NUTRITION AND HEALTH

Handbook of Drug-Nutrient Interactions

Second Edition

Edited by

Joseph I. Boullata
Vincent T. Armenti

Humana Press

HANDBOOK OF DRUG-NUTRIENT INTERACTIONS

SECOND EDITION

NUTRITION AND HEALTH

Adrianne Bendich, PhD, FACN, SERIES EDITOR

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Dedication

This book is dedicated to our families who accepted with good humor the time required to work on the project.

Joseph I. Boullata and Vincent T. Armenti

Acknowledgement

We acknowledge the strong commitment of each of our authors to this project. Additionally, the ongoing support and encouragement from Adrianne Bendich for this topic and project has been invaluable. Finally, we acknowledge Richard Hruska and his staff at Humana Press for the administrative support of the project.

Joseph I. Boullata and Vincent T. Armenti

Series Editor Introduction

The Nutrition and Health Series of books have, as an overriding mission, to provide health professionals with texts that are considered essential because each includes (1) a synthesis of the state of the science; (2) timely, in-depth reviews by the leading researchers in their respective fields; (3) extensive, up-to-date fully annotated reference lists; (4) a detailed index; (5) relevant tables and figures; (6) identification of paradigm shifts and the consequences; (7) virtually no overlap of information between chapters, but targeted, interchapter referrals; (8) suggestions of areas for future research; and (9) balanced, data-driven answers to patient/health professionals questions that are based upon the totality of evidence rather than the findings of any single study.

The goal of the series is to develop volumes that are adopted as the standard text in each area of nutritional sciences that the volume reviews. Evidence of the success of the series is the publication of second, third, and even fourth editions of more than half of the volumes published since the Nutrition and Health Series was initiated in 1997. The series volumes that are considered for second and subsequent editions have clearly demonstrated their value to health professionals. Second editions provide readers with updated information as well as new chapters that contain relevant up-to-date information. Each editor of new and updated volumes has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose trainings are both research and practice oriented, have the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

"*Handbook of Drug–Nutrient Interactions – Second Edition*" edited by Joseph I. Boullata and Vincent T. Armenti fully exemplifies the Nutrition and Health Series' goals. This volume is very timely as about 80% of Americans consume at least one drug – defined as a pharmaceutically active agent – regularly. Moreover, the fastest growing population in the United States as well as globally is that over 60 years of age and especially the oldest-old, those over 80 years of age, and drug use increases with increasing age. Additionally, the aged are at greatest risk for both deficiencies as well as overconsumption of certain nutrients that could be further exacerbated by drug–nutrient interactions. The editors clearly understand the seriousness of the issue of drug–nutrient interactions. They have stated that "In the care of patients, both drug therapy and nutritional therapy are critical. The potential for drugs and nutrients to interact with each other is significant, but unrecognized by many clinicians. These interactions may result in therapeutic failure or adverse effects of the drug, or alterations in the nutritional status of the patient – in either case impacting the patient's outcome."

This important handbook presents a timely review of the latest science concerning drug–nutrient interactions as well as practical, data-driven guidance for the management of at-risk populations exposed to therapeutic interventions. The overarching goal of the editors is to provide fully referenced information to health professionals so they may enhance the nutritional welfare and overall health of clients and patients who may not have been aware of potential unexpected drug–nutrient interactions. This excellent, up-to-date handbook will add great value to the practicing health professional as well as those professionals and students who have an interest in the latest information on the science behind the interactions of nutritional status and drug metabolism and vice versa, the changes in these interactions during the lifespan, and the potential for drug–nutrient interactions, either beneficial or harmful, to modulate the effects of chronic diseases and conditions that are widely seen in the majority of patient populations.

Drs. Boullata and Armenti are internationally recognized leaders in the field of pharmacology and nutrition with particular expertise in clinical approaches to effective management of drug/disease/diet interactions. Dr. Boullata is a recognized leader in the field of nutritional pharmacology, and Dr. Armenti is a transplant surgeon, and they serve as professors of Pharmacology and Therapeutics and of Pathology, Anatomy and Cell Biology, and Surgery respectively. Both editors are excellent communicators and they have worked tirelessly to develop the second edition of their handbook that is already established as the benchmark in the field of clinical nutrition. This volume continues to include extensive, in-depth chapters covering the most important aspects of the complex interactions between dietary components and nutrient requirements and their impact on drug absorption, distribution, and elimination. Drugs used in the treatment of chronic diseases as well as the acute conditions in both men and women are reviewed with the emphasis on the effects of these therapies on nutritional status.

The introductory chapters provide readers with the basics of the complexities involved in drug disposition as the drugs move from the absorptive surface to the blood and then to target organs and organelles in the liver and other organs that contain drug-metabolizing enzymes. Detailed information about dosing and potential drug/nutrient interactions is tabulated. Additionally, a new chapter on drug transporters including informative tables concerning their location and the molecules that are transported into and out of cells has been added to the handbook. Drug-metabolizing enzymes have complex functions. The next chapter describes the actions of many of the 57 functional CYP enzymes in the liver and cites over 300 references. Finally, to assure that all readers have a basic understanding of the human gastrointestinal tract, the last chapter in this part describes the effects of food movements in the GI tract, the release of enzymes and signaling molecules in the mouth through the anus, and the absorption of food in the intestine. Thus, in the first part of the volume, the reader is provided with valuable information about the basics of drug as well as nutrient metabolism and a review of the drug classes and their expected disposition within the body and transport, enzymatic conversions, and potential interactions with dietary constituents.

Part II reviews the influence of nutritional status on drug disposition and effects. Two chapters examine the effects of either under- or over-nutrition (obesity) on drug disposition and their effects. Both comprehensive chapters review relevant classes of drugs that can be most affected by low body weight and obesity or overweight conditions. As more than half the US population is either overweight or obese, this chapter is of great importance when considering drug doses for efficacy.

Part III contains seven chapters that examine the influence of foods, nutrients, and supplements on drug disposition. Co-administration of a drug with a meal can have significant effects on the drug's pharmacokinetics and is especially critical if the drug has a relatively narrow window of efficacy. Specific information about the negative effects of meals on absorption of protease inhibitors as well as the benefits of modified-release oral dosage forms is presented. Practical examples, clinical study designs, and tables describing medications to be taken with and without food are included to better assure that the effect of food on drug efficacy is understood by the health provider. Specific foods and food components have been found to have significant effects on drug absorption and effectiveness. Macronutrients including fat and protein, cruciferous vegetables, grapefruit juice, caffeine, alcohol, vitamins, and certain herbs as well as food preparation, such as charcoal broiling, can all affect drug disposition and are reviewed. Because the effect of grapefruit juice and other juices can affect many drugs, this topic that includes over 200 references, is presented in detail in its own chapter. Certain drugs are poorly absorbed, but absorption is best when taken with food and/or specific nutrients. Certain adverse effects of drugs, such as competing with essential nutrients, can be blunted with dietary changes. These beneficial drug–nutrient interactions are described for the relevant drug classes in the next chapter. Use of dietary supplements has increased dramatically in the United States over the past decade and the variety of supplements and their regulation as well as effects on drug disposition definitely deserved its own chapter. This chapter concentrates on the herbal dietary supplements with the greatest amount of scientific data and includes discussions of garlic, valerian, kava, ginkgo, St. John's Wort, glucosamine/chondroitin, and ginseng. The author has included discussion points as well as responses for the educator or health provider. The next two chapters examine the serious conditions that are associated with enteral and parenteral nutrition and the effects of these nutrient delivery systems to patients who are very often taking one or more medications. Enteral feeding adds complexity to drug pharmacokinetics as co-administration via the tube can result in physical inactivation of the drug and/or modifications to certain nutrients because of exposure to the drug. There is a detailed description of the types of interactions possible between drug and enteral nutrition feeding as well as effects of site of administration, types of enteral formulas and their nutritional components and importantly, a comprehensive tabulation, in 12 tables, of practice guidelines and data on the drugs and their components, such as sorbitol, that may require careful administration to the tube fed patient. Intravenous delivery of nutrients to patients is also obviously complex and challenged further by drug administration. The compatibility and stability of both drug and nutrients are discussed at length, and practice guidelines are provided, as well as 10 informative tables.

Part IV describes the influence of medications on nutritional status and nutrient distribution and effects, and it contains five chapters. The first chapter examines the effects of specific drugs on weight (gain or loss), taste changes, altered GI motility, and metabolic effects, including nutrient depletion. Detailed tables list drugs associated with alterations in taste as well as medications that affect vitamin and mineral status. Because cardiovascular disease is the number one killer in developed nations, and the number and classes of drugs used to treat CVD increase annually, a separate chapter is devoted to the influence of CVD medications on nutritional status. Ten classes of CVD drugs are described in detail with emphasis on their overall effects as well as specific effects of the most commonly used drugs on metabolism and nutritional status. The chapter contains over 200 citations. Drugs that treat neurological illnesses, especially epilepsy, often adversely affect certain B vitamin levels and several are classified as anti-folates. There are also adverse effects on bone and vitamin D status with many of these drugs. Many of the drugs are teratogenic in part a result of their effects on essential nutrients. Parkinsonism, stroke and major brain injury treatments, and nutritional consequences are outlined as well. This informative chapter contains clinical discussions and recommendations. The next chapter provides more in-depth analysis of the physiological roles of folic acid and the effects of drugs that adversely affect folate status. There is also a very useful patient handout that can be used when prescribing an anti-folate such as those included in the comprehensive tables of this chapter. The final chapter in this part reviews the potential effects of drugs on mineral status and includes discussions of sodium, potassium, phosphorus, magnesium, iron, copper, zinc, chromium, selenium, fluoride, iodine, and relevant information on several other trace minerals that are summarized in key tables. The potential for alcohol, illicit drugs, and cigarette smoking to affect mineral status is included as well.

Of particular relevance to clinicians are the chapters in Part V that examine drug nutrient interactions by life stages. Drug–nutrient interactions in infancy and childhood are reviewed with emphasis on the determination of correct dosage levels and dosage forms for the young child. As with the chapter on enteral nutrition, the physical effect of the drug when in contact with infant formula or foods is an important aspect of avoiding adverse reactions. Herb–drug interactions are also included as the use of these products in children has increased in recent years. This chapter contains 13 tables with relevant practice information for the health-care provider. The next chapter in this part reviews drug–nutrient interactions during pregnancy and lactation. Drug effects on the embryo and fetus, placental transfer of drugs, expansion of plasma volume, increases in estrogen and other hormones that can alter metabolic rate, and alterations in renal function, drug effects on appetite and nutrient absorption, drug effects on milk production, drug transfer to breast milk, infant exposure are reviewed, and useful tabulations including information sources on risk of drug use in pregnancy and lactation are provided. The final chapter in this part discusses drug–nutrient interaction in the elderly. This chapter is especially valuable as about one-third of all prescriptions are given to elderly patients who actually make up about 12% of the US population. Drug–nutrient interactions may be of increased risk to the elderly because of the age-related decreases in nutrient absorption, metabolism, and excretion independent of drug use. The chapter provides important insights to help the health provider avoid the real potential for drug-induced adverse health outcomes in elderly patients taking a single or more likely multiple drugs daily. Moreover, the 5 comprehensive tables and more than 250 references provide additional resources to the reader.

The final part of the volume looks at drug–nutrient interactions in individuals who have either chronic diseases or special needs for certain classes of drugs. The chapter on cancer patients is particularly sensitive to the potential for the older as well as newer classes of drugs to affect the precarious health balance in these patients. Tables in the chapter review potential specific drug-induced changes in nutritional status in the cancer patient. Transplant patients also have unique needs, and this chapter provides details about the current antibodies used for transplant induction immediately following transplant and effects on the GI tract – specific issues with transplant of the kidney, liver, pancreas, lung, heart, and small bowel – and concentrates on the nutrient requirements for patients post-transplant. Two chapters examine the effects of the major diseases of the immune system and the effects of chronic infections on nutritional status and then review the nutritional effects of the drugs used to treat these diseases. New and older classes of drugs for HIV and tuberculosis have different effects on the GI tract and nutritional status, and these effects are discussed. There is a comprehensive overview of the human immune system, the effects of specific essential nutrient deficiencies, the effects of major diseases of the immune system with a concentration on autoimmune diseases, including rheumatoid arthritis, diabetes, and lupus, the drugs used in treatment and the interactions of the disease, drug, and nutritional status. Also, there is an in-depth discussion of the importance of pre- and probiotics especially in reference to autoimmune diseases of the GI tract. The seven extensive tables compile information on the major drugs to treat autoimmune diseases as well as infections; the chapter contains more than 300 references.

Drug–nutrient interactions are complex, yet the editors and authors have provided chapters that balance the most technical information with practical discussions of the importance for clients and patients as well as graduate and medical students, health professionals, and academicians. Hallmarks of the chapters include chapter outlines that reflect the content, discussion questions that can guide the reader to the critical areas covered in each chapter, complete definitions of terms with the abbreviation fully defined, and consistent use of terms between chapters. There are over 120 relevant tables, graphs, and figures as well as more than 3800 up-to-date references; all of the 26 chapters include a conclusion section that provides the highlights of major findings. The volume contains a highly annotated index, and within chapters, readers are referred to relevant information in other chapters.

The editors of this comprehensive volume have chosen 42 of the most well-recognized and respected authors who are internationally distinguished researchers, clinicians, and epidemiologists who provide a broad foundation for understanding the role nutritional status, dietary intakes, route of drug administration, life stages of patients, and also disease state and multiple drug use in the background of genetic and clinical aspects of nutritional and therapeutic management of these interactions. Recommendations and practice guidelines are included at the end of relevant chapters.

In conclusion, "*Handbook of Drug–Nutrient Interactions – Second Edition*" edited by Joseph I. Boullata and Vincent T. Armenti provides health professionals in many areas of research and practice with the most up-to-date, well-referenced volume on the importance of the consideration of drug–nutrient interactions for determining the potential for optimal responses to the medicines that are provided to patients. This volume will serve the reader as the benchmark in this complex area of interrelationships between nutritional status, physiological functioning of organ systems, disease status, age, sex, route of administration, and duration and strength of dosage of the myriad of prescription drugs currently available for treatment. Moreover, the interactions between genetic and environmental factors and the numerous co-morbidities seen especially in the aging population are clearly delineated so that students as well as practitioners can better understand the complexities of these interactions. Drs. Boullata and Armenti are applauded for their efforts to develop the most authoritative resource in the field to date, and this excellent text is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, PhD, FACN

Foreword

Interactions between drugs and nutrients can cause an alteration of the pharmacokinetics and pharmacodynamics of a drug or pharmaconutrient that compromises nutritional status as a result of their interplay. This can be either harmful or beneficial. Common adverse events include nutritional deficiencies, drug toxicity, loss of therapeutic efficacy or disease control, and unwanted physiological changes. The working definition of drug–nutrient interactions used in this excellent handbook is broader than often described elsewhere. It is defined as an interaction resulting from a physical, chemical, physiological, or pathophysiological relationship between a drug and a nutrient, multiple nutrients, food in general, or nutritional status. The clinical consequences of an interaction are related to alterations in the disposition and effect of the drug or nutrient.

Rational drug or nutrition therapy requires a management plan based on the correct interpretation of the symptoms and knowledge of the physiological action of the remedy. The physician must therefore make the correct diagnosis and understand the pathophysiology of the disorder before deciding on drug treatment. They should also know enough about the drugs, or receive appropriate pharmaceutical and nutritional advice to select the right drug and administer it in the right dose for the right length of time by the most appropriate route. In addition, the physician must be aware of the potential for both drug–drug and drug–nutrient interactions within the environmental, genetic, and disease-related context.

Pharmaceuticals and pharmaconutrients undergo metabolism through the action of a diverse group of enzymes. The activity of these enzymes is affected by both diet and genotype, and this may be relevant to disease risk, response to diet, and also to optimization of drug dosage in a clinical setting. Dietary factors influence the expression and function of these genes and are likely to have flow-on effects on both drug elimination and disease pathogenesis. Polymorphisms in genes are also critical in determining an individual response to either foods or drugs. Given the number of nutrients and dietary components affecting the immune response, a combined approach involving drugs and pharmaconutrients may become increasingly important in future clinical strategies against illness and disease.

These are exciting times for the pharmaceutical and nutritional sciences. Within the space of only 30 years, I have been privileged to participate in and observe the American Society for Parenteral and Enteral Nutrition (ASPEN) metamorphose from a group of dedicated Americans pioneering advances in nutrition support into a widely respected multidisciplinary international scientific society promoting optimal nutrition *therapy* and pharmaconutrition. These new paradigms encompass the same scientific advances in immunology, molecular biology, nutrigenomics, and substrate metabolism that are being investigated in the development of new pharmaceuticals for therapeutic interventions into the major debilitating diseases of the 21st century. Providing optimal nutrition therapy is as vital to patient outcome as prescribing the correct drug, but as our knowledge of clinical nutrition has expanded, so too have the complexities of the nutrition and drug therapies that patients are prescribed. Incorporating drug–nutrient interaction investigations into new drug development programs may eventually become important for obtaining regulatory approval as well as for improving patient outcome.

The goal of this second edition of the *Handbook of Drug–Nutrient Interactions* is to provide an updated compilation of information on drug–nutrient interactions that will enable health-care providers to better manage their patients. This textbook is intended for use by physicians, pharmacists, nurses, dietitians, and others involved in clinical practice with patients using medication as part of their management regimen. This latest edition, with much new data, will meet its goal by providing both the scientific basis and the clinical relevance with appropriate recommendations for many interactions.

As a researcher and teacher, I particularly appreciate the accessibility and logical simplicity of this reference text which falls naturally into a series of discrete parts: the introductory section provides a basic introduction to drug–nutrient interactions, drug and nutrient dispositions, transporters, and their metabolizing enzymes. This is followed by an important part describing the influence of the extremes of nutritional status, i.e., malnutrition and obesity, on drug disposition and effect. Then a comprehensive part provides a series of chapters on the influence of food and food supplements on drug absorption; fruit juice interactions with medicines; positive drug–nutrient interactions; and enteral and parenteral nutrition. A separate part addresses drugs which influence nutritional status, and a further series of related chapters focus on the role of specific micro- and macro-nutrients in various life stages with particular attention to interactions in infancy and childhood; pregnancy and lactation; and very importantly drug–nutrient interactions in the elderly. Between 10% and 12% of the population in most Western countries is over the age of 65, and it is projected that one in five Americans will be elderly by 2030. However, this relatively small percentage of patients already use more than a third of all medicines prescribed. Moreover, polypharmacy or multiple drug therapy is common in older people. Malnutrition is also more prevalent in the elderly and can be associated with impaired food metabolism, affecting the pharmacokinetics and/or pharmacodynamics of drugs resulting in new drug–nutrient or metabolite interactions.

The editors, Joseph Boullata, PharmD, and Vincent Armenti, MD, PhD, have performed an outstanding service to clinical pharmacology and pharmaconutrition by bringing together a multi-disciplinary group of authors for the second edition of this handbook. The authors, many of whom I am acquainted with through ASPEN, are experts in their designated area. Although predominantly based in North America, they comprise pharmacists, physicians, dietitians, nurses, and nutritionists, who successfully ensure the text is written in a clear, direct, and authoritative style to appeal to their peers throughout the international healthcare community. Their expertise and experience provide not only a comprehensive up-to-date text for the total management of patients on drug and/or nutrition therapy but also an insight into the recent developments in drug–nutrition interactions which will act as a reliable reference for clinicians and students for many years to come.

Gil Hardy, PhD, FRSC

Preface

In the 5 years since publication of the first edition of the *Handbook of Drug–Nutrient Interactions*, new perspectives have emerged and new data have been generated on the subject matter. We have attempted to capture this in the current chapters which have all been revised or are completely new to this edition.

This book is intended for use by physicians, pharmacists, nurses, dietitians, and others whether in training, in clinical practice, in academia, or in research. The book has retained the goals of the previous edition which include improving recognition and management of drug–nutrient interactions. The topic of drug–nutrient interactions is significant for clinicians and researchers alike. For clinicians in particular, the book offers a guide for understanding, identifying or predicting, and ultimately preventing or managing drug–nutrient interactions to optimize patient care. The book provides a scientific look behind many drug–nutrient interactions, examines their relevance, offers recommendations, and suggests research questions to be explored. Although not inclusive of every potential interaction, we hope that the breadth and depth of the book will challenge readers to actively engage in improving the quantity and quality of data in the field. This will help increase the profile of drug–nutrient interactions to that comparable with drug–drug interactions in the care of patients.

We appreciate the dedication of our many authors and those who have provided encouraging comments in the continued development of this reference work. While we welcome new authors who have contributed their expertise and perspective to the book, we remain indebted to the authors from the first edition who set the book in motion, many of whom have worked to revise and update their chapters for this second edition. We were, however, saddened by the loss of Mary Berg, who contributed the original chapter on the *Effects of Antiepileptics on Nutritional Status*, and by the loss of David Fleisher, who helped prepare the chapter on *Drug Absorption with Food.* Each was a leader in the respective subject matter of their chapter and will be greatly missed. As we look forward to the ongoing emergence of new information concerning drug–nutrient interactions, we continue to welcome comments from readers that will improve this book and the care of patients.

Joseph I. Boullata, PharmD, BCNSP
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I

APPROACHING DRUG–NUTRIENT INTERACTIONS

1 An Introduction to Drug–Nutrient Interactions

Joseph I. Boullata

Objectives

- Define the term drug–nutrient interaction in its broadest sense.
- Describe the classification of drug–nutrient interactions with examples of each.
- List possible approaches for identifying, preventing, and managing drug–nutrient interactions.

Key Words: Classification; dietary supplement; drug-nutrient; drug-food; interaction; regulation

1. SCOPE OF THE ISSUE

Advances in the pharmaceutical sciences and nutritional sciences continue unabated. Their application to patient care are expected to generate clinical benefits. Currently there are thousands of drug products commercially available, and approximately 80% of Americans take at least one pharmacologically active agent on a regular basis *(1)*. The sales of pharmaceuticals continue to rise with figures suggesting global sales of over 700 billion U.S. dollars in 2007, nearly 290 billion dollars of that in the United States alone with just over 3.8 trillion prescriptions dispensed *(2)*. Prescription drug use and spending is projected to accelerate significantly despite economic instability *(3)*.

The use of food and nutritional products is more difficult to quantify, although obviously widespread. The availability of food for daily consumption on a global scale averages out to about 2800 kcal per individual *(4)*. Data in the United States suggest mean per capita consumption of 2157 kcal and 81.8 g protein daily *(5)*. Of course actual nutrient consumption is influenced by many factors from availability, cost, and economics to beliefs and preferences, cultural traditions, and geography *(4)*. Environmental factors further influence the nutritional status of populations and individuals.

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Given the widespread use of medication combined with the variability in nutritional status, dietary habits, and food composition, the number of potential interactions between medication and nutrition is overwhelming. Although the number of interactions and permutations may seem infinite and the proportion that may be clinically significant is not clear, scientists and clinicians should not discount the relevance of drug–nutrient interactions to either product development or clinical practice. The prevalence rate for hospital admissions associated with adverse drug reactions in adults ranges from 3.9% to 13.3% *(6)*. The proportion of these that may be drug–nutrient interactions is not known. An ongoing drawback that remains is the absence of properly designed and conducted epidemiologic studies of drug–nutrient interactions *(7)*. This is in large part due to limited or unclear definitions in the literature.

2. DEFINITIONS

The working definition of drug–nutrient interactions used throughout this book is broader than often described elsewhere. It is defined as an interaction resulting from a physical, chemical, physiologic, or pathophysiologic relationship between a drug and a nutrient, multiple nutrients, food in general, or nutritional status *(8)*. An interaction is considered to be clinically significant if it alters pharmacotherapeutic response or compromises nutritional status. The clinical consequences of an interaction are related to alterations in the disposition and effect of the drug or nutrient. The term *disposition* refers to the absorption, distribution, and elimination of a drug or nutrient which can involve physiologic transporters and metabolizing enzymes. And the term *effect* refers to the physiologic action of a drug or nutrient at the level of cellular or subcellular targets. Drug–nutrient interactions can influence health outcomes particularly in vulnerable populations *(9)*.

Several factors may influence the risk for developing a clinically significant drug–nutrient interaction. These include patients with chronic disease who use multiple medications, particularly those drugs with a narrow therapeutic index. The prevalence of medication use in the elderly is widely recognized with consequences that include greater adverse drug effects and drug–nutrient interactions *(10)*. Individuals at either end of the age spectrum, as well as those with genetic variants in drug transporters, enzymes, or receptors, impaired organ function, or poor nutritional status, also have heightened susceptibility to interactions. In this sense, poor nutritional status refers to altered body composition or function resulting from any imbalance between an individual's nutrient requirements and intake – whether the imbalance is due to poor dietary intake or altered nutrient disposition.

Drug–nutrient interactions can be viewed in terms of pharmacokinetics and pharmacodynamics. Drugs and nutrients can influence signal transduction pathways that ultimately impact on drug-metabolizing enzymes and transporters through receptor-mediated gene expression *(11,12)*. The more that is known about drugs serving as substrate, inducer, or inhibitor of various transporters and enzymes in various tissues, the closer that direct or indirect interaction with nutrients that influence these same proteins can be determined or predicted. Pharmacokinetic interactions can involve enzymes and transporters that are implicated in drug absorption, distribution, or elimination. Pharmacokinetic interactions are best defined by changes in drug or nutrient parameters (e.g., bioavailability, volume of distribution, clearance). Pharmacodynamic interactions involve the clinical effect of a drug or physiologic effect of a nutrient. Qualitative or quantitative measures of drug action or of nutritional status help to define pharmacodynamic interactions.

3. PERSPECTIVES

3.1. Historic

For years, the potential for interactions between drug therapy and nutrition was barely mentioned in reference works that probably should have discussed the subject *(13–15)*. This began to change with publication of classic findings such as the influence of vitamin C deficiency on barbiturate action *(16)*, the influence of iron on tetracycline absorption *(17)*, the influence of isonaizid on vitamin B_6 metabolism *(18)*, as well as reviews on the impact of malnutrition on drug disposition *(19)*, the effect of food on drug absorption *(20)*, and the influence of drugs on nutrient disposition *(21)*. This historic perspective has been described in further detail *(22)*. The increased awareness of drug–nutrient interactions has yet to be fully translated and integrated into the general knowledge of clinicians, scientists, and regulators who in turn have the ability to make meaningful contributions to the subject.

3.2. Clinician

Drug interactions contribute to adverse drug effects and can lead to withdrawal of approved drugs from the market *(23)*. Interactions between one drug and another have long been recognized as influencing patient outcomes through altered drug disposition and effect. Drug–nutrient interactions have been considered less significant than drug–drug interactions with the former often limited in scope to the dosing of an oral drug in relation to a meal or perhaps the effect of a drug on body weight or serum glucose and electrolyte concentrations. Surveys suggest poor knowledge of common drug–nutrient interactions among health-care providers, with few offering counseling to most of their patients on the topic *(24,25)*. Some clinicians may recognize specific interactions as individual pieces of information – for example, interactions that interfere with drug absorption (e.g., calcium-containing food products and tetracycline or ciprofloxacin) or other well-described classic interactions (e.g., tyramine-containing foods with monoamine oxidase inhibitors) – but not realize that each can fit into a larger classification system. Generally, product information is not considered an optimal resource for information on drug–nutrient interactions *(26)*. In order for clinicians to recognize, identify, prevent, or manage drug–nutrient interactions that have the potential to influence patient outcome, a more systematic approach to this area of therapeutics is necessary. Such an approach may also be of value to product development.

3.3. Scientist

The science of describing drug–drug interactions has evolved significantly *(27)*. Drug–drug interactions are widely recognized, identified, and managed in practice. The evaluation of drug–drug interactions is also inherent to the drug development process as reflected in guidance documents for industry. Unfortunately, the same may not be said for drug–nutrient interactions yet. The same attention given to the potential for pharmaceutical, pharmacokinetic, or pharmacodynamic drug–drug interactions needs to be afforded to the study of drug–nutrient interactions *(8)*. Drug–nutrient interactions beyond meal effects need to be considered in new drug evaluations as well *(23)*. In the meantime, clinicians should have access to interaction information that allows safe treatment approaches. Because of limited clinical drug–nutrient interaction data generated as part of the drug development process, much will have to be explored in postmarketing observational studies, or from individual case reports, with subsequent mechanistic investigations and descriptions when novel interactions are identified.

3.4. Regulatory

The philosophic approach of the U.S. Food and Drug Administration (FDA) within the framework of the Federal Food, Drug and Cosmetic Act has been to reserve enforcement only when regulatory violations are identified; otherwise, they encourage industry self-regulation *(28)*. As part of that encouragement, the FDA provides guidance for industry on emerging aspects of drug development, approval, and safety. Although the FDA still does not require an evaluation of drug–nutrient interactions in its guidance process for drug development, there may be room for its consideration within the drug interaction guidance *(29,30)*. A good guidance practice document, specific for drug–nutrient interactions, may be less likely to be considered, although the FDA could identify issues and determine whether a working group needs to be developed. Among other features, a discussion of pharmacokinetic and pharmacodynamic endpoints as well as evaluating the degree of change following an interaction (enzyme or transporter) is equally relevant to drug–nutrient interactions *(29)*. Although these can be used to guide characterization of new molecular entities in the drug development process, they can also be applied to a reevaluation of high-risk drugs already in use. New data generated for the latter will require revision to the labeling. Any identification of potential interactions based on early in vitro study helps determine the necessity of subsequent in vivo evaluation. Currently available decision trees can be modified to address drug–nutrient interactions, as can existing criteria (e.g., identifying inhibitor or inducer substrate) *(29)*. For example, an enzyme inhibitor would have to result in a twofold increase in the area under the concentration–time curve (AUC) to be considered “moderate” in its effect.

4. CLASSIFICATION AND DESCRIPTIONS

Based on the working definition provided above, drug–nutrient interactions can be classified into one of five broad categories (Table 1) *(8)*. The many types of drug–nutrient interactions can thus be categorized with each having an identified *precipitating factor* and an *object* of the interaction. In some cases, the drug is the precipitating factor (i.e., causing changes *to* nutritional status), while in others the drug is the object of the interaction (i.e., changes in drug disposition or effect result *from* a nutrient, food, or nutritional status). Drug–nutrient interactions are clinically important if the precipitating factor produces significant change in the

Table 1
Classification of Drug–Nutrient Interactions *(8)*

Precipitating factor	*Object of the interaction*	*Potential consequence*[†]
Nutritional status	Drug	Treatment failure or drug toxicity
Food or food component	Drug	Treatment failure or drug toxicity
Specific nutrient or other dietary supplement ingredient	Drug	Treatment failure or drug toxicity
Drug	Nutritional status	Altered nutritional status
Drug	Specific nutrient	Altered nutrient status

[†] See text for specific examples.

object of the interaction. Interactions that need to be totally avoided are not common; instead close monitoring with modification to the dosing schedules is usually all that is necessary. The nature of any physicochemical or physiologic interaction and its mechanism may be further classified to help in predicting and preventing their occurrence (Table 2) *(31)*. Mechanisms of an interaction relate to the physicochemical attributes of the medication and of the food or nutrient, within the environmental matrix (e.g., the feeding tube or the patient). The consequence of an interaction (altered disposition of a drug or nutrient) is linked to its location. For example, at the gastrointestinal mucosa, an influence on membrane transporters and/or metabolizing enzymes can alter the bioavailability of a drug or nutrient. Another dimension to be considered is that physiologic manifestations of a

Table 2
Location and Mechanisms of Drug–Nutrient Interactions *(31)*

Site of interaction	*Consequence*[†]	*Mechanism of interaction*
In drug (or nutrient) delivery device or gastrointestinal lumen	Reduced bioavailability	Physicochemical reaction and inactivation
Gastrointestinal mucosa	Altered bioavailability	Altered transporter and/or enzyme function
Systemic circulation or tissues	Altered distribution/ effect	Altered transporter, enzyme, or other physiologic function
Organs of excretion	Altered clearance	Antagonism, impairment, or modulation of elimination

[†] Consequence to the drug and/or nutrient.

drug–nutrient interaction may differ based on gene polymorphism (e.g., methotrexate and folic acid) *(32,33)*. The role of polymorphisms in nuclear receptors, metabolizing enzymes, and other proteins needs to be taken into account *(34)*. A brief description of each drug–nutrient interaction category follows with select examples.

4.1. Nutritional Status Influences Drug Disposition

Pharmacokinetic and pharmacodynamic data in special patient populations usually focus on those with renal impairment, hepatic dysfunction, or unique life-stage attributes. Drug disposition is much less frequently assessed based on nutritional status (e.g., protein-calorie malnutrition, obesity, micronutrient deficits), although the influence on drug metabolism has been recognized *(35–37)*. The nutritional status of subjects in clinical drug trials has not always been well described. Drug distribution and clearance are the pharmacokinetic parameters most likely to be influenced by malnutrition. Nutritional status may modify susceptibility to other chemical exposures as well *(9)*. Therapeutic effectiveness or risk for toxicity can be altered by the degree of malnutrition *(38)*.

Reviews on drug class-specific considerations in obesity are welcome, given the ongoing epidemic. Much attention has been paid to antimicrobials in obesity, in view of the clinical repercussions of not accounting for altered drug distribution or clearance *(39)*. This has also been suggested in the case of antibiotics used in undernourished children *(40)*.

During treatment for cellulitis with piperacillin-tazobactam 3.375 g q4h intravenously in a morbidly obese patient (body mass index [BMI] 50 kg/m^2), pharmacokinetic sampling revealed an altered volume of distribution (*V*d) (0.33 L/kg) and clearance (Cl) (27 L/h) for piperacillin, compared with normal values *(41)*. This indicates that the dosing of piperacillin can be based on total body weight, especially if dealing with a *Pseudomnas aeruginosa* minimum inhibitory concentration (MIC) > 8 mg/L *(41)*.

An area of particular concern is the preoperative dosing of antimicrobials to prevent postoperative infection in obese patients undergoing surgical procedures. A 1 g dose of cefazolin as antibiotic prophylaxis for surgery in patients with BMI > 40 kg/m^2 resulted in serum drug concentrations below the MIC for several organisms, but adjustment to 2 g dosing reduced surgical site infection rates from 16.5% to 5.6%, $p<0.03$ *(42)*. Mediastinitis following cardiac surgery in obese patients may also be related to inadequate antimicrobial dosing *(43)*. Cephalosporin clearance may be increased in obesity, requiring repeated dosing during an operation that lasts longer than 2–3 h *(44)*.

Despite high protein binding and distribution predominantly within the extracellular compartment, the pharmacokinetics of ertapenem differ based on BMI *(45)*. Following a standard 1 g intravenous dose, *V*d was significantly higher in normal weight subjects than in obese and severely obese subjects (0.078 L/kg vs 0.063 L/kg and 0.057 L/kg) *(45)*. The significantly lower drug exposure (i.e., $AUC_{0-\infty}$) in the obese and severely obese subjects translates into lower probability of attaining drug exposure targets at a given MIC compared with normal weight subjects *(45)*. Further data are still needed to recommend more optimal drug-dosing schemes for patients with poor nutritional status.

4.2. Food Effect on Drug Disposition

4.2.1. FOOD IN GENERAL

Oral drug administration concurrent with food intake alters the physicochemical conditions within the gastrointestinal tract and may influence the rate and/or extent of drug absorption. The latter is more clinically significant varying with drug properties and meal characteristics. The ability to predict the influence of food on drug disposition has become more grounded in science *(46)*. Prediction based on classifications of physicochemical drug properties (e.g., Biopharmaceutics Classification System [BCS] *(47)* or the Biopharmaceutics Drug Disposition Classification System [BDDCS] *(48)*) together with physiologic variables has become useful. The FDA issued a guidance for industry that expanded drug labeling to include this most basic of information on one aspect of drug–nutrient interactions *(49)*. The recommended test meal using the concept of worst-case scenario contains about 800–1000 kcal with about 50% of calories as fat. While valuable information is provided for clinical use of the marketed medication, it is also in the interest of drug development to identify these interactions early. The BCS data generated in cell culture can often predict human disposition although classifying medication by BDDCS may allow better prediction of food effects *(46,50)*.

The influence of food on a once-daily orally administered iron chelating agent (deferasirox) was recently evaluated *(51)*. This agent may be considered a BCS Class II drug whose bioavailability (~70%) would be predicted to increase with a meal *(52)*. At a dose of 20 mg/kg, the administration of deferasirox was evaluated one-half hour before a high-calorie meal (1000 kcal, 50% fat), one-half hour before or with a more standard breakfast meal (450 kcal, % fat not described), and in a fasted state *(51)*. Drug bioavailability was increased when taken with food, and more so at higher fat content of the meal. Bioavailability was greatest when administered with a standard breakfast (1580 $\mu\text{mol}\cdot\text{h}\cdot\text{L}^{-1}$), followed by a lower exposure when administered one-half hour before either meal (1340 $\mu\text{mol}\cdot\text{h}\cdot\text{L}^{-1}$and 1320 $\mu\text{mol}\cdot\text{h}\cdot\text{L}^{-1}$), and it was lowest in the fasted state (1060 $\mu\text{mol}\cdot\text{h}\cdot\text{L}^{-1}$). The food effect is likely a result of increased solubilization at a more optimal pH, fat content, and surfactant level. From a pharmacodynamic standpoint, the plasma concentrations of iron–drug complex in patients with iron overload were unaffected by food intake *(51)*. The current recommendation is to administer deferasirox 30 min before a meal *(53)*. The magnitude of change in bioavailability would determine how clinically significant the difference is between the fed and fasted states. A similar approach can be taken when describing influences of specific foods or nutrients on drug disposition.

4.2.2. SPECIFIC FOODS OR FOOD COMPONENTS

Specific foods may also have a unique influence on drug disposition. In vitro and in vivo studies help to tease apart possible mechanisms of these interactions.

Di- and trivalent cation-containing dietary products including dairy foods are known to chelate with the fluoroquinolone antibiotics and reduce their bioavailability. This remains true for the newer drugs in this class *(54)*. Cow's milk may also reduce drug bioavailability by its xanthine oxidase content as in the case of mercaptopurine and its transformation to the inactive 6-thiouric acid by the enzyme *(55)*. It is suggested that a 6 h gap should be sufficient to prevent the interaction *(55)*.

Cruciferous vegetables are a dietary source of glucosinolates that are metabolized to isothiocyanates and indoles. The isothiocyanates are not only substrates for but also inducers of glutathione-*S*-transferase (GST) enzymes. The potential for interaction with drugs metabolized through the various GST isoenzymes is not well described. Whether any potential interactions are influenced further by polymorphism in these enzymes will also need to be more closely evaluated. GST genotype may not necessarily predict the influence of dietary sources of isothiocyanates *(56)*.

Soy protein isolates reduce the expression and activity of the cytochrome P450 (CYP)-metabolizing isoenzyme CYP1A1, most likely by a posttranslational reduction of the transcription factor AhR (aryl hydrocarbon receptor) *(57)*. Based on a gene array screening method, soy isoflavones can significantly upregulate two drug transporters and three phase I and two phase II enzymes *(58)*. A soy extract-containing product did not appear to influence losartan pharmacokinetics in healthy subjects, although the supplement product contents were not confirmed *(58a)*.

Several juices can interact with medication at the level of transporters and metabolizing enzymes to a broader degree than first described *(59,60)*. Juices can have an influence on drug disposition based on furanocoumarin and flavonoid content. For some juices, the evidence provided by case reports is only circumstantial and, as in the case of the influence of cranberry juice on warfarin, prospective study may reveal no pharmacokinetic mechanism for an interaction *(61,62)*. The influence on drug transporters and metabolizing enzymes from consuming juices from pureed vegetables remains unknown.

4.2.3. OTHERS

The influence of enteral nutrition on drug disposition and drug effect would also be included in this category of drug–nutrient interactions. A plurality of mechanisms can be involved whereby drug bioavailability may be altered in the presence of enteral nutrition *(63,64)*. Parenteral nutrition although administered directly into a large vein and obviously bypassing the gastrointestinal tract can also interact with medication *(65,66)*. Although technically considered a prescription medication parenteral nutrient admixtures can interact at many levels. The same can be said for individual nutrients (e.g., potassium chloride, magnesium sulfate, multivitamins) administered parenterally.

4.3. Effect of Specific Nutrients or Other Dietary Supplement Ingredients on Drug Disposition

Data are available on drug interactions associated with individual nutrients and with non-nutrient dietary supplement ingredients *(67,68)*. This includes divalent and trivalent cations administered in pharmaceutical dosage forms which can chelate several drugs and reduce bioavailability of both. Sometimes an ex vivo interaction – for example, iron and mycophenolic acid (the active form of mycophenolate mofetil) – as identified in a simple solvent may not occur to a similar or clinically relevant extent in simulated gastric acid *(69)*. Mechanistically, these interactions can otherwise occur because of altered intestinal transport and metabolism or systemic metabolism and excretion, as well as an additive, synergistic, or antagonistic pharmacodynamic effect.

Vitamin D, particularly in its most biologically active form, increases the expression of several phase I and II metabolizing enzymes *(70)*. This is not unexpected given that the vitamin D receptor is a nuclear receptor in the same subfamily as others involved in enzyme induction. The influence of a nutrient on drug disposition may be a positive interaction. One example would be the use of pyridoxine in the prevention or treatment of isoniazid toxicity *(71)*.

Interacting compounds within this category can encompass the various classes of polyphenols and other phytochemicals. These include the flavonoids, phenolic acids, stilbenes, and lignans that may possess therapeutic effects *(72)*. Even bioactive peptides from plants and non-plant food sources may play a role *(73)*. These compounds are found not only in foods but increasingly in dietary supplements. Culinary herbs and spices contain many bioactive compounds including flavonoids, terpenes, and vanilloids, which may carry health benefits but may also influence drug disposition *(74)*. Other flavoring agents may also need to be evaluated. The estimated mean flavonoid intake from dietary sources in the United States is 190 mg/day *(75)*. Risk assessment and safety evaluation of flavonoid intake includes consideration of interactions with drugs *(76)*. Many of these polyphenolic compounds are substrates for drug-metabolizing enzymes and transporters. The inhibitory influence of some polyphenolic compounds may be broad, while others are isoenzyme specific *(77)*. More data are available describing their influence on efflux transporters than on uptake transporters *(78,79)*. An in vitro study using a cell culture overexpressing P-glycoprotein revealed that some phytochemicals (e.g., capsaicin, curcumin, gingerol, resveratrol) have an inhibitory effect on this efflux transporter *(80)*. Some of these and additional phytochemicals found in spices may also influence CYP3A4 metabolism *(81)*. Influences of flavonoids on the expression and activity of several CYP, GST, *N*-acetyltransferase (NAT), sulfotransferase (SULT), and uridine diphosphate glucuronosyltransferase (UGT) enzyme isoforms have been documented in vitro and in vivo *(82)*. For example, numerous in vitro studies suggest that the flavonoids – particularly the flavonol quercetin – are consistently potent inhibitors of cytosolic SULT isozymes relevant to drug metabolism *(82)*. Aside from the usual cautions in interpretation and extrapolation from in vitro and in vivo data, and given discrepant findings, only a few studies in humans are available.

Daidzein is an isoflavone that consumers may use for managing osteoporosis or perimenopausal symptoms. At an oral dose of 200 mg twice daily for 10 days, daidzein increased the bioavailability of theophylline in healthy volunteers and reduced its elimination as a result of diminished CYP1A2 activity *(83)*. The bioavailability of metronidazole may be increased by diosmin (a flavone) and decreased by silymarin (a flavonoid found in milk thistle) in healthy volunteers *(84,85)*. Diosmin, used in the treatment of chronic venous insufficiency and hemorrhoids, also increases the bioavailability of diclofenac possibly through CYP2C9 inhibition *(86)*.

4.4. Influence of Drugs on Global Nutritional Status

4.4.1. FOOD INTAKE AND ABSORPTION

The influence of medication on overall nutritional status can be multifactorial *(87)*. Drugs can influence food intake, digestion, and absorption. A drug may alter food intake by direct effects on the gastrointestinal tract or the gut–brain axis. The mechanism for the sensitivity of gastrointestinal function to drugs has not received much attention *(88)*. When significant, disturbance in gastrointestinal function (e.g., taste disorder, stomatitis, nausea, vomiting, diarrhea) can impair individuals' ability to maintain or improve their nutritional status. Alternatively indirect effects on food intake may occur as a result of drug-induced cognitive disturbances, visual changes, movement disorders, and gait abnormalities when severe. Impaired ability to gather, prepare, or ingest food may play a role *(89,90)*.

4.4.2. METABOLISM

Medication may also be associated with altered metabolic function. Metabolic adverse effects (e.g., weight gain, hyperglycemia, dyslipidemia, osteoporosis) have been documented. Some changes in global nutritional status (e.g., weight gain) may be sought clinically as in the example of megestrol *(91)* but for others it is an adverse event as in the case of antipsychotics *(92)*. Several metabolic adverse effects (i.e., weight gain, hyperglycemia, dyslipidemia) have been associated with the use of the second-generation antipsychotics *(93)*. An evaluation of a large database revealed that weight gain (increased BMI) was significantly more likely with the use of risperidone, quetiapine, and olanzapine compared with first-generation antipsychotic agents, while weight gain was less likely with aripiprazole, ziprasidone, and clozapine *(92)*. In nonobese individuals, the increased body weight and BMI associated with risperidone does not result in a predictable change in lipid profile *(94)*. Pharmacoepidemiologic data suggest that there is no predictable difference between first- and second-generation antispychotics in resultant diabetes *(95)*. Other drugs, for example capecitabine, may cause severe hypertriglyceridemia ($>$ 500 mg/dL), particularly in at-risk individuals *(96)*.

4.5. Influence of Medication on the Status of Specific Nutrients

The influence of medication on the status of a specific nutrient can also be multifactorial *(87)*. Drugs can influence nutrient absorption, distribution, metabolism, and excretion. The significance of changes in nutrient status as a result of medication use will be based in part on the relevance of individual markers. Furthermore, any clinical manifestation may be patient-specific as much as drug-specific. The development of an overt classic nutrient deficiency syndrome would be considered an extremely rare result of an interaction. Instead, some lesser degree of deficit may be associated with clinical manifestations. The concept that some adverse drug effects are directly related to their influence on nutrient status is not new. Drug-induced nutrient deficits may be considered a subclass of adverse drug effects whether dose-related, duration-related, or idiosyncratic in nature. For example, the ability of carbamazepine to alter biotin status by decreasing absorption and increasing clearance may account for some of the idiosyncratic adverse effects observed with this antiepileptic drug *(97–99)*. The influence on the status of a nutrient in these circumstances may or may not be adequately addressed by nutrient supplementation *(100)*.

Carnitine deficiency can occur with valproic acid treatment, resulting in reductions of both plasma-free carnitine and plasma total carnitine concentrations, as well as a reduction in urinary total and free carnitine with chronic valproic acid treatment *(101–103)*. Tissue carnitine depletion during treatment with valproic acid may in part be due to an inhibition of tissue uptake *(104)*. Valproic acid treatment is also associated with altered acylcarnitine subspecies that reflect impaired intermediary metabolism likely responsible for drug-induced hepatotoxicity *(105)*. Valproic acid seems to inhibit the hepatic synthesis of carnitine thereby contributing to a deficiency state. This appears to occur at the level of butyrobetaine hydroxylase but without direct inhibition, likely a result of reduced α-ketoglutarate levels required as a cofactor *(106)*. This deficit may contribute to the drug's adverse effects including hyperammonemia. Management of clinical deficiency has required a significant dose of carnitine in children, in which case symptoms resolved within 1 week of the intervention *(102)*. It has been suggested that oral L-carnitine supplementation be considered for patients with symptomatic valproic acid-associated hyperammonemia, or those with multiple risk factors for valproic acid hepatotoxicity, and infants and children using valproic acid *(107)*. The recommended oral dose of L-carnitine is 100 mg/kg daily to a maximum of 2 g daily. Intravenous administration of L-carnitine is also an option for patients with valproic acid-induced hepatotoxicity or other acute metabolic crises associated with carnitine deficits *(107)*. Supplementation may not be needed in all patients receiving valproic acid who are otherwise healthy and ingest a regular diet *(108)*. An appropriate prophylactic dose has not been described.

Even the use of drugs of addiction may influence nutritional status. For example, cigarette smoking is associated with diminished status of several nutrients including folate, pyridoxine, and vitamin B_{12} even after adjustment for dietary intake in otherwise healthy individuals *(109)*. Tobacco smoking increases biotin metabolism placing women in marginal deficiency, and it has been speculated that this may contribute to teratogenicity *(110)*.

There are some medication regimens that are associated with improvements in nutrient status. For example, the use of highly active antiretroviral therapy in management of HIV infection is associated with improved concentrations of α-carotene, β-carotene, α-tocopherol, vitamin B_{12}, and folate, although these findings were not adjusted for inflammatory state *(111)*. The 3-OH-3-CH_3-glutaryl coenzyme A (HMG-CoA) reductase inhibitors may improve vitamin D status, which may play a role in the drug's therapeutic benefit beyond cholesterol concentration modification *(112)*. The role played by the increased availability of 7-dehydrocholesterol as the vitamin D precursor in the skin following HMG-CoA reductase inhibition is unclear.

Despite improved awareness, definitions, classification schemes, and multiple examples of drug–nutrient interactions available in the literature, further progress should be expected. In order to better recognize, identify, prevent, or manage drug–nutrient interactions, more systematic contributions to the database will be needed from all sectors. These can then be applied in both product development and patient care.

5. MOVING FORWARD

5.1. Product Development and Evaluation

In the process of advancing the drug–nutrient interaction database, one can start with systems already in place. Much can be gathered from the learning curves built in the study of drug–drug interactions, as well as from the advancements in nutrition and food science *(12,27, 113–116)*. For example, strategies for conducting in vitro and in vivo studies, selection of doses and study endpoints, sample size and data analysis considerations are already provided for in guidance documents on drug–drug interactions *(114)*. Additionally a good appreciation of nutritional biochemistry and nutritional pharmacology is necessary. This would include an understanding of the physicochemical properties, kinetics, and cellular functions of each of the nutrients and other dietary components. Practical investigations for integrating pharmacokinetic and pharmacodynamic data will require knowledge of both drug and nutrient disposition.

Knowledge of the affinities of drugs and nutrients for transporters and enzymes has become invaluable. The cellular signaling pathways for the influence on drug-metabolizing enzymes continue to be studied as well *(117)*. The role that nutrients play at this level will also need to be closely evaluated to further develop drug–nutrient interaction models. As an example, a concerted effort is needed to identify or at least to try and predict adverse drug–flavonoid interactions. Validation of in vitro data using in vivo models for both metabolism and transport would be appropriate *(118)*. This would seem prudent especially for those flavonoids used in pharmacologic doses in dietary supplement products. This would occur in parallel with further characterization of the disposition of each flavonoid and its numerous metabolites.

Enterocyte and hepatocyte cell culture systems could be used keeping in mind their limitations. The ability to mechanistically evaluate single and then multiple enzymatic and transporter pathways may provide the ability to help predict clinically relevant drug–nutrient interactions. In vitro systems expressing single drug transporters may not be able to predict the findings from more complex systems or in vivo experiments *(119)*. Even a drug class known to inhibit a metabolizing enzyme may turn out to interfere with uptake transporters as well *(120)*.

Animal models may be useful in examining interactions further, keeping in mind the disadvantage in extrapolation to humans that come with species differences *(121)*. Selecting compounds that are unique to an enzyme or transporter will allow for better evaluation of specific drug–nutrient interactions. However, even this will require further determination of the influence of enzyme or transporter polymorphisms on the results.

DNA chip technology continues to improve and can be a valuable tool to quantitatively evaluate gene expression profiles in various tissues *(11)*. Pharmacogenomic information on absorption, distribution, metabolism, and excretion that may improve drug use can be included in drug labeling and prescriber information *(122)*. Select drug–nutrient interactions that involve pharmacogenomic aspects could easily be included as well. This should be considered in the drug development process when previous data suggest any potential for interaction.

Ultimately the ability to document clinical and experimental drug–nutrient interaction data into accessible databases will make possible the generation and investigation of hypotheses. This will be true whether the data are at the level of a nutrient-sensitive gene, a patient outcome, or the various parameters in between. This may allow for mixed effects modeling and improve predictions of clinically relevant interactions – particularly those that do not develop acutely. The benefit of standardized experimental design with pharmacokinetic and pharmacodynamic studies can be extended to nutrition research generally as has recently been suggested *(123)*. Physiologically based modeling can be used to predict parameters of interest *(124,125)*.

While incorporating drug–nutrient interaction research strategies into the drug development process for new agents is possible, much research will need to be conducted on drugs already in the marketplace. Starting with those drugs having a narrow therapeutic index and those with well-characterized transport and metabolic pathways would seem appropriate. Quantitative prediction of the magnitude of a drug–nutrient interaction based on in vitro data (i.e., in vitro–in vivo correlation) is still not perfect. The magnitude of change in a given kinetic or dynamic parameter will reflect the severity or clinical relevance of an interaction after taking patient (e.g., age, organ function) and drug (e.g., therapeutic index) factors into consideration. For example, the strength of a metabolic interaction could be based on the degree to which the AUC is influenced. Prospective research is also required on the provision of micronutrient supplementation in cases of drug-induced depletion (e.g., pyridoxine therapy concurrent with a regimen of isoniazid or folic acid therapy concurrent with phenytoin).

5.2. Patient Care

5.2.1. Approach

To maximize a drug's benefit while minimizing adverse drug outcomes, it becomes necessary to recognize drug–nutrient interactions systematically as part of the patient assessment process or the drug regimen review. To achieve this, clinicians need to increase their overall level of awareness of drug–nutrient interactions beyond a few isolated examples. There is an expectation that clinicians in health-care systems identify and address drug–nutrient interactions *(126)*. Whether at the institutional level, or at the patient level, more needs to be done. In practice, drug–nutrient interactions can best be identified as part of a thorough assessment of a patient's history and physical examination. A nutritionally focused history and physical exam is important to allow for identification of potential nutrient deficits which can still occur even in high-risk groups using nutrient supplementation *(127)*.

5.2.2. Institutional Level

The current Joint Commission standards for patient care and for medication management are broad based, integrated, and less prescriptive *(126)*. There are no longer specific standards that address drug–nutrient interactions. Several standards relating to patient assessment, patient care plans, medication order review, safe medication administration, patient monitoring, and patient education in a collaborative fashion based on the patient's needs would be interpreted to include a system for drug–nutrient interaction identification and management. An element of performance for standard MM.05.01.01 indicates that all medication orders are reviewed by a pharmacist for "existing or potential interactions between the medication ordered and food and medications the patient is currently taking" *(126)*. Although narrow in definition, it does suggest that an organization perform this evaluation. The current National Patient Safety Goals include one goal to reduce the harm associated with the use of anticoagulation therapy *(128)*. An associated element of performance for this highlighted example describes that the institution's dietary service is notified of all patients receiving warfarin and responds according to an established food–medication interaction program. Clinicians representing all disciplines should be expected to play a role in determining institutional policy and procedures that provide a framework for evaluating drug–nutrient interactions. Responsibilities can be assigned across disciplines based on availability, with the intent of optimizing patient safety.

One approach is to have a subcommittee or working group of the institution's pharmacy and therapeutics committee take the responsibility to develop and maintain a policy and procedure on drug–nutrient interactions. By nature, this would be an interdisciplinary group that would determine in a practical manner which high-risk medications (e.g., antiepileptics, antimicrobials, warfarin) or high-risk patients (e.g., the elderly, obese, transplant recipients) for the institution to manage in terms of drug–nutrient interactions. Procedures for identifying patients with a potential drug–nutrient interaction complete with assigned responsibilities and documentation of each intervention would be critical. Periodic review of the policy, procedure, and interventions by the pharmacy and therapeutics committee would allow any necessary feedback.

The adverse consequences of drug–nutrient interactions (e.g., decreased efficacy, increased toxicity, altered nutritional status) do not discriminate by health-care setting. Special attention would be given to patients at the greatest risk for interactions regardless of the practice setting.

Much has been made about the interactions between food or specific nutrients and the pharmacokinetics or pharmacodynamics of warfarin. The ability to predict or avoid such interactions may still not guarantee optimal anticoagulation given the large number of genes involved in drug disposition and effect that result in the significant interindividual variability in dosing requirements for this drug *(129)*. Warfarin dose requirements are predominantly affected by *CYP2C9* and *VKORC1* genotype, and age *(130)*, while *CYP2C19* genotype does not appear to impact warfarin pharmacodynamics *(131)*. However, drug–nutrient interactions are still significant at the level of intraindividual variability of therapeutic or toxic response.

5.2.3. INDIVIDUAL PRACTITIONER–PATIENT LEVEL

Clinicians can increase the attention paid to a patient's nutritional status and dietary habits before and during drug therapy. A focus on the most commonly used chronic medications, especially those with a narrow therapeutic index and those with active metabolites, makes practical sense. Particular attention could also be paid to medication used in the elderly, the critically ill, or those receiving enteral or parenteral nutrition therapy.

Patient management will be based on the severity of the presenting drug–nutrient interaction or the risk potential for an interaction. In many cases, close monitoring is required, in others the regimen needs to be adjusted. If the therapeutic efficacy of a drug regimen is different than expected, the clinician could evaluate whether this outcome is related to the patient's nutritional status, dietary habits, or specific nutrient or other dietary supplement intake. Similarly, if a change to a patient's overall nutritional status or to the status of a specific nutrient or biomarker occurs, the contribution of the drug regimen could be evaluated closely. A technology-based system for reporting observed drug–nutrient interactions in combination with a broader surveillance database system would be beneficial. Some drug–drug interactions are only recognized with widespread use after the drug is marketed so clinicians should remain just as vigilant for such a possibility with drug–nutrient interactions. Clinicians and scientists should continue to be encouraged to investigate and report drug–nutrient interactions in the literature as well as to the FDA.

As with drug–drug interactions, the clinical significance and severity of drug–nutrient interactions can vary. A rudimentary scoring system was suggested *(8)*. Although this is clearly subjective – and as such beholden to bias and nuances in the evidence available – it is a starting point (Table 3). The ability to assign causation in a clinical case or series would be welcome. Such a proposal has been presented *(132)* and used to successfully evaluate drug–nutrient interactions *(133)*. The drug interaction probability scale was designed to assess the probability of a causal relationship between a drug interaction and an adverse event, and it follows the pattern used in the frequently cited probability scale for adverse drug reactions. With slight modification to account for this chapter's broader definitions of precipitating factors and objects of interaction, the scale is presented in Table 4. This will benefit from wider use, modification if necessary, and further validation. A falsely low probability score is a risk when inadequate data are available to evaluate a potential interaction. This again highlights the need for all clinicians to be vigilant in identifying and documenting drug–nutrient interactions.

A coordinated interdisciplinary team-based approach that includes dietitians, nurses, pharmacists, and physicians is considered critical to managing patients with the potential for drug–nutrient interactions *(134,135)*. Drug–nutrient interaction resources are varied and continually evolving in terms of depth, breadth, and accessibility. Data that are available in textbooks, handbooks, Internet-enabled personal digital assistants, or online sources can be used to help identify or manage drug–nutrient interactions. As was recently suggested for drug–herb interactions *(136)*, effective screening tools would be advantageous in improving the ability to predict clinically significant drug–nutrient interactions, especially those involving enzymes and transporters. Decision support systems integrated into an institution's rules-based informatics systems can also be valuable.

Table 3
A Subjective Approach to Drug–Nutrient Interactions *(8)*

Clinical significance of the interaction	*Severity of the interaction*	
1 – Potentially severe clinical consequence; avoid if possible	1 – Major	Based on the magnitude of change in biomarker, pharmacokinetic parameter, or pharmacodynamic response
2 – Clinical consequence exists; adjust regimen and monitor	2 – Moderate	
3 – Clinical consequence unlikely, or data are insufficient	3 – Minor	

Table 4
The Drug Interaction Probability Scoring System and Scale *(132)*

Question	*Reply* *Yes*	 *Unknown or N/A*	 *No*
• Are there previous *credible* reports of this interaction in humans?	+1	0	−1
• Is the observed interaction consistent with the known interactive properties of the precipitating factor?	+1	0	−1
• Is the observed interaction consistent with the known interactive properties of the object?	+1	0	−1
• Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	+1	0	−1
• Did the interaction remit upon dechallenge of the precipitating factor with no change in the object?	+1	0	−2
○ If so, did the interaction reappear when the precipitating factor was readministered in the presence of continued use of the object?	+2	0	−1
• Are there reasonable alternative causes for the event?[†]	−1	0	+1
• Was the object of the interaction detectable in the blood or other fluids in concentrations consistent with the proposed interaction?	+1	0	0
• Was the drug interaction confirmed by any objective evidence consistent with the effects on the object (other than concentrations from the previous question)?	+1	0	0
• Was the interaction greater when the precipitating factor was increased or less when the precipitating factor was decreased?	+1	0	−1

Total score ___

Score	Probability
<2	Doubtful
2–4	Possible
5–8	Probable
>8	Highly probable

[†] = Consider clinical conditions, other interacting drugs, lack of adherence, risk factors (e.g., age, inappropriate drug doses); an answer of "no" presumes that enough information was presented so that one would expect any alternative causes to be mentioned; when in doubt, use the "unknown or N/A" designation.

6. FINAL THOUGHTS

Based on the working definition of drug–nutrient interactions, the scope of the issue is quite wide and requires ongoing effort at multiple levels. At the most basic level, recognition of drug–nutrient interactions can be improved by including the topic in health-care professional curricula and at postgraduate educational symposia. Furthermore, formalized recognition of drug–nutrient interactions at the level of drug development and regulation will be critical. The drug development process can include the drug–nutrient interaction categories (Table 1) as a framework to generate data (Table 2) that will be useful to clinicians. It will require the work of all clinicians and investigators with an interest in improving patient care. Clinicians investigate drug–nutrient interactions for their clinical relevance, while other investigators evaluate interactions for their mechanism. Once mechanisms are better identified, management approaches for widely recognized drug–nutrient interactions can be offered and evaluated prospectively. As the data become more available, the system of categorizing drug–nutrient interactions, as well as scoring their significance and severity, will become better established. There is no reason that this cannot evolve in the same way that drug–drug interactions have. Good clinical judgment remains the cornerstone until that day. The goal of optimal drug and nutrient management in patient care must be met.

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2 Drug Disposition and Response

Robert B. Raffa

Objectives

- Review basic principles of pharmacokinetics related to the absorption, distribution, metabolism, and elimination of drugs and nutrients.
- Discuss factors that can affect these processes.
- Review basic principles of pharmacodynamics and the quantification of drug and nutrient action.
- Highlight potential pharmacokinetic and pharmacodynamic sites of drug–nutrient interactions.

Key Words: Bioavailability; elimination; pharmacokinetics; pharmacodynamics

1. INTRODUCTION

This chapter presents an overview of drug disposition (pharmacokinetics) and drug action (pharmacodynamics) as a basis for understanding drug–nutrient interactions. *Pharmacokinetics* is the term used to describe the disposition of a drug throughout the body – that is, the drug's absorption, distribution, metabolism, and excretion (ADME). *Pharmacodynamics* is the term used to describe a drug's effect and how that effect is produced (its mechanism of action). A drug–nutrient interaction is medically significant if either the patient's response to the drug or the patient's nutritional status is affected adversely. Therefore, this chapter highlights processes that can contribute to either outcome.

2. PHARMACOKINETICS

A substance can produce an effect only if it can reach its physiological target(s) in sufficient concentration. Hence, the extent and rate of disposition of a drug or a nutrient is important for understanding or predicting the magnitude or the duration of their effect or possible interaction. Several factors affect the absorption and distribution of drugs and nutrients.

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2.1. Absorption

The route by which a substance is introduced into the body affects its pharmacokinetics *(1,2,3)*.

2.1.1. SYSTEMIC ROUTES

Systemic routes of administration are those that deliver the substance with the intent of producing a systemic (on the whole system) effect, rather than a local effect (for example, on the skin). A subdivision of the systemic route of administration is *parenteral*, which refers to systemic routes other than *alimentary* routes (e.g., oral, sublingual, buccal, or rectal). Systemic routes of administration provide an opportunity for drug–nutrient interaction at several levels, including the rate at which drug substance or nutrient is available for absorption (e.g., dissolution rate, degree of ionization, adsorption); the extent of plasma protein binding; and the rate or the route of metabolism.

Oral (PO) administration is generally the simplest, most convenient, safest (because of slower onset of drug effect and ability to reverse a mistake), and often most economical route of administration. Most drugs are well absorbed from the gastrointestinal (GI) tract. The rate and extent of absorption is a function of the physiochemical properties of the substance (e.g., water or lipid solubility), its formulation (e.g., tablet, capsule, liquid, slow-release reservoir, matrix), excipients, physiological environment (e.g., high acidity of the stomach), and metabolism in the gut wall. Alteration of any of these features, for example, as a result of change in diet, lifestyle, age, or health status, can affect absorption. Nutrients and foodstuffs can affect the absorption of a drug by binding to it or by altering the physiologic environment (e.g., pH of the stomach). The simple act of food ingestion, or even its anticipation, can release digestive enzymes that inactivate certain drugs (e.g., penicillins).

The *intravenous* (IV) route of administration delivers the drug directly into the bloodstream. The drug is then delivered to the heart and from there to the general circulation. The IV route bypasses problems of absorption from the GI tract, allows for rapid adjustment of dose to effect, can be used even if the patient is unconscious, and avoids the "first-pass effect" (see below). The related *intraarterial* route of administration, although used much less commonly than IV administration, is useful when infusion of a high concentration of drug into a specific target is desired. Examples include chemotherapeutic agents for the treatment of certain cancers and vasodilators for the treatment of Raynaud's syndrome.

Subcutaneous (SC) administration involves drug delivery into the tissue beneath the skin and its subsequent entry into the blood perfusing the tissue. Absorption following SC administration is generally rapid, depending on blood perfusion of a particular site, and the rate of absorption can be accelerated (e.g., by heating or vasodilators) or slowed (e.g., by cooling, vasoconstrictors, or slow-release formulations).

Intramuscular (IM) administration is generally rapid because of the high vascularity of muscles. It also provides space for drug depots, such as sustained-release formulations, provided a patient has sufficient skeletal muscle.

Inhalation provides one of the most rapid routes of drug administration due to the large surface area and high vascularity of the lungs, provided adequate doses of the active drug reach the distal airway.

Other systemic routes include *intraperitoneal*, which is particularly useful for the administration of drugs to small animals because it provides a rapid, convenient, and reproducible technique, and *transdermal*, because of its convenience and use for extended drug delivery.

2.1.2. TOPICAL ROUTES

Topical routes of administration are generally used for the purpose of local drug action and are generally not sites of drug–nutrient interactions (a possible exception is the reduction of ultraviolet light exposure by sunscreen lotions and the resulting decreased activation of vitamin D). However, if the skin is damaged (such as by abrasions or burns) or if transmucosal passage is significant, the drug does not remain localized to the site of application and administration is akin to systemic administration with the attendant opportunity for a drug–nutrient interaction.

2.1.3. OTHER ROUTES

Direct application of drugs for localized effects to the eye (*ophthalmic* administration), ear (*otic* administration), nerves (*intraneural* administration), spinal cord (e.g., *epidural* or *intrathecal* administration), or brain (e.g., *intracerebroventricular* administration) does not often lead to significant interactions, but any substance that alters the drug's access to specialized compartments particularly via common transporters (e.g., through the blood–brain barrier) can alter the magnitude or the duration of the drug effect.

2.1.4. FACTORS THAT AFFECT ABSORPTION

The rate and extent of absorption of a drug or a nutrient is influenced by the characteristics of the drug or the nutrient and by the characteristics of the patient at the time of administration *(4)*. For example, the rate of dissolution depends on how the product is formulated and also on the person's state of health and other factors, such as diet.

The absorption (and elimination) of substances generally follows either *zero-order* kinetics – i.e., a constant *amount* is absorbed (or eliminated) per unit time (Fig. 1a) – or *first-order* kinetics – i.e., a constant *fraction* is absorbed (or eliminated) per unit time (Fig. 1b). Most currently used drugs follow first-order kinetics.

2.2. Distribution

Once a drug or a nutrient enters the bloodstream, it might bind to a plasma protein (e.g., albumin). In addition, the drug or the nutrient usually must pass some biological barrier in order to reach its site of action.

2.2.1. PLASMA PROTEIN BINDING

Depending on their physicochemical characteristics, drug molecules (D) can form weak, reversible bonds with plasma proteins (P) according to the general equilibrium interaction represented as $D + P \Leftrightarrow DP$ *(5)*. Drug–protein complexes

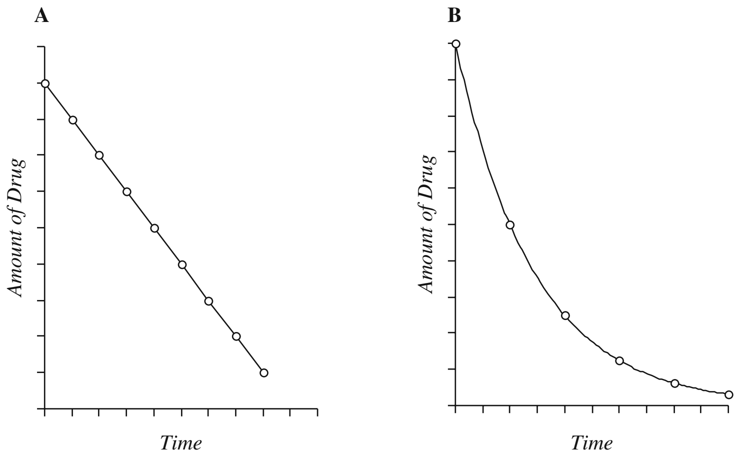

Fig. 1. (**A**) An example of a zero-order kinetics relationship. (**B**) An example of a first-order kinetics relationship.

(DP) have nothing to do with the drug's therapeutic effect, but in some instances can significantly influence the magnitude or the duration of the drug's effect. This is because a plasma protein-bound drug is less likely to reach its site of action, is less likely to be active at its site of action, and is less likely to pass into the renal tubules and be excreted. Every drug binds to plasma proteins to a different extent. The extent depends on the physiochemical properties of the drug and on the amount of plasma proteins in the patient's blood. Drugs that bind avidly with plasma proteins are susceptible to interaction with other drugs and nutrients that also bind to the same sites. Plasma protein binding is saturable (i.e., there is a finite number of such sites) and competition occurs among all substances that have affinity for such sites, introducing a new equilibrium between bound and free drug. Transition from the "bound" to the "free" state can result in a significant increase in the magnitude or the duration of effect. Thus, plasma protein binding is a possible site for interactions.

2.2.2. FIRST-PASS EFFECT

The venous drainage system of the stomach and intestines differs from that of most other organs in a way that has implications for drug–nutrient interactions. The venous drainage of most organs goes directly to the heart, but venous drainage of the GI tract sends blood into the *portal circulation*, which delivers blood to the liver. Hepatic venous drainage then goes to the heart. This is of clinical significance because the liver is a site of active biotransformation (drug metabolism) and a potential site for interactions. Biotransformation in the liver can be extensive (>99% for some commonly used drugs). In some cases, this biotransformation results in the conversion of an inactive parent substance (a *prodrug*) to its active metabolite(s). More often, the metabolites are less active than the parent substance. Once through the liver, the drug and its metabolites follow the venous drainage to the heart and into the systemic circulation. All subsequent pharmacokinetic features are the same as for any other systemically administered substance. Hence, the portal circulation introduces a special influence on distribution during a substance's "first-pass" into the circulation *(6)*. Oral administration of drugs results in the largest first-pass effect. Drugs that are administered IV are not subjected to a first-pass effect.

The extent of first-pass metabolism is an important consideration in drug design, formulation, and dosage regimen. For drugs that undergo high first-pass metabolism, small changes in the rate or the extent of biotransformation (as may occur with interactions) can result in large changes in systemic blood levels. Changes in biotransformation can result from changes in GI and liver function or on hepatic drug-metabolizing enzymes brought about by other drugs, nutrients, or food components.

2.2.3. Blood–Brain Barrier

Many drugs have only limited ability to enter the brain because of their physicochemical properties. The morphologic basis for the blood–brain barrier includes tight junctions between the epithelial cells lining the brain capillaries and transport mechanisms that pump substances out of the brain. In general, the blood–brain barrier restricts the passage of substances that are either too hydrophilic (water soluble) or too lipophilic (fat soluble). Nutritionally required substances can be actively transported across the blood–brain barrier *(7)*.

The permeability of the blood–brain barrier depends on such factors as age, disease, and other influences, including nutritional state. Plasma protein binding is also a factor, since drug molecules highly bound to plasma proteins are less able to traverse the blood–brain barrier. Hence, drug interaction at the level of plasma protein binding can affect blood–brain barrier passage.

2.2.4. Biological Membranes

Biological membranes are bilayer, phospholipid matrices containing cholesterol, proteins, and other constituents. Drugs can be transported around or through these membranes, depending on the properties of the drug and the composition of the particular membrane (*see* Chapter 3). Some mechanisms of drug transport are as follows *(8)*:

Passive diffusion. If a drug is sufficiently lipid soluble, it can diffuse down its concentration gradient (energy is not required, hence the diffusion is "passive"). For weak acids ($HA \Leftrightarrow H^+ + A^-$) and weak bases ($BH^+ \Leftrightarrow H^+ + B$), it is the nonionized form (HA and B respectively) that is more lipid soluble. *Simple diffusion* occurs according to *Fick's law*:

$$\frac{dQ}{dt} = -DA\frac{dC}{dx},$$

where the flux of drug across a membrane is determined by the diffusion constant (D), the surface area (A), and the drug concentration (C). This type of diffusion favors molecules in the uncharged form and is a function of the pH of the environment at the membrane and the pK_a of the drug according to relationships termed the Henderson–Hasselbach equations:

$$\mathrm{p}K_{\mathrm{a}} = \mathrm{pH} + \log\left(\frac{\mathrm{HA}}{\mathrm{A}^{-}}\right)$$

for weak acids and

$$\mathrm{p}K_{\mathrm{a}} = \mathrm{pH} + \log\left(\frac{\mathrm{BH}^{+}}{\mathrm{B}}\right)$$

for weak bases. As described by these equations, absorption of weak acids (e.g., aspirin) is favored over weak bases in the low pH of the stomach. However, the total amount of absorption is usually greater in the intestines due to the much higher surface area. Conversely, the absorption of weak bases is favored in the small intestine (higher pH). Renal excretion follows the same pattern. Weak acids are usually excreted in alkaline urine; weak bases are excreted faster in acidic urine.

Filtration. Some vascular bed capillaries have pores or channels that allow the passage of low-molecular-weight substances, whether they are polar or nonpolar. Such capillaries serve as molecular sieves (filters) that exclude molecules larger than a certain size.

Carrier-mediated (facilitated) diffusion. Transport of some substances across membranes, although by diffusion down a concentration gradient, is facilitated by membrane-associated molecules (carriers). This type of diffusion is generally selective for molecules having specific structures or another property. If the concentration of drug or nutrient exceeds the number of carriers, the process becomes saturated and any further increase in drug or nutrient concentration will not increase the rate of their passage across the membrane.

Active transport. Some molecules are transported across biological membranes against their concentration gradient. Transport in this direction – "up" a concentration gradient – is not favored thermodynamically and, hence, does not occur spontaneously. It requires input of energy, which is commonly supplied by coupled biochemical reactions that, for example, convert ATP to cAMP (catalyzed by $\mathrm{Na}^{+}/\mathrm{K}^{+}$-ATPase). Active transport is similar to carrier-mediated (facilitated) diffusion in that transport is mediated by a membrane-associated macromolecule (pump); it is saturable; and it is usually selective for certain drugs or nutrients (based on size, shape, or other characteristic). It differs in its requirement for energy and the ability to pump against a concentration gradient.

Endocytosis. Some drugs and nutrients can be transported across biological membranes by becoming entrapped (in "pits") and internalized (in "vesicles") with varying degrees of selectivity. For example, sucrose and insulin can be internalized in this manner.

2.2.5. BIOAVAILABILITY

Due to the multiple barriers to absorption, the amount of a drug that enters the systemic circulation is less than the amount administered (with the exception of IV administration). The proportion (expressed either as fraction or percent) of an administered drug dose that reaches the systemic circulation is referred to as the drug's *bioavailability*. Factors that affect a drug's bioavailability include the first-pass effect, the solubility and stability, and the formulation of the drug product (including the quality control of its manufacture). In addition, a person's dietary patterns, nutritional status, and state of health can affect a drug's bioavailability.

2.2.6. Factors that Affect Distribution

Multiple factors affect the distribution of substances in the body. Some are related to the substance itself, such as its physical characteristics (e.g., size, solubility) and its chemical characteristics (e.g., ability to form bonds with plasma proteins or other biochemical substances). Other factors are related to the state of the physiological system, such as concentration of plasma proteins, lipid content of barrier or target tissues, cardiac output, capillary permeability in target or other tissues, and many others. Many of these factors are a function of age, disease, or other influences.

2.3. *Metabolism*

Drugs and nutrients are often biotransformed (metabolized) to other substances (metabolites) by a variety of biochemical reactions in a variety of locations throughout the body *(9)*. Almost all tissues can metabolize drugs, but the liver, GI tract, and lungs are the major sites of drug metabolism of most drugs in humans. The liver plays a predominant role in drug metabolism for two reasons: first, because of its strategic location relative to the portal circulation and second, because it contains high levels of enzymes capable of metabolizing foreign substances (*see* Chapter 4). In general, but not always, metabolites are less active and more water soluble (which favors excretion in the urine) than the parent substance. In some instances, active metabolites are formed from inactive parent drugs, in which case the parent is termed a *prodrug*. The most common chemical reactions that metabolize drugs and nutrients can be conveniently categorized into two broad types: reactions that alter the basic chemical structure of the parent molecule – *Phase 1 reactions*– and reactions that result in the attachment of some endogenous substance to the parent molecule – *Phase 2* or *conjugation* reactions.

2.3.1. Phase 1 Reactions

Phase 1 reactions often occur in the cytosol, mitochondria, and microsomes (a subcellular component containing membrane-associated enzymes on the smooth endoplasmic reticulum) of cells of the liver and other organs.

2.3.1.1. Oxidation. Oxidation (e.g., the addition of oxygen or the removal of hydrogen from the parent molecule) is a common Phase 1-type reaction. Microsomal oxidation is a common mechanism of metabolism of many drugs and nutrients because these substances typically have chemical structures that make them susceptible to oxidation reactions. There is an extensive system (family) of enzymes that are capable of catalyzing oxidation reactions. Primary components of this system are cytochrome P-450 reductase and the many isozymes of cytochrome P-450 (CYP). Examples of microsomal oxidation reactions are *C*-oxidation or *C*-hydroxylation of aliphatic or aromatic groups; *N*- or *O*-dealkylation; *N*-oxidation or *N*-hydroxylation; sulfoxide formation; deamination; and desulfuration. Examples of nonmicrosomal enzymes having important roles in the metabolism of endogenous and exogenous substances include alcohol- and aldehyde dehydrogenase; xanthine oxidase; tyrosine hydroxylase; and monoamine oxidase.

The family of CYP enzymes is particularly important in studying metabolism because of the many drugs and nutrients that are metabolized by these enzymes and, in addition, the potential for drug–nutrient interactions *(10)*. For example, it is estimated that over 90% of presently used drugs are metabolized by one or more of the CYP enzymes. Of the most commonly used drugs, about 50% are metabolized by the CYP3A subfamily; about 25% by the CYP2D6 isozyme; about 15% by the CYP2C9 isozyme; and about 5% by the CYP1A2 isozyme. Because the enzymes are saturable, and can be induced or inhibited, there is significant potential for interactions.

2.3.1.2. Reduction. Reduction reactions (e.g., the addition of hydrogen or the removal of oxygen from the parent molecule) occur both in microsomal and nonmicrosomal fractions of hepatic and other cells. Examples of such reactions include nitro-, azo-, aldehyde-, ketone-, and quinone reduction.

2.3.1.3. Hydrolysis. Hydrolysis-type reactions can occur in multiple locations throughout the body, including the plasma. Examples of some nonmicrosomal hydrolases include esterases, peptidases, and amidases.

2.3.2. PHASE 2 REACTIONS

The coupling (conjugation) of an endogenous substance to a drug or a nutrient molecule typically alters its three-dimensional shape sufficiently to result in a decrease in biological activity. Conjugation also typically results in an increase in water solubility of the substance, which decreases the amount that is reabsorbed through renal tubules and thereby enhances the fraction that is excreted in the urine. Conjugation with glucuronic acid (*glucuronidation*) is the most common conjugation reaction in humans. Other Phase 2 reactions include glycine-, glutamate-, or glutathione-conjugation; *N*-acetylation (acetyl coenzyme A as acetyl donor); *O*-, *S*-, or *N*-methylation (*S*-adenosylmethionine as methyl donor); and sulfate or sulfanilate formation (3′-phosphoadenosine 5′-phosphosulfate as the sulfate donor).

2.3.3. SEQUENCE OF METABOLISM

It is common for a drug to be metabolized through several biotransformation reactions, resulting in the production and the elimination of several or many metabolites, each having its own pharmacokinetic and pharmacodynamic characteristics. It is also common for a substance to undergo a Phase 2-type reaction following a Phase 1-type reaction, but this sequence is not a requirement. It is possible for a Phase 2 reaction to precede a Phase 1 reaction.

2.3.4. INDUCTION OR INHIBITION

Many of the enzymes involved in the biotransformation of drugs and nutrients can be induced (increased in number and activity) or inhibited (reduced in number and activity) by a variety of chemical substances, including themselves and other drugs or nutrients *(11)*. Induction results in an enhanced metabolism of molecules that are biotransformed by the same pathway and results in a decrease in the level of parent molecule and increase in the level of metabolites. The biological effect will be decreased if the parent is more active than its metabolites and increased if the parent is a prodrug. The opposite occurs with enzyme inhibition.

2.3.5. Factors that Affect Metabolism

Multiple factors can affect metabolism *(12)*, including genetics (polymorphisms); the chemical properties of the drug or the nutrient (which determines their susceptibility to the various types of metabolic reactions); the route of administration (which affects, for example, the extent of the first-pass effect); dose (which can exceed the capacity of substrates for conjugation reactions); diet (which can also affect the capacity of substrates for conjugation reactions); age and disease (which can affect hepatic function); and others.

2.4. Elimination

The biological effects of exogenous substances are terminated by the combined processes of redistribution, metabolism, and excretion – i.e., elimination *(13)*. Several factors affect the rate and extent of elimination, and accumulation occurs if the rate of absorption and distribution of a drug or a nutrient exceeds the rate of elimination.

2.4.1. Routes of Elimination

In humans, the kidney is the major route for elimination of many drugs, partly due to the fact that the kidneys receive about 20–25% of the cardiac output. Other sites of elimination include the lungs, the feces, and (usually to a lesser, but no less important, extent) sweat, saliva, blood loss, gastric fluid, breast milk, semen, and others.

Size exclusion prevents plasma proteins – and drug molecules that are bound to them – from passing through the glomerulus of a healthy kidney. The fate of a substance that passes into the nephron depends on the substance's physicochemical properties. Lipophilic substances (such as the nonionized form of weak acids or bases) are more likely to be reabsorbed through the wall of the nephron and back into the circulation. Hydrophilic substances (such as the ionized form of weak acids or bases) are more likely to be excreted in the urine. The pH dependence of ionization is exploited clinically by adjusting the urine pH. Some substances are actively transported across the wall of the nephron either into or out of the lumen of the nephron. Such transport processes are generally saturable and, thus, are possible sites of drug–nutrient interactions.

2.4.2. Rate of Elimination

The elimination of most current drugs follows first-order kinetics (i.e., "exponential decay") in which the drug concentration at any time t (C_t) is related to the original drug concentration (C_o) by the equation $C_t = C_o\ e^{-kt}$. In first-order elimination, equal *fractions* of drug are eliminated in equal times and C_o is reduced by 50% in one *half-life* ($t_{1/2}$). Other drugs are eliminated by zero-order (linear) kinetics. In zero-order elimination, equal *amounts* of drug are eliminated in equal times. In both cases, elimination is a function both of the substance and of the condition of the patient.

2.4.3. CLEARANCE

The rate of elimination (mass/time) of a substance is equal to its concentration (mass/volume) times the "clearance" (volume/time). Clearance is the volume of a compartment (e.g., blood) per unit of time that is "cleared" of the substance due to elimination (e.g., metabolism or excretion). The equation that relates renal plasma clearance (Cl), rate of excretion (R_e), drug concentration in plasma (C_p), and drug concentration in urine (C_u) is:

$$\mathrm{CI}C_p = C_u R_e.$$

2.4.4. EFFECT OF MULTIPLE DOSING

When a drug is administered according to a fixed-interval schedule, the rate of accumulation is predictable from the dose and half-life. For example, following the repeated IV dosing of a drug having first-order elimination kinetics, the mean drug concentration (C_{av}) can be estimated from the dose (D) and the fraction of drug remaining (F) by the equation

$$C_{av} = -D / \ln F.$$

The upper (C_{max}) and lower (C_{min}) bounds can be estimated by

$$D/(1 - F)\,\mathrm{and}\,FD/(1 - F),$$

respectively (Fig. 2). The actual clinical results depend on the patient's individual characteristics.

2.4.5. FACTORS THAT AFFECT ELIMINATION

In addition to the factors already cited, elimination can be accelerated by enzyme induction, increases in urine flow, or by change in urine pH and can be slowed by renal impairment, change in pH, or other patient-specific factors.

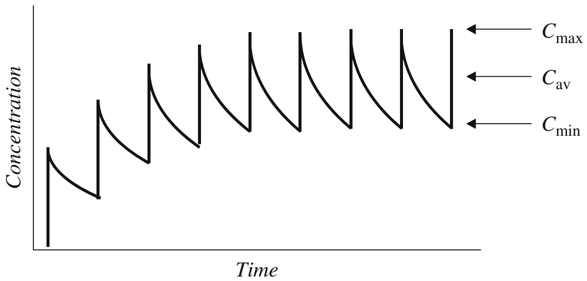

Fig. 2. An example of multiple dosing of a drug having first-order elimination kinetics. C_{max}, C_{av}, and C_{min} are described in the text.

2.5. Pharmacogenetics

Pharmacogenetics (*pharmacogenomics*) is the study of how a person's genetic makeup (*genotype*) influences the way they respond to a drug (their *phenotype* in this regard) and the role genetic differences play in interindividual variability of response to drugs. Many genes that encode drug-metabolizing enzymes, transporters, and receptors are now known to be genetically polymorphic – defined as the ability of a gene to assume multiple forms, where the least common allele occurs in >1% of the population. The variation can be in the gene promoter, the coding region (exons), the noncoding region (introns), or an untranslated gene sequence. A polymorphism in any region can lead to faulty protein structure or expression and there are numerous clinical examples of polymorphic enzymes altering a drug's disposition or effect. *Single nucleotide polymorphisms (SNPs)* are defined as mutations that involve a single DNA base substitution. SNPs are the most common variants in the human genome.

Knowledge of a person's phenotype can facilitate better choice of therapeutic approach and the design of more optimal drug regimens, particularly in patients who may not be achieving the expected effect of a drug.

3. PHARMACODYNAMICS

A substance produces a biological effect by modification or interaction with ongoing physiological processes. In some cases the target is foreign (e.g., bacteria or viruses) or aberrant (cancer cells). In most other cases, the target is part of normal physiology (e.g., enzymes or receptors). Drug actions are quantified and evaluated using dose–response curves.

3.1. Mechanisms of Action

In the broadest sense, drug effects can be categorized into four major mechanisms *(14)*. They can kill invading organisms (e.g., antibiotics or antivirals), they can kill aberrant cells (e.g., many cancer chemotherapies), they can neutralize acids (antacids), and they can modify physiological processes.

3.1.1. ANTIBIOTICS/ANTIVIRALS

Antibiotics and antivirals target biochemical processes of invading organisms. For example, penicillins, cephalosporins, carbapenems, and monobactams, which have chemical structures that contain a β-lactam ring, disrupt cell walls or inhibit their synthesis. Sulfonamides and trimethoprim act on enzymatic pathways, resulting in the inhibition of folic acid synthesis. Aminoglycosides, tetracyclines, chloramphenicol, and erythromycin interfere with mechanisms involved in the synthesis of bacterial proteins. Quinolones inhibit bacterial DNA gyrase. Most antivirals work by inhibiting viral replication. In all cases, the clinical utility is significantly increased when the drug exhibits selectivity for biochemical processes essential to the invading organism, but not essential to humans.

3.1.2. CANCER CHEMOTHERAPY

Much current cancer chemotherapy (antineoplastic agents) involves the use of substances that are cytotoxic. In general, current antineoplastic drugs can be divided into four major classes: alkylating agents, antimetabolites, alkaloids, and antibiotics. Alkylating agents bind covalently to DNA, thereby impeding replication and transcription, leading to cell death. Antimetabolite drugs compete with critical precursors of RNA and DNA synthesis, thereby inhibiting cell proliferation.

Alkaloids inhibit microtubular formation and topoisomerase function, thereby blocking cell division and DNA replication. Certain antibiotics inhibit RNA and DNA synthesis. Many patients receive combinations of these drugs.

3.1.3. ANTACIDS

Excess gastric acidity is reduced by treatment with antacids, which are weak bases that convert gastric (hydrochloric) acid to water and a salt. Most antacids in current use contain aluminum hydroxide, magnesium hydroxide, sodium bicarbonate, or a calcium salt.

3.1.4. MODULATION

The chemical nature of cellular function and communication within and between cells allows for modulation by endogenous chemical substances (drugs and nutrients). The targets of such modulation include enzymes, DNA, and a variety of other molecules involved in the synthesis, storage, metabolism, or elimination of endogenous substances.

3.2. Receptors

Many drugs interact with macromolecular components of cells that then initiate a chain of events that lead to the drug's effect. In the commonly used analogy, the receptor is like a light switch. A better analogy is that a receptor is like a dimmer switch, since there is generally some basal level of activity. A receptor also serves to limit the access to the switch to only a select number of specific molecules (by "lock-and-key" fit).

3.2.1. OCCUPATION THEORY

Receptors are activated when specific molecules (drugs) form weak intermolecular bonds with them – the magnitude of such a drug's effect is related to the number (or the fraction of the total) of receptors that are "occupied" *(15)*. The formation of drug–receptor complexes is usually reversible such that the reaction between drug molecule (D) and receptor molecule (R) is an equilibrium reaction that can be described and characterized – as any other chemical equilibrium reaction – according to the equation $\mathrm{D} + \mathrm{R} \Leftrightarrow \mathrm{DR}$. The "driving force" for the reaction to proceed in the direction of drug–receptor complex depends on the Gibb's free energy difference (ΔG) according to $\Delta G = -RT \ln K_{\mathrm{eq}}$, where R is a constant, T is the temperature (Kelvin), and K_{eq} is the equilibrium constant *(16)*.

3.2.2. AGONISTS AND ANTAGONISTS

The vast majority of chemical substances do not fit a binding site on any receptor. Chemicals that do bind to receptors are said to do so with a certain *affinity*, the magnitude of which is given by the reciprocal of the equilibrium constant and termed the "dissociation constant" (often designated as K_{D}). Only a subset of substances that bind to receptors are capable of eliciting an effect through the receptor, i.e., have *intrinsic activity*. Substances that have affinity and intrinsic activity are termed *agonists* and substances that have affinity, but not intrinsic activity, are termed *antagonists*. Antagonists competitively or noncompetitively inhibit the access of agonists to their receptors. Since receptors mediate the effects of endogenous agonists such as neurotransmitters, hormones, and peptides, antagonist drugs – although lacking intrinsic activity in vitro – can produce biological effects in vivo by attenuating the signal of the endogenous agonist.

3.2.3. SIGNAL FIDELITY

One of the major functions of receptors is to provide the necessary fidelity for accurate and reliable communication between neurons or other cells. The "lock-and-key" requirement restricts access only to molecules of specific three-dimensional shape. The fit is sufficiently flexible, however, that certain molecules (such as drugs) having three-dimensional shapes similar to the endogenous ligand can bind to their receptors (with greater or lesser affinity and intrinsic activity).

3.2.4. "UP-" AND "DOWNREGULATION"

The number of receptors expressed at any given time is the difference between the number synthesized and the number destroyed or internalized and, thus, is a function of the age, health, and other characteristics of the individual. Repeated exposure to an agonist or an antagonist can alter the number of expressed receptors. The change in receptor number is often interpreted as the body's attempt to counteract excess action of an agonist or an antagonist and an effort to reestablish homeostasis. More permanent change in receptor number can result from drug effects at the level of the gene.

3.3. Signal Transduction

Signal transduction refers to the postreceptor sequence of events that lead to an agonist's effect. Transduction mechanisms can be divided broadly into two types: *ionotropic*, in which activation of the receptor leads directly to influx of ions, and *metabotropic*, in which activation of the receptor actuates a series of biochemical *second messengers* that mediate the response *(17)*.

3.3.1. LIGAND-GATED ION CHANNELS

Located on the membranes of excitable cells, ligand-gated ion channel receptors (LGICRs) are comprised of segments of transmembrane proteins that form pores of specific size and shape that allow the passage of certain ions. The magnitude or the rate of flow of ions through the membrane is regulated by the binding of ligand to the receptor. LGICRs usually display selectivity for ions (e.g., Na^+, K^+, Ca^{2+}, or Cl^-) and can be composed of subunits that can be expressed or coupled in different ways in different cells, thus mediating a variety of effects. Examples of LGICRs are the nicotinic cholinergic, $GABA_A$, glutamate, and glycine receptors.

3.3.2. GPCRS

The G-protein-coupled receptors (GPCRs) typically include seven transmembrane regions, an *N*-terminal extracellular region, and a *C*-terminal intracellular region *(18)*. A group of guanosine triphosphate (GTP) protein subtypes are coupled to the receptor. Ligand activation of a GPCR induces GDP–GTP exchange and modulation of associated second messengers such as adenylate cyclase, phosphoinositide pathways, and ion channels. Multiple G-protein subtypes allow for selective responses *(19)*.

3.3.3. TYROSINE KINASE RECEPTORS

Tyrosine kinase receptors span the cell membrane and their self-contained catalytic domain functions as an enzyme. Examples include receptors for certain growth factors and insulin.

3.3.4. NUCLEAR RECEPTORS

A large group of intracellular receptors, referred to as the nuclear receptors, are ligand-dependent transcription factors that regulate gene expression. Along with coreceptors and cofactors, the activation or the inhibition of these receptors influences the synthesis and regulation of proteins (e.g., enzymes and receptors) and other cellular components.

3.4. Dose–Response Curves

The relationship between the dose of a drug and its corresponding response is a useful measure of effect from both a mechanistic and a practical standpoint. For example, given a reaction scheme of the form $D + R \Leftrightarrow DR$, it follows that the shape of the dose–response curve should be hyperbolic, something that is observed for many drugs *(19)*. In addition, certain features of a dose–response curve can yield clinically valuable information, such as a measure of relative potency or efficacy *(20)*.

Several ways of displaying a dose–response curve are described in the following sections. The type of display can affect certain mathematical (statistical) analyses of the data (for details, *see* ref. *(21)*).

3.4.1. QUANTAL

A "quantal" dose–response curve is one in which the dependent variable, usually plotted on the ordinate (y-axis), is measured as an all-or-none outcome (e.g., the number of patients with systolic blood pressure greater than 140 mm Hg).

3.4.2. GRADED

A "graded" dose–response curve is one in which the dependent variable is measured using a continuous scale (e.g., systolic blood pressure in mm Hg). As with a quantal dose–response curve, the set of points on rectangular coordinates derived from plotting the measured effect against the administered dose typically forms a pattern that approximates a rectangular hyperbola (Fig. 3A).

3.4.3. LOG

For practical, and now partly unnecessary but historical, reasons, dose–response curves are commonly constructed by plotting the response against the logarithm (base 10) of the dose. The shape of such curves becomes sigmoidal or "S shaped" (Fig. 3B). This has become so customary that such a plot is often called a dose–response curve, although log(dose)–response curve is more precise.

3.4.4. POTENCY AND EFFICACY

The dose of the drug estimated to produce 50% effect is termed the ED_{50} (or equivalent) for a quantal dose–response curve and the D_{50} (or equivalent) for a graded dose–response curve. *Potency* is a comparative term that refers to the

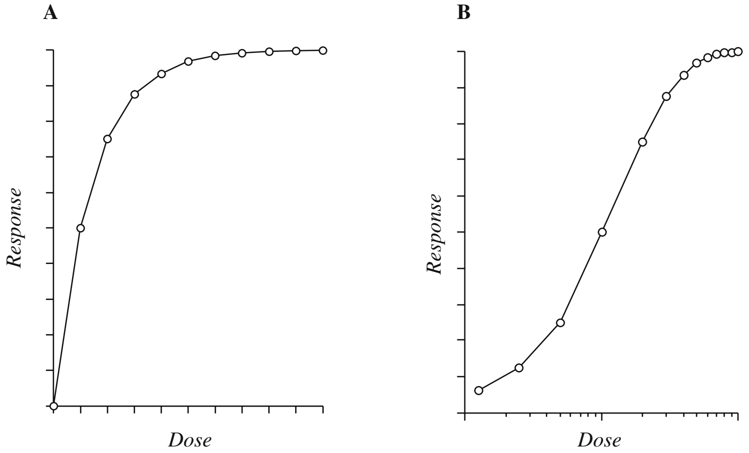

Fig. 3. (**A**) A dose–response curve on rectangular coordinates. (**B**) Quantal or graded dose–response data plotted against $\log_{10}$(dose).

amount of substance that is required to produce a specified level of effect (Fig. 4A). *Efficacy* is a term that refers to a substance's ability to achieve a certain degree of response under specified conditions (Fig. 4B). Potency and efficacy are independent characteristics.

3.4.5. ANTAGONISM

Antagonists, though lacking intrinsic activity, can produce effects when given to a patient because they attenuate the action of an endogenous agonist involved in a pathway that is tonically active. For example, antagonists of the muscarinic cholinergic receptor attenuate the parasympathetic influence on heart rate, with

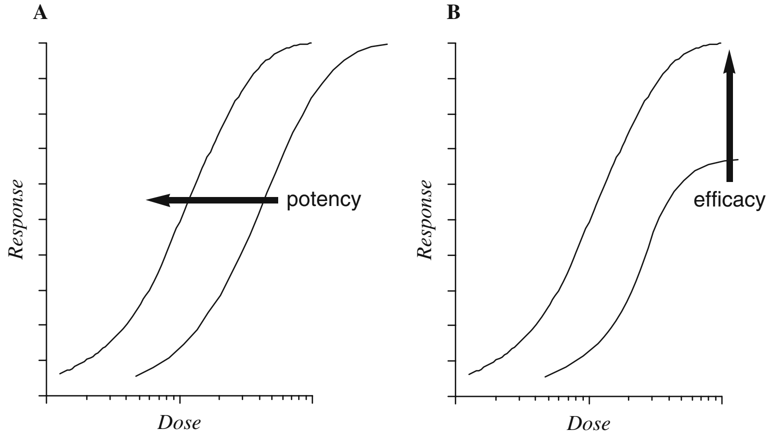

Fig. 4. (**A**) Potency is indicated by the location of a dose–response curve along the x-axis. (**B**) Efficacy is indicated by the maximal-attainable level of effect under specified conditions.

consequent increase in heart rate due to the less-opposed influence of the sympathetic subdivision. Such “effects” of an antagonist can also be characterized by a dose–response curve.

4. CONCLUSION

Drugs are substances taken to defend against invading organisms or to correct aberrant physiological processes, while nutrients are substances taken for maintenance of normal physiological processes. Both types of substance are desirable. Both types of substances also have chemical compositions that, by nature or by design, interact with common sites within the body. Therefore, drug–nutrient interactions can occur. The interactions can be deleterious to the intended action of the drug or to the nutritional status of the patient. Either outcome is undesirable. The principles of drug disposition and response outlined in this chapter provide the basis for understanding, or predicting, such interactions. They further provide a foundation for the more detailed treatments of these interactions presented throughout the rest of this book.

Take Home Points

- In the broadest sense, drugs and nutrients share the feature of being chemical substances that – within a proscribed concentration range – produce a beneficial physiological effect.
- Drugs and nutrients share several common sites of transport within the body (absorption, distribution, metabolism, and elimination), each of which represents a potential site of drug–nutrient interaction.
- Drugs and nutrients produce their effects through similar pharmacodynamic mechanisms (e.g., enzymes and receptors), which can be sites of drug–nutrient interaction.
- The clinical significance of a pharmacokinetic or a pharmacodynamic drug–nutrient interaction can be highly dependent on the individual patient – i.e., a function of patient’s general health, nutritional status, age, etc.
- The basic principles of pharmacokinetics and pharmacodynamics provide a basis for understanding the occurrence and treatment of drug–nutrient interactions.

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3 Drug Transporters

Richard H. Ho and Richard B. Kim

Objectives

- Illustrate the critical importance of uptake and efflux transporters to drug disposition and maintenance of normal physiologic homeostasis.
- Discuss major uptake and efflux transporters involved in the absorption, tissue distribution, and excretion of endobiotic and exobiotic compounds.
- Demonstrate the complexity of tissue-specific expression, overlap, and distribution of transporters are important to drug disposition.
- Highlight the importance of drug transporters to clinically observed drug–drug interactions, drug–nutrient interactions, and drug-mediated adverse effects.
- Underscore the notion that genetic heterogeneity in drug transporter genes contributes to the oft witnessed interindividual variability in drug disposition.

Key Words: uptake transporter; efflux transporter; drug interaction; polymorphism; drug disposition

1. INTRODUCTION

Drug efficacy is dependent on the interplay among multiple processes which govern drug disposition (pharmacokinetics) and response (pharmacodynamics) *(1,2)*. For orally administered drugs, their pharmacologic action is dependent on adequate intestinal absorption and distribution to sites of action, prior to their elimination by metabolic and excretory pathways in organs such as the liver and kidney. Membrane transporters have long been recognized to be an important class of proteins for regulating cellular and physiologic solute and fluid balance and not surprisingly, it has been estimated that nearly 1000 genes encode transport proteins *(3,4)*. Some facilitate the cellular entry of solutes or substrates while others prevent their entry. The goal of this chapter is to summarize the current state of knowledge in the area of human transporters of relevance to drug disposition. The molecular, biochemical, and physiological roles of each transporter will be systematically outlined as well as functional relevance to the drug disposition process. Their potential role in drug–nutrient interactions becomes clear, given common transporters for some drugs, nutrients, and other food components.

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2. TRANSPORTERS AND DRUG DISPOSITION

Drug transporters can be generally separated into two major classes – uptake and efflux transporters (Table 1). As the name suggests, uptake transporters facilitate the movement of drugs into cells. Of relevance to drug uptake are members of the solute carrier (SLC) superfamily that includes the organic anion transporting polypeptide (OATP; *SLCO*) family *(5)*, the organic anion transporter (OAT; *SLC22A*) and the organic cation transporter (OCT; *SLC22A*) family, and the organic cation/carnitine transporter (OCTN; *SLC22A*) family. Efflux transporters, on the other hand, export drugs from the intracellular to the extracellular environment, often against high concentration gradients, thereby requiring energy. Most efflux transporters belong to the ATP-binding cassette (ABC) superfamily of transmembrane proteins and utilize ATP hydrolysis to catalyze substrate translocation across biological membranes. Key members of the ABC transporter superfamily of particular relevance to drug disposition are members of the P-glycoprotein (*ABCB*) family, such as multidrug resistance protein 1 (MDR1; *ABCB1*) and the bile salt export pump (BSEP; *ABCB11*), the multidrug resistance-associated (MRP; *ABCC*) protein family, and the breast cancer resistance protein (BCRP; *ABCG*).

Important to our understanding of transporter-mediated drug disposition is the dynamic interplay between uptake and efflux transporters within any given epithelial cells, where the movement of drugs across such cellular compartments may be impeded or facilitated by the localization of transporters on apical or basolateral membranes. Furthermore, the net directional or vectorial movement is markedly affected by or dependent on the relative expression, activity, and substrate affinity for the individual transporter (Fig. 1). Therefore, it is not surprising to see that the net drug movement across organs such as the liver, kidney, and brain is highly dependent on not only the complement of transporters but also their subcellular localization. Considering that a number of known substrates of both uptake and efflux transporters are environmental toxins or present in plant material, from an evolutionary point of view, a number of transporters currently thought to play an important role in drug disposition appear to have evolved to either enhance toxin elimination or prevent their absorption from the gastrointestinal tract.

3. UPTAKE TRANSPORTERS

3.1. Organic Anion Transporting Polypeptides

The organic anion transporting polypeptides (OATPs) represent a superfamily of important membrane transport proteins that mediate the sodium-independent transport of a diverse range of amphipathic organic compounds including bile salts, steroid conjugates, thyroid hormones, anionic peptides, numerous drugs, and other xenobiotic substances *(5)*. The OATP nomenclature system is based on amino acid sequence identities. Using this approach specific families, subfamilies and individual members can be defined *(10)* (http://www.bioparadigms.org/slc/intro.asp). The general predicted OATP structure consists of proteins with 12 transmembrane (TM) domains with many conserved cysteine residues, *N*-glycosylation sites in extracellular loops 2 and 5, and what is considered to be a consensus

Table 1
Human Drug Transporters

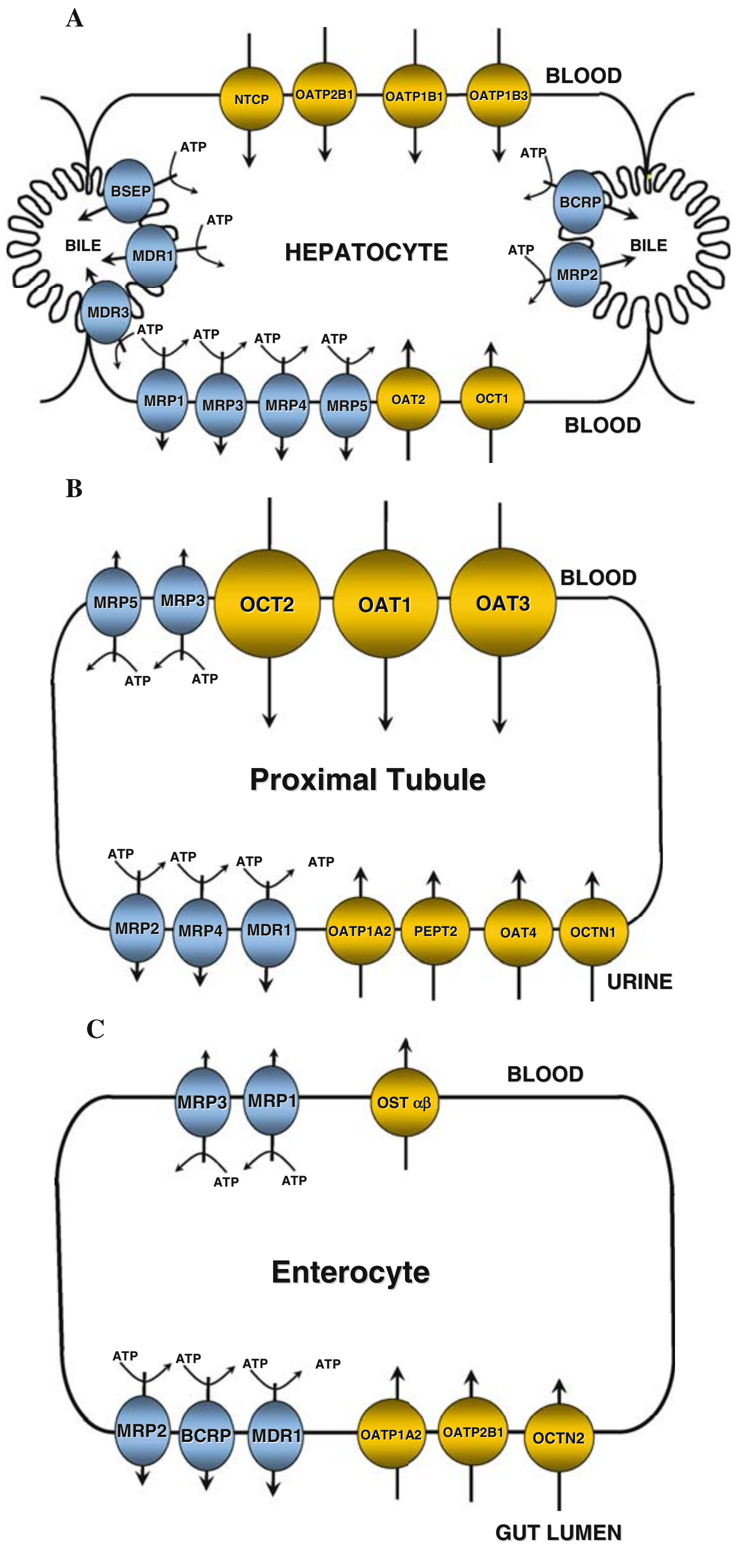
Family	*Member*	*Tissue distribution*	*Cellular localization*	*Examples of typical substrates*	*Important roles*	*References*
SLCO	OATP1A2	Brain, kidney, liver	Basolateral	Fexofenadine, indomethacin, bile salts, hormone conjugates, eicosanoids, deltorphin II	CNS distribution	(*5,10*)
	OATP2B1	Liver, intestine, placenta	Basolateral	Bile salts, digoxin, benzylpenicillin, hormone conjugates		
	OATP1B1	Liver	Basolateral	Benzylpenicillin, pravastatin, rifampicin, methotrexate, bilirubin, bile salts, hormone conjugates, eicosanoids	Hepatic uptake	
	OATP1B3	Liver	Basolateral	Digoxin, methotrexate, rifampicin, bile salts, hormone conjugates, eicosanoids	Hepatic uptake	
SLC22	OAT1	Kidney, brain	Basolateral	Cidofovir, PAH, acyclovir, tetracycline	Renal uptake	(*40*)
	OAT3	Kidney, brain	Basolateral	Cimetidine, PAH, methotrexate, salicylate, valacyclovir, tetracycline	Renal uptake	
	OAT4	Kidney, placenta	Apical	PAH, tetracycline	Renal secretion	
	OCT1	Liver, brain, small intestine	Basolateral	Cimetidine, corticosteroids, quinidine, quinine, midazolam, verapamil	Hepatic/renal uptake	
	OCT2	Kidney, brain, small intestine	Basolateral	Amantadine, choline, dopamine, histamine, norepinephrine, serotonin		
	OCT3	Placenta, liver, adrenal	N.D.	Adrenaline, cimetidine, histamine, noradrenaline		

(*Continued*)

Table 1
(Continued)

Family	*Member*	*Tissue distribution*	*Cellular localization*	*Examples of typical substrates*	*Important roles*	*References*
ABCB	MDR1	Kidney, liver, brain, small intestine	Apical	Digoxin, cyclosporine, taxol, vinca alkaloids, doxorubicin, loperamide, erythromycin, HMG-CoA reductase inhibitors, HIV-1 protease inhibitors	Oral absorption Renal secretion Biliary excretion CNS distribution	*(275)*
	BSEP	Liver	Apical	Bile salts, vinblastine, tamoxifen	Biliary excretion	
ABCC	MRP1	Ubiquitous	Basolateral	Vinca alkaloids, methotrexate, etoposide		*(275)*
	MRP2	Liver, kidney, small intestine	Apical	Vinca alkaloids, methotrexate, pravastatin, ampicillin, ceftriaxone, cisplatin, irinotecan, hormone conjugates	Biliary excretion renal secretion	
	MRP3	Liver, kidney, small intestine	Basolateral	Doxorubicin, vincristine, methotrexate, cisplatin		
ABCG	BCRP	Placenta, liver, small intestine	Apical	Mitoxantrone, doxorubicin, topotecan, methotrexate, irinotecan (SN-38)	Oral absorption, fetal exposure, biliary excretion	*(276)*

N.D., not determined; PAH, para-aminohippuric acid


A
NTCP
OATP2B1
OATP1B1
OATP1B3
BLOOD
ATP
BSEP
ATP
BILE
MDR1
HEPATOCYTE
ATP
BCRP
ATP
MRP2
BILE
MDR3
ATP
ATP
ATP
ATP
MRP1
MRP3
MRP4
MRP5
OAT2
OCT1
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MRP4
MDR1
OATP1A2
PEPT2
OAT4
OCTN1
URINE
C
MRP3
MRP1
OST αβ
BLOOD
ATP
ATP
Enterocyte
ATP
ATP
ATP
ATP
MRP2
BCRP
MDR1
OATP1A2
OATP2B1
OCTN2
GUT LUMEN

Fig. 1. Organ-specific expression of drug transporters. The compartmental expression of transporters in various organs plays a critical role in the drug disposition process. In organs such as the

superfamily signature of D-X-RW-(I,V)-GAWW-X-G-(F,L)-L at the junction between extracellular loop 3 and TM 6 *(5)*. The mechanism of transport appears to consist of anion exchange by coupling the cellular uptake of substrate with the efflux of endogenous conjugates such as bicarbonate, glutathione, and glutathione-*S*-conjugates in a process that seems to be pH dependent and electroneutral *(6–11)*.

3.1.1. OATP1A2 (OATP-A; *SLCO1A2*)

OATP1A2 was the first human member of this family isolated using in situ hybridization screening from a human liver cDNA library. Interestingly, its expression was noted to be strongest in brain and kidney *(12,13)*. Subsequent studies have revealed that OATP1A2 is expressed in the intestine, cholangiocytes, colon cancer cells, as well as in the human hepatoma cell line HepG2 *(14–16)*. Its expression in capillary endothelial cells that make up the blood–brain barrier suggests a potentially important role in the uptake of drugs and neuroactive peptides into the central nervous system *(17)*. Substrates of OATP1A2 include endobiotics such as bile salts, steroid conjugates, the thyroid hormones T4 (thyroxine), T3 (tri-iodothyronine) and rT3 (reverse tri-iodothyronine), and prostaglandin E_2 (PGE_2), and xenobiotics such as bromosulfophthalein (BSP), the opioid receptor agonists [D-penicillamine2,5] enkephalin (DPDPE) and deltorphin II, fexofenadine, ouabain, rocuronium, and the cyanobacterial toxin microcystin *(5)* (Table 1) *(18)*. More recently, OATP1A2 was demonstrated to be expressed on the apical membrane of intestinal enterocytes, suggesting it plays a role in determining bioavailability of orally administered drugs *(19)*. In fact, inhibition of OATP1A2 activity appears to be one mechanism by which dietary constituents such as grapefruit juice cause a nutrient–drug interaction to decrease the oral bioavailability of the antihistamine fexofenadine.

3.1.2. OATP2B1 (OATP-B; *SLCO2B1*)

OATP2B1 was originally isolated from human brain *(20)* and noted to have a near 80% amino acid sequence identity with its rat ortholog *(5)*. Although cloned from a brain library, its strongest expression is in the liver, followed by the spleen, placenta, lung, kidney, heart, ovary, small intestine, and brain *(14,18,21)*. Not surprisingly, OATP2B1 is expressed at the basolateral (sinusoidal) membrane of hepatocytes *(18)*. Relative to other OATPs expressed in the hepatocyte, OATP2B1 appears to have a more restricted substrate specificity, thus its importance in hepatic drug uptake remains to be clarified *(5,22)*. Recent studies suggest that the uptake of substrate drugs may be enhanced in cells exposed to acidic pH *(22)*. Since the physiological pH particularly in the proximal portions of the intestinal epithelial cells is acidic, the role of OATP2B1 in the small intestine might differ from that in other tissues *(23)*.

Fig.1. (Continued) liver (**A**) and kidney (**B**), the coordinated expression and activity of uptake and efflux transporters mediate absorption of exogenous (drugs) and endogenous substrates from the bloodstream in the hepatocyte or proximal tubular cell, respectively. Drugs may then undergo biotransformation or be excreted unchanged into bile or urine. In the intestine (**C**), expression of uptake and efflux transporters in enterocytes serves to either enhance or limit the absorption of drugs from the intestinal lumen, thereby playing a pivotal role in determining the bioavailability of orally administered drugs.

3.1.3. Oatp1b1 (Oatp-C; *Slco1b1*)

This hepatic uptake transporter is considered to be a major pathway to account for the hepatic extraction of many drugs and endogenous compounds. Initially cloned by several groups from human liver *(14,24–26)*, OATP1B1 shares 80% amino acid identity with OATP1B3, but only 65% identity with its rat and mouse ortholog Oatp1b2 *(5)*. OATP1B1 expression appears to be limited to the basolateral membrane of hepatocytes *(14,24–26)*. Its exclusive expression in human liver is consistent with its putative role in the hepatic disposition of endogenous and xenobiotic compounds. OATP1B1 has been functionally characterized using multiple heterologous expression systems including *Xenopus laevis* oocytes *(18,25)*, HEK293 cells *(14,24,26)*, and HeLa cells *(27)*. OATP1B1 has remarkably broad substrate specificity that includes bile salts, conjugated and unconjugated bilirubin, BSP, steroid conjugates, the thyroid hormones T4 and T3, eicosanoids, cyclic peptides, and drugs such as benzylpenicillin, methotrexate, HMG-CoA reductase inhibitors (statins), and rifampicin *(5)*.

3.1.4. Oatp1b3 (Oatp8; *Slco1b3*)

Similar to OATP1B1, OATP1B3 was cloned from human liver and appears to be exclusively expressed at the basolateral membrane of hepatocytes *(28,29)*. In addition, OATP1B3 has been shown to be expressed in various human cancer tissues as well as in different tumor cell lines derived from gastric, colon, pancreas, gallbladder, lung, and brain cancers *(28)*. The pathological significance of OATP1B3 expression in human cancer tissues remains to be investigated and clarified. Similar to OATP1B1, OATP1B3 also transports bile salts, monoglucuronosyl bilirubin, BSP, steroid conjugates, the thyroid hormones T3 and T4, leukotriene C_4 (LTC_4), cyclic peptides, and drugs such as methotrexate and rifampicin *(5)*. However, OATP1B3 also exhibits unique transport properties in that it is able to mediate the cellular uptake of the intestinal peptide cholecystokinin 8 (CCK-8) *(30)*, the opioid peptide deltorphin II *(18)*, and the cardiac glycosides digoxin and ouabain *(18)*.

3.1.5. Other OATPs

There are other OATPs whose spectrum of substrates appears to be much more restricted to endogenous compounds, especially hormones, hormone conjugates, and signaling molecules such as prostaglandins. For example, OATP1C1 (OATP-F; *SLCO1C1*), highly expressed in brain and testis, exhibits high transport affinity for T4 ($K_m \sim 90$ nmol/L) and rT3 ($K_m \sim 130$ nmol/L), suggesting an important role in the delivery and disposition of thyroid hormones in target organs *(31)*. OATP3A1 (OATP-D; *SLCO3A1*) on the other hand is ubiquitously expressed and has also been detected in several cancer cell lines *(14)*, and when transiently expressed, it appears capable of transporting estrone-3-sulfate, PGE_2, and benzylpenicillin *(14)*. Considering the wide tissue distribution, this OATP might serve an as yet undetermined but likely important physiologic function. OATP4A1 (OATP-E; *SLCO4A1*) was isolated from human kidney and brain *(14,32)* and shown to possess 76% amino acid sequence identity with its rodent ortholog Oatp4a1 *(5)*. OATP4A1 mRNA expression is highest in liver, heart, placenta, and pancreas and has been shown to transport taurocholate and the thyroid hormones T3, T4, and rT3 *(32)*. In the placenta it has been localized to the apical surface of the syncytiotrophoblast *(33)*. Another member of the OATP4C subfamily is OATP4C1 (OATP-H; *SLCO4C1*), initially isolated from human kidney and noted to be localized to the basolateral membrane of renal proximal tubular cells *(34)*. OATP4C1 appears capable of transporting the cardiac glycosides digoxin and ouabain, the thyroid hormones T3 and T4, cAMP, and methotrexate *(34)*.

3.2. Major Facilitator Superfamily (SLC22)

While larger, lipophilic, and amphipathic organic anions tend to be transported by the OATPs, small hydrophilic organic anions and cations are more efficiently transported by members of the major facilitator (solute carrier) superfamily (SLC22), which include organic cation transporters (OCT), organic anion transporters (OAT), a urate transporter (URAT), and transporters of carnitine and/or cations (OCTN) *(35)*. These proteins tend to consist of 500–560 amino acids and exhibit common structural features, including 12 alpha-helical TM domains, a large glycosylated extracellular loop between TM 1 and 2, and a large intracellular loop that contains phosphorylation sites between TM 6 and 7 *(36)*.

3.2.1. Organic Cation Transporter 1 (OCT1; *SLC22A1*)

Organic cation transporter substrates are comparatively small (generally with molecular weight <400 Da) monovalent compounds, so-called “Type” I organic cations *(37)*. The OCTs represent facilitative diffusion systems that transport cations bidirectionally independent of H^+ and Na^+ gradients *(38)* with the driving force determining the direction of transport provided by the concentration gradient of the transported substrate and membrane potential. *Oct1* was first cloned from the rat in 1994 *(39)*. In humans, OCT1 is expressed mainly in the liver on the basolateral membrane of hepatocytes where it mediates the hepatic extraction of many cationic drugs. Note that this transporter is also expressed in the heart, skeletal muscle, kidney, placenta, and small intestine *(38)*. Because OCT1 can mediate bidirectional transport, it also likely participates in the release of organic cations from hepatocytes into the portal circulation.

Most OCT substrates are organic cations and weak bases *(38,40)*, but some uncharged compounds and even some anions are also transported. For example, cimetidine, a weak base, is a substrate of human OCT2 *(41)*, while anionic prostaglandins are transported by human OCT1 *(42)*. Common substrates of human OCT1, OCT2, and OCT3 include tetraethylammonium (TEA), the neurotoxin 1-methyl-4-phenylpyridinium (MPP), endogenous compounds such as 5-hydroxytryptamine, noradrenaline, and histamine, and drugs such as phenoxybenzamine, prazosin, o-methyllisoprenanline, procainamide, desipramine, and cimetidine *(38,40)*. Interestingly, *Oct1* knockout mice are fertile and have no overt phenotypic defects *(43–46)*. The tissue concentrations of choline and cimetidine are similar in *Oct1* knockout mice and wild-type mice *(43,46)*. However, the concentrations of TEA, MPP, and metformin in the liver and small intestine are reduced indicating a likely key role for OCT1 in the biliary disposition of certain organic cations.

3.2.2. ORGANIC CATION TRANSPORTER 2 (OCT2; *SLC22A2*)

OCT2 is expressed mainly in the kidney, but is also found in placenta, thymus, adrenal gland, neurons, and choroid plexus *(47–52)*. In rats and humans, OCT2 localizes to the basolateral membrane of renal proximal tubular cells *(52–54)* and mediates the renal excretion of many cationic drugs. Moreover, it is likely that some drugs which undergo glomerular filtration may be reabsorbed in the proximal tubule across the luminal membrane and reenter systemic circulation via OCT2 on the basolateral membrane. Note that human kidneys express an alternatively spliced variant of OCT2 which lacks three C-terminal TMs but is still capable of transporting TEA, MPP, and cimetidine *(55)*. *Oct2* knockout mice demonstrate no significant alteration in terms of levels of TEA in the small intestine, liver, and kidney but decreased accumulation of TEA *(45)*. However, in *Oct1/Oct2* double-knockout mice, TEA secretion in the proximal tubule is abolished, suggesting a critical role of these transporters in rodent kidney *(45)*.

3.2.3. ORGANIC CATION TRANSPORTER 3 (OCT3; *SLC22A3*)

OCT3 is expressed in a number of tissues including skeletal muscle, smooth muscle, liver, placenta, kidney, heart, intestine, spleen, lung, neurons of the brain and sympathetic ganglia, glial cells, and the choroid plexus *(47,56–59)*. Interestingly, tissue levels of MPP were reduced by 75% in the heart in *Oct3* knockout mice compared to wild-type mice *(44)*. Furthermore, after intravenous injection of MPP in pregnant females of an *Oct3* heterozygote cross, accumulation of MPP in *Oct3–/–* fetuses was reduced by 65% compared with wild-type fetuses *(44)*. These data indicate a likely significant role of OCT3 in the uptake of organic cations and substrate drugs into cardiomyocytes and in the transfer of organic cations and drugs across the placenta.

3.2.4. ORGANIC ANION TRANSPORTER 1 (OAT1; *SLC22A6*)

The kidney and liver are the major routes for organic anion elimination. In the kidney, the translocation of organic anions occurs predominantly in proximal tubular cells *(60,61)*. Similar to the liver, the hallmark of the renal organic anion transport system is its multispecific substrate recognition *(60–62)*. Historically, p-aminohippurate (PAH) has been used as a prototypical substrate for this system.

The first PAH uptake transporter was cloned and designated OAT1 in 1997 *(63–65)*. OAT1 mRNA is expressed predominantly in the kidneys and weakly in the brain. OAT1 protein is localized at the basolateral membrane of renal proximal tubular cells. OAT1-mediated PAH uptake appears to be stimulated by an outwardly directed concentration gradient of dicarboxylates such as alpha-ketoglutarate, consistent with the previous notion that OAT1 is an organic anion–dicarboxylate exchanger *(66)*. OAT1 possesses broad substrate specificity including endogenous compounds, such as dicarboxylates, cyclic nucleotides, and prostaglandins, and xenobiotics, such as the antibiotics penicillin and cephalosporin, the antivirals adefovir, cidofovir, and amantadine, nonsteroidal anti-inflammatory drugs such as indomethacin and ibuprofen, loop and thiazide diuretics, angiotensin-converting enzyme inhibitors, and the antineoplastic drugs methotrexate, azathioprine, cyclophosphamide, and doxorubicin *(67)*. Recent studies using *Oat1* knockout mice have confirmed the critical importance of this protein in the organic anion secretory pathway of the renal proximal tubule *(68)*.

3.2.5. Organic Anion Transporter 2 (OAT2; *SLC22A7*)

OAT2 was isolated originally from rat liver as a novel transport protein with unknown function *(69)*. Because of its structural similarities to OAT1, OAT2 was functionally characterized and typical substrates of OAT2 are PAH, salicylate, PGE_2, dicarboxylates, and drugs such as allopurinol, bumetanide, 5-fluorouracil, and paclitaxel *(70)*. OAT2 is expressed predominantly in the liver at the basolateral membrane of hepatocytes and weakly in the kidneys and appears to be involved in the hepatic disposition of some anionic drugs and endobiotics. Recent evidence suggests that its mechanism of transport is consistent with that of OAT1, an organic anion–dimethyldicarboxylate exchanger *(70)*. Nevertheless, little is known about the relevance of this transporter to hepatic or renal drug elimination.

3.2.6. Organic Anion Transporter 3 (OAT3; *SLC22A8*)

OAT3 was initially isolated from rat *(71)* and, by mRNA analysis, was found to be expressed in the kidneys, liver, brain, and eye. In the kidneys, OAT3, like OAT1, is localized to the basolateral membrane of proximal tubular cells *(72)*, while in the brain, OAT3 is expressed on the brush border membrane of choroid plexus cells *(73,74)* and in capillary endothelial cells *(75)*. Like OAT1, OAT3 transports PAH, estrone sulfate, ochratoxin A, and various drugs, including the cationic drug cimetidine *(76,77)*.

3.2.7. Organic Anion Transporter 4 (OAT4; *SLC22A9*)

OAT4 was cloned from human kidney *(78)*. OAT4 mRNA is expressed in the kidneys and is localized at the apical membrane of proximal tubular cells. In the placenta, OAT4 is expressed on the fetal side of the syncytiotrophoblast cells *(79)*. When expressed in *X. laevis* oocytes, OAT4 mediates the sodium-independent, high-affinity transport of estrone sulfate, dehydroepiandrosterone sulfate, ochratoxin A, and PGE_2. A recent study demonstrated that OAT4 functions as an organic anion–dicarboxylate exchanger *(80)*.

4. EFFLUX TRANSPORTERS

4.1. ATP-Binding Cassette Transporter Superfamily

Membrane-bound efflux transporter proteins have emerged as a key defense mechanism for limiting the cellular exposure to potentially toxic xenobiotics. Members of the ATP-binding cassette (ABC) transporter superfamily have been shown to account for efflux transport of a wide variety of compounds across biological membranes, including phospholipids, steroids, polysaccharides, peptides, amino acids, ions, organic anions, bile acids, drugs, and other xenobiotics *(81)*. In humans, 48 ABC genes have been described that are organized into seven subfamilies (A–G) based on sequence homology *(81,82)* (http://www.humanabc.org).

ABC proteins are present in all known living species, with conserved structural motifs consisting of a combination of conserved ABC and TM domains. In mammals, at least four such domains, consisting of two TMs and two ABCs, present within one polypeptide chain (full transporter) or within two separate proteins (half-transporters) have been noted *(83)*. For the half-sized ABC transporters, homodimerization results in a fully functional unit. As inferred by their names, ATP binding and hydrolysis at their nucleotide binding domains (NBDs) generate the energy needed for the translocation of their substrates across membranes *(84)*. Two sequence motifs, Walker A and Walker B, located 100–200 amino acids apart in each NBD are conserved among all ABC transporter superfamily members *(85)*. The lysine residue in the Walker A motif is involved in the binding of the β-phosphate of ATP, while the aspartic acid residue in the Walker B motif interacts with Mg^{2+} *(86,87)*. There is a highly conserved amino acid sequence (ALSGGQ) located between the Walker A and B motifs, referred to as the ABC signature motif (or C motif). The precise function of this sequence has yet to be determined although it has been implicated in ATP recognition, binding, and hydrolysis *(84)*.

4.1.1. Multidrug Resistance Protein 1 (MDR1, P-gp; *ABCB1*)

MDR1 was the first ABC transporter described and without a doubt the most extensively studied ABC transporter to date. MDR1, also widely referred to as P-glycoprotein (P-gp), is a 1280 amino acid protein with a molecular weight of 170 kDa *(88)*. A notable property of this transporter is the diversity of substrates that can be transported, including a vast number of drugs used for various therapeutic applications. Due to its broad substrate specificity and its overexpression in cross-resistant cell lines to various cytotoxic drugs, it was named the multidrug resistance (MDR) protein. Thus it is not surprising to see that many cytotoxic anticancer drugs are transported by MDR1 *(89)*.

MDR1 transports a diverse array of structurally divergent compounds with a tendency toward lipophilic, cationic substrates *(90)*. The list of substrates/inhibitors is continually growing and includes chemotherapeutic drugs, antibiotics, antivirals, calcium channel blockers, and immunosuppressive agents *(90,91)*. Despite its widely appreciated role in chemotherapy resistance via its overexpression in human cancers, MDR1 is also expressed in normal tissues such as the kidney, liver, intestine, and blood–brain barrier, where the normal physiologic function is thought to involve modulation of intestinal absorption, CNS entry, and enhanced secretion of toxic xenobiotics and their metabolites into bile or urine *(92–94)*. Mice have two closely related homologs of *MDR1*, the *Mdr1a* and *Mdr1b* genes. Mice homozygous for disrupted *Mdr1* genes are phenotypically normal but are extremely sensitive to certain drugs, particularly CNS active compounds such as ivermectin *(95,96)*. These studies have led to the determination of a critical role of MDR1 at the level of the blood–brain barrier, since the lack of expression leads to an enhanced drug accumulation within the brain.

In the liver and small intestine, MDR1-mediated excretion appears to be coordinately regulated with enzymes of phase I and phase II metabolism, such as the cytochrome P450 (CYP) family and glutathione-*S*-transferases (GST), respectively *(97)*. In particular, there appears to be an interplay between CYP3A4 and MDR1 in determining the bioavailability of many orally ingested compounds. The CYP3A subfamily is widely recognized as a key determinant of oral drug bioavailability in humans since nearly 50% of all the drugs in clinical use today undergo drug metabolism involving at least some degree of CYP3A-mediated oxidation *(98)* and constitutes a large proportion of all CYP enzymes expressed both in human liver (~30%) and in small intestine (~70%) *(99)* (see Chapter 4). MDR1 and CYP3A4 possess overlapping substrate specificity *(100)* and their coordinated expression is consistent with functional synergy. For example, in small intestine, CYP3A4 and MDR1 are localized on villous enterocytes, with MDR1 expressed on the apical brush border membrane *(101)* and CYP3A4 present in the endoplasmic reticulum just below the apical membrane *(102)*. Therefore, it is easy to envision CYP3A4 metabolizes substrates inside the cell, while MDR1 mediates their efflux in a coordinated fashion thereby limiting systemic exposure to potentially toxic xenobiotics.

4.1.2. BREAST CANCER RESISTANCE PROTEIN (BCRP; *ABCG2*)

BCRP was cloned based on its overexpression in a highly doxorubicin-resistant MCF7 breast cancer cell line (MCF-7/AdrVp) *(103–105)*. BCRP cDNA transfection demonstrated that BCRP could confer resistance to mitoxantrone, doxorubicin, and daunorubicin *(103,106)*. Because the gene was initially isolated from a breast cancer cell line, it was called the breast cancer resistance protein (BCRP) gene. However, as yet there is no indication that BCRP expression is specific for breast cancer cells or that it plays a significant role in chemotherapy resistance during breast cancer therapy. BCRP is an ABC half-transporter with molecular weight ~75 kDa, containing a single amino-terminal ABC followed by six putative TMs *(107)*. Based on comparison with other ABC transporters, it was hypothesized that BCRP functioned as a homo- or heterodimer *(106,108)*. Like MDR1, BCRP possesses broad substrate specificity and can transport hydrophobic, amphipathic molecules, including anticancer agents such as mitoxantrone, topotecan, flavopiridol, and methotrexate, as well as statin drugs, fluorescent dyes, and toxic compounds found in normal food such as pheophorbide A *(109–115)*.

Similar to MDR1, BCRP likely plays an important role in conferring the multidrug resistance phenotype seen in various cancers through its overexpression *(116–119)*. Human BCRP is also expressed in normal tissues, such as the placental syncytiotrophoblast, the apical (canalicular) membrane of liver hepatocytes, and the apical (luminal) membrane of villous intestinal enterocytes, suggesting an excretory function akin to MDR1 *(120)*. Indeed, for some drugs such as topotecan, BCRP has a large effect on its oral bioavailability *(121)*.

4.1.3. BILE SALT EXPORT PUMP (BSEP; *ABCB11*)

This ABC transporter was initially termed sister of P-glycoprotein (Spgp) *(122)* and named for its close sequence homology with MDR1 (P-gp). Recently, this transporter was renamed the bile salt export pump (BSEP) since studies have shown it to be exclusively localized to the canalicular domain of hepatocytes and mediates the high-affinity transport of primary and secondary bile salts *(123–125)*.

In addition to its critical role as a hepatic bile salt export pump, BSEP has been demonstrated to transport a limited number of drugs such as vinblastine, calcein-acetoxymethyl ester *(126)*, and pravastatin *(127)*. Not surprisingly, given its central role in the hepatic bile acid secretion, BSEP has been implicated in drug-induced cholestasis. Several drugs known to cause cholestasis, including glybenclamide (glyburide), troglitazone, and bosentan, have been shown capable of inhibiting BSEP-mediated ATP-dependent bile salt transport in isolated rat liver canalicular membrane vesicles *(128–131)*. In addition, trans-inhibition of BSEP has also been implicated as a mechanism to account for cholestasis induced by the steroid conjugate, estradiol-17β-glucuronide *(132)*.

4.1.4. MULTIDRUG RESISTANCE-ASSOCIATED PROTEIN 1 (MRP1; *ABCC1*)

MRP1 was initially cloned from a multidrug-resistant human small cell lung cancer cell line that did not express MDR1 *(133)*. MRP1 exhibits widespread expression with high levels in muscle, intestine, brain, kidney, lung, and testis, but much lower expression in liver *(134–137)*. MRP1 is localized to the basolateral membranes of polarized epithelial cells including intestinal enterocytes *(138)*, renal distal and collecting tubular cells *(138)*, and hepatocytes *(139,140)*. MRP1 expression has been linked to resistance to chemotherapeutic drugs including daunorubicin, doxorubicin, and vincristine in a range of cancer cell lines *(141–144)*. In contrast to MDR1, MRP1 is capable of transporting hydrophobic drugs or other compounds conjugated to glutathione (GSH), glucuronic acid, or sulfate *(145–148)* or co-transported with reduced GSH *(149,150)*. MRP1 substrates include glutathione conjugates such as LTC_4 and 2,4-dinitrophenyl-S-glutathione (DNP-SG), bilirubin glucuronides, estradiol-17β-glucuronide, and dianionic bile salts *(143,145,151–153)*, suggesting a role for MRP1 in the removal of endogenous metabolites.

Studies have shown that Mrp1 expression on the basolateral membrane of rat hepatocytes is markedly increased following bile duct ligation *(154)*, suggesting its role in facilitating cellular detoxification when normal routes of biliary elimination are limited. Knockout mice lacking *Mrp1* are viable and fertile but show deficiencies in LTC_4-mediated inflammatory reactions, suggesting that secretion of LTC_4 is an important physiological function of MRP1 *(155–157)*. In addition, *Mrp1* knockout mice are more sensitive to the toxicity of intravenously administered etoposide in the oropharyngeal mucosal layer and testicular tubules *(155,158)*. It should be noted that MRP1 may act synergistically with MDR1 in terms of cellular protection against xenobiotics and toxins. There appeared to be significant correlation between MRP1 and MDR1 mRNA levels and resistance to doxorubicin in samples of bladder cancer *(159)*. Both MRP1 and MDR1 expression were markedly higher in tumors after chemotherapeutic treatment compared to untreated tumors. Furthermore, *Mdr1a/1b/Mrp1* triple knockout mice appear to be highly sensitive to intraperitoneally administered vincristine (up to 128-fold) and also to etoposide (3.5-fold), whereas *Mdr1a/1b* deficiency alone resulted in a 16- and 1.75-fold increased sensitivity to these drugs *(160)*.

4.1.5. MULTIDRUG RESISTANCE-ASSOCIATED PROTEIN 2 (MRP2; *ABCC2*)

MRP2 shares 49% amino acid identity with MRP1 *(161)* and was originally cloned from human liver as the canalicular multispecific organic anion transporter (cMOAT) *(162)*. Like MDR1, MRP2 is localized to the apical membrane of target organs such as the liver, intestine, and kidney *(163–165)*. Studies have shown that

MRP2 is involved in transporting a range of both conjugated and unconjugated amphipathic compounds into bile. Like MRP1, MRP2 has broad substrate specificity and transports glutathione conjugates such as LTC_4 and DNP-SG, bilirubin glucuronides, and a number of drugs and conjugated drug metabolites *(152,166,167)*, consistent with MRP2 playing a central role in the secretion of drug metabolites into bile. Note that there are patients with Dubin–Johnson syndrome *(168)* and EHBR (Esai hyperbilirubinemic rat) and TR-/GY rats that lack *MRP2* due to genetic mutations in this transporter *(162,169–171)*. MRP2-defective humans and rats exhibit conjugated hyperbilirubinemia, impaired biliary secretion of glutathione, glutathione conjugates, and bilirubin glucuronides *(170,172–174)*.

As well as transporting endobiotic and xenobiotic metabolites, MRP2 also mediates cellular resistance to other cytotoxic drugs including vincristine, doxorubicin, and cisplatin *(175–177)*. Other MRP2 substrates include the anti-retroviral protease inhibitors *(178,179)*, nucleoside phosphonates *(180)*, and fluoroquinolone antibiotics *(181)*. MRP2 also transports dietary constituents such as the dietary flavonoids quercetin 4′-β-glucoside *(182)* and sulfate conjugates of the tea flavonoid epicatechin *(183)*.

4.1.6. MULTIDRUG RESISTANCE-ASSOCIATED PROTEIN 3 (MRP3; *ABCC3*)

Human MRP3 is most closely related to MRP1, with 58% amino acid identity *(184)* and expressed mainly in liver, but is also present in small intestine, colon, lung, spleen, and kidney *(165,185,186)*. Like MRP1, MRP3 appears to localize to the basolateral membrane in such organs *(187)*. MRP3 possesses significant substrate overlap with MRP2 and BSEP in terms of transporting a wide range of bile salts, including taurocholate, glycocholate, taurolithocholate-3-sulfate, and taurochenodeoxycholate-3-sulfate *(188,189)*.

Human MRP3 can confer resistance to the anticancer drugs etoposide, teniposide, and methotrexate although its role in clinical multidrug resistance is unclear *(187,190)*. MRP3 mediates efficient estradiol-17β-glucuronide transport and moderate DNP-SG and LTC_4 transport *(189,191)*. In *MRP2*/*Mrp2*-deficient patients and rats, and with some pharmacologic-mediated cholestatic states, a strong upregulation of MRP3/Mrp3 is observed in the liver *(165,192,193)*, suggesting a compensatory function for this transporter in terms of eliminating a range of toxic organic anions and glucuronide conjugates.

4.1.7. MULTIDRUG RESISTANCE-ASSOCIATED PROTEIN 4 (MRP4; *ABCC4*)

Human MRP4 shares 30–40% amino acid identity with other MRPs and has been detected in many tissues including jejunum, kidney, brain, lung, and gallbladder *(137,186,194,195)*. MRP4 has been localized to the apical membrane of renal proximal tubular cells *(195)*, but has also been found at the basolateral membrane in tubuloacinar cells of the prostate gland *(196,197)*. MRP4 substrates include folic acid, leucovorin, and methotrexate *(198)* as well as cAMP, cGMP, estradiol-17β-glucuronide, and bile acids *(195,197,199,200)*. The overall significance of MRP4 in drug disposition remains to be clarified, although it has been shown to transport the nucleoside phosphonate analogs PMEG (9-[phosphonylmethoxyethyl] guanine) and adefovir (PMEA; 9-[*2*-phosphonylmethoxyethyl] adenine), as well as azidothymidine monophosphate, from a number of cell lines *(197,201)*. The apical localization of MRP4 in kidney and intestine suggests that MRP4 might mediate renal secretion of nucleoside phosphonate analogs.

4.1.8. Multidrug Resistance-Associated Protein 5 (MRP5; *ABCC5*)

MRP5 shows approximately 33–37% amino acid identity to MRP1-4 *(202)*. Expression of MRP5 is widespread, including colon, liver, kidney, skeletal muscle, and brain *(137,186,203)*. Human MRP5 localizes to the basolateral membrane when stably transfected into MDCKII cells *(204)*, although immunofluorescence microscopy has demonstrated MRP5 to be expressed on the apical (luminal) side of brain capillary endothelial cells *(205)*. MRP5 substrates include DNP-SG, adefovir, the purine analogs 6-mercaptopurine and thioguanine, 5-fluorouracil (5-FU), and methotrexate *(204,206)*.

5. TRANSPORTERS AND TISSUE DISTRIBUTION

Tissue-specific and targeted subcellular localization of transporters appears to be essential to the intestinal absorption and urinary or biliary excretion of many drugs.

5.1. Small Intestine

In the small intestine, enterocytes express a number of transporters critical for enhancing or limiting the absorption of dietary constituents and drugs. MDR1 is a particularly important efflux transporter which limits the bioavailability of substrate by its ability to efflux substrate drugs back to the intestinal lumen. The oral bioavailability of paclitaxel *(207)*, digoxin *(208)*, and HIV-1 protease inhibitors *(209)* is markedly increased in *Mdr1a* knockout mice in comparison to wild-type mice, indicating the importance of this transporter to the bioavailability of many drugs. In humans, extent of intestinal MDR1 expression and activity has been shown to influence attained drug levels after administration of cyclosporine *(210)* and digoxin *(211)*.

5.2. Liver

In the liver, efficient extraction of drugs from the portal blood into hepatocytes is often mediated by uptake transporters expressed on the basolateral (sinusoidal) membrane. Available data strongly suggest that members of the OATP and OCT transporter families are responsible for much of the efficient hepatic extraction of drugs. For example, hepatic uptake of the HMG-CoA reductase inhibitor pravastatin is dependent on OATP1B1 and its activity is thought to be the rate-limiting step in pravastatin hepatic clearance *(212)*. Once a drug gains access into hepatocytes, it often undergoes metabolism mediated by phase I and II enzymes or may be secreted unchanged. Efflux transporters localized on the apical (canalicular) membrane of the hepatocyte, such as MDR1, MRP2, and BCRP, represent the final step in the vectorial transport of drugs from portal circulation into bile.

5.3. Kidney

In the kidney, drug secretion also represents the coordinate function of uptake and efflux transporters localized to the basolateral and apical membranes of proximal tubular cells. Unlike liver, in the kidney, OAT family members appear to be the major determinants of organic anion uptake. OAT substrates include a wide variety of anionic drugs such as β-lactam antibiotics, diuretics, NSAIDs, nucleoside antiviral drugs, and anticancer agents *(213)*. Renal efflux transporters have not been as extensively studied but members of the MRP and OATP families of transporters have been localized to the apical membrane of proximal tubular cells and likely contribute to the urinary elimination of substrate drugs.

5.4. Brain

In organs such as the brain, targeted transporter expression is critical to the maintenance of barrier function. The blood–brain barrier serves a protective function by limiting access of drugs and toxic substances into the CNS. The barrier is maintained by brain capillary endothelial cells, whose closely sealed tight junctions effectively limit entry of drugs via the paracellular route *(214)*. While there are key uptake transporters which facilitate the CNS entry of essential endogenous compounds such as glucose, amino acids, and nucleosides, efflux transporters, such as MDR1, localized to the apical (luminal) side of the blood–brain barrier endothelial cells, prevent CNS entry of substrate drugs *(215)*. The clinical relevance of MDR1 expression at the level of the blood–brain barrier has been shown in studies using *Mdr1a* knockout mice *(95)*, noted to have 80–100-fold greater brain level of drugs such as the neurotoxin ivermectin when compared to wild-type mice *(95)*. Additional studies have demonstrated that the CNS entry of a number of MDR1 drug substrates, such as digoxin, quinidine, tacrolimus, and anti-retroviral protease inhibitors, is markedly greater when MDR1 is deficient at the level of the blood–brain barrier *(209,216,217)*.

6. TRANSPORTERS AND GENETIC HETEROGENEITY

Inherited defects in drug-metabolizing enzymes such as CYP2D6, CYP2C19, and CYP2C9 have long been recognized to be critical to the observed intersubject variation in response to drugs which undergo metabolism by such enzymes *(218)*. Not surprisingly, there is increasing evidence to suggest that genetic heterogeneity in drug transporters may have similar impact on variable drug disposition or response in humans. Numerous polymorphisms have been identified in transporters important to the drug disposition process (Table 2). However, for the most part, studies relating to drug transporter pharmacogenetics have only recently become available or initiated *(218a,218b)*.

6.1. Genetic Polymorphisms in MDR1 (ABCB1)

MDR1 has received the greatest attention in terms of identification and characterization of single nucleotide polymorphisms in relation to drug efficacy. Genetic polymorphisms in the *MDR1* gene were first identified by Kioka et al. from in vitro studies in cancer cells *(219)*. A synonymous polymorphism in exon 26, C3435T, noted to be common in various ethnic groups, was initially shown to correlate with the expressed level of MDR1 protein in the duodenum as determined by Western blot analysis and quantitative immunohistology *(220)*. However, the functional role for this polymorphism still remains controversial. Mechanistically, it has been unclear as to how a synonymous base pair change, which does not alter amino acid coding sequence, could result in altered protein function. A recent study would suggest that the C3435T polymorphism does not result in altered mRNA or

Table 2
Genetic Polymorphisms in Drug Transporters

Gene symbol	*Transporter*	*Polymorphism*	*Allele frequency*	*Potential effects*	*References*
ABCB1	MDR1	C3435T	54% Caucasian 26% African-Americans 53% Asian-Americans	Susceptibility to renal tumors	*(222)*
				Susceptibility to ulcerative colitis	*(224)*
				Susceptibility to Parkinson's disease	*(223)*
				Response in refractory epilepsy	*(225)*
				Overall survival in acute myeloid leukemia	*(281)*
				CD4 response in HIV-1 therapy	*(226)*
				Susceptibility to childhood acute lymphoblastic leukemia	*(282)*
				Increased cyclosporine clearance in renal transplant patients	*(283)*
				Smaller reduction in LDL cholesterol in response to atorvastatin treatment	*(284)*
	MDR1	G2677T	46% Caucasian 6.5% African-Americans	Lower fexofenadine plasma levels in healthy volunteers	*(285)*
				Reduced risk chronic renal dysfunction with calcineurin inhibitors after liver transplantation	*(286)*
				Susceptibility to inflammatory bowel disease	*(287)*
ABCA1	ABCA1	G655A	25% Caucasian	Decreased triglycerides, increased HDL plasma levels, decreased risk of atherosclerosis	*(288)*
		A5397C	Rare	Low levels of HDL-C	*(289,290)*
ABCG2	BCRP	C421A	46% Japanese 14% Caucasian	Decreased protein expression and increased sensitivity to irinotecan (SN-38), mitoxantrone, topotecan in vitro	*(291)*
				Increased plasma levels of diflomotecan in adult cancer patients	*(292)*

(*Continued*)

Table 2
(Continued)

Gene symbol	*Transporter*	*Polymorphism*	*Allele frequency*	*Potential effects*	*References*
SLC22A1	OCT1	C181T	7.2% Caucasian 5.6% Hispanic	Decreased uptake of MPP in vitro	*(293)*
		T262C	0.6% Caucasian	Decreased uptake of MPP in vitro Decreased uptake of serotonin in vitro	*(294)*
		C1022T	8.2% African-Americans 11.7% Asian-Americans	Decreased uptake of MPP in vitro	*(293)*
		G1201A	3.2% Caucasian	Decreased uptake of serotonin in vitro Decreased uptake of MPP in vitro	*(293,294)*
		G1393A	4% Caucasian	Decreased uptake of MPP in vitro	*(293)*
SLC22A2	OCT2	G495A	1% African-Americans	Decreased uptake of MPP in vitro	*(295)*
		C1198T	1.5% African-Americans	Decreased uptake of MPP in vitro	*(295)*
SLCO1B1	OATP1B1	T521C	14% Caucasian	Increased pravastatin plasma levels	*(228–230)*
			16% Japanese	Decreased steroid conjugate uptake in vitro	*(27)*
		G1463C	9% African-Americans	Decreased steroid conjugate uptake in vitro	*(27)*
SLCO1B3	OATP1B3	G1564T	1.9% Caucasian	Impaired protein trafficking to membrane, decreased bile acid transport in vitro	*(296)*
SLCO2B1	OATP2B1	C1457T	30.9% Japanese	Decreased transport of estrone sulfate in vitro	*(227)*

MPP, 1-methyl-4-phenylpyridinium

protein levels, but does alter the conformation of the protein *(221)*, possibly related to affecting the timing of cotranslational folding and insertion of the protein into the membrane, thereby altering the structure of substrate and inhibitor interaction sites.

It should be noted that the C3435T single nucleotide polymorphism in this transporter has been linked to susceptibility to renal cell carcinoma *(222)*, Parkinson's disease *(223)*, inflammatory bowel disease *(224)*, refractory epilepsy *(225)*, and response to anti-retroviral therapy *(226)*. Clearly, additional studies are needed to determine the functional consequences of *MDR1* polymorphisms in vivo to the drug disposition process and disease states*(226a)*, but MDR1 represents an illustrative example of the wide-ranging impact of transporter proteins to clinical medicine.

6.2. Genetic Polymorphisms in OATP1B1 (SLCO1B1)

There are a number of nonsynonymous single nucleotide polymorphisms in OATP1B1 whose allelic frequencies vary by race *(27,227,228)*. A number of the variant alleles that introduced amino acid changes within the transmembrane-spanning domains and extracellular loop 5 have been shown to be associated with a dramatic reduction of V_{max}/K_m values indicating a significant decrease of OATP1B1-mediated transport function *(27)*. Cell surface trafficking defects proved to be responsible for altered transport function of many of these variants *(27)*. Several groups have investigated the in vivo contribution of genetic OATP1B1 variants on pravastatin pharmacokinetics and demonstrated that subjects carrying the *OATP1B1*5* or *OATP1B1*15* allele (*OATP1B1*1b* + *OATP1B1*5*) had increased pravastatin plasma levels compared to individuals carrying the wild-type *OATP1B1*1a* or **1b* allele *(228–230)*. More recently, we confirmed the significance of the *OATP1B1*15* variant to pravastatin pharmacokinetics in European-Americans but also found significant ethnic differences in pravastatin pharmacokinetics between European- and African-Americans *(231)*. These racial differences were not attributable to OATP1B1 genotype or common polymorphisms in MRP2, BCRP, or BSEP, suggesting that polymorphisms in other drug disposition gene(s) may be responsible for the observed ethnic differences. Whether other polymorphisms of OATP1B1 also result in decreased OATP1B1 function in vivo and/or in additional phenotypic alterations remain to be investigated. In the context of the current review, an exhaustive outline of all the relevant transporters and their single nucleotide polymorphisms is not possible. A number of detailed and in-depth reviews are available *(232–237)*.

7. TRANSPORTERS AND DRUG–DRUG/DRUG–NUTRIENT INTERACTIONS

As the number of newly approved drugs increases, medication errors and drug–drug interactions have become a significant source of patient morbidity and, in some cases, mortality. Indeed, it has been estimated that drug interactions alone account for nearly 3% of all hospital admissions *(238)*. Factors such as age, diet, dietary supplement or herbal and alternative therapies may also influence the extent of drug interactions associated with medications. Moreover, inhibition of both drug-metabolizing enzymes as well as transporters (Table 3) is now recognized as the likely mechanism accounting for many drug–drug interactions as transporters and CYP enzymes often share overlapping tissue expression and substrate capacities.

Table 3
Drug–Drug Interactions or Toxicities Involving Drug Transporters

Object Drugs	*Inhibitor/ inducer*	*Measured effect/ toxicity*	*Putative mechanism*	*References*
Penicillin	Probenecid	Decreased renal clearance; prolonged half-life	Inhibition of OATs	*(257)*
ACE inhibitors	Probenecid	Decreased renal clearance; prolonged half-life	Inhibition of OATs	*(257)*
Antiviral drugs	Probenecid	Decreased renal clearance; prolonged half-life	Inhibition of OATs	*(257)*
Procainamide	Cimetidine	Decreased renal clearance; increased AUC	Inhibition of OCT, OAT, OATP	*(257)*
Levofloxacin	Cimetidine	Decreased renal clearance; increased AUC	Inhibition of OCT, OAT, OATP	*(257)*
Dofetilide	Cimetidine	Decreased renal clearance; increased AUC	Inhibition of OCT, OAT, OATP	*(257)*
Fexofenadine	Fruit juices	Decreased plasma levels	Inhibition of OATPs	*(266)*
Methotrexate	NSAIDs	Decreased renal clearance	Inhibition of OAT3	*(262)*
Methotrexate	Probenecid	Decreased renal clearance	Inhibition of OAT3	*(262)*
Loperamide	Quinidine	Increased CNS adverse effects	Inhibition of MDR1	*(254)*
Talinolol	Verapamil	Decreased plasma levels	Inhibition of MDR1	*(277)*
Fexofenadine	Erythromycin	Increased plasma levels	Inhibition of MDR1	*(278)*
Fexofenadine	Rifampicin	Decreased plasma levels	Induction of MDR1	*(279)*
Digoxin	Quinidine	Increased plasma levels, decreased renal clearance	Inhibition of MDR1	*(216)*
Digoxin	Verapamil	Increased plasma levels, decreased renal clearance	Inhibition of MDR1	*(280)*

Digoxin	Talinolol	Increased plasma levels, decreased renal clearance	Inhibition of MDR1	*(250)*
Digoxin	Clarithromycin	Increased plasma levels, decreased renal clearance	Inhibition of MDR1	*(249)*
Digoxin	Statins	Increased plasma levels, decreased renal clearance	Inhibition of MDR1	*(251)*
Digoxin	Rifampicin	Decreased plasma levels	Induction of MDR1	*(252)*
	Troglitazone	Hepatotoxicity	Inhibition of BSEP	*(270)*
	Bosentan	Cholestasis	Inhibition of BSEP	*(128)*
	Estrogens	Cholestasis	Inhibition of BSEP	*(129)*
	Cyclosporine	Cholestasis	Inhibition of BSEP	*(129)*
	Cidofovir	Nephrotoxicity	Inhibition of OAT1	*(271)*
	Adofovir	Nephrotoxicity	Inhibition of OAT1	*(271)*
	Cephaloridine	Nephrotoxicity	Inhibition of OAT1	*(274)*

Another aspect of drug interaction to consider relates to loss of drug efficacy associated with induction of drug-metabolizing enzymes and drug transporters expressed in the intestine and liver *(239)*. It now appears that the expression of drug disposition genes is largely under transcriptional control by members of the nuclear receptor 1 (NR1) family of transcription factors, including constitutive androstane receptor (CAR), pregnane X receptor (PXR), and farnesoid X receptor (FXR) *(239)*. These nuclear receptors share a common signaling mechanism involving ligand binding to the receptor, heterodimerization with the 9-*cis* retinoic acid receptor (RXR), binding of the heterodimer to response elements of target genes, and subsequent initiation of gene transcription *(240)*. For example, PXR appears to be critical for the regulated expression of drug-metabolizing enzymes such as CYP3A4, CYP2B6, and CYP2C9 *(241–244)* as well as the efflux transporter MDR1 *(245)*. More comprehensive reviews of the importance of transcriptional regulation to the drug disposition process have recently been published *(219,246–248)*.

7.1. MDR1 and Drug Interactions

Drug interactions involving the cardiac glycoside digoxin still remain a clinically relevant interaction as the clinical indication for digoxin administration has remained remarkably unchanged over the past century. Despite a wealth of data showing predictable digoxin interactions with concomitant administration of drugs such as quinidine, verapamil, and cyclosporine, only recently has the mechanism underlying this interaction been defined. In vitro and animal studies clearly show digoxin is a high-affinity substrate for MDR1, and interacting drugs have been shown to be MDR1 inhibitors. Indeed, other known MDR1 inhibitors, such as clarithromycin *(249)*, talinolol *(250)*, and atorvastatin *(251)*, have also been shown to increase the area under the plasma concentration time curve (AUC) of digoxin. Due to the cellular membrane domain-specific expression of MDR1, inhibition of intestinal MDR1 activity would be expected to increase digoxin bioavailability, and inhibition of renal and hepatic MDR1 activity to decrease urinary and biliary excretion of digoxin. Conversely, induction of MDR1 associated with rifampin therapy has been shown to lower the digoxin plasma level *(252)*.

One clinically relevant effect of MDR1-associated drug interactions relates to the important role of this transporter in altering the CNS entry of substrate drugs. For example, loperamide is a potent opioid that reduces gut motility by its action at opioid receptors in the gut and is therefore widely used as an anti-diarrheal agent. Due to its localized action to the gut, this drug is available as an over-the-counter medication. The drug is devoid of significant central opioid effects because it is a high-affinity MDR1 substrate, thus normally prevented from intestinal absorption or CNS entry *(253)*. Remarkably, co-administration of loperamide and the MDR1 inhibitor quinidine has been shown to elicit central opioid effects *(254)*. Therefore, inhibition of MDR1 at the level of the blood–brain barrier may result in an unexpected increase in CNS entry of MDR1 substrate drugs. Given the broad spectrum of structurally divergent drugs which have been shown to be transported by MDR1 *(91)*, it is likely that a number of adverse drug effects may be related to alteration in the function of this transporter, especially at the CNS barrier.

7.2. OATs and Drug Interactions

Perhaps the most widely appreciated drug interaction is that of penicillin and probenecid, in which co-administration of probenecid resulted in elevated penicillin serum levels *(255)*. Studies have shown that the high renal clearance of penicillins can be decreased by inhibition of OAT-mediated transport on the basolateral membrane of proximal tubular cells with co-administration of probenecid *(256)*. Similar effects of probenecid co-administration have now been extended to other anionic drugs such as angiotensin-converting enzyme (ACE) inhibitors and anti-retroviral drugs *(257)*.

Another well-known kidney-associated drug interaction relates to methotrexate, a drug widely used in the treatment of various malignancies and rheumatoid arthritis. Methotrexate is eliminated primarily unchanged in urine *(258)*. Interactions between methotrexate and drugs such as NSAIDs, probenecid, and penicillin have been reported and have resulted in severe complications including bone marrow suppression and acute renal failure *(259–261)*. Like penicillin, we now know that the mechanism behind this interaction is likely due to inhibition of OAT-mediated methotrexate transport by these drugs *(262)*.

7.3. OATPs and Fruit Juice–Drug Interactions

Medications and foods are often taken together. Concomitant drug and food intake creates the opportunity for interactions that may change the oral bioavailability and resulting effectiveness or toxicity of a drug (see Chapter 8). The first report of citrus juices' effects on oral drug bioavailability was noted over 15 years ago when grapefruit juice was shown to increase the oral bioavailability and effects of the calcium channel antagonists felodipine and nifedipine *(263)* (see Chapter 10). Felodopine is metabolized by CYP3A4 *(264)* and it was subsequently demonstrated that grapefruit juice caused a major reduction of small intestinal enterocytes CYP3A4 protein expression *(265)*, which was associated with greater than three- and five-fold higher AUC and C_{max} of felodipine, respectively. Furanocumarins in grapefruit juice are thought to function as a mechanism-based inhibitor of enteric CYP3A4.

More recently, it has been shown that certain fruit juices can act as inhibitors of intestinal OATP function. Grapefruit, apple, and orange juices were shown to decrease the overall absorption of the antihistamine fexofenadine, as exhibited by a 70–75% reduction in fexofenadine bioavailability compared to consumption of water *(266)*. A follow-up study demonstrated that OATP1A2 expression in the intestine, fexofenadine transport by OATP1A2 in vitro, and consumption of grapefruit juice concomitantly or 2 h before fexofenadine administration were associated with reduced oral fexofenadine plasma exposure *(19)*. Taken together, fruit juice-mediated inhibition of OATP1A2 activity in the intestine is responsible for decreased bioavailability of fexofenadine when given concomitantly. Although the clinical consequences of these food interactions with fexofenadine have not been fully explored, it is possible that reduced bioavailability of fexofenadine may compromise its efficacy.

8. TRANSPORTER-RELATED ORGAN TOXICITY

In addition to drug–drug interactions, unexpected drug-induced organ toxicities also represent an important subset of adverse drug reactions and may account for a significant proportion of fatal reactions to drugs, estimated to be ~100,000 deaths per year *(267)*. Potential risk factors for the development of drug-induced organ toxicities include age, kidney and liver function, and lifestyle features such as alcohol consumption, smoking, and diet. Interestingly, transporters are now being considered in drug-induced organ toxicities. This is consistent with the function of certain transporters in their elimination of often toxic xenobiotics. Table 3 lists drug-induced organ toxicities which are thought to be mediated at least in part by specific interactions with transporter proteins.

8.1. Inhibition of Bile Salt Transport and Hepatotoxicity

Drug-induced liver injury remains a significant problem for many drugs already in clinical use as well as new drugs under development. The exact mechanisms or pathways by which drug-induced hepatocellular damage occurs, for the most part, have not been fully elucidated. However, there is emerging evidence to suggest that drug-induced cholestasis can result in the intracellular accumulation of bile salts whose detergent actions promote hepatocellular damage by interfering with mitochondrial functions *(268)*. Recent studies have implicated inhibition of certain hepatic transporters as a key determinant of drug-induced cholestasis and hepatocellular injury.

The bile salt export pump (BSEP), an efflux transporter responsible for secretion of bile salts across the canalicular membrane into bile *(123,269)*, appears to be a key target of such drug-induced cholestasis. As noted earlier, in vitro studies have demonstrated that drugs such as cyclosporine, rifampicin, and the oral hypoglycemic agent glybenclamide (glyburide) can directly inhibit rat BSEP-mediated transport of bile salts *(129)*. Bosentan, an endothelin receptor antagonist initially developed for broad indications such as congestive heart failure, was found to cause a dose-dependent cholestatic liver injury and noted to be a potent inhibitor of rat BSEP *(128)*. Similar types of conclusions have been noted for the novel antidiabetic drug troglitazone, first to be marketed among drugs in this class, but subsequently withdrawn from the market due to an unexpected number of drug-induced liver injuries *(270)*.

8.2. Nephrotoxicity and Transporter Involvement

For many renally eliminated drugs such as adefovir and cidofovir, their accumulation in the proximal tubular cells mediated by the OAT family of transporters appears to increase their potential for tubular damage *(271)*. In vitro, cytotoxicity of such agents were noted to be 400–500-fold greater in OAT1-expressing cells than in control cells, suggesting that OAT1-mediated cellular accumulation of adefovir and cidofovir may contribute to their organ-specific toxicity. Similar mechanisms may apply to nephrotoxicity associated with certain β-lactam antibiotics such as cephaloridine *(256)*. Conversely, inhibition of such transporters in some cases may offer a degree of cytoprotection during concomitant use. Indeed, recent studies have demonstrated that probenecid and NSAIDs may reduce toxicity associated with drugs, such as adefovir, cidofovir *(272,273)*, and cephaloridine *(274)*, suggesting that competitive inhibition of OAT transporters may, in some cases, confer nephrotoxicity.

9. CONCLUSIONS AND FUTURE PERSPECTIVES

Drug transporters are increasingly recognized as important proteins that often possess an organ-specific expression pattern to facilitate the absorption, distribution, and subsequent excretion of numerous xeno- and endobiotics. Furthermore, alteration in transporter function by drugs and dietary constituents contributes to drug–drug and drug–nutrient interactions. In addition, genetic variation in drug transporter genes appears to be a major contributor to interindividual variation in drug response. This is an emerging field which appears to be poised to provide important new insights into our understanding of the mechanisms underlying intersubject variability in drug responsiveness. Clearly, the extent of interplay between drug transporters and metabolizing enzymes needs to be assessed in greater detail to better predict or individualize drug therapies.

DISCUSSION POINTS

- The targeted expression of uptake and efflux transporters in organs of importance for drug and nutrient absorption, distribution, and elimination reflects the critical importance of these proteins to overall drug disposition and normal homeostasis.
- The complex interplay amongst drug disposition genes, including those that encode drug transporter and drug-metabolizing enzymes, must be taken into consideration when assessing contributing factors to overall drug or nutrient disposition.
- Modification of transport routes by drug competition or inhibition offers mechanisms by which potentially clinically beneficial or detrimental adverse drug–drug or drug–nutrient interactions may occur.
- A number of polymorphic variants in drug transporter genes have been functionally characterized and not only have significant roles in determining interindividual variation in drug response but also have important implications for response to, susceptibility to, and incidence of various disease states.

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4 Drug-Metabolizing Enzymes

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Objectives

- Define the various superfamilies, subfamilies, and individual drug-metabolizing enzymes and their tissue expression in humans.
- Identify the role of the major drug-metabolizing enzymes in the disposition of medication and other xenobiotics.
- Discuss the potential for interactions that can occur by induction or inhibition of major drug-metabolizing enzymes.

Key Words: Cytochrome P450; drug interaction; glutathione S-transferase; UDP-glucuronosyl transferase

1. INTRODUCTION

A drug interaction occurs when a drug or another substance modifies the pharmacokinetics and/or the pharmacodynamics of a concurrently administered drug. Various types of drug interactions exist, including drug–drug interaction, herb–drug interaction, and food–drug interaction, as well as nutrient–drug interaction *(1–4)*. The underlying mechanism of a pharmacokinetic drug interaction may be due to an alteration in drug absorption, distribution, biotransformation (metabolism), or excretion. Many of the documented pharmacokinetic drug interactions occur at the level of biotransformation by inducing or inhibiting drug-metabolizing enzymes *(5,6)*. Some drug–nutrient interactions may also occur at the level of drug-metabolizing enzymes. A pharmacokinetic drug interaction may result in enhanced drug efficacy. For example, inhibition of drug-metabolizing enzyme is the basis of "boosted" protease inhibitor therapy used clinically in the management of human immunodeficiency virus infection *(7)*. In other instances, a pharmacokinetic drug interaction may lead to therapeutic failure *(8)*, severe adverse events *(9)*, or even fatality *(10)*. In fact, adverse effects due to drug interactions are one of the leading causes of deaths in hospitalized patients *(11)*. Drug interactions also have a high economic cost to the pharmaceutical industry because drugs have been withdrawn

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from the market as a result of adverse consequences *(12)*. This chapter provides an overview of the major classes of drug-metabolizing enzymes, namely cytochrome P450 (CYP), uridine diphosphate glucuronosyltransferases (UGT), and glutathione *S*-transferases (GST). Other classes of drug-metabolizing enzymes include the flavin-containing monooxygenases (FMO), epoxide hydrolases (EH), *N*-acetyltransferases (NAT), sulfotransferases (SULT), and metyltransferases (MT).

2. CYTOCHROME P450

CYP enzymes are a superfamily of heme-containing proteins involved in the biotransformation of numerous drugs and other chemicals, including naturally occurring compounds *(13)*. Each CYP enzyme is denoted by an Arabic numeral designating the family (e.g., CYP1), a letter indicating the subfamily (e.g., CYP1A), and an Arabic numeral representing the individual enzyme (e.g., CYP1A2) *(14)*. The gene coding for the enzyme protein is designated in italics (e.g., *CYP1A2*). Individual enzyme variants that result from gene polymorphism are denoted numerically following an asterisk (e.g., CYP1A2*1). CYP enzymes in the same family have greater than 40% amino acid identity, whereas those in the same subfamily have greater than 55% identity *(14)*. There are 57 functional human CYP genes *(15)*. Members of the CYP1, CYP2, and CYP3 families are CYP enzymes that play a major role in human drug metabolism. The focus of this chapter is on CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP2B6, CYP2E1, and CYP1A2, which collectively account for most of the drug-metabolizing CYP enzymes expressed in human liver *(16)*. According to an estimate *(17)*, this subgroup of individual CYP enzymes is responsible for the biotransformation of most of the drugs in clinical use (Table 1).

Table 1
Major CYP Enzymes in Human Drug Metabolism

Enzyme	*Percentage of prescription drugs metabolized*[a]
CYP3A4	45–50
CYP2D6	25–30
CYP2C9	10
CYP2C19	5
CYP2B6	2–4
CYP2E1	2–4
CYP1A2	2

[a] From Reference *(17)*.

2.1. CYP3A4

The human CYP3A subfamily consists of CYP3A4, CYP3A5, CYP3A7, and CYP3A43. CYP3A4 and CYP3A5 are expressed primarily in adult tissues, whereas CYP3A7 is expressed mainly in fetal tissues *(18)*. By comparison, CYP3A43 has been detected in both fetal and adult tissues *(19)*. CYP3A4 protein has been detected in all human liver samples analyzed to date and it represents, on average, approximately 30% of the total CYP content in adult human liver *(20)*. It is the most abundant CYP3A gene in adult human liver samples, as determined by real-time polymerase chain reaction *(21)*. CYP3A4 is expressed principally in liver *(21)*, although it has also been detected in various extrahepatic tissues *(22)*, most notably in all segments of the small intestine *(23)*.

Approximately 40 single nucleotide polymorphisms have been identified in the *CYP3A4* gene *(24)*. Among the various CYP3A4 allelic variants, CYP3A4*1B (A392→G) is the most common *(25)*. Its expression varies in different ethnic groups, ranging from 0% in Chinese and Japanese to 45% in African-Americans *(26–28)*. However, this particular polymorphism does not appear to have major functional consequences with respect to drug clearance *(26,29,30)*.

Numerous drugs with diverse chemical structures and pharmacological functions are substrates for CYP3A4 (Table 2). Both the expression and the catalytic activity of these enzymes are subject to modulation. CYP3A4 is inducible by many drugs (Table 2), such as rifampin *(31)*, phenobarbital *(32)*, phenytoin *(33)*, carbamazepine *(33)*, and efavirenz *(34)*, in addition to herbal products [e.g., St. John's wort *(35–38)*] and naturally occurring compounds [e.g., hyperforin *(39)*]. A mechanism of CYP3A4 induction involves transactivation of the pregnane X receptor (PXR) *(40)*, which is a nuclear receptor also known as the steroid and xenobiotic receptor *(41)* and the pregnane-activated receptor *(42)*. Many of the CYP3A inducers have been characterized to be activators of PXR *(43)*. For example, St. John's wort activates PXR and this effect is mediated by hyperforin *(44)*. Therefore, determining whether a drug is an activator of PXR allows one to predict its ability to induce CYP3A4. In contrast to enzyme induction in which protein expression is enhanced, CYP3A4 protein levels can be reduced, as demonstrated by studies with grapefruit juice and Seville orange juice. The ingestion of grapefruit juice *(45)* or Seville orange juice *(46)* is associated with a decrease in enterocyte CYP3A protein expression, as shown in biopsy samples taken from human subjects. These effects are attributed to 6′,7′-dihydroxybergamottin *(46)*, which is present in both juices (see Chapter 10). However, grapefruit juice, but not Seville orange juice, enhances the bioavailability of cyclosporine *(46)*. Additionally, the activity of CYP3A enzymes can be altered by the co-administration of drugs, natural products (e.g., goldenseal [*Hydrastis canadensis*]), or other substances (e.g., grapefruit juice) that are inhibitors of these enzymes (Table 2). Clinically significant CYP3A4-mediated drug–drug interactions include the enhanced clearance of indinavir by carbamazepine that may lead to therapeutic failure of the anti-retroviral *(47)* and the reduced clearance and excessive pharmacological effect of a benzodiazepine hynoptic, triazolam, by ketoconazole or itraconazole *(48)*.

2.2. *CYP2D6*

CYP2D6 is the only functional enzyme in the human CYP2D subfamily. It is expressed in human liver, but at a level (2–5% of total CYP content) less than that of CYP3A4, CYP2C9, or CYP1A2. This protein is also present in various extrahepatic tissues, including the gastrointestinal tract *(49)*, brain *(50,51)*, and lung *(52)*, but at much lower levels when compared to the liver.

Table 2
Examples of In Vivo Substrates, Inducer, and Inhibitors of Human CYP3A4

Substrate (Reference)	*Inducer (Reference)*	*Inhibitor (Reference)*
Alfentanil *(220)*	Carbamazepine *(33)*	Amiodarone *(221)*
Alprazolam *(222)*	Efavirenz *(34)*	Clarithromycin *(223)*
Amprenavir *(224)*	Phenobarbital *(32)*	Delavirdine *(225)*
Amitriptyline *(226)*	Phenytoin *(33)*	Diltiazem *(227)*
Bosentan *(228)*	Rifampin *(31)*	Erythromycin *(229)*
Budesonide *(230)*	St. John's wort *(36)*	Goldenseal (*H. canadensis*) *(231)*
Buspirone *(232)*	Troglitazone *(233)*	Grapefruit juice *(234)*
Cyclosporine *(235)*		Indinavir *(236)*
Dextromethorphan *(237)*		Itraconazole *(238)*
Dapsone *(239)*		Ketoconazole *(48)*
Docetaxel *(240)*		Methadone *(241)*
Ethinylestradiol *(242)*		Nelfinavir *(236)*
Erythromycin *(243)*		Nefazodone *(244)*
Felodipine *(245)*		Propofol *(246)*
Indinavir *(47)*		Ritonavir *(247)*
Ifosfamide *(248)*		Troleandomycin *(249)*
Imipramine *(249)*		
Irinotecan *(250)*		
Losartan *(251)*		
Lovastatin *(227)*		
Methylprednisolone *(252)*		
Midazolam *(253)*		
Nelfinavir *(254)*		
Nifedipine *(255)*		
Pimozide *(256)*		
Quinidine *(257)*		
Quinine *(258)*		
Ritonavir *(259)*		
Ropivacaine *(147)*		
Saquinavir *(260)*		
Sildenafil *(261)*		
Simvastatin *(262)*		
Tacrolimus *(263)*		
Triazolam *(48)*		
Verapamil *(264)*		
Vincristine *(265)*		

An important aspect of CYP2D6 is that many allelic variants (>60) of this enzyme have been identified *(53)*, although most are quite rare. CYP2D6*1 is the wild type, whereas CYP2D6*9, CYP2D6*10, CYP2D6*17, CYP2D6*29, CYP2D6*36, and CYP2D6*41 have decreased catalytic activity (intermediate metabolizer phenotype), and others such as CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*7, CYP2D6*8, CYP2D6*14, CYP2D6*18, CYP2D6*21, and CYP2D6*44 have no functional activity (poor metabolizer phenotype) *(53)*. In some individuals, genetic duplication of the CYP2D6*2 or CYP2D6*35 allele results in enhanced functional capacity, which leads to the ultrarapid metabolizer phenotype *(53)*. Ethnic differences exist in the frequency in which the various CYP2D6 alleles are expressed. A striking example is with CYP2D6*10, which is expressed in up to 70% of Chinese subjects, but only in 5% of Caucasians *(54)*. In contrast, CYP2D6*4 is present in approximately 20% of Caucasians *(55)*, but in less than 1% of Japanese subjects *(56)*. For drugs such as codeine, hydrocodone, and oxycodone, the consequences of a poor metabolizer phenotype is particularly significant because these drugs are bioactivated by CYP2D6. In fact, it has been suggested that codeine not be prescribed to a patient with a CYP2D6 poor metabolizer phenotype *(57)*. Conversely, in a patient with a CYP2D6 rapid metabolizer phenotype excessive sedation may develop following codeine administration.

Numerous clinically useful drugs are substrates for CYP2D6 (Table 3), including many of the analgesics, anti-arrhythmics, beta-blockers, anti-depressants, anti-psychotics, and anti-emetics in common use. In contrast to other drug-metabolizing CYP enzymes, CYP2D6 is not inducible. However, CYP2D6-mediated drug clearance appears to be enhanced during pregnancy *(58–60)*. The functional activity of CYP2D6 is subject to inhibition by drugs (e.g., quinidine) and natural products (e.g., goldenseal) (Table 3). In the case of quinidine, it is a potent and enzyme-specific inhibitor of CYP2D6. An example of a CYP2D6-mediated drug–drug interaction is the inhibition of venlafaxine clearance by diphenhydramine *(61)*.

2.3. CYP2C9

The human CYP2C subfamily consists of CYP2C8, CYP2C9, CYP2C18, and CYP2C19. CYP2C9 is the most important CYP2C enzyme with respect to expression and function. Immunoreactive CYP2C9 protein has been detected not only in adult liver *(62)* but also in some fetal liver samples as early as 8–24 weeks of gestation *(63)*. It may account for up to 30% of the hepatic total CYP content in adult liver *(62)*. CYP2C9 is primarily a hepatic enzyme, but it has also been detected in human intestinal microsomes *(64)* at approximately 20% of the CYP3A4 protein content (expressed as pmol per mg microsomal protein) *(23)*. CYP2C9 is important in the in vivo metabolism of many drugs (Tables 1 and 4), including tolbutamide *(65)*, *S*-warfarin *(66)*, phenytoin *(67)*, losartan *(68)*, celecoxib *(69)*, and glyburide *(70)*.

CYP2C9 is subject to genetic polymorphism. More than 30 single nucleotide polymorphisms have been reported to date in the regulatory and coding regions of the *CYP2C9* gene *(53)*. CYP2C9*2 ($\text{Arg}^{144}\rightarrow\text{Cys}^{144}$) and CYP2C9*3 ($\text{Ile}^{359}\rightarrow\text{Leu}^{359}$) are the major CYP2C9 allelic variants of major functional importance. Compared to individuals with the CYP2C9*1 allele (i.e., the wild type), patients with the CYP2C9*2 or CYP2C9*3 allele have a decreased clearance of warfarin and a reduced daily dose requirement for the drug *(66,71,72)*. However, individuals with these alleles do not appear to be more likely to experience severe bleeding complications during long-term therapy *(73)*. The effect of CYP2C9 genetic polymorphism is drug specific. For example, there is no relationship

Table 3
Examples of In Vivo Substrates and Inhibitors of Human CYP2D6

Substrate (Reference)	*Inhibitor (Reference)*
Amitriptyline *(266)*	Amiodarone *(267)*
Atomoxetine *(268)*	Amodiaquine *(269)*
Carvedilol *(270)*	Cimetidine *(271)*
Chlorpheniramine *(272)*	Citalopram *(99)*
Cilostazol *(273)*	Diphenhydramine *(274)*
Citalopram *(275)*	Fluoxetine *(99)*
Clomipramine *(276)*	Fluvoxamine *(99)*
Codeine *(277)*	Goldenseal (*H. canadensis*) *(231)*
Dextromethorphan *(278)*	Methadone *(279)*
Desipramine *(280)*	Moclobemide *(101)*
Dihydrocodone *(281)*	Paroxetine *(99)*
Doxepin *(282)*	Propafenone *(283)*
Encainide *(284)*	Quinidine *(285)*
Flecainide *(286)*	Sertraline *(287)*
Fluoxetine *(288)*	Terbinafine *(289)*
Fluvoxamine *(290)*	
Haloperidol *(291)*	
Hydrocodone *(292)*	
Imipramine *(293)*	
Loratadine *(294)*	
Maprotiline *(295)*	
Methylphendiate *(296)*	
Metoprolol *(297)*	
Mexiletine *(298)*	
Nefazodone *(299)*	
Nicergoline *(300)*	
Nortriptyline *(301)*	
Ondansetron *(302)*	
Oxycodone *(303)*	
Paroxetine *(304)*	
Perhexiline *(305)*	
Perphenazine *(306)*	
Procainamide *(307)*	
Propafenone *(308)*	
Propranolol *(309)*	
Risperidone *(310)*	
Thioridazine *(311)*	
Timolol *(312)*	
Tolterodine *(313)*	
Tramadol *(314)*	
Tropisetron *(315)*	
Venlafaxine *(316)*	
Zuclopenthixol *(306)*	

Table 4
Examples of In Vivo Substrates, Inducers, and Inhibitors of Human CYP2C9

Substrate (Reference)	*Inducer (Reference)*	*Inhibitor (Reference)*
Celecoxib *(69)*	Rifampin *(76)*	Amiodarone *(84)*
Fluvastatin *(317)*		Avasimibe *(318)*
Glimepiride *(319)*		Fluconazole *(81)*
Glyburide *(320)*		Fluvastatin *(83)*
Ibuprofen *(321)*		Miconazole *(82)*
Irbesartan *(322)*		Sulfamethoxazole *(85)*
Lornoxicam *(323)*		Trimethoprim *(85)*
Losartan *(324)*		
Phenytoin *(67)*		
Piroxicam *(325)*		
Tenoxicam *(326)*		
Tolbutamide *(65)*		
Torsemide *(327)*		
S-Warfarin *(66)*		

between CYP2C9 genotype (i.e., CYP2C9*1/*1, CYP2C9*1/*2, CYP2C9*1/*3, CYP2C9*2/*2, CYP2C9*2/*3, and CYP2C9*3/*3) and the metabolism of diclofenac in humans *(74)*. Ethnic differences exist in the frequency distribution of the CYP2C9 allele. The CYP2C9*2 allele is absent in Chinese subjects, but it has been detected in up to 10% of Caucasian Americans *(75)*. By comparison, the CYP2C9*3 allele is expressed in 2–5% of Chinese subjects and in up to 20% of Caucasian Americans *(75)*.

The CYP2C9 enzyme is also subject to both induction and inhibition. Rifampin is an inducer of this enzyme in humans (Table 4), and this drug increases the clearance of CYP2C9 drug substrates, such as tolbutamide *(76)*, phenytoin *(77)*, and *S*-warfarin *(78)*. The transcriptional regulation of CYP2C9 is receptor mediated. Studies from the past several years have shown a role for PXR *(79)*, constitutive androstane receptor (CAR) *(80)*, and glucocorticoid receptor *(80)* in the regulation of CYP2C9 induction. In vivo inhibitors of CYP2C9 include fluconazole *(81)*, miconazole *(82)*, fluvastatin *(83)*, amiodarone *(84)*, sulfamethoxazole *(85)*, and trimethoprim *(85)*. An example of a clinically significant drug–drug interaction involving CYP2C9 is the inhibition of warfarin clearance by fluconazole *(86)*.

2.4. CYP2C19

CYP2C19 is another human CYP2C enzyme of functional importance. It is expressed primarily in human liver, although immunoreactive CYP2C19 protein has also been detected in human intestinal microsomes *(64)*. The developmental expression of hepatic CYP2C19 is similar to that of hepatic CYP2C9, except during the 8–40 week gestation period in which the specific content of CYP2C19 is approximately tenfold greater than that of CYP2C9 *(63)*. Various alleles of CYP2C19 have been identified *(53)*. Some of these alleles (e.g., CYP2C19*2, CYP2C19*3, CYP2C19*4, CYP2C19*6, and CYP2C19*7) are associated with enzymes that have no functional activity, whereas others result in enzymes that have lesser (e.g., CYP2C19*5 and CYP2C19*8) or greater (e.g., CYP2C19*17) catalytic activity *(87,88)*. Ethnic differences exist in the frequencies of the CYP2C19 poor metabolizer phenotype, as assessed by the capacity to metabolize the *p*-hydroxylation of (*S*)-mephenytoin. For example, 12–20% of Asians are poor metabolizers, whereas the frequency is only 2–6% in Caucasians *(89)*. This may translate into a clinical advantage during treatment with the gastric acid-suppressing agent omeprazole.

CYP2C19 catalyzes the metabolism of many drugs in humans (Table 5). It is the major enzyme that metabolizes omeprazole *(90)*, lansoprazole *(91)*, and pantoprazole *(92)*. The enzyme can be induced by rifampin (Table 5), based on the finding that the administration of this drug to human subjects increases the urinary excretion of (*S*)-mephenytoin *(93,94)*. Another inducer of CYP2C19 is artemisinin. This antimalarial agent decreases the area under the concentration–time curve of omeprazole in human subjects *(95)*. A number of drugs have been shown to inhibit CYP2C19 in vivo (Table 5), including omeprazole *(96)*, ticlopidine *(97)*, ketoconazole *(98)*, fluoxetine *(99)*, fluvoxamine *(99)*, isoniazid *(100)*, moclobemide *(101)*, and oral contraceptives *(102)*. Inhibition of CYP2C19 occurs in a gene

Table 5
Examples of In Vivo Substrates, Inducers, and Inhibitors of Human CYP2C19

Substrate (Reference)	*Inducer (Reference)*	*Inhibitor (Reference)*
Amitriptyline *(328)*	Artemisinin *(95)*	Cimetidine *(103)*
Citalopram *(275)*	Rifampin *(93)*	Fluoxetine *(99)*
Clomipramine *(276)*		Fluvoxamine *(329)*
Clopidogrel *(330)*		Isoniazid *(100)*
Cyclophosphamide *(331)*		Ketoconazole *(98)*
Diazepam *(332)*		Moclobemide *(101)*
Fluoxetine *(333)*		Omeprazole *(96)*
Imipramine *(334)*		Oral contraceptives *(102)*
Lansoprazole *(91)*		Ticlopidine *(97)*
Mephobarbital *(335)*		
Moclobemide *(101)*		
Nelfinavir *(336)*		
Omeprazole *(90)*		
Pantoprazole *(69)*		
Phenytoin *(337)*		
Proguanil *(338)*		
Propranolol *(309)*		
Rabeprazole *(339)*		
Sertraline *(340)*		
St. John's wort *(341)*		
Thalidomide *(342)*		
Voriconazole *(343)*		

dose-dependent manner such that the extent of inhibition is the greatest in homozygous extensive metabolizers (CYP2C19*17/*17), intermediate in heterozygous extensive metabolizers, and little or no inhibition in homozygous poor metabolizers *(87)*. Clinically relevant drug–drug interactions involving CYP2C19 include the inhibition of phenytoin metabolism by fluoxetine *(103)*, cimetidine *(103)*, isoniazid *(100)*, and felbamate *(103)*, resulting in increased phenytoin toxicity.

2.5. *CYP2B6*

CYP2B6 is the only functional enzyme in the human CYP2B subfamily. Its expression in human liver is relatively low, with estimates ranging from 0.2% *(20)* to 10% *(104)*, although a large interindividual variability exists at the level of mRNA *(105)* and protein *(106)*. In contrast to some of the other CYP proteins such as CYP2C9, CYP3A4, and CYP3A5, the CYP2B6 protein is not detectable in human intestinal microsomes, as assessed by immunoblot analysis *(23)*. However, extrahepatic CYP2B6 expression has been shown in the nasal mucosa, trachea, and lung *(22)*.

Considerably fewer drugs have been demonstrated as in vivo substrates for CYP2B6 in humans (Table 6). The best characterized CYP2B6 drug substrate is cyclophosphamide, which is a DNA-alkylating prodrug used in the management of a variety of solid tumors. The initial finding that CYP2B6 catalyzes the bioactivation of cyclophosphamide to produce the pharmacologically active phosphoramide mustard *(107)* led to the preclinical development and experimental application of gene-directed enzyme prodrug therapy to the cyclophosphamide/CYP2B6 combination *(108)*. Other important CYP2B6 drug substrates are the anti-retroviral drugs efavirenz and nevirapine and the smoking cessation agent bupropion (Table 6). Pharmacogenetic analysis has shown that the combination of CYP2B6*6, CYP2B6*16, and CYP2B6*18 alleles is associated with decreased capacity to metabolize CYP2B6 substrates *(109)*. The decreased metabolism may lead to the development of systemic toxicity in the case of the pharmacologically active parent drug (e.g., efavirenz), but inadequate drug efficacy in the case where the parent drug is pharmacologically inactive (e.g., cyclophosphamide).

Similar to other mammalian CYP2B enzymes, the human CYP2B6 is highly inducible. The mechanism of CYP2B6 induction involves the action of nuclear

Table 6
Examples of In Vivo Substrates, Inducers, and Inhibitors of Human CYP2B6

Substrate (Reference)	*Inducer (Reference)*	*Inhibitor (Reference)*
Bupropion *(344)*	Artemisinin *(345)*	Clopidogrel *(114)*
Cyclophosphamide *(346)*	Rifampin *(113)*	Hormone replacement therapy* *(347)*
Efavirenz *(109)*		Ticlopidine *(114)*
Mephobarbital *(335)*		
Nevirapine *(348)*		

*Containing 2 mg estradiol valerate and 250 μg levonorgestrel receptors, such as CAR *(110)* and PXR *(111)*. Accordingly, CYP2B6 expression is increased by activators of CAR, such as phenobarbital (as shown in vitro) *(112)*, and by agonists of PXR, such as rifampin (as shown in vivo) *(113)*. CYP2B6-mediated drug clearance may also be influenced by the concurrent administration of an inhibitor of CYP2B6 catalytic activity, as exemplified by the finding that the antiplatelet drugs clopidogrel and ticlopidine decrease the metabolism of bupropion to hydroxybupropion *(114)*.

2.6. CYP2E1

CYP2E1 is expressed in adult *(20,115)* and fetal liver *(116,117)*, in addition to lung *(118)*, placenta *(118)*, and brain *(119)*. Whereas a large number of small molecular weight organic solvents (e.g., ethanol) are substrates for CYP2E1 *(120)*, only a few drugs have been found to be metabolized by CYP2E1 (Table 7). Acetaminophen may be the most important CYP2E1 drug substrate in humans. This enzyme is the predominant CYP catalyst in the in vivo bioactivation of acetaminophen to form *N*-acetyl-*p*-benzoquinone imine *(121)*, which is a reactive intermediate linked to the development of hepatic necrosis *(122)*. Several single nucleotide polymorphisms of the human *CYP2E1* gene have been identified, but they are not associated with functional significance *(123)*. Various factors can influence the activity of this enzyme (Table 7). Chronic alcohol consumption is associated with an increase in hepatic CYP2E1-mediated enzyme activity *(124,125)* and this is accompanied by elevated protein and mRNA expression *(126)*. The levels of this enzyme are also elevated by fasting *(127)*, in individuals with obesity *(127,128)* or diabetes *(129,130)* and in patients with nonalcoholic steatohepatitis *(131)*. This enzyme can also be induced by isoniazid *(124,132)* and all-*trans*-retinoic acid *(133)*. Inhibitors of CYP2E1 are ethanol (acute ingestion) *(134)*, disulfiram *(135)*, chlormethiazole *(136)*, diallyl sulfide *(134)*, watercress *(137)*, broccoli *(138)*, and black tea *(138)*. A clinically significant CYP2E1-mediated

Table 7
Examples of In Vivo Substrates, Inducers, and Inhibitors of Human CYP2E1

Substrate (Reference)	*Inducer (Reference)*	*Inhibitor (Reference)*
Acetaminophen *(121)*	Alcohol (chronic consumption) *(124)*	Alcohol (acute consumption) *(134)*
Chlorzoxazone *(349)*	All-*trans*-retinoic acid *(133)*	Black tea *(138)*
Dapsone *(350)*	Diabetes *(130)*	Broccoli *(138)*
Enflurane *(351)*	Fasting *(127)*	Chlormethiazole *(136)*
Sevoflurane *(352)*	Isoniazid (multiple doses) *(132)*	Diallyl sulfide *(134)*
	Nonalcoholic steatohepatitis *(131)*	Disulfiram *(135)*
	Obesity *(128)*	Isoniazid (single dose) *(132)*
		Watercress *(137)*

drug interaction is the inhibition of acetaminophen bioactivation by acute intake of alcohol *(139)*. Interestingly, this metabolic reaction is enhanced by the consumption of multiple alcoholic drinks prior to ingestion of acetaminophen *(140)*.

2.7. CYP1A2

CYP1A2 is expressed primarily in liver, with little or no known extrahepatic expression *(141)*. This enzyme, which is under the regulatory control of the aryl hydrocarbon receptor *(142)*, is important in the bioactivation of aromatic amines and heterocyclic amines *(143)* and metabolism of clinically useful drugs (Table 8), including clozapine *(144,145)*, mexiletine *(146)*, ropivacaine *(147)*, tacrine *(148)*, theophylline *(149)*, and verapamil *(150)*. Large interindividual differences (up to 100-fold) in human hepatic CYP1A2 protein content have been reported *(151–153)*, which may be due to genetic and/or environmental factors. Allelic variants of CYP1A2 have been identified. The G2964A and C734A polymorphisms are associated with high CYP1A2 inducibility *(154,155)*, whereas the A164C and T2464delT polymorphisms have no effect on CYP1A2 phenotype, as determined by the caffeine metabolic ratio *(156)*. This enzyme is subject to induction by various factors (Table 8), including exposure to environmental pollutants, such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin *(157)*, cigarette smoking *(158)*, consumption of char-broiled meats *(159)* and cruciferous vegetables *(160,161)*, and ingestion of drugs (i.e., carbamazepine *(162)*). The catalytic activity of CYP1A2 can be inhibited by drugs (Table 8), such as ciprofloxacin *(163)*, enoxacin *(164)*, fluvoxamine *(99)*, oltipraz *(165)*, and stiripentol *(166)*. CYP1A2-mediated drug–drug interactions have been reported, for example, the inductive effect of cigarette smoking *(158)* and the inhibitory effect of ciprofloxacin *(163)* on drugs metabolized extensively by CYP1A2.

In contrast to CYP, considerably less is known about the regulation and function of other drug-metabolizing enzymes, such as the UGT and GST enzymes.

Table 8
Examples of In Vivo Substrates, Inducers, and Inhibitors of Human CYP1A2

Substrate (Reference)	*Inducer (Reference)*	*Inhibitor (Reference)*
Caffeine *(353)*	Charcoal-broiled meat *(159)*	Ciprofloxaxin *(163)*
Clozapine *(144)*	Cigarette smoke *(354)*	Enoxacin *(164)*
Lidocaine *(355)*	Cruciferous vegetables *(161)*	Fluvoxamine *(99)*
Melatonin *(356)*	Carbamazepine *(162)*	Oltipraz *(165)*
Mexiletine *(146)*		Stiripentol *(166)*
Ropivacaine *(147)*		
Tacrine *(148)*		
Theophylline *(149)*		
Verapamil *(150)*		

3. URIDINE DIPHOSPHATE GLUCURONOSYLTRANSFERASES

The UGTs are a superfamily of enzymes that catalyze the conjugation of drugs and other substrates with the use of a cofactor containing a glycosyl group (e.g., glucuronic acid, glucose, xylose, and galactose) *(167)*. In general, this type of metabolic reaction results in more polar and, in most cases, less active metabolites. The human UGT genes are categorized into four families, UGT1, UGT2, UGT3, and UGT8 *(167)*. Each UGT gene is denoted by an Arabic number designating the family (e.g., UGT1 family), a letter indicating the subfamily (e.g., UGT1A subfamily), and an Arabic number denoting the individual gene (e.g., *UGT1A1* gene) *(168)*. UGT enzymes in the same family have greater than 45% amino acid identity and those in the same subfamily have greater than 60% identity *(168)*.

Pharmacokinetic studies have shown that many clinically useful drugs undergo glucuronidation in humans (Table 9). Drugs that are glucuronidated at substantial levels ($\geq$50% of the administered dose) include chloramphenicol *(169)*, ketoprofen *(170)*, lamotrigine *(171)*, lorazepam *(172)*, morphine *(173)*, *S*-naproxen *(170)*, oxazepam *(174)*, propofol *(175)*, temazepam *(176)*, zidovudine *(177)*, and zomepirac *(178)*. The extent of drug glucuronidation may be increased or decreased by the concurrent administration of a drug or another substance. For example, rifampin *(179)*, phenobarbital *(180)*, phenytoin *(180)*, carbamazepine *(181)*, and oral contraceptives *(182)* have been reported to enhance the glucuronidation of various drugs. Interestingly, the consumption of watercress, which is a rich source of phenethylisothiocyanate, results in increased glucuronidation of cotinine in smokers *(183)*. Inhibitors of drug glucuronidation include valproic acid *(184)*, salicyclic acid *(185)*, and probenecid *(186)*. While in vitro studies have established the role of various individual UGT enzymes in drug glucuronidation *(187)*, in vivo human studies have been conducted only on UGT1A1, UGT1A6, UGT1A7,

Table 9
In Vivo Drug Glucuronidation by Individual Human UGT Enzymes

Enzyme	*Drug (Reference)*
UGT1A1	Carvedilol *(357)* SN-38 (7-ethyl-10-hydroxycamptothecin)* *(358)*
UGT1A6	Acetaminophen *(359)*
UGT1A7	Mycophenolic acid *(360)* SN-38 (7-ethyl-10-hydroxycamptothecin) *(361)*
UGT1A8	Mycophenolic acid *(194)*
UGT1A9	Mycophenolic acid *(360)*
UGT2B7	Carvedilol *(191)* Diclofenac *(192)* Morphine *(193)* Mycophenolic acid *(194)*
UGT2B15	Lorazepam *(362)*

*SN-38 is an active metabolite of irinotecan

UGT1A8, UGT1A9, UGT2B7, and UGT2B15 (Table 9). Among this subgroup of UGT enzymes, UGT2B7 is the best characterized to date with respect to in vivo glucuronidation of drugs in humans.

3.1. UGT2B7

UGT2B7 has been detected in human liver and various extrahepatic tissues, such as colon, small intestine, kidney, and esophagus *(188)*. Hepatic UGT2B7 protein is detectable in neonates, as assessed by immunoblot analysis of liver microsome samples *(189)*. The hepatic expression of this enzyme increases throughout the developmental period, although a large interindividual variability exists *(189)*. Relative to the other UGT enzymes, UGT2B7 has been shown in vitro to catalyze the glucuronidation of the greatest number of drugs *(190)*. In vivo, a role of UGT2B7 has been indicated in the glucuronidation of carvedilol *(191)*, diclofenac *(192)*, morphine *(193)*, and mycophenolic acid *(194)* in humans. Various alleles of UGT2B7 have been identified. Some of these appear to be linked to an alteration in the extent of drug glucuronidation in vivo. For example, a UGT2B7 promoter variant (–840G>A) is associated with decreased glucuronidation of morphine in patients with sickle cell disease *(193)*. Very little is known about the molecular regulation of UGT2B7 gene expression. However, in vitro experiments with human cell lines have shown that *t*-butylhydroquinone, which is an antioxidant-type inducer, increases UGT2B7 mRNA levels *(195)*, suggesting a role for antioxidant/electrophile response elements in the regulation of UGT2B7. In contrast, the farnesoid X receptor may play a negative role in UGT2B7 expression, as indicated by the finding that transfection of this receptor decreases UGT2B7 promoter activity *(196)*. A correlation exists in the mRNA expression of hepatocyte nuclear factor-1 and UGT2B7 *(197)*, but the biological significance of the finding remains to be determined. A role for the aryl hydrocarbon receptor in the induction of UGT2B7 may be ruled out because 2,3,7,8-tetrachlorodibenzo-*p*-dioxin does not affect UGT2B7 gene expression in the Caco-2 human intestinal carcinoma cell line *(195)*. A role for other receptors, such as PXR, in the regulation of UGT2B7 has not been reported. However, human pharmacokinetic studies have indicated that rifampin, which is a PXR agonist *(43)*, increases the apparent oral clearance of zidovudine *(198)*, which is glucuronidated predominantly by UGT2B7 *(199)*. Other inducers of UGT2B7 are valproic acid *(200)* and resveratrol *(201)*, as demonstrated in cell culture experiments with human cell lines. Drugs shown to inhibit in vivo UGT2B7-mediated activity in humans include fluconazole *(202)* and probenecid *(186)*.

4. GLUTATHIONE *S*-TRANSFERASES

GST enzymes catalyze the glutathione conjugation of drugs and other electrophilic compounds of exogenous and endogenous origin. For many chemicals, including drugs, this represents an important detoxification pathway. There are three families of human GST enzymes: cytosolic, mitochondrial, and microsomal. The cytosolic family consists of 17 genes grouped into 7 subclasses (GSTA, GSTM, GSTP, GSTS, GSTT, GSTZ, and GSTO) *(203)*. The mitochondrial family has one member (K1-1), whereas the microsomal family has six enzymes (MGST2, FLAP, LTC_4S, MGST3, MGST1, and PGES1), but these enzymes are structurally distinct from those in the cytosolic family. Human GST enzymes are expressed in a tissue-dependent manner *(204–207)*. For example, the GSTA1 enzyme is present at high levels in liver, kidney, and testis, but absent in lung, heart, and spleen, whereas the GSTP1 enzyme is expressed in lung, heart, small intestine, and prostate, but undetectable in liver. Most of the studies on the function of GST enzymes have focused on the role of these enzymes in the biotransformation of environmental carcinogens. Much less is known about the specific drugs that are metabolized by GST enzymes, except that the in vitro detoxification of some of the anticancer drugs [e.g., 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), busulfan, chlorambucil, melphalan, and thio-TEPA] is catalyzed by individual GST enzymes *(208)*. Drugs that are known to be in vivo substrates for human GST enzymes include acetaminophen *(209)*, valproic acid *(210)*, and busulfan *(211)*. Polymorphisms in human GST genes have been identified *(212)*. However, the clinical significance of GST polymorphisms on the pharmacokinetics and pharmacodynamics of therapeutic agents is not clear. A study indicated a lack of a relationship between the various GSTA1 alleles and the glutathione conjugation of busulfan *(213)*. Human studies on the induction of GST enzymes are limited. The oral administration of oltipraz, which has been evaluated as a cancer chemopreventive agent, has been shown to increase lymphocyte GST enzyme levels in human volunteers *(214)*. The consumption of brussels sprouts for 1–3 weeks leads to a modest increase in plasma GSTA levels *(215–217)*. Very little is known about the inhibition of GST enzymes in humans. The ingestion (daily for 4 months) of Curcuma extract, which contains the dietary polyphenol curcumin, decreases glutathione *S*-transferase activity in lymphocytes in human volunteers *(218)*. Similarly, eugenol, which is the main constituent of oil of cloves, diminishes human plasma GSTA enzyme activity *(219)*. Overall, much remains to be investigated on the interaction between drugs and individual GST enzymes in humans.

5. CONCLUSION

This overview of CYP, UGT, and GST drug-metabolizing enzymes provides a setting in which to appreciate the various drug–nutrient interactions.

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5 Nutrient Disposition and Response

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Objectives

- Review the mechanisms that control food intake and digestion.
- Review the basic principles of nutrient absorption, distribution, storage, and elimination.
- Briefly discuss the influence of disease on these processes.

Key Words: Absorption; digestion; food intake; macronutrient; micronutrient

1. INTRODUCTION

In order to gain a better understanding for potential drug–nutrient interactions, an appreciation for the mechanisms controlling nutrient intake, digestion, absorption, storage, and elimination is necessary. These mechanisms are regulated by a variety of hormones and digestive enzymes and transporters acting in concert to initiate the consumption and breakdown of food and the availability of the nutrients needed to meet the metabolic demands of life. It is also important to recognize that a myriad of disease states can affect this highly coordinated process.

2. CONTROL OF FOOD INTAKE

A variety of factors, including metabolic demands, environmental cues, appearance of food, psychological states, social traits, and disease states have been shown to play important roles in the ongoing cycle of initiating, maintaining, and terminating food intake *(1,2)*. However, our understanding of the exact mechanism of what controls food intake is continually evolving. For years, a specific anatomic region of the brain was thought to be the only area responsible for this process *(3)*. Experiments with rats were able to illustrate that the stimulation of the lateral hypothalamus elicited a feeling of hunger, while ventromedial stimulation elicited a feeling of satiety. Since these classic studies, the understanding of appetite regulation has evolved from an explanation based on anatomic distribution into one of a complex interaction between the central nervous system (CNS) and the

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Table 1
Summary of Effects of Various Neuropeptides on Feeding

Hunger Promoting Agents	*Satiety Promoting Agents*
Ghrelin	Leptin
Agouti-related protein (AGRP)	Insulin
Neuropeptide Y (NPY)	Cholecystokinin (CCK)
	Glucagon-like peptide-1(GLP-1)
	Peptide YY (PYY)
	α-Melanocyte-stimulating hormone (α-MSH)
	Serotonin (5-HT)

peripheral neuroreceptors. Central modulation is working in concert with afferent sensing and signaling pathways and efferent pathways to control short-term food intake and long-term energy balance (Table 1) *(4)*.

Hunger is the feeling that motivates people to seek food. This driving force is generated by a variety of neuropeptides taking into account the body's overall energy balance, timing of the last meal, taste, smell, and appearance of food, emotions, stressors, gastric volume, exercise, and climate. These neuropeptides originate from the gut, the brain, and the region of the hypothalamus known as the arcuate nucleus. Ghrelin has been a well-studied peptide secreted by the stomach in response to fasting. This hormone stimulates the arcuate nucleus which in turn stimulates the anterior hypothalamus causing the release of neuropeptide Y (NPY) and agouti-related protein. These peptides are potent orexigenic agents producing the desire to consume food.

As one continues to eat, the feeling of hunger is replaced by the feeling of satiety. This is produced by another group of neuropeptides interacting between the arcuate nucleus, the lateral hypothalamus, and the nucleus tractus solitaris of the brainstem. Leptin, insulin, cholecystokinin, glucagon-like peptide-1 (GLP-1), polypeptide YY, and serotonin are released in response to intraluminal nutrients. These hormones promote the binding of propiomelanocortin (POMC) as well as its cleavage product α-melanocyte stimulating hormone to the lateral hypothalamus causing an anorectic sensation. In conjunction, vagal input from the mouth, stomach, and liver helps to further suppress appetite. Leptin is recognized as a major factor in suppressing food intake. This hormone is produced by adipocytes and has the effect of maintaining satiety. For this reason, it has been targeted as a possible drug treatment for obesity. As time passes, the feeling of satiety waxes and is once again replaced by hunger and the cycle begins again.

3. DIGESTION AND ABSORPTION

3.1. Overview

Digestion is the mechanical and chemical breakdown of foodstuff to the nutrients that can be utilized by the body. This process begins with the gastrointestinal (GI) tract which is a tube-like structure consisting of the mouth, esophagus, stomach, small intestine, large intestine, and anus. Although its main function is the digestion and absorption of nutrients (macronutrients – carbohydrate, protein, fat, water; and micronutrients – vitamins, minerals), the GI tract also plays a role in the excretion of waste and maintaining host immune defenses. There are a number of accessory organs that aid the GI tract in carrying out its primary task; these include the salivary glands, the liver, the gallbladder, and the pancreas. A variety of specialized digestive cells which secrete specialized enzymes have evolved to meet the requirements of digestion (Table 2).The GI tract orchestrates the use of these accessory organs and specialized cells in concert to convert carbohydrate, protein, and fat from their complex molecular form into their more usable forms of monosaccharides, amino acids, and free fatty acids. The movement of the digested nutrients from the intestinal lumen into the blood or lymph fluid is called absorption. Absorption is a highly developed process that is very site specific and utilizes a variety of transport systems (i.e., passive, active, or simple diffusion and endocytosis) *(5)*.

3.2. Mouth and Esophagus

Digestion begins in the mouth where mastication decreases the size of the food bolus in preparation for its passage down the esophagus. The sight, smell, and taste of food all lead to the release of amylase from the salivary gland. This enzyme begins the breakdown of dietary starch and remains active until neutralized by the acidic environment of the stomach. Saliva also serves as an antimicrobial and lubricant to aid in speech and swallowing. Swallowing is a coordinated action involving both voluntary and involuntary muscles. The process culminates in the relaxation of the lower esophageal sphincter allowing the deposition of a food bolus into the stomach. Altered physiology of the lower esophageal sphincter leads to the clinical ailment known as acid reflux *(4)*.

3.3. Stomach

The stomach serves the function of a reservoir to prepare food for absorption by the small intestine and thus plays a minimal role in the absorption of nutrients. Ethanol and short-chain fatty acids (SCFAs) are the only products absorbed by the stomach during a meal. The lining of the stomach consists of three distinct types of glandular tissue – cardiac, oxyntic, and antral. The oxyntic gland contains both parietal and chief cells. Parietal cells secrete hydrochloric acid (HCl) and are responsible for maintaining the acid environment of the stomach and secreting intrinsic factor. This latter polypeptide plays an important role in the absorption of vitamin B_{12}. Chief cells release pepsinogen which is responsible for the digestion of proteins. The G cells of the antrum secrete the hormone gastrin responsible for acid production. Mucosal cells throughout the stomach secrete mucus and bicarbonate. All of these gastric cells are under tight neurohormonal regulation. The combination of gastric distention and nutrients in the stomach leads to an increased release of acetylcholine, histamine, and gastrin stimulating the release of HCl and pepsinogen. Pepsinogen is cleaved to its active form pepsin by HCl. The end result is the chemical breakdown of nutrients into smaller molecules. To further maximize digestion, the stomach mixes food particles and gastric juices by continually contracting against the pylorus. This process of mixing and grinding is called

Table 2
Gastrointestinal Hormones

Hormone	*Source*	*Stimulation*	*Inhibition*	*Physiologic actions*
Gastrin	G cells (antrum)	Amino acids Acetylcholine Calcium Alcohol Antral distention pH > 3.0	Somatostatin CCK Secretin VIP GIP pH < 3.0	Targets parietal and chief cells Increases HCL, intrinsic factor, pepsinogen secretion
Somatostatin	D cells (antrum, pancreas)	Acid in duodenum		Many target cells "The great inhibitor"
Gastric inhibitory peptide	K cells (duodenum)	Amino acids Glucose Long-chain fatty acids Decreased pH		Targets parietal cells to decrease H+ and pepsin secretion and beta cells of pancreas to increase insulin release
CCK	I cells (duodenum, jejunum)	Amino acids Fatty acid chains		Gallbladder contraction Relaxation of Sphincter of Oddi Increase pancreatic enzyme secretion
Secretin	S cells (duodenum, jejunum)	Fat Bile pH < 4.0	pH > 4.0 Gastrin	Increase pancreatic bicarbonate release Increase bile flow Inhibits gastrin and HCl release
Vasoactive intestinal peptide	Cells in gut and pancreas	Fat Acetylcholine		Increase intestinal secretion of water and electrolytes and motility Inhibits gastrin release
Insulin	Beta cells (pancreas)	Glucose Glucagon CCK	Somatostatin	Cellular glucose uptake Promotes protein synthesis

Glucagon	Alpha cells (pancreas)	Decreased glucose Increased amino acids, acetylcholine	Increase glucose, insulin, somatostatin	Glycogenolysis Gluconeogenesis Lipolysis Ketogenesis Decreased gastric acid, pancreatic secretion Decreased intestinal and stomach motility Increased LES pressure Decreased MMC
Pancreatic polypeptide	Islet cells (pancreas)	Food Vagal stimulation		Decreased pancreatic and gallbladder secretion
Motilin	Intestinal cells	Duodenal acid Food Vagus input	Somatostatin Secretin PP Duodenal fat	Increased intestinal motility
Peptide YY	Terminal ileum	Fatty meal		Inhibits acid secretion and stomach contraction, gallbladder contraction, and pancreatic secretion
Glucagon-like peptide-2	L cells (ileum and colon)	Food		Regulates growth, proliferation, and maintenance of intestinal mucosa, gastric motility, and nutrient absorption

trituration. The gastric phase of digestion is crucial in the overall absorption of nutrients as proven by a variety of malabsorption syndromes caused by alterations in gastric physiology or anatomy *(5)*.

When a food bolus reaches the stomach, vagal stimulation and gastrin secretion promote gastric motility *(5)*. So as not to exceed the absorptive capacity of the duodenum, the body has developed mechanisms based on food consistency and composition to regulate gastric emptying *(6)*. Normally, food must be broken down to less than 1–2 mm before it may pass through the pylorus. Thus, food that is poorly chewed or is high in fiber or fat will take longer to exit the stomach. The release of the hormone cholecystokinin (CCK) in response to high levels of fat and protein in the lumen of the duodenum also acts to slow gastric emptying. Lastly, the hormone peptide YY is released in response to incompletely digested carbohydrates reaching the terminal ileum and slows gastric emptying *(6)*. This phenomenon is referred to as the "ileal brake."

3.4. Small Intestine

The small intestine consists of the duodenum, jejunum, and ileum. The small bowel has the largest surface area of any part of the GI tract thanks in part to its length (mean ~7 m) and unique anatomic configuration. The entire luminal surface consists of mucosal folds, each with fingerlike projections called villi. On the surface of each villus are more fingerlike projections called microvilli. The result is a surface area of approximately 200 m^2 *(7)*. The small bowel has a unique mechanism of motility. Contents are moved in a back and forth motion called segmentation. This ensures adequate mixing of luminal contents with the surface area. The cells that line the intestinal lumen, called enterocytes, have highly specialized roles in digestion, absorption, storage, and electrolyte balance. Enterocytes are renewed approximately every 3 days *(5)*.

Digestion in the small bowel occurs in two phases – luminal and cellular. The luminal phase involves the help of the liver, gallbladder, and pancreas. As the acidic chyme is expelled from the stomach the pancreas secretes a bicarbonate-rich fluid that acts to raise pH in the duodenum. The neutral environment optimizes the activity of pancreatic digestive enzymes. An enzyme-rich cocktail containing amylase, lipase, phospholipase A2, nucleolytic enzymes, trypsinogen, chymotrypsinogen, elastase, carboxypeptidases, and colipase is excreted by the pancreas in response to partially digested nutrients. Many of these enzymes are stored in an inactive form (zymogens) in order to protect the pancreas against autodigestion. Bile salts are released from the liver and gallbladder in response to lipids. Bile acts to compartmentalize small lipid particles into easily absorbable units called micelles. Also playing roles in the luminal phase are a series of enzymes located on the brush border of enterocytes called ectoenzymes. The end result of the luminal phase is the conversion of carbohydrates into monosaccharides, proteins into amino acids and small peptide fragments, and lipids into free fatty acids and monoglycerides.

The cellular phase of digestion begins as nutrients enter the cytoplasm of enterocytes. Once inside the cell, peptidases breakdown di- and tripeptides into free amino acids. Also present within enterocytes are enzymes used to convert monoglycerides and free fatty acids into triglycerides for incorporation into chylomicrons and distribution throughout the body.

3.5. *Large Intestine*

The colon plays a more limited role in digestion. Nonabsorbed carbohydrates reaching the ascending colon are either actively absorbed or converted to SCFAs by colonic bacteria. This process is called fermentation and helps to provide a fuel source for the cells lining the lumen of the colon. Dietary long-chain fatty acids are not absorbed but their presence affects water absorption and electrolyte balance. In cases where there is limited small bowel, the colon has been shown to adapt its function over time and play a more significant role in absorbing nutrients *(5)*.

3.6. *Regulation*

The process of digestion is regulated by the CNS, GI hormones, central and peripheral neurotransmitters, and paracrine substances *(8)*. This neuronal axis responds to both external (i.e., smell, appearance) and internal (i.e., volume, nutrient content) cues from a meal. Input carried from cranial, vagal, and visceral afferent neurons stimulates the CNS via acetylcholine to increase glandular secretions, gastric motility, and pancreatic exocrine function. G cells of the gastric antrum release the hormone gastrin increasing acid production and gastric motility. Secretin is released in response to a pH less than 4.5 by S cells of the duodenum and jejunum stimulating the secretion of bicarbonate by the exocrine pancreas to neutralize gastric chyme and promote the excretion of bile. Cholecystokinin is released by I cells of the duodenum and jejunum in response to fat or protein in the small bowel. Its action results in the contraction of the gallbladder and the release of pancreatic digestive enzymes. Somatostatin is a paracrine peptide released by D cells of the GI tract and pancreas to reduce overall intestinal secretions, including HCl, pancreatic juice, and blood flow to the GI tract. A variety of other factors including epidermal growth factor, motilin, gastric inhibitory peptide, peptide YY, glucagon-like peptides, bombesin, and pancreatic peptide play smaller roles in helping to regulate GI function *(9)*.

3.7. *Absorption*

Absorption is the net movement of nutrients, including water and electrolytes, from the intestinal mucosa to the vascular and lymphatic systems. The body has developed several mechanisms to facilitate absorption including passive and active transports, simple diffusion, endocytosis, and paracellular movement. Although the entire small bowel has the potential for absorption, the vast majority of nutrients are absorbed by the jejunum. By the time gastric contents have reached the ileum, the process of nutrient absorption is near completion.

4. MACRONUTRIENTS

4.1. *Carbohydrates*

The end result of digestion is the breakdown of complex carbohydrates (starch and fibers) and simple carbohydrates (sugars) into the monosaccharides glucose, fructose, and galactose. These three molecules, all hexoses, share a similar molecular formula. The major enzymes responsible for the digestion of carbohydrates are salivary amylase, pancreatic amylase, and brush border disaccharidases. These enzymes cleave the O–OH bonds between polysaccharides by a process called hydrolysis. After a meal, all carbohydrates are absorbed and only a small portion of resistant starch and dietary fiber remains undigested. These residual products are fermented to SCFA by bacteria in the colon, to be used as an alternative source of energy. For the most part, the absorption of monosaccharides occurs in the small intestine exclusively through a group of hexose transporters *(9)*. Glucose and galactose traverse the apical membrane of enterocytes through a sodium-dependent active transport system called SGLT-1, while fructose enters the epithelial cells, via facilitated diffusion, through a separate transport system called GLUT-5. Once inside the epithelial cell, all three monosaccharides are transported across the basolateral membrane by a passive diffusion transporter called GLUT-2. Once across the basolateral membrane the hexoses are transported by the portal system to the liver where their ultimate fate will be determined. Glucose can be utilized in three different ways by the body: (1) utilized by the cells of the body with the help of insulin and used to meet immediate energy demands via glycolysis, (2) converted to glycogen and stored for later use, or (3) the conversion to fatty acids for energy or storage as triglycerides in adipose tissue. The liver contains one-third of the body's total glycogen stores and muscle contains the remaining two-thirds. During periods of low blood glucose, the liver converts glycogen back to glucose to be used to maintain the energy requirements of the body. Glycogen reserves in muscle are used solely to maintain their own energy requirements. The storage of fatty acid in adipose tissue occurs only when the body's energy needs have been satisfied and glycogen stores filled. Stores of intramyocellular lipids as found in skeletal muscle are considered abnormal.

A recent field of nutritional study focuses on the interaction of nutrients with different genes and their protein products *(10)*. For example, carbohydrates have been shown to effect the production of a variety of proteins. The presence of glucose, galactose, and fructose in the GI tract causes increased expression of their respective hexose transporters *(9)*. Also, increased levels of glucose in blood have been shown to upregulate the production of a myriad of enzymes involved in glycolysis, fructose metabolism, and gluconeogenesis *(9)*. As we gain a better understanding of this field it is possible that nutrient–gene interactions could be used for the identification and targeted treatment of a variety of diseases.

As one begins to understand the physiology of digestion and absorption, it becomes apparent that malabsorption of carbohydrates can result from a variety of diseases. For example, pancreatic insufficiency brought on by chronic pancreatitis, surgical resection, or a congenital condition like cystic fibrosis can lead to insufficient amounts of amylase. Alterations in the function of enterocytes through radiation injury or by celiac disease can affect carbohydrate absorption. And finally, a decrease in bowel surface area caused by congenital short gut, inflammatory bowel disease, or surgical resection can result in inadequate interaction between mucosal cells and nutrients.

4.2. Proteins

Digestion breaks down proteins into individual amino acids and peptides that the body can use. In the stomach, HCl denatures proteins exposing their peptide bonds to the proteolytic enzyme pepsin, breaking down proteins into amino acids and smaller peptide molecules. This digestive process is accelerated in the small intestine by a variety of pancreatic proteases. Enterocytes contain an enzyme on their apical border (enteropeptidase) which acts to convert pancreatic trypsinogen into its active form trypsin. This enzyme also activates the pancreatic zymogens chymotrypsinogen and procarboxypeptidase. This cascade-like action serves to protect the pancreas from autodigestion. Pancreatic proteases work in concert with intestinal peptidase, elastase, and collagenase to further break down proteins to peptide fragments, di- and tripeptides, and single amino acids. Individual amino acid uptake occurs along the brush border membrane through a variety of sodium-dependent transporters. These transporters have a specific affinity for each amino acid based on their electrochemical properties – neutral, dibasic, acidic, or imino. Di- and tripeptides are carried independently across the brush border membrane by a group of substrate-selective carriers. Oligopeptides are also capable of being absorbed; however, once in the cytosol, aminopeptidases break them down to their respective amino acids. The advantage of having the capability to absorb multiple peptide configurations assures the maximal amount of amino acid available to the body. These nutrients then exit the cells through membrane transporters and are carried directly to the liver for subsequent disposition. It is important to note that the rate-limiting step in dietary protein metabolism is the intestinal absorption of amino acids. The body uses nutrient–gene interactions to regulate the number of mucosal cell transporters in response to the dietary load of protein *(9)*. During periods of excessive food intake or in disease states where protein is highly utilized, the number of mucosal cell amino acid transporters increases. The opposite effect is seen during periods of starvation.

Once amino acids reach the liver they are utilized in one of three ways. The first is to replenish the body's protein stores, which are continually being broken down. The second use of amino acids is for the production of energy. The carbon skeletons of amino acids can be converted into intermediates used by the tricarboxylic acid cycle and in gluconeogenesis. The last use of amino acids is in the formation of compounds like nucleotides, neurotransmitters, catecholamines, hemoglobin, and albumin. These uses involve the production of ammonia by transamination or deamination reactions. The toxic by-product of the process is converted to urea by the liver and excreted via the kidneys.

4.3. Lipids

The average Western diet contains 60–100 g of fat daily, most of which consists of triglycerides; the remainder is a combination of sterols, phospholipids, and fat-soluble vitamins. The digestion of lipids begins with the secretion of pancreatic lipase. This enzyme cleaves the 1 and 3 positions along the glycerol backbone to form two free fatty acids and a monoglyceride. The mucosal cells of the duodenum release the hormone CCK in response to an increased concentration of lipids. This hormone is responsible for the release of pancreatic lipase and bile. Bile acts as an emulsifier to help with lipolysis. Once triglycerides are broken down to their constituent monoglycerides and fatty acids, they form bile micelles. These aggregations of bile salts and fatty acids act to orient the hydrophobic portions of the molecules inward and the hydrophilic portions outward toward the aqueous environment.

This orientation allows for easy movement across the watery layer above the brush border and results in more efficient absorption. Once at the apical membrane, the contents of micelles enter the cell by simple diffusion and the micelle recycles back to the intestinal lumen. Short- and medium-chain fatty acids and glycerol are absorbed directly by mucosal cells and are transported to the portal circulation. Phospholipids are absorbed in a similar fashion to triglycerides. Sterols can be absorbed directly by mucosal cells.

Ninety percent of the bile secreted is reabsorbed by the distal small bowel and returned to the liver through portal blood flow. This recirculated bile can then be secreted again or stored in the gallbladder for further use. The route of recycling bile salts is known as the enterohepatic circulation. Once absorbed into the enterocytes, free fatty acids are reassembled into triglycerides and packaged with cholesterol, phospholipids, and protein to form chylomicrons. Chylomicrons act as transport vehicles for the journey through the lymphatic system. Short- and medium-chain fatty acids are more water soluble and are thus able to enter the blood (and bind to albumin) by simple diffusion. Those products of lipid digestion that are absorbed via the blood go directly to the liver and are used for the synthesis of more triglycerides, cholesterols, or other compounds. Those that are absorbed as chylomicrons reach the vascular system through the thoracic duct and have their lipids utilized by cells all over the body or store their fatty acids in adipose tissue. By the time a chylomicron reaches the liver all that remains are proteins and lipid remnants. This chylomicron remnant is then absorbed by the liver and converted into new lipoproteins.

4.4. Water Absorption

The average adult ingests 1–2 L of fluid a day plus an additional 6–7 L from GI secretions. Therefore, the body must be able to absorb large quantities of water. By the time ingesta reach the large intestine, 80% of water has been absorbed *(11)*. The osmotic gradient is the principle by which water is absorbed and is dependent on the absorption of sodium. The absorption of nutrients results in a large accumulation of sodium and other molecules on the anti-luminal side of enterocytes. This causes a high osmotic gradient toward which water flows. The net result is the movement of water between the tight junctions of enterocytes and into the blood. As water moves farther down the GI tract, the tight junction becomes less permeable. Water must travel with the active absorption of sodium.

5. MICRONUTRIENTS

5.1. Vitamins

Vitamins are essential nutrients needed only in small amounts relative to the macronutrients. They are distinguished from carbohydrates, proteins, lipids, and minerals by the fact they are absorbed in their natural organic state. Historically, they have been grouped according to solubility. The fat-soluble vitamins are A (retinol), D (calciferol), E (tocopherols and tocotrienols), and K (phylloquinone and menaquinone). These vitamins are absorbed in a fashion similar to lipids with the help of chylomicrons and can be stored in cells associated with fat. Many require transport proteins as carriers. These vitamins generally are less readily excreted and therefore are needed less frequently. The water-soluble vitamins include all of the B-vitamins plus vitamin C. They travel in the blood and are excreted by the kidneys. These vitamins are absorbed at various sites along the length of the small bowel by both energy-dependent and energy-independent transport systems. Vitamin B_{12} requires intrinsic factor (IF) for its absorption. IF is produced by parietal cells of the stomach. The IF–vitamin complex travels to the terminal ileum where it is absorbed by a specific receptor. Any compromise of IF production or the interaction between B_{12} and IF (i.e., gastrectomy, pancreatic insufficiency, ileal resection) will lead to poor bioavailability of dietary B_{12} and subsequent deficiency. It is important to note that deficiencies are extremely rare given the large hepatic stores of this vitamin but when present they affect multiple organ systems. Fortunately, a balanced diet provides adequate amounts of all vitamins. A list of vitamins, their actions, and physiologic effects of varying concentrations can be found in Table 3.

5.2. Minerals

Minerals are inorganic compounds that are required in small amounts. These compounds play vital roles assisting in energy production, growth, hemoglobin synthesis, as well as the metabolism of carbohydrates, lipids, proteins, and vitamins. Minerals are absorbed and distributed throughout the body without alteration to their chemical structure.

Excessive amounts have the potential to be toxic, thus the body carefully controls their absorption. Minerals are usually divided into two groups, major and minor, depending on their required amounts. Calcium, phosphorous, potassium, sulfur, sodium, chloride, and magnesium are classified as major or macrominerals. Their daily requirements are often described in gram quantities. Iron, zinc, copper, manganese, iodine, and selenium are considered minor or trace minerals and their requirements are measured in milligram or microgram amounts. A normal balanced diet adequately supplies all required amounts of minerals. The following is a brief description of a few minerals.

Calcium absorption is concentration dependent *(12)*. During periods of low calcium ingestion, active absorption occurs in the duodenum. Vitamin D plays an important role in transporting calcium out of enterocytes and into the vascular system. During periods of moderate to high calcium ingestion, the mineral is absorbed by passive diffusion in the jejunum and ileum. The regulation of calcium in the blood falls under the control of parathyroid hormone. An increase in this hormone leads to increased intestinal absorption, decreased renal excretion, and increased bone metabolism.

Phosphorous is the second most abundant mineral in the body. The vast majority is bound to calcium in teeth and bones. It is predominantly absorbed in the upper small intestine by a sodium cotransport system present on the apical surface of brush border cells. The transport system is highly dependent on vitamin D for its activity. There are no known dietary deficiencies of phosphorous because it is so ubiquitous in the food supply.

Iron is absorbed from vegetable (non-heme iron) and meat (heme iron) sources. The average dietary intake is 10–20 mg/day with only 1–2 mg/day being absorbed

Table 3
Vitamins

Vitamin	*Physiologic actions*	*Dietary sources*	*Deficiency*
Thiamin (Vitamin B_1)	Part of coenzyme thiamin pyrophosphate Energy metabolism Role in nerve signal transduction	Whole grains Beans	Common in homeless and alcoholics Beriberi (dry, wet) Wernicke–Korsakoff syndrome
Riboflavin (Vitamin B_2)	Part of coenzyme flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) Energy production	Milk products Whole grains Liver	Adenoflavinosis (inflammation of membranes of GI tract, eyes, skin)
Niacin (Vitamin B_3)	Part of coenzyme nicotinamide adenine dinucleotide (NAD) and NADP Energy metabolism	Precursor is dietary tryptophan	Pellagra (dementia, diarrhea, dermatitis, death) Excess causes flushing
Pyridoxine (Vitamin B_6)	Part of coenzymes pyridoxal phosphate (PLP) and pyridoxamine phosphate (PMP) Amino acid and lipid metabolism Aids in conversion of tryptophan to niacin and serotonin Production of red blood cells	Alcohol acts as an antagonist	Anemia CNS symptoms Dermatitis
Cobalamin (Vitamin B_{12})	Part of coenzyme responsible for new cell synthesis Maintaining nerve cells Breakdown of amino acids and some fatty acids		Anemia Progressive nerve degeneration Sore tongue
Biotin	Part of coenzyme responsible for energy and amino acid metabolism, fat and glycogen synthesis	Avidin from egg whites decreases absorption Present in most foods Also produced by bacteria in GI tract	CNS symptoms Hair loss Rash

Pantothenic acid	Part of coenzyme A used for energy metabolism	Present in variety of foods	Fatigue GI distress CNS symptoms
Folate	Part of coenzyme tetrahydrofolate (THF) and dihydrofolate (DHF) DNA synthesis	Leafy greens Cereals Grains Beans Liver	Anemia GI tract deterioration Important in prevention of neural tube defects during gestation
Ascorbic acid (Vitamin C)	Roles in collagen, thyroxin, amino acid synthesis Acts as an antioxidant Aids absorption of iron	Abundant in citrus fruits and vegetables	Scurvy Poor wound healing Atherosclerosis Bone fragility Loose teeth
Retinol (Vitamin A)	Involved in vision, bone and tooth growth Maintenance of cornea, epithelial cells, mucosal membranes, immunity	Milk, dairy products Precursors are carotenoids found in leafy greens, fruits, and vegetables	Visual problems Suppressed immune function Diarrhea Kidney stones
Calciferol (Vitamin D)	Mineralization of bones	Synthesized by the body Milk, dairy products Fatty fish	Ricketts Osteomalacia Decreased calcium and phosphorous levels
Tocopherols (Vitamin E)	Antioxidant for lipid membrane	Vegetable oils	Erythrocyte hemolysis Extremely high concentrations interfere with blood clotting
Phylloquinone (Vitamin K_1)	Activation of blood clotting proteins through γ-carboxylation of glutamic acid residues	Green leafy vegetables	Bleeding
Menaquinone (Vitamin K_2)		Synthesized by bacteria in gut	

by men and 3–4 mg/day being absorbed by premenopausal women and iron-deficient individuals. Heme iron is the more readily absorbed of the two (10–20% vs. 1–6%). Dietary factors such as phosphates, phytates, and phosphoproteins can render non-heme iron insoluble and impair its absorption. Both dietary forms of iron are mainly absorbed by the duodenum. Some iron remains in enterocytes as ferritin, while the remainder is transported through the blood bound to transferrin. Iron is lost on a daily basis through the exfoliation of mucosal cells. A deficiency in iron is manifested by anemia (microcytic), a decrease in serum ferritin, and increase in serum transferrin levels. Iron overload can be toxic. The genetic disorder hemosiderosis leads to iron deposits in the liver and eventual cirrhosis.

Zinc plays a variety of roles throughout the body including maintaining pancreatic function, wound healing, enzymatic reactions, and blood clotting. Only about 15–40% of dietary zinc is absorbed. Various transporters have been identified for the absorption of zinc, but the exact mechanism still remains incomplete *(13)*. Certain animal proteins have been shown to modulate zinc absorption. Phytates have been shown to chelate zinc and prevent its absorption.

6. FACTORS INFLUENCING NUTRIENT ABSORPTION

6.1. Aging

The effects of aging can have a profound influence on the intake, digestion and absorption of nutrients (see Chapter 22). Aging can impair memory, cognition, and vision making the initiation of food intake more difficult. Tooth loss and decreased sensory input serve to make the act of eating less enjoyable. The metabolic demands of the body change and metabolism declines. Older people have less muscle mass and increased fat, thus protein and carbohydrate consumption takes precedence over fats in the diet. An older person has less total body water content and therefore is more easily subject to dehydration. Vitamin deficiencies are more prevalent in older people. B_{12} deficiency is common because of the increased incidence of atrophic gastritis. As it ages, the body synthesizes less of the active form of vitamin D leading to deficiencies. Osteoporosis can occur from calcium deficiencies. Iron deficiency anemia is also a common problem found in older people secondary to decreased production of gastric HCl. These absorptive problems are often exacerbated by the presence of other comorbid diseases, the use of multiple medicines, or rigid learned dietary habits.

6.2. Disease

The effect of various diseases on absorption and digestion can result in malnutrition and ultimately severe illness. Disease, whether organic or functional, can be found along the entire GI tract and may result from genetic, infectious, or iatrogenic causes. These alterations can affect the luminal factors involved in digestion or impair the function of the brush border cells in absorption. Genetic diseases like cystic fibrosis and lactase deficiency are common throughout the world. Inflammatory conditions like pancreatitis, gastritis, and inflammatory bowel disease also lead to impaired nutrient absorption. Bacterial overgrowth and commonly acquired conditions like celiac disease, diabetes, and infectious gastritis also lead to impaired nutrient uptake. A variety of surgical procedures including gastric resection, short bowel syndrome, ileostomy, or colostomy lead to altered nutrient absorption *(14)*. It is also important to note that diseases affecting other organs like the kidneys, the liver, and gallbladder can also have an effect on nutrient digestion and absorption.

7. CONCLUSION

The absorption and digestion of nutrients is a complex and highly coordinated process. Interactions between the CNS and peripheral nervous systems as well as the GI tract must take place to assure that metabolic demands are met. In an effort to better elucidate the effects of a multitude of diseases involving the GI tract as well as the interventions performed upon it by the medical community, it is paramount that we understand the roles that chemical messengers, GI hormones, digestive enzymes, and mechanical stimuli play. We must also always remember when caring for patients that age, disease processes, and altered physiologic states have profound effects on the milieu of nutrient assimilation. An understanding of the workings of each component, as an individual entity and in the overall picture, will allow for better care of patients. Future efforts in better appreciating drug–nutrient interactions will require this level of knowledge.

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II

INFLUENCE OF NUTRITION STATUS ON DRUG DISPOSITION AND EFFECT

6

Influence of Protein-Calorie Malnutrition on Medication

Charlene W. Compher and Joseph I. Boullata

Objectives

- Describe malnutrition in healthy and ill individuals in the United States.
- Explain how malnutrition can impact drug absorption, distribution, clearance, and effect.
- Provide a compilation of findings regarding the impact of malnutrition on specific drugs.

Key Words: Malnutrition; inflammation; obesity; stunting; wasting; energy

1. INTRODUCTION TO MALNUTRITION

Malnutrition may exist as a chronic problem or as an acute disturbance. The origin of malnutrition can be either primary as a result of inadequate food intake or secondary to other processes *(1)*. Malnutrition, regardless of the etiology, exists if nutrient needs are not being matched by intake. By strict definition overweight and obesity are also considered states of malnutrition. Chronic starvation due to inadequate food supply results in deficits of protein and energy, a syndrome known as protein-energy malnutrition or protein-calorie malnutrition (PCM). Varying degrees of micronutrient deficits are also likely to exist *(1)*. When the predominant deficiency is chronic undersupply of calories, unintentional weight loss occurs in adults or severe growth failure in children *(1)*. When the predominant deficiency is protein, muscle wasting may develop. Some individuals may have combined deficiencies of energy and protein particularly when weight loss or growth failure exists and is complicated by an infection such as measles or diarrheal illness. This additional illness results in an inflammatory response that secondarily reduces serum protein production and results in edema due to low oncotic pressure. In fact, recent efforts at managing diarrheal illnesses in Nigeria may have been a factor in reducing the incidence of kwashiorkor – a specific subtype of PCM *(2)*.

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1.1. Malnutrition in Children

1.1.1. UNDERWEIGHT IN CHILDREN

1.1.1.1. Definitions. Malnutrition in children in the United States is defined by comparison to the Centers for Disease Control and Prevention (CDC) growth charts. These charts are based on data from the ongoing National Health and Nutrition Examination Surveys (NHANES) and include both bottle-fed and breast-fed infants since the year 2000. By these charts, a child with a weight-for-length measurement < 5th percentile is classified as *underweight*. A child whose height- or length-for-age is < 5th percentile is classified as being of *short stature (3)*. These charts are used in clinics to monitor for changes in weight or height status that might signify a new disease or lifestyle problem.

Internationally, the World Health Organization (WHO) uses similar growth charts *(1,4,5)*. These define *wasting* as a child whose weight-for-height is > 2 standard deviations (SD) below the mean. A height-for-age > 2 SD below the reference indicates *stunting (5)*. Severe degrees of wasting and stunting in children are defined as > 3 SD below the reference value *(5)*.

1.1.1.2. Prevalence. The current prevalence of underweight, short stature, and wasting in the United States has not been documented. Malnutrition and food insecurity are closely related to levels of poverty. Nearly 13 million children in the United States lived in families with incomes below the poverty level in 2006 *(6)*. Based on 2005 data in children less than 5 years of age 4.8% were underweight and 6.4% were of short stature in the United States *(3)*.

Internationally, a comparison of other developed countries (Argentina and Italy) with two developing countries (Maldives and Pakistan) revealed that the prevalence of stunting was 4.5% in Argentina and 2.5% in Italy (severe stunting and wasting each at $\leq$ 1% in both countries). By contrast, 37% of children from the Maldives and 27% from Pakistan were stunted, while 20% from the Maldives and 15% from Pakistan were identified as meeting the definition for wasting *(7)*. As can be seen even in developed countries where the prevalence rates are low, undernutrition exists nonetheless. The mortality rate remains above 20% in children with severe malnutrition who are cared for in hospitals *(8)*.

Fetal malnutrition is defined as failure to acquire adequate fat and muscle mass during intrauterine growth *(9)*. This condition is associated with a higher risk of perinatal death as well as chronic diseases (hypertension, diabetes, coronary heart disease) in later life. Fetal malnutrition is more prevalent when the mother is malnourished (BMI <18.5 kg/m^2) *(9)* and has been described as 10% in the United States and up to 20% in India and Nigeria *(9)*. When undernourished pregnant women were supplied with multimicronutrient supplements, the incidence of low birth weight declined from 43.1 to 16.2%, and early neonatal morbidity declined from 28 to 14.8% in a group of 200 malnourished pregnant women in India *(10)*. These studies suggest that neonates are at high risk of malnutrition after birth, and especially in those whose mothers do not have medical care during pregnancy.

More than 50% of deaths in children under five are due to malnutrition. Malnourished children have a 10–20 times greater risk of dying than well-nourished children. Countries with more than 10% of children under five with wasting also have mortality greater than 7%. These countries include Afghanistan, Bangladesh, Cambodia, Congo, Ethiopia, India, Madagascar, and Pakistan. More than 2 million children die in India alone from causes related to undernutrition *(5)*. According to the 2006 WHO report, 20 million children under the age of five years suffer from severe malnutrition, and they die from diarrhea and pneumonia.

1.1.2. Overweight in Children

1.1.2.1. Definition. Given that overweight is epidemic in children in developed countries, the CDC has also developed BMI-for-age and sex charts to screen for this form of malnutrition *(3)*. The BMI is calculated as weight in kg/(height in m)^2. If BMI for age and sex is greater than the 85th but less than 95th percentile, a child is considered as at *risk for overweight* and BMI $>$ 95th percentile indicates *overweight* status. The WHO has developed a similar BMI chart that begins with age 0 and is based on European data *(11)*.

1.1.2.2. Prevalence. By 2003–2004 NHANES data, 34.8% of boys and 32.4% of girls in the United States were either at risk of overweight or overweight, with 17.1% of all children being overweight *(12)*. In children less than 5 years of age, 13.9% were overweight in 2005 *(3)*. By contrast, in the Maldives and Pakistan only 0.2% and 1.2% of children were overweight and 0.2% obese *(7)*.

1.2. Malnutrition in Adults

1.2.1. Underweight

In adults, energy malnutrition is defined by comparison of body weight or body mass index to optimal levels. The BMI is calculated as weight in kg/(height in m)^2. By international agreement, BMI < 18.5 kg/m^2 is considered malnourished and associated with increased mortality risk *(1)*.

Body weight is sometimes compared with predictive equations for "optimum" body weight or for "lean" body weight *(13,14)*. These continue to be widely used and often referred to as "ideal" body weight despite being empirically derived *(15)*. For the Hamwi standard ideal weight for women is 100 lbs for the first 5 feet of height + 5 lbs for each additional inch, while for men, ideal body weight is 106 lbs for first 5 feet of height + 6 lbs for each additional inch *(13)*. For the Devine standard ideal weight for women is 45.5 kg for the first 5 feet of height + 2.3 kg for each additional inch, while for men, ideal body weight is 50 kg for the first 5 feet of height + 2.3 kg for each additional inch *(14)*. With these similar weight standards, an individual whose current weight is 80–89% of ideal is at risk of *mild malnutrition*, and 70–80% ideal is at risk of *moderate malnutrition*, and if $<$ 70% ideal is at risk of *severe malnutrition (16)*. Unfortunately, these standards did not consider non-caucasian ethnic or racial groups and do not consider age. More importantly, they have not been associated with clinical outcomes. Thus, BMI is suggested as a preferred standard.

Unintentional weight loss from usual body weight has been associated with negative clinical outcomes. A loss of $>$ 10% of usual body weight is associated with a threefold increase in mortality after gastric ulcer surgery *(17)*. Weight loss in the elderly, whether in hospital or after discharge, is associated with mortality. Weight loss during hospitalization is common due in part to unfamiliar food intake, medication and disease effects on appetite, and limited intake due to procedures. This degree of weight loss may alter physiologic function even if the BMI is within the desirable limits.

There are no clear data on adult malnutrition in the United States. According to the U.S. Census Bureau, nearly 24 million adults in the United States live in poverty and therefore are at risk for food insecurity and malnutrition *(6)*.

1.2.2. OVERWEIGHT

Rather than undernutrition, the more usual pattern in the general patient population of the United States is normal weight, overweight, or obesity prior to hospital admission *(18)*. Adults with a BMI 25–29.9 kg/m^{2}are considered *overweight* while those with BMI $>$ 30 kg/m^2 are considered *obese (12)* (see Chapter 7). This reality is associated with increased risk of chronic diseases (hypertension, type 2 diabetes mellitus, osteoarthritis, sleep apnea, and several cancers). By the most recent NHANES data, 66.3% of adults were either overweight or obese and 32.9% were obese *(12)*.

1.3. Secondary Malnutrition

While malnutrition can occur as a primary process due to reduced food intake or availability, the more common pattern in developed countries is acute or chronic malnutrition secondary to a disease. Weight loss during acute illness or hospitalization is common. Additionally, rapid development of severely depleted serum protein levels occurs in response to injury, infection, surgical or medical treatments, and prolonged limited intake of protein *(19)*. Such unintentional weight loss is associated with poor surgical outcomes. Patients with critical illness may require intravenous or enteral tube feedings to meet their increased needs for energy, protein, and other nutrients. Subacute and chronic diseases may result in reduced food intake due to physiologic barriers (tumors or adhesions blocking the gastrointestinal tract), reduced nutrient absorption (malabsorption syndromes, surgically induced malabsorption), or loss of appetite (cancer and cardiac cachexia). With aging, any loss of cognitive function or reduced sensory acuity may result in reduced food intake. In addition, some types of malignancy and pulmonary disease (cystic fibrosis) may increase the body's requirement for energy. Treatment for these diseases may also limit a patient's ability to obtain adequate intake (malabsorption due to chemotherapy or radiotherapy, prolonged NPO status, or clear liquid intake for gastrointestinal symptom control). Findings on altered drug disposition related specifically to secondary causes of malnutrition may be found elsewhere *(20–23)*. Following a summary on screening for malnutrition, the remainder of the chapter will focus on primary malnutrition.

1.4. Monitoring or Screening for Malnutrition

1.4.1. PRIMARY MALNUTRITION

While protein and energy have classically defined the syndrome, in the most typical presentation with starvation, the entire food supply is limited such that deficiencies of many other nutrients occur simultaneously *(1)*. A relatively recent observation in developing countries is increasing obesity concurrently with prevalent PCM or micronutrient deficits. In young American children the prevalence of iron deficiency is significantly greater (OR 3.34, 95%CI 1.10, 10.12) in those who are overweight/obese *(24)*. Obesity can occur when caloric supply is adequate to promote chronic diseases (obesity, diabetes, hypertension, and cancer) but the nutrient content of the diet is poor *(25)*.

In hospitalized or institutionalized patients, a nutrition screening tool is sometimes employed to distinguish adult patients with nutritional risk. These tools typically include some component of low body weight, unintentional weight loss, and a physical examination. The Subjective Global Assessment (SGA) includes history of weight loss, appearance of wasted muscle, and fat mass and edema to classify risk *(18)*. The SGA has been validated in surgical patients, renal patients, and the elderly. The British Association of Parenteral and Enteral Nutrition developed the Malnutrition Universal Screening Tool (MUST) that includes a score for low BMI, one for weight loss, and additional points for acute disease-related reduction in food intake *(26)*. When this tool was applied to 1000 adult admissions to a hospital in Glasgow, Scotland, 42% of patients were malnourished and their mortality odds ratio was 2.04 (95% CI 1.22, 3.44) relative to the patients without malnutrition *(27)*.

A third tool used particularly in the elderly is the Mini Nutrition Assessment (MNA). In addition to BMI, patients are screened for using more than 3 prescription drugs daily, independence in activities of daily living, presence of pressure ulcers, and food intake. Malnutrition by the MNA is associated with a threefold greater mortality in hospitalized elderly patients *(28)*. There is no doubt that malnutrition is common and a negative finding in hospitalized and ill subjects. Unfortunately, no single tool has been used widely enough that precise statements about the extent of malnutrition among hospitalized patients can be made *(29)*. Given the prevalence of malnutrition and the widespread use of medication, an appreciation of altered drug disposition is critical to optimal patient care.

1.4.2. Secondary Malnutrition

Serum protein concentration is sometimes used to define malnutrition. Albumin, transferrin, and prealbumin are employed because of their different serum half-lives (21 vs 10 vs 3 days, respectively) but all are negative acute phase reactants. When inflammation occurs due to infection or autoimmune disease, hepatic production of these proteins is reduced while that of positive acute phase reactants (C-reactive protein [CRP], α1-acid glycoprotein, serum amyloid A, procalcitonin, haptoglobin, and many others) are increased *(30)*. Prealbumin concentration classified 41% of patients as malnourished, a similar rate to a detailed nutritional assessment with 83% sensitivity and 77% specificity in a group of 108 hospitalized Italian adults *(31)*. Prealbumin was also inversely associated with CRP and fully 67% of these hospitalized patients had elevated CRP *(31)*. The Prognostic Inflammatory and Nutritional Index (PINI) score has been suggested to include factors that reflect nutrition (albumin) and inflammation (CRP, α1-glycoprotein) *(32)*. A second ratio calculates CRP/prealbumin *(33)*. While these ratios may assist in clarifying the impact of concurrent inflammation on reduced serum concentration of albumin and prealbumin, the ratios are most heavily impacted by the CRP. Low prealbumin alone can increase the ratio perhaps two- to threefold, but even a mild inflammatory response will have a tenfold effect *(30)* making the utility of these proteins to quantitatively define malnutrition questionable.

2. REVIEW OF BASIC SCIENCE

2.1. Physiologic Changes with PCM

Because PCM develops gradually over weeks to months, a series of metabolic and behavioral adaptations occur, with the aim of preserving limited body tissue *(34)*. The adaptive processes include reduced resting energy expenditure due to loss of metabolically active tissue, reduced activity-related energy expenditure as the malnourished individual is too weak for physical exertion, and reduced thermic effect of feeding as caloric supply is limited *(34)*. Thus daily total energy expenditure is reduced. Adaptation involves changes in body composition and function.

Dramatic changes in body composition herald significant malnutrition. A loss of subcutaneous body fat stores occurs, leaving visible bony prominences.

Protein catabolism leads slowly to muscle wasting *(18,34)*, which can be detected in adults by squared off shoulders and limited biceps mass. With severe disease, visceral protein depletion (including reductions in serum total protein and albumin) results from reduced protein synthesis, leading to edema and ascites *(34)*.

With marasmic malnutrition, body fat stores are reduced and total body water increased, as measured by body composition. By the point of marasmic malnutrition, the fat mass has been reduced by 2/3, and the extracellular water expanded 50% *(35)*.

With prolonged severe limitations in nutrient intake, however, the process of adaptation is not successful and the patient succumbs, usually to death from an otherwise minor infection *(1)*. When gradual starvation is not complicated by infection, the body reduces its production of less essential proteins, such as growth and sex hormones, insulin, and thyroid hormone *(34)*. The reduction in thyroid hormone causes a significant decline in metabolic rate and thus energy expenditure. Body cell mass, including red blood cells, T lymphocytes, and complement, is reduced, leading to anemia and fatigue. Reduced immune surveillance, in the setting of an overcrowded, unhygienic environment leaves malnourished individuals at far greater susceptibility to infection *(18,34)*.

Gradual loss in organ function occurs with prolonged, severe malnutrition *(34)*. Blood glucose concentration is initially maintained by the auto-catabolism of body fats to glycerol (and free fatty acids) and of gluconeogenic amino acids. With severe or end-stage PCM or when severe infections limit hepatic function, blood glucose concentrations may drop. Total body potassium and zinc are lost with muscle catabolism. As a result of PCM, muscle mass and its associated minerals and trace elements are lost, leaving the individual with limited metabolic reserve. In addition, the heart and liver are reduced in size and function. These changes can limit the individual's ability to metabolize drugs. Shifts in fluid status may also limit drug excretion. Cardiac output, heart rate, and blood pressure are decreased, with reduced venous return. Renal plasma flow and GFR are limited secondary to reduced cardiac output, but water and electrolyte clearance are unchanged. Diarrhea is common with PCM, for various reasons including limited intestinal secretions, bacterial overgrowth, nutrient deficiencies (particularly of vitamin A or zinc), and villous atrophy *(34)*. Hepatomegaly is associated with steatosis, as nutrient deficiencies prevent the export of fat from hepatocytes. Hepatic production of serum proteins (albumin, prealbumin, and transferrin) is reduced with continuing malnutrition, as are hemoglobin and hematocrit *(34)*. The production of enzymes, including those with a role in drug metabolism, is also reduced *(36–42)*.

2.2. Impact on Medication

With malnutrition, drug absorption, distribution, and clearance are negatively impacted. Changes in drug disposition may vary with the degree of altered body composition and function associated with PCM. In severe PCM, drug absorption may be reduced, protein carriers limited, and metabolism slowed, resulting in higher drug concentrations and a potential for toxicity especially with drugs that have a narrow safety margin. In mild to moderate malnutrition, changes in metabolism may be minimal or of limited clinical significance; however, the clinical data to support this conclusion are very limited.

2.2.1. Absorption

The physical properties of medications, such as lipid solubility, molecular weight, acidity, and biopharmaceutical properties, impact their absorption *(36–42)*. During PCM, however, absorption may be reduced, particularly with children with severe PCM and with alcoholic adults *(43)*. Malabsorption of drugs can occur if the malnutrition problem includes deficiency of zinc or vitamin D, and secondarily generalized malabsorption.

2.2.2. Distribution

In later stages of malnutrition, where hepatic protein synthesis is reduced, protein carriers for drugs may be limited, resulting in greater concentrations of free drug available for tissue use or elimination *(36–42)*. In established kwashiorkor, both extracellular fluid accumulation and low serum albumin concentrations prevail *(1,34)* and may be exacerbated by the liver's inflammatory response to infection further reducing albumin synthesis. In addition to a reduction in carrier availability, the associated fluid shifts and edema may impact drug concentrations or distribution to needed tissues.

2.2.3. Metabolism

Clinical reports to date have described a different pattern in the impact of malnutrition on drugs depending on the severity of malnutrition *(36–42)*. Reports in children have primarily reflected severe PCM (marasmus, kwashiorkor, or marasmic–kwashiorkor) with many children from Africa or the Asian subcontinent. In the few published adult studies, subjects have been mildly to moderately malnourished, likely of much shorter duration, but very small subject numbers.

With the milder forms of malnutrition, oxidative metabolism of drugs is reported as unchanged or increased. By contrast, when the malnutrition has progressed to kwashiorkor, metabolism is consistently reduced.

Antipyrine is exclusively metabolized by the liver, with very limited hepatic extraction, and is a suitable descriptor of overall mixed function oxidase activity *(44)*. The substance is protein bound to a limited degree and its elimination and distribution are not impacted by hypoalbuminemia. In a group of 45 adult patients with inflammatory bowel disease, who had suffered > 10% weight loss and/or reduction in albumin concentration (malnourished = 30 g/L vs 40 g/L in 25 normal controls), cytochrome P450 (CYP) was evaluated by antipyrine metabolism *(44)*. Overall metabolic clearance was reduced, but weight-corrected clearance was unchanged. In 27 of these patients, who were restudied after 30 days of nutritional repletion, clearances were normalized in those who had protein malnutrition but unchanged when the initial deficit was caloric *(44)*. Hepatic blood flow is also reduced in malnourished individuals which would be critical for drugs dependent on blood flow for their metabolism *(45)*.

In 30 undernourished adults hospitalized with peptic ulcer disease or abdominal pain and only mildly hypoalbuminemic, liver biopsy specimens were evaluated for aryl hydrocarbon hydroxylase (AHH) and CYP concentrations *(46)*. CYP was unchanged, but AHH increased in the undernourished men, a pattern suggesting increased ability to activate reactive metabolites concurrent with reduced ability to detoxify them. Unfortunately, levels of expression and activity were not described.

Significant reductions in plasma proteins, hepatic microsomal proteins, and hepatic microsomal CYP have been observed in animal models of PCM *(47)*. The changes in CYP isoenzymes using Western and Northern blot analyses in a rat model of PCM have reported decreases of over 50% in CYP2E1, CYP1A2, CYP2C11, but only slight decreases of CYP3A1/2 *(48)*. There is a significant degree of homology between CYP2C11 and CYP3A proteins in the rat with CYP2C9 and CYP3A proteins in humans. The changes in enzyme extend to hepatic microsomal epoxide hydrolase which increases in activity as well as in mRNA levels in rats with PCM *(49)*.

Male Sprague–Dawley rats were fed either a usual diet (20–25 g/d) or one creating a level of PCM (10–12 g/d) for 8 weeks to determine whether altered hormone secretion is a factor in the altered drug metabolism seen with PCM *(50)*. The diet contained 65.6% of calories as carbohydrate, 15.8% as fat, and 17.6% as protein *(50)*. Although serum albumin concentrations did not change following dietary restriction, both body weight and liver weight decreased significantly, as did the microsomal protein content (mg/g liver) and total CYP mRNA. Evaluation of hepatic pathways of testosterone metabolism revealed significant reduction of V_{max} in four out of five hydroxylating enzymes along with corresponding increases in enzyme affinity *(50)*. The largest capacity normally resides in CYP2C11 which is responsible for 2α-hydroxylation of testosterone, so this activity diminished the most *(50)*. Testosterone 16β-hydroxylation representing CYP2B1 activity remained unchanged by PCM *(50)*. Findings following PCM were less dramatic in adult compared with juvenile animals but significant nonetheless *(50)*. Secretion patterns and serum concentrations of growth hormone were not different between PCM animals and controls *(50)*. Pure protein malnutrition may have different effects on metabolic pathways than does PCM.

2.2.4. Excretion

Renal clearance of drugs may be impacted by protein intake. Since renal tissue is spared until very severe stages of malnutrition, however, most reports to date do not report reduced renal drug clearance with PCM. The possibility that concurrent clinical comorbidities (e.g., hypertension, diabetes, chronic kidney disease, or acute kidney injury) may play a role in altered renal drug clearance, particularly in elderly or metabolically stressed critical care patients, should be considered.

2.2.5. Drug Effects

The therapeutic effectiveness of a drug may be reduced or the risk of toxicity increased due to malnutrition. When absorption is reduced and/or excretion increased adequate drug levels in serum or tissues may not be achieved. When the half-life of a drug is prolonged, due to reduced hepatic metabolism or renal elimination, toxic drug or drug metabolite levels can occur. In malnourished subjects, drugs with a narrow safety margin can produce toxicity at usual dosage levels if the drug's bioavailability is increased due to impaired hepatic function *(42)*. However, if the toxicity of a given drug is due to its metabolite, then the slowing of CYP activity will actually reduce toxicity *(42)*.

3. DATA FROM ANIMAL EXPERIMENTS

A series of animal experiments were designed to examine specific aspects of the impact of severe malnutrition on drug handling and action. Experiments conducted prior to the 1970s verified consistently that oxidation rates of drugs were in general reduced with significant malnutrition *(37)*. More recent experimental findings are discussed below.

3.1. Analgesics

The salicylate analgesics are one class of drugs associated with ototoxicty. Salicylate ototoxicity was enhanced with magnesium and zinc deficiencies *(51)*. Zinc deficiency also enhanced a reversible salicylate-induced nephrotoxicity *(51)*.

Apomorphine is an opioid-related drug used for Parkinson disease. A group of rats were randomized to receive a low-protein diet (0.5%) or standard animal chow for some time *(52)*. Following a dose of apomorphine 2 mg/kg administered intravenously, plasma clearance was significantly reduced in the PCM animals *(52)*. There was also a significant change in drug response in the PCM group following varying intravenous infusions to achieve different steady-state concentrations. Rather than exhibiting bradycardia at low doses and tachycardia at the higher doses, the PCM animals exhibited bradycardia and baseline heart rates at higher concentrations *(52)*. This suggests a desensitization or down-regulation of tachycardia-associated receptors in the PCM rats.

3.2. *Anesthetics*

Ketamine is an anesthetic agent available as a racemic mixture. The two enantiomers have different pharmacokinetic/dynamic properties. The influence of PCM on these properties has been evaluated in a rat model *(53)*. The model used an isocaloric diet with protein intakes of 5.5% (PCM) or 22.5% (controls) for 17–20 days. Animals with PCM had a significantly greater AUC following an 85 mg/kg intramuscular dose of racemic ketamine than did the control animals, as a result of slower clearance (*N*-demethylation) of each enantiomer *(53)*. Exposure to each metabolite (norketamine, dehydronorketamine) was also increased in PCM animals, with significantly higher concentrations of (*S*)-norketamine than (*R*)-norketamine – both active metabolites *(53)*. From a pharmacodynamic perspective, ketamine produced a longer duration of immobilization in the PCM rats *(53)*.

3.3. *Antiepileptics*

Phenytoin disposition was evaluated in a rat model of PCM *(54)*. The model used an isocaloric diet with a protein intake of 5% (PCM) or 23% (controls) for 4 weeks. Following a 25 mg/kg intravenous dose of phenytoin, hydroxylation of the drug to the metabolite HPPH was significantly less in animals with PCM compared with controls, which was also reflected in lower 24-h urinary excretion of the metabolite *(54)*. The intrinsic clearance of phenytoin was slower in the PCM animals. The V_{max} was significantly lower in the PCM animals, with more unchanged phenytoin excreted in the urine *(54)*. The V_d in the central compartment was much larger in this group probably due to increases in unbound drug fraction allowing greater tissue binding *(54)*. There were no improvements of phenytoin pharmacokinetic parameters in this animal model following oral supplementation of the sulfur-containing amino acid cysteine (250 mg/kg twice daily for 1 week) *(54)*. Supplementation of cysteine has improved pharmacokinetic findings in PCM with some other medications *(48)*.

3.4. *Antimicrobial Medication*

Given that infection and malnutrition often co-exist, the influence of PCM on the disposition and effect of antimicrobials is important. Animal data can serve to explain pharmacokinetic alterations in humans or prompt further investigation in humans.

3.4.1. AMINOGLYCOSIDES

The influence of nutritional status on gentamicin ototoxicity was investigated in a guinea pig model *(55)*. Animals were fed a 7% protein diet (PCM) or an 18.5% protein diet (control) prior to exposure to gentamicin alone or in combination with ethacrynic acid. As measured by auditory evoked brainstem responses the PCM animals had significantly greater drug-induced hearing loss than the controls. These differences were not attributed to differences in serum drug concentrations *(55)*.

Gentamicin ototoxicity was enhanced with experimental magnesium and zinc deficiencies in a rat model *(51)*. Magnesium deficiency can induce hearing loss independently of gentamicin, due to low extracellular magnesium concentrations allowing influx and turnover of sodium, potassium, and calcium with a resulting reduction in cochlear blood flow *(51)*. With magnesium deficiency, the hearing loss induced by gentamicin treatment was nearly complete and irreversible in 36% of animals. Enhanced membrane permeability of the hair cells and thus increased ion pumping was the most likely mechanism behind increased ototoxicity with zinc deficiency *(51)*. Experimental dietary potassium depletion in the dog was associated with increased gentamicin nephrotoxicity, with the drug concentrated in the renal cortex of potassium-depleted animals *(56)*. Gentamicin administration also induced urinary potassium wasting *(56)*.

3.4.2. Chloramphenicol

A limitation in protein carriers, which occurs commonly with PCM, reduced chloramphenicol distribution in rats. Hypoproteinemic rats, given a single dose of chloramphenicol, had higher circulating drug concentration, with greater renal than hepatic drug distribution, and diminished plasma half-life *(57)*. The authors speculated that reduced protein binding of the drug allowed the higher drug levels and the shortened half-life.

During malnutrition, the metabolism of chloramphenicol is reduced. In guinea pigs fed a protein-depleted diet, total body and liver weight (but not hepatocyte number) were reduced *(58)*. Hepatic microsomes had reduced conjugation of chloramphenicol, due to a reduced UDP-glucuronidase activity per cell, and reduced response to induction by 3-methylcholanthrene *(58)*. These data suggest that the increased drug levels of chloramphenicol in malnourished patients may in part be due to reduced drug clearance by the liver *(58)*. In malnourished rats treated with chloramphenicol, hepatic microsomal aniline hydroxylase, and aminopyrine-*N*-demethylase activities were markedly reduced *(59)*. Mitochondrial oxidative phosphorylation, which was already inhibited by PCM, was further potentiated by chloramphenicol treatment.

3.4.3. Clarithromycin

This macrolide antibiotic was evaluated in a rat model of PCM *(60)*. Using an isocaloric diet with protein content of 5% (PCM) or 23% (control) for a period of 4 weeks animals received a single dose of clarithromycin 20 mg/kg intravenously. The $AUC_{0-\infty}$ was significantly higher in malnutrition compared with the control animals *(60)*. Total and non-renal drug clearance was significantly slower in the PCM group, as was intrinsic clearance from study of hepatic microsomal fractions, without any change in V_{SS} *(60)*. The percent of drug remaining unmetabolized was higher in the PCM animals *(60)*. Cysteine supplementation (250 mg/kg twice daily by mouth for 1 week) permitted return of all measured pharmacokinetic parameters in PCM animals to the control values *(60)*. This was expected given the return of enzyme activity with cysteine supplementation following the 50% reduction of CYP3A23 as a result of PCM in this model *(48)*. This enzyme has ~73% homology with human CYP3A4 responsible for metabolizing clarithromycin to 14-hydroxy-clarithromycin *(47)*.

3.4.4. Itraconazole

The antifungal agent itraconazole was evaluated using a rat model of PCM *(61)*. The model used an isocaloric diet with protein content of 5% (PCM) or 23%

(controls) for 4 weeks. Animals with PCM had a significantly greater AUC following a 20 mg/kg intravenous dose of itraconazole than did the control animals, with a significantly reduced non-renal drug clearance as a result of suppressed CYP3A1 (-3A23) levels *(61)*. This isoenzyme has ~73% homology to human CYP3A4 *(61)*. It had been previously reported that the expression of this enzyme using Western and Northern blots was reduced in PCM *(48)*. The AUC following a 50 mg/kg oral dose of itraconazole was no different between PCM and control animals possibly because of lesser impact on factors involved in first-pass effect *(61)*. It is interesting to note that alterations in CYP expression were improved in this animal model following oral supplementation of the sulfur-containing amino acid cysteine (250 mg/kg twice daily for 1 week) *(48)*.

3.4.5. OXAZOLIDINONES

Although no animal data on linezolid are available, another newer oxazolidinone (DA-7867) was evaluated in a rat model of PCM *(62)*. The model of dietary protein deficits was 5% (PCM) vs 23% (controls) continued for 4 weeks; designed to be isocaloric, but significant reductions in caloric intake occur in the protein-deprived animals. Following a dose of 10 mg/kg the $AUC_{0-\infty}$ in PCM was significantly smaller than that in the control animals, likely the result of a significantly more rapid total body clearance of the drug *(62)*. Renal clearance of the drug was actually slower in the PCM animals, pointing toward significant increases in gastrointestinal (including biliary) excretion *(62)*. Oral administration of DA-7867 in this model revealed a significantly smaller AUC in the animals with PCM, in part due to reduced intestinal absorption *(62)*.

3.4.6. SULFADIAZENE

A rhesus monkey model was employed to examine the impact of malnutrition on sulfadiazine acetylation by the hepatic phase II conjugation pathway, *(63)*. States of normal nutrition, PCM, and nutritional rehabilitation were induced by change in quantities of diet. Total absorption of sulfadiazine was unchanged, though the peak was delayed in the group with PCM. The peripheral volume of distribution of the drug was reduced, as were the elimination rate constant and clearance rate. These latter two factors resulted in increased drug half-life and AUC in the group with PCM. Acetylation was only measured in hepatic tissue (representing 33% of total acetylation) and appeared unchanged by PCM. The authors suggested that the reduced volume of distribution of drug may be a key factor in reducing drug elimination *(63)*.

3.4.7. ANTI-TUBERCULARS

Isoniazid hepatotoxicity was examined in an experiment with caloric deprivation, PCM, and usual diet in rats *(64)*. After 2 weeks of isoniazid, all animals had transaminitis and proliferation of the rough endoplasmic reticulum in liver tissue. Glutathione activity was reduced in both liver and blood samples, suggesting reduced free radical defense. The isoniazid-induced loss of glutathione activity was further exacerbated by concurrent malnutrition *(64)*. Similar findings were noted in a related experiment testing both isoniazid and rifampicin *(65)*.

3.5. Cardiovascular Agents

The loop diuretics (bumetanide, furosemide, torsemide) have been used to manage volume in the extracellular fluid compartment. Bumetanide was evaluated following intravenous and oral administration in a rat model of dietary protein deficits 5% (PCM) vs 23% (controls) and otherwise isocaloric in content for 4 weeks *(66)*. The oral bioavailability of bumetanide was 73% greater in the PCM animals, probably resulting from reduced first-pass effect *(66)*. Both the excretion of unchanged drug and renal clearance of bumetanide were over 150% greater in the PCM animals relative to the controls following an intravenous dose while non-renal clearance decreased by 28% *(66)*. Incidentally, the urine output, natriuretic effect, and kaluretic effect were not different between groups indicating the possibility that loop diuretics are less efficient in PCM.

Another study by this group using a similar design and model of protein deficits revealed that excretion of unchanged furosemide and renal clearance of the drug were over 160% greater in the PCM animals relative to the controls following an intravenous dose while non-renal clearance decreased by 54% *(67)*. The oral bioavailability of furosemide was 70% greater in the PCM animals *(67)*.

The remaining loop diuretic, torsemide, was also evaluated using the similar design *(68)*. The oral bioavailability of torsemide was over 100% greater in the PCM animals, probably resulting from reduced first-pass effect *(68)*. However, the renal clearance of torsemide was actually less in the PCM animals relative to the controls following an intravenous dose while non-renal clearance decreased by 57% *(68)*. Animals with PCM had a significantly greater $AUC_{0-\infty}$ following a 2 mg/kg intravenous dose of torsemide than the control animals, accounted for by a significant reduction of intrinsic drug clearance possibly because of lower affinity of the drug for its enzyme *(68)*. This diuretic with a low hepatic extraction ratio is metabolized by CYP2C11 in rats (77% homology with human CYP2C9) which is decreased by ~80% in PCM *(68)*. Pharmacodynamic characteristics of torsemide were not significantly different between groups. It is interesting to note that alterations in CYP expression were improved in this animal model following oral supplementation of the sulfur-containing amino acid cysteine (250 mg/kg for 1 week) *(48)*. When these investigators applied the cysteine supplementation to the animal model across several different drugs, the benefit to CYP expression was seen for some agents only.

An agent under evaluation as a treatment for erectile dysfunction, DA-8159, and its active metabolite, DA-8164, were evaluated in a rat model of PCM *(69)*. The model was based on an isocaloric diet with dietary protein intakes of 5% (PCM) vs 23% (controls) continued for 4 weeks. Following both oral and intravenous administration of 30 mg/kg of the parent drug, the $AUC_{0-\infty}$ of the metabolite was significantly lower in PCM animals compared with control animals *(69)*. The significantly lower intrinsic clearance of the parent drug to form the metabolite as seen in hepatic microsomal fractions would explain this finding *(69)*. The metabolite is primarily formed by CYP3A1/2 known to be reduced by at least 50% in this model of PCM *(48)*. When compared with the control animals, the AUC of the parent drug in the PCM animals was significantly greater after oral administration but not significantly different following intravenous administration, probably related to a reduced first-pass effect *(69)*.

3.6. Chemotherapeutic Agents

Several classes of traditional chemotherapeutic agents are associated with significant toxicity and the role that malnutrition plays requires scrutiny. Given the prevalence of PCM in tumor-bearing hosts, a study on the influence of dietary protein 2.5% casein (low protein) vs 21.5% casein (normal protein) for 25 days on the metabolism of a parenterally administered weight-based dose of fluorouracil was conducted in a rat model *(70)*. The activity of hepatic cytosol dihydropyrimidine dehydrogenase was significantly reduced in the low protein animals despite no difference in cytosolic protein content. The metabolic clearance of fluorouracil was significantly reduced in the low protein animals with no difference in volume of distribution, accounting for more than doubling the drug half-life *(70)*. As a result, the low protein animals also experienced greater toxicity (leukopenia, weight loss, diarrhea) and mortality than those fed normal protein diets *(70)*. This would indicate that dosage adjustment would be required in the setting of malnutrition, assuming no significant individual variability in dihydropyrimidine dehydrogenase activity which is known to occur in humans.

In a rabbit model, an isocaloric diet either low in protein (5%) or with normal protein (15%) for 8–12 weeks resulted in significant changes in doxorubicin following a 5 mg/kg intravenous bolus *(71)*. The $AUC_{0-\infty}$ was significantly increased and drug clearance was significantly decreased in the PCM animals, without a significant difference in volume of distribution *(71)*. Doxorubicinol had a prolonged elimination half-life indicating reduced ability to clear the parent drug and its metabolite *(71)*. Doxorubicin was also evaluated in a rat model of PCM *(72)*. The model was based on an isocaloric diet with dietary protein intakes of 5% (PCM) vs 23% (controls) continued for 4 weeks. Following an intravenous bolus dose of doxorubicin 16 mg/kg the $AUC_{0-12\ h}$ in PCM was higher than that in the control animals, with reduced urinary excretion of one of its metabolites suggesting inhibited metabolism *(72)*. There were significant improvements to doxorubicin pharmacokinetic parameters in this animal model following oral supplementation of cysteine (250 mg/kg twice daily for 1 week) *(72)*. Supplementation of cysteine has improved findings with a number of other medications in large part by improving CYP mRNA levels and CYP activity *(48)*.

Methotrexate pharmacokinetics are altered in states of nutritional depletion *(73)*. Non-tumor-bearing rats received protein-free or regular diets for 10 days. Following methotrexate 20 mg/kg administered parenterally, drug concentration was significantly higher in PCM rats. The same design but using tumor-bearing animals again found elevated drug levels in those fed protein-free diets, even in a subset that was allowed nutritional repletion for 2 days *(73)*. Methotrexate was evaluated in rats randomized to an isocaloric diet that was either protein depleted (0.03%) or contained standard protein (22%) for 35 days *(74)*. Following a single 10 mg/kg intraperitoneal dose of methotrexate, the AUC was significantly higher, while peak/time to peak concentrations were significantly greater/later in the PCM group *(74)*. This suggests delay in absorption and clearance of the drug in malnutrition. Significant reductions in creatinine clearance, serum albumin, and fraction of unbound drug were found in the PCM animals *(74)*.

The influence of nutritional status on cisplatin toxicity was investigated in a guinea pig model *(55)*. Animals were fed a 7% protein diet (PCM) or an 18.5% protein diet (control) prior to exposure to medication. As measured by auditory evoked brainstem responses the PCM animals had significantly greater drug-induced hearing losses that were not attributed to differences in serum drug concentrations *(55)*.

Oltipraz is an agent being investigated for its chemopreventative effects. This drug is metabolized by CYP isoenzymes, three of which (CYP1A2, -2C11, -3A) are expressed poorly in rats with PCM *(75)*. As would be expected, animals with PCM had a significantly greater $AUC_{0-\infty}$ following a 10 mg/kg intravenous or a 30 mg/kg oral dose of oltipraz than the control animals, explained by a significant reduction of non-renal intrinsic drug clearance *(75)*. Supplementation with oral cysteine (250 mg/kg) returned most pharmacokinetic parameters to control values *(75)*. Another chemoprotective agent being investigated is 2-allylthio-pyrazine. In the PCM rat the $AUC_{0-\infty}$ was significantly lower than in the control animals likely due to an increased formation of one of the metabolites (M4) *(76)*. Oral cysteine supplementation resulted in an AUC significantly greater than in the PCM or control animals due to reduced production of M4 *(76)*. *S*-methyltransferase is involved in M4 production but the reason for the greater formation of this metabolite in PCM is not clear, although increased enzyme activity cannot be ruled out.

3.7. Gastrointestinal Agents

The proton pump inhibitor omeprazole was evaluated in a rat model of PCM *(77)*. The model was based on an isocaloric diet with dietary protein intakes of 5% (PCM) vs 23% (controls) continued for 4 weeks. Following oral administration of 40 mg/kg and intravenous administration of 20 mg/kg of omeprazole, the AUC of the drug was significantly higher in PCM compared with control animals *(77)*. Findings of a significantly lower total body clearance, non-renal clearance, and a significantly lower intrinsic clearance based on hepatic microsomal fractions explain this finding *(77)*. Omeprazole is primarily metabolized by CYP1A1/2, CYP2D1, and CYP3A1/2 in rats; furthermore both CYP1A2 and CYP3A1/2 have been shown to exhibit significant reductions in this model of PCM *(48)*. There was a return of omeprazole pharmacokinetic parameters toward control values in this animal model following oral supplementation of cysteine (250 mg/kg twice daily for 1 week) *(77)*. Supplementation of cysteine has been associated with improved findings for several other medications in large part by improving CYP mRNA levels and CYP activity *(48)*.

4. CLINICAL EVIDENCE BY MEDICATION

The clinical evidence is rather limited in terms of the number of drugs tested and the range of malnutrition described and is composed almost entirely of pharmacokinetic data from very small numbers of subjects. Thus negative findings may be based on too inadequate of a sample size to say robustly that there is no difference. Given the potential for species differences, findings from animal models need to be compared with published reports in humans before making clinical recommendations based on extrapolations. In the absence of clinical reports describing the influence of PCM on an individual drug, any extrapolation of animal data should take into account species differences in pharmacokinetic and pharmacodynamic properties.

4.1. Analgesics

Acetaminophen is easily absorbed, rapidly distributed, has insignificant protein binding, and is metabolized to non-toxic glucuronide and sulfate products, with subsequent renal elimination *(42,78)*. In children with severe PCM, the biotransformation of acetaminophen was reduced, as evidenced by a prolonged half-life and reduced elimination. This may be expected to increase the formation of toxic reactive intermediates formed through CYP. The authors suggested monitoring drug levels to avoid toxicity in patients with severe PCM *(78)*. By contrast, in adults with milder PCM, acetaminophen toxicity was not greater than in subjects with normal nutrition, even with coadministration of vitamin C *(37)*. Acetaminophen pharmacokinetics were unchanged during a 5-day 500 kcal/day deficit diet in six obese subjects and during a 13-day 1000 kcal/day deficit diet in three obese patients, in a cross-over design study *(79)*. Both of these studies in adults *(78,79)*, however, were seriously underpowered to detect a significant difference if there was one.

The impact of moderate malnutrition in children with rheumatoid arthritis or rheumatic fever on salicylate pharmacokinetics was examined *(80)*. The biotransformation of salicylate and its AUC was reduced, relative to normally nourished controls. The authors suggest kinetic modeling of salicylates in patients with even moderate malnutrition *(80)*.

4.2. Antimicrobial Medication

International guidelines for treating severe malnutrition particularly in children have been expected to reduce case fatality rates but have fallen short with many individuals still succumbing to infection *(81)*. At least half of children with bacteremia die within 48 h of admission despite receiving appropriate antimicrobials based on susceptibility of cultured organisms. While this may be due to a variety of factors, it would be interesting to identify whether medication (antimicrobials) were dosed appropriately based on the altered drug disposition seen in severe malnutrition. All children received intravenous ampicillin 50 mg/kg QID and intramuscular gentamicin 7.5 mg/kg once daily, as well as mebendazole 100 mg Q12H and metronidazole 5 mg/kg Q8H *(81)*. The authors appropriately suggested the need for further pharmacokinetic studies *(81)*.

4.2.1. AMINOGLYCOSIDES

Gentamicin, an aminoglycoside antibiotic with a renal injury profile, is still commonly used for Gram-negative coverage in pediatric practice. In 11 malnourished 3- to 10-month-old infants, gentamicin was metabolized and eliminated normally, but its volume of distribution was increased, likely due to increased total body water, which had replaced muscle mass in starvation *(82)*. In a second group of six malnourished children aged 4–14 years, gentamicin was reported as not different from normally nourished controls *(83)*. The maximal concentration increased by 20%, the clearance was nearly halved, and as a result the half-life was almost doubled.

The number of subjects was very limited and the standard deviations very large, thus these differences were not statistically significant *(83)*. In a third group of six children with severe kwashiorkor, adequate gentamicin concentrations were achieved, though its half-life was prolonged *(84)*. Nutritional rehabilitation was associated with normalization of gentamicin half-life *(84)*.

Based on the findings one would rather administer larger loading doses of aminoglycosides at extended intervals. To further characterize the risk of aminoglycoside use in PCM, over 300 malnourished children less than 5 years of age were randomized to receive gentamicin 5 mg/kg either once daily or in three divided doses *(85)*. Once at steady state a subgroup of these children underwent pharmacokinetic analysis. As expected the gentamicin peak concentrations were significantly higher (11.7 vs 4.7 mg/L, $P<0.001$) and the trough concentrations were significantly lower (0.29 vs 0.48 mg/L, $P<0.001$) in the group receiving the drug once daily *(85)*. Adequate clinical responses did not differ between groups (89 vs 81%, NS) and no child developed nephrotoxcity indicating that once daily dosing would be appropriate in this PCM patient population *(85)*.

In 86 critically ill adult patients, those who had malnutrition (defined as low albumin and >15% weight loss) were treated with parenteral nutrition *(86)*. These malnourished patients had increased Vd with gentamicin, relative to patients without malnutrition, who received intravenous fluids *(86)*. The suspected mechanism was the expanded extracellular fluid space due to hypoalbuminemia, though this study was not controlled in total fluid intake or output. The clearance of gentamicin, however, was not significantly changed. The authors advised to monitor gentamicin drug levels in critically ill patients to ensure adequate serum concentrations while avoiding nephrotoxicity.

Following suggestion that hypoalbuminemia is associated with a higher risk of aminoglycoside nephrotoxicity, amikacin was studied in a large group of patients *(87)*. A total of 113 patients receiving intravenous amikacin for at least 36 h were prospectively evaluated. The incidence of nephrotoxicity was 17.3% in patients with an albumin concentration below 30 g/L and only 2.2% in those with higher albumin levels *(87)*. Of interest there was no difference in the age, sex, weight, diagnosis, blood pressure, or nutritional status between the two groups.

4.2.2. CHLORAMPHENICOL

For the treatment of community-acquired pneumonia in Gambian children under age 5 years, oral chloramphenicol was compared to cotrimoxazole in a prospective clinical trial *(88)*. In 111 children with marasmic malnutrition, the 2 antibiotic regimens performed similarly to normally nourished controls, with 16 treatment failures in each group. The 32 treatment failures were slightly more malnourished (weight 59.3% standard vs 60.7%) than the 79 treatment responders and had a higher percentage of positive blood or lung aspirate cultures (31 vs 13%, $P<0.05$). Serum proteins were not measured *(88)*. This study illustrates the difficulty in separating the impact of malnutrition alone from that of concurrent infection.

In 33 Ethiopian children aged 0.6–6 years, nutritional status was evaluated as 8 normal, 8 marasmic, 8 kwashiorkor, and 9 with marasmic–kwashiorkor malnutrition *(89)*. Drug absorption was erratic, with 30% absorption in marasmic–kwashiorkor and

44% in kwashiorkor. With kwashiorkor, the clearance of chloramphenicol was reduced to approximately half normal, the half-life prolonged, and effective drug concentration increased. The authors suggest individual drug monitoring due to the great inter-individual variation in pharmacokinetics *(89)*.

Chloramphenicol clearance was reduced after its incomplete metabolism in malnourished Ethiopian children *(90)*. The 34 children, who ranged in age from 9 months to 10 years, were screened into three categories of malnutrition. Fourteen were underweight with normal serum protein, 10 were marasmic with slightly reduced serum protein, and 10 had kwashiorkor with marked reduction in serum protein concentration. Unbound chloramphenicol and chloramphenicol succinate were increased in serum, particularly in those with kwashiorkor, where the albumin concentration was significantly reduced. Chloramphenicol monosuccinate clearance was reduced due to limited non-renal clearance, and the fraction of pro-drug excreted unchanged in the urine ranged from 0 to 51% (median 17%). The AUC of chloramphenicol was doubled in the children with marasmus and tripled in those with kwashiorkor, relative to those who were underweight. The authors suggest that if drug monitoring is not possible, measurement of serum total protein may assist in screening for patients who need dosage adjustment *(90)*.

From a retrospective evaluation, pharmacokinetic parameters from 10 malnourished septic children and 10 non-malnourished septic children each treated with chloramphenicol were generated *(91)*. In an additional group of malnourished children with sepsis the model derived from the malnourished patients better predicted peak and trough drug concentrations than the model derived from the non-malnourished group *(91)*. This indicates that a Bayesian modeling program using PCM-specific data is more appropriate (good precision, minimal bias) in drug dosing.

By contrast to the data with malnourished children, chloramphenicol metabolism was not significantly changed from controls with normal nutritional status in six undernourished adults *(92)*, in spite of a significantly lower albumin concentration (29.7 g/L in malnutrition vs 42 g/L in normals). Replication of this study in a larger cohort would help to clarify whether there really is no difference or perhaps the study simply lacked statistical power.

4.2.3. Broad-Spectrum Antibiotics

Malnutrition has a negative impact on wound healing and resistance to infection. In a PRCT of 302 adult surgical patients undergoing contaminated procedures, the benefit of prophylactic broad-spectrum antibiotics (clindamycin and gentamicin just prior to, 8 h after and 16 h post-procedure) on wound infection was evaluated relative to nutritional status *(93)*. With a liberal definition of malnutrition (albumin < 30 g/L, TIBC < 220 mg/dl, or weight loss $> 10\%$), 51.7% of patients were malnourished. The malnourished patients experienced reduced wound infections in response to antibiotic prophylaxis (19.7% of malnourished patients developed wound infection in the absence of antibiotic prophylaxis vs 6.2% with antibiotics, $P<0.01$). This finding was associated with a significant reduction in days of hospital stay in malnourished patients (25.0 without vs 19.5 with prophylactic antibiotics,

$P<0.05$). The patients who did not have malnutrition, however, received no significant benefit in terms of wound infection or length of stay *(93)*. This trial underscores the morbidity and health-care costs associated with malnutrition.

4.2.4. Penicillin

Penicillin is easily absorbed, not metabolized, and renally eliminated *(78,94)*. Alterations in intestinal morphology may also play a role in pharmacokinetic variability. Oral absorption of penicillin V was lower in Ethiopian children than in Swedish children. A cohort of 104 children of varying nutritional status admitted to a hospital in Ethiopia for treatment of bacterial infection were provided with phenoxymethylpenicillin 20 mg/kg orally ($n = 49$) or benzyl penicillin 30 mg/kg intravenously ($n = 37$) or procaine penicillin G 30 mg/kg intramuscularly ($n = 18$) *(95)*. The oral regimens were provided in a fasting state to 26 patients and without feeding restriction to another 23 patients. In the fasted state penicillin bioavailability was greatest for patients with kwashiorkor (83%) than for patients with marasmus (66%) or underweight (36%). In the non-fasted state bioavailability was similarly low (23–30%) regardless of nutritional status. Drug clearance was significantly lower in children who were underweight (15 mL/min·kg) or had marasmus (14 mL/min·kg), kwashiorkor (17 mL/min·kg), or combined PCM (12 mL/min·kg), compared with those with normal weight-for-age (22 mL/min·kg, $P<0.01$) beyond the influence of acute illness alone following intravenous administration. Both peak drug concentrations and AUC were similar in the few patients who received intramuscular injections. In children with severe PCM, penicillin renal clearance was reduced and half-life was increased, compared to normal controls. Both parameters normalized after nutritional rehabilitation *(78,94)*. In a small sample of eight children with kwashiorkor the plasma clearance of penicillin is reduced by 75% most likely due to a reduction in renal drug clearance *(96)*.

4.2.5. Anti-malarials

Quinine has a narrow therapeutic window and is administered orally and intravenously in the treatment of malaria. Given the great worldwide prevalence of malaria and the not infrequent co-existence of malnutrition, any alteration in drug disposition attributed to the infection and/or nutritional status would be important for optimal drug use. Following 8 mg/kg doses of intravenous quinine in an open study of 40 children (2–6 years old) with varying nutritional and infectious status, plasma concentrations of the drug were higher in malnourished children than in controls (AUC 43.5 vs 16.7 mg·h/L, $P<0.05$) *(97)*. This resulted from reductions in both volume of distribution (0.56 vs 1.63 L/kg, $P<0.05$) and clearance (1.7 vs 4.0 mL/min/kg, $P<0.05$) *(97)*. However, the protein-bound drug fraction was increased with higher plasma α_1-acid glycoprotein concentrations in the malnourished children *(97)*. These findings are not significantly different from those seen in children with malaria regardless of nutritional status *(97)*. Erythrocyte uptake of quinine, as measured by RBC:plasma concentrations, was similarly impaired in malnourished children as in those with malaria relative to controls *(97)*. These findings differ from a previous study comparing children with global malnutrition to controls in which free quinine concentrations and volume of distribution were similar between groups, and clearance was significantly higher in the PCM children following 16 mg/kg intramuscular loading dose with a subsequent dosing interval of 12 h *(98)*. Clearance was significantly greater in PCM children compared with controls (4.4 vs 2.3 mL/min/kg, $P<0.05$). The suggestion was made that the dosing interval be increased to 8 h in global malnutrition, but not if protein malnutrition.

Chloroquine pharmacokinetic parameters were measured in eight malnourished adults with mean serum albumin of 30 g/L and seven normal controls with albumin of 37 g/L *(99)*. Drug half-life and distribution were unchanged, but clearance was significantly increased. Similar therapeutic concentrations were achieved, and no increased toxicity was observed, though this trial was subject to Type II statistical error.

The presence of malnutrition increases the burden from malaria *(100)*. Among other deficits, thiamin deficiency remains a clinical problem in some vulnerable populations and is expected to predispose to infection and exacerbate acidosis seen in malaria *(101,102)*. A group of 310 patients undergoing treatment for *Plasmodium falciparum* malaria in Southeast Asia were randomized to chloroquine plus sulfadoxine-pyrimethamine or artesunate plus mefloquine or artemether plus lumefantrine *(101)*. They were also each provided with 1 mg each of thiamin, riboflavin, and pyridoxine as well as ferrous sulfate 200 mg daily *(101)*. Cure rates at day 42 were above 90% in all groups. Using the erythrocyte transketolase activity as a functional marker for thiamin deficits, 30% were identified with thiamin deficiency at baseline. Significant improvements were noted in thiamin status by day 42 and were similar across the three drug treatments although this improvement is only partly due to the supplementation regimen *(101)*.

4.2.6. ANTI-TUBERCULARS

Isoniazid is acetylated by cytosolic N-acetyltransferases predominantly in the liver. Isoniazid absorption was not impaired, but acetylation was slowed in 31 children with PCM *(103)*. The frequency of hepatotoxicity (as evidenced by transaminitis and jaundice), in a cohort of 130 children with PCM followed for 3.5 years, was increased threefold relative to normally nourished controls *(42)*. Hepatic toxicity was not significantly impacted by acetylator status *(42)*. In 13 South African children with tuberculous meningitis, baseline PCM was generally improved after 6 months treatment with nutritional supplementation and a 4-drug regimen (20 mg/kg isoniazid, 20 mg/kg rifampicin, 30 mg/kg pyrazinamide, and 20 mg/kg ethionamide) *(104)*. Isoniazid concentration and systemic elimination did not change after nutritional rehabilitation, though slow, intermediate, and fast acetylators were noted *(104)*. The differences in hepatotoxicity reported by these two studies may reflect the impact of treatment time (6 months vs 3.5 years) and statistical power derived from larger subject numbers.

In eight undernourished adults, who were free of tuberculosis, the peak plasma concentration, AUC, and protein binding of rifampicin were significantly reduced but the half-life was unchanged and renal clearance increased *(105)*. In ten other undernourished adults who had tuberculosis, the AUC and protein binding were reduced further, and GGT levels elevated *(105)*, suggesting that toxicity risk may increase with the combination of malnutrition and disease.

A pharmacokinetic study was conducted in children from Malawi being treated with pyrazinamide (35 mg/kg) or ethambutol (30 mg/kg) three times weekly for tuberculosis in addition to rifampin and isoniazid *(106)*. Both malnutrition and HIV infection were common to these children from 1–14 years of age although none were receiving antiretroviral agents *(106)*. In almost all cases C_{max} did not reach the MIC for *M. tuberculosis*. This was particularly evident for pyrazinamide in the youngest children *(106)*. There was also a non-significant trend toward lower C_{max} and $AUC_{0\text{-}24h}$ for pyrazinamide in malnourished children. A greater C_{max} for ethambutol was noted as nutritional status worsened, but $AUC_{0\text{-}24h}$ was unchanged or lower in malnourished children *(106)*. So while dosing may need to be more aggressive, care should be taken in patients with PCM. More appropriate dosing is important to clinical outcomes for children with tuberculosis.

4.2.7. SULFADIAZINE

Sulfadiazine is 50–55% bound and acetylated in the hepatic cytosol *(78,94)*. In six children with PCM, the rate of drug absorption was reduced, as evidenced by peak blood levels occurring 4–8 h later than in normally nourished controls. Free drug was eliminated at normal rates but acetylated drug elimination was reduced, likely due to limited biotransformation in the malnourished liver. In six undernourished adults *(107)*, sulfadiazine absorption and renal excretion were unchanged, though its metabolism was increased and protein binding reduced (40% vs 54% in normal controls). Therapeutic doses were achieved, however; so specific monitoring was not recommended *(107)*.

4.2.8. TETRACYCLINE

Tetracycline is not biotransformed and is excreted as free drug in the urine *(108)*. Tetracycline pharmacokinetics in eight malnourished adults was compared to six well-nourished controls *(108)*. Oral drug absorption was reduced, and the elimination rate increased *(108)*. The authors proposed reduced protein binding (albumin was significantly lower in the malnourished) as the most likely mechanism, and suggested a more frequent dosing interval in order to obtain therapeutic drug concentrations *(108)*.

4.3. Anti-gout

The impact of dietary protein and caloric intake on the clearance of allopurinol and its metabolite oxypurinol has been examined in a series of small cross-over studies of normally nourished men. Caloric intake had no significant impact on allopurinol or oxypurinol clearance, with observations ranging from 2600 kcal *(109)*, 1600 kcal *(110)*, and 400 kcal *(111)*. Allopurinol clearance also was not impacted by protein intake, but oxypurinol clearance was reduced during periods of limited protein intake *(109–112)*. Protein intake ranged from 0–3 g/kg/d. Clearances of inulin, creatinine, and oxypurinol were reduced on the low-protein-diet treatment (0–0.3 g/kg/d) vs higher protein intake (1.5–3 g/kg/d). No changes in allopurinol absorption, metabolism or excretion were noted, but the clearance of oxypurinol was greatly reduced on the low-protein arm *(112)*, and its half-life increased *(110)*. While these four studies each involved a small number of subjects

(5–7 each) and were conducted by the same group, the consistency of the data is encouraging, and suggests increased risk of toxicity with allopurinol use during periods of limited protein intake.

4.4. Chemotherapeutic Agents

Malnutrition often exists in patients with cancer for many reasons. Whether related to the tumor and its treatment or not, malnourished patients tolerate chemotherapy poorly and have a worse prognosis compared to those in better nutritional status *(113)*. Poor recognition of differences in pharmacokinetics and pharmacodynamics of agents used to manage solid or liquid tumors may contribute to less than optimal management of these patients. Given the narrow therapeutic index for many agents, it makes more sense to dose the drug based on systemic exposure in an individual rather than based on body weight. Many traditional agents used to manage malignancies have been dosed based on body weight or body surface area. However, the data would suggest that dosing based on patient-specific variables (including genetic polymorphisms and nutritional status) makes more sense *(114)*.

No data are available on absorption of chemotherapeutic medication in patients with PCM. From the standpoint of distribution, drugs that are highly protein bound may pose a higher risk for toxicity (assuming no change in drug clearance) in patients with PCM given reductions in plasma protein concentrations. This would include etoposide and teniposide as well as cisplatinum and paclitaxel *(113)*. The elimination half-life of methotrexate is prolonged in undernourished patients compared with well-nourished patients *(115)*. The cardiotoxicity of the anthracyclines may be increased in malnutrition *(116)*.

4.5. Gastrointestinal Agents

The impact of a 7-day, 1000-kcal deficit, 0.3 g protein/kg diet on pharmacokinetics of a single dose of intravenous cimetidine was measured in a cross-over design with a group of five normal volunteers *(117)*. While cimetidine renal clearance was unchanged, fractional excretion of the drug was significantly increased, suggesting net tubular secretion of the drug during the protein- and calorie-restricted diet.

4.6. Immunosuppressants

In children/adolescents requiring cyclosporine for renal transplantation there were significant pharmacokinetic differences based on nutritional status *(118)*. The $AUC_{0-\infty}$ was 52% lower in malnourished patients compared with the well-nourished individuals following a single 3 mg/kg oral dose of cyclosporine which was likely related to the expanded volume of distribution in the malnourished patients (11.1 vs 4.6 L/kg, $P<0.04$) *(118)*. This greater volume of distribution may be accounted for by a relatively larger proportion of body weight as lean mass to which the circulating drug distributes to and binds with *(118)*. These data suggest that a larger loading dose would be needed in poorly nourished children/adolescents, but should be based on individual pharmacokinetic parameters to avoid subtherapeutic or toxic levels.

Although patients requiring maintenance hemodialysis are often poorly nourished, a small study comparing etanercept pharmacokinetics in a group of hemodialysis patients to a group of patients with psoriasis did not find any significant differences *(119)*.

5. LIMITATIONS OF CURRENT DATA

The greatest limitation in currently available data is the dearth of trials comparing the impact of malnutrition on drug action, which leaves health-care providers with limited evidence on which to base practice decisions. Many available studies have examined antibiotics, such as chloramphenicol and tetracycline, that are less commonly used today – while a broad spectrum of newer drugs are in current use with virtually no data on the impact of malnutrition on their action.

The quality of clinical trials is somewhat limited. For ethical reasons, prospective randomized controlled trials of a drug vs placebo in a malnourished cohort with an indication for the drug in question cannot be undertaken. Thus available data are largely from case–control or open-label observations, study designs that are prone to bias. Since both malnutrition and infection can independently impact hepatic protein synthesis and fluid shifts, a further confounder is the impossibility to evaluate independently the impact of infection from that of malnutrition. A further difficulty is finding large enough cohorts of patients with similar degrees of malnutrition to power a comparison of one drug to another.

In the realities of clinical practice, malnutrition proceeds along a continuum that begins with mild, short-term deficits and can progress to severe, protracted losses of fat, muscle and organ function, ending in death. The preponderance of data regarding malnutrition and drugs is from these more extreme degrees of PCM. The few studies with underweight but not wasted children and with critically ill adult patients in conditions of severe metabolic stress suggest that drug distribution and metabolism may be impacted by lesser degrees of malnutrition. Thus we have limited data on which to make decisions about the risk and effectiveness of drug therapy, based on malnutrition.

For clinical purposes, it would be most helpful to see future evaluation of medications using malnutrition stratifications by universally accepted standards, such as the CDC and WHO standards for children and BMI categories for adults. Clinical trials and bedside practice will continue to use height and body weight as surrogates for the much more difficult to obtain body composition measures of metabolically active tissue.

Simple, inexpensive, and rapid feedback methods for monitoring drug concentrations in the field or primary provider's office would be very helpful in high-risk patients.

6. FUTURE RESEARCH NEEDS

Clinical trials with pharmacokinetic modeling of representative members of drug classes are needed in large patient groups with varying degrees of protein and calorie malnutrition. Trials are also needed in cases with single nutrient deficiencies, particularly those with impact on major metabolic pathways.

Animal experiments should be undertaken with measurement of total body water, fat, and protein compartments during PCM and various levels of obesity – to clarify some of the difficult questions regarding drug distribution, sequestration into body compartments, and protein binding. Animal models also could provide a clean experimental evidence base for drug handling during single nutrient deficiencies.

Studies should be considered in subjects with primary malnutrition and in those with secondary malnutrition. Serum albumin is not a good indicator of PCM in drug metabolism studies *(50)*.

Since critically ill patients in current hospital practice have considerable rates of nutritional risk at admission, and nutritional status can worsen during prolonged hospital care, pharmacokinetics studies are indicated in patients with varied levels of metabolic stress so that the concurrent impact of nutritional status on drug effectiveness can be evaluated. Data on the impact of concurrent feeding with enteral or parenteral nutrition therapy in patients with various levels of malnutrition and clinical stressors are sorely lacking and have the potential to radically change medical practice.

Whether the addition of sulfur-containing amino acids (especially cysteine) to a regimen will minimize the impact of PCM on drug disposition remains to be tested in humans. The rationale, based on observations in animal models, is that cysteine and/or glutathione may be required for mRNA levels and expression of select CYP isoenzymes and GST either directly or indirectly by scavenging reactive oxygen species *(60,120)*.

7. CLINICAL RECOMMENDATIONS

First and foremost, all patients who are ill enough to require medications should be screened for malnutrition, using standard parameters. The components of this evaluation, as a minimum, should include evaluation of body weight relative to standards, of serum protein status, and of the likelihood of nutrient deficiencies due to dietary practices. Since all health-care facilities in the United States are required to have a process in place for nutritional screening, it may be possible to obtain a report from the facility's systematic evaluation of patients who are at nutritional risk.

Second, the available research is fairly consistent at recommending the advisability of monitoring for drugs with a narrow safety profile in high-risk patients due to their malnutrition. With the huge prevalence of malnutrition in various disease states (cancer, HIV, geriatrics, to name a few) and clinical settings (intensive care units, skilled nursing facilities, nursing homes, chemotherapy centers), this could be an arduous task. To be successful in this effort, inexpensive and widely available drug monitoring systems for field, clinic, and even home use will need to be developed.

Clearly, since malnutrition alone can lead to death, we should maximize our efforts to minimize time delay in using medications effectively in patients with concurrent malnutrition. A better understanding of the influence of nutritional status on drug disposition and effect would go a long way toward effective clinical management.

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7

Influence of Overweight and Obesity on Medication

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Objectives

- Define and describe the prevalence of overweight and obesity.
- Explain how obesity can impact on drug absorption, distribution, clearance, and effect.
- Provide a compilation of findings regarding the impact of obesity on specific drugs.

Key Words: Body weight; clearance; composition; distribution; obesity

1. INTRODUCTION

Providing appropriate therapeutic drug monitoring requires an understanding of factors that influence drug disposition and effect. In order to make better use of invaluable medication, altered effects of a drug need to be explained or, better yet, predicted prior to use. There are many potential sources of variability that account for differences in drug response between patients. These may include age, gender, and genotype, as well as disease states – both acute and chronic. Included in the latter are states of altered nutritional status. A better understanding of the influence of obesity on drug disposition and drug effect may lead to more measured use of medications in this group of individuals.

1.1. Definitions and Prevalence of Obesity

Obesity is a chronic disorder with a complex pathophysiology involving genetic and environmental factors, which ultimately impact the balance between energy intake and expenditure, and manifests as excess body fat. It is associated with significant risk of morbidity and mortality, as well as increased health-care costs and reduced quality of life. Morbidity includes diabetes which has seen a 61% increase in prevalence over the last 10 years and is expected to accelerate as the obesity epidemic continues *(1–4)*. Obesity is considered a major risk factor for

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coronary heart disease and the second leading cause of preventable death in the United States after tobacco use *(4–6)*. The risk of comorbid disease (e.g., diabetes, heart disease, hypertension, dyslipidemia) is tied to the degree of obesity.

Excessive body weight is best described by the body mass index (BMI) – an expression of an individual's weight relative to their height – in kilograms per meter squared (kg/m^2). The BMI cutpoint defining overweight is 25 kg/m^2 and for obesity is 30 kg/m^2 *(7)*. Obesity, as a disorder of excess body fat (including that stored in the midsection), is best defined in terms of the BMI in combination with waist circumference for adults *(8)*. The BMI and waist circumference are closely linked to health risks associated with overweight (BMI $\geq$ 25 kg/m^2), obesity (BMI $\geq$ 30 kg/m^2), and morbid obesity (BMI $\geq$ 40 kg/m^2) *(9–12)*. Morbidity increases at a BMI of 25 or greater, although this may vary with specific populations. The BMI has been adequately compared to direct measurements of body composition *(13,14)*. Definitions of obesity used in drug investigations often rely on an arbitrary weight cutoff relative to an idealized weight (e.g., actual weight $\geq$ 120% of "ideal" weight). This can be problematic without a standard definition or a substantiated reference weight that could provide a more rational basis for classifying individuals in these studies. An evaluation of various reference weights is discussed further in the next section.

Definitions of obesity in children have been less well defined but proposed age- and gender-specific cutoff values for BMI linked to adult definitions have been developed *(15,16)*. The recent gender-specific BMI-for-age growth curves for those aged 5–19 years can be useful as an appropriate reference particularly as the curves are aligned with adult cutoffs for overweight and obesity at 19 years of age *(16)*. These take into account the changes in BMI distribution with age, therefore age-specific percentiles are used to define overweight and obesity in children. The term overweight in children is defined as a BMI between the 85th and 95th percentile, which is indicative of health risks that vary with multiple factors including body composition *(17)*. When the BMI is $\geq$95th percentile the fat mass of the body is high and defines obesity, with the term severe obesity suggested for those at the 99th percentile *(17)*. When BMI is <85th percentile the fat mass is not likely to pose a health risk *(17)*. The issue in children revolves around how much adiposity is necessary for, and at what point is it excessive during, growth. The linking of percent body fat data with BMI allows for study of relationships between body composition and morbidity in children *(18)*.

Using these definitions, the prevalence of obesity continues to climb across all age groups. Current estimates are that 66% of American adults are overweight (34%) or obese (32%) *(19–21)*. This translates to well over 100 million adults in the United States making it the most prevalent chronic disease. Morbid obesity (BMI $\geq$ 40), associated with the most severe adverse health consequences, has nearly tripled to about 5% in the last 10 years *(20–22)*. And central obesity occurs in 38% of men and 60% of women *(23)*. Both overweight and obesity are also highly prevalent in children and adolescents with rates continuing to rise *(24,25)*. The rates of obesity are reported to be approaching 17% in older children and adolescents in the United States *(25)*. The NHANES data suggest that childhood obesity has doubled, while the rates have tripled for adolescents in a span of 20 years *(26)*. This trend of increasing prevalence of obesity in adults and children is present outside the United

States as well *(27–30)*. Assuming that the trend continues it has been estimated that 75% of adults will be overweight or obese and 24% of children/adolescents will be obese by the year 2015 *(25)*.

Given the higher risk of morbidity in obese individuals, they continue to have higher health-care needs including the wide use of medication. Although the influence of obesity on morbidity and mortality is well described, the influence on drug disposition and effect is not – especially in the absence of regulatory requirements to do so. The difficulty in addressing appropriateness of medication regimens in obese patients is in part based on limited drug-specific data and on varying clinical approaches to describing or even recognizing obesity.

1.2. Assessing Body Weight for Drug Dosing

While not perfect, the most valid and practical indicator of overweight and obesity is the BMI. This tool gained universal approval and was recommended for use in determining body habitus and risk for morbidity and mortality a number of years ago *(31,32)*. BMI is the best predictor of the effect of body weight on health risks but is not easily adapted, and therefore has been considered of little practical use, for the dosing of medications. While weight-based dosing of a drug is less likely to be problematic at a BMI $< 25–30$ kg/m^2, in obesity the use of a patient's actual (i.e., total) body weight may be inappropriate and can increase the risk of adverse effects. But something as basic as which weight measure should then be used for weight-based drug dosing in obese individuals has been fraught with controversy. Numerous dosing terms and predictive equations have been used (Table 1). Their use in pharmacokinetic studies has been reviewed *(33)*. The term *dosing weight* is universally acceptable whether referring to an actual total body weight or an alternative body weight – as one would consider in volume-overloaded or obese patients. The derivation of the best dosing weight for use in obesity is unclear. Adjusting a body weight for dosing in obesity will depend on the substance being evaluated or dosed (e.g., creatinine, nutrient, drug) and how it is handled differently, if at all different, in obesity. Dosing may be based on the total body weight (TBW) or on the lean body weight (LBW) or on some adjusted weight in between LBW and TBW depending on the drug. A body size descriptor should take account of age and ethnicity in addition to height, weight, and gender and remain robust at extremes for each variable *(33)*. The body weight terms described below refer to their original descriptions as summarized in Table 1 *(34–39)*. The reader is encouraged to appreciate the differences between the equations by calculating each body weight term using their own data.

The life insurance industry's actuarial tables, from the earliest versions to those of 1983, are the source of the terms "ideal" and "desirable" body weight. They were derived from data as collected beginning in the 1930s on low-risk, otherwise healthy, young persons able to afford life insurance *(40–43)*, a time when the association between excess body weight and premature death was recognized *(30)*. These data from a limited population sample describing an "ideal" or "desirable" weight for a given height are also reflected in a simple to use regression equation derived from those tables *(34)*. The weight for height provided in the insurance tables or by the equation based on those tables is not an "ideal" to be

Table 1
Equations for Estimating Body Weights *(34–39)*

Body Weight Term	*Equation for Men*	*Equation for Women*
Ideal Weight	52 kg + 1.9 kg/in > 5 ft	49 kg + 1.7 kg/in > 5 ft
Optimum Weight	106 lbs + 6 lbs/in > 5 ft [48.2 kg + 2.7 kg/in > 5 ft]	100 lbs + 5 lbs/in > 5 ft [45.5 + 2.3 kg/in > 5 ft]
Lean Weight	50 kg + 2.3 kg/in > 5 ft	45.5 kg + 2.3 kg/in > 5 ft
Predicted Normal Weight	(1.57)(kg) – (0.0183)(BMI)(kg)	(1.75)(kg) – (0.0242)(BMI)(kg)
Body Cell Mass	$(kg)\,\frac{[79.5 - (0.24)(\mathrm{kg}) - (0.15)(\mathrm{y})]}{73.2}$	$(kg)\,\frac{[69.8 - (0.26)(\mathrm{kg}) - (0.12)(\mathrm{y})]}{73.2}$
Lean Mass	(1.1013)(kg) – (0.01281)(BMI)(kg)	(1.07)(kg) – (0.0148)(BMI)(kg)

kg = kilogram of body weight, in = inches, ft = feet, lbs = pounds, y = years of age, BMI = body mass index in kg/m^2

aimed for, is unrelated to TBW, and is not representative of the general population. The weights based on these tables do not take physiology into account, expecting the same weight for all individuals of the same height, and is not necessarily of any value to drug dosing in obese patients. Additional predictive equations for "optimum" body weight and for "lean" body weight have been described and continue to be widely used *(35,36)*.

The "optimum" body weight equation was described for diabetic persons with a medium-sized frame for use in determining an approximate caloric requirement *(35)*. The suggestion was made to increase by 10% for patients of "heavy" frame and decrease by 10% for those of a "light" frame *(35)*. As can best be determined, this equation is empirically derived but considered adequate for its intended purpose in clinical practice. A role for improving drug dosing in obesity has never been described.

In a case report discussing gentamicin toxicity, the size of the daily dose as a function of body weight was described *(36)*. The weight used to estimate creatinine production was critical in determining creatinine clearance and hence drug dosing. The suggestion was made to use "lean" body weight, with obese patients requiring an adjustment in TBW to derive their lean weight, based on an empiric equation. This equation is one of the most frequently cited for determining a patient's "lean" body weight despite not being based on any actual subject measurements *(34,36)*. The "optimum" and "lean" body weight values derived through these two equations have in recent years been referred to as "ideal" body weight. However, the very concept of "ideal" body weight was questioned years ago in well-supported and valid critiques *(32,44,45)*.

Even though "ideal" body weight may correlate with BMI in overweight and possibly in level I obesity (BMI 30–34.9 kg/m^2) this has not been shown true at all levels of obesity *(46)*. But more to the point, if the purpose is to (1) define a reference "normal" weight with which to compare obese individuals and to (2) derive proposed dosing adjustments for obese subjects, then several factors beyond height and weight need to be considered. To be of most value, a reference weight should be based on actual height/weight data from a representative sample of the entire population or, better yet, be based further on the body composition of such a reference sample. External measures of obesity (i.e., BMI) remain more practical than obtaining body composition data; however, the latter should be used to better define parameters in studies of drug disposition. Body composition is likely much more important for the purpose of drug dosing than height and weight alone. Age and gender influence body composition and should be taken into account in determining "normal" expected body weights. Age and gender influence lean tissue which in turn influences metabolic rate *(38)*. Having designated the term "ideal" body weight as an inappropriate reference point for patients, a focus on lean body mass in its place is needed.

Equations for lean body mass and body cell mass from body composition data have been described that take into account age and the greater absolute lean body mass found in obese patients *(38,39)*. A proportion of the sample populations used to derive these equations were in fact obese, although the numbers of morbidly obese patients were small *(47)*. It has been suggested that the lean body mass equation *(39)* may underpredict true lean body mass of the morbidly obese subject *(47)*. This may require revisiting the data in order to re-adjust the constants *(47)*. Regardless, this remains the only equation that takes fractional fat mass and BMI into account. It is proposed that this equation best reflects lean body mass – until further body composition analysis yields a more accurate predictive equation or population-specific equations *(48)* – and that lean body mass serves as the best predictor of drug dosage *(49)*. So the lean body mass from this equation will be used as the reference standard, for the true LBW, on which to compare TBW between obese and non-obese individuals. For the purposes of understanding drug disposition use the lean body mass equation either in its original format (Table 1) or the more condensed form below *(50)*, where TBW is the total body weight in kg and Ht is the height in cm:

$$\begin{array}{ll} \text{Men} & :(1.10)(\text{TBW}) - (128)(\text{TBW}/\text{Ht})^2 \\ \text{Women} & :(1.07)(\text{TBW}) - (148)(\text{TBW}/\text{Ht})^2 \end{array}$$

Another similar equation developed from a large sample size with wider weight range has been suggested for prospective evaluation. This has been referred to as predicted normal weight (PNW) as a means to exclude excess fat mass *(37)*. It is hoped that improved equations will be developed based on more recent data from a more diverse population coincident with body composition. This data may be available from a broad national sample *(51)*. Such body composition data may be helpful in addressing the dosing issues of obese individuals. Depending on body composition the distribution of a drug under study can be identified and corrections to body weight can be inferred. In this way a dosing weight is based on the characteristic behavior of the drug rather than relative to a standard weight for height. Dosing weight correction factors have been used to adjust body weight to a value between the TBW and the LBW for dosing, although most have not been systematically studied. The general equation often used to adjust body weight is

$$\text{DW}_{\text{OB}} = \text{LBW} + (\text{CF})(\text{TBW} - \text{LBW})$$

where DW_{OB} is dosing weight for obesity, LBW is the lean body weight, CF is a correction factor, and TBW is the total body weight. The LBW will vary depending on the method used to determine it – but again the lean body mass equation is suggested *(50)*. After all, the distribution of body fluid is related to the lean body mass, and overall metabolic activity is also associated with the lean body mass. If a single dosing weight correction factor is used for all obese patients, instead of being individualized to the drug being administered, some drugs may be significantly underdosed while others may be given in overdose. The correction factor is a fraction of the "fat" weight (i.e., beyond LBW) that normalizes the volume of distribution in an obese patient to that in a non-obese patient. Dosing is then based on the excess weight beyond the predicted LBW that a drug's pharmacokinetic characteristics are best correlated with. This relationship is rarely, if ever, evaluated against a patient's actual lean body mass.

What was not recognized early on, and has carried forward virtually unaddressed by continual use of "ideal" body weight, is that not only is "ideal" body weight not necessarily physiologic but that excess weight in obesity is more than just adipose tissue and the composition varies between obese subjects. Unfortunately, there is not an abundance of body composition data. In general, non-obese, middle-aged adults have a fat mass of about 20 kg that corresponds to about 25% of TBW in men and about 33% of TBW in women. Obese individuals have, on average, a larger lean body mass than their non-obese peers, accounting for 20–40% (mean 29%) of the excess weight in obesity *(52)*. In other words, only 60–80% of the excess weight in obesity may be adipose tissue. A description of body composition for a much larger population provides additional data *(53)*. These were otherwise healthy subjects with BMI values between 15 and 35 kg/m^2. While BMI rises with age from 20 to 70 years, a slight decrease was seen in the 70- to 80-year-old age bracket in this cross-sectional study. Fat mass increased in absolute value as well as a percentage of body weight with age up to 70 years as did the BMI. The use of fat mass corrected for height (i.e., fat mass index) might allow use as reference values. Furthermore, the numerous adipose tissue compartments have been characterized using DEXA, MRI, and MRS and may also have age- and gender-dependent patterns *(53,54)*. It may even be possible to distinguish adipose tissue composition phenotype at a specific compartment *(55)*.

Unfortunately, most pharmacokinetic studies in obesity make use of predictive equations without the benefit of actual body composition data (i.e., not physiologically based). In dosing medication, most clinicians make general assumptions for the dosing weight in obese patients focusing on the excess fat. But it is the lean body mass that correlates well with total body water – including the central compartment, metabolic activity – and can be correlated with drug clearance. Clinicians need to keep in mind that obesity can influence the tissue distribution of a drug, its clearance, and its clinical effect. However, this occurs not simply because of excess fat mass but due to other physiologic changes. This might then translate into modified dosing strategies for initial doses and maintenance doses. This is especially important for medications for which minimal effective concentrations or narrow therapeutic indices exist.

Although from a practical standpoint medications that follow weight-based dosing in adults warrant important consideration in obesity, understanding the broader impact of obesity on drug disposition and effect to explain or predict drug effects in obesity is stressed in the remainder of the chapter.

2. BASIC SCIENCE

A review of how obesity impacts drug absorption, distribution, metabolism, excretion, and action should be based on the available science. It is interesting to note the discrepancy that exists across the study of obesity. Despite major improvements in the understanding of the societal, economic, pathologic, and clinical outcomes of obesity, there remains only limited study of pharmacokinetics and pharmacodynamics in this disorder at the current time *(50,56)*. One should understand that it is not a simple task in any human study to clinically assess pharmacokinetics and pharmacodynamics. In hepatic drug metabolism, for example, blood flow, protein binding, and tissue binding are each important factors that need to be taken into account and are also each difficult to assess. Many of the assumptions made may not always be accurate for obese individuals.

In fact, persons with obesity can be considered quite a heterogeneous group. Subjects with a BMI of 30–35 may be quite different than those with a BMI of 45 and greater. A given BMI cannot differentiate the degree of fatness between individuals *(57,58)*. Indeed within a group of individuals at the same BMI there may be differences in body composition that ultimately influence drug distribution and clearance. These physiologic factors among others make for difficulty in modeling drug disposition in obesity.

Variability in fat mass may occur with a number of factors. Fat mass increases as an individual ages. Gender is also a factor with women having higher body fat mass than men in general. Inactive individuals are likely to have higher fat mass than those who are more active. Ethnicity can also be a factor with individuals of Native American, Latin American, and Asian heritage more likely to have higher percent body fat than European Americans, which in turn may have higher percent body fat than Africans or Polynesians *(58–61)*. Percent body fat may differ between individuals of the same BMI *(58,59)*. Even the anatomic distribution of that fat (subcutaneous, visceral, intermuscular), including the blood flow to those depot sites, may vary by gender and ethnicity *(62,63)*. Each of these variables will need to be accounted for in future studies of the influence of obesity on drug disposition and effect. Anatomic and physiologic changes that occur with obesity may impact on a drug's absorption, distribution, and elimination through metabolism or excretion.

2.1. Absorption

Altered gastrointestinal transit time and a higher splanchnic blood flow may modify drug absorption including a reduction in the bioavailability of drugs with high extraction ratios. However, the limited data suggest that oral drug absorption, including drugs with higher extraction ratios, may be no different in obese individuals (e.g., cyclosporine, dexfenfluramine, midazolam, penicillin, propranolol) *(64–67)*. Absorption from transdermal or subcutaneous administration is not well characterized in obesity. Depending on needle length and local fat depot mass, intramuscular injection in many cases may be better characterized as intralipomatous, which has not been well studied either.

2.2. Distribution

The distribution of a drug throughout the body following absorption from the site of administration is determined by several factors – some related to the drug (e.g., lipophilicity, degree of ionization), others related to the body (e.g., blood flow, tissue-binding sites). Plasma protein binding, body composition, tissue size, tissue permeability, and drug affinity for various tissues each determine a drug's distribution. Knowledge of body composition, regional blood flow, and plasma protein binding is necessary.

2.2.1. BODY COMPOSITION

Once considered a passive depot to store excess lipid, it has become clear that adipose tissue is a metabolically active tissue, one of the body's largest endocrine organs with complex functions *(68,69)*. Obese subjects have a larger fat mass and a larger lean body mass in absolute terms compared to non-obese individuals of the same age, height, and gender. In relative terms, lean tissue as a percent of TBW is reduced while percent adipose tissue mass is increased. In other words, not all the excess weight in obesity is made up of fat compared to the non-obese individual. The extra lean tissue makes up about 20–40% of the excess weight, about 29% on average across a BMI range of 29–47 kg/m^2 *(52)*. This increase in lean body mass does not hold for patients with obesity associated with Prader–Willi syndrome or Cushing's syndrome *(52)*. Weight-based drug dosing would need to take into account the relative distribution into various tissue compartments. Total body water in obesity was estimated to include approximately 30% water content in adipose tissue *(70)*. This again likely reflected the 30% extra lean tissue of the excess body weight in obesity. Although lean body mass may be determined through bioelectrical impedance analysis or whole body densitometry, neither of these is yet clinically practical across all settings. An equation that at least takes gender, weight/height, and BMI into account allows a reasonable estimate of lean body mass (*see* Section 1.2). Still the partition of a drug into adipose tissue may vary by body region *(71)*.

2.2.2. Blood Flow

There are increases in blood volume, cardiac output, and organ mass in obesity that also can influence drug distribution. Cardiac output increases to meet the increased peripheral blood flow to tissues, while specific flow remains unchanged. The proportion of cardiac output that reaches the adipose tissue is relatively small (~5%) compared with the blood flow to lean tissue and viscera and might be reduced further with increasing degrees of obesity *(72–74)*. Adipose blood flow may actually be less in morbidly obese individuals compared to the moderately obese or thin *(75)*. It appears that angiotensin II plays a significant role in regulating blood flow to adipose tissue *(76)*.

2.2.3. Protein Binding

Drugs can bind to several circulating proteins – albumin, α_1-acid glycoprotein, and the lipoproteins. Albumin concentrations do not appear to be altered as a result of "moderate" obesity while α_1-acid glycoprotein levels are increased *(77)*. This suggests an inconsistent alteration in drug affinity in obese individuals. The influence of obesity is more likely on α_1-acid glycoprotein than on albumin, thereby decreasing the unbound fraction of basic drugs in some but not all instances *(77–79)*. Drugs bound to α_1-acid glycoprotein may exhibit lower free drug concentrations (e.g., propranolol) or no change in free drug levels (e.g., triazolam, verapamil), while the free levels of drugs bound to albumin do not appear to change (e.g., phenytoin, thiopental). Despite little difference in serum albumin concentrations in obese individuals there may be increased binding of fatty acids to the albumin molecule, thereby potentially altering drug-binding sites. The clinical significance of any changes is unclear. The associated tissue binding that may determine the clinical relevance of alterations in unbound plasma drug is not known. There is a balance of drug affinity between tissue components and plasma proteins that ultimately determine clinical significance. Alterations in the concentration of, or affinity for, plasma proteins may influence drug availability to the tissues where it may be active or may instead be cleared. It may come down to the competition between a drug's binding characteristics in vivo between lean tissue, transport proteins, and adipose tissue. Lipoprotein levels can also be elevated in obese individuals potentially impacting on pharmacokinetics and effect (e.g., cyclosporine) *(80,81)*. The potentially altered tissue perfusion and tissue binding has not been well studied in obesity.

2.2.4. Summing up Distribution

It may be expected based on body composition that lipophilic drugs have a larger volume of distribution (V_D) in obese patients. While this is sometimes the case (e.g., bisoprolol, diazepam, thiopental), it is not always so (e.g., cyclosporine, digoxin, procainamide). Hydrophilic drugs may actually have a larger V_D (e.g., aminoglycosides, ampicillin, cefamandole, cefotaxime, ciprofloxacin, nafcillin) or a similar V_D (e.g., cimetidine, ranitidine) in obese patients. A point to remember is that a drug's lipophilicity, based on its oil-to-water partition coefficient, is only one of several characteristics of a drug and unlikely to be the single driving factor to overcome the other factors (e.g., blood flow, in vivo binding competition) in determining drug distribution on its own *(82,83)*. Lipophilic agents do not necessarily have larger distribution volumes in obese individuals and some may not even be stored in adipose tissue *(84)*. Distribution of a hydrophilic drug into adipose tissue or into the excess lean tissue that supports the excess fat mass may need to be taken into account for dosing. Most hydrophilic drugs distribute to a limited degree into excess adipose tissue, but may more likely distribute into excess lean tissue. Besides increases in fat and lean body mass, obesity is associated with increases in organ mass, cardiac size and output, blood volume and regional flow. Even polar compounds may not behave similarly with regard to volume of distribution and body weight *(83)*.

Antipyrine distributes into body water and exhibits a slightly higher absolute V_D in obese subjects (predicted by a higher *absolute* body water in obese subjects), but significantly reduced V_D when corrected for TBW (predicted by a lower *relative* body water) *(46)*. This important point suggests that comparisons of drug distribution between obese and non-obese individuals should be done on the basis of TBW, that is, the volume normalized to TBW rather than the absolute V_D. A decreased V_D when normalized to TBW indicates a drug that distributes less into the excess adipose tissue. This indicates that antipyrine distributes into the excess body weight above the estimated LBW by a factor of 30% which incidentally correlates with estimates of excess lean tissue in obesity. Ethanol also serves as a marker of total body water. In subjects receiving ethanol 0.4 g/kg intravenously the V_D varied with BMI; from 0.7 L/kg at a BMI of 19 kg/m^2 to 0.45 L/kg at a BMI of 32 kg/m^2 *(85)*.

Development of physiologically based pharmacokinetic/pharmacodynamic models specific for obesity in adults and children have been identified as a need based on the scant available data *(86)*. Compartmental modeling using simultaneous markers of various volume spaces may be necessary to describe the true distribution of drugs in obese individuals regardless of the drug's lipophilicity.

Furthermore, developing physiologically based pharmacokinetic models taking into account each adipose compartment could be invaluable. Regional adipose tissue differences in blood flow have been evaluated in non-obese subjects *(87)*. Based on work in laboratory animals rate constant changes in models cannot be predicted based on the amount of adipose tissue alone *(88)*. The distribution kinetics of theophylline based on a 3-compartment model was simultaneously compared with two reference compounds – urea and inulin, whose distribution volumes represent total body water and extracellular fluid, respectively *(89)*. This animal study demonstrated that theophylline had a preferential binding for tissue, with a tissue:intracellular water partition ratio >1. A similar model enabled accurate prediction of antimicrobial pharmacokinetics in edible tissues of an animal produced for human consumption *(90)*.

2.3. Elimination

The elements that determine elimination of a drug, whether through metabolism or excretion, may be altered in obese individuals. Increased cardiac output, fatty infiltration of the liver, portal inflammation and fibrosis, increased renal plasma and creatinine clearance are all known to occur in obesity *(91–93)*. Additionally adipose tissue itself must be considered metabolically active *(68)*. Metabolism-associated genes may be differentially expressed in obese compared with non-obese individuals *(94,95)*. The metabolic activity may vary between adipose tissue compartments (i.e., omental, subcutaneous) *(96,97)*. So the obesity phenotype may also be a factor in drug disposition.

2.3.1. HEPATIC

The fatty infiltration of the liver could affect hepatic metabolic activity. Fatty infiltration of the liver is more severe with increasing BMI and may impact on the organ's metabolic activity. Using antipyrine as a marker of hepatic oxidative enzyme function, drug half-life was increased in obese individuals compared to lean volunteers *(98)*. However, this was due to an increased apparent V_D, while no change in drug clearance (Cl) was observed *(98)*. The V_D for antipyrine corrected for TBW is significantly reduced in obese patients given distribution limited to lean tissue (described in Section 2.2.4) *(98)*. Given the multiple pathways by which antipyrine can be metabolized it is not clear whether there is actually no change in activity of any specific pathway or whether the measured effect is the resultant net effect across isoenzyme pathways – some increased, others decreased. Drugs which undergo significant first-pass hepatic extraction appear to have similar rates of Cl in obese compared to non-obese individuals indicating that hepatic extraction is not dependent on body weight. Some, but not all, drugs that undergo hepatic oxidation and conjugation may have increased Cl in obesity.

Hepatic drug Cl through phase I metabolic reactions may be increased (e.g., prednisolone), decreased (e.g., methylprednisolone, triazolam), or unchanged in obesity. This variability may be explained by specific enzyme activity. For example, the activity of CYP2E1 may be increased (e.g., chlorzoxazone), while CYP3A activity may be reduced or unchanged (e.g., erythromycin, cortisol) as body mass increases in obesity *(99–103)*. Markers for specific CYP isoenzymes will be necessary to differentiate the impact of obesity on each of them. Based on caffeine as a marker of CYP1A2, there appears to be no difference in activity of this isoenzyme between obese and non-obese individuals *(104)*. All told, there remain very little isoenzyme-specific data.

Some phase II metabolic reactions may be altered. The activity of both glucuronide and sulfate conjugation appears to increase in obese individuals and may impact on drug clearance (e.g., lorazepam, oxazepam) *(105,106)*. On the other hand, activity of glycine conjugation or of acetylation does not appear to be altered by obesity *(107,108)*. Adipose tissue itself possesses metabolic capacity which may be increased based on the larger fat mass. While the findings of altered metabolic enzymes from animal models of obesity are many, the extrapolation of each unique model (e.g., overfeeding vs genetic defect) to the human condition is considered poor *(109,110)*. Based on animal data the significantly reduced $AUC_{0-\infty}$ with a significantly higher V_D and Cl of chlorzoxazone in obese compared with non-obese animals suggests that obesity increases CYP2E1 activity not only in the liver but in adipose tissue as well *(95)*.

2.3.2. RENAL

While using actual body weight may overestimate creatinine clearance predictions, and the empirically derived "ideal" body weight underestimates it, a weight based on a 30% adjustment (correction factor) appears to be the best predictor, although requiring prospective confirmation *(111)*. This reflects the more metabolically active lean tissue, the source of creatinine, rather than renal capacity. Generally, renal drug clearance can be increased in obesity (e.g., aminoglycosides, cefamandole, cefotaxime, cimetidine, ciprofloxacin, lithium, procainamide). This is partly a result of increased glomerular filtration, while indirect evidence suggests that tubular secretion is also increased, thereby further affecting renal drug clearance in obesity *(108,112–114)*. Increased drug clearance is due to increased tubular secretion (e.g., cimetidine, ciprofloxacin, procainamide) and reduced tubular reabsorption (e.g., lithium). Increases in glomerular filtration as measured by creatinine clearance can be increased in obese individuals *(93,115,116)* but have also been reported to be unchanged in some obese patients *(112,117)*. The reasons for this discrepancy are not clear but may relate to variability in body composition (i.e., actual lean body mass) and in renal dysfunction among the various obese subjects and patients.

2.4. Drug Effect

Even after taking any pharmacokinetic changes into account, if a normal drug concentration is subsequently achieved and delivered to the site of action in an obese patient the clinical effect of the drug may still be other than expected. This may occur with alterations in target tissue sensitivity, whether at the level of the drug target or a downstream effect. There may be increased sensitivity to some drugs (e.g., glipizide, glyburide, prednisolone, triazolam) *(79)* and decreased sensitivity to others (e.g., atracurium, verapamil) *(118)*. Receptor expression or affinity may be altered. The drug effect may be more pronounced, including toxic effect, as an extension of pharmackokinetic variables or pharmacodynamics, but is poorly predictable *(119)*. Given the wide number of genes and loci implicated in obesity *(120)*, whether due to mutations, phenotypic associations, or linkages, the possibility exists for associations or overlap with genetic markers of drug metabolism or drug response.

2.5. Integrating the Data for a Clinical Approach to the Obese Patient

Loading doses of a drug will be based on information about a drug's V_D as it relates to TBW (L/kg) (or body composition when possible). On the other hand, *maintenance doses* will be based on the total Cl of the drug from the body (L/h) as documented in obese subjects or patients. When V_D is normalized to TBW the extent of drug distribution into the excess weight, which is of mixed composition, beyond the "lean" weight, has given rise to the figures (correction factors) used to adjust the body weight. This, however, assumes that the subject's LBW is correctly estimated and that excess tissue is adipose alone. This being the case, there should be no expected difference in values between men and women. However, the degree of distribution into the excess weight above the predicted "ideal" or "lean" weight is reported to differ for the hydrophilic analgesic acetaminophen, with men having an apparently higher distribution into the excess tissue *(105)*. This would be accounted for by the higher proportion of lean tissue in men, including more lean tissue in the excess weight above the predicted lean weight.

Therefore, the ratio of TBW-normalized V_D in obese subjects to that in non-obese subjects can help guide which body weight should be used for weight-based loading doses:

V_D/kg TBW_{OB}: V_D/kg $TBW_{Non\text{-}OB}$	Dosing Weight
≥ 1	Actual TBW
0.7 up to 1	An adjusted body weight
<0.7	LBW

For example, the V_D for vecuronium is ~0.5 L/kg TBW in obese patients and ~1 L/kg TBW in non-obese individuals. The ratio of the value in obesity (0.5 L/kg) to the value in controls (1 L/kg) is 0.5, suggesting the use of LBW for the loading dose of this drug. And a similar approach using total body Cl may be possible in guiding which body weight should be used for weight-based maintenance doses in drugs whose activity throughout the dosing interval is concentration dependent:

$Cl_{T\ OB}$:$Cl_{T\ Non\text{-}OB}$	Dosing Weight
≥ 1	Actual TBW
<1	Adjusted or LBW

For example, the Cl for vecuronium is ~16 L/h in obese patients and ~20 L/h in non-obese individuals. The ratio of the value in obesity (16 L/h) to the value in controls (20 L/h) is 0.8, suggesting the use of adjusted or LBW for maintenance doses of this drug. Of course data from well-designed studies examining drug-specific V_D and Cl, as well as drug effect between obese and non-obese individuals, will provide the best guidance compared to the empiric advice above. A review of studies on descriptors of body size in pharmacokinetic parameters identified the greatest success with TBW, an adjusted body weight, and LBW equation as suggested above for V_D and Cl *(33)*. The best single descriptor would be based on drug-specific distribution and Cl. Increased drug sensitivity, despite V_D and Cl parameters otherwise suggesting the use of TBW, supersedes this empiric advice too.

3. CLINICAL EVIDENCE

This section provides an overview of some of the drug-specific data available in the literature to help guide pharmacotherapeutic decision making in patients with obesity.

3.1. Antiepileptic Drugs

The dosing of *phenytoin* can be complex enough in patients with a healthy BMI given the many factors that can impact on its disposition. In obesity the volume of phenytoin's distribution is increased both in absolute terms and when normalized to TBW *(121)*. This indicates that the drug distributes especially into the excess adipose tissue of obese individuals. The significant distribution of phenytoin into adipose tissue sets the stage for potential redistribution from this site *(122)*. The data suggest that a loading dose for phenytoin should be based on an adjusted body weight using a correction factor of greater than 1, in other words dosing based on at least TBW. At the same time the metabolic clearance of phenytoin appears to be increased in obesity *(121)*. This does have the potential to decrease following successful weight loss *(123)*. Conversely, obese individuals have a slightly reduced Cl of *carbamazepine*, which increases following reduction in body weight associated with increased physical activity *(124)*. Whether the increased Cl is due to weight loss itself, a decrease in hepatic fat, or the effect of dietary changes on drug clearance is unclear. Along with a lower Cl, the V_D of carbamazepine is lower in obese individuals when normalized to actual body weight despite a higher absolute V_D *(124,125)*. This suggests that an adjusted body weight may be used for initial dosing of carbamazepine in an obese patient, but that maintenance doses could be administered at longer intervals. Doses of *phenobarbital* should be based on TBW in order to achieve therapeutic concentrations in obesity *(126)*.

3.2. Antimicrobials

Optimal dosing of antimicrobials in obese patients remains challenging. Dosing adjustments of antimicrobials as a class are rarely made based on body weight or degree of obesity but are based instead on drug-specific data. This would include renal function for renally cleared antimicrobials, requiring an estimate of glomerular filtration rate known to be elevated in obesity. This drug-specific information will determine whether adjustments should be made or whether dosing should take actual, lean, or an adjusted body weight into account. A number of findings on the dosing of antimicrobials in obesity have been recently reviewed *(50,127)*. Much is based on the degree of drug distribution into lean and fat mass and on the influence of obesity on drug clearance. Some studies have sought to optimize doses of moderately lipophilic antimicrobials in obese patients *(50)*. Based on a summary of the literature, recommendations for dosing have been provided which include drug-specific correction factors for antimicrobials requiring dose adjustment in obesity *(50,127)*. Given the difficulty in estimating renal function, renal drug clearance of one drug has been used to guide dosing of another drug in morbid obesity *(128)*.

3.2.1. BETA-LACTAMS

For beta-lactam drugs a correction factor of 0.3 is suggested for use in the dosing weight equation – although no clinical study data exist to support this. Using patients as their own control before and after intestinal bypass-associated weight loss, the V_D for *ampicillin* decreased from 0.6 L/kg to 0.41 L/kg, indicating some distribution into adipose tissue for this hydrophilic compound *(129)*. Although the absolute V_D is increased for *nafcillin*, no significant difference is seen in the TBW-normalized V_D or in total Cl in a morbidly obese patient *(130)*. This would imply the potential to dose nafcillin based on actual body weight, and the authors suggest dosing modification upward to 3 g q6h in obesity *(130)*. During treatment for cellulitis with *piperacillin*–tazobactam 3.375 g q4h intravenously in a morbidly obese patient (BMI 50 kg/m^2), pharmacokinetic sampling revealed an altered V_D (0.33 L/kg) and Cl (27 L/h) for piperacillin compared with normal values ($\sim$0.2 L/kg and 13 L/h) *(131)*. So the dosing of piperacillin can be based on TBW, especially if dealing with a *Pseudomonas aeruginosa* MIC $>$ 8 mg/L *(131)*. An area of concern is the pre-operative dosing of antimicrobials to prevent post-operative infection in obese patients undergoing surgical procedures. A 1 g dose of *cefazolin* as antibiotic prophylaxis for surgery in patients with BMI $>$ 40 kg/m^2 resulted in serum drug concentrations below the MIC for several organisms *(132)*. An adjustment to 2 g cefazolin reduced surgical site infection rates from 16.5 to 5.6%, $P < 0.03$ *(132)*. Cephalosporin clearance may also be increased in obesity, requiring repeated dosing during an operation that lasts longer than 2–3 h *(133)*. Mediastinitis following cardiac surgery in obese patients may also be related to inadequate antimicrobial dosing (odds ratio 21 for patients $>$ 75 kg) *(134)*. This was resolved by increasing cefazolin dose to 2 g for prophylaxis in these patients *(134)*. Despite high protein binding and distribution predominantly within the extracellular compartment the pharmacokinetics of *ertapenem* differs based on BMI *(135)*. Following a standard 1 g intravenous dose central compartment V_D was significantly higher in normal weight (BMI 22.5 kg/m^2) subjects than in obese (BMI 33.4 kg/m^2) and severely obese (BMI 43.4 kg/m^2) subjects (0.078 vs 0.063 L/kg and 0.057 L/kg) *(135)*. The significantly lower $AUC_{0\text{-}\infty}$ in the obese and severely obese subjects translates into lower probability of attaining drug exposure targets at a given MIC compared with normal weight subjects *(135)*. The subcutaneous adipose tissue exposure ($AUC_{0-\infty}$) to ertapenem is about 5% of the plasma value *(136)*.

3.2.2. AMINOGLYCOSIDES

The aminoglycosides are quite similar to each other from a physicochemical standpoint exhibiting comparable pharmacokinetic properties. This includes V_D that approximates the extracellular fluid volume. Obese individuals would be expected to exhibit increased absolute V_D given the increase in total body water, but lower values when adjusted for TBW. The typical weight-based dosing of aminoglycosides takes renal function into account in determining a dosing interval. Dosing aminoglycosides in obese patients using actual body weight can result in higher than expected serum concentrations, whereas LBW may result in subtherapeutic levels. A suitable correction factor for establishing a dosing weight that lies between lean and actual weights varies with the study and may differ with degree of obesity and presence of infection. A well-recognized method for predicting *gentamicin* parameters is to use an adjusted dosing weight that incorporates only 40% of the excess weight, that is, a correction factor of 0.4 in the dosing weight equation *(117)*. This would provide the basis for an initial dose of aminoglycoside. Given the variability in correction factors determined for aminoglycoside dosing in obesity *(137)*, it has been suggested that serum concentrations still be used to monitor the patients *(127)*. Aminoglycoside Cl is increased in obesity *(138–140)*. Renal Cl of aminoglycosides may be increased in obesity, but this may be balanced out with the increased V_D, so that if an adequate dose is administered, no change in dosing interval is necessary. Larger doses of *isepamicin* are required in obese, as compared to lean, intensive care unit patients to achieve similar serum concentrations *(141)*. This is despite a slightly lower V_D normalized to TBW, indicating some distribution into the excess adipose tissue.

3.2.3. GLYCOPEPTIDES

Following single-dose administration of *vancomycin*, V_D was higher in morbidly obese patients compared to non-obese individuals *(142)*. The TBW-adjusted V_D was lower in obese patients compared to control subjects. The Cl of vancomycin may be increased in obesity, but may be less pronounced at higher BMI *(115,116,142)*. However, the difference in Cl disappeared when normalized to TBW, suggesting that the actual TBW should be used for dosing vancomycin in obese individuals *(142–144)*. A recent case report of a patient with a BMI > 100 kg/m^2 suggests that the TBW-adjusted V_D was only slightly lower, and the Cl was only modestly elevated compared to values in non-obese patients *(145)*. This again confirms that TBW can be used for dosing vancomycin. Monitoring of serum trough concentrations may help reduce the fear of using such large doses in the face of the variable effect on Cl and could identify patients who may require more frequent dosing to stay ahead of MIC targets. Vancomycin pharmacokinetics in a morbidly obese patient (BMI 66 kg/m^2) was used to estimate renal function and guide the dosing of *daptomycin (128)*. Dosing of daptomycin (6 mg/kg) based on TBW at an interval based on renal function yielded adequate concentrations for clinical efficacy *(128)*. The lower V_D in the patient (0.06 L/kg) than in non-obese subjects would suggest that an adjusted body weight could have been used. Another study comparing daptomycin pharmacokinetics following a 4 mg/kg intravenous dose in 13 obese subjects (BMI 28–58 kg/m^2) and 12 matched controls suggests that TBW could be used for dosing daptomycin in the obese *(146)*.

3.2.4. FLUROQUINOLONES

The fluoroquinolone antimicrobials are widely used. The increased absolute V_D for *ciprofloxacin* in obese individuals becomes slightly below that of controls, proportional to BMI, when normalized to actual body weight *(112)*. This indicates that ciprofloxacin distributes less into the excess adipose tissue than into the fat-free tissue. It has been estimated to distribute into about 45% of the excess body weight (i.e., a correction factor of 0.45) *(112)*. Drug Cl, including renal Cl, is also increased in obese individuals *(112)*. Given both the reduced weight-adjusted V_D and the increased drug Cl for ciprofloxacin in obesity, dosing can be based on an adjusted weight using a correction factor of 0.45 which can provide serum levels within the recommended range *(147)*. Single-dose evaluation of *garenoxacin* in 30 surgical patients (BMI 16–51 kg/m^2) revealed significant distribution into selected tissues including adipose tissue, with tissue:plasma ratio of 0.10–0.53 *(148)*. The much higher V_D of *gemifloxacin* with free drug exposure in tissue greater than in plasma suggests that adipose tissue may serve as a storage site *(149)*. Although no longer marketed, trovafloxacin pharmacokinetics following a single dose in morbidly obese patients appeared similar to non-obese individuals with similar subcutaneous and deep adipose tissue drug concentrations *(150)*. The exposure ($AUC_{0\text{-}\infty}$) to *levofloxacin* is similar in subcutaneous adipose tissue as in plasma using a microdialysis technique following a single 500 mg intravenous dose. This is expected due to interstitial fluid sampling (i.e., not intracellular as may be sampled from tissue biopsy) *(151,152)*.

3.2.5. ANTIFUNGALS

Pharmacokinetic parameters for antifungal agents in obese patients have not been evaluated. *Amphotericin* has been dosed based on TBW given the much greater V_D for this drug in obesity *(153)*. No clear data exist for dosing of the azoles in obese patients, although it has been suggested that V_D and Cl of *fluconazole* are greater in obesity *(154)*. A higher dose of fluconazole is recommended for obese patients based on the higher drug Cl observed in an obese patient compared to data in non-obese patients *(155)*. *Flucytosine* dosing has been based on an estimated LBW in an obese patient that yielded acceptable serum drug concentration *(153)*. This seems rational given the lower V_D normalized to TBW and the reduced Cl identified. In that patient case amphotericin was also used, with maintenance doses based on actual body weight.

3.2.6. ANTIVIRALS

Little information is available on dosing of antiviral agents in obesity. Non-response to *interferon-α* or *peginterferon-α* in patients with hepatitis C genotypes 1 and 4 viral infection is independently associated with BMI $\geq$ 30 kg/m^2 *(156)*. This appears to be explained by an increased expression of an inhibitory factor (i.e., suppressor of cytokine signaling type 3) in obese compared with lean subjects *(156)*.

3.2.7. OTHERS

Despite excellent tissue penetration *linezolid* serum concentrations were reported to be lower in obese patients (BMI 50.8 kg/m^2) *(157)*. This raises concerns about the dose of 600 mg every 12 h against pathogens for which time above the MIC may be inadequate if the V_D is greater. A morbidly obese patient (BMI 86 kg/m^2) receiving this dose of linezolid was reported to have a V_D of 0.47 L/kg compared with 0.6 L/kg in non-obese individuals, suggesting that an adjusted body weight be used *(158)*. For the management of sepsis, dosing of activated *drotrecogin-α* has been based on

TBW although not prospectively evaluated in patients weighing > 135 kg *(159)*. The limited data available for *sulfonamides* and *macrolides* do not establish which weight can be used for dosing in obesity or whether dosing should be different in obese patients. It has been suggested that *antimycobacterial* agents be dosed according to LBW, based on a single case report *(160)*.

3.3. Chemotherapy

3.3.1. BODY SURFACE AREA, BODY WEIGHT, AND SYSTEMIC EXPOSURE

Many drugs used to manage malignancies have a narrow therapeutic index. To limit the interpatient variability and risks associated with many chemotherapeutic agents, body surface area has often been used to guide dosing. Unfortunately, not much data exist to guide dosing in overweight/obese patients with cancer. And similar to the greater population prevalence, approximately one-third of patients with cancer are obese, with its obvious implications for drug dosing.

In obese patients use of the body surface area that incorporates TBW or the Calvert equation which incorporates the Cockroft–Gault equation to dose chemotherapy may result in increased drug exposure with the subsequent risk of treatment toxicity *(161)*. The use of TBW incorporated into body surface area or the Calvert equation for obese patients (BMI 28–45 kg/m^2) with cancer resulted in severe chemotherapy-related toxicity for 11% (1st cycle), with reduction in subsequent doses and toxicity of 7% (2nd cycle) and 4% (3rd cycle) *(162)*. One suggestion to address this has been to incorporate the BMI into a corrected body surface area in estimating chemotherapy drug dosing *(163)*. However, there are little data to support using body surface area over body weight *(162)*, and in fact more support emerging to dose chemotherapeutic agents with traditional targets based on their route of distribution and elimination (i.e., systemic exposure). Data suggest that dosing should be based on patient-specific variables (including genetic polymorphisms and nutritional status) *(164)*. The rationale for using body surface area may be even less clear for calculating doses of oral chemotherapy *(165)*. Standardizing dosing of oral chemotherapy rather than relying on body surface area dosing may improve patient safety *(165)*. It would seem reasonable to dose especially these narrow therapeutic index agents based on systemic drug exposure. But many traditional agents have been dosed based on body surface area or body weight.

Of course a general decrease in drug dose for obese patients because of concern for overdosing may actually increase the risk for therapeutic failure. Obese patients were significantly more likely to receive a reduced chemotherapy dose which was subsequently associated with a significantly worse outcome in pre-menopausal patients with node-positive breast cancer treated with cyclophosphamide, methotrexate, and fluorouracil *(166)*. Tumor drug exposure is related more to the absolute dose in the case of *epirubicin* rather than to a body surface area-normalized dose *(167)*. This is most likely due to a reduced V_D in individuals with higher BMI. In fact drug doses do not need to be reduced in management of breast cancer in obese patients who may be less likely to develop toxicity *(168)*.

3.3.2. Specific Drugs

Ifosfamide may distribute into adipose tissue more than expected, as described by a larger V_D and longer elimination half-life, which may impact on potential for toxicity *(169)*. Encephalopathy subsequent to high-dose (~2 g/m^2) ifosfamide was more common in patients with a higher BMI despite identical body surface area in a small retrospective cohort study *(169a)*. Exposure of *doxorubicin* may also be greater in obese patients compared to non-obese patients, in this case based on decreased drug Cl without a change in V_D *(170,171)*. Another drug with reduced Cl described for obese patients is *cyclophosphamide (172)*. The apparent Cl of *busulfan* was higher in obese patients than non-obese, but an adjusted body weight using a correction factor of 0.25 eliminates any difference and is therefore suggested for dosing this agent *(173,174)*. For the renally eliminated drug *carboplatin*, using an adjusted body weight based on a correction factor of about 0.5 provided the best prediction of drug Cl in obese patients *(175)*. A typical dosing approach resulted in excessive exposures (based on area under the concentration–time curves) to 4-hydroxy-cyclophosphamide, tepa, and carboplatin in a morbidly obese patient *(161)*. It is suggested that an adjusted body weight be used for dosing cyclophosphamide, thiotepa, and carboplatin, with consideration to obtaining drug concentrations. There was a reduced weight-adjusted V_D for all three agents, a slight increase in Cl for cyclophosphamide and thiotepa, but a slightly reduced Cl of carboplatin *(161)*.

3.4. Immunosuppressants

The V_D corrected to TBW is lower in obese individuals for both *prednisolone* and *methylprednisolone* without apparent changes in plasma protein binding to albumin or transcortin *(176,177)*. However, the Cl of prednisolone is increased in obesity and correlates with TBW *(176)*. Although there may be increased Cl of prednisolone in obese patients, the increase in sensitivity to the drug means no dose change is warranted. TBW is used to dose this drug. Conversely, there is a significant reduction in Cl of methylprednisolone with obesity, such that reduced dosing frequency may be needed and LBW is used *(177)*. Infusion of *cortisol* in obese patients who had undergone study of fat area allowed recognition that drug Cl (absolute and body weight corrected) was much higher in those with larger intra-abdominal fat areas *(178)*. *Cyclosporine* may accumulate in adipose tissue, but its pharmacokinetic parameters do not change significantly in obese patients other than a reduced V_D/kg TBW *(66,179)*. This suggests that cyclosporine dosing should be based on LBW in obese individuals *(66,180)*. Based on higher initial *tacrolimus* concentrations following renal transplantation in patients with a larger BMI the suggestion is to use either lower doses or basing doses on “ideal” body weight *(181)*.

3.5. Neuromuscular Blockers

To achieve complete neuromuscular blockade using *succinylcholine* in morbidly obese patients, dosing should be based on TBW rather than on an “ideal” or LBW *(182)*. Given that this drug distributes into extracellular fluid this makes sense; duration of effect may vary depending on pseudocholinesterase activity which may also be directly correlated with BMI *(183)*. *Vecuronium* distributes into lean tissue even in obese patients as indicated by the reduced V_D/kg TBW *(184)*. As a result, dosing of this neuromuscular blocking agent should be based on LBW particularly since prolongation of drug effect has been reported in obese patients *(184)*. Recommendations have been made to dose *rocuronium* on LBW also, based on findings of a lower V_D and Cl in patients with a higher BMI *(185,186)*. While time to onset of rocuronium was slightly shorter in obese women, duration of effect and spontaneous recovery time were no different between obese and normal weight groups *(187)*. Neither the V_D/kg TBW nor the total drug Cl differed between groups, although patients were not morbidly obese (BMI ~34 kg/m^2), indicating that 0.6 mg/kg TBW could be used. In a group of morbidly obese patients (BMI 43.8 kg/m^2) rocuronium at 0.6 mg/kg based on an "ideal" weight resulted in similar duration of action as in a control group compared with dosing based on actual body weight *(188)*. Although the absolute V_D for *atracurium* is unchanged in obesity, it is decreased significantly when normalized to TBW *(118)*. This indicates that dosing should be based on LBW. A possible alteration in protein binding and/or desensitization of acetylcholine receptors may account for the reduced sensitivity of obese patients to atracurium *(118)*. Doses may need to be adjusted upward based on hyposensitivity in these patients. Cisatracurium has become the recommended agent to use in obesity although duration of effect may be prolonged regardless of whether LBW or TBW is used *(189)*. In one group of morbidly obese women (BMI 42.2 kg/m^2) the duration of neuromuscular blockade following cisatracurium dosed at 0.2 mg/kg TBW was prolonged compared to another group of women (BMI 43.5 kg/m^2) in which the dose was 0.2 mg/kg of an "ideal" weight (75 vs 45 min, $P<0.001$) *(190)*. The duration of blockade in non-obese women (BMI 22.1 kg/m^2) following 0.2 mg/kg TBW was intermediate at 59 min which was significantly different than in the two obese groups *(190)*.

3.6. Benzodiazepines

While benzodiazepines as a class are considered highly lipophilic, the impact of obesity on the apparent V_D varies with the specific agent. This does not appear to be an effect of plasma protein binding, which remains no different between obese and control subjects. It was often considered that a correlation existed between the coefficient of distribution into octanol:water and distribution into adipose tissue. *Diazepam*, with the highest octanol:water partition coefficient, and *midazolam* with one of the lowest coefficients each have a significantly higher TBW-adjusted V_D in obese individuals compared to controls, indicating distribution into excess adipose tissue. The V_D of midazolam is significantly larger in obese compared with non-obese subjects, while total Cl is similar *(64)*. Given that drug effect is much more dependent on extent of drug distribution than elimination, single doses should be based on TBW. Use of continuous infusions, however, should be based on a LBW. On the other hand, *lorazepam* and *oxazepam* with intermediate partition coefficients exhibit no difference in V_D adjusted to TBW between obese and control subjects *(46)*. The Cl of benzodiazepines appears to be increased in obese individuals *(46)*. The Cl of lorazepam and oxazepam increases in obese individuals and appears to be correlated with TBW *(106)*. This is documented for diazepam, nitrazepam, and lorazepam which undergo oxidation, nitroreduction, and glucuronidation, respectively. Furthermore, obese subjects are more sensitive to the same dose of *triazolam* than are non-obese individuals *(79)*.

3.7. Anesthetics

Local anesthetics administered via the epidural route may be used to reduce pain during active labor. Obese women often experience higher levels of epidural blockade. A prospective evaluation of *bupivacaine* showed that the effective drug concentration in obese patients (BMI 39.5 kg/m^2) was only 60% (0.067 vs 0.113% w/v, $P<0.001$) of that required in non-obese (BMI 26.3 kg/m^2), and yet the obese patients experienced a significantly higher block level *(191)*. It is not clear whether this is due to a smaller volume of epidural space in obesity.

The very lipophilic agent *propofol* would be expected to distribute predominantly into adipose tissue. However, both absolute and corrected V_D are not significantly different between obese and non-obese individuals *(192)*. This may be accounted for in part by the high hepatic clearance, which appears to be related to TBW. This in turn suggests that propofol maintenance dosing in obese individuals could be based on actual body weight, although cautiously administered given the risk for cardiovascular collapse. A patient's sensitivity to propofol may be associated with degree of body fat; however, this is most likely a lesser factor in the influence of age on propofol pharmacodynamics *(193)*. Physiologically based pharmacokinetic modeling taking into account the variability in obesity may allow for target-controlled infusions with better prediction than compartmental models *(194)*. *Thiopental*, despite being highly lipophilic, may need to be dosed lower in obese patients undergoing anesthesia, not because of V_D, which is clearly larger in these patients even when adjusted to TBW (7.9 vs 1.9 L/kg), or because of Cl which is similar but because of increased drug sensitivity *(195–197)*. Despite a significantly longer elimination half-life attributed to V_D the obese patient should probably receive a dose based on LBW. One paper describes modeling of thiopental disposition with alterations in blood flow and body composition based on available data sets *(71)*. The drug's V_D increases (L/kg TBW), with an adipose tissue:plasma ratio of ~8.5 which may vary for adipose tissue from different body regions *(71)*. It predicts a much lower peak concentration of thiopental in obesity, suggesting that obese patients require 46% higher thiopental doses *(71)*. The volatile anesthetics *halothane* and *enflurane* are metabolized through the liver to a greater extent in obese patients as determined by levels of toxic metabolites, while having prolonged release of metabolites from adipose tissue *(198,199)*. A recent paper describes no difference in emergence and recovery following the less lipophilic anesthetics *desflurane* or *sevoflurane* in morbidly obese patients *(200)*. It should be noted that volatile anesthetics are often avoided in obesity because of ventilation–perfusion mismatch and airway difficulties in these patients.

3.8. Analgesics

The synthetic opioid analgesics are also lipophilic compounds. Use of actual TBW will overestimate *fentanyl* dosing requirements in obese surgical patients *(201)*. Based on an estimated "pharmacokinetic mass" of lean weight drug Cl is linear compared with a non-linear relationship if TBW is used. *Sufentanil* has an elevated V_D/kg TBW but a Cl not much different in the obese compared to non-obese individual *(202)*. This suggests that TBW could be used for dosing sufentanil in obesity, with a reduced maintenance dose based on clinical effect relative to drug redistribution. In a group of obese patients (BMI 35–52.6 kg/m^2) undergoing laparoscopic gastroplasty, sulfentanil was administered as a target-controlled infusion based on pharmacokinetic data in non-obese patients *(203)*. This system overpredicted target drug concentrations particularly at BMI > 40 kg/m^2. However, *remifentanil* has a significantly lower normalized V_D and Cl in obese patients, suggesting that LBW would be more appropriate for dosing and that TBW-based dosing would result in excessively high drug concentrations *(204,205)*. Given the prevalence of obstructive sleep apnea in obesity the degree of sedation is best limited to reduce the risk of airway obstruction.

The over-the-counter analgesic *acetaminophen* is a hydrophilic molecule with an expected lower V_D, adjusted to TBW, in obese subjects *(206)*. The Cl of acetaminophen is increased in obesity, which may necessitate more frequent dosing. So initial dosing of this drug would not have to be increased in obese patients, but could be adjusted. The V_D for *ibuprofen*, once corrected to TBW, is reduced in obese subjects relative to controls and not accounted for by plasma protein binding which remains unchanged *(207)*. Ibuprofen Cl is increased significantly in the obese subjects and correlates with TBW.

3.9. Others

Limited data exist for most other drugs, including those used in cardiovascular, pulmonary, and gastrointestinal illness. *Verapamil* tends to have a larger V_D in obese patients, but not different than normal weight patients when adjusted to TBW, and Cl is not altered suggesting use of TBW *(208,209)*. In addition, obese patients may require higher drug concentrations to achieve similar cardiac effects as that in control patients *(209)*. The distribution volume and the Cl of *digoxin* appear unaffected by obesity based on single-dose studies *(210,211)*. This follows from the limited distribution of the drug into adipose tissue and allows for the continued recommendation to administer digoxin based on LBW. *Lidocaine* distribution normalized to TBW reveals similar values for obese and control subjects and should therefore be dosed based on TBW *(212)*. Intravenous infusions of vasoactive medication are administered using weight-based dosing. A recent search identified only eight research articles covering a mere six medications for which data are very limited *(213)*. The consistent use of a dosing weight in a patient with adjustments made based on close monitoring is suggested *(214)*.

Given the risk for thrombo-embolic disorders in obesity, including post-operative fatalities despite prophylaxis, better evaluation of the dose, timing, and duration of anticoagulants is required *(215,216)*. There is wide variability in the V_D for unfractionated *heparin*, which remains similar when normalized to TBW, suggesting that TBW can be used for weight-based heparin dosing *(217)*. However, the use of heparin for obese patients undergoing cardiopulmonary bypass reached better target-activated clotting time when administered as 300 units/kg LBW compared to those receiving 300 units/kg TBW and also required less protamine for heparin neutralization *(218)*. Low–molecular-weight heparin (*LMWH*) dose and V_D determine the peak drug level, which in turn has been associated with the bleeding risk. Because the V_D for LMWHs is expected to be similar to plasma volume, dosing per kilogram is not expected to differ between obese and non-obese individuals. Only limited study exists thus far in obese patients. Using anti-factor Xa activity as a marker, weight-based dosing is more appropriate than fixed doses in obese patients *(216)*. Enoxaparin 1.5 mg/kg daily or 1 mg/kg twice daily provides predictable anti-Xa responses *(219)*. The pharmacodynamic effect of enoxaparin does not seem to differ between obese and non-obese subjects *(220)*. Based on a preliminary report, dalteparin doses should make use of TBW *(221)*. No apparent difference exists between obese and non-obese individuals in V_D normalized to TBW or in drug Cl. Unfortunately, the effects of obesity on the absorption characteristics have not been examined. Tinzaparin pharmacodynamics is not influenced across body weights of up to 165 kg (BMI $\leq$ 61) when dosed at 75 and 175 units/kg TBW *(222)*. Based on degree of platelet aggregation, with elevated BMI as the only independent predictor of suboptimal platelet response, a higher loading dose of *clopidogrel* may be required following coronary stenting *(223)*. It is not clear if this is a result of altered pharmacokinetics or pharmacodynamics in obesity.

Theophylline, while considered a polar compound, is more lipophilic than caffeine but does not correlate perfectly well with either LBW or TBW. Theophylline salts distribute predominantly into lean tissue even in obese individuals, indicating that loading doses should be based on a LBW *(224,225)*. As drug Cl may be increased in obesity, a close monitoring program should be in place to adjust dosing, particularly if weight loss occurs. Histamine-type-2 receptor *(H_2)-antagonists* as expected by their hydrophilic nature have a much smaller V_D normalized to TBW, but may have an increased Cl *(113,226)*. The Cl may be increased in obesity, in part due to active tubular secretion of the drugs.

A mood-stabilizing drug such as *lithium* with a narrow therapeutic index would be important to evaluate in obesity. Lithium's V_D normalized to actual body weight is considerably smaller in obese individuals, which is in line with the fact that it distributes to lean tissue *(114)*. The Cl of lithium is, however, increased in obesity *(114)*. From these findings it would follow that initial dosing should be based on LBW and that maintenance doses should be larger to maintain therapeutic levels. *Trazodone* is another mood-stabilizing agent but with considerable distribution into adipose tissue based on an increased V_D even when corrected to TBW *(227)*.

3.10. Obesity Treatments

3.10.1. MEDICATIONS

A number of drugs used in the management of obesity have been studied as well. Presumably, appetite suppressants would only be used when indicated and the issue of alterations relative to control individuals would not be relevant. Although no longer on the US market, *dexfenfluramine* was found to distribute proportionally into both the excess fat and the lean tissue, despite being considered lipophilic *(67)*. It appears from limited data that *sibutramine* pharmacokinetics is unchanged in obese individuals compared to non-obese subjects *(228)*. In an open-label study, adolescents receiving *orlistat* therapy to manage obesity also received a multivitamin supplement that included lipid-soluble vitamins *(229,230)*. Nevertheless, serum concentrations of vitamin K and vitamin D were reduced, the latter significantly enough to warrant a recommendation for regular monitoring despite prophylactic supplementation. Levels of vitamin D, vitamin E, and β-carotene can be significantly decreased while vitamin A usually remains unchanged with orlistat *(231)*. The levels of a number of minerals were not influenced by short-term use of orlistat *(232)*. Given the reduction in fat absorption induced by orlistat, several lipophilic drugs have been evaluated in single-dose studies during the course of an orlistat regimen in non-obese subjects *(233,234)*. Absorption of amiodarone was reduced by 27% and cyclosporine by 30%; however, orlistat had no significant effect on the pharmacokinetics of metformin, phentermine, sibutramine, atorvastatin, simvastatin, losartan, amitriptyline, or fluoxetine. Despite clinical efficacy widespread use of *rimonabant* is not expected due to drug-associated mood disorders. Although not indicated for management of obesity, requirements for *levothyroxine* are dependent on lean body mass *(235)*.

Given the ongoing surge in diabetes among obese individuals, it would be wise to study the use of antidiabetic agents in this population. The oral Cl and V_D of *glyburide* and *glipizide* do not appear to be significantly different between obese and non-obese diabetic patients, although some interindividual variability was noted and V_D normalized to TBW was lower for glyburide in obese patients *(236,237)*. Obese patients also appear to be more sensitive to the effects of glyburide requiring lower daily doses to maintain therapeutic effect *(237)*. At a dose of 0.1 unit/kg, insulin aspart pharmacokinetic parameters are not significantly different across BMI categories in patients with type 1 diabetes *(238)*. Insulin glulisine may be less likely to have any shift in action profile than insulin lispro or regular human insulin with increasing subcutaneous fat content *(239)*.

Obese patients may also have cardiovascular disorders requiring drug therapy. Beta-adrenergic receptor antagonists, *β-blockers*, have been studied in obesity with particular attention given to the degree of lipophilicity among agents in this class. Although propranolol is more lipophilic than bisoprolol, the corrected V_D of each drug is reduced in obese subjects consistent with distribution into excess lean tissue rather than excess adipose tissue *(78,240,241)*. There are also no apparent differences between obese and non-obese in V_D or Cl for sotalol, a β-blocker that is much less lipophilic than propranolol or bisoprolol *(242)*. Generally, these agents have a slightly reduced V_D/kg in obese subjects than in controls regardless of the degree of lipophilicity not explained by hemodynamic effects or protein binding but likely correlated with the distribution coefficient of each at physiologic pH *(50)*.

3.10.2. SURGICAL INTERVENTION

Bariatric surgical procedures have helped certain morbidly obese patients reduce their body mass and some comorbid risks. These operations have increased substantially to projections of over 100 000 annually in the United States *(243)*. The most common surgical approaches include gastric bypass, gastric restriction, or intestinal bypass *(244)*. Gastric bypass makes up 88–92%, gastroplasty 7.4–8%, with more significant malabsorptive procedures making up the rest *(243,245)*.

Despite low rates of adjusted hospital complications and mortality, the post-operative gastrointestinal complications include altered nutrient and drug disposition. The malabsorption of nutrients is expected and has been documented for calcium, magnesium, iron, group B vitamins including cobalamin, vitamin D, and other fat-soluble vitamins. Based on the alteration in those portions of the gastrointestinal tract normally responsible for preparing orally administered drugs for absorption, these procedures would be expected to alter drug absorption either by reducing time for disintegration and dissolution or by reducing the surface area and sites for absorption *(246)*.

Following gastric bypass, drug dissolution is likely to vary which can then influence a drug's bioavailability. An in vitro model evaluating 22 medications revealed that 45% would have significantly less dissolution in the gastric environment following gastric bypass *(247)*. Only two drugs evaluated (bupropion, lithium carbonate) had significantly greater dissolution compared with the pre-operative gastric environment *(247)*. A clinical evaluation in patients prior to and following gastric bypass will determine whether these findings translate into differences in drug absorption. This is important given the medication use patterns of these patients *(248)*. Based on serum drug concentrations, the absorption of oral penicillin is apparently not altered following gastroplasty for morbid obesity *(249)*. Even the use of gastric binding may increase the time that a drug spends in the proximal stomach and thereby alter dissolution or detract from the use of modified-release dosage forms *(250)*. Mucosal changes in the excluded stomach following gastric bypass may require management with proton pump inhibitors although it is unclear where the bulk of drug absorption will take place given that the duodenum is bypassed *(251)*. Significant inter-patient variability occurs in the pharmacokinetics of sirolimus, tacrolimus and mycophenolate; the bioavailability of these agents is further compromised following gastric bypass *(251a)*. Jejunal bypass produces significant malabsorption. A patient receiving cyclosporine (oral microemulsion) for liver transplantation experienced significant drug malabsorption compared with other patients following transplantation *(252)*. Dosage adjustment for these immunosuppressants is expected *(251a, 252)*.

3.10.3. OTHER INTERVENTIONS

Liposuction involves administration of a wetting solution into the subcutaneous tissue prior to aspirating that tissue. Epinephrine is included in the solution for hemostatic and vasoconstrictive effects. Each liter of lactated Ringer's solution may include 1 mg epinephrine and 300 mg lidocaine, and often 5–10 L are used in the procedure. As much as 32% of the epinephrine dose may be absorbed systemically *(253)*. And in large-volume liposuction procedures lidocaine may reach anti-arrhythmic levels with as much as 93% absorbed systemically *(253,254)*.

4. LIMITATIONS OF THE DATA AND FUTURE RESEARCH

Altered drug disposition in obese individuals has been described more frequently in the literature in recent years. Unfortunately there is still not a concerted effort to study this and provide clinical recommendations. Regulatory requirements to do so may be needed to advance current knowledge and patient care. Drug dosing guidelines are necessarily based on relatively small studies or case series in moderately obese individuals. There is clearly a paucity of data when it comes to evaluating the effect of obesity in general – let alone specific degrees of obesity or body composition, or bariatric surgery, or the influence of severe weight loss or extreme weight cycling – on the disposition and effect of medications. Much of the data are generated following single dose, rather than repeated doses as used in clinical practice, or from single case reports or case series often involving heterogeneous groups.

It remains difficult to predict the influence of obesity on drug disposition and effect based solely on physicochemical factors (e.g., drug lipophilicity). Dosing recommendations based on single case reports or small case series, as described in the previous sections, cannot be made with as much confidence as those based on more rigorous evaluation in a pharmacokinetic or pharmacodynamic study. There is a clear need for development of physiologically based pharmacokinetic/ pharmacodynamic models specific for obesity. To accomplish this goal more data are required in several areas. One significant area that requires more effort is a method to clinically evaluate body composition of obese patients. A better method to estimate body composition in sub-groups of the obese – by gender, ethnicity, degree of obesity would be welcome. Whole body densitometry, bioelectric impedance, dual-energy X-ray absorptiometry, and other methods can be used to determine lean body mass as long as limitations in technique are accounted for. Estimates may vary depending on data source and patient group *(255)*. This potential interindividual variability needs to be addressed. Also required is to determine, drug by drug, the V_D, Cl, and therapeutic effect in each. It may become important to evaluate drug disposition in patients of similar BMI, body composition, and even ethnic background. Differing body composition should be examined not just between degrees of obesity but also within a group of individuals of the same BMI. The activity of specific CYP isoforms in pre-obese, obese, and morbidly obese subjects should be documented. In this way drug regimens may be better suited to an individual patient to maximize the effectiveness of a drug regimen and limit potential toxicity. Early phase drug studies for new compounds should account for pharmacokinetic differences by body composition. Data in obesity remain an urgent need *(256)* and should be required as part of the new drug approval process *(257)*.

Suggestions made in this chapter regarding the lean body mass equation, use of the V_D normalized to TBW, and total body Cl between obese and non-obese individuals need to be evaluated prospectively. A formal framework for evaluating the influence of body weight and pharmacokinetic/pharmacodynamic parameters that considers all physiologically related variables using a non-linear mixed effects model should be pursued.

5. CONCLUSION AND RECOMMENDATIONS

The practice of using dosing regimens in the obese patient based on data obtained in non-obese individuals may increase the risk of drug toxicity or therapeutic failure. Similarly, generalizations cannot necessarily be made about agents from a related class when data in obesity are only available for one of them. A therapeutic dosing strategy can be developed for obese patients. Specific data describing the independent parameters of V_D and Cl on each drug can be used to determine a therapeutic dosing strategy for the drug in an obese patient. This requires use of drug-specific data in obese individuals (Table 2). Loading doses can be based on V_D data, instead of simply

Table 2
Values in Obesity for Volume of Distribution and Clearance of Select Drugs

Medication	*V_D (L)*	*(L/kg TBW)*	*Cl (L/h)*
Acetaminophen	109	0.81	29
Amikacin	26.5	0.18	9.5
Atracurium	8.6	0.07	26.6
Bisoprolol	182	2	14.8
Carbamazepine	98.4	0.87	1.19
Ciprofloxacin	269	2.46	53.8
Cyclosporine	230	2.5	42
Diazepam	292	2.81	2.3
Digoxin	981	10.7	19.7
Doxorubicin	1119	14	53.5
Gentamicin	23.5	0.17	8.5
Glyburide	47	0.44	3.2
Glipizide	19.5	0.2	2.3
Labetalol	368	3.8	90
Linezolid	135.7	0.47	13.5
Lorazepam	131	1.25	6.1
Methylprednisolone	104	0.9	21.3
Midazolam	311	2.66	28.3
Oxazepam	97	0.84	9.4
Phenytoin	82.2	0.68	3.5
Prednisolone	44.1	0.3	11.1
Propofol	17.9	1.8	1.46
Propranolol	230.5	2.7	44.3
Ranitidine	86	0.8	34.5
Remifentanil	7.5	0.07	186
Sotalol	80	0.9	9.4
Sufentanil	547	5.8	1.25
Theophylline	40.5	0.4	3.3
Thiopental	350	3.5	17.4
Tobramycin	19.2	0.23	7.5
Trazodone	162	1.4	8.7
Vancomycin	43	0.26	11.3
	52	0.32	11.8
Vecuronium	44.7	0.47	15.6
Verapamil	858	7	59.6

V_D = volume of distribution; L = liters; L/kg TBW = liters per kilogram of total body weight; Cl = clearance; L/h = liters per hour

Table 3
Suggested Dosing Weight for Use in Obesity

Medication	*Dosing Weight in Obesity*	
Example	Loading Dose	Maintenance Dose
Aminoglycosides	Adjusted body weight[1]	Adjusted body weight,[1] or by therapeutic response
Amphotericin	Total body weight	Total body weight
Atracurium	Lean body weight	Total body weight
Carbamazepine	Total or Adjusted	Lean body weight
Ciprofloxacin	Adjusted body weight[1]	Adjusted body weight[1]
Cyclosporine	Lean body weight	Lean body weight
Flucytosine	Lean body weight	Lean body weight
Linezolid	Adjusted body weight[1]	Adjusted body weight,[1] or by therapeutic response
Lithium	Lean body weight	Larger than non-obese
Phenytoin	Adjusted body weight[1]	Adjusted body weight[1]
Propofol	Total body weight	Total body weight
Theophylline	Lean body weight	Adjusted body weight[1]
Vancomycin	Total body weight	Total body weight
Vecuronium	Lean body weight	Lean body weight
Verapamil	Total body weight	Lean body weight

[1] Correction factor varies with the drug and study findings.

on degree of lipophilicity, and maintenance doses can be based on drug Cl data. Weight-based approach to loading doses will depend on the distribution of the drug in obese individuals as determined by the V_D/kg compared to that in the non-obese (Table 3). For drugs with a Cl that appears to be correlated with increasing weight, use TBW for dosing and of course consider the need to modify dosing intervals based on pharmacodynamics. On this last point, any available pharmacodynamic data should supplement recommendations based on pharmacokinetic parameters. Close patient monitoring is always required.

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III

INFLUENCE OF FOOD, NUTRIENTS, OR SUPPLEMENTATION ON DRUG DISPOSITION AND EFFECT

8 Drug Absorption with Food

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Objectives

- Describe the factors involved in oral drug absorption and the influences of meal-related variables on those factors.
- Discuss the role that the BCS or BDDCS may play in allowing prediction of meal effects on oral drug bioavailability.
- Describe practical issues in determining the influence of food on oral drug bioavailability within the current regulatory framework.

Key Words: Absorption; bioavailability; dissolution; food; gastrointestinal; permeability

1. INTRODUCTION

Given the convenience of the oral route for drug administration, the large majority of available drug products are oral dosage forms *(1)*. This dictates giving consideration to the timing of drug administration with respect to food intake. There are several reasons for taking a drug with a meal or nutrient beverage. It may be expedient for clinical staff in an institutional setting to administer a drug at a time when meals are provided for inpatients. Outpatient adherence to a prescribed drug dosage regimen may be aided with administration at regular mealtimes. Some drugs are irritating in the gastrointestinal tract and their administration with food or a nutrient beverage can diminish this effect as compared to administration with water.

For some drugs however, administration with a meal can alter oral drug absorption and, possibly, therapeutic effect compared to drug administration in the fasted state with water. In such cases, oral drug–meal interactions can be described as pharmacokinetic and possibly pharmacodynamic in nature.

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One of the more dramatic pharmacodynamic drug–nutrient interactions with significant clinical repercussions may occur following administration of a monoamine oxidase inhibitor with a meal containing tryptamine or tyramine. A patient receiving oral tranylcypromine therapy who ingests wine and cheese as a meal component *(2)* illustrates a classic example for such an interaction requiring emergency care for the resultant hypertensive crisis. This extreme example illustrates an interaction in which a meal component alters clinical response to oral drug administration. This requires that marketed drug product information contain warnings and special prescription labeling.

Pharmacokinetic interactions are reflected by meal influences on drug plasma levels and are the focus of this chapter. Clinically significant changes correspond to maximum drug plasma levels varying above or below the therapeutic range with meal administration. These changes are often mediated by the influence of a meal on the *extent* of drug absorption and are most serious for drugs with a narrow therapeutic window for which effective under- or overdosing can critically impact patient health. Such changes, if known for a drug, dictate prescription labeling with a statement to take the drug with (or without) food and patient counseling on the timing of oral drug administration with respect to a meal. A more common pharmacokinetic effect is represented by a reduction in *rate* of drug absorption manifest as a delay in therapeutic drug concentrations from meal-induced reductions in gastric emptying without a change in systemic availability and extent of absorption. While this interaction is not of concern for many drugs, a meal-induced delay in absorption may be a significant clinical event to a patient on an oral analgesic drug hoping to achieve rapid pain relief.

Following initial review of this topic *(3)*, a number of recent review articles on drug–food interactions are available in the literature *(4–12)*. Since this text is intended more for health-care professionals rather than for drug development scientists in the pharmaceutical industry, this review is geared toward the patient care perspective. A listing of timing of drug administration with respect to meal

Table 1
Medications to be Administered on an Empty Stomach[a]

Generic Name	*Brand Name*	*Clinical Effect/Reason*
Azithromycin capsules	Zithromax	Food decreases absorption of capsules by 50%; taken on an empty stomach. Tablets and suspension can be taken without regard to meals.
Bisphosphonates		
• Alendronate	Fosamax	Dairy products/food can impair absorption; administer 2 h prior to meal
• Etidronate	Didronel	
• Ibandronate	Boniva	
• Risedronate	Actonel	

Dextroamphetamine	Adderall	Acidic foods/juices will impair absorption
Digoxin	Lanoxin	Food delays absorption and may decrease peak concentrations; take consistently with respect to meals
Diltiazem	Tiazac, Cardizem	Absorption is increased in the fasting state; administer before meals
Furosemide	Lasix	Absorption is increased in the fasting state
Glipizide	Glucotrol XL	Increased absorption and improved clinical effect when administered 30 min prior to meal
Levothyroxine	Levoxyl, Synthroid	Absorption is increased in the fasting state; take at same time daily and consistently with respect to meals
Metronidazole	Flagyl	Food decreases the peak concentration and time to peak
Phenytoin	Dilantin	Food alters absorption; taken consistently with respect to meals
Proton pump inhibitors		
• Esomeprazole	Nexium	Administer before meals to improve absorption and maximize clinical effect
• Lansoprazole	Prevacid	
• Omeprazole	Prilosec	
• Pantoprazole	Protonix	
• Rabeprazole	Aciphex	
Quinolones		
• Ciprofloxacin	Cipro	Cations (Ca, Fe, Zn, etc.), antacids, and dairy products will decrease absorption
• Norfloxacin	Noroxin	
Tetracyclines		
• Doxycycline	Vibramycin	Absorption is significantly impaired by iron/milk/food
• Minocycline	Minocin	
• Tetracycline	Sumycin	
Theophylline	TheoDur, TheoBid, SloBid	Food may decrease absorption; taken consistently with respect to meals
Warfarin	Coumadin	Food alters absorption; taken consistently with respect to meals
Zafirlukast	Accolate	Food decreases absorption by up to 40%
Zolpidem	Ambien	Food may delay the onset of action

[a] List is based on 2006 Top 200 brand/generic prescribing by prescription volume. Note that drug/food interactions may exist for other medications not included on this list (e.g., anti-HIV medications). Many medications also have interactions with grapefruit juice.

Table 2
Medications to be Administered with Food[a]

Generic Name	*Brand Name*	*Clinical Effect*
Amoxicillin/ clavulanate	Augmentin	Food increases absorption and decreases GI upset
Carbamazepine	Tegretol	Food increases absorption
Carvedilol	Coreg	Food decreases risk for orthostatic hypotension
Divalproex	Depakote	Food will decrease GI upset
Fenofibrate	Tricor	Food increases bioavailability
Glucocorticoids		
• Methylprednisolone	Medrol	Food will decrease GI upset
• Prednisone		
Glyburide/ metformin	Glucovance	Food will decrease GI upset from metformin
Labetalol	Normodyne	Food increases absorption; taken consistently with respect to meals
Metformin	Glucophage (reg and XR)	Food will decrease GI upset
Metoprolol	Toprol, Toprol XL	Food increases absorption; taken consistently with respect to meals
Niacin	Niaspan	Food decreases GI upset
Nitrofurantoin	MacroBid	Food improves tolerance and increases bioavailability
Nonsteroidal Agents		
• Celecoxib	Celebrex	Food will decrease GI upset
• Diclofenac	Voltaren	
• Etodolac	Lodine	
• Ibuprofen	Motrin	
• Meloxicam	Mobic	
• Nabumetone	Relafen	
• Naproxen	Naprosyn	
• Various others		
Potassium chloride	K-Dur, Klor-Con	Food will decrease GI upset
Tamsulosin	Flomax	Food alters bioavailability; take consistently 30 min after same meal daily
Trazodone	Desyrel	Food increases absorption by 20%
Venlafaxine	Effexor	Food will decrease GI upset

[a] List is based on 2006 Top 200 brand/generic prescribing by prescription volume. Note that drug/food interactions may exist for other medications not included on this list (e.g., anti-HIV medications). Many medications also have interactions with grapefruit juice.

effects on the pharmacokinetics of the most commonly prescribed oral drugs is provided (Tables 1 and 2). In addition, guidelines for clinical meal-effect studies are outlined based on regulatory considerations.

2. REVIEW OF BASIC SCIENCE

For an orally administered drug to become systemically bioavailable it must have acceptable properties and overcome a number of barriers. The drug's dissolution rate, solubility in gastrointestinal (GI) fluids, and intestinal permeability are critical parameters, while GI secretions, GI transit, and first-pass extraction as well as presence of food can impact on drug bioavailability *(12a)*. Drugs vary in their degree of solubility and permeability and can be classified using these properties *(13,14)*. The Biopharmaceutics Classification System (BCS) or the Biopharmaceutics Drug Disposition Classification System (BDDCS) may allow for general predictions of the influence of GI changes including food intake on drug absorption (Table 3a,3b) *(9,13–15)*.

The potential for a meal to influence drug absorption depends on the physicochemical properties of the drug and dosage form as well as meal effects on GI physiology. Drug properties and the rate of drug release from the dosage form into solution in the GI tract define rate-limiting steps in the drug absorption process. Drug dissolution, gastric emptying, and intestinal permeability determine the rate of absorption. However, both intestinal and hepatic first-pass metabolism can couple with these absorption rate limits to affect systemic drug availability. Each of these rate limits can be influenced by meal input.

The extent of drug absorption is determined by drug residence time at sites of absorption and sites of chemical degradation and enzymatic metabolism in the GI tract. Some drugs are unstable in stomach acid so gastric residence time is a critical physiologic variable *(16)*. Since gastrointestinal pH is region dependent, and ionizable drug solubility is a function of pH, drug dissolution and precipitation can impact drug availability in solution for absorption. Further, GI pH can affect intestinal permeability of ionizable drugs. Both drug intestinal permeability and metabolism may be saturable as well as region dependent so at a given dosage, administered fluid volume, gastric emptying, and intestinal transit combine to play a role in rate and extent of drug absorption. Each of these variables can be influenced by meal input.

2.1. Drug Absorption

Drug absorption depends on the physicochemical properties of an individual agent as well as on the properties of the dosage form that contains the active drug.

2.1.1. DEPENDENCE ON DRUG PROPERTIES

The food effect is expected to be most pronounced for drugs whose GI absorption is solubility-limited. The solubility – aqueous or lipid – is a key drug property in determining rate limits to intestinal drug absorption. Many drugs owe some of their potency to their ability to permeate cell membranes and gain access to sites of

Table 3a
Biopharmaceutics Classification System and Predicted Food Effect *(9,13,14)*

BCS Class	*Solubility*	*Permeability*	*Examples*	*Absorption Effect by Food*	*Mechanism*
I	High	High	Acetaminophen, levofloxacin, verapamil	↓ Rate, Ø Extent	↓ Gastric emptying
II	Low	High	Carbamazepine, ciprofloxacin, warfarin	↓ Rate (bases), ↑ Rate (acids),	Altered solubility, ↑ gastric pH
				↑ Extent (others)	↑ Volume & solubilization in dietary fats and mixed micelles
III	High	Low	Atenolol, lisinopril, ranitidine	Generally little effect	Ø, ↓ Intestinal drug concentrations
IV	Low	Low	Ganciclovir, indinavir, mebendazole	Not predictable	N/A

Table 3b
Biopharmaceutics Drug Disposition Classification System and Predicted Food Effect *(14)*

BDDCS Class	*Solubility*	*Metabolism*	*Examples*	*Absorption Effect by Food*	*Mechanism*
1	High	Extensive	Acetaminophen, verapamil	Minimal effect on bioavailability	Absorption dominated by passive diffusion
2	Low	Extensive	Carbamazepine, mebendazole, warfarin	Increased bioavailability	Often substrates for enzymes and efflux transporters which may be inhibited
3	High	Poor	Atenolol, levofloxacin, lisinopril, ranitidine	Reduced bioavailability	Reliant on uptake transporters which may be inhibited
4	Low	Poor	Amphotericin, ciprofloxacin, furosemide	Not predictable	N/A

pharmacological action. Good membrane permeability is generally a function of good lipid solubility (lipophilicity). This is accompanied by poor hydrophilicity (referring to aqueous solubility) so the absorption rate of lipophilic drugs is limited by poor dissolution into the aqueous media of the GI tract. Dosage formulation can sometimes reduce this problem since drug dissolution rate also depends on the powder drug surface area exposed to water. Drug powder surface area can be increased by micronization and for a low-dose drug like digoxin (0.25 mg; BCS Class II or III; BDDCS Class 4); this greatly improves drug absorption into the systemic circulation. Some increase in absorption via micronization is observed for a high-dose drug like griseofulvin (500 mg; BCS Class III or IV, BDDCS Class 2) but the improvement is only modest. Enhancing drug absorption through increased dissolution at the drug particle surface area depends on the amount of drug that can be dissolved within the small intestine during transit time. This is, of course, more difficult to achieve at higher doses.

As would be expected, many lipophilic drugs are better absorbed when administered with a fat-containing meal. Absorption may increase as a direct function of meal fat content. A good example of this is the first-marketed HIV-protease inhibitor, saquinavir. This drug was approved quickly in spite of the fact that an oral dose administered with water resulted in only 5–10% of this high-dose drug reaching the systemic circulation. It was observed that when patients took this medication with a high-fat meal, systemic availability increased five- to tenfold. Newer dosage forms take advantage of this by putting the drug in a lipid vehicle inside a soft-gel capsule *(17)*.

Hydrophilic drugs possess good aqueous solubility and can dissolve quickly but do not permeate lipid membranes very readily. The absorption of these drugs is therefore limited by membrane permeability rather than dissolution rate. Co-administration with meals does not typically affect the absorption of hydrophilic drugs. Some hydrophilic drugs are exceptional and have high membrane permeability due to membrane transport by nutrient carriers. Several amino acid and small peptide drugs fall into this category. While it might be anticipated that protein meals would inhibit the absorption of these drugs, this has not been observed in clinical practice *(18)*.

Another class of hydrophilic drugs with good membrane permeability includes compounds of sufficiently small molecular size (< 200 Da) that permeate membrane paracellular pathways. Since neither dissolution nor membrane permeation is rate limiting to absorption, gastric emptying controls the rate of absorption of these smaller hydrophilic drugs (e.g., acetaminophen) *(19)*. The effect of meal intake on gastric emptying rate is a point to be discussed in a later section of this chapter.

Drugs may also have both poor dissolution rates and poor membrane permeability. Such drugs are not poorly water-soluble because they are lipophilic but rather because they have a high capacity to form intermolecular hydrogen bonds. Such compounds tend to have high melting points and form poorly dissolving crystals. While food can negatively affect the absorption of such compounds, they rarely make it to the market as oral drug products since their properties dictate poor oral absorption even in the fasted state *(20)*.

2.1.2. Dependence on Dosage Form Properties

Some of the most clinically significant food effects on oral drug delivery have been in association with the administration of modified-release dosage formulations of drugs with narrow therapeutic indices *(21–23)*. Since these formulations typically contain very high doses of highly permeable drugs, meal component interactions with formulation components that alter the intended release rate can produce an effective under- or overdose. In the extreme, meal-induced "dose dumping" as a bolus drug release process of the entire dose of a modified-release formulation can result in toxicity in individual patients *(24)*.

Less dramatic meal effects on modified-release dosage forms are seen as meal-controlled delays in oral drug delivery to the systemic circulation. Since non-disintegrating particles greater than 2 mm in diameter do not empty from the stomach with the gastric liquid contents *(25)*, oral drug delivery from dosage forms with these physical properties may be influenced by meal intake. Such dosage forms are subject to emptying with the timing of the interdigestive migrating motility complex (IMMC) under the control of the circulating gut peptide, motilin *(26)*. Following administration of a meal, this complex is disrupted and gastric emptying is influenced by other gut peptides *(27)* as regulated by caloric density and intestinal feedback control *(28)*. Gastric emptying control by IMMC is not re-established until most of the meal calories have been emptied. As a result, with high-caloric density input, gastric emptying of non-disintegrating dosage forms greater than 2 mm in diameter may experience substantial time lags before emptying into the intestine. Such delays in absorption may be reflected in delayed drug plasma levels *(29)*.

2.2. Meal Effects

A meal may influence GI transit and drug absorption. Although mean small intestinal transit time (between 3 and 4 h) is remarkably independent of fasted versus fed-state conditions *(30)* several drugs *(31,32)*, drug excipients *(33)*, and over-the-counter products *(34)* have been shown to influence the extent of drug absorption via influences on intestinal transit. Careful studies have shown that a drug's small intestinal residence time in human subjects is approximately 200 min whether it is administered with or without a meal *(30)*. However, gastric emptying rate is a function of fed or fasted state. Both volume and caloric density of a meal play a role.

2.2.1. Administered Volume

In many studies of meal effects on drug absorption, a comparison of fasted versus fed conditions is not controlled for administered volume *(9)*. This aspect is certainly consistent with the variability in patient fluid intake with oral drug administration of prescription drugs and may therefore represent a legitimate statistical comparison. Although studies uncontrolled for meal volume may verify whether or not there is a significant food effect on oral drug bioavailability, fasted-state pharmacokinetics may depend on administered volume for several reasons. When a drug is administered with a noncaloric aqueous liquid, the rate of human gastric emptying of liquid containing dissolved drug and small drug particles is first order and dependent on the volume load after an initial lag period. When drug is administered with small volumes of fluid in the range of 60 mL (2 fl oz), emptying of the gastric contents is more dependent on the IMMC than is the case when larger volumes in the range of 240 mL (8 fl oz) are administered *(35)*. Thus, emptying of a drug contained in the gastric fluid contents will be more erratic with respect to the time of drug administration for smaller than larger co-administered fluid volumes. In addition, the first-order gastric emptying of larger volumes is more rapid than for smaller volumes for all phases of the IMMC.

Meal administration is typically high volume, but intestinal feedback control dictates that the gastric emptying rate and the subsequent drug delivery to absorption sites in the small intestine is a function of caloric load or density (kcal/mL). Furthermore, if fasted-state drug administration is conducted under low volume conditions compared to the typical high volumes consumed with meal administration, initial intestinal drug concentrations will be much higher in the fasted-state condition as compared to meal co-administration. In addition, certain meals may dictate significant gastric, intestinal, biliary, and pancreatic secretions that can further dilute fed-state drug concentrations as compared to the fasted state. For those drugs that show nonlinear characteristics as a function of local concentrations, such differences in the volume of administration can complicate the interpretation of food-effect studies. It would be advisable to administer the same volume of noncaloric fluid in fasted-state studies as the volume of meal administered in fed-state studies. While this only controls initial conditions, since meals will influence GI fluid absorption and secretions, a more mechanistic comparison is offered when meal-effect studies control for volume.

2.2.2. CALORIC LOAD

Caloric feedback signals from the intestine that control gastric emptying have been studied for simple carbohydrate, fat, and protein meals. Triggers for these signals include sodium-monosaccharide co-transport *(36)*, peptide digestion *(37)*, and chylomicron formation *(38)*. The magnitude of the signal and the extent of gastric emptying inhibition are a function of the extent of nutrient and intestinal sensor contact down the length of intestine *(39,40)* and therefore depend on both digestion and initial caloric load. The pattern of calorie-regulated gastric emptying is different than for volume-controlled gastric emptying *(35)* and has been studied in most detail for simple glucose meals *(41)*. With respect to oral drug delivery, calorie intake will result in a different volumetric input rate from drug contained in the gastric liquid into the intestine than for noncaloric liquid intake. This will, in turn, influence differences in rates of co-administered drug delivery to sites of absorption and first pass elimination in the upper intestine with nutrient versus noncaloric input. Even a very low-fat meal (166 kcal, 0.44 g fat) significantly improves both rate and extent of absorption of a low solubility lipophilic drug (e.g., quazepam) compared to the fasted state, although making no difference to two other lipophilic benzodiazepines *(42)*. Caloric control of intestinal drug delivery rates from gastric emptying can result in less variability in oral drug pharmacokinetic profiles compared to drug administration with small volumes of noncaloric fluid. This is the case since the timing of gastric emptying with an IMMC will be highly variable with respect to the time of oral drug administration. For example, not only does the bioavailability of rifalazil improve with food but the variability decreases as well *(43)*.

2.2.3. Meal Type

Although different meal types provide a similar rate of fluid delivery from the stomach to the small intestine based on caloric density *(44)*, intestinal fluid volumes and resultant drug concentrations depend strongly on meal type. Simple carbohydrate meals may result in substantial water absorption in the small intestine *(45)* that may, in theory, result in more concentrated drug solutions in the intestinal lumen. Protein meals promote higher intestinal fluid volumes as the result of significant pancreatic secretions *(37)* which may, in theory, result in more dilute drug solutions. Even greater intestinal volumes should result from intake of high-fat meals since pancreatic and biliary secretions will be stimulated to a greater extent than with other meal types *(46)*. Bile secretion in response to food is rapid and results in lipid degradation products by the proximal jejunum *(47)*. Dietary lipids and bile acids explain in large part the significantly higher solubility of poorly soluble drugs in intestinal fluids during the fed state *(48)*. The fed-state balance between intestinal fluid secretion and intestinal water absorption is very much a function of the rate at which complex meals are converted to simple nutrients. Simple carbohydrates tend to be rapidly broken down in the upper GI tract, while protein and fat digestion are slower processes *(46)*. The greater extent of upper intestinal water absorption observed with simple carbohydrate meals as compared to protein meals is the result of both differences in the rate of digestion and differences in the absorption pathways of the resultant elementary nutrients. Most monosaccharides are absorbed by sodium-dependent co-transporters, which promote intestinal water absorption *(49)*. While a number of sodium-dependent transporters support amino acid transport, many intestinal amino acid transporters utilize sodium-independent mechanisms for mucosal absorption *(50)*.

2.3. Physical–Chemical Interactions in the Gastrointestinal Tract

Absorption of drugs that are co-administered with meals may be altered both by meal component influences on GI physiology and by meal component influences on drug and dosage form properties.

2.3.1. Meal Viscosity

Although this factor is certainly related to meal type based on digestibility, the fact that meal viscosity can be studied independent of caloric input dictates consideration as an additional meal-effect factor. As opposed to the effect of high fluid volume intake resulting in local gastric pressure distention, which speeds gastric emptying, high viscosity intake slows gastric emptying *(51)*. If insufficient digestion occurs in the gastric contents to substantially reduce the solution viscosity entering the small intestine, several factors may effect drug absorption following oral administration. First, higher viscosity may increase upper intestinal residence time. In addition, based on the inverse dependence of solute diffusivity on medium viscosity, diffusion of dissolved drug from the intestinal lumen to sites of absorption at the intestinal membrane will be slowed. Finally, high viscosity can slow drug dissolution rate by decreasing solute diffusion away from the solid drug interface *(52)*.

2.3.2. Meal Effects on Gastrointestinal pH

Medium pH can impact both the solubility and membrane permeability of ionizable drugs. Since meal intake may alter gastric and upper intestinal pH, the ionization state of weak acid and weak base drugs with pKa in the range of GI pH variation will be affected. Since non-ionized drug has greater membrane permeability than ionized drug, nutrient effects on mucosal microclimate pH might be expected to influence the absorption of drugs in this class. Enterocyte metabolism of glucose lowers microclimate pH via sodium–proton exchange *(53)*. However, little overall effect on drug absorption is observed.

Food effects on weak acid drugs are not common *(4)*, since ionized drug promotes high solution concentrations in the intestine and permeability of the non-ionized compound is frequently high enough to shift ionization equilibrium toward favorable absorption. The previously marketed nonsteroidal anti-inflammatory drug (NSAID), bromfenac, may be exceptional in this regard *(54)*. This drug showed a reduced analgesic effect when administered with a meal. This unusual meal effect for a weak acid drug with a pK_a within normal GI pH variability may be a function of the exceptionally low dose of bromfenac as compared to other NSAIDs.

The potential for meal effects on weak base drugs, with pK_a in the range of GI pH variation, is greater than for weak acids. This is a function of their potential to precipitate at intestinal pH or high gastric pH as promoted by some types of meals *(55)*.

2.3.3. Meal Calcium Content

There is experimental evidence that the stomach controls the rate of soluble calcium delivery to the small intestine. This element of intestinal feedback control has been verified indirectly by observations on the rate of gastric emptying of calcium chelators. The observation of feedback control appears to be an indirect effect of the capacity of calcium chelators to remove ionic calcium from the tight junctions *(36)*. In isolated intestinal tissue and cell culture, removal of calcium from the tight junctions may result in an increase in paracellular solute transport *(56)*. A defense mechanism to slow the delivery of calcium chelators from the stomach would thus serve a protective feedback control function. Since a number of simple nutrients resulting from fat digestion sequester calcium *(36)*, this may provide a parallel feedback control mechanism to that of caloric content in controlling the rate of gastric emptying. In addition to the influence of this factor on the rate of gastric delivery to the small intestine and the availability of the paracellular pathway for absorption, calcium is known to bind a number of drugs, like tetracycline, reducing their availability for absorption in the intestine *(57)*.

2.3.4. DRUG BINDING TO MEAL AND BILIARY COMPONENTS

Drug binding, complexation and micellar sequestration, including bile acid interactions, can reduce effective drug concentration in the intestinal lumen and thereby reduce absorption. Over-the-counter product influences include antacid effects on drug binding, oil emulsion product effects on drug sequestration and fiber effects on viscosity; these may mediate a number of these interactions.

Drug binding to nutrient components has been most often cited with drug co-administration with enteral nutrition products. These interactions may include both reversible and irreversible binding components when drug–nutrient co-administration is through nasogastric tubes *(58)*. Drug binding to the protein component of common enteral nutrition formulations has also been reported *(59)*.

2.3.5. MEAL EFFECTS ON FIRST-PASS ELIMINATION

The significant clinical impact of grapefruit juice on the oral bioavailability of several drugs *(60)* brought meal component effects on first-pass drug elimination to the forefront of food-effect studies. Other fruit juices have since been studied. This is an example of a meal component directly inhibiting the activity of first-pass elimination factors dictating an increase in oral bioavailability. Such inhibitory effects can lead to dramatic increases in oral drug delivery with risk for toxicity *(61)*. Meal input can influence drug first-pass elimination elements through saturation as well as inhibition. It has been stressed that oral drug dosage form administration factors, including co-administered meals, influence drug concentration gradients that are the driving forces for drug absorption. For example, meal lipid solubilization of an orally administered drug may serve to increase lipophilic drug concentration in the GI lumen. Oral bioavailability is further determined by intestinal and hepatic transporters and enzymes with activities that may or may not be saturated as a function of local drug concentration gradients. By impacting local drug concentration gradients around first-order to zero-order transition points for saturable absorption and first-pass elimination components, meals can exert an effect on oral bioavailability independent of inhibition on first-pass elimination.

2.3.5.1. First-Pass Metabolism. Meals can affect both intestinal and hepatic first-pass metabolism. With regard to nutrient component inhibitory effects, phase I drug-metabolizing pathways have been observed to be impacted to a greater extent than phase II metabolic pathways *(62)*. Since grapefruit juice inhibits the cytochrome P450-3A4 isoenzyme (CYP3A4) which is responsible for the intestinal metabolism of the greatest number of drugs and drug candidates, this elimination element has been the focus of drug–nutrient interaction studies. Drug candidate screening now includes human hepatocyte, microsomal, or recombinant enzyme metabolism data. Since CYP3A4 is a component of this screening, a measure of the potential for intestinal metabolism is also available. Caco-2 monolayers enhanced in CYP3A4 have been developed to screen drug candidate intestinal metabolism coupled to membrane influx and efflux transporters *(63)*. It has been further recognized that grapefruit juice may also inhibit influx transporters (e.g., OATP) and efflux transporters (e.g., P-glycoprotein) *(64)*. Basic studies to isolate the grapefruit juice component responsible for CYP3A4 inhibition have focused on furanocoumarins acting as mechanism-based inhibitors, but have generated even broader investigations of elementary nutrient factors that might impact the important drug-metabolizing enzyme and coupled transporters *(64,65)*.

Other drug oxidizing enzymes in the intestine *(66)* and liver *(67)* may be influenced by nutrient intake. In animal studies, it was reported that methionine and cysteine inhibited flavin monooxygenase (FMO)-mediated cimetidine sulfoxidation *(68)*. This interaction is less important in humans and cimetidine's safety further reduces its clinical significance. The absorption of a narrow therapeutic index drug that undergoes FMO-mediated sulfoxidation is not influenced by meal intake *(69)*. However, for a new drug entity, the screening of a battery of metabolizing enzymes and further basic investigations on elementary nutrient effects on metabolism may yet uncover meal effects on drug-metabolizing enzymes other than CYP3A4.

2.3.5.2. Permeability Limitations Due to Intestinal Efflux. Research has implicated P-glycoprotein (Pgp)-mediated drug export as a factor limiting intestinal permeability of some compounds *(70)*. Although cell culture data may overestimate the in vivo activity in some cases *(1)*, this has led to further investigations on the effect of nutrients on this elimination pathway *(71)*. Inhibition of Pgp by dietary flavanoid components has been reported *(72)*. The influence of grapefruit juice on Pgp activity was mentioned in the previous section. Because Pgp substrates are typically hydrophobic and poorly water soluble, saturation of Pgp is difficult to achieve. However, elevated drug concentrations through meal lipid solubilization could lead to a nonlinear concentration dependence of Pgp-mediated drug export *(73)*. For lipophilic compounds that are Pgp substrates, the combined effects of increased permeability via Pgp inhibition with an increase in drug concentration through solubilization by a high-fat meal might be projected to substantially increase absorptive flux. Most Pgp substrates are neutral or weak base hydrophobic compounds *(74)*. Some weak acid drugs are substrates for intestinal multidrug resistance protein (MDR1 = Pgp) and multidrug resistance-associated proteins (MRP1-5) that belong to the ATP-binding cassette (ABC) superfamily of membrane transporters *(75)*. There may be additional intestinal membrane proteins mediating drug and/or drug metabolite export yet to be identified that could interact with the nutrient components of a meal *(76)*.

There is evidence that drug metabolites are substrates for intestinal exporters and it is proposed that intestinal metabolism and mediated mucosal efflux are coupled processes in intestinal drug elimination *(77)*. The function of such coupling, with respect to CYP3A4 and Pgp, is suggested to promote efficient intestinal elimination *(78)*. Since most metabolites are less hydrophobic than their parent drug, they might be weaker substrates for Pgp. Efficient intracellular metabolite production would set up a favorable metabolite-to-drug ratio minimizing potential competition for Pgp export *(79)*. Some inhibitors of Pgp are also inhibitors of CYP3A4 and these include some compounds that are meal components *(80,81)*. Given the possibilities of inhibition and saturation of coupled intestinal drug elimination components, the impact of meal intake on first-pass metabolism may be mechanistically complex.

2.3.6. Meal Effects and Region-Dependent Absorption

Many drugs possess sufficient lipophilicity to promote high permeability throughout the small and large intestine *(82,83)*. However, for some compounds, intestinal absorption and elimination may not be a homogeneous or even a continuous process throughout the entire small intestine. This is the case for some drugs that are absorbed by a carrier-mediated process *(84)* and is generally true for drugs of moderate lipophilicity as a function of a reduction in absorbing surface area in the lower small intestine *(85)*. For small hydrophilic compounds predominantly absorbed through paracellular pathways, it would be anticipated that permeability would decrease with distance down the intestine since paracellular pathways become more restricted by the tight junctions *(86)*. However, this has not been confirmed with the paracellular marker compound mannitol *(87)* and regulation of this pathway may be variable as a function of intestinal region *(88)*. What may prove to be a significant factor in regionally dependent drug absorption are differences in drug elimination as a function of intestinal region *(79)*. Furthermore, resultant differences in the rate of absorption and elimination in different regions of the intestine can dictate variability in the rate of drug presentation to the liver.

Studies have indicated that region dependence in the absorption of some drugs may underlie a significant meal effect on systemic drug availability following oral administration *(79,89)*. When drug absorption is better in the upper small intestine than in the mid and lower regions, meal factors that serve to reduce drug availability to the absorbing membrane may produce negative effects on systemic availability. These factors may include drug-binding interactions with meal components or any physical hindrance to drug transport provided by meal intake in the upper intestine that reduces drug availability to sites of absorption. Reduced drug absorption in the upper intestine can result in delivery of lower drug concentrations to sites of first-pass elimination. It is possible that drug administration without meals may provide intestinal concentrations sufficient to saturate first-pass metabolism, while administration with a meal results in drug concentrations below first-pass saturation levels. Based on a limited set of studies, the potential for a negative meal effect is more likely if there is region-dependent absorption.

2.3.7. Meal Effects on Splanchnic Blood Flow

Just as nutrient effects on region-dependent drug absorption should alter rate of drug delivery to sites of first-pass elimination, meal effects on splanchnic blood flow would be anticipated to alter the rate, and possibly extent, of first-pass drug elimination. This may be the case with meal effects on alcohol elimination and possibly underlie varying meal effects on high first-pass drugs like propranolol.

3. CLINICAL EVIDENCE – THE CASE OF THE PROTEASE INHIBITORS

The first HIV-protease inhibitor on the market was saquinavir. The need for treatment with this drug class dictated approval in spite of a low 5% oral bioavailability. This was due to the low intrinsic solubility and high first-pass metabolism of this drug. Although orally administered as the mesylate salt at 600–800 mg three times a day, this low pK_a weak base drug may dissolve in the acid pH of the stomach but would enter the upper small intestine at concentrations three orders of magnitude above its intrinsic solubility. Such a high level of supersaturation promotes the potential for intestinal precipitation. Observations that saquinavir administration with a high-fat meal increased oral bioavailability five- to tenfold *(90)* led to the development of a lipid-melt soft-gel capsule formulation that similarly increased oral bioavailability *(17)*. Although no longer marketed, this tremendous increase in bioavailability, as a function of dosage formulation, was likely due to a combination of solubilization of the drug in the intestine by lipid meal components and the resultant saturation of some elements of first-pass elimination, particularly in the intestine. Saturation of intestinal CYP3A4 and Pgp should result in a faster rate of absorption and a higher rate of drug presentation in the portal vein to the liver.

The third drug marketed in this class of compounds was indinavir, which showed a decrease in bioavailability when administered with meals *(91)*. Goals in the molecular design of this drug included the addition of a weak base moiety with higher pK_a to increase its solubility. It is administered as a sulfate salt at a dosing regimen similar to that of saquinavir. As was the goal of this molecular design ploy, it is likely that indinavir achieves higher concentrations in the GI tract and a higher driving force for absorption as compared to saquinavir when administered without meals. The higher intestinal indinavir concentrations compared to saquinavir saturate elements of first-pass elimination resulting in oral indinavir bioavailability tenfold higher than the initial saquinavir product. However, when the drug is administered with a high-caloric meal, a 60% reduction in indinavir bioavailability is observed. When the drug is administered with a light meal of low caloric density, the meal effect can be minimized *(91)*.

Possible contributions to a negative meal effect on indinavir were investigated in HIV-infected patients as a function of meal type *(55)*. Indinavir plasma levels and gastric pH were simultaneously measured as a function of time after oral indinavir administration. In this clinical study, protein meals produced the greatest and most statistically consistent reduction in oral indinavir bioavailability as compared to administration with an equal volume of water. Gastric pH, as measured by radiotelemetry in these patients, showed that the protein meal caused a lengthy (4 h) pH elevation (around $pH = 6$ over this time period) as compared to other meal types or drug administration with water. Only slight pH elevations of short duration were observed with the other meals since they offer little buffer capacity to gastric acid secretion. It is suggested that the protein meal will provide the greatest potential for poor dissolution and/or precipitation of indinavir in the stomach as a function of elevated pH.

All meal types produced a significant negative meal effect on indinavir oral bioavailability, though not to as great an extent or as consistently from patient-to-patient as the protein meal. Meal types studied in addition to the high-caloric protein meal included high-caloric carbohydrate and high-caloric lipid meals as well as a noncaloric viscous meal. It is likely that high-caloric density meals, as well as high viscosity meals slow gastric emptying and the rate of drug transport in the intestinal lumen to sites of first-pass elimination to an extent that they are no longer saturated.

Other contributions to the negative meal effect have been investigated in isolated animal and tissue experiments to include influences of intestinal regional differences *(79)*. In the case of indinavir, rat intestinal perfusion studies show high permeability in the upper intestine and dramatically reduced permeability in the lower small intestine. The drug is metabolized by CYP3A4 in both the upper intestine and the liver, and the predominant intestinal metabolite is excreted into the intestinal lumen. Interestingly, no metabolism is observed in the lower small intestine and metabolism is greatly reduced in the mid-jejunum as compared to the upper jejunum. Indinavir is also a substrate for intestinal Pgp and this may account for its poor permeability in the lower intestine where Pgp exports drug that is absorbed into the enterocyte back to the intestinal lumen. The fact that CYP3A4 metabolism dominates indinavir elimination in the upper small intestine while Pgp efflux controls its elimination in the lower small intestine permits some mechanistic studies in the rat. Reaction-coupled transport in the form of cellular metabolism subsequent to cell entry increases the rate of indinavir absorption into the enterocyte by increasing the concentration gradient driving force for cellular entry. If metabolites compete with drug for export by Pgp, this could promote drug absorption across enterocytes in the upper small intestine while there would be no such competition in the lower small intestine *(79)*.

Continued elimination as the drug moves down the intestine will depend on regional CYP3A4 and efflux activity as well as on changes in drug concentration down the intestinal tract. Meal effects on the rate of drug delivery to these sites of first-pass elimination might be anticipated to produce alterations in bioavailability. The potential for a positive meal effect from lipid-enhanced solubility compared to negative meal effects from slowed delivery to saturable sites of first-pass elimination may also be determined by variation in these elimination factors as a function of intestinal region. Some evidence for this might be gleaned by a comparison of indinavir with nelfinavir, the fourth HIV-protease inhibitor to reach the market. Nelfinavir shows a positive meal effect similar to saquinavir *(92)*. In rat intestinal perfusion of upper jejunum compared to lower ileum, nelfinavir showed no region-dependent permeability as compared to the dramatic regional permeability differences cited above for indinavir *(79)*.

4. PRACTICAL ISSUES AND REGULATORY CONSIDERATIONS

Food and drug intakes often coincide because meals habitually serve as temporal reminders to patients of timely drug administration. Drugs may also be intentionally co-administered with meals to minimize GI side effects, a common practice for certain drug classes (e.g., NSAIDS). Administration of drugs concomitantly with or in close proximity to meals could result in a significant decrease or increase in the overall rate and extent of drug absorption and, as a consequence, may occasionally compromise efficacy or lead to adverse effects. These situations justify drug administration under a fasted state. High doses of Theo-24, a formulation that allows for once daily theophylline administration, and ibandronate, a bisphosphonate for improving bone mineral density are examples in this category *(93)*. On the other hand, when changes in the rate and extent of absorption lead to lower side effects or improved efficacy, concomitant administration with meals is desirable and is generally recommended (e.g., atovaquone) *(93)*. Often, changes in rate and extent of drug absorption resulting from drug-food interactions are unlikely to be clinically significant. In such cases, FDA-approved labels are either silent with respect to how the drug should be administered or may state that the drug could be taken without regards to meals (e.g., losartan) *(93)*. Regulatory agencies generally make these assessments and recommendations after reviewing food-effect bioavailability studies for new drug applications (NDAs), factoring in their exposure–response relationships and clinical safety and efficacy information submitted with the sponsors' registration dossier.

Food intake may influence drug exposure owing to the effect that meal components have on the physiological system, which, in turn, may influence absorption (e.g., grapefruit juice may increase exposure through enzyme and/or efflux inhibition; high-fat, high-calorie meals prolong gastric emptying time and may also affect drug solubility). Drugs may also physically or chemically bind to specific food items (e.g., digoxin bioavailability may be lower with a high-fiber meal) and as a result may affect drug exposure. In the following sections, guidelines for meal-effect studies are provided from a regulatory perspective.

4.1. Drug Classification and Food Effects

4.1.1. Bioavailability

Various physicochemical and physiological bases for oral drug-meal/food interactions have been alluded to in this chapter (i.e., including delayed gastric emptying, secretions affecting GI pH and solubilization, changes in splanchnic blood flow, meal components affecting metabolism or transport systems and chelation or complexation processes). Prediction of changes in drug exposure due to GI perturbations has been attempted using BCS of drugs *(13)* and may be approached using the BDDCS classification *(14)*.

It has been postulated that important food effects on bioavailability are least likely to occur with many rapidly dissolving, immediate-release drug products containing highly soluble and highly permeable drug substances (BCS Class I) (Table 3a,b). This is thought to be a consequence of pH- and site-independent absorption of Class I drug substances, their insensitivity to differences in dissolution and their extensive absorption *(94)*. Because the proximal intestinal region is the primary site of drug absorption, a Class I drug may undergo delayed absorption owing to meal-related prolonged gastric emptying time (resulting in longer T_{max} and lower C_{max}) with an overall unchanged extent of absorption (AUC) (e.g., immediate-release theophylline) *(95)*. This concept seems to hold true unless the drug undergoes high first-pass elimination, or is highly adsorbed, complexed or unstable in the gastric milieu. Immediate-release propranolol and metoprolol are BCS Class I drugs that undergo high first-pass elimination. A large increase in the extent of absorption is observed when these drugs are administered with food *(96)*. The latter is partly attributable to the splanchnic blood flow changes caused by meal intake. Because dissolution of low solubility drugs may be enhanced with food, bioavailability may be superior, if taken with meals (e.g., carbamazepine) *(97)*. In general however, for immediate-release drug products of BCS Classes II, III, and IV with low solubility or low permeability food effects are most likely to result from a more complex combination of factors that influence the in vivo dissolution of the drug product and/or the absorption of the drug substance. In all cases, because the relative direction and/or the magnitude of food effects on formulation bioavailability are difficult to predict, and because the regulatory agency assesses the clinical implications of this change, a food-effect study is recommended for all new chemical entities, irrespective of their classification.

4.1.2. BIOEQUIVALENCE

Formulation factors are expected to play a minor role in bioavailability of Class I drug products because they rapidly dissolve in a wide pH-range environment and are well absorbed. While food can affect C_{max} and T_{max} by delaying gastric emptying and prolonging intestinal transit time or in certain instances increasing bioavailability, the food effect on these measures is expected to be similar for different formulations of the same Class I drug, provided they have a rapid and similar dissolution. As a result, these products should be bioequivalent under both fasted as well as fed conditions. Although an increase in exposure is observed for propranolol and metoprolol when concomitantly administered with meals, various immediate-release formulations were shown to be bioequivalent under both fasted and fed conditions. In the case of Class II, III, and IV drugs, excipients or interactions between excipients and the food-induced changes in gut physiology can contribute to food effects and consequently may influence the demonstration of bioequivalence *(98)*. When new formulations are developed with the intention of interchangeability, appropriate documentation of therapeutic equivalence *(99)* is required.

4.2. Food Effects on Modified-Release Formulations

4.2.1. BIOAVAILABILITY

Administration of a drug product with food may change the bioavailability by affecting either the drug substance or the formulation. In practice, it is difficult to determine the exact mechanism by which food changes the bioavailability of a drug product without performing specific mechanistic studies. The underlying BCS principles involving the expected influence of food apply primarily to immediate-release formulations where the drug is released instantaneously from the dosage form. In these instances, solubility and permeability limit the rate of absorption.

Unlike the conventional immediate-release formulations, modified-release products are specially designed in that the formulation and manufacturing variables control the release rate of the drug from the dosage form. As a consequence, these factors may play a key role in determining the outcome of a food-effect bioavailability study, irrespective of the BCS classification of the drug substance. Systemic availability of a drug from the modified-release product under fed conditions is complex. It consists of a combination of the physiological effects of meals on drug release (affecting disintegration, dissolution, degradation, or diffusion) from these dosage forms, as well as the effect of meals on drug absorption, after it is released from the modified-release product.

Modified-release oral dosage forms (e.g., delayed-release, sustained-release, products) are predominantly designed to provide therapeutic advantages over conventional immediate-release formulations. These include curtailing frequent dosing intervals, minimizing peak and trough plasma concentrations, and overcoming the instability at gastric pH. During the late 1970s to early 1980s, extensive experience with development of several modified-release dosage forms demonstrated that integrity of these products in the physiological environment of a fed state could present a challenge for formulation scientists. Theophylline is a noteworthy example for which a number of modified-release preparations were tested. Owing to its narrow therapeutic window of use, food effects on formulation robustness drew considerable attention of the scientific community. Immediate-release theophylline formulations have a minimal food effect on overall drug exposure. However, when prepared as modified-release formulations, these effects became formulation dependent. For instance, it was shown that rate as well as extent of absorption was increased when Theo-24 was administered with a high-calorie meal (800–1000 calories, 50% fat) yet a light meal had a minimal effect. Temporal separation of meals and drug administration helped minimize the food effect. In another example, although absorption from Theo-Dur sprinkles was reduced, food effect from Theobid-Duracap remained unchanged *(21)*.

Modified-release products may contain large amounts of drug, designed to be delivered over a prolonged period of time. Lack of formulation integrity or robustness may bear upon its safe and effective use. Findings from modified-release theophylline studies during the 1970s and 1980s served as a testimony to this concern and reinforced the need for thorough in vivo formulation evaluation before proceeding with further drug development. In fact, for regulatory purposes at the U.S. FDA, oral modified-release dosage forms are required to demonstrate lack of dose dumping, a phenomenon exemplifying the untimely release of an undesirable and unintended amount of drug from the modified-release dosage form *(100)*. To date, in vitro tests have not been consistently predictive of either the extent of in vivo food effect or the dose dumping with the modified-release formulations. The FDA therefore recommends that a tangible in vivo food-effect study be conducted with all new modified-release formulations. This study serves to fulfill the regulatory requirement of a test for dose dumping. Sponsors of all modified-release dosage forms generally conduct one or more food-effect studies with the formulation under development. When food effect is identified, sponsors generally attempt to understand the source of interaction (i.e., whether food effect is due to the drug substance or formulation). For certain drug products, insight into the temporal relationship between food and drug intake and impact of different meal types on drug exposure may be deemed clinically useful. The sponsors are encouraged to understand this relationship and when appropriate, to specify these in the dosage and administration instructions of the package inserts to optimize therapeutic benefits of the drug *(101,102)*.

4.2.2. Bioequivalence

It has been demonstrated that various modified-release formulations of the same drug could exhibit different food effects. Some examples are theophylline and nifedipine modified-release formulations (refer to theophylline labels for Theo-24 and Uniphyl, nifedipine labels for Adalat CC and Procardia XL) *(93)*. When new modified-release formulations are developed with the intention of interchangeability, it is critical to demonstrate bioequivalence under both fed and fasted conditions.

4.3. Regulatory Studies Under Fed Conditions

Concomitant food and drug intake could result in clinically significant effects that may warrant appropriate study design considerations in the clinical trials. Information on food administration in relation to drug intake also serves to optimize efficacy and safety once drugs are approved, by providing important and useful directions to patients regarding dosage and administration in package inserts. FDA recommends that food-effect bioavailability studies be conducted for all new drugs and drug products during the Investigational New Drug (IND) period. The purpose of such a study is to assess the effects of food on the rate and extent of absorption of a drug when the drug product is administered shortly after a meal as compared to administration under fasting conditions.

When generic equivalents of approved new drugs are developed, the manufacturer is required to submit an Abbreviated New Drug Application (ANDA). The FDA requires demonstration of interchangeability between the ANDA and the reference-listed drug. The bioequivalence studies in support of interchangeability are recommended under both fasted and fed states, with a few exceptions.

4.4. The Food-Effect Bioavailability and Fed Bioequivalence Studies Guidance

Study design variables are central to the outcome of a food-effect bioavailability study. Food effects on bioavailability are generally greatest when the drug product is administered shortly after a meal is ingested. The nutrient and caloric contents of the meal, the meal volume, and the meal temperature can cause physiological changes in the GI tract in a way that affects drug product transit time, drug dissolution, luminal diffusion, drug permeability, and systemic availability. In general, meals that are high in total calories and fat content are more likely to affect the GI physiology and thereby result in a larger influence on the bioavailability of a drug substance or drug product. A survey of food-effect studies in NDAs for immediate-release and modified-release products reviewed by FDA revealed that important study design variables were not consistent in these studies and yet package inserts were not reflective of these irregularities. The FDA was also aware that the meal recommended for the food-effect bioavailability studies was of a higher caloric content than the fed bioequivalence study meal. These findings provided the impetus for harmonization through a formal guidance development from the regulatory agency addressing study design issues, data analysis, and labeling for studies under fed conditions.

FDA published a guidance document for industry *(103)* that provides recommendations on (1) when food-effect bioavailability studies should be conducted as part of INDs and NDAs and (2) when fed bioequivalence studies should be conducted as part of ANDAs. This guidance applies to both immediate-release and modified-release drug products and provides recommendations for food-effect bioavailability and fed bioequivalence study designs, data analysis, and product labeling.

4.4.1. Recommendations for Immediate-Release Drug Products

The guidance recommends that a food-effect bioavailability study be conducted for all new chemical entities during the IND period for INDs and NDAs. These studies should be conducted early in the drug development process to guide and select formulations for further development. Food-effect bioavailability information should be available to help design clinical safety and efficacy studies and to provide information for appropriate sections of product labels such as the one entitled “Clinical Pharmacology” and “Dosage and Administration.”

Two study approaches are required for ANDAs. In addition to a bioequivalence study under fasting conditions comparing the ANDA formulation to the reference-listed drug, a bioequivalence study under fed conditions is also recommended for all orally administered immediate-release drug products. The following exceptions exist:

- when both test product and reference-listed drug are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (BCS Class I); or
- when the “Dosage and Administration” section of the reference-listed drug label states that the product should be taken only on an empty stomach; or,
- when the reference-listed drug label does not make any statements about the effect of food on absorption or administration.

4.4.2. Recommendations for Modified-Release Drug Products

The guidance recommends that food-effect bioavailability for NDAs and fed bioequivalence studies for ANDAs be performed for all modified-release dosage forms. This section provides general considerations for designing food-effect bioavailability and fed bioequivalence studies. Sponsors may choose to use alternative study designs with scientific rationale and justification. They may also consider additional studies for a better understanding of the drug product and to provide optimal labeling statements for dosage and administration (e.g., different meals and different times of drug intake in relation to meals). In studying modified-release dosage forms, consideration should be given to the possibility that co-administration with food can result in dose dumping, creating a potential safety risk for the study subjects.

4.4.3. OVERVIEW OF THE GUIDANCE

4.4.3.1. General Design. The guidance document recommends a randomized, balanced, single-dose, two-treatment (fed vs fasting), two-period, two-sequence crossover design for studying the effects of food on the bioavailability of either an immediate-release or a modified-release drug product. The formulation to be tested should be administered on an empty stomach (fasting condition) in one period and following a test meal (fed condition) in the other period. A similar, two-treatment, two-period, two-sequence crossover design is recommend for a fed bioequivalence study except that the treatments should consist of both test and reference formulations administered following a test meal (fed condition). An adequate washout period should separate the two treatments in both the food-effect bioavailability and the fed bioequivalence studies.

4.4.3.2. Subject Selection. Both food-effect bioavailability and fed bioequivalence studies can be carried out in healthy volunteers drawn from the general population. Studies in the patient population are also appropriate if safety concerns preclude the enrollment of healthy subjects. A sufficient number of subjects should complete the study to achieve adequate power for a statistical assessment of food effects on bioavailability to claim an absence of food effect or to claim bioequivalence in a fed bioequivalence study. A minimum of 12 subjects should complete the food-effect bioavailability and fed bioequivalence studies.

4.4.3.3. Dosage Strength. In general, the highest strength of a drug product intended to be marketed should be tested in food-effect bioavailability and fed bioequivalence studies. In some cases, clinical safety concerns can prevent the use of the highest strength and warrant the use of lower strengths of the dosage form. For products with multiple strengths in ANDAs, if a fed bioequivalence study has been performed on the highest strength, bioequivalence determination of one or more lower strengths can be waived based on dissolution profile comparisons *(99)*.

4.4.3.4. Test Meal. In evaluating the exposure changes of new drugs (INDs/NDAs) due to food intake, the FDA seeks information on the “worst case scenario” (i.e., the largest food effect likely resulting from co-administration of drugs with meals). This information is evaluated in the landscape of safety and efficacy of the drug and appropriate directions for use are incorporated in clinical trials and once the drug is approved these directions are provided in the labeling. Additional studies may be conducted if deemed useful. FDA recommends that the fed bioequivalence study for ANDAs be conducted with a meal likely to provide maximal GI perturbation, as well.

The FDA recommends a high-fat (approximately 50% of caloric content of the meal) and high-calorie (approximately 800–1000 calories) meal for food-effect bioavailability and fed bioequivalence studies. This test meal should derive approximately 150, 250, and 500–600 calories from protein, carbohydrate, and fat, respectively. An example test meal would be two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk. Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity. In NDAs, it is recognized that a sponsor can choose to conduct food-effect bioavailability studies using meals with different combinations of fats, carbohydrates, and proteins for exploratory or label purposes. However, one of the meals for the food-effect bioavailability studies should be the high-fat, high-calorie test meal described above.

4.4.3.5. Administration. *Fasted Treatments*: Following an overnight fast of at least 10 h, subjects should be administered the drug product with 240 mL (8 fl oz) of water. No food should be allowed for at least 4 h post-dose. Water can be allowed as desired except for 1 h before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

Fed Treatments: Following an overnight fast of at least 10 h, subjects should start the recommended meal 30 min prior to administration of the drug product. Study subjects should eat this meal in 30 min or less; however, the drug product should be administered 30 min after start of the meal. The drug product should be administered with 240 mL (8 fl oz) of water. No food should be allowed for at least 4 h post-dose. Water can be allowed as desired except for 1 h before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

4.4.3.6. Sample Collection. Timed samples in biological fluid, usually plasma, should be collected from the subjects for both fasted and fed treatment periods to permit characterization of the complete shape of the plasma concentration-time profile for the parent drug. It may be advisable to measure other moieties in the plasma, such as active metabolites *(99)*.

4.4.3.7. Data Analysis. Food-effect bioavailability studies may be exploratory and descriptive or a sponsor may want to use a food-effect bioavailability study to make a label claim. The following exposure measures and pharmacokinetic parameters should be obtained from the resulting concentration-time curves for the test and reference products in food-effect bioavailability and fed bioequivalence studies:

Total exposure or area under the concentration-time curve ($AUC_{0-\infty}$, AUC_{0-t})
Peak exposure (C_{max})
Time to peak exposure (T_{max})
Lag-time (t_{lag}) for modified-release products, if present
Terminal elimination half-life ($t½\beta$)
Other relevant pharmacokinetic parameters

An equivalence approach is recommended for food-effect bioavailability (to make a claim of no food effects) and fed bioequivalence studies, analyzing data using an average criterion for AUC and C_{max}. Log-transformation of exposure measurements (AUC, C_{max}) prior to analysis is recommended. The 90% confidence interval for the ratio of population geometric means between test and reference products should be provided for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} *(104)*. For IND or

NDA food-effect bioavailability studies, the fasted treatment serves as the reference. For ANDA fed bioequivalence studies, the reference-listed drug administered under fed condition serves as the reference treatment.

5. DRUG PRODUCT LABELING ON FOOD EFFECTS

The results of food effect on drug exposure from food-effect bioavailability studies should be evaluated for clinical relevance and appropriately described in package inserts.

For an NDA, if the 90% confidence interval for the ratio of population geometric means between fed and fasted treatments, based on log-transformed data, is not contained in the equivalence limits of 80–125% for either $AUC_{0-\infty}$ ($AUC_{0-t}$when appropriate) or C_{max}, an absence of food effect on bioavailability is not established. In these situations, the sponsor should provide specific recommendations on the clinical significance of the food effect based on what is known from the total clinical database about dose–response (exposure–response) and/or pharmacokinetic–pharmacodynamic relationships of the drug under study. For example, a food-effect bioavailability study of rifalazil revealed that the 90% confidence interval of the fat-containing meals are outside the 80–125% limits based on C_{max} and $AUC_{0-\infty}$ *(43)*. Therefore bioequivalence does not exist between the fed and fasted states, and rifalazil should be dosed with fat-containing food in upcoming clinical trials and recommended in relevant communications with the FDA. The sponsor should also indicate the clinical relevance of any difference in T_{max} and t_{lag}. The results of the food-effect bioavailability study should be reported factually in the “Clinical Pharmacology” section of the labeling and should form the basis for making label recommendations (e.g., *take only on an empty stomach*) in the “Dosage and Administration” section of the labeling. When important, other sections of the label may include pertinent information about interactions with meals. The following are two examples of general language for the package insert:

1. A food-effect study involving administration of [the drug product] to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} and AUC were increased 57% and 45%, respectively, under fed conditions. This increase in exposure can be clinically significant, and therefore [the drug] should be taken only on an empty stomach (1 h before or 2 h after a meal).
2. A food-effect study involving administration of [the drug product] to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} was decreased 15% while the AUC remained unchanged. This decrease in exposure is not clinically significant, and therefore [the drug] could be taken without regard to meals.

An absence of food effect on bioavailability is indicated when the 90% confidence interval for the ratio of population geometric means between fed and fasted treatments, based on log-transformed data, is contained in the equivalence limits of 80–125% for $AUC_{0-\infty}$ (AUC_{0-t} when appropriate) and C_{max}. In this case, a sponsor can make a specific claim in the “Clinical Pharmacology” or “Dosage and Administration” section of the label that no food effect on bioavailability is expected provided that the T_{max} differences between the fasted and fed treatments are not clinically relevant. The following is an example of language for the package insert:

1. The C_{max} and AUC data from a food-effect study involving administration of [*the drug product*] to healthy volunteers under fasting conditions and with a high-fat meal indicated that exposure to the drug is not affected by food. Therefore, [the drug product] may be taken without regard to meals.

For an ANDA, bioequivalence of a test product to the reference-listed drug product under fed conditions is met with the following criterion: the 90% confidence interval for the ratio of population geometric means between the test and the reference-listed drug product, based on log-transformed data, is contained in the bioequivalence limits of 80–125% for AUC and C_{max}. Although no criterion applies to T_{max}, the T_{max} values for the test and reference products are expected to be comparable based on clinical relevance.

5.1. Labeling Examples from Approved Products

Historically, food-effect bioavailability studies have generated useful information on optimal dosing instructions for patients with regard to meals. The examples described in Tables 4–10 demonstrate the significance and utility of meal types, meal timing, and other general information on drug intake with meals. Note that these examples are relevant excerpts from some approved labels; for complete information, refer to the respective package inserts *(105)*.

Table 4
Didanosine Labeling Information

VIDEX® EC (didanosine) Delayed-released Capsules
VIDEX® (didanosine) Pediatric Powder for Oral Solution
DOSAGE AND ADMINISTRATION
VIDEX® EC should be administered on an empty stomach
VIDEX® should be administered on an empty stomach, at least 30 min before or 2 h after eating.

Table 5
Boniva Labeling Information

BONIVA® (ibandronate sodium) Tablets
DOSAGE AND ADMINISTRATION
To maximize absorption and clinical benefit, BONIVA® should be taken at least 60 min before the first food or drink (other than water) of the day or before taking any oral medication or supplementation, including calcium, antacids, or vitamins

Table 6
Letairis Labeling Information

LETAIRIS® (ambrisentan) Tablets
DOSAGE AND ADMINISTRATION
Initiate treatment at 5 mg once daily with or without food, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated

Table 7
Mepron Labeling Information

MEPRON® (atovaquone) Suspension
DOSAGE AND ADMINISTRATION
Dosage: *Prevention of PCP: Adults and Adolescents (13–16 Years):* The recommended oral dose is 1500 mg (10 mL) once daily administered with a meal.
Treatment of Mild-to-Moderate PCP: Adults and Adolescents (13–16 Years): The recommended oral dose is 750 mg (5 mL) administered with meals twice daily for 21 days (total daily dose 1500 mg).
Note: Failure to administer MEPRON Suspension with meals may result in lower plasma atovaquone concentrations and may limit response to therapy.

Table 8
Tekturna Labeling Information

TEKTURNA® (aliskiren) Tablets
DOSAGE AND ADMINISTRATION
Patients should establish a routine pattern for taking TEKTURNA® with regard to meals. High-fat meals decrease absorption substantially.

Table 9
Tasigna Labeling Information

TASIGNA® (nilotinib) Capsules
DOSAGE AND ADMINISTRATION
TASIGNA® should be taken orally (400 mg) twice daily, approximately 12 h apart and should not be taken with food. The capsules should be swallowed whole with water. No food should be consumed for at least 2 h before the dose is taken, and no food should be consumed for at least 1 h after.

Table 10
Kuvan Labeling Information

KUVAN® (sapropterin dihydrochloride) Tablets
DOSAGE AND ADMINISTRATION
KUVAN® tablets should be administered orally with food to increase absorption, preferably at the same time each day. KUVAN® tablets should be dissolved in 120–240 mL (4–8 fl oz) of water or apple juice and taken within 15 min of dissolution.

6. FUTURE RESEARCH

In the process of drug discovery and drug development many models have been generated to use available evidence to predict the influence of food on a drug substance or formulation intended for oral administration *(9,12a,13–15,106)*. Much of the data involves an evaluation of the physicochemical properties of the drug and its in vitro behavior. Better in-silico models are being considered that will include in vivo data from human intestinal fluid perfusion studies *(1)*. Issues that need to be further examined include the effects of specific food types and nutrients, the segmental effects of food, and the influence of limited bile secretion (e.g., cholecystectomy), pancreatic juice (e.g., partial pancreatectomy), or bowel surface area (e.g., gastric bypass).

7. CONCLUDING REMARKS AND RECOMMENDATIONS

Food-effect bioavailability studies provide insights into the exposure changes due to concomitant intake of drugs and meals. Exposure–response relationships translate these changes into clinical relevance, and guide clinical trial designs. The resulting information also supports dosage and administration instructions for patients once drugs are approved by providing directions in the package inserts on whether or not the drug could be taken with meals or if temporal relationships between drugs and meals are critical to optimize efficacy and safety. Interactions with specific foods (e.g., grapefruit juice) and nutrients (e.g., calcium supplements) may need to be studied separately and are generally based on theoretical expectations of physicochemical or physiological mechanisms for interactions with specific drugs. Patients are more informed about disease states and drugs than ever before. Patients and health-care providers need a good understanding of the potential for drug–food interactions in order to guide drug therapy. Information in package inserts and the evolving literature can offer this guidance toward optimal therapy.

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9

Effects of Specific Foods and Dietary Components on Drug Metabolism

Karl E. Anderson

Objectives

- Describe the major dietary components known to alter drug metabolism.
- Indicate the magnitude of changes in drug metabolism that can be induced by drugs.
- Understand why diet–drug interactions are difficult to recognize in patients and have been studied mostly in healthy subjects and laboratory animals.

Key Words: Dietary components; drug metabolism; protein; tyramine; vegetable

1. INTRODUCTION

This chapter provides an overview of the effects of specific food components on the metabolism and action of medications in humans. Although drug–food interactions are becoming better defined and understood, progress has continued to be relatively slow, and research has been less active than for drug–drug interactions *(1)*.

Effects of diet on pharmacokinetics are most important clinically for drugs that have a narrow therapeutic index and when the effect of a drug closely reflects its plasma concentration. For such drugs, a diet-induced change in kinetics may, at any given dosage level, alter plasma drug levels sufficiently to render the drug either ineffective or toxic. In contrast, a change in drug metabolism for a drug with a broad therapeutic window is likely to have little effect on efficacy or safety. Attention to food–drug interactions has been considered important by the Joint Commission, which is an indication of their clinical relevance *(2)*.

2. STUDIES IN HEALTHY SUBJECTS AND OBSERVATIONS IN PATIENTS

Some drug–nutrient interactions have been recognized in patients undergoing treatment for medical or psychiatric conditions. However, many clinically relevant drug–nutrient interactions are difficult to recognize and study in patients, because

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effects of diet on drug metabolism may not be recognized and be attributed to other causes instead. Observations in patients are also likely to be confounded by underlying illness, organ dysfunction, alterations in fluid distribution, and exposure to multiple drugs. These concurrent confounding factors can limit recognition of diet-induced effects. Moreover, dietary variations are often complex and difficult to accurately determine in the clinical setting. Therefore, it is not surprising that many such effects have been first recognized in studies of healthy subjects under controlled experimental conditions. Studies in healthy subjects have also been important for documenting and explaining the underlying mechanisms for such interactions. Even if it remains difficult to recognize specific occurrences of such interactions in individual patients, and such interactions are demonstrated mostly in healthy subjects, it is important to warn patients and health professionals of their potential for complicating drug therapy in clinical practice. Children and the elderly may be at higher risk for complications due to drug–food interactions *(3)*. Interactions between diet and cancer chemotherapeutic agents may be important, but have been little studied *(4)*.

3. DRUG METABOLIC PATHWAYS LIKELY TO BE AFFECTED BY DIET

Foods, vegetables in particular, are a complex mixture of chemicals, many of which do not provide recognized nutritional value to the host. Nutritive components and nonnutritive chemicals may have unwanted effects on metabolic processes, including pathways of drug metabolism. Effects of some dietary substances resemble the more easily recognized effects of certain drugs on the metabolism of other drugs. Indeed, many drugs are derived from chemicals in plants. Therefore, it is not surprising that drug–nutrient and drug–drug interactions have many common features and can be of similar magnitude *(5)*.

The cytochrome P450 (CYP) enzymes found in the endoplasmic reticulum of cells in the liver and intestinal mucosa are important for many diet–drug interactions. These enzymes are also important for many drug–drug interactions, because many drugs can either inhibit or induce one or more of these enzymes and thereby greatly influence the metabolism and clearance of other drugs (see Chapter 4). CYP enzymes are a large family of hemoproteins that oxidize both exogenous and endogenous chemicals. The enzyme reactions require both molecular oxygen and NADPH. CYP-catalyzed reactions are termed mixed function oxidase or monooxygenase reactions because only one atom of the oxygen molecule is utilized for oxidizing the substrate, whereas the other oxygen atom reacts with protons to form water *(6)*.

Diets and their components may, like drugs, induce or inhibit these important enzymes. Effects of diet on drugs that are metabolized by CYP enzymes have been most studied in humans *(6)*. Effects on the conjugating enzymes and on the transporter P-glycoprotein are also important for some drugs and dietary factors. It is likely that many unknown effects of diet on drug metabolism remain to be discovered both by clinical observations and in careful metabolic studies. Additional studies are particularly needed in the elderly and in patients with specific diseases that can affect diet and nutritional status *(7)*.

4. STUDIES IN ANIMALS AND HUMANS

Some effects of diet and nutrition on drug metabolism were initially recognized in animals, particularly rodents *(8–11)*, and such observations in animals have predicted effects of diet observed later in humans *(6)*. But it is difficult to extrapolate the conclusions of animal studies to humans, because of the major differences between species in CYP and other drug-metabolizing enzymes. In addition, differences in CYP enzymes between male and female rodents are prominent but much less important in humans *(12)*.

In addition to being more relevant, studies in humans have other advantages. Human subjects are more compliant with dietary changes especially during short-term studies in a supervised setting, making it possible to make a specific change in dietary composition without altering other components and total energy intake. Therefore, it is possible to observe effects of a change in diet without a confounding effect of a change in the total amount of energy consumed. Such studies are quite difficult in animals, without resorting to study design strategies such as pair feeding.

Effects of diet have been studied for only a small proportion of the drugs available for clinical usage. Many drugs are metabolized by several different CYP enzymes and also by conjugating enzymes. Other pathways, such as transport by P-glycoprotein, may also be influenced by diet. Although effects of diet components on the metabolism of some drugs are well documented, it is not always evident which specific enzyme isoform is affected, and it remains difficult to extrapolate from one drug substrate to another.

4.1. Effects of Dietary Protein, Carbohydrate, and Fat

The first recognized effect of diet on human drug metabolism was seen in crossover studies in healthy male subjects. Dietary protein and carbohydrate were exchanged sequentially, while keeping fat and total energy constant *(13,14)*. Metabolic clearances of both antipyrine and theophylline were more rapid, and plasma levels of these drugs declined more rapidly, during the high-protein diet. These drugs were chosen for study because their clearances are dependent on metabolic transformations by CYP enzymes in the liver. The metabolism of these drugs may especially reflect activity of hepatic CYP1A2 *(12)*.

In further studies, the addition of a pure protein supplement (100 g sodium caseinate each day for 2 weeks) to a calculated well-balanced diet in two subjects increased the rates of metabolism of antipyrine and theophylline, while in two other subjects a supplement of carbohydrate (200 g sucrose daily for 2 weeks) had the opposite effect *(14)*. Increasing the protein content of the diet also accelerated the metabolism of propranolol *(15)* and perhaps aminopyrine and caffeine *(16)*. An effect of protein on theophylline and propranolol clearance has been shown to occur in both women and men *(15)*.

Further studies compared the effects of high-carbohydrate, high-fat, and high-protein diets on drug metabolism *(17)*. Composition of the three diets permitted observations on the effects of the isocaloric substitution of fat for carbohydrate while keeping protein constant at 10% of total calories and the substitution of dietary protein for fat while keeping carbohydrate constant at 20% of total calories in the six healthy male subjects. As shown in Table 1, metabolic clearances for

Table 1
Drug Metabolism During Diets High in Protein, Carbohydrate, or Fat *(17)*

	Diet Composition			*Clearance* $(mL \cdot min^{-1}\, kg^{-1})$	
Diet	*% Protein*	*% Fat*	*% Carbohydrate*	*Antipyrine*	*Theophylline*
High carbohydrate	10	10	80	0.57±0.02	0.76±0.06
High fat	10	70	20	0.59±0.02	0.74±0.04
High protein	50	30	20	0.71±0.05*†	0.98±0.08¶

Each calculated diet was consumed in the order shown by six normal male subjects, and antipyrine metabolism was studied on day 10 and theophylline metabolism on day 14 of each dietary period. Clearance values (means ± SE) during the high-protein dietary period were significantly different from the high-carbohydrate dietary period (*$p<0.005$) and the high-fat dietary period (†$p<0.01$, ¶$p<0.02$, paired t-test).

antipyrine and theophylline were greater during the high-protein dietary period than during the other two diets, as in previous studies, but there were no differences in the drug clearances between the high-fat and the high-carbohydrate dietary periods. The conclusion was that the substitution of protein for either fat or carbohydrate can increase drug oxidation rates, whereas exchanging carbohydrate and fat has no major effect *(17)*.

The lack of an effect of carbohydrate and fat, including both saturated and unsaturated fats, was confirmed in an additional study in nine normal males *(17)*. Large isocaloric exchanges of carbohydrate for either unsaturated fat (corn oil) or saturated fat (butter) were accomplished while maintaining dietary protein constant at 15% of total calories. No significant changes in the metabolism of antipyrine and theophylline were observed *(17)*. Others have confirmed that substituting saturated and unsaturated fat in the diet of normal subjects has no effect on the metabolism of antipyrine *(18)*. Therefore, isocaloric exchanges of saturated fat, unsaturated fat, and carbohydrate do not appear to influence the metabolism of at least some substrates for CYP enzymes in humans. Changes in dietary fat can influence hepatic drug oxidation in animals *(9)*. It remains possible that some CYP enzymes or other enzymes important in drug metabolism may be influenced by dietary fat.

Thus, protein content of the diet appears to be more important for regulating oxidative drug metabolism in humans than carbohydrate or fat. Moreover, studies at different intakes of total calories indicate that dietary protein can influence drug oxidation rates at levels of energy intake other than that needed to maintain body weight *(19)*. Protein content of the diet may influence drug metabolism in patients with cirrhosis *(20)* as well as other clinical settings. For example, in hospitalized children with asthma, clearance of theophylline was greater during a high-protein diet than during two diets lower in protein content. Theophylline levels were higher and wheezing episodes and requirements for additional medications less frequent during a low-protein diet (Table 2) *(21, 21a)*. In adults with obstructive pulmonary disease, theophylline concentrations were lower during a high-protein diet than

Table 2

Theophylline Clearances and Serum Concentrations and the Total Number of Wheezing Episodes Occurring in Children with Asthma During Diets Differing in Protein Content *(21,21a)*

	Diet Composition			*Theophylline*		
Diet	*% Protein*	*% Fat*	*% Carbohydrate*	*Clearance* $(L \cdot kg^{-1}\ min^{-1})$	*Steady-state serum concentration* $(\mu g\ mL^{-1})$	*Wheezing episodes*
Normal	6–8	35	57–60	0.059±0.015	14.04±3.97	22
High protein	14–20	20	60–66	0.071±0.019*	10.66±3.43	17
High carbohydrate	2–3	20	77–88	0.048±0.016*	17.24±5.68	9

After steady-state serum concentrations of theophylline of 10–20 µg/mL were achieved, children (age 7–14 years) were fed the three test diets in the order shown, each for 12 days (with 2 days on a usual diet between each of the test diets). Values for theophylline clearance and concentration are means ± SD.

Significantly different from results obtained during the normal diet ($p<0.001$, paired t-test).

Table 3
Effects of Dietary Brussels Sprouts and Cabbage on Antipyrine Metabolism in Healthy Subjects *(56)*

Diet	*Antipyrine Clearance*
	(L h^{-1})
Control (first time)	3.09 ± 0.31
Brussels sprouts and cabbage	3.44 ± 0.32*
Control (second time)	2.98 ± 0.33

Each diet was fed to 10 healthy subjects in the sequence shown. Values are means ± SE.

*Significantly different from both control diet periods ($p<0.002$, paired t-test).

Table 4
Effects of Brussels Sprouts and Cabbage on Phenacetin Metabolism in Healthy Subjects *(56)*

Diet	*Phenacetin AUC*
	(μg·h mL^{-1})
Control (first time)	5283 ± 1864
Brussels sprouts and cabbage	2718 ± 779*
Control (second time)	4391 ± 1506

Diets were fed to 10 subjects in the order shown. Values for area under the plasma concentration vs. time curve (AUC) are means ± SE for 0–7 h.

* Plasma phenacetin concentrations were significantly lower at 3, 4, 5, and 7 h and plasma levels of total *N*-acetyl-*p*-aminophenol were significantly higher at 1, 2, and 7 h during the test diet period than during both control diet periods ($p<0.05$–0.001, paired t-test).

Table 5
Effect of Charcoal-Broiled Beef on Phenacetin Metabolism in Healthy Subjects *(107)*

Diet	*Phenacetin AUC*
	(μg·min mL^{-1})
Control (first time)	170 ± 40
Charcoal-broiled beef	37 ± 8*
Control (second time)	174 ± 53

Each diet was consumed by nine subjects in the order shown. Values for area under the plasma concentration vs. time curve (AUC) are means ± SE for 0–7 h.

*Significantly different during the test diet than during control diet periods ($p<0.01$, first time; $p<0.025$, second time; paired t-test).

during a high-carbohydrate diet *(22)*. Warfarin dose requirements were reported to be higher in several patients placed prospectively on high-protein–low-carbohydrate diets, but it is not known if this was due to a change in warfarin absorption, a change in warfarin metabolism *(23,24)*, or if changes in vitamin K intake may have played a role *(25)*.

The exact mechanism whereby dietary protein accelerates drug oxidation in humans is not established. While human studies have mostly involved solid food diets, it is unlikely that nonnutritive components of the diet were responsible for the effects ascribed to protein. The effects of feeding high-protein diets have been observed by different investigators that presumably were not uniform in terms of the solid foods in the experimental diets. Moreover, a protein supplement had the same effect as a high-protein diet in healthy subjects *(14)*. Effects of dietary protein on drug metabolism in humans were corroborated by earlier studies of high-protein diets in rodents, although the results in rodents are more complex due to marked sex differences that are not found in humans. Because the diets for the human studies were adequate in all essential nutrients, the substantial effects on drug metabolism were not due to the correction of deficiencies in protein or other nutrients. Impaired gastrointestinal absorption or altered distribution after absorption of the test drugs has also not been a factor in such studies *(26)*.

The mechanisms of protein and effects on CYP enzymes in laboratory animals are also not known *(6)*. High-protein intakes augment hepatic microsomal CYP content, liver weight, and mitotic indices in rodents *(8,27)*. These effects are reminiscent of the inducing effects of phenobarbital. Certain amino acids such as tryptophan and oxidized sulfur amino acids may increase liver protein synthesis and induce the mixed function oxidase system in laboratory animals and in liver cell cultures *(28–32)*. The role of an indirect effect through orphan receptors (e.g., pregnane X receptor, PXR) is not yet clear. Under some circumstances, effects of high-carbohydrate and fat diets on drug-metabolizing enzymes may be attributed to increased fat accumulation in hepatocytes *(11)*.

The metabolism of steroid hormones occurs primarily in the liver through CYP enzymes, microsomal reductases, and conjugating enzymes *(33)*. Dietary effects on these enzymes might also be expected. Indeed, an increase in the protein-to-carbohydrate ratio of the diet can increase estrogen 2-hydroxylation *(34)* and decrease androgen 5α-reduction in healthy subjects *(35)*. The same dietary change may alter the plasma concentrations of testosterone and cortisol in a reciprocal fashion and produce parallel changes in the binding globulins for these steroids *(36)*. These effects mimic those induced by phenobarbital in humans *(37)*.

Dietary protein can also alter the disposition of drugs that are cleared primarily by the kidneys, by influencing renal plasma flow, creatinine clearance, and renal tubular transport *(38,39)*. Renal tubular transport of basic drugs or drug metabolites may be especially reduced. For example, allopurinol is readily absorbed from the gastrointestinal tract and rapidly converted by hepatic xanthine oxidase or aldehyde oxidase to its major metabolite, oxypurinol, which is then excreted largely unchanged in the urine. Berlinger and coworkers studied the pharmacokinetics of allopurinol in normal subjects during consumption of high-protein and low-protein diets. A marked increase in area under the curve for oxypurinol and a decrease in renal clearance of this metabolite were demonstrated in healthy subjects during a low-protein diet compared to a high-protein diet. It was postulated that protein restriction produced an increase in the net tubular reabsorption of oxypurinol *(40)*. Therefore, in some patients treated with allopurinol, dietary restriction may enhance the retention of oxypurinol and increase the likelihood of adverse effects.

Protein and other specific food components in the diet can also enhance or interfere with the absorption of some drugs. For example, theophylline absorption has been reported to be faster after a high-protein meal than after a high-carbohydrate or high-fat meal *(41)*. The buffering capacity of protein is greater than for carbohydrate and fat. Therefore, a high-protein diet may enhance the bioavailability of acid-labile drugs to a greater extent than a lower protein diet.

A dietary component can influence delivery of a drug to its central site of action. For example, a low-protein diet can benefit patients with Parkinson's disease during treatment with levodopa by reducing unpredictable fluctuations in response (the "on–off" phenomenon) *(42–45)*. Levodopa absorption and blood levels are not affected by protein restriction, indicating that the effect occurs at a more central level *(46,47)*. Rather, a high-protein intake provides amino acids, especially large neutral amino acids, which inhibit the transport of levodopa across the blood–brain barrier by the aromatic amino acid transporter *(48)*. This leads to reduced brain dopamine formation from exogenous levodopa *(49)*. A protein redistribution diet, with protein restriction during the day and unrestricted intake near bedtime, was found to be beneficial in clinical studies *(45,46, 50–52)*. But deficiencies may develop if intakes of protein or other nutrients are marginal prior to the dietary change *(53)*. A diet balanced in protein and carbohydrate has also been advocated *(54)*. As described later, efficacy of levodopa can also be affected by vitamin B_6 intake.

4.2. Cruciferous Vegetables

Cruciferous vegetables, such as cabbage and Brussels sprouts, and alfalfa meal when added to the diet of laboratory animals were found to markedly induce chemical oxidations *(55–57)*. The inducing effects of cruciferous vegetables were accounted for primarily by indoles, including indole-3-carbinol and indole-3-acetonitrile *(58)*. Certain strains of cabbage and Brussels sprouts are particularly rich in these inducing substances. These vegetables and indoles have effects on the metabolism of environmental carcinogens such as aflatoxin B_1 and binding of their metabolites to DNA *(59–61)*.

These observations led to studies of drug oxidation and conjugation in normal subjects on calculated diets. Brussels sprouts and cabbage were substituted for other vegetables shown not to enhance mixed function oxidation in animals. The cruciferous vegetables significantly enhanced the oxidative metabolism of antipyrine (Table 3) and phenacetin (Table 4) *(56)* and the conjugation of acetaminophen *(62)*.

Variations in vitamin K intake from foods including cruciferous vegetables, as well as vitamin supplements, can significantly influence the stability of long-term anticoagulation with warfarin *(63,64)*. Furthermore, a diet rich in Brussels sprouts can enhance the elimination rate of warfarin *(65)*. A prospective dietary intervention study in patients on a stabilized dose of warfarin demonstrated that alterations in vitamin K content of the diet can lead to clinically relevant changes in the INR *(66)*. Low and erratic intakes of vitamin K may especially place patients at risk for unstable control of anticoagulation *(67)*. Coumarins in some herbal teas may enhance and vitamin K in smokeless tobacco products reduce the in vivo effects of coumarin anticoagulants *(2,68)*. In one patient, an unexpected increase in INR during warfarin therapy was attributed to an effect of orlistat to decrease vitamin K absorption *(69)*. Taking royal jelly as a dietary supplement was associated with an otherwise unexplained increase in INR and bleeding in one patient, although a mechanism was not established *(70)*. Maintaining a reasonably constant intake of foods and supplements containing vitamin K and other substances that can influence the metabolism and effects of these anticoagulant drugs can help to keep the prothrombin time within the desired therapeutic range during long-term anticoagulation.

Watercress, also considered a cruciferous vegetable, contains a glucosinolate precursor of phenethyl-isothiocyanate, which is appreciably absorbed by humans *(71)* and can impair CYP2E1 activity and the metabolism of drugs such as chlorzoxazone *(72)*. This drug is commonly used as an in vivo probe for CYP2E1 activity in human study subjects. In 10 such subjects, a single ingestion of a watercress homogenate (50 g) increased the area under the chlorzoxazone plasma concentration–time curve by 56% and prolonged the chlorzoxazone elimination half-life by 53%; similar and somewhat greater effects were seen with the known CYP2E1 inhibitor isoniazid *(73)*. A watercress homogenate (50 g) significantly reduced the peak plasma concentration and area under the plasma concentration–time curve for the oxidative metabolites of acetaminophen, which appear as cysteine and mercapturate conjugates, as well as their total urinary excretion. Formation and excretion of the major glucuronide and sulfate conjugates of this drug were not affected *(74)*.

4.3. Grapefruit Juice

The effect of grapefruit juice on metabolism of drugs that are metabolized by CYP3A4 has become perhaps the best-known drug–food interaction and is discussed in detail elsewhere (see Chapter 10). The initial serendipitous observation of this effect occurred in 1989 when grapefruit juice was used as a vehicle in a study of the effects of alcohol on felodipine metabolism *(75)*. It was noted that grapefruit juice decreased the oral clearance of this calcium channel blocker and enhanced the area under the plasma concentration vs. time curve. Because the bioavailability of the drug was increased, its systemic exposure and pharmacodynamic effect increased. Subsequently, interactions between a variety of drugs and grapefruit juice were studied *(76)*.

Grapefruit juice contains furanocoumarins and other substances that can inhibit CYP3A and to some extent other CYP isoforms. Significant CYP3A inhibition by grapefruit juice occurs in the small intestine. As a result, drugs that are substantially metabolized by CYP3A during absorption from the intestinal lumen are most notably affected by grapefruit juice. Drugs administered parenterally are not expected to be affected. Inhibition is both reversible and irreversible. Recovery from irreversible inhibition requires synthesis of new enzyme, and the limited information available suggests this may take up to 72 h after grapefruit juice exposure *(76)*. Inhibition by grapefruit juice is clinically important when drug response closely reflects plasma concentration, as is the case for calcium channel blockers.

Because this interaction occurs primarily with drugs that are subject to extensive first-pass metabolism by CYP3A in the intestine, there are many drugs that are not affected. As a result, it is often possible within a class of drugs to choose an alternative that is not subject to inhibition by grapefruit juice or to predict whether this interaction might occur based on the known pharmacokinetic features and pathways of a drug's metabolism. Examples of drug groups where such choices can be made include calcium channel blockers, HMG-CoA reductase inhibitors, sedative-hypnotics and anxiolytics, psychotropics, and antihistamines *(76)*. However, it must be kept in mind that inhibition of CYP3A4 may not be the only mechanism whereby grapefruit juice affects drug metabolism. Drug transporters such as P-glycoprotein in enterocytes may also be affected, and this mechanism may be more important than CYP3A4 inhibition for some drugs such as cyclosporin *(76,77)*. In addition, grapefruit can inhibit organic anion transporting polypeptides at least in vitro, which might decrease oral drug bioavailability *(78)*.

4.4. Herbs

Herbs are dietary supplements that are complex and incompletely characterized mixtures of chemicals. These compounds have considerable potential for causing unrecognized changes in drug metabolism and are discussed elsewhere in this book (see Chapter 12). Reports of possible drug–herb interactions have often been incomplete, and further studies are needed *(79–82)*. Use of nonvitamin, nonmineral supplements is changing in the population and is often incompletely recorded in patient medical records. Moreover, patients are often not aware of potential interactions of these supplements with drugs *(83)*. It may be especially important to identify risks for interactions in certain populations, such as the elderly, who are often taking multiple prescription drugs and over-the-counter supplements *(84)*, and in patients undergoing cancer chemotherapy *(85)*.

Interactions of herbs with warfarin are in general poorly documented *(82)*. Bleeding has been reported when warfarin is combined with ginkgo (*Ginkgo biloba*) *(82)*. However, a controlled prospective study failed to confirm such an effect *(86)*. Examples of other herbs reported to interact with warfarin to cause bleeding include dong quai (*Angelica sinensis*) *(87)* and danshen (*Salvia miltiorrhiza*) *(88)*.

St. John's wort (*Hypericum perforatum*) can cause induction of CYP3A4 and 2E1 *(89)*, possibly 2C9 and 1A2, and P-glycoprotein and decrease the blood concentrations or effects of drugs such as digoxin, theophylline, cyclosporin, protease inhibitors (e.g., indinivir and nevirapine), coumarin-derived anticoagulants, amitriptyline, and oral contraceptives *(10,79,90–92)*.The inducing effect on CYP3A4 is greater in women than men *(89)*. Serotonin syndrome has been noted in patients who take St. John's wort along with serotonin-reuptake inhibitors, nefazodone, or triptans *(79,90,91)*. Garlic oil was found to reduce CYP2E1 in healthy subjects *(89)*.

Ginseng has been reported to induce mania in patients taking antidepressants *(79,93)*. Heavy betel nut (*Areca catechu*) consumption may precipitate extrapyramidal side effects with schizophrenic patients on neuroleptic drugs *(94)*. Yohimbine (*Pausinystalia yohimbe*) may increase risk of hypertension in patients taking tricyclic antidepressants *(79)*. Licorice (*Glycyrrhiza glabra*) may potentiate oral and topical corticosteroids *(79)* and digitalis *(95)*. Heavy intake of licorice products can be an inapparent cause of hypertension that is resistant to drug therapy *(96)*.

Because herbal products are not subject to consistent standardization and regulation, their content is often variable and uncertain. Many of the chemical components of these plant products and their effects on drug disposition and action remain unknown. Therefore, it is widely recommended that patients taking prescribed drugs should not take herbal remedies, unless authorized by their physicians *(79,91)*.

4.5. Methylxanthines

Methylxanthines such as caffeine (1,3,7-trimethylxanthine) are common natural, nonnutritive components of foods and especially beverages such as coffee and tea. Caffeine is added to many popular carbonated beverages. The closely related drug theophylline (1,3-dimethylxanthine) is used as a bronchodilator in treating asthma and related pulmonary conditions.

These and other methylxanthines are extensively metabolized by CYP enzymes. When ingested regularly, these substances can also accumulate and influence drug metabolism. Effects on drug metabolism are complex and may involve saturation and inhibition as well as induction of hepatic enzymes that metabolize methylxanthines and other drugs and chemicals. For example, with repeated doses, theobromine (3,7-dimethylxanthine), a major methylxanthine in chocolate, lowers its own metabolism by saturating or inhibiting hepatic enzymes; but several days after the last repeated dose, induction of theobromine hepatic metabolism can be demonstrated *(97)*. Theobromine induction of its own metabolism was shown to occur in rats as well *(98)*. Theophylline also can induce its own metabolism in humans *(99)*. Studies in healthy subjects indicate that a pool of methylxanthines derived from the diet may compete with theophylline for common saturable metabolic pathways *(100)*.

Cola nuts, which are reported to contain 2.3% caffeine, are commonly chewed in Africa and elsewhere for stimulant effects. Antipyrine half-life was prolonged by cola nut chewing in a cross-sectional study employing multiple regression analysis in Gambian villagers *(101)*. However, this effect was not seen in a controlled study in normal male volunteers in the United States *(102)*. This difference is not explained, but it is possible that other nutritional factors influenced metabolism of the test drug antipyrine in the West African study.

An interaction between caffeine and clozapine, both of which are CYP1A2 substrates, has been demonstrated in schizophrenic patients *(103)*. In seven subjects on monotherapy, clozapine concentrations were lower after they were changed to a caffeine-free diet for 5 days. Therefore, habitual caffeine intakes can alter the metabolism of this drug. The findings suggest that caffeine intake should be medically supervised and levels of clozapine monitored in some schizophrenic patients *(103)*.

4.6. Food Preparation

Chemical changes in foods are induced during cooking particularly at high temperatures, and the consumed chemical products may be absorbed and then influence drug metabolic pathways. For example, charcoal broiling of meats leads to formation of polycyclic aromatic hydrocarbons similar to those found in cigarette smoke. Polycyclic aromatic hydrocarbons in cigarette smoke probably account for enhanced drug oxidation rates in smokers *(104)*.

These chemicals are products of incomplete combustion and are produced during charcoal broiling when drippings contact the hot coals and are then volatilized and redeposited on the meat *(105)*. Oral administration of such compounds to rats increases benzo(*a*)pyrene hydroxylase activity in the intestine and liver. Moreover, feeding charcoal-broiled beef induces intestinal metabolism of phenacetin in the rat *(106)*.

Charcoal-broiled beef can have substantial effects on the metabolism of drugs such as phenacetin, theophylline, and antipyrine in healthy subjects *(107–109)*. Pharmacokinetics of these drugs was studied during periods of daily ingestion of standard portions of hamburger (8 oz) and steak (6 oz) that were broiled over charcoal and fed twice daily as part of a calculated test diet and again during control diet periods, when aluminum foil was placed under the meat and drippings aspirated by hand to prevent their falling onto the burning charcoal. Phenacetin plasma concentrations were markedly reduced by consumption of charcoal-broiled beef (Table 5), and the ratio of the major metabolite of phenacetin, *N*-acetyl-*p*-aminophenol (acetaminophen), to phenacetin was increased *(107)*. Therefore, both charcoal-broiled beef and cigarette smoking enhance phenacetin *O*-dealkylation in humans. In a separate study, clearance of antipyrine and theophylline was increased by consumption of charcoal-broiled beef *(108)*. Clinical usage of phenacetin has been largely replaced by acetaminophen, which is metabolized primarily by conjugation. Acetaminophen metabolism was not influenced by consumption of charcoal-broiled beef *(110)*.

4.7. Tyramine and Related Substances

Hypertensive reactions may occur in patients using monoamine oxidase (MAO) inhibitors after ingestion of foods containing tyramine, such as some highly flavored cheeses. These “tyramine reactions” or “cheese reactions” are among the best-known drug–food interactions *(111)*. They began to be reported with use of the irreversible MAO inhibitors from about 1961. By about 1965 the underlying mechanisms were understood to involve tyramine-provoked hypertension, and fairly simple dietary precautions could be recommended *(112,113)*. However, fear of these sometimes severe reactions persisted and greatly limited the use of first-generation, non-selective MAO inhibitors as antidepressants, such as tranylcypromine, pargyline, phenelzine, selegiline (deprenyl), and isocarboxazide *(111,112)*.

Manifestations of these sudden and dramatic reactions may include hypertension with palpation, nausea, vomiting, and headache. The potentially life-threatening hypertensive crises, which may occur within 1 h of ingestion of the tyramine-containing food, are described as resembling the paroxysmal symptoms of pheochromocytomas, which are neuroendocrine tumors that intermittently release catecholamines into the circulation *(111)*.

Tyramine and other phenylethylamines are formed from tyrosine due to the actions of bacterial and fungal tyrosine decarboxylase. MAO in the intestine and liver normally oxidatively deaminates phenylethylamines that are absorbed from the diet. When MAO is inhibited in these tissues by a drug, dietary phenylethylamines can be absorbed systemically and displace norepinephrine from storage vesicles in the nervous system. Large amounts of this neurotransmitter are then released into synapses, which can lead to severe acute hypertension and additional complications such as myocardial infarction and thrombotic or hemorrhagic stroke (2). Paradoxically, the interaction between cheddar cheese and tranylcypromine was used to therapeutic advantage in two patients with severe postural hypotension *(114)*.

Although highly flavored cheeses, such as cheddar, are most commonly associated with this adverse drug interaction, other high-protein foods that have started to ferment may also contain large amounts of tyramine or other phenylethylamines (2). These include pickled herring, yeast preparations, broad beans, and certain wines (e.g., Chianti) and beers *(115,116)*. Amounts of these substances in foods and beers can vary greatly from sample to sample. Tap lager beers prepared by bottom fermentation may contain amounts of tyramine that are significant even for moderate levels of beer consumption and have been implicated in hypertensive reactions to MAO inhibitors *(115)*.

Rates of absorption and delivery of dietary phenylethylamines to the systemic circulation can be greatly affected by other foods in the meal. Iron deficiency is said to increase susceptibility to these reactions. Concurrent sympathomimetic drugs may also exacerbate tyramine reactions. Reactions related to ingestion of broad beans (fava beans) may be due in part to their content of dopa or its amine derivative dopamine (2).

Other drugs with weak MAO-inhibiting properties, such as furazolidine (an antiprotozoal) and meperidine (an opioid analgesic) have also been implicated in tyramine reactions (2). The antimicrobial linezolid is a reversible and nonselective MAO inhibitor with interaction potential. Procarbazine has been reported to cause hypertension in patients consuming tyramine-containing foods while taking this drug for Hodgkin's disease *(117)*. Isoniazid (an antituberculosis drug) is a weak MAO inhibitor that may cause tyramine reactions in combination with tricyclic antidepressants *(118)*.

Strategies to avoid tyramine reactions in patients taking MAO inhibitors have included dietary restrictions and development of new pharmaceutical products *(119)*. Based on analysis of phenylethylamine content of foods and case reports of diet-related hypertensive reactions, rational guidelines for diet planning and counseling of patients on MAO inhibitor drug regimens have been described. Some confidence in the safe use of these drugs may be provided by beginning dietary counseling before drug therapy, keeping tyramine intake below 5 mg, and recommending consumption of only fresh foods. Any food rich in aromatic amino acids can become high in tyramine with aging or when microbial contamination is followed by prolonged storage or if spoilage occurs *(113)*. It has been recommended that all tap (draft) beers should be avoided even at modest levels of consumption *(116)*. Dietary compliance should be monitored and dietary restrictions continued 4 weeks after completion of drug therapy *(113)*.

Altering the route of drug administration has been explored. For example, a selegiline transdermal system when used for treating depression apparently allows inhibition of central nervous system MAO type A and type B (MAO-A and MAO-B) enzymes while avoiding inhibition of intestinal and liver MAO-A enzyme. Transdermal administration of this drug to adults with major depression was reported to not significantly increase sensitivity to dietary tyramine *(120)*.

Pharmaceutical strategies of particular interest include combining MAO inhibitors with tricyclic antidepressants and development of new selective and reversible MAO inhibitors. Effectiveness of such approaches can be assessed by the tyramine pressor test *(119)*. Selegiline is approved as adjunctive treatment of Parkinson's disease using lower doses (e.g., 10 mg/day by mouth) than is used for depression. When used in this manner, selegiline does not inhibit intestinal and hepatic MAO-A and is therefore a selective, irreversible cerebral MAO-B inhibitor without significant risk of the tyramine reaction *(121,122)*. However, this dose-dependent selectivity is not absolute, and a few hypertensive reactions have been reported even at the recommended doses for Parkinson disease, and there is some selectivity retained at higher doses as well *(123,124)*. Rapidly reversible MAO-A inhibitors, such as moclobemide, a novel benzamide, are reported to carry less risk of a hypertensive reaction and yet appear to be effective antidepressants *(123,125)*, but with doses above 900 mg/day the risk of interaction with dietary tyramine may be significant *(126)*.

4.8. Alcohol

Adverse reactions develop soon after alcohol is consumed in patients treated with tetraethylthiuram disulfide (disulfiram). For this reason, the drug has been used in alcohol treatment programs as an adjunctive means of encouraging abstinence. The unpleasant manifestations of this drug–food interaction may include flushing, headache, nausea, vomiting, weakness, vertigo, hypotension, blurred vision, and seizures. The drug inhibits the enzyme aldehyde dehydrogenase, which oxidizes acetaldehyde that is derived from alcohol. Cyanamide is a disulfiram-like drug that has been used for the management of alcoholism in some countries such as Japan, but has been associated with adverse effects on the liver *(127)*. The disulfiram reaction has been reproduced using acetaldehyde and has therefore been termed the "acetaldehyde syndrome." It can occur with ingestion of foods cooked with wine, wine vinegar, or wine-containing desserts *(128)*.

Other drugs have been found to cause disulfiram-like reactions in association with alcohol (2). These drugs, some of which are aldehyde dehydrogenase inhibitors, include cyanamide, metronidazole, sulfonylureas *(129)*, griseofulvin *(130)*, procarbazine, some cephalosporin antibiotics, and possibly ketoconazole *(131)*. Some mushrooms contain inhibitors of aldehyde dehydrogenase and may cause such reactions *(132,133)*. Inhibitors of this enzyme may be found in other foods, such as cabbage *(134)*.

The potential for metronidazole to cause a disulfiram-like reaction has been questioned, based on lack of convincing case reports or evidence for inhibition of hepatic alcohol dehydrogenase *(135,136)*. This drug may increase acetaldehyde production in the colon, at least in rats *(137)*.

Cephalosporin antibiotics have differing effects on the liver alcohol dehydrogenase and circulating acetaldehyde levels *(138,139)*. Those reported to cause disulfiram-like reactions include cefoperazone, moxalactam, ceftriaxone, cefonicid, and cefmetazole *(140–142)*. Reactive metabolites rather than the parent drugs are thought to be responsible for the enzyme inhibition *(143)*. Drugs with a *N*-methyltetrazole-thiol side chain in the 3′-position and certain other side chains are particularly associated with this reaction. Drugs with these structural features can also inhibit vitamin K epoxide reductase (VKOR) and cause coagulopathies (hypoprothrombinemia and bleeding), particularly in patients with vitamin K deficiency *(140,144–147)*. Vitamin K administration can prevent this drug-induced coagulopathy.

4.9. Vitamins

A number of vitamin deficiencies alter hepatic mixed function oxidation in laboratory animals *(8,9,11,148)*. Therefore, it is likely that ingestion of vitamins to correct evident or subtle vitamin deficiencies may alter drug metabolism. But there are few studies in humans, and the observations in animals are difficult to translate to human populations due to marked species differences in drug metabolism. There is also some potential for large doses of vitamins to alter drug metabolism in subjects without vitamin deficiencies.

The effects of vitamin C have been most studied in humans. Several species, including humans, guinea pigs, and other primates, as well as some strains of rats, are unable to synthesize vitamin C and therefore require small amounts in the diet. Interrelationships between vitamin C and CYP enzymes were examined in some detail in early studies *(149)*. Depletion of this vitamin in the guinea pig and in a rat strain unable to synthesize ascorbic acid impairs oxidative drug metabolism and reduces CYP and most associated enzyme activities *(150,151)*. Amounts of ascorbic acid required for optimal CYP induction by exogenous chemicals (e.g., polychlorinated biphenyls) exceed the amounts required to maintain induced levels of mixed function oxidase activities *(151)*.

Observations in a few patient populations suggest that vitamin C deficiency impairs drug metabolism in humans. For example, antipyrine half-lives were longer in liver disease patients with low leukocyte ascorbate levels than in patients with higher ascorbate levels *(152)*. Ascorbic acid supplementation of elderly patients *(153)* and diabetics *(154)* with low initial leukocyte or serum ascorbate levels resulted in shortening of antipyrine half-lives. It is possible that additional nutritional deficiencies contributed to impaired drug metabolism in these studies.

Studies in healthy subjects have not found a substantial effect of vitamin C deficiency. For example, subclinical vitamin C deficiency of short duration in five male volunteers had no significant effect on antipyrine metabolism *(155)*. In 10 elderly subjects who underwent ascorbate depletion for 4 weeks, there was also no significant change in caffeine metabolism *(156)*. It is possible that effects on drug metabolism occur in humans only with more severe deficiency of vitamin C than was induced in these experiments.

Large doses of vitamin C can decrease mono-oxygenase activities in animals *(157)*. Such effects have been little studied in humans. Vitamin C administered in large doses increased antipyrine clearance in one study *(158)* but not in another *(159)*. A small influence on warfarin disposition was not considered clinically significant *(160)*. Large doses of this vitamin may have effects on nonoxidative pathways of drug metabolism. For example, the vitamin may reduce sulfate conjugation of drugs such as salicylamide and acetaminophen by competing for available sulfate *(161,162)*. High doses of vitamin C may reduce steady-state indinavir plasma concentrations *(163)*.

Because reactive oxygen species may be involved in the clearance of the antibiotic linezolid, the effects of dietary antioxidants were studied in humans. However, daily oral doses of 1000 mg vitamin C or 800 IU of vitamin E were found not to alter the pharmacokinetics of this drug in healthy subjects *(164)*.

Administration of vitamin B_6 can enhance the peripheral conversion of levodopa to dopamine by dopa-decarboxylase, a pyridoxine-requiring enzyme, such that less is available to cross the blood–brain barrier for conversion there to dopamine. Dopamine itself does not cross the blood–brain barrier. Carbidopa, an inhibitor of peripheral dopamine decarboxylase, which enhances the efficacy and reduces side effects of levodopa, also prevents the reduction in efficacy of levodopa by exogenous vitamin B_6 *(165)*.

There is some evidence that fortification of the US diet with folate since 1997 to prevent neural tube defects may have contributed to higher methotrexate dosing in patients with rheumatoid arthritis. If real, this suggests an effect of folate on drug action rather than disposition *(166)*.

5. CONCLUSIONS AND IMPLICATIONS

It is apparent that the variety of macronutrients and micronutrients found in foods can have major effects on the metabolism and effects of some drugs. There is incomplete understanding of many of these interactions, because experimental and clinical observations are incomplete. It is likely also that there are many specific effects of dietary components on drug metabolism and actions that remain to be discovered. Given the complex mixture of chemicals found in foods and the large number of new drugs that come to market yearly, interactions between dietary components and drugs will require continued attention from both investigators and health professionals in the future.

Studies in healthy subjects indicated that diet may explain part of the intra-individual variations in drug metabolism rates that occur over time *(167)*. Further studies in relevant patient populations on the effects on drug metabolism of naturally occurring dietary variations are needed.

As knowledge of these interactions increases, there will be an increasing need for physicians, pharmacists, and drug manufacturers to provide information on drug–-nutrient interactions to patients. It must be kept in mind that public understanding of diet and nutrition is less than desirable, and compliance with dietary recommendations is often not satisfactory. Compliance is particularly difficult for individuals who are physically or mentally impaired or do not normally prepare their own food. Therefore, monitoring strategies may be considered for some drugs that are particularly affected by changes in diet.

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10

Grapefruit and Other Fruit Juices Interactions with Medicines

David G. Bailey

Objectives

- Provide a comprehensive overview of the clinical interactions of grapefruit or other fruit juices with medications to cause altered pharmacokinetics and potential clinical drug response.
- Focus primarily on the extensive literature of interactions determined by modulation of drug metabolism mediated by intestinal CYP3A4. Established/predicted and interacting/non-interacting medications, important adverse events and possible beneficial effects and clinical recommendations are discussed.
- Address more recent research on interactions determined most likely by changed presystemic efflux/uptake drug transport.

Key Words: Bioavailability; citrus juice; drug metabolism; grapefruit; organic anion transporting polypeptides; P-glycoprotein

1. INTRODUCTION

Medications and food are often taken together. Linking drug administration to a regular event like a meal can improve adherence of the patient to the treatment regimen, especially in the elderly. However, certain foods can create an interaction that can increase or decrease systemic drug availability resulting in altered clinical effects.

Our research on fruit juice–drug interactions began with a single crucial unexpected secondary observation in one clinical study that resulted in a highly novel follow-up investigation more than 25 years ago *(1,2)*. The finding was that grapefruit juice could markedly augment oral drug bioavailability. The mechanism was inhibition of drug metabolism, which was likely the first finding of a food producing such an effect in humans *(1–3)*. Subsequently, many scientists followed up this finding with hundreds of original research articles that investigated a range of related and relevant issues. It was discovered that grapefruit primarily attenuated the activity of intestinal cytochrome P450 isoenzyme 3A4 (CYP3A4), which

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provided early endorsement of the gut as a central site of drug metabolism *(4)*. Moreover, grapefruit has been shown to interact with more than 50 medications, some of which are highly utilized or essential for treatment of serious medical conditions, by causing reduction in the normal extent of first-pass metabolism. In an attempt to eliminate the possibility of a marked boost in oral drug systemic availability and resulting unintentional serious overdose/toxicity, some drug product monographs and a prescription vial label now caution against consumption of grapefruit during pharmacotherapy. Since individuals over 50 years of age are the prime purchasers of grapefruit, are commonly prescribed the affected drugs, have a marked pharmacokinetic interaction and are less able to compensate for excessive plasma drug concentration, they appear to be a particularly vulnerable patient population *(5)*. Furthermore, numerous articles in the lay press have made the topic of grapefruit–drug interactions very familiar to the general population. Thus, the original finding of grapefruit-mediated inhibition of intestinal drug metabolism to augment oral drug bioavailability has attained significant scientific, clinical and mainstream stature. It may also have been instrumental in initiating a significant shift in the perception of the potential importance of food, especially fruit juices, in drug interactions.

2. REVIEW OF BASIC SCIENCE

2.1. Drug Metabolism and Grapefruit Juice Effect

Metabolism of a drug to another chemical substance that becomes less active or more readily eliminated by the kidney is a well-established mechanism for terminating the effects of a drug *(6)*. A key step of drug metabolism is commonly oxidation by a member of the family of enzymes known as the cytochrome P450s (CYPs) (see Chapter 4). The enzyme, CYP3A4, oxidizes about 50% of all drugs *(7)*. Moreover, the location of CYP3A4 in apical enterocytes of the small intestine and in hepatocytes of the liver means that this enzyme is well situated to inactivate orally administered drug during passage from the gut into the systemic circulation, a process known as first-pass or presystemic drug metabolism *(8,9)*. The result can be a markedly reduced oral bioavailability (the percent of the oral dose of drug that reaches the systemic circulation unchanged) and clinical effect of the medication. This concept is illustrated in Fig. 1. The calcium antagonist, felodipine, is normally completely absorbed from the gastrointestinal tract *(10)*. However, sequential metabolism of felodipine in the small intestinal wall and liver by CYP3A4 results in a lower mean oral bioavailability of 15%. The clinical dose is thereby corrected for this effect. In the case of felodipine, 10 mg orally is administered to obtain the equivalent response of 1.5 mg intravenously. The concern is that consumption of a substance that alters the activity of enteric and/or hepatic CYP3A4 might substantially change oral drug bioavailability sufficiently to risk adverse effects (loss of efficacy or overdose toxicity).

The discovery that grapefruit juice could markedly increase oral drug systemic availability was initially suggested by an unanticipated finding in an interaction study that we designed to investigate the effect of ethanol on the pharmacokinetics and pharmacodynamics of the dihydropyridine calcium channel antagonist,

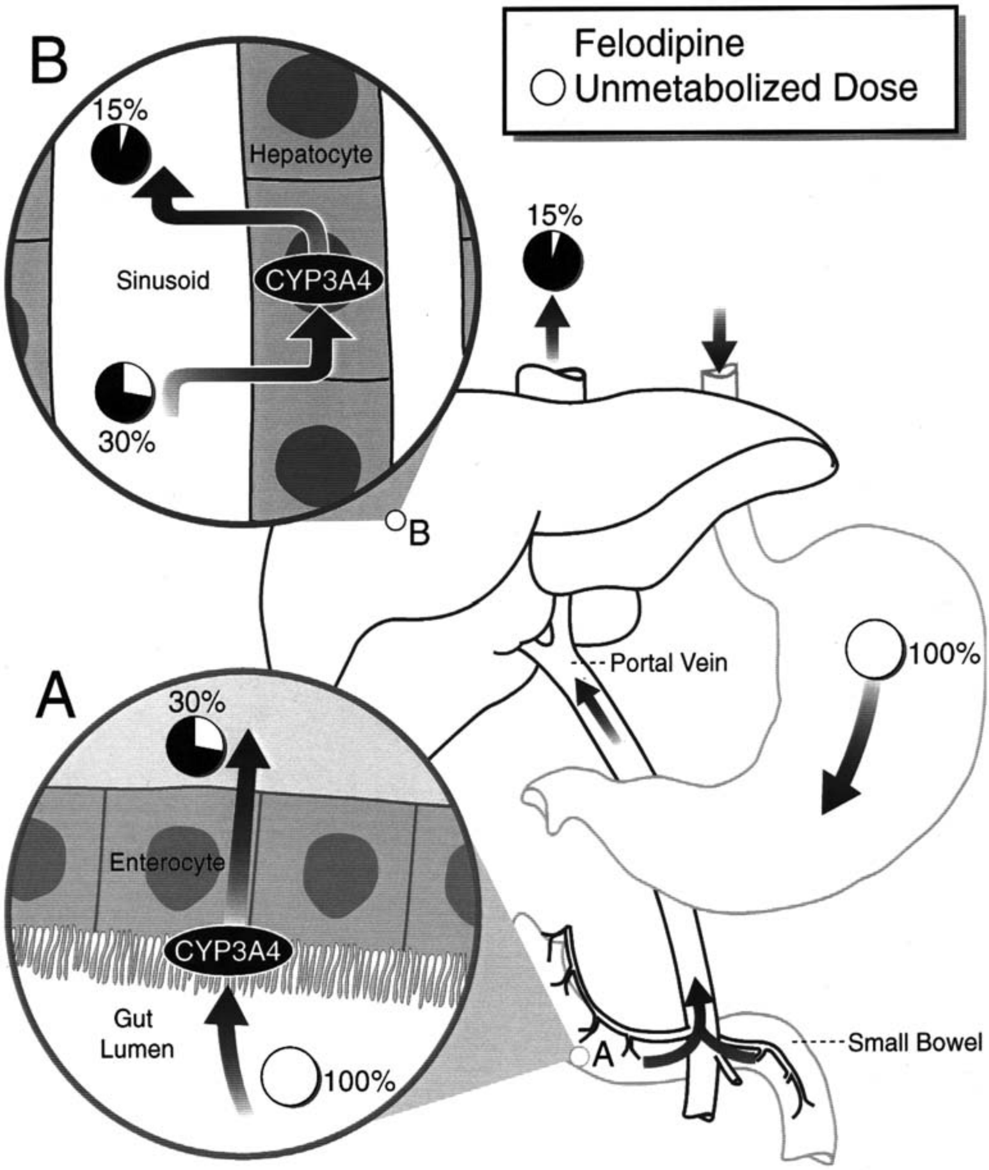
Felodipine
○ Unmetabolized Dose
B
15%
Hepatocyte
Sinusoid
CYP3A4
30%
15%
B
Portal Vein
100%
A
30%
Enterocyte
CYP3A4
Gut
Lumen
100%
A
Small Bowel

Fig. 1. Sequential presystemic felodipine metabolism by CYP3A4 in apical enterocytes of the small bowel (**A**) and then the hepatocytes of the liver (**B**). The percent of unmetabolized felodipine is presented before and after passage through the gut wall and the liver.

felodipine *(1)*. In this subject-blinded investigation, grapefruit juice had been chosen to mask the taste of the ethanol. Results showed that plasma felodipine concentrations were not different between the groups receiving the treatment (ethanol in grapefruit juice) and control (grapefruit juice). However, both groups had plasma felodipine concentrations that were several-fold higher than those observed in other pharmacokinetic investigations in which the same dose of felodipine was given. A systematic examination for obvious possible causes, such as incorrect dose or error in the drug assay, did not resolve this discrepancy. However, these previous investigations had not administered felodipine with grapefruit juice. As a result, we conducted a pilot project in a single volunteer [DGB] to judge the possible role of the juice. Plasma felodipine concentrations were more than fivefold higher with grapefruit juice compared to those with water *(3)*.

A formal clinical study involving patients with untreated borderline hypertension established the interaction *(2)*. This finding underlined the importance of follow-up on unexpected observations in research. The peak concentration ($C_{\mathbf{max}}$) and area under the plasma drug concentration–time curve (AUC) of felodipine with grapefruit juice were essentially threefold compared to those with orange juice or water. As little as a single normal amount of juice (200 mL) or one fresh grapefruit is now known to produce this effect *(3,11)*. Moreover, it appears that there can be sufficient grapefruit in orange marmalade to produce severe overdose toxicity for certain drugs *(12)*. The elimination half-life ($t_{1/2}$), i.e. rate of drug removal from the systemic circulation, of felodipine was not affected *(3)*. Also, the intravenous pharmacokinetics of felodipine with grapefruit juice was not changed *(13)*. Thus, grapefruit juice primarily inhibited presystemic, rather than systemic, metabolism of felodipine. The mechanism was a reduced activity of the primary and secondary pathways of felodipine metabolism, both of which are mediated by CYP3A4, during first-pass *(14)*.

Administration of grapefruit juice (250 mL) caused mean 62% reduction of enterocyte CYP3A4 protein content *(4)*. This provided early endorsement of the gastrointestinal tract as a central site of drug metabolism. Subjects with the highest enterocyte content of CYP3A4 before grapefruit juice had the largest reduction of this enzyme and greatest increase in felodipine $C_{\mathbf{max}}$ with the juice. In contrast, liver CYP3A4 activity, as measured by the erythromycin breath test, was not altered. Intestinal content of other drug-metabolizing enzymes (CYP2D6, CYP1A1) was not affected. Thus, grapefruit juice appeared to inhibit intestinal CYP3A4 activity selectively.

Decreased expression of intestinal CYP3A4 implied that the interaction was not simply the result of competition for metabolism between felodipine and inhibitory substrate(s) in grapefruit juice. Since the content of enterocyte CYP3A4 mRNA was not changed, the interaction likely did not result from decreased production of CYP3A4 protein *(4)*. Rather, it indicated that the inhibitory effect was caused by enhanced degradation of this enzyme. This effect could have been caused by one or more substances in grapefruit juice that was initially metabolized by CYP3A4 to a reactive intermediate(s) and then bonded covalently to the enzyme, a process termed “suicide” or “mechanism-based” inhibition *(3)*. The structurally modified and inactivated CYP3A4 might then be expected to undergo rapid proteolysis within the cell. Consequently, the return of CYP3A4 activity would require de novo enzyme synthesis. Since reduced intestinal CYP3A4 protein by grapefruit juice did not cause increased CYP3A4 mRNA, it indicated that there was not an effective feedback mechanism within the enterocyte to up-regulate CYP3A4 synthesis. Thus, it might be predicted that return of CYP3A4 activity would require enterocyte replacement. This could cause prolonged inhibition of CYP3A4-mediated drug metabolism by grapefruit juice.

The duration of inhibitory activity of grapefruit juice has been evaluated. In the initial study, consumption of a single glass (200 mL) of grapefruit juice at various time intervals before felodipine administration showed that the pharmacokinetic interaction was maximal when administration occurred simultaneously or within 4 h of previous juice consumption *(15)*. Then, the extent of the interaction declined slowly with increasing time interval. The disappearance half-life of grapefruit juice's inhibitory effect on CYP3A4-mediated drug metabolism was estimated at 12 h *(3)*. Increased felodipine $C_{\mathbf{max}}$ was still evident when this volume of grapefruit juice was consumed 24 h beforehand. Subsequently, other studies using different drug probes that included nisoldipine, simvastatin or midazolam confirmed the long duration of effect of grapefruit juice *(16–18)*. In the case of nisoldipine, increased drug AUC was observed up to 72 h after a 7-day pretreatment period with grapefruit juice (200 mL) three times daily *(16)*. For midazolam, the recovery half-life was estimated to be 23 h for a single 300 mL volume of grapefruit juice *(18)*.

Because grapefruit juice produced a long duration of inhibition of intestinal CYP3A4 activity, repeated administration of juice might be expected to cause a cumulative increase in the magnitude of pharmacokinetic interaction. Under single-dose conditions, mean felodipine $C_{\mathbf{max}}$ and AUC with a glass of grapefruit juice (250 mL) were 3.5-fold and 2.7-fold, respectively, compared to those with water *(4)*. During repeated juice consumption, grapefruit juice (250 mL three times daily for 5 days) further increased felodipine $C_{\mathbf{max}}$ and AUC to 5.4-fold and 3.5-fold, respectively, of those relative to single-dose administration of felodipine with water. Thus, repeated administration of grapefruit juice can cause a cumulative increase in the magnitude of the pharmacokinetic drug interaction.

3. CLINICAL EVIDENCE

3.1. Drug Interactions with Grapefruit Juice

Many drugs from a broad range of therapeutic categories have been examined for a possible interaction with grapefruit juice. Those that have increased oral bioavailability with grapefruit juice are listed in Table 1 *(1–5, 11–112)*. Medications without enhanced bioavailability are shown in Table 2 *(113–138)*. Comparisons between Tables 1 and 2 supported the concept that medications interacting with grapefruit juice have inherently low to intermediate oral bioavailability (<5–60%) and undergo presystemic metabolism primarily mediated by CYP3A4. In general, drugs with lower intrinsic bioavailability will experience a greater magnitude of interaction.

3.2. Adverse Drug Effects with Grapefruit Juice

3.2.1. TORSADES DE POINTES

The antiarrhythmic agents, amiodarone and quinidine, and the antimalarial drug, halofantrine, can produce QTc interval prolongation and associated risk of developing the life-threatening cardiac ventricular arrhythmia, torsades de pointes. Other medications that produced this serious drug effect including the non-sedating antihistamines, astemizole and terfenadine, and the gastrointestinal prokinetic

Table 1
Drugs with Increased Oral Bioavailability with Grapefruit Juice from Inhibition of Intestinal CYP3A4

Anti-infective Agents
- Albendazole *(19)*
- Artemether *(20–22)*
- Erythromycin *(23)*
- Halofantrine *(24)*
- Praziquantil *(25)*
- Primaquine *(26)*
- Saquinavir *(27)*

Anti-inflammatory Agents
- Methyprednisolone *(28)*

Antilipemic Agents
- Atorvastatin *(29–31)*
- Lovastatin *(32–34)*
- Simvastatin *(17,35,36)*

Cardiovascular Agents
- Amiodarone *(37)*
- Carvedilol *(38)*
- Felodipine *(1–5,11,13–15,39–50)*
- Manidipine *(51)*
- Nifedipine *(2,52–56)*
- Nimodipine *(57)*
- Nicardipine *(58)*
- Nisoldipine *(16,59,60)*
- Nitrendipine *(61,62)*
- Sildenafil *(63)*
- Verapamil *(64–66)*

Central Nervous System Agents
- Alfentanil *(67)*
- Buspirone *(68)*
- Carbamazepine *(69)*
- Dextromethorphan *(70)*
- Diazepam *(71)*
- Fluvoxamine *(72)*
- Methadone *(73)*
- Midazolam *(18,74–78)*
- Quazepam *(79)*
- Scopolamine *(80)*
- Sertraline *(81)*
- Triazolam *(79,82–84)*

Estrogens
- Ethinylestradiol *(85)*

Gastrointestinal Agents
- Cisapride *(86–89)*

Histamine H_1 Antagonists
- Terfenadine *(90–93)*

Immunosuppresive Agents
- Cyclosporine *(94–108)*
- Tacrolimus *(12,109–111)*

Oral Antidiabetic Agents
- Repaglinide *(112)*

agent, cisapride, have been removed from the market because of this concern. The risk of developing this arrhythmia appears to be increased in conditions where plasma concentrations of these drugs are elevated.

Mean oral bioavailability of amiodarone is normally variable among individuals (range: 20–80%) as a result of extensive first-pass metabolism *(139)*. *N*-desethylamiodarone (*N*-DEA) is the major metabolite formed by CYP3A4 *(140)*. This metabolite appears to have significant antiarrhythmic properties. Mean amiodarone $C_{\mathbf{max}}$ and AUC, respectively, with grapefruit juice (300 mL at 0 h, 3 h and 9 h relative to drug administration) were 1.8-fold and 1.5-fold compared to those with amiodarone alone *(37)*. This resulted in plasma amiodarone concentrations that exceeded recommended therapeutic levels. Plasma *N*-DEA concentrations were decreased to undetectable levels, and prolongation of QTc interval was less with concomitant grapefruit juice. Inhibition of *N*-DEA

Table 2
Drugs with No Change in Oral Bioavailability with Grapefruit Juice

Antiasthmatic Agents
- Theophylline *(113–114)*

Anticoagulants
- Acenocoumarin *(115)*
- Warfarin *(116)*

Anti-infective Agents
- Amprenavir *(117)*
- Clarithromycin *(118)*
- Indinivir *(119,120)*
- Quinine *(121)*

Anti-inflammatory Agents
- Prednisone *(98)*

Antilipemic Agents
- Pravastatin *(29,31)*
- Pitavastatin *(30)*

Cardiovascular Agents
- Amlodipine *(122,123)*
- Diltiazem *(124,125)*
- Propafenone *(126)**
- Quinidine *(127,128)**

Central Nervous System Agents
- Alprazolam *(129)*
- Clomipramine *(130)*
- Clozapine *(131–133)*
- Haloperidol *(134)*
- Phenytoin *(135)*

Hormones
- 17β – estradiol *(136)*
- Levothyroxine *(137)*

Oral Antidiabetic Agents
- Glibenclamide *(138)*

* See text for discussion of concern for potential interaction

production might decrease the beneficial action of amiodarone, or conversely, it might reduce the unwanted proarrhythmic effects linked to QTc prolongation. Because the clinical outcome is not clear, consumption of grapefruit juice should be avoided in patients receiving amiodarone.

Quinidine has relatively high absolute oral bioavailability (about 70%), but it has a narrow therapeutic range of effective and safe plasma drug concentrations *(141, 142)*. In one single-dose study, grapefruit juice (240 mL) did not change mean quinidine $C_{\mathbf{max}}$ or AUC; however, it decreased 3-hydroxyquinidine AUC compared to water *(127)*. In another study, chronic consumption of grapefruit juice (250 mL twice daily) reduced the oral clearance of quinidine and 3-hydroxy and N-oxide metabolites to 0.85, 0.81 and 0.73 of those with water *(128)*. Thus, grapefruit juice appears to have a small effect on mean pharmacokinetics of quinidine. However, even modestly elevated plasma quinidine concentrations have the potential to cause serious side effects. Thus, it seems reasonable to avoid grapefruit juice consumption during therapy with quinidine until proven safe.

Halofantrine has a mean oral bioavailability of 10% and is metabolized to the less cardiotoxic metabolite, *N*-debutylhalofantrine, by CYP3A4 *(143–145)*. When it was administered as a single dose after grapefruit juice (250 mL once daily for 3 days and once at 12 h before drug), halofantrine $C_{\mathbf{max}}$ and AUC were 3.2-fold and 2.8-fold higher, respectively, those with water *(24)*. *N*-Debutylhalofantrine AUC was decreased to 0.4-fold that observed after water. Maximum QTc interval prolongation with halofantrine was increased to a mean 31 ms with grapefruit juice compared to 17 ms with water. It was concluded that grapefruit juice consumption should be contraindicated during administration of halofantrine.

Other drugs can cause QTc prolongation and have the pharmacokinetic properties of low to moderate oral bioavailability from CYP3A4-mediated presystemic metabolism. They include the upper gastrointestinal motility modifier, domperidone; the antipsychotic drug, pimozide; the urinary tract antispasmodic drug, solifenacin; and the antitumour drug, sunitinib. An adverse interaction with these drugs and grapefruit juice to cause QTc prolongation seems predictable (Table 3).

Table 3
Drugs with Potential for Increased Oral Bioavailability with Grapefruit Juice from Inhibition of Intestinal CYP3A4

Anticancer Agents
Cyclophosphamide
Dasatinib
Ifosfamide
Imatinib
Sunitinib
Trofosfamide
Anti-inflammatory Agents
Budesonide *(176,177)*
Cardiovascular Agents
Clopidogrel
Ergotamine
Propafenone
Tadalafil
Vardenafil
Central Nervous System Agents
Pimozide
Sibutramine
Gastrointestinal Agents
Domperidone
Immunosuppressants
Sirolimus (rapamycin)
Urinary Tract Agents
Darifenacin
Solifenacin
Tamsulosin

3.2.2. RHABDOMYOLYSIS

HMG-CoA reductase inhibitors belong to an important class of cholesterol-lowering medications. However, they can cause significant toxicity. Unwanted effects range from diffuse myalgia and elevated creatine phosphokinase to severe skeletal muscle degeneration (rhabdomyolysis) and associated acute renal failure. These effects can occur when the plasma concentration of HMG-CoA reductase inhibitor is markedly elevated. Atorvastatin, lovastatin and simvastatin are extensively metabolized by CYP3A4 and have low oral systemic availability.

Atorvastatin is administered as the active acid form and has a mean absolute oral bioavailability of 12% *(146)*. The AUC of a single oral dose of atorvastatin was increased and ranged from a mean of 1.8-fold to 2.5-fold compared to that with water following consumption of grapefruit juice three times per day for 2–4 days *(29–31)*. However, the AUC of an active metabolite of atorvastatin was approximately halved.

Simvastatin and lovastatin are inactive lactones that both have an absolute oral bioavailability of less than 5% *(32,147)*. They undergo conversion to the active acid derivative, during systemic absorption. However, most of the simvastatin and lovastatin are transformed to inactive metabolites through the action of CYP3A4.

Consumption of grapefruit juice at a relatively high volume (400 mL three times daily for 3 days) or at a more usual amount (200 mL once daily for 3 days) prior to co-administration of the corresponding quantity of juice with a single dose of simvastatin increased the AUCs of simvastatin acid to 7.0-fold or 3.3-fold, respectively, compared to that when simvastatin was ingested with water *(17,35,36)*. Moreover, 10 days consumption of one fresh grapefruit per day in an athletic and healthy 40-year-old woman stabilized on a relatively high dose (80 mg) of simvastatin caused rhabdomyolysis as evidenced by dramatically high creatine phosphokinase (12,640 Units/L) and myoglobin (6,453 Units/L) and a markedly low walking distance of less than 20 m *(148)*.

Ingestion of grapefruit juice at comparatively high quantity (400 mL three times daily for 3 days) followed by co-administration with a single dose of lovastatin augmented lovastatin acid to fivefold compared to that with water *(32)*. Consumption of a more usual amount of grapefruit juice (200 mL once daily for 3 days) at breakfast followed by the administration of a single dose of lovastatin in the evening increased the AUC of lovastatin acid to 1.6-fold that with water *(33)*. Although the interval between the last glass of juice and the intake of lovastatin was not specified, it appears likely that the observed extent of the interaction may substantially underpredict that with concomitant juice and lovastatin ingestion *(34)*. Consequently, it is recommended that consumption of grapefruit juice should be avoided entirely during therapy with atorvastatin, lovastatin or simvastatin.

Pravastatin and rosuvastatin are metabolized to only a minor extent. Moreover, pravastatin did not interact with grapefruit juice *(29,31)*. The interaction between rosuvastatin and grapefruit juice has not been reported. However, co-administration of rosuvastatin with the potent CYP3A4 inhibitor, itraconazole, did not result in a pharmacokinetic interaction *(149)*. Fluvastatin has essentially complete oral bioavailability and is predominantly metabolized by CYP2C9. Thus, pravastatin, rosuvastatin or fluvastatin might serve as alternative agents when there is concern for a potential interaction with grapefruit juice.

3.2.3. SYMPTOMATIC HYPOTENSION

Dihydropyridine calcium channel antagonists are selective arteriolar vasodilators that are often employed in the management of hypertension or other cardiovascular disorders. Adverse clinical consequences of excessive vasodilatation from elevated plasma concentration of the dihydropyridines include headache, ankle edema and facial flushing. Although these effects are generally not considered to be serious, they could be sufficiently unpleasant to decrease patient adherence to the treatment regimen and to negate drug benefit. At the other extreme, adverse drug events from excessive vasodilatation may result in symptomatic hypotension or myocardial infarction.

Several dihydropyridines have low inherent oral bioavailability and are inactivated, at least in part, by CYP3A4-mediated metabolism. In middle-aged subjects with untreated borderline hypertension, mean felodipine AUC with grapefruit juice was 2.8-fold compared to that with water *(2)*. This was associated with enhanced diastolic blood pressure reduction and increased heart rate and frequency of vasodilatation-related side events. In healthy elderly individuals (70–83 years of age), mean oral felodipine AUC with grapefruit juice was fourfold compared to that with water, supporting the importance of intestinal CYP3A4-mediated drug metabolism in this age group *(5)*. In contrast with the effect in middle-age individuals, there was enhanced reduction of both systolic and diastolic blood pressure in the elderly. Although some tachycardia was apparent in both age groups, lower systolic blood pressure in only the elderly may have resulted from attenuated baroreceptor reflex responsiveness that is known to occur with aging *(150)*. This likely also explains the greater blood pressure lowering effects of felodipine in the elderly *(151)*. Since the elderly are the prime purchasers of grapefruit juice, demonstrate a marked pharmacokinetic interaction, are often prescribed affected drugs and less able to compensate for excessive plasma drug concentration, there is particular concern for grapefruit–drug interactions in this population.

Other dihydropyridine calcium channel antagonists that interact with grapefruit juice include manidipine *(51)*, nifedipine *(2,52–56,60)*, nimodipine *(57)*, nicardipine *(58)*, nisolidipine *(16,59,60)* and nitrendipine *(61,62)*. Average dihydropyridine $C_{\mathbf{max}}$ and AUC with grapefruit juice ranged from 1.5-fold to 4.0-fold those with water under single-dose conditions. In contrast, amlodipine had a negligible pharmacokinetic interaction with grapefruit juice *(122,123)*. The most likely reason is amlodipine's inherently high (80%) oral bioavailability.

Sildenafil is used to treat erectile dysfunction by causing vasodilatation of smooth muscle of the corpus cavernosa. At therapeutic drug concentration, sildenafil inhibits a particular isoform of phosphodiesterase (PDE5) to selectively increase intracellular cyclic guanosine monophosphate (cGMP) concentration in this tissue. At higher drug concentration, the selectivity of sildenafil for PDE5 is lost and other isoforms of PDE are inhibited, resulting in a more generalized increase in intracellular cGMP and systemic vasodilatation. Organic nitrates can also increase intracellular cGMP concentration, but this is by a mechanism involving stimulation of cGMP production. The combined effects of sildenafil and nitrates can be sufficient to cause symptomatic hypotension, myocardial infarction or sudden death. Sildenafil has intermediate oral bioavailability (mean: 41%, range: 25–63%) and is eliminated extensively through metabolism mediated by CYP3A4

(152,153). The primary metabolite (*N*-desmethylsildenafil) is approximately 50% as potent as the parent drug. Sildenafil and desmethylsildenafil AUCs with grapefruit juice (250 mL) given 1 h before and together with drug were a mean 1.2-fold compared to those with water in a single-dose study *(63)*. Mean decrease in systolic and diastolic blood pressure and increase in heart rate were not different between treatments. However, sildenafil AUC with grapefruit juice ranged from 0.8-fold to 2.6-fold compared to those with water among individuals. The authors concluded that the small mean increase in the oral bioavailability of sildenafil and active metabolite by grapefruit juice would probably not produce more enhanced therapeutic or adverse effects. However, variability in the extent of the pharmacokinetic interaction among individuals, in the amount of CYP3A4 inhibitors among brands and batches of grapefruit juice and in the volume of juice consumed make the effect less predictable. It is therefore recommended that the combination of sildenafil and grapefruit juice should be avoided.

Other drugs with the potential to cause hypotension and to possess grapefruit juice-interacting pharmacokinetic properties include the newer erectile dysfunction agents, tadalafil and vardenafil, and the alpha$_1$ adrenoreceptor blocker used for treatment of urinary tract symptoms associated with benign prostatic hyperplasia, tamsulosin (Table 3).

3.2.4. DYSRHYTHMIA

Verapamil depresses atrio-ventricular conduction and myocardial contractility and moderately dilates arteriolar smooth muscle. Verapamil is a racemic mixture of *S*- and *R*-enantiomers. The *S*-enantiomer is more pharmacologically active. Verapamil undergoes stereoselective first-pass metabolism involving CYP3A4 that results in variable bioavailability of 13–34% for the *S*-enantiomer and 33–65% for the *R*-enantiomer among individuals.

The interaction between grapefruit juice and verapamil has been assessed in several investigations. In one study, administration of a single glass of grapefruit juice (200 mL) to 10 hypertensive patients receiving chronic short-acting verapamil resulted in increased AUC ratio of the racemic parent drug to major active dealkylated metabolite, norverapamil, indicative of inhibition of CYP3A4-mediated verapamil metabolism *(64)*. However, the absolute pharmacokinetic values for verapmil and norverapamil were not statistically changed. In a second study, grapefruit juice (200 mL twice daily for 5 days) increased steady-state plasma concentrations of both *S*- and *R*-enantiomers of verapamil compared to an orange juice control *(65)*. Mean AUC and $C_{\mathbf{max}}$ of *S*-verapamil with grapefruit juice were 1.4-fold and 1.6-fold those with orange juice, respectively. The effect was similar for *R*-verapamil. Considerable inter-subject variability in the magnitude of the pharmacokinetic interaction was apparent. No change in the mean pharmacodynamics of verapamil (PR interval, blood pressure and heart rate) was observed. In a third study, grapefruit juice (1 L/day for 3 days) augmented the steady-state plasma concentration of *S*,*R*-verapamil administered in the prolonged release drug formulation *(66)*. Mean verapamil AUC and $C_{\mathbf{max}}$ with grapefruit juice were 2.5-fold and 2.6-fold compared to those with water. The increases were slightly greater for verapamil than for norverapamil. Prolongation of PR interval above

350 ms occurred in 2 of the 24 individuals in the group receiving grapefruit juice. Overall, the results of these studies show that a pharmacokinetic interaction between grapefruit juice and verapamil can occur under most conditions. However, a pharmacodynamic interaction was evident only during repeated high volume grapefruit juice and chronic verapamil administration. Nevertheless, the high variability of the pharmacokinetic interaction among individuals suggests that a clinically relevant interaction may occur with verapamil under single dose and more usual volumes of grapefruit juice administration.

3.2.5. Loss of Drug Efficacy

Losartan and its active metabolite, E-3174, antagonize the vasoconstrictor and aldosterone-stimulating effects of angiotensin II by blocking the binding of angiotensin II to AT_1 receptors found in many tissues, including vascular smooth muscle. Losartan undergoes substantial first-pass metabolism, resulting in a mean absolute oral bioavailability of 33%. CYP3A4 and CYP2C9 convert losartan to E-3174, which has four times the inhibitory activity in vitro and is responsible for the majority of the antagonism at the angiotensin II receptor clinically. Since grapefruit juice substantially reduced the AUC of E-3174, the therapeutic effectiveness of losartan may be decreased *(154)*.

Carvedilol combines non-selective beta-receptor and alpha-1 receptor blockade in a single racemic drug. Beta-receptor blockade is attributed to the *S*-enantiomer, while alpha-1 receptor blockade is present in equal potency in both enantiomers. Because heart failure can worsen when beta- and alpha-receptor blockade are excessive, care must be taken in situations where plasma *S*,*R*-carvedilol concentrations are increased. Racemic carvedilol has only a 25–35% absolute oral bioavailability because of presystemic metabolism. This process is stereoselective and results in plasma concentrations of *S*-carvedilol that are twofold to threefold lower than those of *R*-carvedilol. Since glucuronidation as well as oxidation by CYP2D6 and CYP2C9 appear to be the major pathways of drug elimination, it might be predicted that grapefruit juice would not significantly interact with carvedilol. Results of a clinical investigation showed that mean AUC of *S*,*R*-carvedilol with grapefruit juice (300 mL) was 1.2-fold compared to that with water under single-dose conditions *(38)*. Unfortunately, the magnitude of the interaction among individuals and the effect on each enantiomer was not reported. Since dosage and effect of carvedilol must be carefully individualized and closely monitored by a physician experienced in the treatment of heart failure, this makes a recommendation about grapefruit juice use in this setting unclear. For no other reason than to eliminate factors that might prevent establishment of a stable dose-response relationship, it seems reasonable to indicate that patients with heart failure receiving carvedilol should avoid grapefruit juice intake.

3.3. Potentially Beneficial Drug Effects with Grapefruit Juice

3.3.1. Drug Cost Savings

Cyclosporine is an immunosuppressive agent useful in preventing organ rejection following transplantation. It is crucial that plasma cyclosporine concentrations are maintained within a narrow range so as to have adequate drug concentration to prevent transplant rejection but not to have sufficiently high concentration to cause renal toxicity. Cyclosporine is very expensive and must be taken on a daily basis for many years. Cyclosporine has a 30–40% oral bioavailability. Theoretically, increasing cyclosporine bioavailability could result in reduced drug dose and associated cost. Since cyclosporine is metabolized by CYP3A4, grapefruit juice might be useful in this situation. Indeed, numerous investigations have shown that grapefruit juice can increase cyclosporine bioavailability *(94–108)*. However, the effect was variable among studies. Since there is the absolute need for consistency of effect, differences in the content of active ingredients among batches and suppliers of the juice may be an important factor for this variability *(155)*. Consequently, it may not be possible to maintain a uniform effect on cyclosporine bioavailability within any particular patient. Thus, grapefruit juice is currently not recommended as a means to reduce drug cost in this circumstance.

3.3.2. MAINTENANCE OF DRUG EFFECTIVENESS

Artemether is an antimalarial drug with fast onset of action, few side effects and good activity against multidrug resistant parasites. However, it has a high relapse rate during monotherapy. Since there is marked reduction in plasma drug concentrations on repeated administration, induction of its own metabolism (autoinduction) is considered the cause of loss of efficacy. Artemether undergoes high presystemic metabolism by CYP3A4. During single-dose administration, grapefruit juice increased the oral bioavailability of artemether compared to water *(20)*. After 5 days of concomitant grapefruit juice administration, higher plasma artemether concentrations were observed compared to those with 5 days of water *(21)*. However, both grapefruit juice and water produced decreased oral bioavailability of artemether over this time period. Thus, grapefruit juice improved the oral bioavailability of artemether under conditions of single and repeated administration. However, grapefruit did not totally abolish the autoinduction of artemether. Nevertheless, it prolonged effective plasma drug concentrations. Oral treatment with artemether may be more effective when the medication is taken with grapefruit juice *(22)*.

3.3.3. ENHANCED DRUG EFFICACY

Protease inhibitors are antiretroviral drugs used in the treatment of HIV-1 infection. Saquinavir has very low oral bioavailability (1–2%) and is a substrate for CYP3A4. Since it does not appear to have important toxicity at high plasma drug concentration, any increase in saquinavir bioavailability has the potential to produce enhanced drug benefit. Saquinavir AUC with grapefruit juice was twofold that with water *(27)*. Although saquinavir with grapefruit might produce some therapeutic benefits compared to saquinavir alone, the extent of the interaction was minor compared to the 58-fold increase with ritonavir *(156)*.

3.4. Drug Interactions with Other Fruit Juices

The search for other fruit juices creating a drug interaction by inhibition of CYP3A4 logically required determination of the active ingredient(s) in grapefruit juice. Citrus fruits contain a number of flavonoids, furanocoumarins, liminoids and other polyphenolic compounds. The key in vitro finding was that it might be the furanocoumarins *(157)*. Numerous studies have subsequently established that several furanocoumarins in grapefruit are irreversible "mechanism-based" inhibitors of CYP3A4 *(158–166)*.

3.4.1. SEVILLE ORANGE JUICE

Seville orange, which is commonly found in marmalades, contained two of the major furanocoumarins in grapefruit, bergamottin and 6',7'-dihydroxybergamottin *(43)*. A clinical study testing the effect of 240 mL of Seville orange juice and dilute grapefruit juice, which contained equivalent total molar concentrations of these two furanocoumarins, was conducted *(43)*. These juices increased the AUC of felodipine to 176 and 193% compared to that with the negative control, common orange juice, respectively. Seville orange and grapefruit juices also produced similar changes in the pharmacokinetics of the primary metabolite, dehydrofelodipine, consistent with the same mechanism of inactivation of intestinal CYP3A4. It was suggested that bergamottin and/or 6',7'-dihydroxybergamottin may be "marker substances" in foods to predict this type of interaction. Moreover, marmalades containing Seville orange may produce clinically relevant drug interactions. As a further indicator of the role played by the furanocoumarins, a furanocoumarin-free grapefruit juice was developed and evaluated. When tested against original grapefruit juice and orange juice as a control in healthy volunteers taking felodipine or cyclosporine, the AUC and $C_{\max}$ were only increased with the original grapefruit juice, with no difference between furanocoumarin-free juice or control *(165,166)*.

3.4.2. PUMMELO OR POMELO JUICE

Pummelo or pomelo (*Citrus grandis* (L.)) is a citrus fruit closely related to grapefruit (*Citrus paradise* Macf). Fruit juice of the pummelo was found to have substantial furanocoumarin content and to cause inhibition of CYP3A4-mediated testosterone 6β-hydroxylation by human liver microsomes *(167)*. Pummelo juice 250 mL augmented the AUC and $C_{\mathbf{max}}$ of felodipine to 200 and 206% of those with water in 12 healthy male Chinese volunteers *(167)*. This supports yet another fruit juice producing this type of interaction. Clinically, pummelo juice 240 mL increased the AUC and $C_{\mathbf{max}}$ of cyclosporine to 119.4% [$p < 0.05$] and 112.1% [$p < 0.05$], respectively, compared to those with water *(168)*. In a case report involving a renal transplant patient, pummelo juice induced an increase in the blood concentrations of another immunosuppressant, tacrolimus *(169)*. This juice was also shown to be a potent inhibitor of CYP2C9 with a value for 50% inhibition (IC_{50}) for dihydroxybergamottin much lower than for bergamottin *(170)*.

3.4.3. LIME JUICE

Lime juice was found to contain high bergamottin content, but essentially no 6',7'-dihydroxybergamottin *(45)*. In a study of eight healthy volunteers assessing the potential for a clinical drug interaction, lime and grapefruit juices had measured concentrations of bergamottin of 100 and 25 μmol/L, respectively *(45)*. Overall, lime juice 250 mL at one-fourth strength caused one-third the increase in the oral bioavailability of felodipine compared to grapefruit juice. It more than doubled the AUC and $C_{\mathbf{max}}$ of felodipine in the two study subjects who had the greatest increase with grapefruit juice. Thus, lime juice and bergamottin seem to have clinical activity. Consumption of as little as 62 mL of lime juice may produce a relevant drug interaction in grapefruit juice-sensitive individuals.

3.4.4. POMEGRANATE JUICE

Pomegranate and grapefruit caused 50% inhibition [IC_{50}] of in vitro CYP3A activity at very low juice concentrations [0.61 and 0.55% strength, respectively] under competitive conditions *(78)*. However, only grapefruit juice produced mechanism-based inhibition. Pomegranate juice 240 mL did not alter the pharmacokinetics of intravenous or oral midazolam compared to water. However, grapefruit juice 240 mL increased the AUC and C_{max} of oral midazolam to 153 and 136% compared to those with water, respectively. Using carbamazepine as a probe with the 10,11-epoxide as a marker, pomegranate juice inhibited CYP3A activity in human liver microsomes to a similar extent as grapefruit juice in a dose-dependent manner *(171)*. Testing in an animal model revealed increased AUC of the parent drug and the 10,11-epoxide with no suggestion of pomegranate juice influencing carbamazepine absorption *(171)*. This indicated a post-luminal effect with recovery of enzyme activity requiring 3 days. The results provide additional support that the ability to cause mechanism-based enzyme inhibition is an important predictor of juice-mediated drug interactions clinically.

3.4.5. TANGERINE JUICE

Tangeretin is a flavonoid that stimulates the in vitro catalytic activity of CYP3A4 and is found in high levels in tangerine juice. It increased the conversion of midazolam to 1′-hydroxymidazolam by up to 212% by human liver microsomes and to 152% by recombinant CYP3A4 *(172)*. However, tangerine juice 200 mL did not alter the total AUC of midazolam or AUC ratio of 1′-hydroxymidazolam/midazolam. It appears that tangerine juice will not likely have any appreciable effect on CYP3A4-mediated drug metabolism in humans.

3.4.6. CRANBERRY JUICE

Case reports implied that cranberry juice might increase the anticoagulant effect of warfarin *(173–177)*. Cranberry juice or water 200 mL ingested three times daily for 10 days was followed by concomitant administration of *R*- and *S*-warfarin, tizanidine and midazolam, which are probes of CYP2C9, CYP1A2 and CYP3A4, respectively *(178)*. Cranberry juice did not alter the AUC or C_{max} of the probes or metabolites or the anticoagulant effect of warfarin. Moreover, cranberry juice 240 mL did not influence the disposition of cyclosporine *(168)*. Cranberry juice-mediated pharmacokinetic or pharmacodynamic interaction with warfarin seems questionable.

3.4.7. OTHERS

Further evidence that grapefruit or other juices are not alone comes from a recent case report describing a transplant patient experiencing significant variability in serum cyclosporine concentrations attributed directly to ingestion of a citrus soda considered to contain furanocoumarins *(179)*.

4. LIMITATIONS OF THE DATA

4.1. Incomplete List of Drugs Interacting with Grapefruit Juice

A substantial number of drugs have been assessed for an interaction with grapefruit juice. However, there are many more medications that have not been studied. Nevertheless, it is possible to predict the likelihood of an interaction for other drugs. Because grapefruit juice enhances oral drug bioavailability, the suspected medication should have an inherent absolute bioavailability that is normally low or intermediate (<70%). Additionally, there should be accompanying data to indicate that the drug is extensively metabolized by CYP3A4. A number of drugs with the potential to interact with grapefruit juice have been discussed previously.

4.2. Adverse Effects with Grapefruit Juice

The glucocorticoid, budesonide, is available as an oral controlled release formulation designed to optimize drug delivery to the ileum and colon for the treatment of mild to moderate symptoms of Crohn's disease *(180)*. Although it is well absorbed, oral budesonide has low systemic availability ranging from 9 to 21% as a result of extensive first-pass elimination mediated by CYP3A4 that produces metabolites with negligible glucocorticoid activity. Grapefruit juice consumption would very likely markedly augment the oral bioavailability of budesonide *(180,181)*. Although this may not produce clinically relevant problems during acute grapefruit juice consumption, there is the concern for significant adverse effects (hyperglycemia, Cushingoid features, adrenal suppression) associated with chronic grapefruit juice and budesonide ingestion.

The antiplatelet agent, clopidogrel, is an irreversible inhibitor of ADP-induced platelet aggregation and is used for secondary prevention of vascular events in patients with a history of symptomatic atherosclerotic disease. It is rapidly converted to at least one active metabolite, and this results in a plasma clopidogrel concentration that is normally not detectable following oral administration. Findings have shown that concomitant administration of a CYP3A4 inhibitor, erythromycin or troleandomycin, attenuated platelet aggregation inhibition; whereas, pretreatment with a CYP3A4 inducer, rifampin, enhanced the inhibition of platelet aggregation *(182)*. Consequently, the active metabolite(s) of clopidogrel is likely formed by CYP3A4. Because clopidrogel has negligible oral bioavailability, extensive presystemic metabolism by intestinal CYP3A4 might be expected. Consequently, grapefruit juice could reduce formation of the active metabolite(s) and attenuate the therapeutic benefit of clopidogrel.

Cyclophosphamide, ifosfamide and trofosfamide are anticancer alkylating agents that undergo extensive metabolism to yield both active (4-hydroxylated) and therapeutically inactive but neurotoxic (*N*-dechloroethylated) metabolites mediated mainly through the action of CYP3A4 *(183–186)*. The manufacturer of cyclophosphamide notes that the absolute oral systemic availability is 74%. Importantly, the alkylating activity of cyclophosphamide was 3.5-fold greater with oral administration than that with intravenous dosing. Thus, the intestinal tract appears to be a key site for the metabolic activation process. Consequently, the manufacturer recommends avoidance of grapefruit or grapefruit juice during therapy to prevent possible impairment in the conversion of cyclophosphamide to the active metabolite(s). Similarly, ifosfamide has been estimated to have incomplete oral bioavailability (~37%) and to be more cancerotoxic after oral than intravenous administration. Avoidance of grapefruit and juice is recommended for cyclophosphamide, ifosfamide and possibly trofosfamide.

Darifenacin is a muscarinic (M_3 selective) receptor antagonist, which is indicated for reduction of smooth muscle contraction in patients with overactive bladder. Although darifenacin appears to be well absorbed after administration, the mean oral bioavailability is normally 15% from first-pass metabolism mediated by CYP3A4 and possibly CYP2D6 *(187,188)*. None of the major metabolites appears to contribute to overall clinical effect. Since concomitant administration of ketoconazole and erythromycin increased the mean $C_{\mathbf{max}}$ of darifenacin by 9.5-fold and 2.3-fold, respectively, grapefruit juice would be predicted to produce a relevant pharmacokinetic interaction, which would likely enhance the primary effect of the drug and increase the frequency of dry mouth and constipation. A marked pharmacokinetic interaction in susceptible patients may precipitate acute urinary retention, gastrointestinal obstructive disorders, glaucoma or anti-muscarinic effects related to cardiac, visual or cognitive function.

Ergotamine is an alkaloid used to treat migraine headache. Serious toxicity can occur during therapy. Ergotism is a syndrome referred to as “St Anthony’s Fire” and is characterized by vascular ischemia and neurological compromise as a result of excessive ergotamine concentration. Cases of gangrene and stroke have been reported that have resulted in amputation or death. Ergotamine appears to have low oral bioavailability and is a substrate of CYP3A4 *(189)*. Toxicity has occurred in patients concomitantly receiving standard doses of ergotamine with the CYP3A4 inhibitors, clarithromycin, ritonavir or triacetyloleandomycin *(190)*. Thus, an interaction between ergotamine and grapefruit juice appears probable, and this combination should be avoided. Alternatively, better options than ergotamine exist for the treatment of migraine headache, including the class of drugs known as triptans. There does not appear to be an interaction between most drugs of this class and grapefruit juice.

Imatinib is a protein tyrosine kinase inhibitor indicated for the treatment of certain patients with leukemia. It has been reported to have good oral bioavailability and is metabolized mainly by CYP3A4 to the *N*-demethylated piperazine derivative, which has similar in vitro potency to the parent imatinib. However, coadministration of a single dose of ketoconazole increased the mean $C_{\mathbf{max}}$ and AUC of imatinib by 26 and 40% in healthy subjects *(191)*. The manufacturer recommends caution when administering imatinib with inhibitors of the CYP3A4 family (e.g., ketoconazole, erythromycin, clarithromycin, itraconazole and grapefruit juice) as they may decrease metabolism and increase drug concentrations. Dasatinib is also a CYP3A4 substrate and has a similar warning by the manufacturer.

Propafenone undergoes presystemic metabolism resulting in an absolute oral bioavailability that ranges markedly from 3 to 40%. Normally, the major route of elimination is metabolism by CYP2D6, and the minor route involves metabolism by CYP3A4. However, the activity of CYP2D6 varies markedly among individuals.

Genetic mutations can result in CYP2D6 activity that is substantially reduced or absent, a phenomenon known as "genetic polymorphism". The frequency–activity distribution curve of CYP2D6 is divided into two basic populations classified as extensive (EM) or poor (PM) metabolizers. The incidence of CYP2D6 PM is 5–10% in Caucasians and about 1% in Asians. Preliminary data indicate that CYP3A4 inhibitors, erythromycin, ketoconazole or grapefruit juice, can increase plasma propafenone concentrations in individuals who are CYP2D6 PM *(126)*. Symptoms of propafenone overdose include bradycardia, hypotension, conduction disturbances, ventricular tachycardia and/or fibrillation, somnolence or convulsions. This may explain the adverse interaction reported in a patient taking propafenone for 4 years who experienced convulsions 2 days after starting treatment with the CYP3A4 inhibitor, ketoconazole *(192)*. Thus, grapefruit juice may potentially cause propafenone toxicity in individuals who are CYP2D6 PM.

Sibutramine reduces body weight by enhancing satiety and inducing thermogenesis through inhibition of neuronal reuptake of serotonin and noradrenaline. Sibutramine appears to undergo extensive CYP3A4-mediated presystemic metabolism to active metabolites. Concomitant administration of the CYP3A4 inhibitors, ketoconazole or erythromycin, produced mean sibutramine $C_{\mathbf{max}}$ that were twofold or threefold, respectively, compared to those with sibutramine alone *(193)*. The $C_{\mathbf{max}}$ of at least one active metabolite was also increased. Systolic and diastolic blood pressures and heart rate were increased compared to sibutramine alone. Since caution is recommended for administration of sibutramine with CYP3A4 inhibitors, it may be also appropriate to include avoidance of grapefruit juice. As patients might consider the "grapefruit diet" as an adjunct to weight reduction, this precaution appears particularly relevant.

Sirolimus (rapamycin) is an immunosuppressant with a low oral bioavailability averaging 20% that is a substrate for CYP3A4 and P-glycoprotein *(194)*. A single-dose pharmacokinetic interaction study showed that the AUC and $C_{\mathbf{max}}$ of sirolimus with diltiazem were 160 and 143% of those with water, respectively *(195)*. Moreover, two case reports have demonstrated a marked increase in trough blood concentrations of sirolimus with clarithromycin or itraconazole *(196,197)*. Thus, grapefruit juice would likely cause a marked increase in the oral bioavailability of sirolimus.

5. FUTURE RESEARCH NEEDS

5.1. Other Enzymes and Fruit Juices

Although most attention has been focused on CYP3A4 given its role in metabolism of about half of all drugs, other enzymes may also be influenced by compounds found in fruit juices.

5.1.1. CYP1A2

Naringin is a major flavonoid in grapefruit juice that can be converted to the aglycone naringenin. The latter compound may contribute to CYP1A2 inhibition *(198)*. Clinically significant interactions with CYP1A2 substrates have not been documented.

5.1.2. CYP2C9

Both grapefruit juice and pummelo juice were evaluated for their inhibitory influence on CYP2C9 at juice concentrations of 25, 5 and 1% *(170)*. Grapefruit juice (1% dilution) inhibited CYP2C9 by 48%, but the same dilution of pummelo juice resulted in 74% inhibition. At higher concentrations, CYP2C9 inhibition was complete for both juices. The IC_{50} values of the furanocoumarins for CYP2C9 were lower than they were for CYP3A4. This included paradisin A (0.18 μmol/L), dihydroxybergamottin (1.58 μmol/L) and bergamottin (4.51 μmol/L) *(170)*.

5.1.3. CYP2D6

Both grapefruit juice and pummelo juice were evaluated for their inhibitory influence on CYP2D6 at juice concentrations of 25, 5 and 1% *(170)*. Pummelo juice (1% dilution) inhibited CYP2D6 poorly at ~13%, while grapefruit juice was even less inhibitory. At the highest juice concentration (25% dilution), CYP2D6 inhibition was 73–90% with grapefruit and pummelo juice. The IC_{50} values of the furanocoumarins for CYP2D6 were 0.30 μmol/L (paradisin A), 5.63 μmol/L (dihydroxybergomottin) and 11.74 μmol/L (bergamottin) *(170)*.

5.1.4. Esterases

Grapefruit juice inhibits esterase activity and can influence the activation of ester prodrugs such as enalapril and lovastatin *(199)*. The flavonoids (e.g., kaempferol and naringenin) in grapefruit juice have been identified as being responsible, at least in part, for the inhibitory effect on esterase activity *(200)*. This would have the potential to increase bioavailability of enalaprilat and lovastatin acid.

5.1.5. UGT1A1

Uridine diphosphate glucuronosyl transferases (UGT) catalyze drug conjugation reactions. Among the 4 UGT gene families, UGT1A enzymes conjugate several endogenous (e.g., bilirubin) and exogenous (e.g., carvedilol) compounds. Polymorphisms of UGT1A1 include UGT1A1*28 (7 TA repeats) resulting in lower levels of conjugated metabolites. Findings from an epidemiologic study suggest that citrus fruit consumption may increase the activity of UGT1A1*28 *(200a)* based on lower serum bilirubin. It remains to be seen whether this will be clinically relevant for medication.

5.2. Drug Transporters and Fruit Juices

Drug transporters can be generally separated into two major classes – uptake and efflux transporters *(201–206)* (see Chapter 3). Members of the solute carrier (SLC) superfamily are uptake transporters that facilitate the translocation of drugs into cells. They comprise the organic anion transporting polypeptides (OATPs), organic anion transporters (OATs), organic cation transporters (OCTs), organic cation/ carnitine transporters (OCTNs) and peptide transporters (PEPTs). The efflux transporters export drugs from the intracellular to the extracellular environment. Members of this ATP-binding cassette (ABC) superfamily can pump drugs out of the cell against a marked concentration gradient. They comprise the P-glycoprotein family (P-glycoprotein or MDR1), the bile salt export pump (BSEP), multidrug resistance-associated protein family (MRP1, MRP2 and MRP3) and the breast cancer resistance protein (BCRP). Several furanocoumarins and flavonoids found in fruit juices are likely more potent inhibitors of OATP than P-glycoprotein.

5.2.1. P-GLYCOPROTEIN

P-glycoprotein was first observed in tumour cells and caused resistance to chemotherapeutic agents. Subsequently, it was shown to play an important physiological role. P-glycoprotein is located in a number of tissues where it can affect both drug elimination (gastrointestinal tract, liver and kidney) and drug distribution (brain and testes). Regarding the systemic availability of drugs, P-glycoprotein is located on the luminal surface of epithelial cells of the small intestine and the bile canalicular membrane of the liver, where it can limit absorption from the gut and facilitate first-pass removal into bile.

The clinical effect of grapefruit juice on P-glycoprotein has not been extensively documented. However, grapefruit juice did modestly enhance the oral bioavailability of the non-metabolized P-glycoprotein substrate, digoxin, to 109% [$p = 0.01$] compared to that with water in humans *(207)*. This small increase prompted the authors to conclude that grapefruit juice did not produce meaningful inhibition of presystemic intestinal or hepatic P-glycoprotein activity. However, digoxin normally has an oral bioavailability of 70–80%. Thus, inhibition of P-glycoprotein at these sites would not be expected to enhance the oral absorption of digoxin markedly.

The issue of the effect of grapefruit juice on the clinical activity of P-glycoprotein is currently difficult to assess due to the lack of an established ideal probe. Such a probe would possess the profile of good safety, low inherent oral bioavailability and disposition determined nearly entirely by P-glycoprotein. The angiotensin II receptor blockers, candesartan, eprosartan, telmisartan and valsartan, are relatively safe and have been reported to have absolute oral bioavailabilities of 15, 13, 43 and 23%, respectively. They are excreted essentially unchanged. Biliary clearance appears to be important for systemic elimination. Since P-glycoprotein at the bile canalicular membrane likely plays an important role, one of these drugs might prove to be an appropriate probe to study the effect of grapefruit juice on the activity of presystemic P-glycoprotein. However, this has yet to be determined.

In addition to lack of clinical data on the effect of grapefruit juice on P-glycoprotein-mediated drug absorption, this juice also did not appear to alter the intestinal expression of P-glycoprotein in humans *(4,208)*. If grapefruit juice were subsequently shown to inhibit presystemic P-glycoprotein activity, the mechanism would likely be different from that involved in inactivation of CYP3A4. Flavonoid content (e.g., nobiletin, tangeritin) of orange juice may be involved in P-glycoprotein inhibition based on a Caco-2 cell model *(166)*.

5.2.2. ORGANIC ANION TRANSPORTING POLYPEPTIDES (OATPS)

Passive diffusion has previously been considered the major method for drug uptake. However, more recent findings indicate that drug transporters including the OATPs appear to play an important role. In the small intestine, OATP transporters are located on the luminal membrane of enterocytes and enable drug uptake from the gastrointestinal tract into the portal circulation. In the liver, they are found on the sinusoidal membrane and facilitate the movement of drug from the portal circulation into hepatocytes. Thus, these transporters have the potential to affect the systemic availability of certain medications. Recently, OATP1A2 (OATP-A) was found in healthy human small intestine *(208)*. It was co-localized with P-glycoprotein to the apical membrane of enterocytes and detected along the whole crypt–villus axis with the greatest expression at the villus tip.

The non-sedating antihistamine, fexofenadine, is a zwitterion possessing pronounced polarity over a wide pH range from uninterrupted ionization. It is exceptionally hydrophilic, which would likely greatly impede passive drug diffusion from the gut into the portal circulation *(209)*. It is also chemically stable and undergoes negligible metabolism in humans. Fexofenadine was identified as a substrate for P-glycoprotein-mediated efflux *(201–206)*. Additionally, it was found to undergo cellular uptake by human OATP1A2 *(210)*. Moreover, OATP1A2 was the only human uptake carrier capable of fexofenadine transport *(208)*. Clinically, fexofenadine has an estimated mean absolute oral bioavailability of 33%, which appears to be largely dependent on the interplay of P-glycoprotein and OATP1A2 in the small intestine and liver. Consequently, fexofenadine is likely a useful probe to assess the effect of inhibitors on the in vitro and clinical activities of P-glycoprotein and OATP1A2.

Grapefruit juice was assessed for in vitro effect on transport activity *(211)*. This juice at 5% normal strength, which maintained cellular integrity, essentially nullified fexofenadine uptake by human OATP1A2. Moreover, grapefruit at one-tenth this concentration (0.5% normal strength) caused more than 50% reduction. In contrast, grapefruit juice at 5% normal strength did not alter digoxin transport. Thus, grapefruit juice at low juice concentration produced substantial and preferential inhibition of OATP1A2 compared to P-glycoprotein drug transport.

The initial study in human subjects tested the effect of a relatively high volume of grapefruit juice (1200 mL ingested over a 3 h period), in order to assess possible maximal clinical effect *(211)*. It decreased the oral systemic availability of fexofenadine to 33% of that observed with water. Volume–effect relationships were evaluated subsequently *(209)*. Grapefruit juice 300 mL decreased the AUC and $C_{\mathbf{max}}$ of fexofenadine to 58 and 53%, respectively. Consequently, a single and more commonly consumed volume of grapefruit juice had the potential to diminish oral drug bioavailability sufficiently to be pertinent clinically.

Clinical mechanisms of the interaction might include reduced fexofenadine (1) dissolution from the tablet, (2) transfer from the stomach to the intestinal site of absorption, (3) passage through the intestinal wall into the portal circulation and/or (4) conveyance through the liver into the systemic circulation. Because of the physiochemical properties of fexofenadine, it seemed unlikely that decreased drug dissolution was a logical basis for the interaction. Since the $t_{\mathbf{max}}$ values of fexofenadine were not different among treatments, reduced transit of drug from the stomach to the intestinal site of absorption was also a doubtful cause. Given that fexofenadine has high polarity and ionization over a wide pH range, it might be predicted that passive diffusion through the intestinal wall would be normally negligible. Consequently, the absorption of fexofenadine from the small intestine into the portal circulation would likely depend on the (1) innate activities of OATP1A2 relative to P-glycoprotein and/or (2) duration of exposure of fexofenadine to these transporters. Thus, an effect of the juice to reduce either could be an explanation for the interaction. Moreover, OATP1A2 has not been detected in the liver and inhibition of it or P-glycoprotein there would tend to increase, rather than to decrease, systemic drug availability.

If the mechanism were to involve inhibition of intestinal OATP1A2, the likely cause would be specific ingredients in the juice. In vitro screening showed that naringin, which is the foremost flavonoid (subclass: flavanone) in grapefruit juice, caused concentration-dependent inhibition of human OATP1A2 with half-maximal inhibition (IC_{50}) of 3.6 μmol/L *(212)*. Naringin IC_{50} was essentially 600-fold lower than that causing equivalent in vitro inhibition of P-glycoprotein and 300-fold less than the concentration often found in grapefruit juice. Thus, a flavanone in grapefruit juice might be the chief causative constituent.

Naringin has been used commercially in certain food products and given safely as the pure substance to humans in several studies *(41,59)*. Thus, an aqueous solution of naringin at the same concentration as that measured in the tested grapefruit juice (1200 μmol/L) was investigated *(212)*. The aqueous solution of pure naringin and grapefruit juice (300 mL) decreased mean fexofenadine bioavailability to 75% ($p < 0.05$) and 55% ($p < 0.001$) of that with water, respectively. Thus, naringin was clinically active and accounted for about half the reduction observed with grapefruit juice. It appears to be the first reported dietary constituent to modulate drug transport in humans and to have sufficient safety, selectivity and clinical activity to be an inhibitor probe of intestinal OATP1A2 activity.

This research into the interaction between grapefruit juice and fexofenadine supported a new mechanism of food–drug interactions. Grapefruit juice also decreased the oral bioavailability of other medications, indicating that this type of interaction may be relevant to a wide range of medications (Table 4). These included the non-metabolized and hydrophilic beta-blockers, acebutolol, celiprolol and talinolol *(212a,213,214)*. Grapefruit juice additionally reduced the oral bioavailability of the anticancer agent, etoposide, and the hormone, thyroxine, which raises the additional clinical concern of loss of or reduced efficacy of medications essential for the treatment of serious medical conditions *(215,215a)*. Furthermore, acebutolol, celiprolol and thyroxine undergo in vitro uptake transport mediated by OATP1A2 *(215b,215c)*.

5.2.3. OTHER FRUIT JUICES

5.2.3.1. Orange Juice. Orange juice was evaluated for inhibitory effect on in vitro drug transport activity *(211)*. At 0.5% normal strength, it caused more than 50% reduction of uptake transport of fexofenadine by human OATP1A2. Ten times higher concentration of orange juice was required for the equivalent 50% lower efflux transport of digoxin by P-glycoprotein. Thus, orange juice at low juice concentration also produced substantial and preferential inhibition of OATP1A2 compared to P-glycoprotein drug transport. Moreover, the major flavanone in orange juice, hesperidin, caused concentration-dependent inhibition of human OATP1A2 with an IC_{50} of 2.7 μmol/L, which is about 40-fold less than the concentration often found in this juice *(212)*.

Orange juice at relatively high volume (1200 mL ingested over a 3 h period) decreased the oral systemic availability of fexofenadine to 28% of that observed with water *(211)*. Such a large volume used to assess maximum clinical effect might

Table 4
Drugs with Decreased Oral Bioavailability with Fruit Juices from Possible Inhibition of Intestinal OATP1A2

Grapefruit Juice
- Acebutolol *(212a)*
- Celiprolol *(206)*
- Fexofenadine *(202,204,205)*
- Etoposide *(208)*
- Talinolol *(207)*
- Thyroxine *(215a)*

Orange Juice
- Atenolol *(209)*
- Celiprolol *(210)*
- Ciprofloxacin *(211)*
- Clofazimine *(212)*
- Fexofenadine *(204)*
- Itraconazole *(213)*
- Levofloxacin *(214)*

Apple Juice
- Cyclosporine *(215)*
- Fexofenadine *(204)*

raise the possibility that mechanisms other than direct inhibition of intestinal OATP1A2 play a major role. For example, the osmotic effect of non-specific ingredients in the juice might retain fluid in the gastrointestinal tract. The result could be decreased exposure to OATP1A2 from the combination of reduced intestinal drug concentration and transit time.

Orange juice not only reduced the oral bioavailability of fexofenadine but other studies have shown that a more typical amount of juice significantly decreased the systemic availability of a range of other drugs (Table 4). These include atenolol, celiprolol, ciprofloxacin, clofazimine, itraconazole and levofloxacin *(216–221)*. Since atenolol, celiprolol, ciprofloxacin and levofloxacin undergo OATP1A2-mediated transport, the interaction appears likely to involve inhibition of intestinal OATP1A2 *(215b,221a)*. An ethyl acetate extract of orange juice as well as several isolated components (e.g. heptamethoxyflavone, nobiletin and tangeretin) inhibited the efflux of vinblastine via P-glycoprotein and the efflux of saquinavir via MPR2 in an intestinal cell culture system *(222)*.

5.2.3.2. Apple Juice. Apple juice produced a much different effect on in vitro drug transport compared to grapefruit juice or orange juice *(211)*. At 5% normal strength, apple juice only reduced OATP1A2-mediated fexofenadine uptake to about 70% and increased P-glycoprotein-mediated digoxin efflux transport to 125% of those of control. Moreover, a single major flavonoid in apple juice is not readily apparent. Despite these in vitro findings, apple juice at relatively high volume (1200 mL ingested over a 3 h period) markedly decreased the oral systemic availability of fexofenadine to 23% of that observed with water *(211)*. Thus, the mechanism of action of apple juice is not clear. However, apple juice has also been shown to cause a clinically relevant reduction in the oral bioavailability of cyclosporine *(223)*.

6. CLINICAL RECOMMENDATIONS

Drug-related issues such as pharmacokinetics, mechanism of elimination and toxicity play critical roles when assessing potential risk of an interaction with grapefruit juice. If a medication has low oral bioavailability from high presystemic metabolism mediated by CYP3A4 and can produce serious overdose toxicity, it appears mandatory to advise against concomitant consumption of grapefruit juice. Although this may not cause altered drug response in most instances, it is often difficult to predict. Consequently, avoiding the combination will definitely prevent toxicity. Also, alternative medications that don't interact with grapefruit juice are often available.

Patient-related issues affect the clinical importance of the interaction. The magnitude of pharmacokinetic interaction is normally markedly variable. For example, felodipine AUC with grapefruit juice can range from no change to at least eightfold that with water among individuals *(3,4,14,39,45,224)*. Moreover, the magnitude of this effect appears to be substantially reproducible within individuals, at least within a 1-month interval of retesting *(39)*. In this case, factors inherent to the individual accounted for essentially half the variability in the extent of the interaction. Since subjects with the highest amount of intestinal CYP3A4 before consuming grapefruit juice were the ones that showed the greatest increase in plasma felodipine concentration, this is likely one logical and important factor *(4)*. Unfortunately, there are no routine clinical tests available to estimate the extent of pharmacokinetic interaction before exposure. Pre-existing medical conditions can also affect clinical response. For example, dihydropyridines produce an antihypertensive effect dependent on pretreatment blood pressure. The greatest reduction in blood pressure occurs in patients with the highest pretreatment blood pressure *(151,225)*. These patients are likely at greater risk of developing cardiovascular ischemic symptoms with the combination of a dihydropyridine and grapefruit juice. Age appears to affect susceptibility to drug interactions as well. For example, elderly patients have demonstrated enhanced antihypertensive effect to dihydropyridines compared to younger individuals *(2,5)*. As mentioned previously, this may result from reduced autonomic responsiveness from age-related decreased baroreceptor sensitivity *(150)*. Since the elderly are the group most often prescribed medications and are major consumers of grapefruit juice, the potential for a relevant unwanted grapefruit juice–drug interaction in this population appears substantial.

Administration-related issues require consideration as well. First, grapefruit juice appears to have the potential to interact only with drugs that are administered orally *(13,94)*. Second, commercial white grapefruit juice from frozen concentrate, diluted from concentrate or fresh frozen has been shown to interact with felodipine *(1–5,13–15,39–50)*. Segments from unprocessed grapefruit can do the same *(11)*. Thus, any form of grapefruit should be considered to produce a drug interaction. Third, consumption of as little as a single glass of a normal amount of regular-strength grapefruit juice (200 mL) can produce a clinically relevant increase in oral drug bioavailability *(3,15,40)*. Since administration of the same volume of double-strength juice did not substantially enhance this effect, it appears that just 200 mL of regular-strength grapefruit juice can produce near-maximal acute pharmacokinetic interaction *(40)*. Fourth, chronic consumption of a normal amount of grapefruit juice several times daily should be considered to produce a cumulative inhibitory effect on intestinal CYP3A4 and enhance the magnitude of the drug interaction *(4)*. Fifth, high consumption of grapefruit juice may also inhibit hepatic CYP3A4 *(83)*. Sixth, the amount of active ingredient(s) in grapefruit may vary among batches and lots that may affect reproducibility of the interaction *(155)*. Seventh, grapefruit juice has a very long duration of action *(15–18)*. A glass of grapefruit juice consumed yesterday has the potential to augment the oral bioavailability of drug administered today. Thus, it is recommended that grapefruit juice consumption should best be avoided entirely during pharmacotherapy, rather than just for concomitant juice and drug administration, when there is a concern for drug toxicity from excessive plasma drug concentration.

Continued study of fruit and juice contents *(226,227)* as well as the influence of those compounds on drug metabolism and transport *(198)* is clearly necessary. Recommendations regarding other juices must await further clinical data.

DISCUSSION POINTS

Grapefruit can increase the oral bioavailability of certain drugs.

- Discuss the mechanism of the interaction and inherent characteristics of affected drugs.
- Discuss factors determining the clinical importance of such a pharmacokinetic interaction and several specific interactions that are known to be particularly clinically important.
- Discuss approaches to avoid clinically relevant grapefruit–drug interactions.

Other fruit juices have the potential to augment the oral bioavailability of drugs affected by grapefruit juice.

- Discuss the common active ingredients that these other fruit juices have with grapefruit juice.
- Name the other fruit juices that have been shown to have this effect.
- Name the fruit juices that have been demonstrated not to have this effect.

Grapefruit and other juices can also decrease the oral bioavailability of different drugs.

- Discuss possible mechanisms that cause this interaction and the inherent characteristics of affected drugs.
- Discuss circumstances when a reduction in oral drug bioavailability can be particularly clinically relevant.
- Name the other fruit juices that have been shown to decrease oral drug bioavailability.
- Discuss what may be common active ingredients in grapefruit and other fruit juices.

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11

Positive Drug–Nutrient Interactions

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Objectives

- Identify the drug–food and drug–nutrient interactions that result in enhanced positive drug effects
- Discuss the mechanisms of positive drug–food and drug–nutrient interactions
- Identify patient-specific clinical conditions that may benefit from positive drug–food and drug–nutrient interactions

Key Words: Bioavailability; drug effect; physicochemical; physiologic; toxicity

1. INTRODUCTION

Drug–nutrient interactions are often the result of physical and chemical interactions between drugs and nutrients. These interactions are influenced by factors of a physicochemical nature (e.g., pH, dissolution, disintegration, binding) or physiological determinants (e.g., absorption, elimination, gastrointestinal transit time, gastrointestinal secretions, splanchnic blood flow, liver enzyme inhibition or induction) *(1,2)*. Clinically significant negative drug–nutrient interactions may result in therapeutic failure, drug toxicity, or nutrient deficiency. Less commonly considered are drug–nutrient interactions that may significantly enhance drug effect, reduce drug toxicity, or reduce gastrointestinal drug intolerance. This chapter focuses on beneficial and clinically relevant drug–food and drug–nutrient interactions that improve serum drug concentrations, enhance therapeutic drug effects, or reduce or prevent severe drug toxicities (Table 1). Although data describing positive effects of food on drug absorption are commonly recognized, there are also examples of specific nutrients that improve drug absorption, enhance drug effect, and reduce drug toxicity.

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Table 1
Summary of Relevant Drug–Nutrient and Drug–Food Interactions that May Optimize Drug Effect (in the order they appear in the text)

Drug	*Diet/Nutrient*	*Proposed Mechanism of Interaction*	*Relevant Effects*	*Recommendations*
Albendazole	Fatty meal	Increased solubility and absorption	Increased plasma and tissue drug concentrations Enhanced therapeutic effect	Should be taken with food when treating systemic infections
Mebendazole	Meals	Increased absorption	Increased target drug concentrations Enhanced therapeutic effect	Should be taken with food when treating systemic infections
Cefuroxime	Meals	Increased absorption with decreased gastric pH	Increased plasma concentrations Bactericidal activity not affected	Suspension should be taken with food Tablets can be taken with or without food
Nitrofurantoin	Meals	Increased dissolution and absorption	Increased duration of urinary concentrations Reduced peak plasma concentrations Improved gastrointestinal tolerance	Should be taken with food
Griseofulvin	Fatty meal	Increased disintegration and absorption	Increased plasma concentrations Enhanced therapeutic effect	Should be taken with food
Itraconazole (capsules)	Meals, Acidic beverages	Increased solubility and absorption in acidic medium	Increased plasma concentrations Enhanced therapeutic effect	Capsules should be taken with food or an acidic beverage Oral solution should be taken on empty stomach
Posaconazole	Meals, Nutritional supplements	Increased absorption	Increased therapeutic effect	Should be taken with meals or nutritional supplement Otherwise, consider alternate therapy or monitor patient closely for breakthrough of fungal infection
Atovaquone	Fatty meal	Increased solubility and absorption	Increased plasma concentrations Enhanced therapeutic effect	Should be taken with food
Nitazoxanide	Meals	Increased absorption	Enhanced therapeutic effect	Should be taken with food (oral tablet and solution)
Atazanavir	Meals	Increased absorption and decreased gastric pH	Increased plasma concentrations	Should be taken with food
Darunavir	Meals	Increased absorption	Enhanced therapeutic effect	Should be taken with food

Lopinavir (oral solution)	Meals	Increased absorption	Enhanced therapeutic effect	Oral solution should be taken with food Oral tablets can be taken with or without food
Nelfinavir	Meals	Increased absorption	Enhanced therapeutic effect	Should be taken with food
Saquinavir	Meals	Increased dissolution, disintegration, and absorption	Enhanced therapeutic effect	Should be taken with food or within 2 h after a meal
Fenofibrate	Fatty meal	Increased absorption	Enhanced therapeutic effect	Lofibra$^{\circledR}$ and Lipofen$^{\circledR}$ should be taken with food Tricor$^{\circledR}$, Triglide$^{\circledR}$ and Antara$^{\circledR}$ can be taken with or without food
Isotretinoin	Meals	Increased solubility and absorption	Increased plasma concentrations Enhanced therapeutic effect	Should be taken with food
Mesalamine/ Olsalazine	Meals	Delays the presence of the active metabolite 5-aminosalicylic acid in the gut	Persistently high local therapeutic 5-aminosalicylic acid concentration in colon	Should be taken with food
Misoprostol	Meals	Reduced absorption rat Reduced peak plasma concentrations	Reduced frequency of diarrhea	Should be taken with food
Iron	Ascorbic acid	Inhibition of iron chelation to phytates Reduction of iron to the ferrous form	Increased iron absorption	Coadminister ascorbic acid (100–200 mg/day) with iron in patients who are poor absorbers
Fluorouracil (5-FU)	Folic acid	Increased levels of reduced folate metabolites	Possible reduction of 5-FU toxicity and modulation of 5-FU activity	Efficacy and safety not established
Methotrexate	Folic acid	Increased levels of reduced folate metabolites	Reduced low dose methotrexate toxicity in the treatment of rheumatoid arthritis	Weekly folic acid doses of 1 mg, 5 mg, and 27.5 mg have been used with low-dose methotrexate regimens
Isoniazid	Pyridoxine	Increased pyridoxal phosphate availability	Prevention of isoniazid-induced peripheral neuropathy	Coadminister prophylactic pyridoxine to adults (50 mg/day) and children (1–2 mg/kg/day) receiving isoniazid
Docetaxel	Calcitriol	Possible enhanced antitumor activities	Improved patient survival, bone pain, and quality of life	Used mostly in clinical studies in patients with androgen-independent prostate cancer (AIPC)
Statins	Plant stanols	Blockage of cholesterol absorption	Reduced serum cholesterol and low density lipoprotein (LDL) concentrations	Use stanols 2–3 times/day in diet or as adjunct to lipid-lowering therapy

2. EFFECTS OF FOOD ON DRUG ABSORPTION

2.1. Anthelmintics

2.1.1. ALBENDAZOLE

Albendazole is a broad-spectrum anthelmintic agent effective against larval and adult stages of trematodes and cestodes *(3)*. Albendazole is available commercially as oral tablets. Because of its low aqueous solubility, albendazole is poorly absorbed from the gastrointestinal tract. However, administration with a fatty meal enhances albendazole solubility and thereby increases its bioavailability.

Fatty meals increase the oral bioavailability of albendazole up to fivefold as compared with the fasting state. Maximal plasma concentrations of albendazole sulfoxide (the primary active metabolite) were achieved in 2–5 h with albendazole 400 mg doses during treatment of patients with hydatid disease *(4)*. In a study that assessed the bioavailability of albendazole in six patients with hydatid disease, mean plasma albendazole concentrations were 4.5 times higher when albendazole was administered with breakfast as compared with fasting *(5)*. In another study of adult patients with onchocerciasis, plasma albendazole sulfoxide concentrations increased fourfold when albendazole was administered with breakfast (43.1 g of fat) instead of on an empty stomach *(6)*. However, when albendazole was given with 20 mL of olive oil in 100 mL of milk to four adult volunteers, plasma albendazole sulfoxide concentrations increased 3.5-fold in one subject whereas only small changes occurred in the other three subjects *(7)*.

Albendazole absorption is significantly increased when taken with food. Albendazole should be administered with fatty meals to increase its concentrations within tissues and hydatid cysts *(4)*. However, administration of albendazole on an empty stomach is preferable when intraluminal effects are desired to treat susceptible intestinal parasites *(3,5)*.

2.1.2. MEBENDAZOLE

Mebendazole is a broad-spectrum anthelmintic agent that is available as oral chewable tablets. Mebendazole is poorly absorbed from the gastrointestinal tract, but its absorption is increased when administered with food *(3)*. When used for the treatment of echinococcosis, systemic bioavailability and intracystic mebendazole concentrations are essential to achieve therapeutic effect.

Administration of mebendazole 1.5 g with a fatty meal to three healthy volunteers resulted in an eightfold increase in plasma mebendazole concentrations. When administered in the fasting state, plasma mebendazole concentrations remained <17 nmol/L in two subjects and reached 17 nmol/L in the third subject. When the same dose was administered with a standard breakfast (2 slices of ham, 2 fried eggs, 10 g butter, jam, bread, and coffee), plasma mebendazole concentrations rose within 2–4 h to 91 nmol/L, 112 nmol/L, and 142 nmol/L in the three subjects, respectively *(8)*. Mixing mebendazole with olive oil also increased the drug's bioavailability to a greater level than giving the tablets or suspension with a standard breakfast *(9)*. A wide variability in mebendazole absorption was reported in patients treated for hydatid cysts. Although plasma mebendazole concentrations were higher when mebendazole was given with food, the difference was not found to be significant *(10)*.

When taken with food, higher plasma mebendazole concentrations are achieved. This is a desirable effect for the treatment of hydatid cysts. Mebendazole tablets can be chewed, swallowed whole, or crushed and mixed with food *(11)*.

2.2. Antibiotics

2.2.1. CEFUROXIME

Cefuroxime is a broad-spectrum beta-lactam antibiotic belonging to the second-generation cephalosporins. Cefuroxime has broad activity against susceptible bacteria that cause infections of the upper and lower respiratory tract, skin and soft tissues, and the genitourinary tract *(12)*. Cefuroxime is available as the prodrug cefuroxime axetil in oral suspension and tablet dosage forms and as crystalline cefuroxime for intravenous administration *(13)*. Due to the enhanced lipid solubility of the prodrug, oral cefuroxime axetil is rapidly absorbed from the gastrointestinal tract and is hydrolyzed to active cefuroxime once in the bloodstream *(12–14)*. However, the oral tablet and suspension forms of cefuroxime axetil are not bioequivalent and cannot be used interchangeably *(13)*. The safety and the efficacy of oral cefuroxime tablet and suspension were established in separate clinical trials, and the dosage forms have different therapeutic indications *(12,13)*. Since the cefuroxime axetil oral tablet first became available, it has been reformulated several times due to absorption problems *(14)*. Food *(15–17)* and milk *(18)* have been shown to enhance cefuroxime axetil bioavailability, but the exact mechanism of this effect remains unknown.

A randomized, crossover, open label study evaluated the effects of food and fasting on cefuroxime bioavailability in healthy volunteers. The mean cefuroxime absolute bioavailability during fasting was 32–35%. There was a 34% relative increase in bioavailability when cefuroxime axetil was taken with food (area under the plasma concentration-time curve, AUC: 50 μg·h/mL) as compared to fasting (AUC: 36.4 μg·h/mL). Food also resulted in increases of the peak plasma concentrations ($C_{\max}$: 13.9 μg/mL vs. 9.9 μg/mL) and time-to-peak concentration ($T_{\max}$: 2.7 h vs. 2.1 h, respectively) compared to fasting. Cefuroxime elimination half-life was not significantly changed *(15)*. In another study, similar effects of food on cefuroxime absorption were observed. A single 500 mg dose of cefuroxime axetil taken with food resulted in increased absolute cefuroxime bioavailability from 36 to 52%, corresponding to a 45% relative increase. A linear correlation was also observed between single doses of cefuroxime ranging from 125 to 1000 mg given with food and both the AUC ($r^2 = 0.958$) and $C_{\max}$ ($r^2 = 0.943$) *(16)*.

A study evaluated the effects of food and increased gastric pH (with administration of ranitidine and sodium bicarbonate) on cefuroxime absorption in six healthy volunteers. When cefuroxime was administrated with food, cefuroxime bioavailability increased despite the anticipated negative effects of a higher gastric pH on cefuroxime absorption. Cefuroxime AUC significantly increased with food as compared to fasting (39.8 ± 2.9 μg·h/mL vs. 23.4 ± 2.9 μg·h/mL, $p < 0.05$); $T_{\max}$ was significantly longer when cefuroxime was taken with food as compared to fasting (13.6 ± 1.0 h vs. 7.3 ± 0.8 h, $p < 0.05$); and $C_{\max}$ was slightly higher in the fed state with a statistically significant difference as compared to fasting (1.5 ± 0.1 mg/L vs. 1.4 ± 0.152 mg/L, $p < 0.05$) *(19)*.

In a study that evaluated the effects of food on cefuroxime serum concentrations and the minimum inhibitory concentration (MIC), serum cefuroxime concentrations were at or above the MIC of common respiratory pathogens for much of the dosing interval *(17)*. This suggests that administration of cefuroxime axetil with food achieves adequate serum concentrations for the effective treatment of susceptible organisms *(12–17)*.

Pharmacokinetic differences exist between the cefuroxime tablet and suspension forms to the point that they are not bioequivalent *(12–20)*. The AUC and $C_{\max}$ for cefuroxime suspension average 91 and 71% respectively, of that for the tablet *(12)*. When given with meals, cefuroxime had a significantly lower AUC for oral cefuroxime suspension as compared to the tablet (10.22 μg·h/mL vs. 14.02 μg·h/mL, respectively; $p = 0.001$). Food resulted in significantly lower $C_{\max}$ with cefuroxime suspension as compared to the tablet (2.48 μg/mL vs. 4.04 μg/mL, respectively; $p = 0.001$). Despite these differences, serum cefuroxime bactericidal activities were not affected and remained similar with both dosage forms *(20)*. Because bacteriological and clinical responses to cefuroxime axetil tablets are independent of food ingestion, tablets may be administered without regard to meals. Pharmacokinetic, efficacy, and safety studies of cefuroxime axetil suspension in pediatric patients were conducted in the fed state. No kinetic data on the suspension formulation are available when administered under fasting conditions in pediatrics *(13)*.

In summary, cefuroxime axetil tablets and suspension are not bioequivalent and cannot be substituted on a milligram-per-milligram basis. Oral cefuroxime axetil tablets can be administered with or without food. Oral cefuroxime suspension should be taken with food *(13)*.

2.2.2. NITROFURANTOIN

Nitrofurantion is a broad-spectrum bactericidal agent that exerts its effects by possibly interfering with bacterial carbohydrate metabolism *(21,22)* or cell wall synthesis *(23)*. Nitrofurantoin is used for the treatment of uncomplicated urinary tract infections caused by susceptible microorganisms. Nitrofurantoin is available in different oral formulations including a combination formulation of nitrofurantoin monohydrate (75% of the drug) and macrocrystals (25% of the drug) in oral capsules (Macrobid®), nitrofurantoin macrocrystalline oral capsules (Macrodantin®), and microcrystalline oral suspension (Furadantin®) *(24–26)*. A tablet formulation of nitrofurantoin was previously manufactured but is no longer available.

Oral nitrofurantoin is absorbed in the small intestines. Because serum nitrofurantoin concentrations are usually low or undetectable in patients with normal renal function *(21,27,28)*, urinary nitrofurantoin levels are typically used to assess nitrofurantoin absorption *(29)*. Macrocrystalline nitrofurantoin has a slower dissolution and absorption rate than nitrofurantoin monohydrate. Food, however, increases the bioavailability of nitrofurantoin by about 40% *(24)* and substantially increases the duration of therapeutic nitrofurantoin urine concentrations *(21)*.

The effects of food on nitrofurantoin absorption in macrocrystalline and microcrystalline tablets were evaluated in a study of four healthy volunteers. Nitrofurantoin 100 mg single oral dose was administered either following an 8-h overnight fast or immediately after breakfast. Serial urinary specimens were collected to measure nitrofurantoin urine concentrations. Study results showed that food delayed nitrofurantoin absorption in the macrocrystalline form but did not have a significant effect on the rate of absorption of the microcrystalline form. Food also resulted in increased maximum urine excretion rate of macrocrystalline nitrofurantoin but did not have a significant effect on the rate of excretion of the microcrystalline form. Compared to fasting, food increased nitrofurantoin bioavailability by an average of 30 and 80% of the microcrystalline and macrocrystalline forms, respectively *(30)*.

Another study compared the effects of food on the oral bioavailability of nitrofurantoin in three different microcrystalline tablets, a macrocrystalline capsule, and an aqueous microcrystalline suspension. The percent of a single 100 mg oral dose recovered in the urine was significantly greater when administered with food as compared to the fasting state for the microcrystalline tablets ($p < 0.05$) and the macrocrystalline capsule ($p < 0.05$). Food increased the bioavailability of the tablets and the macrocrystalline capsule by 23–40 and 85%, respectively. Although the bioavailability of the microcrystalline suspension was also increased with food, it was not statistically significant. Compared to fasting, food also significantly increased the mean duration of therapeutic urinary concentrations of nitrofurantoin macrocrystalline capsules ($p < 0.05$). Food also increased the duration of therapeutic urinary concentrations of the microcrystalline suspension, but the difference was not statistically significant compared to the fasted state. Nitrofurantoin administration with food improved the uniformity of nitrofurantoin absorption and decreased the coefficients of variation. It was hypothesized that by decreasing the rate of gastric emptying, food increased nitrofurantoin residence in the stomach thereby increasing drug dissolution that makes nitrofurantoin more readily absorbed in the small intestines *(31)*.

In summary, food delays nitrofurantoin delivery to the intestines thereby increasing its absorption and reducing its peak plasma concentrations *(26,31)*. Nitrofurantoin macrocrystals are more slowly absorbed than the microcrystals *(29,32)*. Therefore, the macrocrystals are better tolerated and are associated with less nausea and vomiting *(33–35)*. Nitrofurantoin should be administered with food to enhance its absorption, increase the duration of nitrofurantoin urinary concentrations, and improve gastrointestinal tolerance *(24)*.

2.3. Antifungals

2.3.1. GRISEOFULVIN

Griseofulvin is an oral antifungal agent used for the treatment of tinea infections. Because of its low aqueous solubility, griseofulvin absorption is slow, irregular, and incomplete, especially when taken on an empty stomach *(36)*. However, griseofulvin absorption increases twofold when taken with fatty meals *(37)*. Food increases griseofulvin absorption by increasing its disintegration and de-aggregation *(38)*.

In a study of 12 adult volunteers who each received a single dose of griseofulvin 500 mg tablet, there was a significant increase in griseofulvin bioavailability of

70 and 120% when taken with a low-fat (29.3% calories from fat) and high-fat (52.4% calories from fat) meals, respectively, compared to fasting ($p < 0.01$) *(39)*. However, one older study, using urinary excretion data, concluded that fatty meals increase the rate but not the extent of griseofulvin absorption, and that griseofulvin follows a circadian rhythm of absorption regardless of dietary fat content *(40)*.

Griseofulvin absorption also varies with the dosage form used. A crossover study of four healthy volunteers compared the absorption of two different dosage forms consisting of microsize and ultramicrosize griseofulvin tablets taken with or without food. When taken on an empty stomach, griseofulvin $C_{\max}$ of the ultramicrosize formulation was about 70% of the microsize formulation. When taken with food, griseofulvin $C_{\max}$ was 136% of the microsize formulation and about twice the $C_{\max}$ for the ultramicrosize formulation. The rate and the extent of griseofulvin bioavailability were similar for both formulations when taken with food *(38)*.

In summary, optimal plasma griseofulvin concentrations are attained when griseofulvin is administered with a high-fat meal. Taking griseofulvin with meals maximizes its absorption and enhances therapeutic drug effect.

2.3.2. ITRACONAZOLE

Itraconazole is a triazole antifungal used for treating superficial and systemic fungal infections. Itraconazole is available as oral solution and capsule formulations. Each oral itraconazole dosage form has specific indications *(41)*. Injectable itraconazole has been discontinued by the manufacturer for sales and distribution in the United States. Itraconazole is a highly lipophilic, extremely weak base that is almost insoluble in water and requires an acidic medium for optimal oral absorption *(42,43)*. The bioavailability of oral itraconazole also depends on the dosage form and the presence or absence of food. Whereas food enhances itraconazole capsule dissolution and absorption *(44,45)*, oral itraconazole solution is already in the dissolved form and is better absorbed when taken on empty stomach *(46)*.

In one study, the bioavailability of itraconazole capsules increased from 40% with fasting to 102% when administered with meals *(44)*. In another study of 27 healthy volunteers, a single dose of itraconazole 200 mg capsule was administered with or without food. Pharmacokinetic parameters were analyzed for itraconazole and its active metabolite hydroxyitraconazole. The AUC for itraconazole and hydroxyitraconazole was higher when the drug was administered with food (3423 ± 1154 ng·h/mL and 7978 ± 2648 ng·h/mL, respectively) as compared to fasting (2094 ± 905 ng·h/mL and 5191 ± 2489 ng·h/mL, respectively). The $C_{\max}$ for itraconazole with fasting was 59% of that with food (140 ± 65 ng/mL and 239 ± 85 ng/mL, respectively), and $C_{\max}$ for hydroxyitraconazole with fasting was 72% of that with food (286 ± 101 ng/mL and 397 ± 103 ng/mL, respectively) *(41)*.

The absorption of oral itraconazole capsules is decreased with increasing gastric pH such as in patients receiving gastric acid inhibitors (antacids, H_2-receptor antagonists, proton pump inhibitors). In patients with hypochlorhydria, coadministration of oral itraconazole capsules with an acidic beverage (e.g., cola) increased itraconazole bioavailability *(47,48)*. Following the administration of a single 100 mg dose of itraconazole capsules with 325 mL of water or an acidic cola beverage (pH = 2.5), the itraconazole AUC was significantly higher with cola (2.02 ± 1.41 μg·h/mL) than with water (1.12 ± 1.09 μg·h/mL) ($p < 0.05$). Itraconazole $C_{\max}$ was also significantly higher with cola than with water (0.31 ± 0.18 μg/mL vs. 0.14 ± 0.9 μg/mL, respectively; $p < 0.05$), and $T_{\max}$ was significantly longer (3.38 ± 0.79 h vs. 2.56 ± 0.62 h; $p < 0.05$) *(48)*.

In contrast to itraconazole capsules, itraconazole oral solution does not require food or an acidic medium to increase its absorption. Significantly higher itraconazole and hydroxyitraconazole AUC and $C_{\max}$ and shorter $T_{\max}$ occur when itraconazole oral solution is taken on an empty stomach rather than with food *(42)*. Following administration of oral itraconazole solution at a dose of 200 mg/day, respective mean itraconazole and hydroxyitraconazole concentrations were 43 and 38% higher when the drug was taken with food as compared to fasting *(46)*. The AUC with a single 100 mg dose of itraconazole oral solution was significantly higher when administered during fasting (2379 ± 1353 ng·h/mL) as compared to the fed state (1713 ± 741 ng·h/mL). $C_{\max}$ was also significantly higher in the fasting state as compared to the fed state (349 ± 239 ng/mL vs. 147 ± 74 ng/mL; $p = 0.006$). Additionally, $T_{\max}$ was significantly shorter during fasting as compared to the fed state (1.7 ± 0.5 h vs. 3.8 ± 1.4 h; $p = 0.0001$) *(42)*.

In summary, oral itraconazole capsules should be taken with a full meal for maximal absorption. However, oral itraconazole solution is better absorbed when taken on empty stomach at least 2 h before or 2 h after a meal. Oral itraconazole solution provides an alternative to itraconazole capsules in patients who have difficulty swallowing the capsule or in those whose oral intake is restricted *(41,45)*. The optimal serum itraconazole and hydroxyitraconazole concentrations are not known; however itraconazole oral solution is associated with higher serum drug concentrations compared to oral capsules *(49)*. Administration of itraconazole with cola enhances itraconazole capsule absorption in patients receiving acid suppression therapy *(47)*. Patients receiving medications that alter gastric pH should take itraconazole oral capsules with a cola beverage.

2.3.3. Posaconazole

Posaconazole is a triazole antifungal agent that works by blocking the synthesis of ergosterol, one of the key compounds in the fungal cell membrane. Posaconazole is FDA labeled for the prophylaxis of invasive *Aspergillus* or *Candida* infections in patients who are at risk of developing systemic infections due to an immunocompromised state *(50)*. Posaconazole is insoluble in water and is commercially available as a suspension for oral administration. It is well absorbed from the gastrointestinal tract with a proportional increase in AUC and $C_{\max}$with increasing doses up to 800 mg daily. Steady-state plasma posaconazole concentrations are reached after 7–10 days of therapy with a $T_{\max}$ ranging from 5.8 to 8.8 h *(51)*.

A study evaluated the difference in absorption of posaconazole oral suspension and tablet formulations and the effect of food and its fat content on posaconazole bioavailability *(52)*. In this randomized, open label, four-way crossover study, 20 healthy male volunteers received posaconazole 200 mg oral tablets administered with a high-fat breakfast (841 calories, 52% fat), or posaconazole 200 mg oral suspension administered with a high-fat breakfast, low-fat breakfast (461 calories, 0% fat), or after a 10-h fast. Absorption was significantly better with the oral suspension compared to the tablets with a 37% increase in AUC ($p = 0.001$) and 23% increase in $C_{\max}$($p = 0.004$). In addition, the AUC and $C_{\max}$ of the oral suspension were 4 times greater with the high-fat meal compared with the fasted state ($p < 0.001$). Administration with the low-fat meal also increased posaconazole absorption (2.6 times) and $C_{\max}$ (3 times) compared to the fasted state ($p < 0.001$). Pharmacokinetic profiles were similar between the high-fat and nonfat meals, suggesting that posaconazole should be administered with meals regardless of fat content and that the suspension should be used over the tablets to enhance absorption. A related study found that concomitant administration of antacids with posaconazole had no significant effect on posaconazole bioavailability under fasting or nonfasting conditions *(53)*.

Patients who receive posaconazole are often severely ill and may have difficulty eating. It would not be uncommon for these patients to receive their nutritional needs through enteral tube feedings. For this reason, a study evaluated the effect of a nutritional supplement (Boost Plus®, Novartis Nutrition Corp.) on the bioavailability of posaconazole *(54)*. In a randomized, crossover study, 20 healthy subjects received 400 mg of posaconazole oral suspension either after an overnight fast or with 8 ounces of the nutritional supplement (360 calories, 34% fat). Coadministration of posaconazole with the nutritional supplement resulted in a threefold increase in posaconazole $C_{\max}$ and a 2.6-fold increase in AUC compared to the fasted state. There was no difference in posaconazole $T_{\max}$ or half-life between the two groups.

In summary, posaconazole is a highly lipophilic compound for which administration with food results in a clinically significant increase in bioavailability. Posaconazole should always be administered with food regardless of fat content, or with a nutritional supplement to ensure adequate plasma posaconazole concentrations. If the patient cannot meet these feeding requirements, the manufacturer of posaconazole recommends that another antifungal agent be considered or that the patient be closely monitored for breakthrough fungal infections *(50)*.

2.4. Antiprotozoals

2.4.1. ATOVAQUONE

Atovaquone is an antiprotozoal agent available as an oral suspension. It is used as a second-line agent for the treatment or prophylaxis of mild to moderate *Pneumocystis carinii* pneumonia in patients who are intolerant of trimethoprim-sulfamethoxazole (cotrimoxazole). Atovaquone is highly lipophilic with a low aqueous solubility making it slowly and irregularly absorbed on an empty stomach. Atovaquone bioavailability is enhanced when taken with a fatty meal. The previously marketed atovaquone tablet resulted in irregular absorption and subtherapeutic plasma concentrations. As such, manufacturing of atovaquone tablets (Mepron®) was discontinued once the suspension became commercially available. Atovaquone suspension exhibits double the bioavailability compared to the tablet *(55)*, resulting in increased atovaquone AUC and $C_{\max}$ *(56)*.

In a prospective, open label, crossover study of 10 healthy volunteers, the bioavailability of atovaquone (single 750 mg dose of suspension) was enhanced when administered following breakfast (fat content 21 g) or with an oral liquid nutrition supplement (Sustacal Plus®, Mead Johnson Nutritionals: fat content 28 g). The

AUC of atovaquone following breakfast (103.8 μg·h/mL) and Sustacal Plus® (118.8 μg·h/mL) was significantly higher when compared to administration under fasting conditions (43.4 μg·h/mL) ($p < 0.0001$). This corresponds to a mean increase in atovaquone bioavailability by 502 and 505% following breakfast and Sustacal Plus®, respectively *(57)*.

Two studies investigated the effect of food on the pharmacokinetics of atovaquone suspension in patients infected with HIV *(58,59)*. In an open label, dose escalation study including 22 HIV-infected patients, administration of atovaquone with breakfast (fat content 23 g) increased average atovaquone steady-state plasma concentrations by 1.3- to 1.7-fold as compared to fasting *(58)*. Similarly, a single- and multiple-dose pharmacokinetic study in HIV-infected patients showed food to increase atovaquone bioavailability by 1.4-fold. However, an increased incidence of rash was observed when higher plasma atovaquone concentrations were achieved with the 1000 mg twice daily dose taken with food *(59)*.

In summary, the rate and the extent of atovaquone absorption are significantly increased when taken with food, especially fatty meals. As such, atovaquone should be administered with meals to increase its absorption and improve its therapeutic effects *(55)*.

2.4.2. Nitazoxanide

Nitazoxanide is an antiprotozoal agent that is FDA labeled for the treatment of diarrhea associated with cryptosporidiosis (caused by *Cryptosporidium parvum*) and giardiasis (caused by *Giardia lamblia*). Nitazoxanide is practically insoluble in water. It is available in oral tablet (500 mg) and suspension (100 mg/5 mL) formulations which are not bioequivalent. The relative bioavailability of nitazoxanide suspension is 70% compared to the tablet. Although specific data on the bioavailability of nitazoxanide are lacking, nitazoxanide is metabolized in the gut wall, liver, and plasma. Nitazoxanide is rapidly converted to the active metabolite tizoxanide that is ultimately excreted in the urine, bile, and feces. About 67% of the parent nitazoxanide is excreted in the feces *(60)*.

Food significantly increases the absorption of nitazoxanide. Administration of nitazoxanide tablets with food resulted in a twofold increase in the AUC of tizoxanide and the metabolite tizoxanide glucuronide, and a 50% increase in $C_{\max}$. Administration of nitazoxanide oral suspension with food resulted in a 45–50% increase in AUC of tizoxanide and tizoxanide glucuronide and an increase in $C_{\max}$ by up to 10% *(60)*. A study in 32 healthy volunteers evaluated the absorption of nitazoxanide following the administration of a single oral nitazoxanide dose of 1 g, 2 g, 3 g, or 4 g first under fasting conditions, and a week later with breakfast. Study results showed that food approximately doubled the plasma concentrations of tizoxanide and tizoxanide glucuronide irrespective of the administered dose *(61)*.

In clinical trials, nitazoxanide was administered with food that substantially increased drug absorption. Therefore, nitazoxanide oral tablets and suspension should be taken with food.

2.5. Antiretrovirals

2.5.1. ATAZANAVIR

Atazanavir is an HIV-1 protease inhibitor that is indicated for the treatment of HIV-1 infection when used in combination with other antiretroviral agents. Atazanavir selectively inhibits virus-specific processing of HIV-1 infected cells, thereby preventing the formation of mature virons *(62)*.

Pharmacokinetic data supporting the effect of food on the absorption of atazanavir capsules are limited to information found in the product labeling, but are worthy of mention. Atazanavir is rapidly absorbed after oral administration. Steady-state plasma atazanavir concentrations are achieved after 4–8 days of continuous therapy. Absorption is significantly increased when atazanavir is administered with food as compared to the fasting state. This may in part be due to improved atazanavir solubility with decreasing pH. When a single dose of atazanavir 400 mg was administered with a light meal, the AUC of atazanavir increased by 70%, and $C_{\max}$ increased by 57% relative to fasting. When administered with a high-fat meal, the AUC of atazanavir increased by 35% with no change in $C_{\max}$ relative to the fasting state. In both cases (light meal or high-fat meal), there was a decrease in the coefficient of variation for AUC and $C_{\max}$ by approximately one-half compared to the fasting state *(62)*.

These data suggest that administration of atazanavir with food increases its bioavailability and reduces pharmacokinetic variability. Therefore, it is recommended that atazanavir be taken with food to enhance its absorption *(62)*.

2.5.2. DARUNAVIR

Darunavir ethanolate (Prezista®), a protease inhibitor antiretroviral agent used for treatment of HIV-1 infection, is marketed as 300 mg oral tablets. The usual adult darunavir dose is 600 mg (two tablets) twice daily taken together with ritonavir 100 mg. Ritonavir, another anti-HIV protease inhibitor, is coadministered at a low dose with darunavir because it inhibits darunavir metabolism through the CYP3A4 isoenzyme and increases its plasma concentrations. Ritonavir increases the absolute systemic bioavailability of darunavir from 37 to 82% *(63)*.

Food increases the bioavailability of darunavir. Regardless of the type of meal (range 240 kcal with 12 g fat to 928 kcal with 56 g fat), taking darunavir with food along with ritonavir increased the AUC and $C_{\max}$ of darunavir by about 30% *(63)*. An open label, randomized, crossover study evaluated the effects of different meal types on the pharmacokinetic profile of darunavir in healthy adult volunteers who were given the darunavir/ritonavir combination. Darunavir was taken after a period of fasting for at least 10 h, immediately following a standard breakfast (533 kcal, 21 g fat, 67 g carbohydrate, 19 g protein), following a high-fat breakfast (928 kcal, 56 g fat, 65 g carbohydrate, 41 g protein), after a protein-rich nutritional drink (250 kcal, 8.4 g fat, 33.4 g carbohydrate, 10.5 g protein), or after coffee with croissant (240 kcal, 12 g fat, 28 g carbohydrate, 5 g protein). Study results showed that the AUC and $C_{\max}$ for darunavir were 30% lower under fasting conditions compared to when darunavir was taken with a standard breakfast. There were no significant differences in the AUC and $C_{\max}$ for darunavir when taken with the different types of meals *(64)*.

In summary, darunavir should only be used in combination with ritonavir. Food increases darunavir absorption regardless of the meal composition. Therefore, the combination of darunavir/ritonavir should be consistently taken with food, in order to achieve optimal therapeutic drug effects *(63)*.

2.5.3. LOPINAVIR

Lopinavir is a protease inhibitor antiretroviral agent used for the treatment of HIV-1 infection. It is only marketed in a co-formulation with ritonavir, a structurally related protease inhibitor. Ritonavir inhibits the principal isoenzyme CYP3A4 that metabolizes lopinavir; it is, therefore, combined with a low lopinavir dose to decrease lopinavir metabolism and increase its plasma concentrations, thereby enhancing its anti-HIV activity *(65)*.The lopinavir/ritonavir co-formulation is marketed as Kaletra®and is available as oral tablets (lopinavir 200 mg/ritonavir 50 mg) and oral solution (lopinavir 80 mg/ritonavir 20 mg per 1 mL) *(66)*. The main antiviral activity of Kaletra®is due to lopinavir.

Originally, the lopinavir/ritonavir formulation was available in oral soft gelatin capsules that required a daily dosing of six capsules taken with food. Because of patient compliance issues and storage requirements, the lopinavir/ritonavir oral capsules were replaced with a tablet formulation that was manufactured using a special melt extrusion technology that limits the excipient mass. The tablet formulation has significantly improved bioavailability under various meal conditions and is bioequivalent to the oral soft gelatin capsule when taken after a moderate fat meal. The tablet formulation also reduced the number of lopinavir/ritonavir doses to four tablets daily that can be easily stored at room temperature *(66,67)*. The absorption of Kaletra®oral tablets is not significantly affected by the presence of moderate or high-fat meals, but there is less variability and more consistent lopinavir and ritonavir absorption when administered with food compared to the fasted state *(67)*. However, the absorption of lopinavir in Kaletra®oral solution is substantially increased when taken with food. Compared to fasting, administration of Kaletra®oral solution with a moderate fat meal (500–682 kcal, 23–25% fat) increased lopinavir AUC by 80% and $C_{\max}$ by 54%. Taking Kaletra®oral solution with a high-fat meal (872 kcal, 56% fat) further increased lopinavir AUC by 130% and $C_{\max}$ by 56%, relative to fasting *(66)*.

Because the bioavailability of lopinavir oral solution is significantly increased when taken with moderate to high fat containing meals, Kaletra® oral solution must be taken with food to improve therapeutic drug effects. Kaletra® oral tablets can be taken with or without food.

2.5.4. NELFINAVIR

Nelfinavir is a protease inhibitor antiretroviral agent used for treatment of HIV-1 infection. Nelfinavir is available as oral tablet (250 mg, 625 mg) and powder (50 mg/g) formulations that have similar bioavailability. Food increases nelfinavir absorption and decreases nelfinavir pharmacokinetic variability compared to the fasting state *(68)*.

A study in healthy volunteers evaluated the pharmacokinetics of a single nelfinavir dose of 1250 mg (5 × 250 mg tablets) taken under fasting conditions or with three different meals. Study results showed that nelfinavir AUC, $C_{\max}$, and $T_{\max}$ increased with higher caloric and fat intake. Compared to the fasting state, a low calorie and fat meal (125 kcal, 20% fat) caused an increase in the AUC and $C_{\max}$ of nelfinavir by 2.2- and 2-fold, respectively. Further increases in nelfinavir bioavailability occurred with a meal that provided higher calories (500 kcal, 20% fat) leading to a 3.1-fold increase in AUC and 2.3-fold increase in $C_{\max}$. A meal with even higher calories and fat content (1000 kcal, 50% fat) was associated with a higher 5.2-fold increase in AUC and 3.3-fold increase in $C_{\max}$. Similar pharmacokinetic results on nelfinavir absorption were obtained from another study in healthy volunteers that evaluated the effects of low (20%) vs. high (50%) fat meals with similar calorie intake (500 kcal) on *(68)*.

Although the effect of food on the pharmacokinetics of the 625 mg nelfinavir tablet has not been separately evaluated, a crossover study that compared the effects of food (standard breakfast at 820 kcal) on a single dose administration of nelfinavir 1250 mg (5 × 250 mg tablets vs. 2 × 625 mg tablets) showed that compared to fasting, food caused a six- and eightfold increase in nelfinavir absorption for the 250 mg and 625 mg tablet, respectively *(69)*.

In summary, nelfinavir bioavailability is higher when the drug is taken with high calorie or high-fat meals. For optimal absorption and enhanced therapeutic effects, nelfinavir should be taken with meals.

2.5.5. SAQUINAVIR

Saquinavir is an antiretroviral agent used for treatment of HIV-1 infection. It is available in oral capsules as saquinavir mesylate (Invirase®) and in soft capsules as saquinavir (Fortovase®). The two dosage forms are not bioequivalent and cannot be used interchangeably. Fortovase® has better bioavailability as compared to Invirase®. Following administration of single 600 mg doses of saquinavir, the relative bioavailability of Fortovase® was 331% as compared to Invirase®. Food, however, substantially increases saquinavir absorption with either dosage form *(70,71)*. Administration of saquinavir with food was reported to increase saquinavir bioavailability by 1800% *(72)*.

In a study of six healthy volunteers who received saquinavir in a single 600 mg dose, a 6.7-fold increase in AUC was reported when saquinavir was administered with food as compared to fasting. Mean 24-h saquinavir AUC increased from 24 ng·h/mL with fasting to 161 ng·h/mL following breakfast (1006 kcal, 57 g fat, 60 g carbohydrate, 48 g protein). The 24-h AUC and $C_{\max}$ were on average twofold higher following a higher calorie and fat meal (943 kcal, 54 g fat) than a lower calorie and fat meal (355 kcal, 8 g fat) *(70)*. In another study of 12 healthy volunteers who received a single dose of Fortovase® 800 mg, the mean 12-h AUC increased from 167 ng·h/mL with fasting to 1120 ng·h/mL when saquinavir was taken with breakfast (1006 kcal, 57 g fat, 60 g carbohydrate, 48 g protein) *(71)*.

In summary, food increases saquinavir bioavailability by increasing drug dissolution and disintegration *(73)*. As such, Fortovase® and Invirase®should be taken with food or within 2 h after a meal *(70,71)*. Due to its improved absorption, Fortovase® should be used as the saquinavir formulation of choice in an antiretroviral regimen.

2.6. Fenofibrate

Fenofibrate is a fibric acid derivative prodrug that is rapidly hydrolyzed to its major pharmacologically active metabolite, fenofibric acid. Fenofibrate reduces serum total cholesterol, low-density lipoprotein cholesterol (LDL), very low-density lipoprotein cholesterol (VLDL), and triglycerides, and increases high-density lipoprotein cholesterol (HDL) in patients with dyslipidemia. Fenofibrate also increases urinary uric acid excretion via a different mechanism, hence its off-label use in the treatment of hyperuricemia and gout *(74,75)*. The FDA-labeled indication of fenofibrate is for the treatment of hypercholesterolemia, hypertriglyceridemia, and mixed dyslipidemia (types IV and V) in adjunct to a low-fat diet *(76)*.

Fenofibrate is well absorbed from the gastrointestinal tract with $C_{\max}$ attained 6–8 h after oral administration. Fenofibrate is a neutral lipophilic compound that is practically insoluble in aqueous solution for injection, thus the lack of data on the drug's absolute bioavailability. The variable bioavailability and dissolution problems of fenofibrate have led to manufacturing innovations in oral fenofibrate formulations. Fenofibrate is available in various tablet and capsule formulations that have different bioavailability profiles and are not bioequivalent on a milligram-for-milligram basis. The bioavailability of the original non-micronized tablet was improved by micronization, conferring about a 30% increase in bioavailability. Fenofibrate capsules contain micronized fenofibrate particles that disperse and aggregate randomly to excipients. With the fenofibrate microcoated micronized tablet formulation, fenofibrate is coated directly into an inert excipient core which improved its in vitro dissolution by 46% owing to it its higher bioavailability over the non-microcoated micronized capsules. Plasma fenofibric acid concentrations that are achieved following administration of the 54 mg or 160 mg microcoated micronized tablets are equivalent under fed conditions to those achieved with the 67 mg or 200 mg micronized capsules, respectively. The extent of absorption of fenofibrate micronized capsules or micronized microcoated tablets is increased by about 35% under fed conditions compared to fasting *(74,77)*.

Commercially available fenofibrate products can be classified based on their formulation and whether they should be taken with or without regards to meals. Fenofibrate formulations that should be taken with food include micronized capsules (Lofibra® 67 mg, 134 mg, 200 mg), microcoated micronized tablets (Lofibra® 54 mg, 160 mg), and CIP-fenofibrate hard gelatin capsules (Lipofen® 50 mg, 100 mg, 150 mg) *(78–80)*. Fenofibrate formulations that can be taken with or without meals include nanoparticle tablets (Tricor® 48 mg, 145 mg), Insoluble Drug Delivery®-Microparticle (IDD-P) tablets (Triglide® 50 mg, 160 mg), and micronized capsules (Antara® 43 mg, 130 mg) *(76,81,82)*.

The CIP-fenofibrate formulation (Lipofen®) is a newly developed drug delivery technology (Lidose) that increased fenofibrate bioavailability by about 25% compared to the micronized form. The CIP-fenofibrate 150 mg capsule is bioequivalent to 160 mg micronized microcoated tablet (Tricor®) under low- and high-fat-fed conditions. When compared to fasting conditions, the extent of Lipofen®absorption increased by about 25% when taken with a low-fat meal and by 58% with a high-fat meal *(80)*. Similarly, the nanoparticle technology used in the reformulation of Tricor® allowed faster drug dissolution that improved its absorption and allowed the drug to be taken with or without food. On the other hand, the formulation of the IDD-P tablets uses a technology of preparing fenofibrate microparticles that are stabilized with phospholipid-surface-modifying agents to prevent the re-aggregation of microparticles. This preserves the expanded drug surface area of microparticles and increases its dissolution for better absorption. Single-dose pharmacokinetic studies of the fenofibrate IDD-P formulation in healthy adults showed similar AUC for fenofibrate under fed or fasting conditions *(83)*. Although the micronized capsules in Antara® are better absorbed with a high-fat meal, the package insert states that Antara® capsules may be taken without regard to meals. When Antara® was administered with a high-fat meal, there was a 26% increase of the fenofibric acid AUC and a 108% increase in $C_{\max}$ compared to the fasting state. However, the AUC of fenofibric acid was unaffected when Antara® was taken with a low-fat meal or under fasting conditions. $T_{\max}$ was also unaffected in the presence of a low-fat meal. Although Antara® absorption was increased when taken with a fat-rich meal, the approval of Antara® to be administered without regard to meals was based on data from clinical studies that showed comparable outcomes on serum triglycerides and cholesterol concentrations when Antara® 130 mg was taken once daily with or between meals *(82)*. A study of an investigational sustained-release fenofibrate 250 mg capsule showed a significant increase in AUC (3.34-fold) and $C_{\max}$ (3.82-fold) when taken with a high-fat meal compared to fasting ($p < 0.01$). There was also a significant increase in AUC (2.45-fold) and $C_{\max}$ (2.89-fold) when the same formulation was given with a standard breakfast compared to fasting ($p < 0.01$) *(84)*.

In summary, many different fenofibrate oral formulations are commercially available and they are not bioequivalent. The difference in bioequivalence should be considered when a patient is switched from one fenofibrate formulation to another. Lofibra® and Lipofen® should be taken with meals to improve absorption and optimize therapeutic effects. Tricor®, Triglide®, and Antara® can be taken with or without food.

2.7. Isotretinoin

Isotretinoin is a synthetic analog of vitamin A that is available in oral capsules and used for the treatment of cystic acne. Isotretinoin is a highly lipophilic drug with maximal isotretinoin absorption achieved when administered with a fatty meal *(85)*.

The effects of food and fasting on isotretinoin bioavailability were evaluated in a randomized, crossover study of 20 healthy, male volunteers. Isotretinoin 80 mg was administered either during a complete fast, 1 h before a standard breakfast, with a standard breakfast, or 1 h after a standard breakfast. Each treatment was separated by a washout period. Study results showed that isotretinoin bioavailability increased by about 1.5- to 2-fold when isotretinoin was administered 1 h before, with, or 1 h after breakfast, as compared to fasting. Mean isotretinoin $C_{\max}$ increased 1.6- to 2.4-fold in the presence of food. $T_{\max}$ was slightly delayed by 0.8–1.6 h. The investigators related the positive effects of food on isotretinoin absorption to the increased bile flow that enhances isotretinoin solubility *(86)*.

In summary, isotretinoin bioavailability is increased when taken with food. Consistent intake of isotretinoin with meals is recommended in order to optimize isotretinoin clinical effects.

2.8. Mesalamine/Olsalazine

Mesalamine (5-aminosalicylic acid) is an oral agent indicated for the treatment of chronic inflammatory bowel disease. The exact mechanism of action of mesalamine is unknown, but may be due to its local effects that decrease colonic inflammation by blocking the cyclooxygenase enzyme and inhibiting prostaglandin production in the colonic mucosa. Several different formulations of mesalamine are available on the market. Delayed-release tablets (Lialda®, Asacol®) and controlled-release capsules (Pentasa®) are minimally absorbed (20–30%). In addition, the delayed-release tablets are coated with an acrylic-based resin that only dissolves at a pH of 7 or higher, releasing mesalamine in the terminal ileum. When the delayed-release tablets are given with a high-fat meal, target exposure and absorption are delayed, and there is an increase in systemic exposure to mesalamine (91% increase in $C_{\max}$ and 16% increase in AUC) *(87)*. Despite enhanced absorption, the effects of mesalamine are believed to be due to its local effects in the colonic mucosa and not due to its systemic concentration.

Olsalazine (Dipentum®) is a prodrug containing two azo-bound molecules of mesalamine that is cleaved by bacteria in the colon to form mesalamine (5-aminosalicylic acid). Olsalazine is used for the maintenance of remission of ulcerative colitis in patients who are intolerant to sulfasalazine. The oral bioavailability of the olsalazine is limited at <3%. Oral absorption of 5-aminosalicylic acid is also very slow, which leaves high local therapeutic drug concentrations in the colon. Of a 1 g dose of olsalazine, more than 0.9 g of 5-aminosalicylic acid reaches the colon where it exerts its effects *(88)*. Food does not affect the bioavailability of olsalazine or 5-aminosalicylic acid *(89)*. However, because the efficacy of olsalazine is dependent on the colonic concentration of 5-aminosalicylic acid and is independent of serum drug concentrations, taking olsalazine with food increases drug efficacy by prolonging the presence of 5-aminosalicylic acid in the gut *(88)*.

Because the pharmacologic action of mesalamine and olsalazine depends on the local effects of 5-aminosalicylic acid, they should be taken with food to maximize local colonic effects in patients with ulcerative colitis *(87,88)*.

2.9. Misoprostol

Misoprostol is a prostaglandin E_1 analog that is primarily used for preventing gastric ulceration in patients treated with nonsteroidal antiinflammatory drugs (NSAIDs). Misoprostol is available as oral tablets. Gastrointestinal side effects such as diarrhea and abdominal pain are common with misoprostol therapy. Diarrhea is dose-related and may sometimes require discontinuation of misoprostol therapy. The incidence of diarrhea with misoprostol 800 μg/day in patients treated with NSAIDs ranges between 14 and 40%. Administration of misoprostol after meals slows the rate of misoprostol absorption and thus reduces the frequency of diarrhea *(90)*.

In a randomized, open label, crossover study of 12 healthy volunteers, misoprostol absorption was studied when taken with a high-fat meal or during fasting. Study results showed that food decreases the rate of misoprostol absorption without significantly affecting the amount or extent of misoprostol absorption. Food significantly increased misoprostol $T_{\max}$ compared to fasting (64 ± 79 min vs. 14 ± 8 min; $p< 0.05$). Food, however, decreased misoprostol $C_{\max}$ (303 ± 176 pg/mL) compared to fasting (811 ± 317 pg/mL) ($p < 0.05$). Because achieving a rapid, high $C_{\max}$ of the active misoprostol metabolite (misoprostol acid) may result in increased side effects (diarrhea, abdominal pain), these effects can be minimized when misoprostol is taken with food *(91)*.

The effects of misoprostol on bowel motility were evaluated in a double-blind, crossover study of 12 healthy volunteers. Study results showed that oral-to-cecal transit time (measured by H_2 breath test following lactulose administration) was shortened by 57 and 18% when misoprostol was administered before and after meals, respectively. The mean oral-to-cecal transit time was significantly shorter when misoprostol 400 μg was taken before meals compared to after meals ($p < 0.001$) and to placebo ($p < 0.001$). Although other parameters such as stool frequency, fecal fat and bile acids, and fecal weight showed differences between treatments, these differences were not found to be significant *(92)*.

In summary, administration of misoprostol before or after meals decreases the C_{max} of the active metabolite misoprostol acid without affecting misoprostol bioavailability *(91)*. Misoprostol should then be taken with food to reduce the incidence of diarrhea *(90)*.

3. EFFECTS OF SPECIFIC NUTRIENTS ON DRUG ABSORPTION

3.1. Ascorbic Acid and Iron

Iron deficiency anemia can affect all age groups, especially children and women of childbearing age. There are two forms of iron found in the diet – heme iron from meat and non-heme iron from cereals, fruits, and vegetables. Heme iron accounts for about 10–15% of iron intake when consuming a meat-rich diet whereas most of the remaining dietary iron is in the non-heme form. Factors that increase (e.g., ascorbic acid) or decrease (e.g., phytates) non-heme iron absorption do not, however, affect heme iron absorption *(93)*. Ferrous iron (Fe^{2+}) is better absorbed than ferric iron (Fe^{3+}). Most dietary iron is in the ferric state, but factors such as gastric acidity, dietary ascorbic acid, and other reducing substances convert ferric iron to ferrous iron. When considering oral iron supplements, the amount of iron absorbed depends on the type of iron salt used (sulfate vs. fumarate vs. gluconate), iron dose administered, and body iron stores. For instance, 10–35% of an oral iron dose is normally absorbed, whereas up to 80–95% of iron is absorbed in patients with iron deficiency anemia *(94)*.

Iron absorption is significantly reduced by the presence of phytate in the diet. Phytates or hexaphosphates are natural components of vegetables and cereals that bind iron in the gastrointestinal tract to form insoluble and unabsorbable compounds. Ascorbic acid inhibits iron chelation to phytates and also reduces iron to the ferrous form, making it more available for absorption *(94)*. The amount of ascorbic acid needed to inhibit phytate binding to iron depends on the amount of phytate present in the gastrointestinal tract *(95,96)*. The greater the amount of phytate that is present, the more ascorbic acid is required to reverse the inhibition. With meals containing no phytates, ascorbic acid increases iron absorption by about 60% *(97)*. When phytates were added into wheat rolls at 2 mg, 25 mg, and 250 mg, iron absorption was inhibited by 18, 64, and 82%, respectively. When coadministered with 50 mg of ascorbic acid, absolute iron absorption was highest when the rolls contained no phytates, and was lowest when the rolls contained 250 mg of phytates. It is estimated that about 80 mg of ascorbic acid is needed to counteract the effects of 25 mg of phytates, and a few hundred milligrams of ascorbic acid are required to counteract the effects of 250 mg of phytates *(98)*. The average North American person consumes about 750 mg of phytates daily, although wide individual and geographical variation exist *(99)*.

Iron absorption was increased two- to threefold when 50 mg of ascorbic acid was added twice daily to each meal *(93–96)*. The first 50–100 mg doses of ascorbic acid appear to have the most significant effects on iron absorption. Higher doses have little additional effects *(97)*. Administration of ascorbic acid at doses of 500 mg twice daily after meals for 2 months significantly improved iron status in strict vegetarians *(100)*. However, there was no significant effect on serum ferritin levels when higher ascorbic acid doses of 1 g twice daily were given to adults consuming a well-balanced diet. The lack of significant response with higher ascorbic acid doses may indicate that iron reserves are maintained under tight control regardless of the mechanisms that enhance iron bioavailability *(101)*. Also, ascorbic acid supplementation may have little effect on improving iron absorption in well-nourished, iron-replete subjects.

The effects of ascorbic acid on iron retention were also evaluated in a study of premenopausal women following induction of iron depletion by a low iron diet and phlebotomy. Women in this study consumed a low iron diet that provided 5 mg of elemental iron per 2000 calories for 67–88 days. At the end of the low iron diet period, subjects were divided into three groups to receive a diet containing either 13.7 mg of iron per 2000 calories, supplemental ascorbic acid 500 mg 3 times daily with meals, or a placebo supplement for a total of 5.5 weeks. Study results showed significant improvement in apparent iron absorption (defined as the difference between dietary and fecal iron) with ascorbic acid supplementation compared to placebo. Blood analysis at the end of 5 weeks showed ascorbic acid supplementation to have also improved hemoglobin, serum iron concentration, and erythrocyte protoporphyrins. Ascorbic acid had no effect on improving serum ferritin, transferrin saturation, hematocrit, or total iron-binding capacity *(102)*.

The effect of ascorbic acid on iron absorption was also reported in 54 preschool Indian children who had iron deficiency. Ascorbic acid supplemented at a dose of 100 mg twice daily given with meals for 60 days resulted in a significant improvement in hemoglobin ($p < 0.001$) and red cell morphology as compared with placebo ($p < 0.01$) *(103)*. In another study of 65 Chinese children with mild iron deficiency anemia who were consuming a predominantly vegetarian diet, daily ascorbic acid supplementation at 50 mg, 100 mg, and 150 mg had similar effects on improving iron status *(104)*.

The fraction of iron in ferritin and ferric hydroxide that enters the non-heme dietary iron is also influenced by diet composition. One study compared the absorption of iron from ferritin iron and ferric hydroxide in 35 multiparous women. When administered in water, the geometric mean iron absorption was 0.7 and 2.4% from ferritin iron and ferric hydroxide, respectively. With the presence of ascorbic acid 100 mg in dietary maize porridge, iron absorption increased to 12.1% for ferritin and 10.5% for ferric hydroxide, compared to 0.4% for both compounds with maize porridge without ascorbic acid *(105)*.

Ascorbic acid in fruit juices and vegetables is as effective as equal amounts of synthetic ascorbic acid in enhancing iron absorption *(96)*. In a study that evaluated the effect of fruit and fruit juices on iron absorption from a rice diet containing 0.4 mg of iron, juices of citrus fruits with higher ascorbic acid content resulted in higher amounts of iron absorbed *(106)*.

Iron supplements are commercially available in different salt forms (gluconate, fumarate, sulfate) each providing different amounts of elemental iron *(107)*. Iron sulfate, the most widely prescribed oral iron supplement, is usually given in 1–3 daily doses. Most clinical evidence of enhanced iron absorption with ascorbic acid is with iron sulfate. *(94,108)*. Coadministration of ascorbic acid 100–200 mg/day with iron supplements enhances iron absorption, particularly in anemic patients *(94)*. Patients who absorb iron poorly, such as those with gastrectomy, would most benefit from ascorbic acid supplementation during oral iron therapy *(109)*. Various combinations of commercial iron and ascorbic acid formulations can be found, such as Fero-Grad-500® (timed release tablet containing ferrous sulfate 105 mg with sodium ascorbate 500 mg), Vitelle Irospan® (timed release tablet and capsule containing ferrous sulfate exsiccated 65 mg with ascorbic acid 150 mg), Hemaspan® (containing ferrous fumarate 110 mg with ascorbic acid 200 mg), and Cevi-Fer® (timed release capsule containing ferrous fumarate 20 mg with ascorbic acid 300 mg). Slow-release iron formulations may result in portions of the dose bypassing the intestinal sites of absorption.

4. EFFECTS OF SPECIFIC NUTRIENTS ON REDUCING DRUG TOXICITY

4.1. Folic Acid and Fluorouracil

Fluorouracil (5-FU) is a fluorinated pyrimidine antineoplastic antimetabolite used in the palliative management of colorectal, gastric, pancreatic, breast, ovarian, and head and neck cancers. 5-FU exerts its effects primarily through its active metabolite fluorodeoxyuridine monophosphate that inhibits thymidylate synthase, a key enzyme in pyrimidine synthesis. Leucovorin, a modulator of 5-FU activity, is typically administered intravenously in combination with 5-FU to enhance 5-FU activity. Leucovorin enhances thymidylate synthase inhibition through increasing the intracellular pool of folates that stabilize the thymidylate synthase–fluorodeoxyuridine monophosphate complex *(110,111)*. Because reduced folate metabolites enhance 5-FU antitumor activity, folic acid has been proposed as an alternative to leucovorin as long as it generates the same plasma metabolite levels. Animal studies have shown potential modulating effects for folic acid in mice with lymphocytic leukemia treated with 5-FU *(112)*. However, human studies evaluating the role of folic acid as possible modulator of 5-FU activity are limited.

A crossover, randomized pharmacokinetic study evaluated the metabolism of folic acid and its ability to yield reduced folates. The study included 10 adult volunteers who were divided into two groups. One group received folic acid at doses of 25 mg/m^2 and the other group received 125 mg/m^2. After a 2-week washout period, the same group received the same folic acid dose by the alternative route. Serial blood samples were collected over 24 h following folic acid administration. Plasma samples were analyzed for folic acid and for reduced folate metabolite concentrations. Study results showed a twofold increase in plasma reduced folate concentrations with the higher oral folic acid dose as compared to the lower dose. In comparison with other studies using leucovorin, the same reduced folate metabolites were generated following folic acid administration. Folic acid at 125 mg/m^2 was at least as effective as leucovorin in increasing plasma reduced folate concentrations. However, folic acid metabolites accumulated at a slower rate and persisted longer than leucovorin metabolites. Based on these results and considering the short half-life of 5-FU, the study concluded that folic acid offers a potential therapeutic alternative to leucovorin in modulating 5-FU efficacy. It was also concluded that giving folic acid 4–6 h before 5-FU allows enough time for effective accumulation of reduced folate metabolites *(113)*.

A clinical study combining 5-FU and high-dose folic acid yielded disappointing results. The study included 22 patients with metastatic colorectal cancer who received a weekly dose of 5-FU 600 mg/m^2 (maximum 1 g) administered 1 h after an intravenous folic acid dose. The starting folic acid dose was 40 mg/m^2 intravenously escalated based on tolerance to the maximum dose of 140 mg/m^2. Study results showed a low response rate and severe toxicities with the combination therapy of folic acid and 5-FU, as compared to 5-FU alone. Only four patients had partial responses for a mean duration of 4 months; no patient had a complete response. Severe diarrhea requiring hospitalization was reported in 12 patients and also caused 3 patients to drop out of the study. Two patients developed leukopenia and later died from sepsis. The study concluded that the use of folic acid with 5-FU could not be justified and that further studies were still needed. There was no clear explanation for the low response rate and high toxicities encountered in this study. The 5-FU dose was within the usual recommended dose. Mean serum folate concentrations at 1 h after folic acid administration were 11 nmol/L higher than the in vitro optimal levels for stabilization of the thymidylate synthase–fluorodeoxyuridine monophosphate complex. However, interpretation of these levels is difficult because serum folate levels do not necessarily correlate with intracellular folate concentrations. Also, it was unknown whether folic acid or the folic acid dose could have contributed to these effects, or even if patients with colorectal cancer are more sensitive to the combination therapy *(114)*. For instance, severe gastrointestinal toxicities (e.g., stomatitis and diarrhea) are more commonly seen in patients with colorectal cancer who are treated with leucovorin and 5-FU, as compared to 5-FU alone. Additionally, it remains unknown whether reductase enzyme phenotype plays any role in the findings. The C677T genotype codes for a poorly functional MTHFR that allows accumulation of 5,10-methylenetetrahydrofolate which increase the thymidylate synthase effects of 5-FU and drug-induced myelosuppression (115). For safety reasons, it is generally recommended that patients who develop gastrointestinal toxicity not be initiated or continued on leucovorin therapy with 5-FU and that patients should be monitored closely until diarrhea resolves *(116)*.

At present, intravenous leucovorin remains the agent of choice for modulation of 5-FU effect. The safety, efficacy, optimal dose, and dosing schedule for folic acid as a modulator of 5-FU activity remain unknown. Studies comparing leucovorin to folic acid are needed before folic acid can be recommended as a safe and effective modulator of 5-FU effect in the treatment of cancer.

4.2. *Folic Acid and Methotrexate*

Methotrexate is an antineoplastic antimetabolite used for the treatment of certain cancers. It is also used for treating psoriasis and rheumatoid arthritis (RA). Methotrexate use in RA is based on its antiinflammatory, immunosuppressive, and antiproliferative effects. A low methotrexate dose of 5–25 mg/wk is often used for short- and long-term treatment of adults with RA *(117,118)*. Higher methotrexate doses are exceptionally used when efficacy is not achieved at low doses. Significant toxicities, especially bone marrow suppression, occur at methotrexate doses exceeding 20 mg/wk *(119)*. Dose-related hematological, gastrointestinal, hepatic, and pulmonary toxicities frequently lead to cessation of methotrexate therapy *(120,121)*.

Methotrexate is structurally similar to folic acid. Methotrexate inhibits the dihydrofolate reductase enzyme that reduces folic acid to tetrahydrofolic acid. This results in decreased intracellular levels of reduced folates and inhibition of deoxyribonucleic acid (DNA) synthesis and cellular replication *(120,121)*. The resultant folate depletion and inhibition of folate-dependent enzymes contribute to methotrexate toxicities in nontarget tissues. Diarrhea, stomatitis, and leukopenia are manifestations of methotrexate toxicity that mimic the symptoms of folic acid deficiency *(122)*. Thus, adequate folate supplementation is crucial to reduce methotrexate toxicity.

Leucovorin (folinic acid) is a chemically active reduced folate derivative that is used clinically as a folate rescue to counteract methotrexate toxicity. Low oral doses of leucovorin at 2.5–5 mg/wk are used in combination with low-dose methotrexate *(123)*. Low leucovorin doses reduce methotrexate toxicity without altering its efficacy. However, higher leucovorin doses (45 mg/wk) may counteract methotrexate efficacy and result in worsening of RA *(124)*. As such, folic acid has been investigated as a possible substitute for leucovorin. Compared to methotrexate, folic acid has a lower affinity to the dihydrofolate reductase enzyme. This gives folic acid the advantage of reducing methotrexate toxicity without counteracting its efficacy.

Low plasma and erythrocyte folate and high homocysteine levels were reported in patients treated with methotrexate without folate supplementation *(125,126)*. Plasma homocysteine levels decreased following folic acid or folinic acid supplementation

(126). Reducing homocysteine levels may have long-term cardiovascular protective effect because hyperhomocysteinemia may be a risk factor for cardiovascular disease *(127)*.

The optimal dose and the timing of folic acid supplementation in relation to methotrexate therapy are still debatable. Although weekly folic acid doses of 1 mg *(128)* and 5 mg *(120)* were shown to reduce low-dose methotrexate toxicity, higher doses were suggested to sufficiently prevent methotrexate toxicity *(129)*. The effects of folic acid on reducing low-dose methotrexate toxicity were evaluated in a double-blind, placebo-controlled trial of 79 patients with RA. Oral folic acid doses of 1 mg/day (5 mg/wk) or 5.5 mg/day (27.5 mg/wk) were given 5 days a week on days not coinciding with methotrexate administration. Study results showed that either folic acid dose resulted in lower toxicity scores compared to placebo ($p < 0.001$). Neither folic acid dose interfered with methotrexate efficacy as assessed by joint indices and grip strengths *(121)*. However, results of another study using folic acid doses at 5 mg/day for 13 consecutive days along with weekly intramuscular methotrexate showed alterations in methotrexate pharmacokinetics. There was a significant decrease in plasma methotrexate concentrations and increased total methotrexate clearance. Study investigators concluded that decreased plasma methotrexate concentrations were possibly due to folic acid-induced increased cellular methotrexate uptake *(130)*. Based on these results, the question remains about the optimal folic acid dose that reduces methotrexate toxicity without interfering with its efficacy.

A meta-analysis of seven double-blind, randomized, controlled studies was conducted to evaluate the effects of folic acid or folinic acid on the toxicity of low-dose methotrexate (< 20 mg/wk) in patients with RA. Results of the meta-analysis showed a 79% reduction in methotrexate-induced mucosal and gastrointestinal toxicity with folic acid supplementation. A clinically, but not statistically, significant 42% reduction of the same side effects was seen with folinic acid. Similar effects were also achieved with low- and high-dose folic acid (1–27.5 mg/wk) or folinic acid (1–20 mg/wk). However, high folinic acid doses were associated with increased tender and swollen joint count, a possible indication of decreased response to methotrexate *(120)*. The protective effects of folic acid reported in the meta-analysis *(120)* were not, however, replicated in a later individual study *(131)*. In a 48-week, multicenter, randomized, double-blind, placebo-controlled study, folic acid 1 mg/day and folinic acid 2.5 mg/wk reduced the incidence of elevated liver enzymes without affecting the incidence, severity, or duration of other toxicities including mucosal and gastrointestinal side effects *(131)*.

Based on available data, folic acid supplementation appears to reduce low-dose methotrexate toxicity *(129)* and results in less frequent interruption of methotrexate therapy *(131)*. Relying on dietary folic acid intake alone may not be sufficient to prevent methotrexate toxicity *(132)*. Because folic acid supplements are safe, effective, and less expensive than folinic acid *(133)*, weekly oral folic acid supplementation given on non-methotrexate days appears an appropriate substitute to leucovorin. Although there is no agreement on the optimal folic acid dose, clinical studies reported weekly folic acid doses of 1 mg, 5 mg, and 27.5 mg to be safe and effective in reducing low-dose methotrexate toxicity *(120)*. Baseline patient folate status, methotrexate dose, duration of methotrexate therapy, and possibly reductase (DHFR, MTHFR) enzyme phenotypes should play a role in determining the optimal protective dose of folic acid. Reports of possible liver protective effects of folic acid are encouraging and require further exploration *(134)*.

4.3. Pyridoxine and Isoniazid

Isoniazid is an antimycobacterial agent used for the treatment and prophylaxis of *Mycobacterium tuberculosis* infections. Peripheral neuropathy is the most common side effect of isoniazid therapy *(135)*. Peripheral neuropathy is dose-related and is most likely to occur in slow acetylators, chronic alcoholics, and malnourished, uremic, and diabetic patients. Signs and symptoms of peripheral neuropathy include paresthesias of the feet and hands, muscle weakness, and diminished or exaggerated reflexes. The mechanism of isoniazid-induced peripheral neuropathy is likely related to isoniazid-induced pyridoxine deficiency or to isoniazid blocking the effect of pyridoxal phosphate synthesis by inhibition of pyridoxine kinase activity *(136,137)*. Vitamin B_6 exists in the body as pyridoxine, pyridoxal, and pyridoxamine *(138)*. Pyridoxine kinase is the enzyme that converts pyridoxal to pyridoxal phosphate *(136,137)*. Pyridoxal phosphate is the active byproduct of pyridoxal metabolism that acts as a coenzyme in the metabolism of neurotransmitters. Reduced pyridoxal phosphate availability during isoniazid therapy is believed to cause a reduction in neurotransmitter synthesis (including gamma-amino butyric acid) that eventually leads to peripheral neuropathy *(137)*.

The incidence of peripheral neuropathy correlates with the isoniazid dose and the presence or absence of patient-specific factors. Peripheral neuropathy occurs in about 1–2% of patients treated with the usual isoniazid doses of 3–5 mg/kg/day *(135)*. The incidence of peripheral neuropathy increases to 40% with isoniazid doses of 20 mg/kg/day *(136)*. In malnourished patients, even low isoniazid doses of 4–6 mg/kg/day may cause peripheral neuropathy in up to 20% of patients *(137)*. Peripheral neuropathy does not usually appear until 6 months of isoniazid therapy *(135)*, but it could appear earlier in malnourished patients or those with preexisting pyridoxine deficiency *(139)*.

It is common practice to supplement pyridoxine at doses of 15–50 mg/day, during the course of isoniazid therapy. Higher pyridoxine doses of 100 mg/day are required in patients treated with hemodialysis. Increased pyridoxine requirements during hemodialysis likely result from reduced pyridoxine metabolism to active pyridoxal phosphate and increased dialysis clearance of pyridoxal phosphate *(140)*. Pyridoxine has also been used to prevent or treat isoniazid-induced psychosis *(138,141)* and seizures *(142,143)*. Seizures are the major toxic reactions of isoniazid overdose *(135)*. In case of isoniazid overdose, intravenous pyridoxine doses of 1 g for each 1 g of isoniazid dose ingested were used without evidence of pyridoxine toxicity *(143,144)*.

In summary, peripheral neuropathy rarely occurs in well-nourished patients treated with isoniazid doses up to 5 mg/kg/day *(145)*. Adult patients treated with isoniazid, especially those at high risk for peripheral neuropathy, should receive prophylactic oral pyridoxine doses of 50 mg/day *(135)*. Although high pyridoxine doses can possibly reduce isoniazid activity *(146)* or even cause neuropathy *(147)*, pyridoxine doses of 100–200 mg/day have been safely used to treat isoniazid-induced peripheral neuropathy *(137,146)*. The practice of avoiding pyridoxine prophylaxis in children receiving isoniazid should be discouraged, especially in malnourished children *(148)*. Children treated with isoniazid may be supplemented with oral pyridoxine at a dose of 1–2 mg/kg/day *(149)*.

5. EFFECTS OF SPECIFIC NUTRIENTS ON ENHANCING DRUG EFFECT

5.1. Calcitriol and Docetaxel

Docetaxel is an antineoplastic mitotic inhibitor used in the treatment of breast, ovarian, head and neck, nonsmall cell, and hormone refractory androgen-independent prostate cancer (AIPC). In patients with AIPC, docetaxel-based therapy in conjunction with other chemotherapy agents improved patient survival, bone pain, and quality of life. The antineoplastic activity of docetaxel may be significantly enhanced when given in combination with calcitriol (1,25-dihydroxy-vitamin D). Calcitriol is the most biologically active form of vitamin D that exerts its antitumor activity at supraphysiologic concentrations. At the cellular level, calcitriol exerts its antitumor effects via a genomic pathway that is mediated by the vitamin D receptor present in many tissues and via cytoplasmic signaling pathways through protein kinases, lipases, and prostaglandins. Clinically, several mechanisms are proposed for calcitriol antineoplastic activities that varied with tumor and experimental models. These include induction of cell apoptosis, inhibition of differentiation and proliferation, and reduction in angiogenesis and invasiveness. In experimental and clinical studies, combining calcitriol with other cytotoxic agents (e.g., paclitaxel, docetaxel, cisplatin, carboplatin, mitoxantrone, and platinum compounds) has shown synergistic and/or additive antitumor effects in certain types of cancer. When combined with glucocorticoids, calcitriol-mediated inhibition of tumor cell growth and cycle cell arrest were also enhanced *(150,151)*.

The antineoplastic effects of calcitriol are dose dependent and occur at concentrations that exceed the physiologic calcitriol range. Calcitriol concentrations $\geq$ 1 nmol/L are required for in vitro antineoplastic activity. Clinically, achieving these high calcitriol concentrations with high daily calcitriol doses resulted in hypercalcemia, a limiting toxicity of intensive calcitriol regimen. Therefore, daily dosing was replaced with weekly oral calcitriol administration with the goal of avoiding hypercalcemia while still achieving high calcitriol concentrations. In a phase I study, weekly oral calcitriol dose escalation from 0.06 μg/kg to 2.8 μg/kg achieved higher blood calcitriol concentrations from 3.7 to 6 nmol/L without a dose-limiting toxicity. With weekly calcitriol dosing at 60 μg, self-limited hypercalcemia was observed. There was no dose-limiting toxicity observed with single calcitriol doses up to 165 μg *(150)*.

Data are emerging on the beneficial role of a weekly high calcitriol dose in combination with docetaxel for the treatment of patients with AIPC. Preliminary human data also show a possible beneficial effect of a combined regimen using calcitriol and docetaxel for improving the quality of life and pain relief of AIPC-treated patients *(152)*. A single center, phase II study evaluated the role of combining calcitriol and docetaxel in the treatment of 11 patients with AIPC. Oral calcitriol was administered weekly at 0.5 μg/kg on day 1 followed by intravenous docetaxel 36 mg/m^2 on day 2 for 6 consecutive weeks of an 8-week cycle. The five patients who completed the 8-week cycle had at least a 50% reduction in prostate-specific antigen (PSA) *(153)*. Another phase II study of 37 patients with AIPC used a similar dosing regimen of calcitriol and docetaxel. The PSA response rate was 81% (30 of 37 patients); 59% of patients (22 of 37 patients) had $> 75\%$ reduction in PSA. Overall, 1-year patient survival was 89%, and treatment related toxicities were no different than with a single dose docetaxel *(154)*.

Because the commercial calcitriol (Rocaltrol®) formulation is available in 0.5 μg capsules, a large number of capsules (about 70–100) is required for each weekly high calcitriol dose. An investigational high-concentration calcitriol formulation (DN-101) was developed to overcome this limitation. A double-blind, randomized, international, multicenter, phase II study (Androgen Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere = ASCENT-1) of 250 patients with AIPC compared the effects of combining docetaxel with the DN-101 formulation or with placebo. Oral DN-101 45 μg or placebo was given on day 1 before intravenous docetaxel was administered on day 2 at weekly doses 36 mg/m^2 for 3 weeks of a 4-week cycle. The primary study endpoint was a 50% reduction in PSA confirmed 4 weeks later within 6 months. The primary endpoint was reached in 59% of DN-101-treated patients compared to 48% of placebo-treated patients ($p = 0.16$). At any time during the study, overall PSA response rates were 63% in DN-101-treated patients compared to 52% in placebo-treated patients ($p = 0.07$). An adjusted survival analysis showed improved survival in the DN-101 group compared to placebo (hazard ratio 0.67). The incidence of grade 3 and 4 adverse events (hematologic and non-hematologic) was significantly lower in the DN-101 group compared to placebo (58% vs. 70%, respectively; $p = 0.065$). In the DN-101 group, there were significantly fewer serious adverse events (2.4 % vs. 9.6%; $p = 0.02$) and thromboembolic events compared to placebo (1.6% vs. 7.2%; $p = 0.03$). Study investigators concluded that DN-101 treatment in combination with docetaxel does not increase docetaxel toxicity. Although the docetaxel and DN-101 combination improved survival of AIPC patients, this requires further confirmation in other studies because survival was not a primary endpoint of this ASCENT-1 study *(155)*. Currently, a phase III study (ASCENT-2) including 900 patients with AIPC is underway comparing weekly DN-101 with weekly docetaxel to the standard 3-weekly docetaxel 75 mg/m^2 with prednisone. Results of the ASCENT-2 study may better define the role of high-dose calcitriol in the treatment of AIPC. Calcitriol use as adjunctive therapy for specific malignancies primarily remains investigational at this time.

5.2. Plant Stanols and Statins

The management of dyslipidemia combines drug therapy with lifestyle modifications. HMG-CoA reductase inhibitors (statins) are the most widely prescribed agents to lower serum LDL concentration. Besides reducing saturated fat, trans fat, and cholesterol intake, an alternate or adjunct approach in managing hypercholesterolemia is inhibiting cholesterol absorption with dietary inclusion of plant sterols and stanols. Plant sterols and stanols block dietary and biliary cholesterol absorption in the small intestines with subsequent reduction of serum cholesterol and LDL concentrations *(156,157)*.

Plant sterols (phytosterols) are naturally occurring plant constituents. They are 28-carbon (campesterol) and 29-carbon (sitosterol and stigmasterol) sterols found in edible oils, nuts, and seeds. Plant stanols are saturated derivatives of plant sterols, with sitostanol being the most common. Sitostanol is found mainly in wood pulp, tall oil, and to a lesser extent, in soybean oil.

The Western diet provides about 100–300 mg/day of plant sterols and 20–50 mg/day of plant stanols. Plant stanols and sterols have been incorporated into various food products, including margarine and salad dressing. They are more commonly used in Europe than in the United States. Although plant stanols and sterols have been shown to be equally effective in reducing serum cholesterol concentrations *(156)*, the compounds have inherent differences. For instance, plant stanols are preferable over plant sterols because they are relatively unabsorbed from the gastrointestinal tract. Although plant sterols are poorly absorbed, daily sterol intake of 3.24 g increases serum sitosterol and campesterol by 40 and 70%, respectively. Because of concerns that plant sterols and their byproducts may initiate the development of atherosclerosis, plant stanols appear safer substances, especially during long-term consumption *(158)*.

Plant stanols have been used as adjunctive therapy with statins to manage hypercholesterolemia. Because statins inhibit cholesterol synthesis and stanols block cholesterol absorption, an additive effect of combining the two agents would be anticipated to further lower serum cholesterol concentrations. The combined effects of statins and plant stanols are equivalent to a one- to twofold increase in statin dose *(159)*. A double-blind, placebo-controlled study evaluated the effects of adding dietary plant stanol esters (esterified plant stanols) to statin therapy *(160)*. One-hundred-sixty-seven adults with serum LDL cholesterol concentrations $\geq$ 130 mg/dL and total cholesterol concentrations $\leq$ 350 mg/dL who had been receiving a stable dose of a statin for at least 90 days were included in the study. Subjects were randomized to receive either dietary canola oil-based spread in three servings that provided 5.1 g/day of plant stanol ester (equivalent to 3 g/day of plant stanols) or placebo for a period of 8 weeks. Study results showed plant stanols in combination with statins significantly reduced serum total cholesterol (12% vs. 5%, $p < 0.0001$) and LDL concentrations (17% vs. 7%, $p < 0.0001$) compared to placebo. There were no changes in serum triglyceride or HDL concentrations. Plant stanols were well tolerated *(160)*.

Plant sterols have also been studied. A double-blind, randomized, multicenter study evaluated the effects of plant sterol ester margarine on serum LDL cholesterol concentrations when combined with a statin drug in subjects with hypercholesterolemia (baseline LDL cholesterol $\geq$ 97 mg/dL) *(161)*. The study design used four parallel treatment arms with four daily treatment options of placebo with regular margarine 25 g ($n = 38$), placebo with sterol ester margarine 25 g (2 g of plant sterol; $n = 39$), cerivastatin 0.4 mg with regular margarine 25 g ($n = 38$), and cerivastatin 0.4 mg with sterol ester margarine 25 g ($n = 37$). Study results at the end of 4 weeks showed that cerivastatin significantly reduced serum LDL cholesterol by 32%

compared to placebo ($p < 0.0001$). Sterol ester margarine reduced serum LDL cholesterol concentrations by 8% compared to regular margarine ($p < 0.0001$). There was an additive effect of sterol ester margarine with cerivastatin that resulted in a 39% reduction in serum LDL cholesterol concentrations. All treatments were well tolerated. Study investigators concluded that adding sterol ester margarine to statin therapy reduces serum LDL cholesterol that is equivalent to doubling the statin dose *(161)*.

The effects of plant sterols were also investigated in patients with familial hypercholesterolemia. Patients with heterozygous familial hypercholesterolemia have markedly elevated serum cholesterol concentrations and require lifelong intensive dietary and lifestyle modifications with intensive lipid-lowering drug therapy for hypercholesterolemia. A double-blind, randomized, placebo-controlled, crossover study with two consecutive periods of 8 weeks compared the effects of plant sterol intake at 2.5 g/day in fat spread to placebo on plasma lipid and lipoprotein concentrations *(162)*. Thirty patients with heterozygous familial hypercholesterolemia were concurrently treated with a statin drug, and 32 patients with type IIa primary hypercholesterolemia with total serum cholesterol concentrations > 250 mg/dL were not being treated with lipid-lowering agents. Because of possible carryover effects at the end of the two 8-week study periods, data analysis was limited to the first phase of treatment. At the end of the first 8 weeks, serum LDL cholesterol concentrations had significantly decreased by 10% with sterol treatment compared to no decrease in the placebo group ($p < 0.0001$). There was no difference in response between patients receiving or not receiving concomitant statin therapy *(162)*. The lack of combined effects between plant stanols and sterols with statins in patients with heterozygous familial hypercholesterolemia was replicated in another study of children with heterozygous familial hypercholesterolemia. Combined inhibition of cholesterol absorption by plant stanol ester intake at 2 g/day and inhibition of cholesterol synthesis with pravastatin therapy (40 mg/day) in these patients did not significantly improve serum cholesterol concentrations, especially in patients with the highest serum cholesterol concentrations *(163)*. It was postulated that high baseline serum cholesterol concentrations, possible enhanced cholesterol absorption by statins as detected by increased cholesterol absorption markers, and reduced biliary secretion of plant sterols may be contributing factors to the lack of significant combined effects between plant stanol esters and statins in patients with heterozygous familial hypercholesterolemia *(163)*.

Maximum lowering of serum LDL concentrations appears to be achieved with plant stanol esters at 2 g/day; higher doses are unlikely to provide additional efficacy *(164)*. When considering statin therapy alone or in combination with stanols, doubling the statin dose would reduce serum LDL concentrations by an additional 6%, whereas a 10% reduction in LDL concentrations is achieved when statins are combined with stanols. Also, doubling the statin dose carries the risk of hepatic and muscle toxicity. Therefore, adding plant stanols to statin therapy appears a safer alternative *(159,160,164)*. A possible limiting factor to stanol efficacy alone is related to liver upregulation of its LDL receptor activity to increase LDL synthesis in response to decreased cholesterol levels in liver cells *(165)*. The magnitude of this compensatory effect remains unknown.

Because plant sterols are not water-soluble but dissolve better in fat, most clinical studies of sterol-containing foods have been brands of stanol-enriched margarine. However, patients with hypercholesterolemia commonly avoid using margarine products to limit their fat intake, and using stanol-containing margarine is not convenient when eating out at a restaurant. A placebo-controlled study evaluated the effect of a daily dispersible tablet formulation containing a 1.8 g dose of soy stanols on serum LDL cholesterol in 26 subjects who were already eating a heart-healthy diet and taking statin drugs. To help them dissolve in water and get to their targets in the intestines, stanols were combined with lecithin and compressed into the investigational tablet formulation. Following 9 weeks of therapy, study results showed that the addition of plant stanols in a tablet decreased serum LDL cholesterol concentrations by an additional 9.1% and serum total cholesterol by 12.2 mg/dL *(166)*.

Currently, a commercial product of plant stanol esters (Benecol®) is available in spreads (regular and light) and Chews. Benecol®spread is taken with meals in 2–3 daily servings (1 serving = 1 tablespoon = 0.85 g of plant stanol esters). Benecol®Chews are usually taken as two Chews twice daily with meals and snacks (1 Chew = 0.85 g of plant stanol esters). There are also several multi-ingredient products available as nutritional supplements that contain plant stanols and sterols. However, the exact quantities of ingredients in these products are less well defined. The overall efficacy of plant stanols and sterols on lowering serum cholesterol remains modest, especially with the associated compensatory increase in liver cholesterol synthesis *(165)*. Also, stanol-enriched diets do not appear to have any significant effects on lowering serum triglyceride concentrations *(167)*.

The relatively high cost of plant stanol and sterol products and the need to consume them several times daily make them less appealing to the consumer. However, data are emerging on the cost-effectiveness of dietary supplementation of plant stanol and sterols. A European study evaluated the cost-effectiveness in Euros per quality adjusted life years (€/QALY) of the daily intake of dietary plant stanol ester spread in combination with and without statin drugs in preventing coronary heart disease (CHD). This was based on conducting two meta-analyses of randomized, placebo-controlled clinical studies: one meta-analysis evaluated the reduction of total serum cholesterol concentrations with the use of stanol esters alone and another meta-analysis evaluated reduction of total serum cholesterol concentrations with the use of stanol ester spread in combination with statin therapy. Health-care data from Finland were used to determine age- and gender-specific CHD risk factors. Study results showed that regular use of plant stanol ester spreads alone (assuming consumption of 2 g stanol/day) and in combination with statins reduced serum total cholesterol concentrations by about 14 mg/dL and 15 mg/dL, respectively. Regular use of plant stanol ester spreads was found to be cost-effective in preventing CHD in adult males and older age women with total serum cholesterol concentrations $\geq$ 194 mg/dL. Based on the assumption that changes in serum cholesterol concentrations are converted to changes in the incidence of CHD events using the CHD risk equations, the base case cost (€/QALY) gained ranged from €7,436 to €20,999 in men and from €34,327 to €112,151 in women *(168)*.

6. CONCLUSIONS

6.1. Limitations of Current Data

Data on clinically beneficial drug–nutrient and drug–food interactions are scarce. Well-designed clinical studies of positive drug–nutrient interactions are few, and mainly focused on certain drugs and nutrients. A limitation to the available data on beneficial drug–food and drug–nutrient interactions is that many studies were performed in healthy individuals and/or with small sample size populations. Because disease states may alter the normal physiology of organ functions that ultimately affect drug and nutrient disposition, data from healthy subjects may not always be replicated in sick individuals.

6.2. Research Needs

The list of commonly recognized positive drug–nutrient and drug–food interactions that optimize drug effects is limited, considering the extensive number of drugs available and their potential interactions with various nutrients and foods. Future avenues should include research that focuses on identifying the potential benefits of nutrients that enhance therapeutic drug effect and prevent drug toxicity, determining the populations that may benefit from these positive interactions, and defining the appropriate nutrient intake and drug dosing to achieve the clinically desired beneficial effects. Prospective randomized controlled studies in patients with different disease states and consuming different nutrients are needed to further explore the arena of clinically beneficial drug–nutrient interactions.

6.3. Clinical Recommendations

Drug–nutrient and drug–food interactions can cause increased or decreased drug effects. Beneficial drug–nutrient and drug–food interactions can enhance therapeutic drug effect and reduce or prevent drug toxicity. Clinicians should be aware of these positive drug–nutrient and drug–food interactions and should apply them to patient-specific clinical conditions when clinically indicated. Clinicians should also counsel patients about the appropriate nutrient or food intake to improve the safety and efficacy of drug therapy.

DISCUSSION POINTS

Drug–nutrient and drug–food interactions are often the result of physical and chemical interactions between drugs and nutrients.

- Discuss the factors that can influence drug–nutrient and drug–food interactions.
- Discuss the mechanisms of positive drug–nutrient and drug–food interactions.

Positive drug–nutrient interactions can improve serum drug concentrations, enhance therapeutic drug effects, or reduce or prevent adverse drug events.

- Discuss which nutrients can have a positive influence on drug effects.
- Discuss how nutrients can reduce drug toxicity.

Certain foods can enhance the absorption of certain drugs.

- Discuss how a fatty meal can affect the absorption of certain drugs to enhance their therapeutic effect.

Several of the antiretroviral drugs should be administered with food.

- Discuss the advantages of administering these antiretroviral drugs with food.

Plant stanols and sterols have been used in patients with hypercholesterolemia.

- Discuss the differences, including advantages and disadvantages, of plant stanols vs. plant sterols for the management of hypercholesterolemia.
- Discuss the rationale behind using plant stanols in combination with statin therapy.

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12 Interaction of Natural Products with Medication and Nutrients

Lingtak-Neander Chan

Objectives

- Discuss the current regulations concerning the manufacturing and marketing of dietary supplements in the United States.
- Discuss the prevalence of dietary supplement use.
- Describe the most common dietary supplements with a potential for having an interaction with a medication based on the current clinical and scientific literature

Key Words: Dietary supplement; dynamic; herbal; kinetic; natural product

1. BACKGROUND

Driven by the desire to prevent certain illnesses and the belief that supplementation of vitamins, herbal remedies, or other natural products is an effective means to achieve good health, the interest and the demand by the public on the use of dietary supplements have continued to rise over the past decade. According to the figures published in 2007, the U.S. dietary supplement industry is a $22.5 billion annual business, on a sales volume that has quintupled since 1994 when the Dietary Supplement Health and Education Act (DSHEA) was first signed into law *(1)*. Dietary supplements come in a variety of dosage forms, such as tablets, capsules, powders, energy bars, or beverages. With the relatively open regulation, today's dietary supplements include not only nutrient derivatives (i.e., vitamins, minerals, amino acids) but also substances such as herbs, botanical extracts, hormones, and enzymes that may not be part of the regular human diet. Many of these compounds may have disease-modifying and pharmacological activities. This suggests the potential for interactions with other therapeutic agents which may lead to adverse clinical outcomes. For the purpose of this chapter, only the term *dietary supplement* will be used in preference to the term natural health product.

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1.1. Definition of Dietary Supplements

According to DSHEA, which amended the Food, Drug, and Cosmetic Act, a dietary supplement is *(2)* "…a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, mineral, herbs or other botanicals, amino acids, a dietary substance used by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any ingredient described above; and intended for ingestion in the form of a capsule, powder, soft gel, or gel cap, and not represented as a conventional food or as sole item of a meal or diet."

The DSHEA was enacted in 1994 and changed the framework for regulating dietary supplements as a unique entity. The stimulus for the change was the response to the public's desire and demand, in that many people considered these products beneficial to their health. Although the intent was to increase the availability of – and information about – these products, in effect, this act eliminated the premarket safety evaluations for dietary supplements. Under this act and the regulations currently in effect, dietary supplements are not required to undergo the rigorous testing for safety and efficacy before being marketed, including identification of interactions, which is currently required of all prescription medication. The U.S. Food and Drug Administration (FDA) regulatory framework leaves the manufacturer responsible for maintaining data supporting any product claims in the labeling. The FDA's postmarketing responsibilities include monitoring safety, through voluntary dietary supplement adverse event reporting, and overseeing product information, such as labeling, claims, package inserts, and accompanying literature. The Federal Trade Commission regulates dietary supplement advertising. Thus, the DSHEA places the burden of proof on the FDA if it wishes to take any regulatory action against a supplement. The government must show that the supplement presents a "significant or unreasonable risk of illness or injury" under the conditions recommended or suggested in labeling (or under ordinary conditions of use if the labeling is silent). The DSHEA's regulatory framework, unlike the system involved in drug regulation requiring extensive premarketing evaluation of safety and efficacy, is primarily a "postmarket" program similar to the bulk of food regulation.

While the goal to ease the access of dietary supplements to the public is achieved by DSHEA, product safety and false claims have become the primary concerns for both consumers and clinicians. Reports such as the deaths linking the use of ephedra-containing supplements in athletes highlight potential dangers associated with dietary supplements *(3–8)*. In addition, product contamination is increasingly becoming a concern since many dietary supplements contain ingredients grown or manufactured overseas *(9–11)*. Currently, overseas facilities that manufacture, process, pack, or hold the ingredients for the dietary supplements marketed in the United States are only required to register their facility with the FDA. The manufacturing process and the conditions for storage and packaging are not subject to routine inspection and approval prior to the marketing of the products *(12)*.

Some of these concerns have been partially addressed by the recent amendments and new laws. The passage of the Dietary Supplement and Nonprescription Drug Consumer Protection Act in December 2007, which amends the Federal Food, Drug, and Cosmetic Act with respect to serious adverse event reporting for dietary supplements and nonprescription drugs, is one of the few steps aimed toward improving safety *(13)*. The Act requires the manufacturers of dietary supplements to notify the FDA about serious adverse events related to their products. It also requires manufacturers to include contact information, either in the form of a telephone number or address on the product label, for the consumers to contact the manufacturer with questions and complaints. In addition, the final rule on the current good manufacturing practices (cGMP) for dietary supplements issued by the FDA has been in effect since June 2008 *(14)*. Under the cGMP rule, manufacturers are required to:

- Employ qualified employees and supervisors;
- Design and construct their physical plant in a manner to protect dietary ingredients and dietary supplements from becoming adulterated during manufacturing, packaging, labeling, and holding;
- Use equipment and utensils that are of appropriate design, construction, and workmanship for the intended use;
- Establish and use master manufacturing and batch production records;
- Establish procedures for quality control operations;
- Hold and distribute dietary supplements and materials used to manufacture dietary supplements under appropriate conditions of temperature, humidity, light, and sanitation so that the quality of the dietary supplement is not affected;
- Keep a written record of each product complaint related to cGMPs; and
- Retain records for 1 year past the shelf life date, if shelf life dating is used, or 2 years beyond the date of distribution of the last batch of dietary supplements associated with those records.

Undoubtedly, these changes reflect only the initial steps to increase public safety regarding the use of dietary supplements while maintaining their ease of access by the public. Nevertheless, the effectiveness and the adequacy of these measures remain highly debated among legislators, health advocates, and practitioners.

1.2. Prevalence of Dietary Supplement Use

As a result of the DSHEA, use and sales of dietary supplements in the United States have increased dramatically. The results of a survey of Americans conducted in 1999 showed that at least 9.6% of the responders have turned to herbal medicine as a form of alternative medicine second only to prayer *(15)*. The belief that taking dietary supplements is an effective way to maintain good health and prevent health problems has further increased the widespread use and overall sales of these products. Data published in 2005 showed that 74% of the responders to a survey believed vitamin and mineral supplementation are effective in disease prevention. Close to 70% of the responders use dietary supplements with the intention of improving their existing health problems. Among people who use dietary supplements for specific purposes, arthritis/joint pain is the leading health condition *(16,17)*. Other common preexisting conditions include osteoporosis, frequent cold and flu, lack of energy, menopause issues, memory problems, gastrointestinal disturbances, overweight, and depression *(17,18)*. In terms of sales volume, condition-specific supplements with a claim for sports/energy/weight loss had a highest sales volume according to the data in 2005, whereas products with a claim for cancer prevention had the highest increase in sales volume. According to market survey and the current trend, it is believed that products with an antioxidant claim on the labels will also experience a significant growth in market shares and sales volume *(17)*.

The use of dietary supplements is very common in the general population *(17,19)*. Among the most likely users of dietary supplements are middle-aged Caucasian women and the elderly with preexisting medical conditions or chronic diseases. Many of these individuals are taking at least one medication concurrently. Results from marketing surveys also suggest that the aging baby boomers are the most rapidly expanding group of consumers of dietary supplements *(17)*. Additionally, patients who have recovered from other serious illness are also very likely to use dietary supplements. Between 64 and 81% of cancer survivors report using any vitamin or mineral supplements and 26–77% report using any multivitamins *(17,20–25)*. With the widespread use of dietary supplements by the general public, especially among people who may be taking multiple prescription drugs for chronic illnesses, the potential for these patients experiencing drug–nutrient interactions is high and the resulting adverse reactions can be serious. The concern is substantiated by the findings from the studies conducted in different health clinics. For example, it is reported that approximately one-third of the anticoagulation clinic patients receiving chronic warfarin therapy use nonvitamin dietary supplements on a regular basis *(26)*. The number of patients using vitamin-containing supplements is believed to be much higher. The supplements most commonly used by these patients include glucosamine/chondroitin, omega-3 fatty acid/fish oil, cranberry extract, coenzyme Q10, and green tea extracts. Many of these supplements have been reported to interact with warfarin *(26–29)*. In another study aimed at assessing the most common clinically significant drug–nutrient interactions among patients using dietary supplements and prescription medications concurrently, the incidence of dietary supplement use was 40%. Out of the 710 dietary supplement users, a total of 369 potential interactions were identified among 236 patients. Twenty-nine percent of these interactions were classified as clinically significant and important interactions *(30)*. In a Medicare population consisting of 5052 participants, 14.4% combined the use of supplements with conventional drugs with as many as 1179 observed combinations having risk for an adverse interaction *(31)*. The incidence is much higher when the data are generalized to the population, although the usage is highly variable among different ethnic groups and the clinical significance of the interactions is more difficult to determine *(32–34)*. Likewise, a survey conducted in 979 preoperative patients undergoing anesthesia showed that 17.4% reported current use of herbal or selected dietary supplements *(35)*. In reality, the actual number of patients using dietary supplements may be underrepresented in these studies because not all patients readily report use of these products to their physicians and other health care providers. Additionally, patients tend to underreport use of these products on written questionnaires, and it is common that the medical team or primary care provider is unaware of the use of dietary supplements by patients *(36,37)*. Because such a large number of people are using dietary supplementation concomitantly with prescription medication, the stage is set for significant and potentially dangerous interactions that may result in serious complications and adverse events. When dietary supplement–drug interactions are encountered by health care providers, they are rarely reported *(38)*.

Ideally, classification and characterization of drug–nutrient interactions based on the mechanism of interaction would offer the most practical approach to identify and manage the interactions *(39)* (Table 1) (see Chapter 1). Unfortunately, the complexity of products, paucity of clinical trials, void of product standardization,

Table 1
Classification, Characterization, and Examples of Drug–Nutrient Interactions

Category	*Description*
Type I	Ex vivo bioinactivation
Type II	Absorption
IIA	Metabolism
IIB	Transport
IIC	Complexation
Type III	Physiologic disposition
Type IV	Elimination

Likely mechanisms of some reported drug–dietary supplement interactions:
Danshen – Type II interaction

- Enhanced theophylline oral absorption

Dong Quai – Type II or Type III interaction

- Increased anticoagulant effect of warfarin

Garlic – Type II interaction

- Decreased saquinavir and ritonavir (both protease inhibitors) absorption and increased clearance
- Increased anticoagulant effect of warfarin
- Increased hypoglycemic effect of chlorpropamide

Ginseng – possible Type III interaction

- Precipitated CNS side effects of phenelzine and benzodiazepines

Ginkgo – possible Type III interaction

- Counteract the antihypertensive effect of thiazide diuretics
- Increased anticoagulant effect of warfarin

Kava – possible Type III interaction

- Precipitated CNS side effects of alprazolam
- Affected efficacy of levodopa

St. John's Wort – Type IIA, IIB, and III interactions
Each oral itraconazole dosage form has specific indications *(41)*

- Immunosuppressive agents: Cyclosporine, tacrolimus
- Tyrosine kinase inhibitor: Imantinib
- Anticholesterol: Simvastatin
- Antihistamines: Fexofenadine
- Antifungal: Voriconazole
- Topoisomerase I inhibitor: Irinotecan
- Protease inhibitor: Indinavir
- Others: Digoxin, methadone, nefazodone, paroxetine, sertraline, theophylline, verapamil, warfarin

and lack of product dose reproducibility limit the ability to accurately delineate, characterize, and quantify these interactions *(39–40)*. Therefore, a specific recommendation regarding a particular drug–dietary supplement pair is rarely available. Most of the time, the practical approach toward drug–nutrient interaction includes a combination of conducting a thorough literature search, with careful review of the patient's clinical conditions and concurrent medications, and then exercising good clinical judgment. A suggested strategy is summarized in Table 2.

Table 2
Strategy in Approaching a Possible Interaction Between a Drug and a Dietary Supplement

1. Determine the possible symptoms associated with the object compound, which could be the drug or the dietary supplement (e.g., cardiovascular effects, elevated liver function tests, CNS disturbances, electrolyte abnormalities). Compare the patient's symptoms and clinical presentation to see if an interaction is plausible. If an interaction is likely, discontinue the compound that is responsible for the symptoms and provide supportive care if applicable.
2. Research the literature to determine if the potential interaction has been confirmed through clinical investigations. If yes, the likelihood of the interaction is high.
3. If no clinical investigation exists, determine if there is any published case report or letter regarding the interaction pair.
4. If neither clinical investigation nor case report can be found, consider researching the online registry or the FDA MedWatch program *(175)*.
5. If no existing report is available, determine whether a possible mechanism of interaction between the compounds exists.
6. Assessment tools such as Drug Interaction Probability Scale *(176)* can be used to determine whether a drug interaction is a likely explanation for the observe event.

2. SCIENTIFIC PRINCIPLES

2.1. Confounding Issues with Dietary Supplements

Unlike drugs, but more like conventional foods, premarketing clinical evaluations for safety and effectiveness for dietary supplements are not required by the FDA. This creates a concern that the quality and consistency of the products may vary among manufacturers, or even between two batches from the same manufacturer. Additionally, the labeling of these products may not reflect the actual ingredients present in the formulation. A wide array of compounds were found in the products ranging from undeclared pharmaceuticals such as ephedrine and chlorpheniramine, to toxic levels of heavy metals including lead and arsenic in some Asian patent medicinal products sold in California as dietary supplements *(40)*. A review of 25 commercially available ginseng preparations found that although the labeled plant products were in fact present in the preparation, the concentrations of these compounds differed from labeled amounts *(41)*. Also, a study of steroid-containing supplements found a disparity between the labeled amount of steroids in the product and the actual quantity within it. One product tested even contained testosterone, which is a class III controlled substance in the United States *(42)*. This inter- and intra-manufacturer variation limits not only the accuracy for clinicians to predict clinical response but also the accuracy and reliability to report and predict drug interactions with these supplements. More importantly, the questionable product purity and labeling accuracy further confounds health care professionals' ability to accurately identify and manage potential interactions and adverse reactions associated with FDA-approved medications. For example, a documented interaction between a supplement product and a medication may be the result of a poorly formulated product rather than the labeled active ingredient per se. These issues are unlikely to be changed unless further amendments to DSHEA take place.

2.2. *Observed and Reported Mechanism of Interactions*

Dietary supplements may interact with drugs through different mechanisms. Like other types of drug–drug interactions, dietary supplements may act as the precipitant agent and thus can affect the pharmacokinetics and pharmacodynamics of a medication (object drug). Pharmacokinetic interactions involve altering the absorption, distribution, and elimination of the drugs, whereas pharmacodynamic interactions affect the pharmacological or biological action of the drugs. A clinically significant pharmacokinetic interaction often leads to a pharmacodynamic interaction, although the reverse is not always true. For example, a supplement that inhibits the metabolism of warfarin (pharmacokinetic interaction) will likely increase the pharmacodynamic effect of warfarin, potentially increasing risk for bleeding. Nevertheless, a supplement may also increase bleeding risk without affecting warfarin pharmacokinetic through inhibition of platelet function. Some supplements may cause pharmacokinetic interactions with certain drugs but pharmacodynamic interactions with others. For instance, St. John's wort (SJW) increases the intestinal and hepatic metabolism of drugs such as carbamazepine and cyclosporine (pharmacokinetic interactions), whereas it interacts with tricyclic and some serotonergic antidepressants by potentiating their effect on the neurotransmitters (pharmacodynamic interactions).

2.3. *Quality of Data Available*

Because of the difficulties associated with studying herbal products, the literature currently available to classify these interactions is quite limited. Although some clinical pharmacokinetic and pharmacodynamic studies are available, the majority of the evidence consists mainly of case series and anecdotal reports. From the pharmacokinetic standpoint, dietary supplements can have profound effects on the absorption, distribution, elimination, or clearance of the object drug through metabolic inhibition or induction of specific enzymes and transporters. Mechanisms by which the absorption of a drug is changed by a dietary supplement include binding in the gastrointestinal tract and inhibition/induction of presystemic effect, which may include metabolism and transport of the drug in the intestinal epithelium and liver. Since these changes affect the oral bioavailability of the object drugs, only drugs that are administered orally or enterally are expected to be affected. A considerable number of dietary supplements have been identified as potent inhibitors of the cytochrome P450 (CYP) enzyme system, the most important phase I enzyme family responsible for the biotransformation of many biogenic amines, steroids, cholesterol, and most prescription drugs *(43–47)* (see Chapter 4). Some herbs and nutrient supplements also affect the functions of cell membrane transporters. For example, SJW induces intestinal P-glycoprotein (P-gp) *(48–52)*. P-gp is an adenosine-5'-triphospate (ATP)-dependent efflux pump encoded by the multidrug resistant-1 gene, which is located on chromosome 7. It belongs to the ATP-binding cassette transporter family and is highly expressed in the gastrointestinal tract, the renal tubule, the blood–brain barrier, the liver, and several other tissues (see Chapter 3). P-gp is highly expressed and functionally active in the intestinal epithelial tissues. Its primary function involves active transport of specific xenobiotics, drugs, chemicals, or even certain food substances that have already been absorbed by the epithelial cells back into the gut lumen *(53–57)*. This is an intrinsic defense mechanism of the human body to decrease the exposure to xenobiotics (in other words, "foreign" compounds). Many drugs, especially those with low oral bioavailability, are substrates of P-gp, and modulation of intestinal P-gp activity can directly alter their absorption. Cyclosporine, digoxin, most dihydropyridine calcium channel blockers, and a number of protease inhibitors are examples of P-gp substrates. Induction of P-gp by SJW can decrease the systemic absorption of digoxin leading to subtherapeutic serum concentrations and potentially treatment failure. SJW also induces CYP3A4, an enzyme responsible for the elimination of indinavir, a protease inhibitor *(47,58)*. This decreases the oral absorption and increases the metabolic elimination of indinavir potentially leading to treatment failure for human immunodeficiency virus (HIV). Some dietary supplements can also alter the elimination rate of a drug by interfering with its hepatic metabolism, biliary excretion and enterohepatic recirculation, or renal excretion. In these cases, both orally and parenterally administered drugs may be affected. Again, SJW is a classic example of a supplement that may interact with drugs administered both orally and parenterally. On the contrary, some supplements may interact with an object drug by potentiating their pharmacological effects on specific receptors. Therefore, dietary supplements can interact with a patient's medication regimen through multiple different mechanisms and may have a profound effect on the patient's treatment outcome. Clinicians should carefully review the literature and attempt to understand the mechanism of interaction whenever possible in order to optimize the clinical management of a patient with drug–nutrient interactions.

3. ESTABLISHED EVIDENCE

A recent study suggests that the most common dietary supplements with a potential for interaction include garlic, valerian, kava, ginkgo, SJW, glucosamine, and ginseng. The most common prescription medication classes with a potential for interaction are antithrombotic medications (e.g., warfarin), sedatives, antidepressant

Table 3
A list of dietary supplements capable of precipitating drug interactions

Alfalfa (*Medicago sativa*)	Echinacea
Aloe (*Aloe vera*)	Elder
Angelica sp. (e.g., Bai Zhi, Dong Quai)	Fenugreek
Arnica flower	Feverfew
Betel nut	Flaxseed
Boldo	Garcinia
Black cohosh	Garlic
Bromelain	Ginger
Caffeine (herbal caffeine)	Ginkgo
Camellia (e.g., green tea extract)	Ginseng
Capsicum	Grape seed extract
Cascara	Hawthorn
Cat's claw	Juniper
Chamomile	Kava
Chlorella	Lemon balm
Chondroitin	Licorice
Clover	Papaya extract
Cocoa	Quercetin
CoEnzyme Q10	Saw palmetto
Cranberry extract	St. John's wort
Danshen	Valerian
Devil's claw	Yohimbe

It is important to point out that many of these interactions are considered *possible* drug interactions as this is mostly a collection of case reports of adverse reactions associated with the use of these dietary supplements; in addition, the purity of the supplements in many of these anecdotal reports can neither be quantified nor be confirmed; clinicians should perform an updated search of the literature and relevant databases whenever a concern or suspicion of drug–dietary supplementation interaction arises *(177,178)*.

agents, and antidiabetic agents *(30)*. The mechanism of interactions for these commonly used supplements will be briefly discussed. Other potential drug–dietary supplement interactions are summarized in Table 3.

3.1. Garlic

Used for centuries as a flavoring ingredient in food, garlic is believed to carry many beneficial effects. In the ancient world, garlic had a variety of uses, including managing common ailments, headaches and body weakness, epilepsy, and even to clean the arteries *(59)*. This is very much in line with some of the more modern therapeutic indications for garlic, which include hypertension, hypercholesterolemia, atherosclerosis, to improve circulation, and even as a blood thinner *(60–62)*. The primary active component in garlic is thought to be allicin, which is only formed when garlic is crushed. Cooking or heating destroys the necessary enzymes for the formation of allicin. However, there still are a number of other components found within garlic products with potential activity.

In vitro data suggest that garlic may inhibit CYP2C9, CYP2C19, CYP2D6, and CYP3A isoenzymes *(63)*. In contrast, an in vivo study in nine healthy volunteers, which examined the chronic administration of garlic (greater than 3 weeks), showed that garlic decreased the systemic exposure and maximum concentrations of saquinavir, a protease inhibitor that is a known substrate of the CYP3A4 *(64)*. However, the exact mechanism of the decrease was unable to be determined from this trial. Furthermore, garlic had a bimodal effect on the serum concentrations of subjects tested. Six subjects showed a decreased saquinavir systemic exposure, measured by the area under the concentration–time curve (AUC) during treatment with garlic, which later returned to just below their baseline upon discontinuation of garlic. The AUC of the three other subjects was unchanged while on garlic, but dropped significantly after the discontinuation of garlic. The reason for this bimodal distribution in subjects was unable to be determined. Because the overall maximal plasma concentration ($C_{\max}$) and the AUC were decreased, the data imply that chronic ingestion of garlic may have an induction effect on CYP3A4 in the intestinal mucosa. However, because saquinavir is also a P-gp substrate, an effect on P-gp at this time cannot be ruled out. Another trial that evaluated the effect of a variety of herbal products, including garlic, on substrates of various different CYP isoenzymes in healthy volunteers found that garlic had no significant effect on the CYP3A4 isoenzyme but did indeed have an inhibitory effect on the CYP2E1 metabolic pathway *(65)*. Garlic inhibits the activity of CYP2E1, an enzyme responsible for the metabolism of many inhalation anesthetic agents, and to a lesser extent, acetaminophen and ethanol *(66–69)*. Therefore, it is possible that in patients who use garlic oil on a chronic basis, the dosing requirement of anesthetic agents for surgery may be decreased. The impact of garlic on other CYP enzymes appears to be much less, with clinically significant interactions involving drugs metabolized by CYP2D6 and CYP3A4 appearing less likely *(70)*.

Garlic can interact with antithrombotic drugs through pharmacodynamic mechanisms. It prevents platelet aggregation by suppressing cyclooxygenase activity and the formation of thromboxane A2. Garlic also suppresses the mobilization of intraplatelet calcium ions and increases cAMP and cGMP concentrations. Furthermore, garlic acts directly on the GPIIb/IIIa receptors and reduces the ability of platelets to bind to fibrinogen *(60)*. Collectively, all these mechanisms suggest that garlic inhibits platelet aggregation and may increase the risk of bleeding in patients taking antithrombotic drugs such as ticlopidine, clopidogrel, and warfarin.

3.2. Valerian

Supplements containing valerian are often marketed as a sleep aid, a sedative, an anxiolytic, and a gastrointestinal spasmolytic. Less common applications include muscular cramping, uterine cramping, and headache. Pharmacological studies suggest that valerian extracts affect γ-aminobutyric acid-type A ($\mathrm{GABA_A}$) receptors, with possible additional action on inducing the release of the inhibitory neurotransmitter GABA in the brain *(71–75)*. Based on in vitro data, valerian exhibits inhibitory effect on CYP3A4 *(76)*. Subsequent clinical data have shown that the inhibitory effect is likely not clinically significant. Data from clinical pharmacokinetic study suggest that valerian causes clinically insignificant changes to the activity of CYP1A2, CYP2D6, CYP2E1, and CYP3A4 *(77,78)*. Likewise, repeated administration of valerian (*Valeriana officinalis*) also has shown minimal effects on CYP3A4 activity and no effect on CYP2D6 activity in healthy volunteers *(78)*. Therefore, current knowledge suggests that the potential for valerian causing pharmacokinetic interactions with CYP substrates appears fairly low.

However, because of the action on the GABA receptor, valerian may cause pharmacodynamic interaction with other drugs that depress cognitive function. It may also synergize the sedative effect of other drugs. For example, valerian has been shown to prolong thiopental- and pentobarbital-induced sleep. It may be prudent to avoid concurrent use of valerian with sedative agents and antiepileptic agents.

3.3. Kava

Kava (*Piper methysticum*) is a large-leaved Pacific island plant in the pepper family. It has been marketed and promoted primarily as an anxiolytic agent. Other uses include insomnia, promotion of relaxation, and relief of menopausal symptoms *(79–81)*. The primary constituent of commercially available kava is a group of compounds belonging to the family of kavalactones *(82)*. Based on in vitro data, extracts of kava and several of the individual kavalactones are potent inhibitors of the CYP enzymes, which include CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 *(83)*. The clinical significance of kava on CYP inhibition is implicated by a published case report describing a man who developed coma after concurrent ingestion of kava and alprazolam, a known CYP3A4 substrate *(84)*. In addition to pharmacokinetic interactions via CYP enzyme system, pharmacodynamic interactions between kava and other drugs have also been reported. An increased duration and frequency of mental status deterioration has been suspected in cases involving a patient with Parkinson's disease taking levodopa and kava concurrently *(85–86)*. Dystonia and dyskinesia have been reported in patients using kava. The symptoms are reversed by an anticholinergic drug biperiden *(86)*. There is also evidence that kava may reversibly inhibit monoamine oxidase-B and platelet aggregation, whereas some kavalactones have demonstrated inhibitory effect of GABA receptors, sodium channels, and calcium ion channels *(87–92)*. Although the number of clinical investigations is limited, caution is warranted when kava is used in combination with drugs, particularly those metabolized by CYP3A4 or with psychotropic effects.

In 2002, many European countries suspended the sales of kava products following a series of reports describing serious hepatotoxicity with fatalities. The mechanism of hepatotoxicity remains highly debated. The extract of kava or the process to extract kava, not the herb itself, is the suspected cause for these adverse reactions *(93–103)*. In March 2002, the FDA issued a warning to health care providers regarding the potential risk of severe liver injury associated with the use of kava-containing dietary supplements *(104)*. Nevertheless, kava remains available for sale in the United States and is widely available for purchase over the Internet.

3.4. Ginkgo

Ginkgo is a popular herb that is derived from the dried leaves of *Ginkgo biloba* or maidenhair, a tree that is native to China, but can be cultivated in Europe, Asia, and

North America. Use of this herb dates back to the very beginnings of ancient Chinese medicine. Today, the herb is used for a variety of purposes including cognition, memory, cerebral vascular disease, peripheral vascular disease, and multiple sclerosis, to name a few. The active components of *Ginkgo biloba* are extracted from the leaves, which contain ginkgolides A, B, C, J, and M, and bilobalide *(105)*.

In terms of specific drug interactions with ginkgo, there are a number of case reports documenting possible interactions between ginkgo and the anticoagulants warfarin and aspirin *(106–107)*. In the reported cases, bleeding seems to be the most common result of the concomitant use of ginkgo with other anticoagulant agents. This reaction may in part be exacerbated by the fact that various ginkolides are capable of inhibiting platelet-activating factor *(108)*. There has been a number of case reports of ginkgo attributed to an increased risk of serious bleeding events *(109)*. It may be possible that the cumulative effects of ginkgo's inhibition of platelet-activating factor with other anticoagulants are responsible for the reaction. Because of the potential for ginkgo to increase the risk of bleeding, clinicians should recommend that patients avoid the use of this herb with any anticoagulant therapy or prior to any scheduled surgery.

Metabolically, there are conflicting results regarding the potential for ginkgo to affect CYP. *Gingko biloba* leaf extract has been shown to increase the absorption and pharmacodynamic effect of nifedipine, a CYP3A4 substrate *(110)*. However, a published trial examining ginkgo's effects on a number of different CYP substrates found that the herb had no significant effect on any of the CYP isoenzymes *(67)*. Likewise, no interactions between ginkgo extract and CYP2C9 substrates were observed in clinical investigation with healthy volunteers *(111)*. Therefore, it is not expected to alter the metabolism of warfarin. It is possible that different formulations of ginkgo with differing concentrations and combinations of phytochemicals might be responsible for the discrepancy. With current knowledge, it could be concluded that pharmacokinetic interactions attributable to ginkgo are not the result of phytochemical-mediated effects on CYP isoforms. Nevertheless, ginkgo did potentiate the bleeding time prolongation effect of cilostazol, a phosphodiesterase inhibitor with antiplatelet effects *(112)*. Caution should be exercised when ginkgo is used in patients receiving antithrombotic therapy, especially antiplatelet agents.

3.5. St. John's Wort

SJW is one of the most investigated and understood medicinal plants with regard to its potential and mechanism to cause specific interactions with prescription medications. Its scientific name is *Hypericum perforatum*. The name SJW exists because the bloom time of this plant coincides with the time of the feast of St. John the Baptist in June. This herb has been used for thousands of years topically for many ailments, including minor burns and wounds and in more recent times as an oral extract to treat mild depression. SJW is a perennial weed that can be found throughout Europe, Asia, North Africa, and in North America *(113–117)*. The product tends to be standardized in terms of its hypericin content, but as with other herbal products, there have been published reports of discrepancies between labeled content and actual content assayed *(118)*. In addition to hypericin, a number of its derivatives and metabolites, such as hyperforin, chlorogenic acid, and quercetin, may also contribute to its clinical effect.

The dramatic ability of SJW to alter the concentrations of concomitantly administered medications is thought to occur through two major mechanisms. First, SJW has the ability to induce intestinal transporter (e.g., P-gp) activity. Second, the herb can increase the activity of CYP3A4 and CYP2B6 through pregnane X receptor activation *(67,119–125)*. CYP3A4 is an enzyme responsible for the metabolism of a majority of prescription agents, and its induction has important clinical implications. Although CYP2B6 activity is also increased by hyperforin, there are very few medications identified to be CYP2B6 substrates. Therefore, the clinical relevance of CYP2B6 induction remains to be determined. In the human small intestine, CYP3A4 and P-gp function as a coupled system to reduce xenobiotic exposures by the host. This coupling system has the most significant influence on the absorption of substances that are substrates of both CYP3A4 and P-gp. Drug molecules that "escape" the initial extraction by the intestinal CYP3A4 enzymes and are absorbed into the epithelial cells can be excreted back into the gut lumen by P-gp, potentially reexposing them to gut-wall metabolism multiple times. Induction of both P-gp and CYP3A4 by SJW may lead to a dramatic reduction in oral bioavailability of drugs and can have grave implications for narrow therapeutic index agents. Decreased oral absorption may lead to subtherapeutic serum concentrations of medicinal agents resulting in treatment failure.

Even the induction of CYP3A4 alone may have grave complications for narrow therapeutic index agents. SJW may cause up to a sixfold induction of CYP3A4 activity. CYP3A4 is the most important phase I oxidative enzyme in humans accounting for the metabolism of more than 50% of prescription drugs currently used. CYP3A4 is ubiquitous with the most significant concentrations found in a variety of tissues including the liver and intestinal epithelium *(126)*. However, in terms of drug metabolism, the most significant locale for CYP3A4 is the liver and intestine. An induction of CYP3A4 in the intestinal epithelium can increase the presystemic metabolism of medicinal agents preventing their absorption. This can lead to an overall decrease in the total bioavailability of an orally administered agent. Also, an induction of CYP3A4 in the liver will increase the systemic elimination of medicinal agents primarily metabolized by this enzyme system. This could lead to a decrease in the systemic exposure of the agent and potentially lost efficacy. Like P-gp, this effect is especially true for narrow therapeutic index agents.

In addition to pharmacokinetic studies, a number of clinical trials and case reports have corroborated the interaction between SJW and prescription medication with a narrow therapeutic index that is substrate for P-gp, CYP3A4, or both. Several studies have demonstrated a positive pharmacokinetic interaction between oral contraceptive agents and SJW, although the significance of pharmacodynamic effects, especially on the contraceptive efficacy of the newer, more potent hormones, remains controversial *(127–130)*. All these results confirm that SJW has a strong potential to alter therapeutic effects and drug concentrations. The alteration in therapeutic concentrations in some cases potentially has very deleterious and dangerous consequences for affected patients. For example, a decrease in the therapeutic concentrations of indinavir, a protease inhibitor used in the treatment of HIV disease, may lead to an increase in HIV viral load or viral resistance indicating treatment failure. Additionally, subtherapeutic concentrations of cyclosporine or tacrolimus, medications used by organ transplant recipients to prevent rejection, can lead to organ rejection and significant morbidity or even mortality for these patients.

Because of the potential for SJW to induce P-gp and CYP3A4, it is probably prudent to avoid using SJW in patients treated with prescription medications that are substrates of these two systems. Most importantly, it would be imperative to avoid narrow therapeutic index agents transported by P-gp or metabolized by CYP3A4 in order to avoid a dangerous interaction. Patients should be carefully counseled about the potential risks of initiating therapy with SJW, and health care professionals should be vigilant about the potential risks associated with this herbal product.

Outside the realm of pharmacokinetic interactions, SJW may also interact with a number of medications based on pharmacodynamic properties. The agents that are particularly at risk for causing this type of reaction are antidepressants, including selective serotonin reuptake inhibitors (SSRIs), namely paroxetine and sertraline, and agents such as trazodone or nefazodone. There have been a number of cases of the combination of these agents with SJW causing symptoms consistent with that of excess serotonin or serotonin syndrome *(131,132)*. This reaction is thought to occur because of hyperforin, a component of SJW that may inhibit the reuptake of serotonin. This, in combination with a prescription SSRI or other prescription agent that inhibits the reuptake of serotonin, may have an additive effect and predispose one to the serotonin syndrome. The potential for dangerous complications owing to serotonin syndrome cannot be understated, and deaths have occurred as a result of this syndrome. Patients who are currently being treated with SSRIs or other antidepressants that increase the concentrations of serotonin should be warned of this potential interaction and should be advised not to use SJW with these prescription medications.

3.6. Glucosamine/Chrondoitin

Glucosamine and chondroitin sulfate are the most widely used dietary supplements for osteoarthritis and joint disorders with estimated sales around $730 million in 2004 *(133–136)*. Glucosamine is an amino monosaccharide, which participates in the constitution of glycosaminoglycans such as chondroitin. Chondroitin, an extracellular polysaccharide, is an important structural component of cartilage *(137,138)*. Despite showing limited efficacy in a multicenter, double-blind, placebo trial glucosamine hydrochloride or sulfate continues to be widely used as a supplement for joint health either alone or together with chondroitin sulfate *(139,140)*. In addition, glucosamine-supplemented food products (e.g., glucosamine-enhanced orange juice) are also available in the United States. Glucosamine is approved as a prescription drug for the treatment of osteoarthritis by regulatory agencies in Europe.

A large number of reports have implicated a potential interaction between warfarin and glucosamine with or without chondroitin sulfate. In patients who have been stabilized on chronic warfarin therapy, the addition of glucosamine can increase the international normalized ratio (INR) value, in some cases up to two times the baseline value *(141–144)*. This would significantly increase the risk of bleeding. The mechanism of this interaction has not been elucidated. The onset of the interaction is usually within a few weeks after initiation of glucosamine/chondroitin therapy. Upon discontinuation of the supplement, the patient's INR returns to baseline and remains stable with the presupplementation warfarin doses. Therefore, it is advisable for patients receiving chronic warfarin therapy to use alternative agents for joint pain. If the patient or care provider chooses to use glucosamine, close monitoring of INR, especially in the first 4 weeks after initiation of glucosamine, is necessary to minimize the risk of bleeding from excessive anticoagulation.

3.7. Ginseng

Ginseng is one of the most popular herbal supplements in the United States. There are a number of different species of ginseng. However, the most studied forms of ginseng include just three species: *Panax ginseng* (Asian ginseng), *Panax quinquefolius* (American ginseng), and *Panax japonicus*(Japanese ginseng) *(145)*. These species can be found in many dosage forms including alcoholic extracts, fresh root, teas, capsules, and in combination products with other mineral, vitamin, and herbal ingredients *(146)*. Ginseng has been used therapeutically for thousands of years in Asia for a variety of illnesses and ailments. Some of these uses vary from more traditional ones (e.g., increase general well-being) to now include use to improve vitality, immune function, cognitive function, cardiovascular function, physical performance, sexual performance, and even the treatment of cancer *(147)*. Compounds known as the ginsenosides are thought to be responsible for the therapeutic activity of ginseng. However, because of the complexity of actions of these compounds as well as the activity of non-ginsenoside compounds contained within the herb, the overall activity of the herb is very complex *(145)*. The potential interactions with prescription medication are even less well understood. Reports of an interaction between ginseng and the oral anticoagulant agent warfarin exist *(148)*. A 74-year-old man with a mechanical heart valve was being anticoagulated with warfarin with an INR value within the therapeutic range for more than 5 years before deciding to begin taking ginseng capsules. All of his other medications and diet remained the same. Two weeks after taking the ginseng capsules, the patient's INR dropped to a subtherapeutic level. On discontinuation of the ginseng product, the patient's INR returned to the therapeutic level and continued to remain within the therapeutic range. Doses of warfarin were not adjusted. An animal study examining the interaction with warfarin and ginseng found conflicting results *(149)*. Several studies have shown that ginseng affects CYP2C9, resulting in altered clinical effect of warfarin *(150–154)*. These reports suggest that the use of ginseng supplements should be discouraged in patients on warfarin therapy.

Similar to the cases of warfarin and ginseng, the human experience with an interaction between ginseng and phenelzine is only documented in case report form. Phenelzine is a monoamine oxidase inhibitor with many known food and drug interactions. It is used for the treatment of depression. In the cases reported, upon addition of ginseng products to therapy with phenelzine, patients developed tremulousness, headache, and sleeplessness. The symptoms improved with discontinuation of the ginseng. While still being treated with phenelzine, one of these patients was inadvertently rechallenged with ginseng many years later and experienced similar results *(155–157)*.

A case report by Becker suggested that a ginseng product containing germanium may decrease the diuretic effect of furosemide. However, it is important to point out that exposure to germanium, a heavy metal, may itself lead to renal failure. It is, therefore, unclear, based on this case report, whether a true drug–herb interaction was present *(158)*.

3.8. Other Emerging Drug Interactions with Dietary Supplements

Although it is well known that a number of drugs have the potential to cause hypovitaminosis, it is less appreciated that dietary supplementation with vitamins may affect drug disposition. Other nutrients may also interact with drugs—altering absorption, metabolism, and pharmacodynamic effects. Unfortunately, most of the data are obtained from case reports, including single patients and animal models, or from in vitro investigations. The two better documented vitamins include folic acid and vitamin E (α-tocopherol).

It has been established that patients receiving chronic therapy with phenytoin carry a 50% risk of folate deficiency. Ironically, supplementation of 1 mg/d folic acid may lead to a significant decrease in serum phenytoin concentrations in 15–50% of the patients. This interaction between folic acid and phenytoin (see Chapters 17 and 18) may involve the bilateral interdependent transport and possible metabolic processes *(159)*. Although the exact mechanism is unknown, pharmacokinetic analysis of phenytoin suggests that folic acid may increase the affinity of the metabolic enzyme(s) involved in the elimination of the phenytoin without causing overall enzymatic induction *(160)*. Although it is important to monitor for any signs of folic acid deficiency (such as megaloblastic anemia) in patients receiving long-term phenytoin therapy, it is as important to closely follow their serum phenytoin concentration should folate supplementation be deemed necessary in order to avoid breakthrough seizures secondary to subtherapeutic serum phenytoin concentrations.

The mechanism of Vitamin E interactions with drugs is of particular interest. The enhanced oral absorption of cyclosporine by water-soluble vitamin E was first reported in pediatric patients after liver transplantation *(161,162)*. Subsequently, a more formal observation trial took place in liver transplant recipients. In 26 patients who failed to achieve therapeutic blood cyclosporine concentrations despite prolonged intravenous administration or provision of daily oral cyclosporine doses higher than the normally recommended range (>10 mg/kg/d for adults and >30 mg/kg/d for children), concurrent administration of 6.25 IU/kg of vitamin E liquid (*d*-α-tocopheryl-polyethylene-glycol-1000 succinate [TPGS]) before each oral dose of cyclosporine led to a significant improvement in cyclosporine absorption. TPGS coadministration resulted in a reduction of daily cyclosporine dose by 28.3% in 19 adult patients and 31.7% in 7 pediatric patients. Steady-state, whole-blood cyclosporine trough concentrations were all significantly increased. Patients who previously required intravenous administration of cyclosporine were all successfully converted to oral therapy *(163)*.

Although it was initially thought that TPGS acted as a vehicle to allow lipophilic drugs, such as cyclosporine, to be more readily absorbed, subsequent investigations showed that TPGS is a P-gp inhibitor *(164,165)*. This mechanism implies that coadministration of vitamin E liquid may increase the absorption of a significant number of drugs. Vitamin E capsule (α-tocopheryl acetate) has not been shown to cause similar drug interactions *(166)*. It is reasonable to conclude, however, that vitamin supplementation may not appear to be completely without risks.

Omega-3 fatty acid supplements from fish oil have also been implicated to increase the risk of bleeding in patients taking warfarin *(167–169)*. The mechanism has not been determined. Iron repletion in iron-deficient patients with chronic renal failure receiving hemodialysis may also lead to an overall increase in CYP3A4 activity *(170)*.

4. SUMMARY

The area of dietary supplements is a growing topic of interest within the public and the medical community. Dietary supplement use has continually increased over the last decade. With the high health care costs and the public desire to maintain better health, it is expected that this trend will continue in the coming years. While the supportive evidence linking the regular use of dietary supplements and clinical benefits is generally lacking, the potential risks associated with these products cannot be overlooked. Many suspected drug interactions between dietary supplements and drugs have been reported in the literature. The mechanisms of some of these interactions have been determined and confirmed with scientific methods which allow clinicians to better predict the significance of potential interactions. Clinicians should also be reminded that the knowledge in this area is also greatly limited by publication bias toward reports with positive interactions (e.g., the change in pharmacodynamic or clinical effect with the use of dietary supplements). Until recently, reports concerning the absence of an interaction between two compounds (i.e., negative interactions) are rarely written by clinicians or accepted for publication *(171–173)*. Nevertheless, the quality of the data often remains questionable since the purity of the products cannot be ensured, and much knowledge has yet to be gained through continued research. Screening tools may be able to help predict metabolic interactions *(174)*. From the practice standpoint, clinicians can also help advance the knowledge in this area by reporting suspected and observed interactions and adverse reactions *(175,176)* through public databases such as the MedWatch program (www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm), the ClotCare International Registry of Interactions Between Oral Anticoagulants and Dietary Supplements online registry (www.clotcare.com), and the medical and scientific literature.

DISCUSSION POINTS

1. Are manufacturers of dietary supplements required by law to submit proof of product safety to the FDA before a new dietary supplement product is being marketed in the United States, even if the product is manufactured outside the United States?	No. Under DSHEA, proof of product safety is not required before a dietary supplement is marketed, even if the ingredients and the manufacturing process are outside the United States. The manufacturing facility, however, has to be registered with the FDA.
2. Are medically indigent individuals more likely to use dietary supplements than an individual with insurance coverage?	It has been reported that over 30% of the medical indigent individuals with multiple medication conditions use dietary supplement. But it is not known whether medical indigence is an independent factor for increased dietary supplement use. It is possible that the relative usage of dietary supplements is actually lower in indigent patients than those who have prescription drug insurance coverage because these products are not inexpensive. The demographic of the routine dietary supplement users (i.e., educated individuals and cancer patients) also appears to suggest that medical indigence may not be an independent factor for dietary supplement use.
3. Where can consumers or clinicians find information concerning the potency and purity of a particular brand or lot of dietary supplement?	Currently, the law does not require dietary supplement manufacturers to provide a record on file, either in the public domain or government offices regarding the purity and potency of any of their dietary supplement product. The most likely channel to obtain such information is through the product manufacturer.
4. SJW is known to increase the metabolism and clearance of many drugs. How long does it usually take for the induction effect to subside metabolism of other drug?	Pharmacokinetic studies suggest that it takes at least 2 weeks after the discontinuation of SJW for the activity of the induced drug metabolism enzymes to return to the pre-SJW state.

5. I suspect that a drug–nutrient interaction has occurred in a patient. But I cannot find any published research or clinical report regarding this suspected interaction. What should I do?	The most important step is to assess whether an adverse event has/will likely occur. If so, determine if there is any action that can be taken to improve/restore the effect of the object drug. Discontinuation of the supplement is highly recommended unless the risks of discontinuation outweigh the benefits. Closely monitor the clinical effects of the object drug. Because the research in this area is very limited and drug–nutrient interactions are often under-reported, the absence of any published evidence does not imply the evidence of absence. Good clinical judgment must be exercised in reviewing every case of possible drug–nutrient interactions. If the suspicion is high, the case should be reported to the government agencies or the literature.

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13

Drug–Nutrient Interactions in Patients Receiving Enteral Nutrition

Carol J. Rollins

Objectives

- Describe enteral nutrition and discuss its indications, routes of administration, administration regimens, and safety issues.
- Define different classes of interactions that can occur between enteral nutrition and medication – including those that are specific to administration, formulation, drug, or disease.
- Describe appropriate medication administration in the patient receiving enteral nutrition therapy.

Key Words: Compatibility; enteral nutrition; feeding tube; pharmaceutical; stability

1. INTRODUCTION

Malnourished patients and those at risk of malnutrition are candidates for nutrition intervention. This includes previously well-nourished patients who have been or will be without oral intake for 3–5 days (pediatric populations) or 5–10 days (adults). Enteral nutrition (EN), which is synonymous with tube feeding, should be considered when a patient cannot, will not, or should not consume appropriate quantities of nutrients by mouth to prevent malnutrition. There are few absolute contraindications to tube feeding other than a bowel obstruction that cannot be bypassed. However, conditions such as diffuse peritonitis, intractable vomiting, intractable diarrhea, and ischemia of the small bowel may be contraindications to EN therapy *(1)*. Most other conditions allow at least some nutrients to be delivered enterally.

Advances in enteral formulas and tube placement techniques over the past two decades allow full nutrition therapy via EN today, where parenteral nutrition was previously the norm (e.g., patients with pancreatitis). Some patients tolerate only partial EN therapy and require both EN and parenteral nutrition to achieve full support. Other patients require EN as a supplement to inadequate oral intake. Once

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EN is started, it is most often continued until the patient is able to meet their nutrient requirements by mouth. Thus, EN therapy is relatively common in the hospital setting, "step-down" facilities for rehabilitation or skilled nursing care, and other patient care facilities. A large population also receives home enteral nutrition (HEN). In 1992, it was estimated that 152,000 people received HEN therapy *(2)*. The number is estimated to be much greater today although there is no centralized data collection that allows accurate determination of the number of HEN patients.

As the population of patients receiving EN in various settings grows, the potential for interactions between drugs and EN increases. The interaction can involve components of the EN formula or administration techniques. Such drug–nutrient interactions have the potential to adversely affect patient outcomes when feeding tubes occlude, inadequate drug is absorbed, or nutrient provision is compromised. To understand the potential for drug–nutrient interactions in patients receiving EN therapy, it is first necessary to have a basic understanding of EN. This chapter provides a brief overview of EN, then reviews available data, discusses problems in extrapolating available data to current practice, and provides recommendations for managing drug–nutrient interactions in patients receiving EN therapy.

2. REVIEW OF ENTERAL NUTRITION BASICS

2.1. Tube Placement

EN therapy is characterized by both the route of tube placement and the site of feeding. Tubes can be placed through the nares or by ostomy formation. The route of tube placement per se is unlikely to influence drug–nutrient interactions in patients receiving EN therapy. Tube size and length, however, may be determined by the route of placement, and these characteristics in turn can affect the risk of tube occlusion when drugs are administered via the tube. Nasal placement requires that a long, small-bore tube be passed through the nares, pharynx, and esophagus. Tubes are described by both length (cm) and diameter (French units, with 1 Fr = 0.33 mm). Tubes used in adults are typically 8–10 French (Fr); pediatric tubes may be as small as 2 Fr for young children. Polyurethane is the preferred material for nasal tubes. These tubes remain soft and flexible when exposed to gastric acid rather than becoming brittle as do polyethylene or polyvinyl chloride tubes. Polyurethane tubes are less likely to collapse when aspiration is attempted and less likely to occlude than silicone tubes due to their larger internal diameter for a given Fr size. In general, the risk of tube occlusion decreases with increasing internal tube diameter regardless of the tube material and with increasing external diameter (i.e., Fr size) for a specified feeding tube material. Patients expected to require EN for a short duration of time are most appropriate for nasal placement of the tube. Bedside techniques are generally effective for tube placement through the nares, although radiological guidance may be necessary in some patients.

Feeding ostomies (i.e., enterostomies) are reserved for patients requiring long-term EN therapy. The definition of "long term" ranges from a minimum of 4 weeks to at least 6 months duration for EN therapy depending on specific patient characteristics, the type of enterostomy, and physician preferences *(3)*. Percutaneous techniques using endoscopy or radiography (fluoroscopy, ultrasound, or computed tomography [CT]) and surgical procedures are available for enterostomy formation. Passage of an endoscope into the stomach or small bowel and transillumination to the skin surface are required to perform endoscopic enterostomy techniques. Conditions precluding endoscopic enterostomy include morbid obesity, peritoneal dialysis, hepatomegaly, and portal hypertension *(4)*. Massive ascites, coagulopathy, and a history of Crohn's disease or radiation enteritis (i.e., patients at high risk of enterocutaneous fistula formation) hinder enterostomy formation by any method, percutaneous or surgical. Percutaneous enterostomies are generally favored in patients who do not require laparotomy for another purpose since general anesthesia is not required for percutaneous procedures. Tubes used for enterostomies vary from 5 Fr to 28 Fr depending on the type of tube and site of placement. Percutaneous endoscopic gastrostomy (PEG) and surgical gastrostomy tubes are the largest; needle catheter jejunostomy tubes and those used in infants are the smallest. Most tubes used today for needle catheter jejunostomies are at least 7 Fr or 8 Fr to reduce the risk of tube occlusion. To avoid jejunal obstruction, jejunostomy tube size is generally a maximum of 16 Fr in adults. Tubes used in children vary considerably in size based on the child's weight and the type of tube. Most of the tubes used for young children are quite small and more prone to occlusion than tubes used for adolescents and adults. Silicone is the preferred material in tubes designed for feeding ostomies, but red rubber tubes and Foley catheters made of latex continue to be used (though not recommended) for replacement tubes in enterostomies. Ease and safety of tube replacement depend on the exact procedure used for initial tube placement and the time since tube placement. Needle catheter jejunostomy tubes generally require laparotomy for placement and for replacement, if an occlusion occurs that cannot be reversed. Gastrostomy tubes placed through a stoma (e.g., Janeway gastrostomy) are easily removed and replaced.

2.2. Site of Feeding

The name of a feeding tube indicates both the proximal route of placement (i.e., nasal or ostomy) and the distal site of feeding. Location of the tube's distal tip determines the site of feeding – gastric, duodenal, or jejunal. Tube placement into the stomach is easier than into the small bowel with either nasal or enterostomy techniques. Gastric feeding is considered more physiologic than post-pyloric (i.e., duodenal or jejunal) feeding since most normal gastrointestinal (GI) functions, except those of the mouth and esophagus, are utilized. However, post-pyloric feeding is generally more appropriate for patients with gastric dysfunction (e.g., gastroparesis, gastric atony) and when minimal pancreatic stimulation is desired (e.g., pancreatitis). Post-pyloric tube placement may facilitate early postoperative enteral feeding since the small bowel regains function more quickly after surgery than the stomach. For patients at risk of aspiration, including those with poor gag reflex, neurological injury, or delayed gastric emptying and those on mechanical ventilation, post-pyloric feeding is suggested since this may reduce the risk of aspiration *(1,5,6)*. However, most studies have failed to show a difference in the incidence of aspiration between gastric and post-pyloric feeding, although the post-pyloric location may play a role in aspiration risk *(7,8)*. EN formula from nasoduodenal feeding and the tubes themselves can migrate back into the stomach from a position just beyond the pylorus. Formula and tubes placed past the ligament of Treitz (i.e., jejunal placement) are much less likely to migrate into the stomach. The site of feeding is an important consideration for drug–nutrient interactions in patients receiving EN when the feeding tube is used for drug administration.

2.3. Administration Regimens for Enteral Feeding

The administration regimen selected for EN therapy depends on the site of feeding, patient tolerance to feeding volume, and fluid requirements. The regimen includes the method of administration as well as the flush volume and frequency necessary to provide adequate fluids. Gastric feeding offers more options for formula administration than post-pyloric feeding. There are four general administration methods: continuous, cyclic, intermittent, and bolus. Continuous administration and cyclic administration are used for both gastric and post-pyloric feeding, while intermittent and bolus regimens are reserved for gastric feeding. Continuous infusion is the most common administration method for hospitalized patients. The consistent rate of infusion over 24 h minimizes the volume of formula per hour and may reduce the risk of feeding intolerance. Patients receiving post-pyloric feeding are particularly prone to feeding intolerance with high infusion rates and/or fluctuations in rate or volume of feeding. Intolerance generally manifests as abdominal pain and cramping with or without diarrhea. The small bowel gradually adapts to larger volumes thereby allowing transition to a cyclic regimen for many HEN patients with post-pyloric feeding tubes. Patients receiving gastric feeding can generally transition from continuous administration to a cyclic regimen faster than those receiving post-pyloric feeding and with less risk of intolerance. Cyclic regimens are convenient for many HEN patients since formula infuses at a constant rate but for less than 24 h per day. A typical cyclic regimen infuses for 8–12 h at night so the patient is not encumbered by feeding during daytime hours when they are most likely to be active. Intermittent administration and bolus administration provide EN formula in a pattern similar to that of meals, with a few to several discrete feedings daily depending on tolerance to volume. The volume provided per feeding is considerably higher than the hourly rate for continuous administration or cyclic regimens; therefore, the intermittent and bolus regimens are rarely tolerated by patients with post-pyloric feeding tubes. The major difference between intermittent and bolus feeding is the rate of administration. Intermittent feedings are infused over 30–60 min, while bolus feedings typically infuse over 5–10 min. The administration method selected for EN induces physiologic responses by the GI tract that can influence drug–nutrient interactions. In addition, the risk of physical interactions between drugs and formula can be influenced by the feeding method.

2.4. Safety

Given the many opportunities for adverse outcomes in the process of EN therapy, evidence-based safe practice guidelines have recently been developed by the American Society for Parenteral and Enteral Nutrition *(9)*. These guidelines cover best practices for enteral access as well as ordering, labeling, preparing, and administering EN *(9)*. Medication administration recommendations are also included. Further documents review appropriate administration of medication for patients receiving EN *(10)*.

3. CLASSES OF INTERACTIONS

Interactions between drugs and EN therapy can be defined as direct interactions between drugs and enteral formula, or they can be defined more broadly as any effect of a drug on EN therapy or any effect of EN on a drug that results in altered response to the other therapy. Using the broader definition, interactions can be divided into several categories or classes as listed in Table 1. These categories are not mutually exclusive as one class of interaction could be associated with another class. For example, a *physical* interaction that results in precipitation of a drug could lead to altered absorption, a *pharmacokinetic* interaction. Many *pharmacokinetic* interactions are, in fact, the result of another class of interaction. Factors contributing to the various classes of interactions can be organized into groups based on the moiety of EN therapy involved (Table 2). These groups serve as a logical basis for reviewing drug–nutrient interactions in patients receiving EN therapy, although there is considerable overlap between some groups.

Table 1
Mechanistic Categories of Drug–Nutrient Interactions in Patients Receiving Enteral Nutrition

Category of Interaction	*Description/Definition*
Physical	Changes in physical appearance, viscosity, or consistency of a drug and/or enteral formula that result in adverse outcomes such as feeding tube occlusion when the drug and formula are allowed to commingle
Pharmaceutical	Inappropriate changes in the drug dosage form to allow administration through a feeding tube that causes inadequate drug delivery, toxicity, or irritation of the GI tract
Pharmacologic	The expected effects of a drug based on the drug's mechanism of action interfere with nutrient absorption or induce intolerance to enteral feeding
Physiologic	A physiological response to a drug that causes intolerance to EN therapy and is not related to the purpose for which the drug is administered A physiological response to an enteral formula that is not related to the nutritional content and results in altered efficacy of a drug Physiologic interactions may also be referred to as side effects or adverse effects of the drug or formula
Pharmacokinetic	Changes in absorption, distribution, metabolism, or elimination of a drug or nutrient due to another drug or nutrient
Pathophysiologic	Changes in the response to a drug or nutrient due to development or alteration of a disease process (e.g., malnutrition) by a drug or nutrient

Table 2
Factors Contributing to Drug–Nutrient Interactions

- Administration-related factors
  - Tube characteristics
  - French size, length, material
- Administration regimen
  - Method – continuous, cyclic, intermittent, bolus
  - Flush protocol – water vs other fluid, frequency, volume
- Site of feeding
  - Gastric, duodenal, jejunal
- Drug-related factors
  - Dosage forms
  - State – solid, liquid
  - Specific dosage forms
    - Tablet – simple compressed, film-coated, enteric-coated, extended duration, sublingual, buccal
    - Capsule – hard gelatin (contains powder, granules, beads, or pellets), soft gelatin (contains liquid)
    - Solution – drug is in solution, does not specify liquid carrier or solubilizing agent for drug
    - Elixir – drug is in solution, contains alcohol to solubilize drug
    - Syrup – drug is in solution, contains high concentration of sugar
    - Suspension – fine particles of solid drug suspended in liquid
  - Excipients – sorbitol, alcohol, other solubilizing agents, stabilizers, flavorings
  - Osmolality – described in mOsm/kg of water
  - Viscosity – described in mPa·s (equivalent to cP)
- The absorptive environment
  - Solubility – acid, base
    – hydrophilic, lipophilic
- Therapeutic index – narrow therapeutic index drugs
- Formula-related factors
  - Protein content
    - Complexity – intact, hydrolyzed
    - Source – caseinate, isolated milk protein, soy, whey
  - Components influencing GI motility
    - Fat content
    - Osmolality
    - Viscosity – fiber content and caloric density
  - Vitamin K content
- Disease state-related factors
  - Visceral protein status
  - GI motility – gastric emptying and small bowel transit time

3.1. Administration-Related Factors

3.1.1. TUBE CHARACTERISTICS

Tube size and length can affect the risk of tube occlusion when drugs are administered via the tube. Long tubes with a small internal diameter are most prone to occlusion. For a given tube material, smaller Fr size correlates with increased risk of tube occlusion. Formula characteristics such as viscosity and drug characteristics such as dosage form are synergistic with tube size and length in causing tube occlusion, a form of *physical* interaction.

3.1.2. ADMINISTRATION REGIMEN

Drug–nutrient interactions can be affected by the EN administration regimen in several ways. The first is by the presence of enteral formula or lack thereof at the time drugs are administered. Failure to stop a continuous infusion of EN formula and flush the tube prior to drug administration contributes to *physical* interactions between formula and drugs that often result in tube occlusion. Second, the choice of flush fluid significantly affects the risk of *physical* interactions that contribute to tube occlusion. Water is the preferred fluid for flushing feeding tubes. Carbonated beverages are no better than water as a flush solution and have the potential to interact with formula or drugs *(11)*. Acidic fluids such as fruit juice can cause clumping, curdling, and other physical changes in enteral formula; cranberry juice is particularly problematic as a flush solution *(12,13)*. Adequate flush volume must be used to clear the feeding tube of formula or drug and flushing should occur before, after, and between drugs. Table 3 provides general guidelines for drug administration in patients receiving EN therapy, including recommended flush volumes for nasogastric and small bowel tubes in adults (steps 7–8). Despite the risk of tube occlusion or other complications when drug administration guidelines are not followed, adherence to such guidelines remains woefully inadequate *(14)*.

Starting and stopping continuous infusion EN formula to allow an hour or more separation between formula administration and drug administration can be difficult. The net result of holding formula administration too long is that patients receive less than the prescribed enteral formula volume. Over time, this could result in malnutrition (undernutrition) with concomitant alterations in drug response, a *pathophysiologic* interaction. When formula is not held long enough after administration of specific drugs (e.g., phenytoin, warfarin) *pharmacokinetic* interactions that result in reduced efficacy may occur. In this case, it may be easier to assure that drug and formula administration are separated by an appropriate time period and that adequate formula is delivered when the formula is administered periodically (i.e., intermittent or bolus regimen).

The feeding regimen can result in *physiologic* interactions mediated by the GI tract's response to feeding. Patterns of GI motility and secretion can be divided into "fed" and "unfed" patterns. The fed pattern is associated with slower transit from

Table 3
Guidelines for Drug Administration in Patients Receiving Enteral Nutrition

1. Administer drugs by the oral route whenever possible. Consider alternate routes (e.g., rectal, sublingual, buccal, transdermal) when drugs are available in these forms and the patient cannot swallow the drug. Some oral dosage forms are effective when administered by the sublingual or rectal route (e.g., sustained release morphine tablets administered rectally). Consider cost to benefit in the selection of alternate dosage forms.
2. Oral liquid dosage forms are generally preferred, if available, when drugs must be administered through the feeding tube. However, other dosage forms may be preferred when the liquid is associated with a high risk of physical incompatibility and/or GI intolerance.

Problematic oral liquids that should generally be ***avoided*** include

- syrups with a pH of 4 or less.
- possibly elixirs with a pH of 4 or less.
- oil-based products (e.g., MCT oil, cyclosporin).
- products with a high sorbitol content. Cumulative sorbitol dose should be no more than 5 g/day. Consider an alternative dosage form (e.g., crushed tablet) if sorbitol content cannot be determined and patient has abdominal cramping, bloating, or diarrhea.
- some specific formulations that the manufacturer states should not be administered through a feeding tube (e.g., clarithromycin suspension is a microgranular formulation and erythromycin suspension is a microcapsular formulation that are not to be administered through feeding tubes due to risk of tube occlusion).

3. Oral liquid dosages must be properly prepared to administer through a feeding tube.
   - dilute viscous products with 30–50 mL water (minimum 50:50 volume:volume) prior to administration (e.g., phenytoin suspension and carbamazepine suspension).
   - dilute hypertonic or irritating products prior to administration using a minimum of 30 mL, preferably more, of water. Hypertonic products may require dilution with more than 100 mL of water to reach an osmolality of approximately 300 mOsm/kg, the goal osmolality if possible.
   - divide doses of hypertonic or irritating products into 2–4 smaller doses administered at least 1 h apart when this does not alter therapeutic efficacy (e.g., divide 60 mmol (mEq) liquid potassium chloride into 3 doses of 20 mmol (mEq) each).
4. Select appropriate solid dosage forms for administration through the feeding tube, including most
   - immediate release, compressed tablets.
   - capsules that contain powdered drug.
   - capsules containing beads or pellets that are an immediate release form of drug that can be crushed.
   - coated tablets or capsules designed to protect the oral mucosa from dyes, irritants, or bad taste.

   The dosing schedule must be adjusted if the dosage form is changed from one with a prolonged duration of action to an immediate release form.
5. Oral solid dosage forms that should NOT be administered through a feeding tube include
   - sublingual products.

- buccal products.
- enteric-coated products.*
- dosage forms designed for a prolonged duration of action.*
- any product which cannot be dissolved or adequately crushed to form a slurry that can pass through the feeding tube without occluding the tube.

6. Prepare solid dosage forms properly for administration through a feeding tube.
   - tablets – crush to a fine powder and mix with 30–50 mL of warm water (15 mL minimum) for administration.
   - capsules – open **hard gelatin capsules** containing powder and mix the powder with 30–50 mL of warm water (10 mL minimum) before administration through the tube. Hard gelatin capsules containing beads or pellets are usually long-acting dosage forms that should not be crushed. These products can be administered only through large bore tubes that have openings large enough to permit intact beads to pass through (i.e., 14 Fr or larger gastrostomy and PEG tubes, possibly jejunostomies).
   - capsules – dissolve **soft gelatin capsules** in warm water using adequate volume (suggest 30 mL minimum) to keep the gelatin dissolved during administration. Liquid contents can also be aspirated from these capsules and mixed with 10–15 mL water for administration, although some of the drug may remain in the capsule when the aspiration method is used.
7. Use only water for mixing and flushing.
   - tap water is only acceptable if it meets municipal water quality standards, including adequate microbial quality; otherwise particulate-free water should be used.
   - immunocompromised patients may require water containing no microbes or other particulates (i.e., sterile water).
   - do not mix drugs directly with enteral formula. Exceptions to this rule include sodium chloride as table salt and some electrolyte injections.
8. Administer each drug separately with a minimum 5 mL flush of water between each sequentially administered drug. Do not mix drugs together before administration as this increases the risk of interactions and incompatibility.
9. Flush the tube adequately with water before and after administering drugs.
   - nasogastric tubes require a minimum of 15 mL for flushes with 30 mL recommended.
   - tubes in the small bowel require a minimum of 20 mL for flushes with 30–50 mL recommended.
   - use the recommended flush volume whenever possible, especially to clear the tube after drug administration.
10. Administer the dissolved drug or drug–water slurry using a 30–60 mL syringe and allowing gravity flow to empty the syringe. Use only a gentle push on the syringe plunger when necessary to aid flow. Excessive pressure on the syringe can damage the feeding tube.
11. Hold feedings for the recommended time period before and after administration of specific drugs.
    - carbamazepine – hold formula administration for 2 h before and after drug administration.

(Continued)

Table 3
(Continued)

- ciprofloxacin – hold formula for at least 1 h before and 2 h after drug administration.
- penicillin V potassium – hold formula for at least 1 h before and 2 h after drug administration.
- phenytoin – hold formula administration for 1–2 h before and after drug administration.
- warfarin – hold formula for at least 1 h before after drug administration.

12. Assess response to drugs using clinical parameters and therapeutic drug monitoring as appropriate.
13. Assess response to EN therapy.

* It may be possible to administer coated pellets, beads, or granules contained in hard gelatin capsules by opening the capsule and delivering the pieces via a feeding tube with an internal diameter and distal ports of adequate size to allow the pieces to pass through. An acidic fruit juice could be used to flush the tube immediately after administering an enteric-coated product, then follow this with the usual flush of water.

Note: Volumes for dilution and flushing are for adult patients. Reduce dilution volumes for pediatric doses to a minimum of 50:50 volume:volume; use at least 5 mL for dilution when fluid restriction is not required. Flush volume must be adequate to clear drug from the tube and will depend on the tube length and internal diameter. Follow the manufacturer's recommendation for flush volume to maintain tube patency.

the stomach to the small bowel and increased presence of digestive enzymes and GI tract secretions. Based on individual drug and dosage form characteristics the "fed" state may be better or worse than the "unfed" state for drug absorption, hence recommendations to take a drug with or without food (see Chapter 8). The influences of tube feeding on drug availability are likely to be similar to outcomes with food, at least for intermittent feeding. Interestingly, continuous infusion of enteral formula into the stomach appears to produce an "unfed" (i.e., fasting) pattern within the GI tract for some drugs. A study in which hydralazine was administered to eight healthy subjects with continuous infusion enteral formula via nasogastric tube demonstrated pharmacokinetic parameters similar to those in the fasted state *(15)*. Hydralazine pharmacokinetic parameters with bolus feeding were similar to those observed following a standard breakfast in this study. There is little evidence to document reduced absorption when the majority of drugs to be taken on an empty stomach are administered with continuous tube feeding. Therefore, the decision to hold tube feeding for a period of time, usually an hour, before and after drug administration must consider the potential for inadequate enteral formula delivery as well as the consequences of inadequate drug absorption. It may be prudent to hold feedings before and after critical medications to be taken on an empty stomach (e.g., ofloxacin for a serious infection). For other drugs, it may be better to continue feeding, monitor response to the drug, and only hold feedings if the patient fails to respond adequately to the drug.

3.1.3. The Site of Feeding

Substances administered through feeding tubes bypass specific regions of the GI tract and avoid exposure to the environment at those locations. Drugs require adequate dissolution to have an opportunity to be absorbed. Dissolution in turn may depend on numerous factors (e.g., drug particle surface area, diffusion layer thickness, solubility in gastric juice, bile, or pancreatic secretions). The site of feeding determines the physiologic conditions which are avoided and those to which a drug or nutrient is exposed. Table 4 outlines the physiologic conditions and functions normally performed relative to drugs and foods at various sites along the GI tract. The absorptive environment is established by the site of feeding and has a major impact on *pharmacokinetic* interactions of drugs, absorption in particular. Drugs intended for a local effect in the stomach (e.g., antacids, sucralfate) should not be administered through a post-pyloric tube as they will not be able to exert their pharmacologic effect.

Table 4
Physiologic Conditions and Functions at Sites Within the GI Tract

Site	*Major Secretions*	*Activity Related to Drugs*	*Activity Related to Foods*
Mouth	Saliva Salivary amylase	Disintegration of solid forms started	Maceration; Carbohydrate digestion started
Esophagus	None	Transport to stomach; Disintegration continues	Transport to stomach; Continue carbohydrate digestion
Stomach	Gastrin Gastric acid (HCl) Pepsinogen (pepsin) Gastric lipase Intrinsic factor	Disintegration; dissolution of acid soluble drugs; some absorption of small, lipophilic molecules and nonpolar weak acids that are soluble in low pH	Mixing; chyme formation; carbohydrate digestion; begin protein digestion; release nutrients from food; reduction of iron (Fe^{+3}) few nutrients absorbed
Duodenum	Gut hormones[a] Pancreatic enzymes[b] Bile	Disintegration of enteric coated drugs; dissolution of drugs soluble at pH 5–7; Passive absorption of drugs in solution	Osmolality and pH of chyme control gastric emptying; carbohydrate, protein, and fat digestion; absorption of protein, fats, and many micronutrients

(Continued)

Table 4
(Continued)

Site	*Major Secretions*	*Activity Related to Drugs*	*Activity Related to Foods*
Jejunum	VIP[c] Aminopeptidases Dipeptidases Disaccharidases	Dissolution of drugs soluble at pH 5–7; passive absorption of most drugs occurs to some extent	Absorption of carbohydrate, protein, fat, and many micronutrients
Ileum	Aminopeptidases Dipeptidases Disaccharidases	Continued dissolution of drugs soluble at pH 5–7; passive absorption of most drugs occurs to some extent	Absorption of carbohydrate, protein, fat, and many micronutrients; site of active absorption for vitamin B_{12}; reabsorption of bile acids

[a] Gastrin, gastric inhibitory polypeptide (GIP), motilin, glucagon, pancreatic polypeptide, secretin, and cholecystokinin

[b] Trypsinogen (trypsin), chymotrypsinogen (chymotrypsin), procarboxypeptidase (carboxypeptidase A and B), elastase, collagenase, ribonuclease, deoxyribonuclease, alpha-amylase, lipase, cholesterol esterase

[c] Vasoactive intestinal polypeptide

3.2. Drug-Related Factors

3.2.1. DOSAGE FORMS

The term “dosage form” refers to the drug product which encompasses the active drug molecule itself plus all the inert ingredients (i.e., excipients) needed to produce a stable, efficacious, nontoxic product for administration to a patient. Common dosage forms include those intended for oral administration which take the form of capsules, tablets, powders, suspensions, and solutions (including elixirs and syrups). Subsets of solid dosage forms (tablets and capsules) designed for specific purposes are also available, as listed in Table 2. Liquid dosage forms that are commonly administered through feeding tubes are included in Table 2 as well. Solid dosage forms must be altered by crushing or otherwise obtaining a fine powder that can be mixed with purified water to form a slurry for administration through a feeding tube. When changes in the pharmaceutical dosage form result in reduced efficacy, increased toxicity, or increases in other adverse effects, a *pharmaceutical* interaction has occurred. Enteric-coated and extended duration solid dosage forms are most prone to *pharmaceutical* interactions. Some products may contain coated, delayed-release and immediate-release particles in the same solid dosage form including some orally disintegrating tablets. Other coatings (e.g., film coatings) can also be troublesome as they tend to remain intact despite crushing of the tablet. Table 5 lists several accessory terms associated with dosage forms that should not be crushed and provides examples of drugs using these terms. Lists of drugs that should not be crushed or otherwise altered are also available in the literature *(16,17)*.

Table 5
Terms Associated with Dosage Forms that Should Not be Crushed

Accessory Term	*Meaning of term*	*Examples*
CD	Controlled dosing/delivery	Cardizem CD*
CR	Controlled release	DynaCirc CR, Norpace CR, Sinemet CR
ER	Extended release	
Extentab	Slow release	Dimetane Extentab
LA	Long acting	Entex LA, Inderal LA
ODT	Orally disintegrating tablets[†]	Prevacid Solutab
Repetab	Slow release	Proventil Repetab
SA	Sustained action	Choledyl SA, Tedral SA
Sequel	Slow release	Diamox Sequels, Ferro-Sequel
Spansule	Slow release	Feosol Spansule
Sprinkle	Slow release	Theo-Dur Sprinkle*
SR	Sustained release	Calan SR, Cardizem SR*, Isoptin SR, Pronestyl SR, Wellbutrin SR
Timecaps	Slow release	Nitrocine Timecaps
TR	Time release	Rondec TR, Triaminic TR
XL	Extended release	Ditropan XL, Glucotrol XL, Procardia XL, Ritalin XL
XR	Extended release	Dilacor XR, Tegretol XR
Enteric-coated	Enteric-coated	Creon*, Pancrease*, Pancrease MT*, Prevacid*, Prilosec*, Prozac*, Verelan*

* These drugs are microencapsulated dosage forms with pellets, beads, or granules in a hard gelatin capsule. The capsule can be opened and the pieces administered via a feeding tube with adequate diameter and distal port size to allow the pieces to pass through. For enteric-coated products, the tube could be flushed with an acidic juice before the usual flush with water.

[†] Not all ODT products contain enteric-coated particles

Enteric coating is designed to resist gastric acid and dissolve in the higher pH of the small bowel. Enteric coating is used when the drug is acid labile, causes mucosal or gastric irritation, stains teeth or mucosa or when exposure to acid results in toxic metabolites. Tablets are the most common enteric-coated dosage form. In addition, microencapsulated dosage forms consisting of enteric-coated pellets, beads, or granules enclosed in hard gelatin capsules are available. Crushing enteric-coated tablets or microencapsulated dosages removes the protection afforded by the coating thereby exposing the drug to gastric acid or the body to irritants or toxins when the crushed product is administered by mouth or into the stomach by tube.

For products delivered into the jejunum through a feeding tube, the enteric coating is not necessary. However, crushing enteric-coated dosage forms is still problematic for what might be considered a *physical* interaction. Enteric coatings are troublesome to crush, tending to form fragments that clump together when mixed with water and occluding the tube if administration through the tube is attempted. Whenever possible, alternative routes or dosage forms should be used rather than attempting to administer an enteric-coated drug through a feeding tube. Nonetheless, when the dosage form is small and the internal diameter and distal ports of the feeding tube are of adequate size (i.e., $\geq$ 14 Fr gastrostomy or jejunostomy tubes), it may be possible to administer the dosage form through the tube. Some microencapsulated dosages can be removed from their outer capsule and delivered through the feeding tube. Table 5 notes some of these products. Pouring the pieces from the capsule down the tube has been suggested *(17)*; however, some pieces may adhere to the inside of the tube with this method unless a vigorous flush with an acidic juice follows the pieces. Another suggestion is to suspend the pieces in an acidic fruit juice for administration. This method also poses some risk of tube clogging. Neither method should be attempted with small diameter tubes, especially tubes that require surgical replacement (i.e., needle catheter jejunostomies). For some drugs to be administered through a jejunostomy tube, it may be possible to dissolve the enteric coating using bicarbonate solution, then crush or dissolve the drug to form a slurry.

Dosage forms designed to provide an extended duration of action should not be crushed or otherwise altered for administration via a feeding tube. These dosage forms contain several doses of drug in one tablet or capsule. Drug is released in the GI tract over several hours thus reducing the number of times a drug must be administered to once or twice daily. Crushing or dissolving an extended duration dosage form delivers all the drug as an immediate release, consequently causing an “overdose” initially and no drug activity several hours later. Side effects or toxicity of the drug may be increased and disease control may be erratic. As with enteric-coated drugs, it may be possible to administer certain extended release dosage forms through large-bore feeding tubes. Pellets, beads, or granules that are coated to create an extended release of drug and enclosed in a hard gelatin capsule can often be removed from their outer capsule and delivered through a feeding tube with an internal diameter and distal ports of adequate size. However, the consequences of possible tube occlusion should be considered before administering these dosage forms that are more a convenience than a necessity.

Administration through a feeding tube of dosage forms not intended to be swallowed often results in a *pharmaceutical* interaction with altered bioavailability of the drug. Sublingual and buccal dosages are designed for absorption through tissues in the mouth where exposure to gastric acid and hepatic metabolism prior to systemic circulation are not a concern. As such, the amount of drug in most of these dosage forms can be relatively small compared to dosage forms that are swallowed. Likewise, intravenous dosage forms are not designed to withstand gastric acid, digestive enzymes, or other conditions within the GI tract, and substantial loss of drug can occur with administration through a feeding tube.

Excipients are additional ingredients in a dosage form that are intended to solubilize, stabilize, bind, dilute, flavor, sweeten, or otherwise allow drugs to be converted to usable dosage forms. Although not intended to produce a response by the body, some excipients can cause undesirable physiologic responses (e.g., diarrhea). Such unintended responses to a drug administered through a feeding tube that occur in people with a wide range of conditions requiring EN therapy are classified as *physiologic* interactions. When these unintended responses are the result of exacerbating a disease process, the interactions are considered to be *pathophysiologic*. Wheat or cornstarch used as a binder in tablets, for example, could result in bloating, abdominal pain, and diarrhea for a patient with gluten-induced enteropathy (i.e., Celiac disease) but would cause no symptoms in most people. Alcohol, lactose, carbohydrates, and dyes are other excipients of concern for some patient populations. The excipient of most concern for people receiving EN therapy is sorbitol.

Sorbitol is a sugar alcohol used as a solubilizing agent, to prevent crystallization of sucrose, and as a "sugar-free" sweetener in liquid dosage forms. However, sorbitol doses of 20–50 g are used as a purgative agent and cause severe cramping and diarrhea in most people. Doses of only 5–10 g cause GI symptoms such as bloating and flatulence in a sizable share of the population *(18)*. Several case reports of GI intolerance secondary to cumulative sorbitol doses can be found in the literature. Thus, care must be taken to avoid excessive cumulative sorbitol intake from multiple drugs *(19–21)*. All dosage forms and doses of a given drug should be evaluated since there can be clinically significant differences in sorbitol content, as shown in Table 6. For example, use of furosemide solution 10 mg/5 mL to administer 40 mg furosemide daily would contribute 9.6 g sorbitol while furosemide solution 40 mg/5 mL from the same manufacturer would result in only 2.4 g sorbitol daily. Therapeutic equivalents for the drug should be considered if necessary. A patient receiving 1200 mg cimetidine daily for erosive esophagitis would receive 11.2 g sorbitol using the 300 mg/5 mL

Table 6
Sorbitol Content of Selected Liquid Dosage Forms

Classification Generic Name	*Brand and Dosage Form*	*Concentration per 5 mL*	*Manufacturer*[a]	*Sorbitol (g/mL)*[b]
Analgesics				
Acetaminophen	Tylenol infant's drops (100 mg/mL)	500 mg	McNeil	none
	Tylenol children's elixir	160 mg	McNeil	0.2
	Tylenol children's suspension	160 mg	McNeil	0.2
	Tylenol extra strength liquid	167 mg	McNeil	0.2
Ibuprofen	Pedia-profen suspension	100 mg	McNeil	0.3
Naproxen	Naprosyn suspension	125 mg	Roche	0.1
Antibiotics				
Nitrofurantoin	Furadantin suspension	25 mg	PG	0.14
Tetracycline	Sumycin suspension	125 mg	Apothecon	0.3

(Continued)

Table 6
(Continued)

Classification Generic Name	*Brand and Dosage Form*	*Concentration per 5 mL*	*Manufacturer*[a]	*Sorbitol (g/mL)*[b]
Trimethoprim/ Sulfamethoxazole (TMP/SMZ)	Bactrim pediatric suspension	[*40* mg TMP + 200 mg SMZ]	Roche	0.07
	Septra suspension		GW	0.45
	TMP/SMZ		Biocraft	0.07
Antiepilepties				
Carbamazepine	Tegretol suspension	100 mg	Novartis	0.12
Phenobarbital	Phenobarbital elixir	15 mg and 20 mg	Lilly	none
Phenytoin	Dilantin-30 suspension	30 mg	Parke-Davis	none
	Dilantin-125 suspension	125 mg	Parke-Davis	none
Primadone	Mysoline suspension	250 mg	WA	none
Valproic acid	Depakene syrup	250 mg	Abbott	0.15
Antidiarrheals				
Loperamide	Imodium A–D	1 mg	McNeil	none
	Loperamide oral solution	1 mg	Roxane	none
Bronchodilators				
Aminophylline	Aminophylline oral liquid	105 mg	Roxane	0.14
Theophylline	Elixophylline elixir (80 mg/15 mL)	27 mg	Forest	none
	Slo-Phyllin 80 syrup (80 mg/15 mL)	27 mg	RPR	0.58
	Theoclear-80 syrup (80 mg/15 mL)	27 mg	Central	0.8
	Theolair liquid (80 mg/15 mL)	27 mg	3 M Pharma	0.1
	Theophylline solution (80 mg/15 mL)	27 mg	Roxane	0.46
Theophylline/ Guaifenesin	Elixophylline GG elixir	[*27* mg theoph. + 100 mg guaifen.]	Forest	0.46
	Slo-Phyllin GG syrup		RPR	0.12
Diuretics				
Chlorothiazide	Diuril oral suspension	250 mg	Merck	none
Furosemide	Furosemide solution	10 mg	Roxane	0.48
	Furosemide solution	40 mg	Roxane	0.48
	Lasix oral solution	10 mg	HMR	none
Hydrochlorothiazide	Hydrochlorothiazide solution	50 mg	Roxane	none

GI Stimulants				
Metoclopramide	Metoclopramide syrup	5 mg	Biocraft	0.4
	Metoclopramide oral solution	5 mg	Roxane	0.25
	Metoclopramide Intensol	10 mg	Roxane	0.25
Histamine (H_2) Antagonist				
Cimetidine	Tagamet liquid	300 mg	SKB	0.56
Famotidine	Pepcid oral suspension	40 mg	Merck	none
Ranitidine	Zantac syrup (15 mg/mL)	75 mg	GW	0.1
Sedative/Hypnotics				
Diazepam	Diazepam oral solution	5 mg	Roxane	none
	Diazepam Intensol (2 mg/mL)	10 mg	Roxane	none
Diphenhydramine	Benadryl elixir (cherry)	12.5 mg	Warner Lambert	none
	Benadryl elixir, diet	12.5 mg	Warner Lambert	0.45
Lorazepam	Lorazepam Intensol (2 mg/mL)	10 mg	Roxane	none

[a] BI, Boehringer Ingelheim; BMS, Bristol–Myers Squibb; GW, Glaxo Wellcome; BW, HMR, Hoechst-Marion Roussel; PG, Procter & Gamble; RPR, Rhone-Poulenc Rorer; SKB, SmithKlein Beecham; WA, Wyeth-Ayerst

[b] Determine daily sorbitol dose by calculating the total mL/day of drug, then multiply by the grams of sorbitol per mL. For example, the calculation for a patient receiving 320 mg acetaminophen four times daily using Tylenol Children's suspension (160 mg/5 mL concentration) is as follows: 10 mL/dose × 0.2 g/mL × 4 doses/day = 8 g/day.

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Tagamet® liquid. Changing to the therapeutic equivalent ranitidine at an equivalent dose of 600 mg daily, the patient would receive only 4 g sorbitol from 150 mg/5 mL Zantac® syrup. A therapeutically equivalent dose of famotidine as Pepcid® oral suspension would provide no sorbitol at all.

Most drugs available without prescription now include a list of inert ingredients (albeit without quantities) on the label but a large percentage of prescription medications do not. Excipients may be classified as proprietary information by the manufacturer although oftentimes the medical information department will answer whether a specific excipient is or is not present in a specific product. The amount of an excipient present may be much more difficult to obtain. Table 6 contains the sorbitol content of a few selected drugs based on information provided by the manufacturer. In recent years, the trend has been toward elimination of sorbitol in some classes of drugs, especially pediatric antibiotics. Table 7 lists several

Table 7
Liquid Antibiotic Preparations Reported to Contain No Sorbitol

Generic Name	*Brand and Dosage Form*	*Concentration (per 5 mL)*	*Manufacturer*[a]
Amoxicillin	Various brands of suspension	125 mg and 250 mg	Apothecon, Biocraft, Lederle, SKB, WA
Amoxicillin	Amoxil and Trimox pediatric drops	250 mg (50 mg/mL)	SKB, Apothecon
Ampicillin	Various brands of suspension	125 mg and 250 mg	Apohecon, Biocraft, Lederle
Azithromycin	Zithromax 100 suspension	100 mg	Pfizer
	Zithromax 100 suspension	200 mg	Pfizer
Cefaclor	Ceclor suspension	125 mg, 187 mg, 250 mg	Lilly
Cefadroxil	Duricef suspension	125 mg and 250 mg	BMS
Cefuroxime	Ceftin suspension	125 mg and 250 mg	GW
Cephalexin	Cephalexin suspension	125 mg and 250 mg	Lederle, Biocraft
	Keflex oral suspension	125 mg and 250 mg	Dista
Cephradine	Velosef suspension	125 mg and 250 mg	BMS
Ciprofloxacin	Cipro oral suspension	250 mg and 500 mg	Bayer
Clarithromycin	Biaxin suspension	125 mg and 250 mg	Abbott
Clindamycin	Cleocin pediatric oral solution	75 mg	Upjohn
Dicloxacillin	Dynapen and Pathocil suspensions	62.5 mg	Apothecon, WA
Doxycycline	Vibramycin monohydrate suspension	25 mg	Pfizer
	Vibramycin calcium syrup	50 mg	Pfizer
Erythromycin ethylsuccinate	EES 200	200 mg	Abbott
	EES 400	400 mg	Abbott
	EryPed suspension drops	200 mg and 400 mg	Abbott
Erythromycin/ sulfisoxazole	EES/sulfisoxazole suspension	200 mg /600 mg	Lederle
	Pediazole	200 mg /600 mg	Ross
Loracarbef	Lorabid suspension	100 mg and 200 mg	Lilly

Penicillin VK	Various brands of suspension	125 mg	Biocraft, SKB, WA
	Veetids oral suspension	125 mg and 250 mg	Apothacon
Sulfisoxazole	Gantrisin pediatric suspension	500 mg	Roche
Vancomycin	Vancocin oral solution	1 g bottle	Lilly

[a]BI, Boehringer Ingelheim; BMS, Bristol–Myers Squibb; GW, Glaxo Wellcome; BW, HMR, Hoechst-Marion Roussel; RPR, Rhone-Poulenc Rorer; SKB, SmithKlein Beecham; WA, Wyeth-Ayerst

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liquid antibiotic preparations that contain no sorbitol. However, published information listing quantities of specific excipients such as dyes and sweeteners *(22)*, carbohydrate *(23)*, or sorbitol *(24,25)*, or statements that none of a particular excipient is present in specific products must be interpreted with caution. Excipients are often manufacturer specific and may change frequently depending on market availability and cost. The best method to determine whether a product currently on the market contains a particular excipient is to contact the manufacturer and request the information for the care of a specific patient.

Osmolality of liquid dosage forms is somewhat related to the drug itself but more to the number and types of excipients. Hyperosmolar drug products can cause symptoms including nausea, vomiting, diarrhea, bloating, cramping, and abdominal pain that are attributed to EN intolerance, thereby resulting in a *physiologic* interaction *(26–29)*. Liquid dosage forms often have an osmolality of 3000 mOsm/kg or higher *(17,26,29,30)*. Small amounts of hyperosmolar liquid delivered to the stomach are diluted by gastric fluid prior to being emptied into the duodenum, and the rate of delivery is controlled by osmoregulators in the duodenum. Hyperosmolar liquid delivered directly into the small bowel, however, must be diluted by an influx of water. The greater the volume of hyperosmolar liquid and the higher the osmolality, the greater the risk that cramping and diarrhea will result. Diluting the hyperosmolar liquid prior to administration reduces the risk of cramping and diarrhea. For small bowel administration, the desired osmolality is approximately 300 mOsm/kg. The volume of water needed for dilution can be calculated by dividing the drug osmolality by 300 then multiplying by the drug volume (mL) required to deliver the dose. The drug volume in mL is then subtracted from the first number to arrive at the mL of water for dilution. For example, a 500 mg dose of acetaminophen elixir (65 mg/mL) with an osmolality of 5400 mOsm/kg requires dilution with 131 mL of water to have an osmolality of about 300 mOsm/kg *(30)*.

$$\left(\frac{5400\ \text{mOsm/kg}}{300\ \text{mOsm/kg}} \times \frac{500\ \text{mg}}{65\ \text{mg/mL}}\right) - 7.7\ \text{mL} = 131\ \text{mL}$$

Using the minimum dose of drug necessary to achieve the desired response minimizes the amount of water needed as a diluent. Dividing the ordered dose into two to four doses spread over a few hours can also reduce the impact of hyperosmolar drugs on GI intolerance, but this approach should only be considered if drug efficacy will not be adversely affected. For example, an 80 mmol dose of potassium chloride can be divided into four doses of 20 mmol each spread over several hours with little impact on overall effectiveness. Many “once-daily” doses can be divided into two half doses administered 2–3 h apart with minimal change in effectiveness.

Certain dosage forms appear to be troublesome with respect to *physical* interactions between drugs and EN formulas. About one-third of all drugs tested have demonstrated some degree of *physical* interaction with enteral formulas *(30–36)*. Syrups, elixirs, and oil-base liquid dosage forms are most often reported to cause physical changes such as curdling, clumping, gelling, emulsion separation, precipitation, increased viscosity, and reduced viscosity. The drug itself is probably of minimal importance except to define the pH and/or solubilizing agent (e.g., alcohol) required for a stable, soluble liquid dosage form. In studies where pH was determined, an association between low pH and physical interaction with intact protein formulas was noted with 9 of 11 incompatible products at pH 4 or below *(30–32)*. Acidic syrups were more likely to interact than acidic elixirs (3/4 syrups vs 2/5 elixirs). Of the 25 drugs reported as incompatible with enteral formula, pH was available for 18 and only two of these products had a pH above 6; both were antacids (Riopan and Mylanta II at pH 7.5) *(30–34)*. Another in vitro study that evaluated drug vehicles (water, simple syrup, 9% alcohol elixir, and 25% alcohol elixir) buffered to pH 2, 7, or 11, and formulas containing single protein sources (caseinates, soy, and whey) found that syrups were problematic at both acidic and neutral pH while elixirs caused undesirable physical changes only at an acidic pH *(37)*. This suggests that pharmaceutical syrups, regardless of the drug or pH, must be used with caution when administered through a feeding tube.

Methods of avoiding *physical* interactions between drugs and enteral formula are summarized in Table 8. One of the most effective methods is to prevent physical contact between the drug and formula. This can be accomplished by flushing feeding tubes appropriately (Table 3) and by using routes of drug administration other than the feeding tube whenever feasible. Oral drug administration can be used when there is no contraindication to fluids by mouth and is the preferred route whenever possible *(17,29,30)*. Instant dissolving tablets that do not require water may be another option for drugs that are available in this form, such as the antiemetic ondansetron (Zofran®) and some nonprescription analgesics. Other routes that are available for some drugs include transdermal, sublingual, and rectal. Parenteral drug administration is the least desirable alternative to drug administration via the feeding tube due to increased cost and venous access issues. Likewise, cost of certain other alternative dosage forms (e.g., transdermal systems) can be

Table 8

Methods to Avoid or Minimize Drug–Nutrient Interactions in Patients Receiving Enteral Nutrition

	Type of Drug–Nutrient Interaction				
Method	*Physical*	*Pharmaceutical*	*Pharmacologic*	*Physiologic*	*Pharmacokinetic*
Avoid mixing drug and formula	+/+	0	0	0	+/+
Change route of administration to:					
Oral	+/+	+/+	0	?	+/+
Parenteral	+/0	+/0	0	+/0	+/0
Transdermal patch	+/–	+/–	0	+/–	+/–
Rectal suppository	+/+	+/+	0	+/+	+/+
Other	+/?	+/?	0	+/?	+/?
Change dosage form	+/?	+/?	0	+/?	+/?
Change to therapeutic equivalent	+/?	+/?	+/?	+/?	+/?
Change enteral formula	+/0	0	0	+/?	+/?
Use minimum dose necessary	?	0	+/+	+/+	+/+
Dilute the drug	0	0	0	+/+	0
Treat with adjunct therapy	0	0	+/?	+/?	0

+/+ effective in preventing interaction and minimal change in cost; first-line method.
+/? effective in preventing interaction; cost may be higher, lower, or equivalent.
+/– effective in preventing interaction; usually significantly more expensive.
+/0 effective in preventing interaction; typically the last option due to significant increase in cost and other potential issues.
? possibly effective in some instances.
0 not effective in preventing this type of interaction.

prohibitive for some patients. When the drug ordered does not have alternative routes and/or dosage forms that are available and cost effective, a therapeutically equivalent drug may be available in more desirable dosage forms. Properly prepared compressed tablets, hard gelatin capsules, or soft gelatin capsules are preferable to "high-risk" liquid dosage forms in many cases and often are the most cost effective means of providing a drug via the feeding tube. When drugs must be administered through a feeding tube, flushing with water before and after drug administration is essential to prevent tube occlusion. Liquids such as fruit juices should never be used as the flush solution, although a rare drug might be mixed in an acidic juice for administration.

Viscous liquid dosage forms (e.g., suspensions) have a tendency to coat the inside of feeding tubes, and drug may even remain adherent to the tube after flushing with water. The net result is reduced drug delivery and absorption, a *pharmacokinetic* interaction. Separate in vitro studies using simulated administration of phenytoin and carbamazepine suspensions through feeding tubes found better drug recovery with diluted suspensions than with undiluted suspensions *(38,39)*. Carbamazepine suspension diluted 50:50 with water, saline, or 5% dextrose solution did not appear to coat the tubes either before or after flushing with water, saline, or dextrose solution *(38)*. Undiluted suspension clung to the tube before flushing but was no longer visible after the tubes were flushed. However, significantly less carbamazepine was recovered in the effluents when undiluted suspension was administered, suggesting that drug remained in the polyvinyl chloride tubes. Polyvinyl chloride nasogastric tubes and silicone PEG tubes used in studies with phenytoin produced essentially the same results *(39,40)*. However, when diluted phenytoin was administered through a PEG tube with latex coating, phenytoin recovery was decreased perhaps because of increased solubility and concomitantly increased binding to the latex *(41)*. Thus, tube material may be an important factor in reduced drug recovery although polyurethane, the most common material for nasal tubes, has not been evaluated, but polyurethane is generally not associated with significant adsorption of drugs to the tube. Diluting with water (50:50) prior to administering viscous liquid dosage forms through a nonlatex feeding tube is unlikely to cause any harm and may prevent erratic serum drug concentrations; therefore, at least a 50:50 dilution of viscous dosage forms with water should be the standard of practice. Further investigation is necessary to determine if this is an appropriate practice for a latex tube.

3.2.2. The Absorptive Environment

The environment to which a drug is exposed has a significant impact on *pharmacokinetic* interactions of drugs and the amount of drug ultimately available to the body. Drugs typically must be in solution for passive absorption to occur, and most drugs are absorbed by this method. Absorption then relies on the degree of permeability which may also be determined by the environment. Before absorption can occur, solid dosage forms generally undergo a two-step process consisting of disintegration and dissolution. Disintegration entails breakup of the dosage form into granules that then separate further into fine particles exposing a large surface area to the environment. Drugs formulated as powders and those crushed to a fine powder by mechanical action prior to administration through a feeding tube require dissolution but not disintegration. The large surface area of powders and fine particles aids in dissolution. Liquid dosage forms may already be in solution (e.g., elixirs, syrups) or may require dissolution but not disintegration (e.g., suspensions). Soft gelatin capsules contain a drug in solution or in an oil albeit the capsule itself must be dissolved in warm water or the liquid contents extracted for administration through a feeding tube.

Drugs and formula delivered via feeding tube bypass the mouth and esophagus, where the processes of disintegration and digestion begin, as noted in Table 4. This is of little consequence when the drugs are prepared as a slurry of fine particles in water or in liquid dosage forms that do not require disintegration. Enteral formulas are liquid foods that do not require maceration. Minimal digestion of carbohydrates occurs in the mouth and esophagus. Drugs and nutrients administered through duodenal or jejunal tubes, however, circumvent the stomach and are exposed to a very different environment than those that pass through the stomach. Depending on chemical characteristics of the drug or nutrient, bypassing the stomach may alter pharmacokinetic parameters and ultimately increase or decrease the quantity of the substance that can be absorbed.

3.2.2.1. Stomach. Substances that enter the stomach are mixed with gastric acid and digestive enzymes. Oral drugs in solid dosage forms that have not disintegrated during passage through the esophagus generally complete that process in the stomach, and some drugs undergo dissolution. Drugs that are not soluble in an acidic environment must enter the small bowel before dissolution begins. Weak to moderately acidic drugs (e.g., acetazolamide, tolbutamide, warfarin) that are soluble at the pH of gastric acid are largely in a nonionized form that can be absorbed by passive diffusion. Those that are poorly soluble at the gastric pH (e.g., phenobarbital) are unlikely to be absorbed to any measurable extent from the stomach. Drugs that are weak bases (e.g., meperidine, procainamide, reserpine) are mostly in an ionized form in a low pH environment and are typically not absorbed although they may be relatively soluble in acid. Lipid-soluble, small, nonelectrolyte substances (e.g., alcohol) are absorbed from the stomach. However, the stomach provides a relatively small contribution to overall absorption of any substance due to the small surface area and limited blood flow here relative to the small bowel.

3.2.2.2. Small Bowel. Absorption from the small bowel requires that materials first enter the small bowel and that disintegration and dissolution of drugs be completed if this has not already occurred. In most cases, disintegration is complete when drugs enter the small bowel; the notable exception being enteric-coated drugs. In contrast, dissolution is complete only for drugs that are freely soluble in acid. Many drugs have undergone only partial dissolution or are not dissolved at all when they enter the small bowel. For readily absorbed drugs and nutrients delivered through gastric feeding tubes or by the oral route, gastric emptying controls the rate at which substances enter the small bowel and, therefore, is the rate-limiting step for absorption. Gastric emptying is highly variable and influenced by a number of factors *(42–44)*. Table 9 lists several drugs, enteral formula characteristics, and

Table 9
Factors Influencing GI Motility

	Gastric Emptying		*Small Bowel Motility*	
Factor	*Delayed*	*Increased*	*Decreased*	*Increased*
Formula Characteristics				
High fat (long-chain triglycerides)	X			
High protein	X (< fat)			
High viscosity (e.g., fiber)	X			
Liquid consistency		X		
Large particles or tablets	X			
Large volume	X			X
Hypotonic osmolarity (< 250 mOsm/L)	X			
Osmolarity over 800 mOsm/L	X			X
Low pH	X			X
Drugs				
Anticholinergic agents	X		X	
Atropine, belladonna, benztropine,				
Biperiden, ethopropazine,				
Hyoscyamine, procyclidine,				
Scopolamine, trihexphenidyl		X		X
Cholinergic agonists				
Bethanechol, cisapride[a]		X		X
Dopamine agonists		X		X
Levodopa, metoclopramide				
Motilin agonist				
Erythomycin				
Mucosal irritants		X		
Salicylic acid				
Narcotic agents	X		X	
Morphine, others				
Octreotide	X		X	
Disease States and Conditions				
Autonomic neuropathy	X			
Diabetic gastropathy	X			
Dumping syndrome		X		X
Duodenal ulcers		X		
Gastric surgery		X		
Billroth I and II				
Gastroesophageal reflux disease				
Irritable bowel syndrome				
– Diarrhea predominant				X
– Constipation predominant			X	
Partial gastrectomy		X		X
Peptic ulcer disease	X			

Pyloric obstruction	X	
Stenosis, gastric cancer		
Scleroderma	X	X
Vagotomy	X	

[a] Cisapride has only been available under a limited access investigational protocol from the manufacturer since July 14, 2001, due to cardiac toxicity.

disease states that can influence gastric emptying rate and GI motility. Anything which alters gastric emptying rate is expected to alter the rate of absorption for most drugs and nutrients in a similar manner; slowed gastric emptying slows the rate of absorption while rapid gastric emptying increases the rate of absorption.

3.2.2.3. Gastric Administration. Effects of altered gastric emptying rate on extent of absorption (i.e., percent absorbed or bioavailability) are more variable and may be more difficult to predict than the effects on rate of absorption. Extent of absorption may be increased, decreased, or unchanged for either slow or rapid gastric emptying depending on the drug or nutrient characteristics and the absorption mechanisms. Table 10 shows expected effects of various factors on extent of absorption when gastric emptying rate is decreased. Effects of rapid gastric emptying are much more difficult to predict and may depend on the drug dosage form

Table 10
Change in Extent of Absorption with Decreased Gastric Emptying Rate

Extent of Absorption	*Example*
Increased Extent of Absorption	
Active absorption in upper GI tract	Riboflavin
Significant absorption in upper GI tract	Ciprofloxacin
Poor solubility in stomach and small bowel, acid stable	Griseofulvin Carbamazepine
Release from food, binding to another substance in the stomach is required	Cobalamin
Soluble in gastric pH but not small bowel (pH 5–7)	Ketoconazole, Tetracycline
Absorption from the stomach (weak acid; small nonelectrolyte)	Alcohol
No Effect on Extent of Absorption	
Enteric-coated tablet or granules	Multiple products
Decreased Extent of Absorption	
Acid labile	Ampicillin
Poor solubility in stomach and small bowel, acid labile	Digoxin

as well as on small bowel transit time. Dosage forms that require time for disintegration have the least opportunity for absorption when both gastric emptying and GI motility are rapid. With normal small bowel motility, rapid gastric emptying is expected to reduce absorption to the greatest extent when an acidic medium is required for dissolution or is otherwise necessary for absorption (e.g., ketoconazole, itraconazole, tetracycline). More than one factor may influence the extent of absorption for a given drug or nutrient. For example, slow gastric emptying increases the extent of riboflavin absorption by at least two mechanisms. Riboflavin is released from foods in the stomach and absorbed by a saturable transport process in the upper GI tract (i.e., duodenum and jejunum). Slow gastric emptying allows more time to free riboflavin from foods, thereby making more riboflavin available to absorption sites. In addition, riboflavin enters the region containing transport sites at a reduced rate and over an extended time period. The net effect is that a larger percentage of riboflavin is absorbed because fewer transport sites are “occupied” or saturated when the “free” riboflavin reaches these sites. In general, slow gastric emptying allows more complete release of vitamins from the food matrix while food is in the stomach. Release of vitamins from the food matrix continues in the small bowel as digestion progresses. The majority of vitamins are absorbed by passive transport throughout much of the small bowel; thus, incomplete release from the food matrix prior to entering the small bowel is of limited clinical significance to overall absorption. In fact, jejunal feeding with nonhydrolyzed formulas is routine and has not resulted in vitamin deficiencies.

Gastric emptying rate is most likely to influence drug absorption through effects on solubility. Slow gastric emptying increases the extent of dissolution for drugs that are only soluble in an acidic environment (e.g., tetracycline) and for relatively insoluble drugs (e.g., carbamazepine, digoxin, griseofulvin, spironolactone). The extent of absorption increases when these drugs are acid stable (e.g., carbamazepine, griseofulvin) but decreases when the drug is acid labile (e.g., digoxin). In general, exposure to gastric acid increases destruction of acid-labile drugs (e.g., ampicillin, digoxin, omeprazole), and bioavailability is reduced when gastric emptying is slow unless the drug is protected by enteric coating. Substances that can be absorbed from the stomach (i.e., weak acids in solution and small lipid-soluble nonelectrolytes) will be absorbed to a greater extent with longer exposure to the gastric mucosa, although this rarely has clinical significance since the majority of absorption still occurs in the larger surface area of the small bowel.

3.2.2.4. Post-pyloric Administration. Administration of drugs through post-pyloric tubes, either duodenal or jejunal, bypasses conditions in the stomach and eliminates the effect of gastric emptying on rate of absorption. A major consequence of bypassing the stomach is reduced exposure to acid. The pH in the proximal duodenum is approximately 4–5 and increases to near neutral in the distal duodenum as gastric acids are neutralized by bile salts and pancreatic secretions entering the duodenum. The jejunum is neutral to slightly alkaline. With increasing pH, most basic drugs transform from an ionized, nonabsorbable state to a primarily non-ionized state that can be absorbed. Acidic drugs generally become more ionized and less absorbable. Nonetheless, the jejunum and the ileum remain the major sites of absorption for all except highly acidic drugs because of the immense absorptive surface area in these regions.

Drugs that are only soluble in an acid environment or otherwise require exposure to an acidic environment for proper absorption (e.g., ketoconazole, itraconazole, tetracycline) may be ineffective when administered through a feeding tube placed into the small bowel. The more distal the tube, the greater the potential problem. Mixing these drugs with an acidic fluid (e.g., dilute vinegar, ascorbic acid, fruit juice) should, theoretically, improve absorption but documentation supporting this assumption is lacking. In contrast, low itraconazole concentrations were noted in a case report when an extemporaneously prepared suspension with an acidic pH was administered through a post-pyloric feeding tube *(45)*. It is unclear whether the low itraconazole concentrations in this case were due to poor absorption because the acidic medium used for the drug was ineffective or because of poor GI perfusion in a critically ill patient.

A reduced extent of absorption is expected when poorly soluble drugs are delivered into the duodenum or jejunum because the time available for dissolution is decreased. The more distal is the site of drug delivery, the less time there is for dissolution to occur; thus, jejunal administration may be more problematic than duodenal administration. Use of a dosage form that does not require dissolution (e.g., elixir, syrup, dissolved soft gelatin capsule) can overcome this problem and may result in greater drug absorption than gastric administration for acid-labile drugs. In one small study with digoxin, significantly more hydrolytic metabolites (2.9% vs 0.6%) were noted after oral ingestion vs administration into the jejunum *(46)*. Recovery of nonmetabolized digoxin was higher with jejunal administration (96.3% vs 90.8%), suggesting a need for lower doses when digoxin is administered into the jejunum through a feeding tube. Bypassing the stomach avoids acid hydrolysis of digoxin; therefore, more drug is available for absorption. Therapeutic drug monitoring should be performed within a couple of days whenever digoxin dosing changes from oral or gastric administration to post-pyloric administration or vice versa.

The further a feeding tube is placed into the small bowel, the more important it becomes to consider the site(s) of drug or nutrient absorption. When substantial absorption occurs in the duodenum, delivery of a drug or nutrient into the jejunum could significantly reduce the extent of absorption. An example of this is seen with ciprofloxacin where healthy volunteers absorb up to 40% of an oral dose in the duodenum *(47)*. Administration of ciprofloxacin into the duodenum results in better absorption than delivery into the stomach in both healthy volunteers and ICU patients *(48)*. Jejunal administration results in lower serum concentrations than those found after oral administration *(49,50)*. The majority of drugs are absorbed by passive diffusion which is typically not limited to a specific segment of the GI tract, although chemical characteristics of a drug can influence absorption at different pHs. Unfortunately, published data rarely specify the percent of drug absorbed in specific segments of the GI tract (i.e., stomach, duodenum, jejunum, ileum, and colon), and few studies have compared serum drug concentrations following administration by mouth compared with administration through tubes at different sites within the GI tract.

Most water-soluble vitamins are absorbed by passive diffusion primarily in the upper small bowel, but absorption is rarely limited to the duodenum and may extend into the ileum, depending on transit time. Thus, delivery of nutrients into the jejunum has little impact on the amount of most water-soluble vitamins absorbed. Minerals generally require facilitated absorption or active transport because most form chelates or complexes that are too large to be absorbed efficiently by passive diffusion. Calcium, phosphorus, iron, and most trace minerals are most efficiently absorbed from the slightly acidic upper GI tract and demonstrate limited absorption in the ileum. Release of minerals from the food matrix and formation of the complexes normally occurs in the stomach; thus, theoretically jejunal administration could compromise absorption. However, routine use of nonhydrolyzed formulas for jejunal feeding has not resulted in reports of mineral deficiencies.

Administration of drugs that stimulate GI motility, as listed in Table 9, could reduce nutrient absorption by reducing GI transit time. For example, diarrhea may develop in a patient receiving metoclopramide or erythromycin. Although erythromycin may have been ordered to treat an infection, its mechanism of action still includes activity as a motilin agonist. When the mechanism of action for a drug interferes with nutrient absorption or induces enteral feeding intolerance, this is classified as a *pharmacologic* interaction. Pharmacologic effects on the GI tract must be considered in drug selection to minimize such interactions. Other methods of handling *pharmacologic* interactions are included in Table 8.

3.2.3. THERAPEUTIC INDEX

Drugs with a relatively small therapeutic range are more likely to result in patient harm when drug–nutrient interactions are not anticipated and managed appropriately. Drugs for which serum drug monitoring is performed are typically drugs with a small therapeutic range and *pharmacokinetic* interactions are of most concern. With only a small range of concentrations within the efficacious but nontoxic range, small changes in absorption can have significant changes in therapeutic outcome. Phenytoin, carbamazepine, and digoxin are among the “narrow” therapeutic index drugs of concern when administered through a feeding tube. These drugs are discussed in Section 4.

3.3. Formula-Related Factors

3.3.1. PROTEIN CONTENT

Complexity of the protein source (i.e., intact protein vs hydrolyzed protein or free amino acids) appears to play a key role in *physical* interactions between drugs and enteral formulas. Intact proteins are complex, highly ordered chemical structures that rely on various bonds and electrostatic attractions to maintain their order and shape. Exposure to acids, salts, alcohol, or heat can result in breaking of bonds, conformational change, and loss of tertiary configuration with “unfolding” of proteins, a process referred to as denaturation. Curdling of milk on exposure to acid is an example of protein denaturation and of the differences among proteins in susceptibility to denaturation. Casein undergoes denaturation on exposure to acid, and the resulting changes in protein solubility and viscosity are visible as clumps or curds. On the other hand, whey proteins do not denature and remain fluid unless a very strong acid is used. The source of protein determines the pH at which denaturation begins and the sensitivity of the protein to various salts and alcohols. Whey protein is the most acid stable of the intact protein sources routinely used in enteral formulas (i.e., caseinates, soy, or whey), and whey-based formulas are the least likely to be physically incompatible with drugs *(37)*. Casein and caseinates tend to form large clumps and curds similar to curdled milk, while soy protein forms finer precipitates.

Protein denaturation explains many of the observations related to *physical* interaction or incompatibility between drugs and enteral formulas. Nearly all of the drug-formula incompatibilities reported are with formulas containing intact protein, predominantly casein or caseinates, and no drug has been identified that is incompatible with hydrolyzed protein formulas while being compatible with intact protein formulas. Acidic syrups and elixirs are the most problematic dosage forms and both acid and alcohol can cause protein denaturation. Formulas containing hydrolyzed protein rarely result in physical incompatibility except with oil-based products. Of 25 drugs reported as incompatible with one or more formulas tested in an in vitro study, only 3 were incompatible with hydrolyzed protein formulas *(30–34)*. Two of these three drugs were oil-based products (i.e., mandelamine suspension and MCT oil). Hydrolyzed proteins and free amino acids lack the complex chemical structure of intact proteins; thus, they are not subject to the same changes in structure and shape as intact proteins. Enteral formulas containing hydrolyzed proteins are, however, an emulsion much like intact protein formulas. The interaction with oil-based drugs is more likely related to disruption of the emulsion than to effects on the hydrolyzed protein. Nitrogen content (i.e., protein concentration) and dilution of the enteral formula are not expected to alter denaturation and do not appear to influence the risk of physical incompatibility between drugs and formulas *(31)*. Likewise, fiber is not expected to alter protein denaturation and does not appear to be a significant factor for incompatibility *(30)*. The source of fiber in the formulas studied was soy polysaccharide, a predominantly insoluble fiber. Addition of soluble fiber to a formula is not expected to alter protein denaturation anymore than insoluble fiber. At least theoretically, however, addition of some soluble fibers (e.g., pectin, banana flakes, and apple flakes) to a formula at the bedside could increase the risk of tube occlusion by gel formation, especially if an acidic drug is allowed to mix with formula. The fiber content of enteral formulas has recently expanded in both type and dose; the implications of which are not yet clear.

Interactions between drugs and formula that result in *physical* incompatibility are a major contributor to tube occlusion and loss of enteral access. Feeding tube occlusion can compromise drug and nutrient provision to patients receiving EN therapy. Despite several studies that have assessed enteral formula compatibility with drugs in liquid dosage forms, relatively few formulas and drugs have been evaluated *(30–36)*. The names of enteral formulas included in these compatibility studies are commonly seen in the marketplace today (e.g., Ensure, Osmolite); however, most formulas have been reformulated with different nutrient sources and ratios than formulas of the same name used in the studies. Drug formulations may also have changed over the years. Therefore, care must be exercised when interpreting enteral formula–drug compatibility studies relative to current practice. Tube occlusion is not a measured outcome in these studies; in vitro observations are typically reported. Most data are subjective descriptions of changes in the formula's physical appearance, although viscosity measurements are sometimes included. Nonetheless, when these observations are combined with data on chemical stability of formula components and drug characteristics, a few generalizations emerge. Table 11 summarizes generalizations related to *physical* interactions between drugs and enteral formulas that are applicable to current practice and may help the practitioner avoid many of these interactions.

Table 11
Summary of Factors and Their Degree of Contributing to Drug–Formula Physical Interactions

Protein complexity is a critical factor in drug–formula physical interactions.
- Caseinates appear to be most prone to physical interactions, followed closely by soy protein.
- Whey protein is the intact protein source least likely to be incompatible.
- Hydrolyzed proteins and amino acids rarely result in interactions except with oil-based products.

The drug vehicle for liquid dosage forms is a critical factor in drug–formula physical interactions.
- Acidic liquids are highly prone to interactions.
- Syrups are likely to be incompatible, especially when the pH of 4 or less.
- Alcohol contributes to interactions, especially with a low pH; thus acidic elixirs are problematic.
- Oil-based products are incompatible.

Drug–formula physical interactions do not appear to be influenced by:
- Nitrogen content.
- Fiber content.
- Dilution of the enteral formula.

Hepatic drug clearance may be influenced by the amount of protein provided by EN therapy. Animal studies indicated that protein intake can modify hepatic microsomal mixed-function oxidase system activity *(44,51,52)*. High protein intake stimulates this enzyme activity, thus increasing clearance of certain drugs (see Chapters 4 and 9). Niacin, riboflavin, and large doses of vitamin C may also increase enzymatic activity. Low protein intake may reduce renal plasma flow and creatinine clearance, thus decreasing renal elimination of certain drugs. However, much more research is needed in this area before any definitive statements can be made regarding clinical impact of these observations. Most studies concerning dietary effects on the mixed-function oxidases have been performed in animals.

3.3.2. COMPONENTS INFLUENCING GI MOTILITY

Formula components and characteristics that alter GI motility, as listed in Table 9, result in *pharmacokinetic* interactions when drug absorption is changed. Fats, especially long-chain fatty acids, slow gastric emptying to a greater extent than protein, and protein has a greater influence than carbohydrates. High osmolality also slows gastric emptying, as does increased formula viscosity. Calorically dense formulas (i.e., 2 kcal/mL) have both an increased viscosity and an increased concentration of macronutrients that can slow gastric emptying. As discussed in Section 3.2.2, slowed gastric emptying generally slows absorption of drugs administered by mouth or by a gastric feeding tube. Effects on extent of drug absorption are related to the drug's solubility and acid stability.

For drugs delivered through a post-pyloric feeding tube, formula effects on gastric emptying are irrelevant, but effects on small bowel motility may change drug absorption. Formulas with a high osmolality delivered into the small bowel can cause nausea, vomiting, diarrhea, and abdominal pain as water rapidly enters the bowel to dilute the formula. Likewise, rapid administration or significant fluctuation in volume of formula into the small bowel can cause diarrhea. When diarrhea shortens bowel transit time, drug absorption can be reduced, especially when the drug must undergo dissolution in the small bowel. Use of dosage forms where the drug is in solution (e.g., elixirs, syrups) may reduce the impact on absorption in these situations.

3.3.3. VITAMIN K CONTENT

Formulas with a high vitamin K content can antagonize the anticoagulant effect of warfarin, a significant *pharmacologic* interaction in which a nutrient interferes with a drug's mechanism of action. Warfarin acts by inhibiting formation of the vitamin K-dependent clotting factors (II, VII, IX, and X) in the liver and can overcome the typical daily intake of vitamin K in the diet. The amount of vitamin K in the diet may vary considerably. Data from national dietary surveys in the United States over the past 20 years report average dietary intake between 70 and 125 μg vitamin K daily, although previous data indicated intake of 300–500 μg vitamin K from the Western diet *(53–55)*. This interaction is best avoided by careful selection of the enteral formula for patients receiving warfarin therapy. Since the initial reports of warfarin resistance in the early 1980s, most formulas have reduced their vitamin K content *(56–60)*. Table 12 lists the current vitamin K content of several enteral formulas. It is probably best to avoid formulas containing over 100 μg of vitamin K per 1000 kcal in patients requiring warfarin anticoagulation, although this recommendation has not been tested in controlled trials. Patients with

Table 12
Selected Enteral Formulas and Vitamin K Content[a]

Vitamin K: 50 μg or less/1000 calories[b]
Pediatric Formulas
Nutren Junior (Nestle)
Peptamen Junior (Nestle)
Intact Protein Formulas
TwoCal HN (Abbott)
Osmolite (Abbott)
Nutren 1.0 [with or without fiber] (Nestle)
Nutren 1.5 and 2.0 (Nestle)
Replete [with or without fiber] (Nestle)

(Continued)

Table 12
(Continued)

Vitamin K: 50 μg or less/1000 calories[b]
Specialized Formulas
Critical care
Crucial (Nestle)
Glucose control
Glytrol (Nestle)
Pulmonary function
NutriVent (Nestle)
Renal dysfunction
NutriRenal (Nestle)
Nepro (Abbott)
Suplena (Abbott)
Hydrolyzed protein/free amino acids
f.a.a. (Nestle)
Peptamen products (Nestle)
Vitamin K: 51–75 μg/1000 calories[b]
Pediatric formulas
Pediasure [with or without fiber] (Abbott)
Intact protein formulas
Ensure Plus (Abbott)
Jevity 1, 1.2, and 1.5 Cal (Abbott)
Osmolite 1.5 Cal (Abbott)
Osmolite 1 Cal (Abbott)
ProBalance (Nestle)
Osmolite 1.2 Cal (Abbott)
Specialized formulas
Critical care
Pivot 1.5 Cal (Abbott)
Glucose control
Glucerna (Abbott)
Pulmonary function
Pulmocare (Abbott)
Oxepa (Abbott)
Hydrolyzed protein/free amino acids
Perative (Abbott)
Vital HN (Abbott)
Vitamin K: 76–100 μg/1000 calories[b]
Intact protein formulas
Carnation Instant Breakfast (Nestle) with 2% milk
Carnation Instant Breakfast (Nestle) ready to drink
Promote [with or without fiber] (Abbott)
Ensure High Protein (Abbott)

Specialized formulas
Glucose control
Glucerna Select (Abbott)
Hydrolyzed protein/free amino acids
Optimental (Abbott)

Vitamin K: 101–150 μg/1000 calories[c]

Intact protein formulas
Carnation Instant Breakfast Essentials (Nestle)
No sugar added with 2% milk or non-fat milk

[a] Formulas in each category are listed from least to most vitamin K per 1000 calories. Always confirm current vitamin K content with the product label and current manufacturer's data since vitamin K content of enteral formulas can change.

[b] Formulas with low to moderate vitamin K content are generally safe to use in patients receiving warfarin therapy.

[c] Formulas with higher vitamin K content should be used cautiously in patients receiving warfarin therapy. Consider comparable formulas with lower vitamin K content for patients with warfarin therapy.

disruption of normal vitamin K production by GI flora (i.e., antibiotic-induced diarrhea, gut decontamination prior to chemotherapy) may be at less risk of warfarin resistance secondary to excess vitamin K intake. Separating warfarin administration from formula administration does not prevent warfarin resistance secondary to high vitamin K intake. However, there is evidence that holding enteral feeding for at least an hour before and after warfarin administration can reduce the risk of warfarin resistance in patients receiving EN therapy *(29,61–63)*. This likely reflects a separate *pharmacokinetic* interaction between warfarin and enteral formula that would also account for reports of warfarin resistance in formulas with a low to modest vitamin K content.

3.4. Disease-Related Factors

3.4.1. Visceral Protein Status

Malnutrition is the most important disease process in relation to drug–nutrient interactions in patients receiving EN therapy. The effects of malnutrition on drug–nutrient interactions are not specific to patients receiving EN therapy, but the majority of patients started on EN are malnourished or at high risk of malnutrition. *Pathophysiologic* interactions in many disease processes are likely mediated through development of malnutrition, especially protein malnutrition. The decreased visceral protein status and the increased edema that are noted with protein malnutrition can significantly alter pharmacokinetic parameters of drugs and may alter nutrient absorption. Drugs that are highly bound to albumin (e.g., warfarin) are particularly susceptible to *pathophysiologic* interactions. As serum albumin concentrations decrease, drug distribution is altered and toxicity may be increased.

Metabolism may be reduced in severe protein malnutrition since production of enzymes necessary for metabolism may be reduced. There are probably many effects of malnutrition on drug–nutrient interactions, but less research than necessary has focused on this subject (see Chapter 6).

3.4.2. GI MOTILITY

Multiple disease processes can increase or decrease GI motility, as indicated in Table 9. As discussed in Section 3.2.2, gastric emptying rate often controls the rate of drug absorption when drugs are taken by mouth or administered to the stomach and may influence absorption of specific nutrients. Effects on extent of absorption depend on specific drug characteristics. Small bowel transit time can be altered by the pharmacologic effects of drugs, and drug absorption can be altered by changes in transit time. For example, 48% of patients in a pentobarbital-induced coma experienced feeding intolerance that was not associated with dose, timing, or duration *(64)*. The effects of altered GI motility on drug–nutrient interactions are not specific to patients receiving EN therapy, but many patients receiving EN have abnormal GI motility. Therefore, the practitioner managing EN therapy must be alert to possible problems related to drug and nutrient absorption in patients with abnormal GI motility who are receiving EN therapy.

4. SPECIFIC DRUGS

Several drugs of key clinical importance relative to drug–nutrient interactions in patients receiving EN therapy are discussed below. *Pharmacokinetic* interactions involving absorption occur with all of the drugs, although *pharmacologic* interactions can also occur with warfarin. Mechanisms responsible for these interactions are often inadequately defined; studies documenting the interactions are few, small, and not as rigorous as is desired for evidence-based recommendations. Table 3, step 11 includes recommendations for holding formula administration with specific drugs, and Table 8 contains a summary of methods to handle *pharmacokinetic* and *pharmacologic* interactions, as well as the other classes of drug–nutrient interactions without reference to specific drugs.

4.1. Phenytoin

Phenytoin was one of the first drugs noted to have a significant interaction with enteral formula, and this interaction continues to be classified as clinically significant *(65)*. Numerous studies have evaluated this interaction since Bauer's initial report *(66)*. A review of in vivo and in vitro studies, case reports, and letters found four prospective, randomized, controlled studies that do not support the existence of an interaction *(67)*. All four studies were in a small number of healthy volunteers (i.e., 6–10), and only one study used continuous feeding through a nasogastric tube *(67,68)*. The remaining 25 reports and studies provide evidence of an interaction in patients, although none of these are prospective, randomized, controlled studies. The mechanism of the interaction has not been delineated despite multiple theories including binding to the enteral administration tubing or with an enteral formula component *(40,69)* and various pH-related explanations *(41,70,71)*. Protein complexity does not appear to be an important factor as the interaction has been reported with both intact protein and hydrolyzed protein formulas *(72,73)*. Methods reported to reduce the interaction include stopping feeding for an hour before and after administration of phenytoin *(74)*, clamping the feeding tube for an hour after drug administration *(75)*, diluting phenytoin suspension prior to administration *(39)*, opening phenytoin capsules and administering the contents through the tube *(76)*, and using a commercial meat-based formula with a bolus feeding schedule *(69)*.

None of the suggested methods can assure therapeutic phenytoin concentrations, but stopping feeding for at least an hour before and after the phenytoin dose appears to most consistently produce therapeutic concentrations with reasonable drug doses. Holding formula for 2 h on each side of the phenytoin dose has been more effective than holding for 1 h in some studies, but this increases the risk of inadequate formula delivery *(66)*. Therefore, a 2 h hold time may be best reserved for patients in whom a 1 h hold fails to prevent subtherapeutic concentrations. Clamping the tube for an hour after the phenytoin dose must be studied in a prospective, randomized manner before this method can be routinely recommended. However, a retrospective review of brain-injured patients receiving phenytoin through gastrostomy tubes noted significantly higher serum phenytoin concentrations when the tube was clamped after the drug dose vs uninterrupted feeding *(75)*. Diluting phenytoin suspension prior to administration through a feeding tube improves phenytoin delivery in vitro compared to undiluted suspension *(39)*. The dilution factor in this study was approximately threefold with water on a volume:volume basis. As discussed in Section 3.2.1, dilution of viscous suspensions such as phenytoin at least 50:50 with water prior to administration through a feeding tube should be a standard of practice, especially for small bore nasal tubes. The effectiveness of using capsule contents administered through a feeding tube is not adequately studied as only seven healthy volunteers were included in the study suggesting this approach, and formula was ingested on an intermittent oral schedule *(76)*. Administration of a capsule's contents through a small-bore tube may cause occlusion, and the potential benefits are probably not adequate to balance potential risks with an unproven method. Commercial meat-based formula is relatively expensive compared to standard intact protein formulas, is often not covered by third-party payers, and may require delivery through a large-bore tube. Only five healthy volunteers were included in the study with meat-based formula, and intermittent ingestion of the formula occurred rather than administration via a feeding tube *(69)*. Thus, use of a meat-based formula requires more rigorous evaluation before this method can be routinely recommended. Regardless of the method(s) used to minimize the phenytoin–enteral formula interaction, serum phenytoin concentrations require close monitoring to avoid subtherapeutic concentration during EN therapy and potentially toxic concentrations when EN therapy is discontinued. Serum concentrations should be monitored once to twice weekly during the initiation and discontinuation of EN therapy or until the patient is therapeutically stable on phenytoin. Close clinical observation for signs and symptoms of inadequate disease control and drug toxicity are also warranted. When serum albumin is below 3 g/dL, monitoring of free phenytoin concentration should be considered to avoid potentially toxic levels from decreased binding of drug to albumin *(77)*.

4.2. Carbamazepine

Dissolution is the rate-limiting step for absorption of carbamazepine. Anything which slows gastric emptying, such as food, allows more time for dissolution and is expected to increase absorption. However, there is concern that EN therapy decreases carbamazepine absorption and may place patients at risk of inadequate disease control when EN is required. Evidence supporting an interaction between EN therapy and carbamazepine is sparse. Studies in patients receiving tube feeding are lacking, and few in vivo studies are available.

One randomized, crossover study with seven healthy men reported a relative bioavailability of 90% for carbamazepine suspension administered by nasogastric tube with continuous feeding vs oral intake following an overnight fast *(78)*. Pharmacokinetic parameters were not significantly different, although serum carbamazepine concentrations were lower with feeding and significantly lower at 8 h. The maximum serum concentration approached significance for being lower with feeding. The small size of this study most likely prevented statistically significant findings. With the same intact protein formula and use of carbamazepine compressed or chewable tablets, recovery of drug after mixing with formula for an hour was 58% *(79)*. Drug recovery was 79% from simulated gastric juice alone and 75% from simulated intestinal fluid alone. Addition of formula to the simulated gastric juice increased drug recovery (85%) but decreased recovery from simulated intestinal fluid (59%). Carbamazepine recovery from formula alone was essentially the same as from formula plus simulated intestinal fluid. Such an in vitro study design cannot account for effects of gastric emptying rate, which could increase absorption above that from "gastric juice" in this study, especially if slow gastric emptying improved dissolution. On the other hand, concern is raised that administration of carbamazepine through a post-pyloric tube may result in subtherapeutic drug concentrations whether or not formula is present in the small bowel. Holding formula for 2 h on each side of the carbamezepine dose has been recommended to minimize the interaction with carbamazepine in the clinical setting *(80,81)*. However, carbamazepine has not been shown to bind with a component of enteral formula either in vivo or in vitro. Studies in patients with feeding tubes are needed to document the incidence of an enteral formula–carbamazepine interaction and to determine the best method of managing the interaction when it occurs. Not acknowledging the interaction could result in serious complications for patients receiving carbamazepine through feeding tubes.

The limited data available suggest that an interaction is most likely to be clinically significant when drug is administered through a post-pyloric tube. Formula should be held for 2 h before and after drug administration in this population. It is less clear that holding formula with drug administration through a gastric tube is necessary and it may be best to hold formula on a case-by-case basis when maintaining a therapeutic carbamazepine concentration is difficult. Carbamazepine suspension should be diluted 50:50 with water, as discussed in Section 3.2.1 *(38)*. However, it is unclear if the difference in drug recovery occurs with non-polyvinyl chloride tubes and with standard flush volumes as compared to the large flush volumes (i.e., two 50 mL flushes) used in this study.

4.3. Fluoroquinolones

Several studies have evaluated fluoroquinolone bioavailability in either healthy volunteers or patients receiving EN therapy. Most studies have evaluated ciprofloxacin and indicate lower bioavailability when quinolones are administered with enteral formula. One of three small studies in healthy volunteers failed to detect a difference in bioavailability, despite using a nasogastric tube for drug delivery in two segments of the crossover design *(82)*. Other studies in healthy volunteers found a 25–28% reduction in ciprofloxacin bioavailability with intact protein formula *(83,84)*. Hydrolyzed protein formula was not evaluated in these or other studies. In hospitalized patients, bioavailability decreased 27–67% depending on the site of feeding*(48)*. The greatest decrease is seen with jejunal feeding, as discussed in Section 3.2.2 *(49,50)*. Decreased bioavailability is also noted in critically ill patients receiving continuous EN therapy and ciprofloxacin via nasogastric tube *(85,86)*. The clinical significance of this decrease in bioavailability is not clear since ciprofloxacin concentrations have been reported to remain above the minimum inhibitory concentration for many pathogens *(87)*. However, larger studies are needed to confirm adequate drug concentrations (AUC:MIC) for treatment of major pathogens for which ciprofloxacin is selected before the decrease in bioavailability can be considered clinically irrelevant. Inadequate antibiotic concentrations could result in significant patient morbidity and potentially mortality.

The interaction between fluoroquinolones and enteral formula appears to be drug dependent and influenced by the hydrophilicity of the drug. In 13 healthy volunteers, ofloxacin was found to have 90% bioavailability with an intact protein formula compared to 72% bioavailability for ciprofloxacin *(83)*. Gatifloxacin bioavailability does not appear to be altered with concomitant enteral feeding into the stomach, although a wide range of bioavailability may occur with critical illness *(88)*. Immediate loss of unbound antibiotic was noted in an in vitro study when quinolone antibiotics were mixed with intact protein formula *(89)*. Recovery was about 54% for ofloxacin, 39% for levofloxacin, and 17.5% for ciprofloxacin. Loss of drug did not appear to correlate with cation content of the formula, suggesting that binding of quinolones with divalent cations (i.e., calcium and magnesium) may not be responsible for the interaction. Loss of drug from binding to the feeding tube itself does not seem to be a problem and no specific component of the enteral formula has been identified as binding drug *(90)*.

Holding formula for 1 h or more before and 2 h after the dose is the recommended method to minimize effects of enteral feeding on serum concentrations of ciprofloxacin and norfloxacin *(65,80,81)*. Holding the formula for 2 h before and 4 h after fluoroquinolone administration, or administering the drug intravenously, has also been suggested*(15)*. Although less hydrophilic quinolones appear to be less affected by an interaction with enteral formula, the safest approach is to hold formula for at least 1 h before and 2 h after quinolone administration through a feeding tube unless there is documentation of excellent bioavailability, as is the case for gatifloxacin *(88)*. Thus, a therapeutically appropriate quinolone with less frequent dosing may often be a better choice for patients receiving EN therapy. Using a different antibiotic with appropriate coverage for the infection would be another option to avoid the interaction. It is important to note that the commercially available 5 and 10% CIPRO oral suspension (ciprofloxacin from Bayer Corporation) "should not be administered through feeding tubes due to its physical characteristics" as per literature included in the package *(91)*.

4.4. Warfarin

The *pharmacologic* interaction between warfarin and vitamin K in enteral formulas was addressed in Section 3.3. A second *pharmacokinetic* interaction was also mentioned as possibly explaining the continued problem of warfarin resistance after reduction of vitamin K content in most enteral formulas more than 10 years ago *(60–63)*. A retrospective crossover case series in six ICU patients revealed that the change in INR during a pair of 3-day observation periods was significantly improved when feedings were held for 1 h before and after warfarin administration compared to co-administration – despite similar drug doses *(63)*. Warfarin has been reported to bind to some filterable component of the formula, but this specific mechanism of warfarin resistance has not been adequately studied *(62)*. Protein is the most likely filterable component to be involved with warfarin binding, especially since warfarin is a highly protein-bound drug. Assuming protein is the binding component, formulas containing free amino acids would not be expected to cause warfarin resistance; hydrolyzed proteins might, depending on the length of remaining peptide chains. Neither free amino acid nor hydrolyzed protein formulas have been evaluated. Holding formula administration for an hour before and after warfarin administration should be an effective method of managing the *pharmacokinetic* interaction *(61,63)*. Warfarin therapy must be carefully monitored for an alteration in anticoagulant response whenever EN therapy is initiated or discontinued and when formula changes occur to assure patient safety.

4.5. Theophylline

Theophylline elimination is increased with high protein intake and decreased by a high carbohydrate, low protein diet *(92)*. Rate and extent of absorption may be affected by food with rapid release of some sustained release preparations when taken with food (see Chapters 8 and 9). Effects of EN therapy on theophylline are poorly studied although one small study suggested that continuous nasogastric feeding interfered with theophylline absorption *(93)*. Nevertheless, holding formula administration for 1 h before and 2 h after drug administration is recommended *(80,81)*. Two single-dose studies in healthy volunteers found no difference in extent of absorption for sustained-release theophylline preparations with intact protein formula taken by mouth (100 mL every hour for a total of 10 h) compared to fasting *(94,95)*. Studies are not available in healthy volunteers with feeding tubes in place or in patients receiving EN therapy. Studies are necessary to determine whether holding formula administration before and after theophylline administration provides any clinical benefit. At this time, it is difficult to justify holding formula unless the patient has experienced erratic theophylline serum concentrations or inadequate disease control after initiation of EN therapy.

4.6. Levothyroxin

A *pharmacokinetic* interaction involving absorption has been reported between soy protein and levothyroxin sodium *(80,81)*. Interference with drug absorption results in higher than expected fecal loss of levothyroxin sodium with soy protein formulas. Soy polysaccharide is the most common fiber source in enteral formulas, but its effect on levothyroxin sodium pharmacokinetics has not been assessed. Several enteral formulas contain soy protein. Without more definitive information, it is probably best to avoid enteral formulas containing soy protein in patients receiving levothyroxin. A large percentage of formulas containing fiber contain soy polysaccharide; thus, it may not be practical to avoid soy polysaccharide when a fiber-containing formula is appropriate. It is prudent to monitor thyroid function within several days for patients receiving levothyroxin sodium who start EN therapy since this is a poorly studied interaction, but it is most important if the formula contains soy products. On the other hand, a change in clinical status that warrants initiation of EN therapy probably warrants evaluation of the patient's levothyroxine dose whether the formula contains soy products or not.

4.7. Penicillin V Potassium

Directions for penicillin V potassium recommend the drug be taken on an empty stomach since decreased absorption occurs with food *(96)*. Absorption is reported to be 30–80% and erratic with feeding *(80,81)*. Holding administration of formula for 1 h before and 2 h after administering, the drug is recommended to mitigate this *pharmacokinetic* interaction. However, studies in patients receiving EN therapy are lacking as are studies in any population receiving the drug and enteral formula through a feeding tube. Recommendations for holding formula administration follow guidelines for taking the drug on an empty stomach, generally recognized as 1 h before a meal or 2 h after. Selecting another antibiotic that provides appropriate coverage and site penetration also would be an appropriate method of managing the interaction.

5. CONCLUSION

Using a broad definition, drug–nutrient interactions in patients receiving EN therapy fall into several categories including physical, pharmaceutical, pharmacologic, physiologic, pharmacokinetic, and pathophysiologic interactions. Physical compatibility, pharmaceutical issues, and osmotic characteristics have received the most attention, but even these topics are poorly researched. Unfortunately, in this age of evidence-based medicine, expert opinion and consensus rather than strong research data still dominate the domain of drug–nutrient interactions in patients receiving EN therapy. Data identifying interactions between drugs and enteral formula components or administration techniques are minimal and sometimes conflicting. Likewise, evidence supporting techniques used to manage drug–nutrient interactions in patients receiving EN therapy is often limited. Available data may be old and may not be applicable to products in use today. Well-designed prospective human studies in patients with feeding tubes in place are difficult to find. Research is needed on essentially every aspect of drug–nutrient interactions in this patient population. Until such research is completed, extrapolation from pharmaceutical principles and pharmacokinetic theories, case reports, and in vitro data will remain the mainstay of evidence for identifying and managing drug–nutrient interactions in patients receiving EN therapy. The practitioner must be ever vigilant for drug–nutrient interactions that interfere with appropriate drug and nutritional therapy in patients receiving EN. Nevertheless, the specific steps discussed throughout this chapter and summarized in Tables 3 and 8 can reduce the risk of interactions and adverse outcomes for patients.

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14 Drug–Nutrient Interactions in Patients Receiving Parenteral Nutrition

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Objectives

- Describe parenteral nutrition and discuss its indications and routes of administration.
- Define stability and compatibility as it relates to parenteral drugs and nutrition.
- Determine the stability of drugs admixed with parenteral nutrition or co-infused by Y-site administration.
- Discuss the guidelines for safe administration of drugs with parenteral nutrition.

Key Words: Admixture; compatibility; parenteral nutrition; stability

1. INTRODUCTION

Parenteral nutrition (PN) is a complex nutrition therapy applied in a variety of health-care settings. Patient conditions where PN is used frequently require medications to treat or control symptoms of disease. It has been known for some time that medications used in patients receiving PN often interfere with the success of this nutritional intervention *(1)*. The purpose of this chapter is to describe the following: the indications and use of PN, issues related to compatibility and stability of medications with PN, and the influence of PN on the pharmacokinetic and pharmacodynamic effect of medications.

2. PARENTERAL NUTRITION

2.1. Definitions

Parenteral nutrition is best described as the administration of nutrients intravenously *(2)*. It has been used in adult, pediatric, geriatric, and neonatal patients located in the hospital, home, nursing home, or extended care facility. PN is a complex formulation made up of more than 40 different chemical compounds (nutrients) that impart specific stability and compatibility issues. *Compatibility* refers to the combining of two or more chemical products such that the physical

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integrity of the products is not altered *(2)*. *Stability* is the extent to which a product retains the same physicochemical properties and characteristics that it possessed at the time of its manufacture throughout its period of storage and use *(2)*. Incompatibility occurs as either a concentration-dependent precipitation or acid–base reaction that results in the physical alteration of the products when combined together. Serious harm and death have been attributed to incompatibilities resulting from improperly compounded PN *(3)*. Incompatibility of a mixture or instability of a nutrient or drug also has the potential to influence therapeutic effect.

There are two types of PN: 2-in-1 and 3-in-1 formulations. A 2-in-1 PN solution is the combination of the two macronutrients dextrose and amino acids along with electrolytes, vitamins, and trace elements in the same infusion container while the intravenous fat emulsions (IVFE) are administered separately. IVFE is an intravenous fat-in-water emulsion of oil, egg yolk phosphatide, and glycerin. Because it is an oil-in-water emulsion, when it is admixed in PN as a 3-in-1 formulation (i.e., all three macronutrients in one infusion container) – also known as "total nutrient admixture" or TNA – it remains an emulsion with its stability being dictated predominantly by its emulsifier content.

PN admixtures are hypertonic relative to body fluids and, if administered inappropriately, may result in venous thrombosis, suppurative thrombophlebitis, and extravasation. The osmolarity is dependent on the dextrose, amino acid, and electrolyte content. The osmolar contribution of dextrose is approximately 5 mOsm/g. Amino acids yield about 10 mOsm/g and electrolytes provide 1 mOsm/mEq of individual electrolyte additive. The final osmolarity of PN dictates the venous access site where the fluid may be safely administered. Generally, the maximum osmolarity tolerated by peripheral vein is 900 mOsm/L *(4)*. The usual PN has an osmolarity >1000 mOsm/L and, therefore, must be delivered into a large diameter vein, usually the superior vena cava adjacent to the right atrium (central vein PN, CPN). The rate of blood flow in these large vessels rapidly dilutes the hypertonic parenteral feeding formulation to that of body fluids, minimizing venous complications of its infusion. Peripheral PN (PPN) is delivered into a peripheral vein, usually of the hand or forearm. It has a similar composition to CPN but lower concentrations of nutrient components are required to allow for safe peripheral administration. Therefore, PPN usually requires large fluid volumes to be administered. Since venous tolerance continues to be a concern, this route for PN is reserved for those with mild to moderate malnutrition who require treatment for short periods of time (<2 weeks).

2.2. Indications for PN

PN is used in patients who are malnourished or may become malnourished during prolonged periods of inadequate oral intake. Because PN is associated with both complications of venous access (mechanical and/or infectious) and metabolism (fluid, electrolyte, acid–base, glucose, or fat homeostasis in the short term and additionally vitamin and trace element homeostasis in the long term), it is reserved for those patients in whom the risk-to-benefit is appropriate. In general, PN is used in patients who have temporary or permanent malfunction of the gastrointestinal tract. The conditions in which enteral nutrition is contraindicated

Table 1
Conditions Usually Requiring Parenteral Nutrition

Complete intestinal obstruction
Paralytic ileus (unless localized to the stomach)
High-output intestinal fistula (volume >500 mL/day)
Severe, intractable diarrhea (volume >1500 mL/day)
Short bowel syndrome
Severe hemodynamic instability

include the following: paralytic ileus, mesenteric ischemia, small bowel obstruction, or enterocutaneous fistula (Table 1). Other conditions in which a trial of enteral nutrition has failed with appropriate tube placement (post-pyloric) usually require PN. Examples of such conditions are those with pancreatitis, malabsorption conditions, or critical illness where mesenteric ischemia may be a contributing factor.

3. COMPATIBILITY AND STABILITY OF DRUGS WITH PN

3.1. General

Compatibility and stability problems associated with PN and medication use are dependent on the composition of PN and sample formulas. Table 2 provides specific components of PN formulations. The content of amino acid formulations (Table 3) and IVFE (Table 4) is noteworthy, since these also contribute a multitude of different chemical compounds to the final PN formulation *(5)*. The variability in content resulted in the recommendation that brand names for the amino acid and IVFE products be included in patient-specific PN orders and labels *(6)*.

Tables 5 and 6 provide sample formulas evaluated for drug–PN compatibility *(7,8)*. Since compatibility is dependent on the type of PN and its contents, the table

Table 2
Components of Parenteral Nutrition

Macronutrient	Dextrose injection Amino acids injection Intravenous fat emulsion
Micronutrient	
Electrolytes	Sodium (as chloride, acetate, and phosphate salt) Potassium (as chloride, acetate, and phosphate salt) Magnesium (as sulfate and chloride salt)
Vitamins	Calcium gluconate (only salt recommended for PN admixture) Parenteral multivitamins (fat soluble: A, D, E, and K. Water soluble: thiamin, riboflavin, niacin, pyridoxine, vitamin B_{12}, folic acid, biotin, pantothenic acid, and ascorbic acid)
Trace elements	Multiple trace element products (include zinc, copper, chromium, manganese, and selenium)

Table 3
Amino Acid Formulations

*Type of Amino Acid Formulation**	*Commercial Product (Manufacturer)*	*Comments*
Standard solution	Aminosyn (Abbott) Aminosyn II (Abbott) Freamine III (Braun) Travasol (Baxter)	Contains a balanced amount of essential and non-essential amino acids for general use. Considered to be of high biological value
Hepatic formula	Aminosyn HF (Abbott) Hepatamine (Braun)	Formulas with higher amounts of branched-chain amino acids and a lower content of aromatic amino acids
Renal failure	Aminosyn RF (Abbott) RenAmine (Baxter) NephrAmine (Braun)	Products with higher content of essential amino acids with or without additional histidine and arginine
Metabolic stress/ trauma	Aminosyn HBC (Abbott) BranchAmin (Baxter) FreAmine HBC (Braun)	Contains a higher content of branched-chain amino acids
Pediatrics	Aminosyn PF (Abbott) Trophamine (Braun) Premasol (Baxter)	Contains a lower content of methionine, phenylalanine, and glycine. Also contains taurine, glutamate, and aspartate

* Specific concentrations of each component differ between commercial products within each formulation type

provides sample PPN and CPN formulas with or without IVFE. The formulas are presented in accordance with the Safe Practice Guidelines *(6)* developed by the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.), in a 1 L total volume so the total daily dose also represents the concentration of ingredient per liter. It is important to represent PN formulas in this manner because misinterpretation of the formula as patients transfer across health-care organizations has resulted in patient harm. From this perspective, it is important to represent the PN formula in a manner that facilitates its interpretation related to the dose of nutrient (content). To meet the nutrient needs of patients

Table 4
Composition of Intravenous Fat Emulsions in the United States

Component or Characteristic	*Intralipid (Baxter)*	*Liposyn III (Hospira)*
Oil (%)	Soybean (10, 20, 30)	Soybean (10, 20, 30)
Egg yolk phosphatide (%)	1.2	1.2
Glycerin (%)	2.25	2.5
Fatty acids (%)		
Linoleic acid	50	54.5
Oleic acid	26	22.4
Palmitic acid	10	10.5
Linolenic acid	5	8.3
Stearic acid	3.5	4.2
Osmolarity (mOsm/L)	260–268	284–292
Approximate pH	8	8.3
Fat particle size (μm)	0.5	0.4

Table 5
Composition of 2-in-1 PN Solutions *(7)*

	Formulas	
Component and Unit	*Peripheral Line*	*Central Line*
Amino acids Injection Product[a] (g)	35	42.5
Dextrose (g)	50	250
Multivitamins[b] (mL)	10	10
Trace elements[c] (mL)	1	1
Electrolyte[d] content		
Sodium (mEq)	41	44
Potassium (mEq)	40	30–40
Calcium (mEq)	5–9	5–9
Magnesium (mEq)	8	8
Chloride (mEq)	65–78	43–65
Acetate (mEq)	25–31	30–38
Phosphorous (mmol)	3.5	10–15

[a] Products tested: Aminosyn II 10%, Abbott Laboratories; FreAmine III 10%, Braun Laboratories

[b] M.V.I.-12, AstraZeneca

[c] Abbott, containing zinc 0.8 mg/mL, manganese 0.16 mg/mL, copper 0.2 mg/mL, and chromium 2 μg/mL as the chloride salts

[d] Provided from the addition of the following electrolyte salts: potassium phosphate, sodium chloride, potassium chloride, and magnesium sulfate

ranging in weight from 50 to 100 kg, volumes of 1.5–2.5 L of these formulas would need to be administered. For compatibility purposes, the manner by which chemicals react are most often influenced by their concentration and

Table 6
Composition of 3-in-1 PN Formulas *(8)*

Component and Unit	*Formulas* *Peripheral Line*	*Central Line*
Amino acids injection product[a] (g)	30	49
Dextrose (g)	50	200
IVFE[b] (g)	20	35
Multivitamins[c] (mL)	10	10
Trace elements[d] (mL)	1	1
Electrolyte[e] content		
Sodium (mEq)	43	40
Potassium (mEq)	40	40
Calcium (mEq)	5–9	5–9
Magnesium (mEq)	8	8
Chloride (mEq)	35–45	35–45
Acetate (mEq)	42–52	45–68
Phosphorous (mmol)	7.5–15	10–15

[a] Products tested: Aminosyn II 10%, Abbott Laboratories; FreAmine III 10%, Braun Laboratories

[b] Products tested: Intralipid, Kabi Pharmacia, Inc.; Liposyn II and Liposyn III, Abbott Laboratories

[c] M.V.I.-12, AstraZeneca

[d] Abbott, containing zinc 0.8 mg/mL, manganese 0.16 mg/mL, copper 0.2 mg/mL, and chromium 2 μg/mL as the chloride salts

[e] Provided from the addition of the following electrolyte salts: potassium phosphate, sodium chloride, potassium chloride, and magnesium sulfate

environmental factors such as exposure to light and temperature. Therefore, the concentration of ingredients (quantity per liter) is necessary to assess compatibility of medications with PN.

3.2. Admixture Compatibility and Stability

Due to the high level of formula variability and patient-specific customization of PN formulas *(7)*, it is not feasible to test the compatibility of medications with every PN formulation that could be used in clinical practice. The complex nature of PN contributes to a high probability of incompatibilities when it is used as a vehicle for drug administration or when it is co-infused via the same intravenous catheter. These incompatibilities could result in precipitation in the venous catheter causing malfunction of the catheter or, if administered, pulmonary emboli. Therefore, admixture of medications with PN is not advised. However, there are periods when there is no other alternative. In these cases, the following guidelines should be followed:

- Assure the medication is stable and compatible with the PN formulation for the period beginning with pharmacy admixture through completion of its infusion (usually 24–36 h).
- Assure the PN remains stable and compatible with the medication additive.

- Assure the clinical effect of the drug is maintained if infused continuously with PN and the dose of medication has been stabilized prior to PN admixture.
- Assure that there is a stable PN infusion rate.
- The PN should be labeled appropriately and reviewed in concert with the patient's medication profile to avoid therapeutic duplication or abrupt discontinuation of medication therapy if the PN is discontinued.

In general, only histamine type-2 (H_2) receptor antagonists and insulin have been admixed with 3-in-1 PN *(5,9)*. These drugs may also be admixed with 2-in-1 PN. Other drugs demonstrating stability, compatibility, and clinical effect when admixed with 2-in-1 PN include heparin, aminophylline, hydromorphone, hydrochloric acid (maximum concentration: 100 mEq/L), and iron dextran *(5,9)*. Unfortunately, an evaluation of nutrient stability in these admixtures is not typically performed.

3.3. Co-infusion Compatibility and Stability

Co-administration with PN is often considered for intravenous medications that would otherwise be administered via continuous infusion or as individual doses into an existing intravenous catheter (i.e., "piggyback"). This technique involves Y-site administration with the drug administered either as a piggyback, continuous infusion, or intravenous push at the Y-site injection port of the venous access device. Simulated studies of Y-site compatibility of medications with PN use a 1:1 volume ratio of drug with PN. In adults, the time of drug exposure to PN is short due to the rapid infusion of the medication and PN. In pediatrics, the time of contact is longer due to the slower infusion rate of drug and PN. Trissel and co-workers have studied the compatibility of medications with 2-in-1 and 3-in-1 PN formulations *(7,8)*. This information along with past reviews *(5)* is the basis for the compatibility data for Tables 7, 8, 9, and 10. Compatibility is provided for 2-in-1 admixtures (Tables 7 and 9) as well as 3-in-1 (Tables 8 and 10) formulations. If the drug is not listed in any of these tables, it has not been studied for compatibility and, therefore, should not be administered by this technique. If a drug is not compatible with PN or if no compatibility information exists, some options to consider for administration are to use a separate lumen of a multi-lumen central venous catheter or cycle the PN and administer the drug when the PN is not infusing. It is important to note the type of reactions observed for incompatible mixtures of drugs and PN. For 2-in-1 solutions, reactions varied from the formation of a gross flocculent or yellow precipitate (amphotericin B) to turbidity or color change *(9)*. Incompatibility for 3-in-1 or TNA admixtures frequently occurred as a result of damage to the emulsion integrity and the possibility of the formation of free oil *(9)*. Twenty-three of 106 commonly used drugs were incompatible when studied against 9 different 3-in-1 formulations based on visual inspection *(8)*. Evaluations of drug stability or nutrient stability were not performed.

In some instances, the incompatibility may be due to a single PN component, as in the case of the interaction between ceftriaxone and calcium. It has been known for some time that ceftriaxone has high calcium-binding affinity *(10)*. Fatal reactions associated with a precipitate of cetriaxone–calcium salt have occurred in neonates receiving the antimicrobial co-administered with calcium-containing

Table 7
Y-Site Injection Compatibility (1:1 Mixture): Drugs Compatible with 2-in-1 Solutions *(5,7–9)*

- Amikacin sulfate
- Aminophylline
- Amoxicillin sodium
- Ampicillin
- Ampicillin/sulbactam
- Atracurium besylate
- Aztreonam
- Bumetanide
- Buprenorphine HCl
- Butorphanol tartrate
- Calcium gluconate
- Carboplatin
- Cefazolin sodium
- Cefepime
- Cefotaxime
- Cefoxitin
- Ceftazidime
- Ceftizoxime
- Ceftriaxone sodium
- Cefuroxime
- Chlramphenicol sodium succinate
- Chlorpramazine HCl
- Cimetidine HCl
- Clindamycin phosphate
- Clonazepam
- Cyclophosphamide
- Dexamethasone sodium phosphate
- Digoxin
- Diphenhydramine HCl
- Dobutamine HCl
- Dopamine HCl
- Doxycycline
- Droperidol
- Enalaprilat
- Epinephrine HCl
- Erythromycin lactobionate
- Famotidine HCl
- Fentanyl citrate
- Fluconazole
- Folic acid
- Gentamicin sulfate
- Granisetron HCl
- Haloperidol lactate
- Heparin sulfate
- Hydrocortisone sodium phosphate
- Hydrocortisone sodium succinate
- Hydromorphone HCl
- Hydroxyzine HCl
- Idarubicin HCl
- Ifosfamide
- IL-2
- Imipenem–cilastatin sodium
- Insulin, regular
- Iron dextran
- Isoproterenol HCl
- Kanamycin sulfate
- Leucovorin calcium
- Levorphanol tartrate
- Lidocaine HCl
- Linezolid
- Lorazepam
- Magnesium sulfate
- Mannitol
- Meperidine HCl
- Mesna
- Methyldopate HCl
- Methylprednisolone sodium succinate
- Metronidazole
- Milrinone lactate
- Morphine sulfate
- Multivitamins
- Nafcillin sodium
- Netilmicin sulfate
- Nitroglycerin
- Norepinephrine bitartrate
- Octreotide acetate
- Ofloxacin
- Ondansetron HCl
- Oxacillin sodium
- Paclitaxel
- Penicillin G
- Penicillin G potassium
- Pentobarbital sodium
- Phenobarbital sodium
- Piperacillin sodium
- Piperacillin sodium–tazobactam
- Potassium chloride
- Prochlorperazine edisylate
- Propofol
- Ranitidine HCl
- Sargramostim
- Sodium nitroprusside
- Tacrolimus
- Ticarcillin disodium
- Ticarcillin disodium–clavulanate potassium
- Tobramycin sulfate
- Trimethoprim–sulfamethoxazole
- Urokinase
- Vancomycin HCl
- Vecuronium bromide
- Zidovudine

solutions including PN *(11,12)*. This may even occur when administered through different infusion lines. Although the reaction had not been reported in older children or adults, the initial contraindication to the use of ceftriaxone in patients receiving calcium-containing PN was broad nonetheless *(11)*. Following further study the absolute contraindication to concomitant use of ceftriaxone and intravenous calcium-containing preparations remains for neonates (≤28 days of age). For all other age groups the recommendation is to avoid simultaneous administration via Y-site, or sequential administration without thorough flushing of the line between infusions *(11a)*.

Table 8

Y-Site Injection Compatibility (1:1 Mixture): Drugs Compatible with 3-in-1 (TNA) Formulations *(5,7–9)*

Amikacin sulfate
Aminophylline
Amoxicillin Sodium
Ampicillin
Ampicillin/sulbactam
Aztreonam
Bumetanide
Buprenorphine HCl
Butorphanol tartrate
Calcium gluconate
Carboplatin
Cefazolin sodium
Cefotaxime
Cefoxitin
Ceftazidime
Ceftizoxime
Ceftriaxone sodium
Cefuroxime
Chlorpramazine HCl
Cimetidine HCl
Cisplatin
Clindamycin phosphate
Cyclophosphamide
Cytarabine
Dexamethasone sodium phosphate
Digoxin
Diphenhydramine HCl
Dobutamine HCl
Enalaprilat
Erythromycin lactobionate
Famotidine HCl
Fentanyl citrate
Fluconazole
Furosemide
Gentamicin sulfate
Granisetron HCl
Hydrocortisone sodium phosphate
Hydrocortisone sodium succinate
Hydroxyzine HCl
Ifosfamide
Imipenem–cilastatin sodium
Insulin, regular
Isoproterenol HCl
Kanamycin sulfate
Leucovorin calcium
Levorphanol tartrate
Lidocaine HCl
Magnesium sulfate
Mannitol
Meperidine HCl
Meropenem
Mesna
Methotrexate sodium
Methylprednisolone sodium succinate
Metronidazole
Morphine sulfate[a]
Nafcillin sodium
Netilmicin sulfate
Nitroglycerin
Norepinephrine bitartrate
Octreotide acetate
Ofloxacin
Oxacillin sodium
Paclitaxel
Penicillin G potassium
Piperacillin sodium
Piperacillin sodium–tazobactam
Potassium chloride
Prochlorperazine edisylate
Promethazine HCl
Ranitidine HCl
Sodium bicarbonate
Sodium nitroprusside
Tacrolimus
Ticarcillin disodium
Ticarcillin disodium–clavulanate potassium
Tobramycin sulfate
Trimethoprim–sulfamethoxazole
Vancomycin HCl
Zidovudine

[a] Morphine sulfate incompatible at concentrations of 15 mg/mL but compatible at a concentration of 1 mg/mL *(7)*.

Table 9

Y-Site Injection Compatibility (1:1 Mixture): Drugs Incompatible with 2-in-1 Solutions *(5,7–9)*

Acyclovir
Amphotericin B
Cefazolin sodium
Cisplatin
Cyclosporine
Cytarabine
Doxorubicin
Fluorouracil
Furosemide
Ganciclovir sodium
Immunoglobulin
Methotrexate sodium
Metoclopramide HCl
Midazolam HCl
Minocycline HCl
Mitoxantrone HCl
Phenytoin sodium
Potassium phosphate
Promethazine HCl
Sodium bicarbonate
Sodium phosphate

Table 10
Y-Site Injection Compatibility (1:1 Mixture): Drugs Incompatible with 3-in-1 (TNA) Formulations *(5,7–9)*

Acyclovir
Amphotericin B
Cyclosporine
Dopamine HCl
Doxorubicin
Doxycycline hyclate
Droperidol
Fluorouracil
Ganciclovir sodium
Haloperidol
Heparin
Hydrochloric acid
Hydromorphone
Iron dextran
Levorphanol tartrate
Lorazepam
Methyldopate HCl
Midazolam HCl
Minocycline HCl
Morphine[a] sulfate
Nalbuphine HCl
Ondansetron HCl
Pentobarbital sodium
Phenobarbital sodium
Phenytoin sodium
Potassium phosphate
Sodium phosphate

[a] Morphine sulfate incompatible at concentrations of 15 mg/mL but compatible at a concentration of 1 mg/mL *(7)*.

Lists of medication compatibility are often made as a matter of health-care provider convenience. However, compatibility for a specific formula is very much dependent on the PN composition, the drug, its concentration, time of exposure in the access catheter, and environmental temperature as well as exposure to light. Because of the complexity of drug–PN compatibility, original research reports regarding experimental conditions and assay determinations should be reviewed for similarities/differences of conditions for use at a specific institution or place of administration, especially if it is to be in the home *(5)*. Trissel's *Handbook of Injectable Drugs (9)* provides a comprehensive table of drug–PN compatibility providing experimental conditions, PN formulations, and original citations for the compatibility information.

Since there is a potential for serious harm caused by the incompatible mixture of drugs with PN, safe practice guidelines *(6)* have been developed and should be followed. These are quoted below:

- The responsible pharmacist should verify that the administration of drugs with PN either admixed in the PN or co-infused through the same intravenous tubing is safe, clinically appropriate, stable, and free from incompatibilities.
- If there is no information concerning compatibility of the medication with PN, it should be administered separately from the PN.
- Compatibility information should be evaluated according to concentration of the medication used and whether the base formulation is a 2-in-1 or a TNA (3-in-1).

4. INFLUENCE OF PN ON PHARMACODYNAMICS AND PHARMACOKINETICS OF DRUGS

4.1. Glycemic Control

The predominant influence of PN on drug action is related to glucose control. Abnormalities in glucose homeostasis have led to serious harm and death associated with PN *(13)*. Wolfe et al. determined the rate of maximum rate of glucose oxidation in patients receiving PN to be 4–5 mg/kg/min *(14)*. Rosemarin et al. *(15)* found that hyperglycemia was associated with glucose infusion rates that exceeded 4–5 mg/kg/min.

Therefore, the ability to control glucose in PN patients is dependent on the dose of glucose prescribed. This is particularly important as it relates to the current practice of maintaining normal glucose values in critically ill patients *(16)* and values <150 mg/dL for other patient types. These concepts will influence the indication, route, and type of drug uses to control blood glucose. In some circumstances, insulin may be required. In other cases such as the insulin-dependent diabetic, the type and route of administration may need to be revised because the parenteral route of nutrition, bypasses physiologic regulation through the enterohepatic route. In practice, there are variable approaches to glucose management, so guidelines have been developed to facilitate safe practices in glucose control for PN patients *(6)*.

- Insulin use in PN should be done in a consistent manner according to a method that health-care personnel have adequate knowledge.

A.S.P.E.N. Safe Practices for PN outline issues related to hyperglycemia and PN as follows:

- Diabetic patients receiving PN have a fivefold increase in catheter-related infections than non-diabetic patients *(17)*.
- Administration of carbohydrate calories in excess or 4–5 mg/kg/min or 20–25 kcal/kg/day exceeds the mean oxidation rate of glucose predisposing to hyperglycemia.
- A reasonable target glucose level is between 100 and 150 mg/dL.
- Diabetic patients should not receive more than 100–150 g of dextrose on day 1 of PN. No more than 100 g per day should be given to patients who have been previously treated with insulin, oral hypoglycemic agents, or patients with fasting glucose levels >200 mg/dL.
- A reasonable starting dose of insulin (Note: only regular human insulin may be safely admixed with PN) is 0.1 units per gram of dextrose. If the patient is hyperglycemic, a dose of 0.15 units per gram of dextrose should be used.
- Capillary glucose should be measured every 6 h with appropriately dosed sliding scale insulin coverage to maintain glucose in the goal range.

4.2. Oral Anticoagulants

Another potential effect of PN on drug action is the inclusion of vitamin K_1 (phylloquinone; phytonadione) in parenteral multivitamin products as recently mandated by the FDA *(18)*. The concern for PN is not so much the dose of vitamin K in the product but that not all multivitamin products contain vitamin K, and IVFEs contain variable amounts of vitamin K depending on the product. This can create problems as the patient transfers from one health-care setting to another which may use a different IVFE product or multivitamin product.

4.3. Influence of PN on Drug Elimination

Drugs are eliminated from the body via metabolism (especially hepatic) and/or excretion (hepatic, renal). The pathways involving enzymes and transporters are in part dependent on nutritional status. Any influence of PN on drug elimination may have clinical consequences. It is difficult to distill the effects of baseline nutritional status and underlying disease from PN components on enzyme function. Just by correcting malnutrition, PN may normalize drug metabolism that had been previously altered by malnutrition. PN-associated liver disease represents hepatic injury/inflammation and may also influence hepatic function including drug metabolism. It has also been suggested that administration of PN itself increases pro-inflammatory cytokines which could contribute to depressed cytochrome P450 enzyme (CYP) expression and activity *(19)*. In animal models, administration of lipid-free PN seems to play a role in the significant influence on enzyme protein synthesis and function and additionally is iso-enzyme specific *(20)*. While IVFE prevented the CYP downregulation seen in animal models *(21)*, the effect in animals extends to significant reductions in phase 2 (i.e., conjugation) drug metabolism *(22)*.

Malnourished patients receiving PN repletion have exhibited increased (corrected) activity in CYP metabolic activity *(23)*. The CYP enzyme system is sensitive to PN regimens with significantly decreased activity noted in patients receiving post-operative PN from dextrose-based compared with isonitrogenous mixed dextrose–lipid formulations or a control group receiving IV fluids *(24)*. Recent reviews underscore that an exact mechanism(s) is still not completely understood *(25,26)*. The effects may be nutrient specific. The inclusion of glutamine in PN formulations attenuates the PN-associated suppression of CYP3A and CYP2C activity *(27)*. Choline-supplemented PN increases the activity of CYP2E1 compared with unsupplemented PN *(28)*. Preliminary findings suggest that intravenous iron may increase hepatic CYP3A4 activity as seen in a subset of patients requiring hemodialysis with low baseline activity *(29)*. The influence of PN on drug metabolizing enzymes and on drug transporters, including those at the liver responsible for excretion, is an area that could have significant clinical impact and requires further study.

4.4. Others

Finally, PN is a hyperosmolar fluid infused intravenously that could influence the volume of total body and extracellular fluid. If not closely monitored, changes in extracellular fluid volume could influence drugs that are predominantly distributed to that space (e.g., aminoglycoside and β-lactam antibiotics). Also, long-term PN may adversely affect hepatobiliary function thereby having the potential to effect drugs that undergo hepatobiliary metabolism and excretion.

5. SUMMARY

Numerous factors influence the stability and compatibility of drugs and PN. The PN composition, the chemical nature of the drug, the time of contact of drug with PN, and environmental conditions influence whether a drug can be safely administered with PN. Drug interactions with PN may be significant. The interaction may result in a decrease in clinical drug and/or nutrient effect, occlusion of the venous catheter, or symptoms or death caused by infused particulates. Safe practices *(6)* for drug administration with PN have been developed to assist organizations in developing systems to minimize or avoid drug–nutrient interactions with PN.

DISCUSSION POINTS

Drug–nutrient interactions in patients receiving parenteral nutrition:

- PN is a complex admixture of over 40 different chemical compounds.
- PN is used in malnourished patients when the gastrointestinal tract in not functional or should not be used.
- Drug compatibility with PN is dependent on whether the PN is a 2-in-1 or 3-in-1 formula.
- Drug–PN incompatibilities could result in the formation of a precipitate that causes catheter malfunction or pulmonary emboli if infused.
- The effect of a drug may be influenced by PN administration as a result of clinical effect (hyperglycemia), alteration in hepatic metabolism, or changes in the volume of body fluid compartments.

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IV

INFLUENCE OF MEDICATION ON NUTRITION STATUS, NUTRIENT DISPOSITION, AND EFFECT

15 Drug-Induced Changes to Nutritional Status

Jane M. Gervasio

Objectives

- Identify drugs associated with alterations in weight and their subsequent effect on growth.
- Understand varying taste alterations and their effect on nutrition intake.
- Recognize the differing drugs' mechanisms of action or their adverse effects and the varying nutritional complications which may ensue.

Key Words: Body weight; gastrointestinal; metabolism; nutritional status; taste

1. INTRODUCTION

Drug-induced changes to nutritional status may be a direct or an indirect consequence of a chemical class or specific medication. Recognizing and acknowledging drug-induced changes to nutritional status is imperative for optimal patient care. Changes to overall nutritional status or to nutrient-specific status can be multifactorial. Medication may affect the patient's nutritional status by altering body weight and growth, altering taste perception (thereby decreasing intake), decreasing nutrient absorption, altering macronutrient metabolism, or depleting essential vitamins and minerals. Either as a result of the drug's mechanism of action or by its adverse effect profile, a patient's nutritional status may be affected. Drug-induced changes to nutritional status may be considered a subclass of adverse drug effects *(1)*.

2. DRUGS ASSOCIATED WITH WEIGHT GAIN

Treatment with medication for therapeutic purposes may result in an adverse effect of weight gain. The most commonly reported agents include psychotropics, antidiabetic drugs, corticosteroids, estrogen, and oral contraceptives, as well as alcohol, β-blockers, and cyproheptadine *(2–4)*.

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2.1. Psychotropic Agents

Psychotropic medications are the most commonly reported group associated with weight gain. This drug-induced weight gain can result in increased risk for diabetes, coronary artery disease, and other health-related problems *(5)*. Negative self-image from the weight gain can further complicate the patient's success with psychotropic therapy *(6)*. Psychotropic medications associated with large weight gain include chlorpromazine, clozapine, olanzapine, valproate products, lithium, amitriptyline, imipramine, mirtazapine, risperidone, and ziprasidone though many of the remaining antipsychotic and antidepressant drugs have also been associated with some weight gain *(7)*.

2.2. Antidiabetic Agents

Insulin, sulfonylureas, and thiazolidinediones administered for diabetes control are also associated with weight gain. Studies have reported weight increases from 0.8 to 6.6 kg after the start of the medication. Additionally, the higher dosages were associated with greater weight gain. Most weight gain reached a plateau effect by 6–12 months *(2)*.

2.3. Steroids

Reported adverse effects of testosterone, testosterone derivatives, and selective estrogen receptor modulators include weight gain. Subsequently, they have been used purposefully to facilitate weight gain in the malnourished patient. Oxandrolone, a testosterone derivative, is FDA approved to promote weight gain in patients who have lost weight as a result of chronic infection, surgery, or severe trauma *(8)*. Smoked marijuana, oral dronabinol, megestrol acetate, and anabolic steroids have been successfully used for the promotion of weight gain in anorexia–cachexia syndromes including HIV/AIDS and cancer *(9–11)*. Testosterone therapy allows for reduction in fat mass while lean body mass increases in HIV-positive patients with low testosterone levels and abdominal obesity *(12)*.

2.4. Management

The clinician must assess true weight gain from the medication before changing or initiating new treatment. Patients starting hormone replacement therapy associate weight gain with their medication when, in fact, it may solely be due to their entrance into menopause *(13)*. Continuous replacement therapy may reduce central fat accumulation, but influences on body weight may depend on body composition before treatment *(14,15)*. Patients experiencing relief from symptoms of depression may eat more or overindulge. Patient education concerning body changes, proper diet, and exercise must be incorporated into the overall care of the patient.

Drug-associated weight gain does not regress easily, particularly given the high degree of adiposity in the weight gain. The extent of weight change depends on the specific drug, the dosage, and the duration of treatment *(7)*. The clinician must assess each patient's clinical presentation. Lower dosages or alternative medications within a therapeutic category may need to be instituted. For example, psychotropic medications such as fluoxetine, isocarboxazide, lamotrigine, and topiramate are associated with weight loss and may be an alternative to other medications. Lower dose oral contraceptives and estrogen products may alleviate the problem of increased weight seen with this class of drugs *(16)*.

3. DRUGS ASSOCIATED WITH WEIGHT LOSS

3.1. Stimulants

Drugs associated with weight loss are predominantly central nervous system stimulants. While the stimulants' anorexic properties have been used for weight loss in obese patients, many times it is an unwanted adverse effect. Children receiving stimulant medications for attention deficit hyperactivity disorder may also have minor growth suppression as well as weight loss but this does not appear to affect adult height or weight *(17)*. More common drug stimulants are listed in Table 1.

Table 1
Drug Stimulants

Amphetamine
Armodafinil
Caffeine
Dextramphetamine
Doxapram
Ergotamine
Lisdexamfetamine
Methamphetamine
Methylphenidate
Modafinil
Theophylline

3.2. Others

Serotonergic drugs, including selective serotonin reuptake inhibitors (SSRI) and serotonin receptor agonists (SRA), have been reported to cause weight loss in non-obese and obese individuals. The effect is strongly associated with hypophagia and is probably mediated by the hypothalamic melanocortin system *(18)*. While drugs like fenfluramine and dexfenfluramine, both voluntarily removed from the market, were manufactured for the sole purpose of weight loss, SSRI and SRA are marketed for other medical conditions. Unrelated to a serotonin or norepinephrine mechanism, the antiepileptic drug topiramate has been shown in short-term evaluations to reduce body weight in patients with obesity *(19,20)*. Lamotrigine, another antiepileptic agent, is associated with weight loss as seen in the treatment of bipolar disorder *(21)*. The side effect of appetite suppression from these drugs may be of benefit or consequence when selecting a medication for treatment. The health-care practitioner must evaluate the patient before initiation of the medication.

Other medications that may exhibit an anorexic adverse effect include the antihistamines, bethionol, dacarbazine, epirubicin, etoposide, fluvoxamine, perhixiline, pimozide, sibutramine, temozalomide, trazodone, and zonisamide.

3.3. Drugs with Potentially Excessive Social Use

Evidence that caffeine and caffeinated beverages (cola, tea, coffee) result in weight loss is lacking. Caffeine has been shown to cause greater thermogenesis, lipolysis, fat oxidation, and insulin secretion in non-obese individuals than in obese individuals *(22)*. Additionally, weight loss may be induced from increases in physical activity and improved exercise performances associated with caffeine and caffeinated beverages *(23)*. Further research is necessary before caffeine and caffeinated beverages should be recommended for weight loss. However, in patients presenting with weight loss or anorexia, decreasing consumption of caffeine may be warranted.

Alcohol intake in women and nicotine intake in both men and women are associated with lower body weight. The mechanism of action of alcohol or nicotine weight loss is unknown. Perkins and colleagues *(24)* showed a significant thermogenic effect with nicotine alone or in combination with alcohol in men but not women. Alcohol alone in either men or women and nicotine alone in women showed no thermogenic effect. Hence, it is speculated that in women, nicotine acts by suppressing appetite but more research is still needed.

3.4. Management

The clinician must ascertain whether a patient's weight loss is related to a medication or indicative of another underlying condition. Any advantages in continuing a medication must be balanced against the patient's unwanted weight loss. Lower dosages or alternative medications may be necessary. Drug holidays in children receiving stimulants may be indicated *(25)*.

4. ALTERED TASTE PERCEPTION

4.1. Drug Induced

Medication-induced changes to an individual's perception of taste can result in decreased oral intake and weight loss *(26,27)*. Taste is mediated by chemosensory nerves that respond to stimulatory chemicals by direct receptor binding, opening ion channels, or second messenger systems using cyclic nucleotides and phosphorylated inositol *(28,29)*. Medications disrupting these cellular processes may result in symptoms of ageusia (loss of taste), dysgeusia (distortion of taste), hypogeusia (decreased sense of taste), and phantogeusia (gustatory hallucination) (Table 2) *(28–31)*.

Dry mouth (xerostomia) is also associated with altering taste perception. Xerostomia results from the suppression of saliva production. Decreased saliva

Table 2
Drug-Induced Taste Disorders

Drug	*Taste Defect*	*Drug*	*Taste Defect*
Acemetacin	D	Bretylium	H-salt
Acetazolamide	D-acid	Bromocriptine	P
Acetylsulfosalicyclic	D	Bupropion	D
Adriamycin	D	Butorphonol	D
Albuterol	D	Cadmium	D-metallic
Alcohol		Calcifediol	D-metallic
Allopurinol	D-metallic	Calcitriol	D-metallic
Alprazolam	H	Calcitonin	D-metallic, P-salt
Ambifylline	D-bitter	Calcium salts	D-metallic
Amethocaine	D-bitter/ sweet	Captopril	A, D-bitter, P-metallic/ salt/sweet
Amezinium	D	Carbamazepine	A, H, P
Amiloride	A, D-salt, H	Carbenicillin	D
Amiodarone	D	Carbimazole	H
Amiloride	A, D-salt	Carboplatin	H
Amitriptyline	H	Carmustine	D-metallic
Amlodipine	D	Cefacetrile	D, H
Amonafide	D	Cefadroxil	D
Amphotericin B	H, P-metallic	Cefamondole	D
Amphetamine	D-bitter/sweet	Cefpirome	D
Ampicillin	H	Cefodizime	D
Amrinone	H	Cefpodoxime	D
Amydricaine	D-sweet	Ceftriazone	P-metallic
Anisotropin	A	Cephalexin	D
Antimony	D-bitter	Chlorhexidine	D, H-salt
Antithrombin III	D	Chlormezanone	A, H, P
Apomorphine	D-metallic	Chlorthalidone	D
Apraclonidine	D	Cholestyramine	D
Aspirin	D-bitter, H	Choline magnesium trisalicylate	A
Auranofin	H, D-metallic		
Azathioprine	H	Cilazapril	D
Azelastine	D-bitter, metallic	Cimetidine	H, P
Azothioprine	P	Ciprofloxacin	D
Azithromycin	D	Cisplatin	A,D, H
Aztreonam	D	Clarithromycin	H
Bacampicillin	H	Clomipramine	D
Baclofen	A, H, P	Clofibrate	H
Beclomethasone	A, H	Cocaine	D-sweet, H
Benoxaprofen	A	Colchicine	H
Benzocaine	D-sour	Corticosterones	H
Bepridil	D	Cyclobenzaprine	P
Bevacizumab	D	Dantrolene	D
Biguanides	D-metallic, H	Daunorubicin	D
Bismuth	D-metallic	Deferoxamine	D
Bleomycin	A, D, H	Desipramine	D

(*Continued*)

Table 2
(Continued)

Drug	*Taste Defect*	*Drug*	*Taste Defect*
Dexamphetamine	D	Flurazepam	D-metallic, bitter
Diazepam	H	Flurbiprofen	D
Diazoxide	A,D,H	Foscarnet	D
Diclofenac	D	Fluphenazine	P
Dicyclomine	A	Fosinopril	H
Didanosine	D, H	Furosemide	D-sweet, H, P-sweet
Dilitiazem	A,D, H	Gallium	D-metallic
Dimethyl sulfoxide	D	Glipizide	D
Dinitrophenol	H	Glycopyrrolate	A
Dinoprostone	D	Gold salts	A, D-metallic, P
Dinitrophenol	D-salt	Granisetron	D
Dipyridamole	D-metallic, P-salt	Griseofulvin	D, H
Disulfiram	D, P-metallic	Guanfecine	D
Dicyclomine	A	Hydralazine	D
Dorzolamide	D	Hydrochlorothiazide	A,D
Doxazosin	D	Hydrocortisone	H
Doxepin	H	Hyoscyamine	A
Doxorubicin	D, H	Ibuprofen	D, H
Duloxetine	D	Idoxuridine	D
EDTA	D	Imipramine	H
Enalapril	A, D-metallic, H, P-salt	Inamrinone	D, H
		Indomethacin	H
Ergocalciferol	P-metallic	Insulin	A, H
Esmolol	D	Interferon-α	D, P
Esomeprazole	D	Interferon-γ	D-metallic
Estazolam	D	Interleukin-2	H
Ethacrynic acid	H	Iodine	D-metallic
Ethambutol	D-metallic, H, P-metallic	Isococaine	D-sweet
		Isopropamide	A
Ethchlorvynol	P	Isosorbide Nitrates	P
Ethionamide	D-metallic	Isotretinoin	D, H
Etidronate	A, H	Ketoprofen	D, H
Etodolac	D	Ketoralac	D
Etretinate	D	Labetalol	D
Eucaine	D-sweet, H	Lansoprazole	D
Famotidine	D	Lead	D-metallic
Felbamate	D	Levamisole	D-metallic
Fenfluramine	D	Levodopa	D-bitter, H, P
Filgrastim	D	Levofloxacin	D
Flecainide	D	Lidocaine	D-sweet, H
Flosequinan	D	Lincomycin	D, H
Flunisolide	A, D, H	Lisdexamfetamine	D
5-Fluorouracil	D-sweet, H	Lisinopril	D, H
Fluoxetine	D	Lithium	D-metallic
Fluphenazine	P	Lomefloxacin	A

Lomustine	D
Loratadine	D
Losartan	A, D-salt/sour/sweet
Lovastatin	A
Mazindol	D
Mefenamic acid	H
Mercury	D-metallic
Methscopolamine	D
Methimazole	A, H
Methocarbamol	D-metallic
Methotrexate	H, D-metallic
Methscopolamine	A
Methyldopa	D-metallic, H, P-metallic
Methylthiouracil	H
Metoclopramide	H
Metolazone	P-metallic
Metronidazole	D-metallic, H, P-metallic
Mexiletine	D
Minocycline	D
Misoprostol	D
Monoctanion	D-metallic
Moracizine	P
Moxifloxacin	D
Nabumetone	D
Nedocromic	D-bitter
Nickel	D-metallic
Nicotine	D
Nifedipine	A, D-metallic, H
Niridozole	D
Nitroglycerin	A, D, H
Norfloxacin	D-bitter
Nortriptyline	D
Nuproxen	D
Nylidrin	D-metallic
Ofloxacin	A, D
Omega fatty acids	D
Omeprazole	D
Opiates	A
Oxaprozin	H, P
Oxazepam	H
Oxyfedrine	D, H
Palifermin	D
Paroxetine	D
Penicillamine	A, D-metallic/salt, H
Pentamidine	D-metallic, H, P-metallic
Pentazocine	D
Pergolide	D
Perindopril	A, D-bitter
Phendimetrazine	D
Phenformin	D-metallic
Phenindione	D, H
Phentermine	D
Phenylbutazone	A, H, P
Phenytoin	H
Piperacillin	H
Pirbuterol	D, H
Piroxicam	H
Pravastatin	D
Procainamide	P
Procaine PCN	D-metallic, H
Promethazine	H
Propafenone	D-metallic, bitter
Propranolol	A, D, H
Propylthiouracil	A, D, H
Protirelin	D-metallic
Pseudoephedrine	D
Quinapril	D
Ramelteon	D
Rifabutin	A
Rimantadine	D, H
Risperidone	P
Scopolamine	H
Selegiline	D
Selenium	D-metallic
Sertraline	D
Sodium lauryl sulfate	H
Spironolactone	A, H
Stibogluconate	D-metallic
Streptomycin	H
Sucralfate	H
Sulfasalazine	H, D-sweet, P-metallic
Sulindac	A, D-metallic, P-metallic
Sumatriptan	D-bitter
Tacrine	D
Tegafur	D-metallic
Telithromycin	D
Tellurium	D-metallic
Temsirolimus	D
Terbinafine	A, H

(*Continued*)

Table 2
(Continued)

Drug	*Taste Defect*	*Drug*	*Taste Defect*
Terfenadine	D	Trichlormethiazide	H
Tetracycline	D-metallic	Tridihexethyl chloride.	A
Thallium	D-metallic	Trihexyphenidyl	H
Thiamazole	A	Trifluoperazine	P
Thiouracil	H	Trimipramine	P
Tiagabine	D	Varenicline	D
Tinidazole	D	Venlafaxine	D, H
Tiopronin	A, D	Vincristine	H
Tocainide	D-metallic	Vitamin D	D-metallic
Tolbutamide	D	Vorinostat	D
Tramadol	D	Zalcitabine	D
Tranylcypromine	D	Zidovudine	D
Trazodone	P	Zinc oxide	D-metallic
Triamterene	H	Zolpidem	D
Triazolam	A, D	Zopiclone	A, D-bitter

D=dysgeusia; H=hypogeusia; A=aguesia; P=phantogeusia; EDTA=ethylenediaminetetraacetic acid

production alters the ion concentrations between the saliva and the plasma resulting in decreased taste sensation. Many drugs are associated with xerostomia, especially those medications with anticholinergic properties. Medications often associated with xerostomia include amitriptyline, brompheniramine, bumetanide, cetirizine, cyclopentolate, cyproheptadine, didanosine, diphenhydramine, flecainide, flunitrazepam, granisetron, imipramine, isoniazid, loratadine, mesalamine, molindone, nizatidine, nomifensine, nortriptyline, ondansetron, olanzapine, orphenadrine, oxybutinin, pentoxyfylline, procainamide, propantheline, rimantadine, selegiline, sertraline, terfenadine, trazodone, and trimethobenzamide *(29)*.

4.2. Management

If the offending medications cannot be discontinued or the dosage decreased, supplemental therapy may be offered. Masking techniques including chewing sugarless gum or using lozenges or breath mints to help alleviate dry mouth or altered taste may be tried. Artificial saliva spray and pilocarpine oral tablets have successfully been used for xerostomia. Davies and colleagues *(32)* reported statistically significant improvement in xerostomia symptoms with pilocarpine 5 mg three times a day over artificial saliva spray. Though both therapies improved dry mouth symptoms, many patients preferred the convenience of the saliva spray *(32)*.

Betaine-containing toothpaste has been reported to reduce xerostoma in patients with chronic dry mouth. In a double-blind, crossover study, 60% of patients reported improvement from their symptoms of dry mouth after using toothpaste containing betaine. No changes were reported in saliva flow rates, oral mucosa, or mouth microflora *(33)*.

Conflicting reports have been shown using zinc supplementation for the treatment of taste disturbances *(31,34)*. Impaired taste sensation is a clinical manifestation of zinc deficiency. A variety of etiological factors have been attributed to zinc deficiency including drug therapy. If the patient is experiencing taste disturbances from zinc deficiency, administration of zinc sulfate may be beneficial. The implementation of zinc therapy is not indicated for everyone. Souder et al. *(35)* reported 34% of patients with chemosensory disorders were treated with zinc but only 6% of those patients experienced any relief of symptoms. Careful assessment of the underlying cause of the taste disturbance must be performed.

5. DRUGS ALTERING GASTROINTESTINAL FUNCTION

5.1. Overview of Gastrointestinal Function

One of the primary functions of the gastrointestinal (GI) tract is to provide the body with a continual supply of water, electrolytes, and other nutrients. The GI tract is composed of the following layers: (1) the serosa, (2) a longitudinal muscle layer, (3) a circular muscle layer, (4) the submucosa, and (5) the mucosa. The innervations of the GI tract are supported by the enteric nervous system. The enteric nervous system controls most of the GI functions under the direction of the autonomic nervous system. Sympathetic and parasympathetic nervous signals from the brain to the GI tract strongly affect the degree of activity of the enteric nervous system. Acetylcholine and norepinephrine are the primary neurotransmitters for the parasympathetic and sympathetic system, respectively. Additional GI neurotransmitter receptors include cholinergic, histaminic, dopaminergic, opiate, serotonergic, and benzodiazepine receptors. Any drug affecting these neurotransmitters, either centrally or locally, can affect GI tract function *(36,37)*. Ultimately, drugs altering the GI tract function of absorbing nutrients will affect nutritional status.

5.2. Drug-Induced Emesis

Prolonged or severe vomiting will alter the absorption of nutrients. While vomiting is a reported side effect from numerous medications, it is usually not lingering. Tolerance to a medication or alternative therapy usually is rendered and nutritional complications are not a concern. Nutritional complications become a concern when vomiting is prolonged or severe, most notably from cytotoxic chemotherapy. Cytotoxic chemotherapy may be highly emetogenic. Chemotherapy agents associated with the most emetogenic potential include aldesleukin, altretamine, carboplatin, carmustine, cisplatin, cyclophosphamide, dacarbazine, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, lomustine, mechlorethamine, mitoxantrone, pentostatin, and streptozocin *(36)*.

5.3. Drug-Induced Motility Disturbances

5.3.1. INCREASED MOTILITY

Medications that increase the motility of the GI tract or cause GI intolerance may result in abdominal pain, cramping, or diarrhea. Similar to vomiting, if these adverse effects are prolonged or severe, altered nutrient absorption may result. Furthermore, patients experiencing abdominal pain and cramping from a medication may decrease nutrient intake simply due to decreased appetite. Nutrient losses resulting from prolonged or severe diarrhea are due to increased oral–cecal transit or decreased GI absorption time. Aspirin, other nonsteroidal anti-inflammatory agents, and iron are notorious for causing GI irritation. Medications associated with increasing motility include metoclopramide, erythromycin, and cisapride.

Patients may become tolerant of the offending medication. If adverse effects do not subside, alternative therapy may be instituted or the medication discontinued. Antidiarrheal medications may be introduced but careful consideration must be given to potential contraindications. Resulting decreases in GI motility from antidiarrheal medications may cause constipation and bowel obstruction.

5.3.2. DECREASED MOTILITY

As previously mentioned, decreased GI motility may also result in inadequate delivery of nutrients. Decreased GI motility is associated with opioids and anticholinergic medication or those with anticholinergic effects. Opioids increase the resting tone of smooth muscles in the GI tract resulting in delayed gastric emptying and decreased peristaltic movement *(37)*. The effectiveness of opioids for the relief of pain is often limited by its side effect of GI dysfunction. Implementation of stool softeners or laxatives may be indicated. Novel selective peripheral opioid receptor antagonists (e.g., alvimopan) may be considered in managing opioid-induced bowel dysfunction in the acute care setting *(38,39)*.

Anticholinergic agents decrease GI motility by blocking the action of acetylcholine at the parasympathetic receptor sites. Several anticholinergic medications are currently available and are in use including atropine, belladonna, benztropine, hyoscyamine, ipratropium, isopropamide, oxybutynin, scopolamine, and trihexyphenidyl. Other commonly prescribed medications with anticholinergic effects include psychotropic agents such as amitriptyline, diphenhydramine, imipramine, olanzapine, procainamide, and zotepine. In patients where severe constipation or bowel obstruction occurs, these medications should be discontinued and alternative therapy instituted.

6. DRUG-INDUCED METABOLIC EFFECTS

Alterations in metabolic function or macronutrient status of a patient may be attributed to medication as well. Drug-induced alterations in glucose and lipid metabolism have been reported with several medications. Acute metabolic changes may range from transient to life threatening for the patient. Drug-induced osteoporosis and pancreatitis may be chronic consequences of exposure to some medication.

6.1. Hyperglycemia

Drug-induced hyperglycemia may result from fluctuations in a patient's metabolism. Drug-induced episodes of hyperglycemia may worsen glucose control in the diabetic patient as well as increase patient risk for developing hyperglycemia and subsequent diabetes. Since the introduction of antipsychotic medication, alterations in glucose metabolism have been reported. Medications for schizophrenia or schizoaffective disorders are associated with increases in blood glucose concentrations and type 2 diabetes. The atypical or second-generation antipsychotic drugs, including clozapine, olanzapine, and risperidone, have a stronger diabetogenic effect than the classical antipsychotics (e.g., haloperidol). Cohen et al. reported that among 200 mainly Caucasian patients with schizophrenia or schizoaffective disorder, 7% suffered from hyperglycemia and 14.5% from diabetes. The prevalence of diabetes was significantly greater compared with the general population *(40)*.

Beta-blockers, especially in patients with type 2 diabetes, have been reported to cause hyperglycemia resulting in part from inhibition of insulin release *(41)*. Corticosteroids are associated with decreased peripheral utilization of glucose, promotion of gluconeogenesis, and accelerated synthesis of glucose. Hyperglycemia reported from the use of oral contraceptives is associated with decreased insulin receptor binding or a post-receptor defect in insulin actions *(42)*. New-onset diabetes has been associated with immunosuppressant agents – particularly corticosteroids and calcineurin inhibitors (e.g., cyclosporine, tacrolimus) – used following organ transplantation *(43)*. The rapamycin derivative sirolimus may also be associated with new-onset diabetes *(44)*. Other commonly reported drugs implicated in the induction of hyperglycemia include alcohol, caffeine, calcium channel blockers, growth hormone, morphine, nicotine, phenytoin, protease inhibitors, second-generation antipsychotics, sympathomimetic amines, thiazide diuretics, theophylline, and thyroid products *(45,46)*. The fluoroquinolone antibiotics have been associated to varying degrees with hyperglycemia as well as hypoglycemia *(47)*.

6.2. Hypoglycemia

Not surprisingly, the most common causes of drug-induced hypoglycemia are insulin, sulfonylureas, and thiazolidinediones when used for treatment of hyperglycemia *(48)*. While excessive alcohol intake induces glucose intolerance, alcoholic hypoglycemia is the better known alteration of carbohydrate metabolism *(49)*. The increased oxidation of ethanol results in reduced gluconeogenesis, hypoglycemia, and ketoacidosis.

Serotonin reuptake inhibitors have been reported to cause hypoglycemia. A case report of hypoglycemia resulted from self-intoxication with a serotonin–norepinephrine reuptake inhibitor (venlafaxine) and oxazepam *(50,51)*. Additional medications associated with hypoglycemia include the anabolic steroids, angiotensin-converting enzyme inhibitors, calcium channel blockers, insulin-like growth factor 1 (IGF-1), salicylates, tetracycline, and warfarin *(46,48,52)*.

6.3. Lipid Changes

Drugs may adversely affect a patient's serum lipid profile. Anabolic agents, beta-blockers, diuretics, progestins, combined oral contraceptives containing progestins, danazol, immunosuppressive agents, protease inhibitors, and enzyme-inducing anticonvulsants negatively affect serum lipid profiles. They increase total cholesterol, low-density lipoprotein cholesterol, and triglycerides by up to 40, 50, and 300%, respectively *(53)*.

6.4. Protein Effects

Anabolic agents including growth hormone, anabolic steroids, and IGF-1 affect protein synthesis. Growth hormone's effect on protein metabolism includes increasing protein synthesis without affecting protein degradation *(54)*. IGF-1 promotes growth function as well as having insulin-like metabolic action including inhibition of lipolysis in adipose tissue and stimulation of glucose and amino acid transport into muscle *(55)*. Anabolic steroids have been shown to improve nitrogen retention and restore muscle mass in HIV/AIDS, trauma, and thermally injured patients *(56–59)*.

Corticosteroids, including inhaled corticosteroids, have been associated with a decreased rate of growth in children, especially with high-dose, long-term treatment. Corticosteroids decrease the secretion of growth hormone as well as decrease the tissue's sensitivity to its effect *(60)*.

Alcohol may also induce protein loss by inhibiting intestinal protein absorption and increasing urinary nitrogen excretion. Negative nitrogen balances have been reported in patients consuming alcohol and the catabolic effects continued for 1 week after the abstinence of alcohol *(49)*.

7. DRUG-INDUCED NUTRIENT DEPLETIONS

Changes in a patient's nutrient status may not necessarily be directly due to the medication but may instead be due to a nutrient deficiency resulting from the medication. Multiple drugs, including alcohol and illicit drugs, have been reported to cause electrolyte, mineral, and vitamin deficiencies. Tables 3 and 4 are a select list of drug-induced nutrient depletions from more extensive lists that are regularly updated *(30,61)*. See other chapters for greater detail on interactions that impact on folate status (Chapter 18) and mineral status (Chapter 19).

Table 3
Drug-Induced Mineral Depletion

Mineral/Electrolyte Deficiencies

Hypocalcemia

Alendronate
Alvimopan
Amphotericin B
Antacids
Bleomycin
Bumetanide
Calcitonin
Carboplatin
Cholestyramine
Cisplatin
Cimetidine
Citrate salts
Clodronate
Codeine
Corticosteroids
Corticotropin
Cytarabine
Daunorubicin
Didanosine
Digoxin
Diethylstilbestrol
Doxorubicin
Edetate disodium
Estrogens
Ethacrynic acid
Etidronate
Famotidine
Fluocortolone
Fluorouracil
Foscarnet
Furosemide
Gentamicin
Hydroclorothiazide
Ibandronate
Interferon
Isoniazid
Lansoprazole
Leucovorin
Magnesium
Mineral oil
Nizatadine
Pamidronate
Pentobarbital
Pentamidine
Phenobarbital
Phenytoin
Phosphates
Polymyxin B
Plicamycin
Propylthiouracil
Ranitidine
Risedronate
Rituximab
Saline laxatives
Sargramostim
Sodium polystyrene Sulfonate
Sulfonamides
Terbutline
Tetracyclines
Tobramycin
Torsemide
Triamterene
Zoledronic acid

Hypomagnesemia

Albuterol
Amphotericin B
Bumetanide
Carboplatin
Chlorothiazide
Cholestyramine
Cisplatin
Corticostroids
Cyclosporine
Dextrose
Didanosine
Digoxin
Docusate
Estrogen
Ethacrynic acid
Ethanol
Foscarnet
Furosemide
Gentamicin
Hydrochlorothiazide
Oral contraceptives
Pamidronate
Penicillamine
Pentamidine
Phosphates
Sargramostim
Sulfonamides
Tacrolimus
Tetracylines
Tobramycin
Zoledronic acid

Hypophosphatemia

Alendronate
Antacids
Arginine
Calcium
Cefotetan
Demeclocycline
Dextrose
Digoxin
Ethanol
Felbamate
Magnesium
Pamidronate
Sevelamer
Sirolimus
Tacrolimus

(*Continued*)

Table 3
(Continued)

Mineral/Electrolyte Deficiencies

Cholestyramine
Cisplatin
Foscarnet
Ifosfamide
Lanthanum carbonate
Zoledronic acid

Hypokalemia

Acetazolamide
Activated charcoal
Albuterol
Amiloride
Ammonium chloride
Amphotericin B
Aspirin
Betamethasone
Bisacodyl
Bumetanide
Carbenicillin
Carboplatin
Carmustine
Chlorothiazide
Chlorpropamide
Chlorthalidone
Cisplatin
Colchicine
Corticosteroids
Corticotropin
Cortisone
Cyanocobalamin
Cytarabine
Desirudin
Dexamethasone
Dextrose
Didanosine
Digoxin immune fab
Dobutamine
Doxorubicin
Ethacrynic acid
Fluconazole
Fluoxetine
Foscarnet
Furosemide
Ganciclovir
Gentamicin
Hydrochlorothiazide
Hydrocortisone
Insulin
Isoflurane
Isosorbide mononitrate
Itraconazole
Levalbuterol
Levodopa/carbidopa
Lithium
Methylprednisolone
Mezlocillin
Nafcillin
Nifedipine
Ondansetron
Oxacillin
Pamidronate
Penicillin G
Phosphates
Piperacillin
Polymyxin B
Prednisolone
Prednisone
Risperidone
Saline laxatives
Sargramostim
Sirolimus
Sodium bicarbonate
Sodium lactate
Sodium polystyrene Sulfonate
Sotalol
Tacrolimus
Testosterone
Theophylline
Ticarcillin
Tobramycin
Torsemide
Triamcinolone
Vincristine

Zinc Deficiency

Antivirals
Captopril
Corticosteroids
Deferiprone
Edetate calcium disodium
Estrogen
Ethambutol
Folic acid
Hydrochlorothiazide
Oral contraceptives
Potassium-sparing diuretics
Thiazides
Valproic acid

Iron Deficiency

Aspirin
Calcium
Cholestyramine
Deferoxamine
Erythropoietins
Ethanol
Indomethacin
Neomycin
Sulfonamides
Tetracyclines

Copper Deficiency

Antacids
Antivirals
Ethambutol
Zinc salts

Selenium Deficiency

Clozapine
Valproic acid

Table 4
Drug-Induced Vitamin Depletion

Vitamin Deficiencies

Folic Acid Deficiency

Aspirin
Carbamazepine
Celecoxib
Cholestyramine
Corticosteriods
H2 blockers
Indomethacin
Methotrexate
NSAIDs
Oral contraceptives
Phenytoin
Potassium-sparing diuretics
Primidone
Pyridoxine
Sulfasalazine
Valproic acid

Vitamin A (Retinol) Deficiency

Cholestyramine
Ethanol
Mineral oil
Neomycin
Orlistat

Vitamin B_1 (Thiamin) Deficiency

Aminoglycosides
Cephalosporins
Digoxin
Ethanol
Fluoroquinolones
Loop diuretics
Phenytoin
Sulfonamides
Tetracyclines

Vitamin B_2 (Riboflavin) Deficiency

Aminoglycosides
Cephalosporins
Fluoroquinolones
Oral contraceptives
Phenothiazines
Sulfonamides
Tetracyclines

Vitamin B_3 (Niacin) Deficiency

Aminoglycosides
Cephalosporins
Cholestyramine
Colestipol
Ethanol
Fluoroquinolones
Isoniazid
Sulfonamides
Tetracyclines
Valproic acid

Vitamin B_6 (Pyridoxine) Deficiency

Aminoglycosides
Cephalosporins
Estrogen
Ethanol
Fluoroquinolones
Hydralazine
Isoniazid
Loop diuretics
Oral contraceptives
Sulfonamides
Tetracyclines
Theophylline

Vitamin B_{12} (Cyanocobalamin) Deficiency

Aminoglycosides
Antivirals
Cephalosporins
Cholestyramine
Colchicine
Ethanol
Fluoroquinolones
H2 blockers
Metformin
Neomycin
Oral contraceptives
Phenytoin
Proton pump inhibitors
Sulfonamides
Tetracyclines

(*Continued*)

Table 4
(Continued)

Vitamin Deficiencies

Vitamin C Deficiency
Aspirin

Vitamin D Deficiency
Mineral oil
Orlistat

Vitamin E Deficiency
Aspirin
Cholestyramine
Colestipol
Corticosteroids
Loop diuretics
Oral contraceptives
Orlistat

Vitamin K Deficiency
Aminoglycosides
Barbiturates
Cephalosporins (cefotetan)
Cefoperazone
Cholestyramine
Fluoroquinolones
Mineral oil
Orlistat
Phenytoin
Sulfonamides
Tetracyclines

8. SUMMARY

Drugs and chemicals may alter a patient's nutritional status in a multitude of ways. Clinicians need to recognize which medications have the potential to disrupt the patient's nutritional status. Patients must be assessed to determine if a change in their nutritional status is related to a drug-induced complication. Drug dosages may need to be decreased, alternative medications incorporated, drug holidays offered, or the offending medication discontinued. Medications will continue to be identified as causes for changes in nutritional status. Further research must be conducted to identify new or alternative agents with fewer adverse effects or better resources to control these nutritional changes.

DISCUSSION POINTS

- Medications administered for mental disorders and diabetes are associated with weight gain. Discuss the disadvantages of weight gain in these populations. How does the adverse effect compromise treatment in these populations? How might it serve as an advantage? Similarly, how might medications associated with weight loss be used?
- Caffeine, alcohol, and nicotine have associated weight loss. Discuss what the research has shown and where additional research is needed.
- Many drugs have been associated with altering taste perception. Discuss the various treatments to combat this problem.
- Alterations to the gastrointestinal tract include nausea/vomiting and diarrhea/constipations. Which medications have a higher propensity to cause these side effects and what types of interventions may be utilized to relieve these symptoms?
- Discuss the drugs associated with inducing hyperglycemia, hypoglycemia, lipid changes, and catabolism.

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16 Influence of Cardiovascular Medication on Nutritional Status

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Objectives

- Review effects of food on absorption of cardiovascular medications.
- Describe interactions of cardiovascular medication with nutrients.
- Describe cardiovascular medications' effects on nutritional status or specific nutrients.

Key Words: Angiotensin; antithrombotic; cardiovascular; diuretic; vasoactive

1. INTRODUCTION

Cardiovascular diseases are the number one cause of mortality in the United States *(1)*. Current recommendations for treatment of cardiovascular diseases include many medications; patients will often require a complex multi-drug regimen *(2–7)*. The sheer number of drugs used increases the likelihood for drug–nutrient interactions. This chapter will describe the effects on overall nutritional status or nutrient-specific status from acute or chronic use of cardiovascular agents. In addition, it will address the effects of food, food components, and nutrient or dietary supplements on cardiovascular agents. The reader is advised to use the information provided here in combination with their clinical expertise to determine the relevance of these interactions in providing patient care.

The chapter reviews information on each of the following drug classes as a whole as well as on the individual agents within the class when drug-specific data are available:

1. Antiadrenergic agents
2. Antiarrhythmic agents
3. Antithrombotic agents
4. Calcium channel blocking agents
5. Cardiac glycosides
6. Diuretics

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7. Renin–angiotensin–aldosterone system agents
8. Lipid modulating agents
9. Organic nitrates
10. Vasoactive agents

Each section provides the available information for drugs within the class. Drug–nutrient interactions for each drug include the following categories: effect of nutritional status, food/food component effect, or nutrient/dietary supplement effect on drug disposition, as well as drug effect on nutritional status or effect on specific nutrients *(8)*. In some sections, classifications will be combined.

2. ANTIADRENERGIC AGENTS

2.1. β-Blockers and α/β-Adrenergic Blocking Agents

2.1.1. GENERAL

Beta (β)-blockers comprise a relatively large class of antihypertensive drugs with effects on cardiac conduction and contractility. β-Blocker administration remains a standard of care in patients with angina pectoris, following myocardial infarction, and those with left ventricular dysfunction *(3,5,6)*.

2.1.1.1. Influence of Obesity. The pharmacokinetics of β-blockers can be influenced by obesity since potential alterations include changes in drug distribution, biotransformation, and excretion. Studies have examined whether pharmacokinetic parameters of lipophilic β-blockers (i.e., propranolol) in comparison to hydrophilic β-blockers (i.e., atenolol) would be different in obese patients. In general, the volume of distribution (Vd) of β-blockers at steady state expressed in L/kg total body weight is always slightly smaller in obese than in non-obese patients *(9)*. Compared to lean patients, obese patients appear to have an approximately 24% larger absolute Vd (in L) but a 23% smaller weight-normalized Vd (in L/kg), suggesting that lipophilic β-blockers diffuse less into excess adipose tissue than into lean tissue *(9)* (see Chapter 7). One article suggests that it is not only the lipophilic property of the drug that influences diffusion into adipose tissue but also the extent of blood flow to the adipose tissue which may be decreased by some β-blockers *(2)*. Another study examined whether serum lipid profile could influence pharmacokinetics and pharmacodynamics of lipophilic propranolol and hydrophilic atenolol in obese subjects with or without hyperlipidemia *(10)*. The study found that there was a trend toward increased Vd, bioavailability (F) and clearance (Cl)/F of propranolol in obese patients with hyperlipidemia. Additionally, the area under the serum concentration over time curve (AUC), the mean maximal plasma concentration ($C_{\max}$), and the oral clearance were significantly lower in obese patients receiving water-soluble atenolol. Pharmacodynamically, the effects of β-blockers on heart rate, systolic blood pressure, and diastolic blood pressure were similar. Findings of this study and peer review suggest that plasma concentrations of β-blockers do not reliably predict cardiovascular activities and clinically the differences were not relevant *(10,11)*.

2.1.1.2. Influence on Nutritional Parameters. One of the drawbacks against the primary use of β-blockers in overweight hypertensive patients is the possibility of weight gain. A systematic analysis evaluated eight prospective randomized controlled trials that lasted greater than 6 months. The median difference in body weight was found to be 1.2 kg (–0.4 to 3.5 kg); however, regression analysis suggested that most of the initial weight gain was during the first few months and no further weight gain compared to control was apparent afterward. An accompanying editorial questioned whether β-blockers put on weight or rather hinder attempts of hypertensive patients to lose weight with side effects of fatigue, reluctance to start new tasks, depression, difficulty breathing, and numb feet *(12,13)*. Furthermore, no evaluations of β-adrenergic receptor phenotype were performed.

Nonselective β-blockers (e.g., nadolol) have been associated with increased serum triglycerides and reductions in high-density lipoprotein cholesterol. Agents with intrinsic sympathomimetic activity (e.g., acebutolol) have little or no effects on lipids, whereas cardioselective β-blockers (e.g., atenolol) have intermediate effects. β-Blockers have been shown to lower morbidity and mortality so their effects on cholesterol have little clinical significance. These changes in serum lipid profile are not sustained with chronic therapy *(14,15)*.

Insulin release and glycogenolysis are adrenergically mediated through unopposed stimulation of the β_2-receptor; therefore, blockade of β_2-receptors may reduce either process and cause hyperglycemia. Third-generation β-blockers, carvedilol and nebivolol, possess vasodilator actions through such proposed mechanisms as nitric oxide release, antioxidant effects, and calcium blockade that may improve insulin sensitivity *(16)*.

All β-blockers can mask the symptoms of hypoglycemia which are mediated through epinephrine release (i.e., hunger, tremor, and palpitations). Thus β-blockers can cause adverse effects on glucose homeostasis in diabetes, including worsening of insulin sensitivity and potential masking of the epinephrine-mediated symptoms of hypoglycemia; these problems are usually easily managed and are not absolute contraindications for β-blockers use *(7)*.

Stimulation of the β_2-receptors by epinephrine promotes the movement of extracellular potassium into the cells, thereby lowering the plasma potassium concentration. Nonselective β-blockers (such as propranolol) are more likely to exert this effect since they block both β_1- and β_2-receptors; as compared to selective β-blockers which, at low doses, affect only β1 receptors. In most cases, the administration of β-blockers is associated with only a minor elevation in the plasma potassium concentration of less than 0.5 mmol/L, as the potassium that cannot enter the cells is excreted in the urine. True hyperkalemia is rare, unless associated with a superimposed problem such as a marked potassium load, severe exercise (which is associated with the release of potassium from the cells into the extracellular fluid), hypoaldosteronism, or end-stage renal disease. Hyperkalemia has also been reported in renal transplant recipients treated with labetalol *(17–20)*.

2.1.2. ACEBUTOLOL

Although the peak drug concentration and rate of absorption decrease slightly with food, the effect on acebutolol AUC is not significant *(21)*.

2.1.3. ATENOLOL

Bioavailability of atenolol given by nasogastric tube in the postoperative period was assessed in 18 patients scheduled for abdominal surgery. The study reported 36% reduction in the atenolol AUC and 46% reduction in the peak concentration of atenolol in the postoperative period compared to preoperative values given. Based on these findings, the authors concluded that reduced cardiac morbidity related to intravenous atenolol in the immediate postoperative period cannot be expected when the drug is given by nasogastric tube *(22)*.

2.1.4. CARVEDILOL

The rate of absorption is decreased when carvedilol is administered with food; however, there is no significant difference in overall bioavailability. Taking carvedilol with food may minimize the risk of orthostatic hypotension *(23)*.

2.1.5. PROPRANOLOL

Administration of propranolol with protein-rich foods increases the bioavailability by about 50% (no change in plasma binding, half-life, time to peak concentration, or the amount of unchanged drug in the urine) *(24)*.

2.1.6. OTHERS

The absolute bioavailability of *betaxolol* is approximately 89% and appears to be unaffected by the concomitant ingestion of food or alcohol *(25)*. The absolute bioavailability of *bisoprolol* fumarate is not affected by the presence of food *(26)*. The absolute bioavailability of *labetalol* is increased when administered with food *(27)*. The bioavailability of *metoprolol* succinate is not significantly affected by food. For the immediate-release formulation, metoprolol tartrate, patients should be advised to take metoprolol with or immediately following meals *(28,29)*. Food does not affect the rate or extent of *nadolol* absorption *(30)*. The bioavailability of *pindolol* is not significantly affected by co-administration of food *(31)*.

2.2. Centrally Acting Antiadrenergics

2.2.1. GENERAL

Methyldopa and clonidine are the two most commonly used agents in this class. These agents stimulate alpha-adrenoreceptors in the brain stem which causes a decrease in sympathetic outflow from the central nervous system resulting in decreases in peripheral resistance, renal vascular resistance, heart rate, and blood pressure. A major side effect in this class that may alter dietary habits is dry mouth *(32)*. Generally these drugs are used as last line agents for treatment of resistant hypertension.

2.2.2. CLONIDINE

Patients with short bowel syndrome have significant fluid losses. Clonidine, an alpha-2 agonist, is effective for the treatment of chronic diarrhea resulting from long-standing diabetes and thus has been studied to determine if it is effective in decreasing fecal water and sodium losses in eight parenteral nutrition-dependent patients with proximal jejunostomy. The results showed that transdermal administration of 0.3 mg clonidine is associated with a clinically modest but statistically significant decrease in fecal weight in patients with short bowel syndrome and high-output proximal jejunostomy that require chronic parenteral fluid infusion *(33)*.

In two studies, clonidine premedication showed attenuation of hyperglycemic response to surgery. This is probably due to inhibition of surgical stress-induced release of catecholamines and cortisol *(34,35)*. Hypoglycemia has also been reported with clonidine testing for growth hormone deficiency in children. Most likely mechanism is blunting of the counterregulatory response to hypoglycemia through decrease in cortisol levels and decreased sympathomimetic outflow *(36)*.

2.3. Peripherally Acting Antiadrenergics

2.3.1. GENERAL

Antihypertensive effects of these drugs occur through blockade of peripheral alpha-receptor causing overall relaxation of vascular smooth muscle and decreasing peripheral resistance. Specific food-related drug interactions in this class are described below.

2.3.2. DOXAZOSIN

The effects of food on the absorption of doxazosin were studied in a crossover study of 12 hypertensive subjects. A reduction of 12% in the AUC and 18% in mean maximum plasma concentration was observed when doxazosin was administered with food; however, neither of these differences was statistically significant *(37)*.

2.3.3. TERAZOSIN

Food delays the time to peak concentration by about 1 h; however, it has little or no effect on the extent of absorption of terazosin *(38)*.

3. ANTIARRHYTHMIC MEDICATIONS

3.1. General

Antiarrhythmic medications are used in the treatment or prevention of cardiac arrhythmias. Drug-induced torsades de pointes (TdP) is a potentially fatal cardiac arrhythmia. Antiarrhythmic agents which prolong the QT interval have a more than 1% chance of causing TdP *(39)*. Additional risk factors for TdP include hypokalemia and severe hypomagnesemia and, therefore, electrolyte abnormalities and nutritional states which may cause these electrolyte abnormalities must be monitored closely in patients receiving antiarrhythmic medications *(39)*.

3.2. Amiodarone

An open-label, single-dose, crossover study in 30 healthy men found that a standard high-fat breakfast significantly increased the rate and extent of absorption (AUC increased 2.4-fold) of amiodarone relative to fasting *(40,41)*. Several case reports suggest that amiodarone can induce hyperglycemia; however, one prospective trial in a group of 10 patients on amiodarone therapy followed over a 9-month period found no evidence of significant glucose intolerance *(42–44)*. Recommendations do not list hyperglycemia as a potential side effect of amiodarone *(40)*.

3.3. Disopyramide

Several case reports describe significant hypoglycemia in patients receiving disopyramide *(45–49)*. The risk for hypoglycemia is increased in patients with chronic malnutrition, congestive heart failure, hepatic, or renal impairment. The risk is additive in patients receiving other medications known to cause hypoglycemia *(50)*.

3.4. Flecainide

Although food does not affect absorption, milk may inhibit the absorption of flecainide in infants. As a result, a reduction in dose may be necessary if milk is removed from the infant's diet *(51)*.

3.5. Lidocaine

In patients receiving lidocaine, the Vd increases with obesity and, therefore, total body weight should be used to calculate loading doses. Maintenance infusions should be calculated based on an "ideal" body weight as the clearance is determined by hepatic blood flow and is not changed by increases in body weight *(52)*.

3.6. Procainamide

The Vd for procainamide correlates best with "ideal" body weight and, therefore, a measure of lean body weight should be used to calculate loading doses for obese patients receiving procainamide *(53)*.

3.7. Propafenone

Propafenone undergoes metabolism by the polymorphic oxidative enzyme CYP2D6. One single-dose study evaluating the effect of breakfast on the absorption of propafenone found that administering propafenone with food did not affect the plasma concentration in subjects who were "slow" metabolizers (intrinsic clearance <0.5 L/min) of propafenone; however, "rapid" metabolizers demonstrated a significant 2.5-fold increase in the AUC *(54)*. Despite evidence of increased absorption demonstrated in single-dose studies, multiple-dose studies in healthy volunteers did not demonstrate significant differences in bioavailability *(55)*.

3.8. Quinidine

Quinidine absorption may differ depending on the oral salt administered. The overall absorption of quinidine sulfate was not affected when administered with a balanced meal in nine healthy male subjects; however, the rate of absorption was decreased (44% increase in time to $C_{\max}$) *(56)*. Another study evaluating the absorption of quinidine sulfate in eight healthy volunteers (five women, three men) confirmed that overall bioavailability was not affected by a standard breakfast; however, the rate of absorption was again decreased *(57)*. The authors postulate that this decrease in the rate of absorption may result in a dampening of undesirable side effects when quinidine sulfate is administered with food *(57)*.

The absorption of quinidine gluconate was unaffected by administration with a standard breakfast in 9 healthy volunteers; however, a more recent study of 15 healthy men found that administration of quinidine gluconate with a low-fat or high-fat breakfast increased both the rate and extent of bioavailability *(58,59)*. Recommendations state that food increases the rate and extent of absorption by 27 and 17%, respectively *(60)*. Recommendations for quinidine gluconate also state that a decrease in dietary salt may increase drug concentrations and, therefore, changes in dietary salt intake should be avoided *(60)*.

Several reports document the risk of hypoglycemia in patients receiving quinine for the treatment of malaria *(61–63)*. Quinidine, the diastereoisomer of quinine, has also been found to increase insulin release and decrease plasma glucose concentrations, although to a lesser extent than quinine *(64,65)*. Despite these studies, the manufacturer recommendations make no mention of the risk of hypoglycemia in patients receiving quinidine therapy *(60)*.

3.9. Sotalol

Obesity had no significant effect on any clinical (heart rate, blood pressure, cardiac index) or pharmacokinetic (AUC, Vd, Cl) parameters in 6 obese patients receiving intravenous sotalol as compared to 12 healthy non-obese volunteers *(66)*. A study in five healthy subjects found that absorption was decreased by 20% when administered with a meal, especially with milk *(67, 68)*.

4. ANTITHROMBOTIC AGENTS

This class of medication includes several different agents that affect blood hemostasis each with differing mechanisms of action that include antiplatelet, anticoagulant, and thrombolytic activity. These medications are used to treat and prevent diseases where blood clotting is involved such as myocardial infarction, peripheral vascular disease, deep vein thrombosis, and pulmonary embolism.

4.1. Aspirin

To evaluate whether obesity affects salicylate kinetics, a crossover study in 40 subjects (20 obese, mean weight 113 kg; 20 controls, mean weight 67 kg) matched for age, sex, height, and smoking habits were administered a single 650 mg dose of aspirin intravenously and then orally *(69)*. Following parenteral administration, the Vd (in L) of total salicylate was 19% higher in obese patients ($p<0.05$); however, upon correction for total weight the Vd was actually smaller in obese subjects (0.14 L/kg vs 0.19 L/kg, $p<0.001$), indicating that any weight-based dosing should use an adjusted or lean body weight. Following the oral administration of aspirin, $C_{\max}$ was significantly lower in the obese subjects compared to normal subjects (27 vs 36 μg/mL, $p<0.002$); however, the overall bioavailability of salicylate was not significantly different between the two groups. Despite the changes observed in Vd and $C_{\max}$, the overall extent of absorption and clearance of salicylate was not significantly different in obese patients compared to healthy volunteers and, therefore, the authors conclude that salicylate dosage does not need to be adjusted in proportion to total body weight. A more recent study in 21 nondiabetic subjects found that inhibition of platelet aggregation by aspirin was less in obese insulin-resistant patients compared to matched normal-weight patients *(70)*. Following oral administration of 50 mg of aspirin, platelet aggregation induced by adenosine diphosphate (ADP) concentrations of 2 μmol/L were 74 ± 6% for the non-obese group and 91 ± 1% for the obese group ($p<0.01$) *(70)*.

Several studies have evaluated the effects of food on the absorption of aspirin *(71–73)*. One study found that a standard breakfast reduced bioavailability (as measured by salicylate levels) of a single dose of 491 mg aspirin tablet by 15% *(71)*. Another study found that administration of a 650 mg tablet of aspirin in a fasting state (as compared with a high-carbohydrate, high-protein, or high-fat meal) resulted in higher salicylate levels during the first hour following administration *(73)*. Overall bioavailability was higher in the patients who took aspirin with a high-fat meal and in patients who took aspirin on an empty stomach with 250 mL water. A third study evaluated the absorption of conventional tablets and enteric-coated tablets in the fasting and fed conditions and found that 1 g of aspirin administered as an enteric-coated product had decreased absorption when administered with food during the fourth to eighth hour following dosing ($p<0.05$); however, overall salicylate recovered over 48 h was not statistically significantly different (with food 878 mg vs fasting 959 mg) *(72)*. Decreased absorption of the conventional aspirin tablet was observed during the first to second hour following dosing; however, no difference was found over the 48 h. The manufacturer for Aggrenox® (dipyridamole/aspirin capsules) states that although a 50% decrease in $C_{\max}$ of aspirin occurred when Aggrenox® was taken with a high-fat meal, there was no difference in AUC at steady state and no difference in the degree of cyclooxygenase inhibition and therefore is not clinically relevant *(74)*. The reduction in $C_{\max}$ would only be relevant if aspirin were being administered for acute pain. An analysis of several beverages (water, tea, coffee, orange juice, milk, beer, and distilled alcohol) on salicylate absorption in five healthy volunteers found that alcohol (whisky, rum, or vodka) increased absorption while milk and beer decreased absorption *(75)*.

One unusual effect that aspirin can have on food is an increased hypersensitivity response. Several reports suggest that aspirin can increase and enhance type I allergic reactions in patients with pre-existing food allergies and food-dependent exercise-induced anaphylaxis *(76–79)*.

Studies evaluating the effects of dietary supplements on aspirin were summarized in a recent review article *(80)*. Dietary supplements that have significant effects on aspirin include the following: *n*-3 fatty acids (increase antiplatelet effects and bleeding risk), vitamin E (increase antiplatelet effect and increase bleeding risk), and tamarind (increased bioavailability by 516%) *(80)*. An additional observational study of 255 patients hospitalized with cardiovascular disease found that patients using aspirin were more often deficient in vitamin B_{12} compared to nonusers *(81)*. There are also some studies which suggest that aspirin, in doses ranging from 800 mg to 3 g, may decrease the absorption of vitamin C (ascorbic acid) from the gut *(82–84)*.

Case reports suggest aspirin as a potential cause of hypoglycemia and an analysis in six healthy volunteers found that aspirin decreases the jejunal absorption of glucose by 50% *(85–87)*. Another study found that aspirin administration in non-insulin-dependent diabetic patients ($n = 18$) resulted in an increase in insulin mobilization and a decrease in blood glucose levels *(88)*. In both healthy and type 2 diabetic patients, aspirin (3 g/day for 3 days) increased plasma insulin levels although it reduced tissue sensitivity to insulin. In the diabetic patients aspirin also reduced hepatic glucose production *(89)*.

4.2. Cilostazole

In a study of healthy male volunteers, the $C_{\max}$ and AUC of cilostazol (two 50 mg tablets) were increased by 90 and 25%, respectively ($p<0.05$) when administered with a high-fat (62% fat) breakfast consisting of two fried eggs, two pieces of bacon, two pieces of toast with butter, whole milk, and hash browns *(90)*.

4.3. Clopidogrel

A study evaluated whether body mass index (BMI) affected platelet response to a clopidogrel loading dose *(91)*. Forty-eight patients (29 with BMI > 25 kg/m^2 and 19 with BMI < 25 kg/m^2) who had been on aspirin therapy (100–250 mg/day) for at least 7 days were administered 300 mg of clopidogrel. Platelet aggregation (as induced by 6 μmol/L ADP) was assessed at baseline, 10 min, 4 h, and 24 h following clopidogrel administration. While both groups demonstrated significant reduction in platelet aggregation at 4 h, only the normal-weight patients continued to demonstrate a significant decrease in platelet aggregation at 24 h. The aggregation was significantly higher in the obese group compared to the normal-weight group at 24 h (38.5±13.6 vs 25.8±15.6%; $p = 0.02$) and the percentage inhibition of platelet aggregation at 24 h was suboptimal (<40%) in a higher percentage of obese patients (59%) compared to the normal-weight patients (26%) ($p = 0.04$). The findings of this study suggest that a dose of 300 mg may not be sufficient in obese patients and that a higher dose may be necessary to achieve optimal inhibition of platelet aggregation.

Although the manufacturer states that there is no effect of food on the bioavailability of clopidogrel, a study in healthy male subjects found that administration of clopidogrel with a standard high-fat breakfast (two eggs fried in butter, two strips of bacon, two slices buttered toast, hash brown potatoes, and whole milk) increased the $C_{\max}$ and AUC by 6.1-fold and 9.2-fold, respectively *(92,93)*.

4.4. Dipyridamole

The manufacturer of Aggrenox® (aspirin/extended-release dipyridamole) states that although peak plasma levels and total absorption of dipyridamole were decreased by 20–30% when taken with a high-fat meal, the degree of inhibition of adenosine uptake was similar and, therefore, the effect is not clinically significant *(74)*.

4.5. *Fondaparinux*

The manufacturer recommendations state that fondaparinux should not be used for prophylaxis in patients weighing less than 50 kg due to an increased risk of bleeding *(94)*.

4.6. *Heparin*

4.6.1. EFFECT OF HEPARIN ON NUTRITION STATUS

Heparin causes aldosterone suppression which can lead to hyperkalemia in 7–8% of patients treated with heparin *(95)*. The majority of reports included in a review of the published data of heparin-induced hyperkalemia were of patients receiving unfractionated heparin *(95)*. Recent studies suggest that the risk of hyperkalemia appears to be less with low-molecular-weight heparin (LMWH) products *(96–100)*.

4.6.2. INFLUENCE OF NUTRITION ON HEPARIN

Caution must be used when administering fixed-dose LMWH products to underweight patients. After a single subcutaneous dose of enoxaparin 40 mg, the anti-factor Xa exposure was 27% higher in low-weight men (<57 kg) and 52% higher in low-weight women (<45 kg) *(101)*.

The safety and efficacy of LMWH in obese patients was recently reviewed in an article that included information from nine trials using LMWH in obese patients *(102)*. The literature suggests that LMWH can be used safely in patients with BMI greater than 30 kg/m^2. The highest weight (when available) in the studies was 182 kg. The manufacturer recommendations for enoxaparin state that the mean AUC of anti-factor Xa activity is marginally higher in obese healthy volunteers (BMI 30–48 kg/m^2) as compared to non-obese healthy volunteers administered 1.5 mg/kg once daily; however, the product labeling neither provides dosing information for obese patients nor specifies a maximum recommended dose *(101)*. The manufacturer recommendations for tinzaparin state that although a prospective study of heavy/obese subjects (101–165 kg; BMI 26–61 kg/m^2) demonstrated similar anti-Xa activity in obese and normal-weight volunteers, clinical trial experience is limited in patients with a BMI $>$ 40 kg/m^2 *(103)*.

4.7. *Warfarin*

Warfarin is the most widely used oral anticoagulant in the United States. Warfarin exerts its effects by inhibiting synthesis of vitamin K-dependent clotting factors II, VII, IX, and X and protein C, S, and Z in the liver *(104)*. Since vitamin K is found in many foods, patients receiving warfarin are sensitive to *fluctuating* levels of dietary vitamin K intake. It was estimated that vitamin K intake of more than 250 μg/day decreases warfarin response in anticoagulated patients consuming regular diets. Similarly another study estimated that each 100 μg in the daily dietary intake of vitamin K reduced the international normalized ratio (INR) by 0.2 *(105, 106)*. Thus, patients consuming an increased amount of green vegetables or vegetable oils, known to have high vitamin K content, can have reduced anticoagulant response to warfarin. This, however, does not mean that patients should avoid eating green leafy vegetables or salad dressing. This is a popular misconception among patients and some clinicians. *Consistency* in the intake of vitamin K-containing foods should be stressed to patients in order to avoid fluctuations in warfarin response *(107,108)*. In fact, several studies have shown that poor intake of dietary vitamin K is associated with instability of anticoagulation *(109,110)*. In the vitamin K-depleted patients, as little as 25 μg/day vitamin K in a multivitamin tablet was enough to have significant impact on anticoagulation control *(111,112)*. Several small studies have investigated whether administration of vitamin K 100–500 μg/day augments anticoagulation control to reduce variation in the INR. They concluded supplementation with low daily dose of vitamin K significantly increases anticoagulation control *(113–116)*. Recent guidelines recommend that patients receiving long term warfarin with a variable INR response that is not attributable to any of the known causes for instability receive a low-dose oral vitamin K (100-200 μg) daily. This should coincide with close monitoring of the INR and drug dose adjustment to the initial lowering of the INR *(107)*.

Besides green leafy vegetables, certain unusual culprits have been reported in the literature as having high content of vitamin K. These include green tea, avocado (large amounts), and sushi-containing seaweed *(117,118)*.

Enteral feedings have also been implicated to alter the bioavailability of warfarin (see Chapter 13). The interaction in the early 1980s resulted from the high vitamin K content from tube feeding products, since then manufacturers have reformulated the products to contain less vitamin K. Despite this change, additional case reports of warfarin-enteral feedings have been published. Because the vitamin K content is low in the tube feeding products, it is hypothesized that the drug interaction more likely results from the binding between warfarin and proteins in the feeding products *(119)*.

Soy is widely advocated as a health food for antihypertensive, antihyperlipidemic, and more recently alternative hormone therapy. One case report describes a drug interaction with warfarin and soy protein (given as soymilk) leading to subtherapeutic INR values. The exact mechanism of decline in INR is not known, the authors speculate alteration in drug absorption, metabolism, and biliary excretion by the isoflavones genistein and daidzein in soy protein *(120)*.

Another popular trend in the United States is the use of high-protein, low-carbohydrate diets. Two cases of decreased INR after initiation of a high-protein, low-carbohydrate diet have been reported. High-protein diets can increase serum albumin levels and this may lead to more warfarin binding to serum albumin, thereby decreasing the anticoagulant effect *(121)*.

A probable interaction between mango fruit and warfarin was reported to have increased the anticoagulant effect among 13 male patients. Possible mechanisms for this interaction include the high vitamin A content and its relation to CYP2C19 inhibition and the presence of other components in the mango. Further studies are needed to confirm this interaction *(122)*. Interactions between fruit juices and warfarin have also been evaluated (see Chapter 10).

No case reports of garlic or ginger interaction with warfarin were identified. However, both of these natural foods have been associated with decreased platelet aggregation and episodes of prolonged bleeding (see Chapter 12). Therefore, in theory concomitant use of these foods with warfarin may increase bleeding risk *(123)*.

5. CALCIUM CHANNEL BLOCKERS

5.1. General

Calcium channel blockers (CCB) inhibit the elevation of intracellular calcium required for contraction in the vascular smooth muscle. In general, CCB can be divided into two major subcategories, dihydropyridines and nondihydropyridines. The dihydropyridines are potent vasodilators and have little or no negative effect upon cardiac contractility or conduction, whereas nondihydropyridines (e.g., verapamil, diltiazem) do have effect on cardiac contractility or conduction.

The influence of gastrointestinal (GI) motility and transport processes on the pharmacokinetics of drugs, particularly when given as extended-release formulations, has received little attention. A study evaluated the influence of GI transit times on the pharmacokinetics of three calcium channel blockers, 240 mg diltiazem, 10 mg felodipine, and 5 mg amlodipine, recommended for once-daily dosing. Patients were divided into slow (>35 h) or rapid (<15 h) GI transit times, assessed by the metal detector method (EAS II). The AUC and concentration at 24 h of diltiazem were significantly less in the rapid vs the slow group (1135 vs 1705 ng/mL*h, $p<0.05$, and 22.8 vs 49.5 ng/mL, $p<0.05$, respectively). No significant difference in AUC, $C_{\max}$, and tmax were found between the groups for felodipine and amlodipine. The authors concluded that the pharmacokinetics of the CCB with once-daily formulation characteristics are sensitive to GI transit if these processes are rapid enough to interfere with the formulation-specific release profile *(124)*.

Two studies investigated the effects of calcium supplementation on hypertension. In the first study calcium (1200 mg/day) was given for 8 weeks in 30 hospitalized patients with essential hypertension receiving oral manidipine or intravenous nicardipine. The average systolic and diastolic blood pressures were not decreased or enhanced by calcium supplementation *(125)*. The second study administered 1 g of elemental calcium and administration of 2 mg bid lacidipine or placebo to healthy male subjects *(126)*. No significant difference in the effect of lacidipine vs placebo on standing or recumbent systolic or diastolic blood pressure or heart rate was found between the placebo and calcium groups.

Peripheral edema is a common adverse effect of dihydropyridine CCBs. It is also observed with verapamil and diltiazem, however, to a lesser extent. The incidence is dose dependent and may be as high as 80% with very high doses of dihydropyridine calcium antagonists *(127)*. The etiology of CCB-induced peripheral edema is not completely understood; however, it most likely involves increase in capillary hydrostatic pressure with consequent transcapillary fluid loss that results from a relatively more pronounced vasodilatation in precapillary than postcapillary resistance vessels *(128)*. The edema is not associated with salt and water retention; in fact dihydropyridines are natriuretic, and usually treatment with diuretic therapy does not improve the edema *(129)*.

Constipation is a common side effect of verapamil. This effect can occur in over 25% of patients *(130)*. A study evaluated whether nifedipine and verapamil inhibit the sigmoid colon myoelectric response to eating in healthy volunteers. The results showed that nifedipine strongly inhibited the sigmoid myoelectric response to the meal. There was also significant response in those taking verapamil compared to placebo, although to a much lesser extent than in those taking nifedipine. Since verapamil clinically has been implicated to a greater extent to cause constipation, the authors conclude that verapamil probably displays other mechanisms (reduced colonic transit, increased water absorption) in causing this adverse event *(131)*.

5.2. Amlodipine

Forty healthy volunteers were enrolled in an open-label, single-dose, randomized, two-way crossover study, with 14 day washout period between doses of amlodipine/atorvastatin 10/80 mg tablets under fed or fasted conditions. The bioavailability of amlodipine from Caduet® (amlodipine/atorvastatin) was not affected by food *(132)*. The rate of atorvastatin absorption decreased with food intake; however, food did not significantly affect the extent of absorption.

5.3. Felodipine

Food affects the bioavailability of felodipine. When felodipine was administered with either a high fat or carbohydrate diet, the $C_{\max}$ is increased by approximately 60% although the overall AUC is unchanged. When felodipine was administered after a light meal (orange juice, toast, and cereal), however, there is no effect on felodipine's pharmacokinetics *(133)*.

Peppermint oil which contains menthol, a widely used flavoring ingredient present in a variety of commercial products, was shown to inhibit the CYP3A activity in rat and human liver microsomes and to enhance the oral bioavailability of the CYP3A4 substrate felodipine in people. Therefore, a study evaluated the effect of menthol on the pharmacokinetics and pharmacodynamics of felodipine in 11 healthy subjects *(134)*. The results of the study found there were no differences in dehydrofelodipine, the inactive metabolite of felodipine, and felodipine $C_{\max}$ and $AUC_{0\text{-}24h}$ values when co-administered with menthol or placebo. For pharmacodynamic evaluation, only eight female subjects' cardiovascular data were analyzed due to technical problems. There was no difference in heart rate or blood pressure between the two treatments.

5.4. Isradipine

Administration of isradipine with food significantly increases the time to peak by about an hour, but has no effect on the total bioavailability of the drug *(135)*. For the controlled release product DynaCirc® there was no evidence of dose dumping either in presence or absence of food though bioavailability was decreased by 25% in the presence of food *(136)*.

5.5. Nifedipine

The effect of food on nifedipine depends on the formulation. Bioavailability of sustained-release nifedipine preparations is increased by 28–31% when administered with food. However, bioavailability of modified release Adalat Retard and controlled release Adalat Oros formulations is not significantly affected by food *(137,138)*. Another study showed similar results for Adalat Oros; however, for nifedipine (Sandoz) Retard formulation, food interaction was detected showing a threefold increase in the mean $C_{\max}$ when compared to values obtained in fasting subjects *(139)*. Significant food interaction was also demonstrated with modified release Adalat Coral formulation compared to Adalat Oros which are preparations marketed in the European Union.

Significant dose-dumping effect was observed after fed administration of Coral, resulting in nearly three- to fourfold increase in plasma nifedipine concentrations *(140)*. The clinical relevance of food interactions with nifedipine is formulation specific and products should not be used interchangeably. Change in administration condition (with or without food) can lead to changes in pharmacologic and therapeutic effect.

5.6. *Verapamil*

Controlled-onset extended-release verapamil (COER-verapamil) is developed to control the release of the calcium antagonist, verapamil, in synchrony with the circadian rhythm of blood pressure and heart rate. Although studies have evaluated the safety and efficacy in the general population, studies have not been performed in obese patients known to be at higher risk for cardiovascular events. Patients were randomized to receive COER-verapamil (180–540 mg at bedtime) or placebo for 4–8 weeks and stratified according to BMI (“obese”$>$ 28 kg/m^2). The hemodynamic effects of COER-verapamil assessed by blood pressure, heart rate, and rate-pressure product in obese ($n = 166$, average BMI = 32.8 kg/m^2) and non-obese ($n = 115$, average BMI = 25 kg/m^2) were similar *(141)*. Two notable exceptions in terms of adverse effect profile in the obese patients were the significantly lower rates of constipation and fatigue compared to non-obese group. The authors concluded that COER-verapamil is effective in reducing blood pressure, heart rate, and rate-pressure product independently of BMI *(141)*.

In 12 healthy volunteers the effects of high-protein food on the bioavailability of the racemate and individual *S*-, *R*-enantiomers of verapamil were investigated. The results showed that food had no effect on any parameter of bioavailability for both the racemate and the individual enantiomers of verapamil except t_{max} which was significantly prolonged after food intake. Clinical efficacy is not related to food intake except for a slight prolongation in the time to onset of the pharmacologic effects *(142)*.

5.7. *Manidipine*

Food significantly improved the absorption with an increase in AUC from 19.1 to 27.2 ng/h/mL, but did not modify the rate of absorption of manidipine. Increase in bioavailability of manidipine administered with food is related to its high lipophilicity and may be explained by a solubilization effect by food and bile secretions *(143)*.

6. CARDIAC GLYCOSIDES

The main effect of cardiac glycosides is increased contractility of cardiac muscle and decreased heart rate. Digoxin is the cardiac glycoside most often prescribed and is used in the treatment of heart failure and for rate control in patients with atrial fibrillation.

The effect of dietary fiber on digoxin absorption was evaluated in five healthy women *(144)*. A 0.8 mg β-acetyl-digoxin tablet was administered along with a formula diet (614 kcal, 19 g fat, 75.4 g carbohydrate, 30 g protein) and each of the following: 10 g wheat bran, 5 g microcrystalline cellulose, 5 g pectin, 5 g carrageenan, and 5 g carob seed flour. Although none of the fiber substances were found to lower overall digoxin concentrations, the carob seed flour significantly increased the serum digoxin concentrations. In addition, the wheat bran, cellulose, and pectin increased the time to peak serum digoxin concentration. Two additional studies evaluated the effect of dietary fiber on digoxin absorption and found that, although there was a slight decrease in digoxin serum concentrations, it was not clinically significant *(145,146)*.

The influence of obesity on digoxin distribution was evaluated in a study of 29 patients (16 obese, mean weight 100.2±36.8 kg; 13 controls, mean weight 64.6±10.5 kg) *(147)*. Patients were given a single 5 min infusion of 0.75 mg digoxin followed by serial blood samples drawn up to 96 h following the infusion. The Vd, elimination half-life, and total clearance were calculated for each patient. The absolute Vd, total Cl and elimination half-life were similar in the two groups and it is recommended that digoxin loading and maintenance doses be calculated based on an "ideal" body weight in obese patients.

7. DIURETICS

Diuretics are a class of agents used to decrease fluid volume in patients with hypervolemia from various causes. They are most commonly used for the treatment of heart failure and hypertension.

7.1. Diazoxide

The recommendations for diazoxide state that the majority of patients treated with diazoxide will experience transient hyperglycemia; however, treatment is usually only necessary in patients with pre-existing diabetes mellitus *(148)*. Blood glucose should be monitored closely, particularly in those patients receiving multiple injections.

7.2. Loop Diuretics

A review article summarized the effects of food on loop diuretic absorption *(149)*. Six studies were described which evaluated the effect of food on furosemide absorption and each found that food decreased the overall absorption of furosemide. Despite a consistent finding of decreased absorption, only one study demonstrated a resultant decrease in diuresis. Bumetanide and torsemide bioavailability appears not to be affected by administration with food *(149,150)*.

The loop diuretics by their mechanism of action can lead to urinary loss of potassium, sodium, calcium, and magnesium, and close monitoring and supplementation are necessary *(151–153)*.

Several studies have evaluated the effect of diuretic therapy on thiamin status. A study in six volunteers found that furosemide (1, 3, and 10 mg) doubled the rate of urinary thiamin excretion which correlated with urine flow rate *(154)*. Additional studies observed that administration of furosemide in hospitalized patients predicted decrease in thiamin status ($F = 4.06$, $p < 0.001$) and that patients receiving high-dose furosemide (mean 120 ± 40 mg/day) and low-dose furosemide (mean 40 mg/day) were severely deficient in thiamin (96 and 57%, respectively, with thiamin pyrophosphate effect [TPPE] percentage >25%) *(155,156)*. The clinical effect of this deficiency has been evaluated. One study of 38 heart failure patients receiving furosemide (mean dose 242 ± 216 mg/day) or bumetanide (mean daily dose not reported) found that biochemical evidence of severe thiamin deficiency (thiamin pyrophosphate effect > 25% stimulation) was found in seven patients. There was a nonsignificant trend for patients with thiamin deficiency to have lower percentages of left ventricular ejection fractions *(157)*. A case–control study found that 23 patients with heart failure on long-term furosemide therapy (dose range 80–240 mg daily) were more likely to have thiamin deficiency (TPPE > 15%) compared to a matched control group (21 of 23 in heart failure group vs 2 of 16 in control group, $p<0.001$) *(158)*. When six of the heart failure patients were given parenteral thiamin (100 mg twice daily), the mean TPPE decreased to normal (27.0±3.8 to 4.5±1.3%, $p<0.001$) and left ventricular ejection fraction increased from 24±4.3 to 37±2.4% in four out of five patients who underwent echocardiography (one remained unchanged). No change in cardiac output was noted. A prospective, double-blind randomized study evaluated the effect of 1 week of daily intravenous thiamin HCl (200 mg) compared to placebo (normal saline) in heart failure patients receiving furosemide (mean daily dose for placebo 108 ± 45 mg/day and for thiamin treatment 120 ± 36 mg/day) *(159)*. This portion of the study was followed by a 6-week open-label period in which all patients received 200 mg of oral thiamin daily. Fifteen of the 27 patients included in the study had baseline TPPE higher than 15%. There was no change in TPPE in the placebo group after 1 week; however, the thiamin-treated group decreased from 11.7 ± 6.5 to 5.4 ± 3.2% ($p<0.01$). Mean left ventricular ejection fraction (LVEF) increased in the thiamin-treated group (0.28 ± 0.11 to 0.32 ± 0.09, $p<0.05$) but not in the placebo group. The mean LVEF also increased 22% ($p<0.01$ compared to baseline) after the 6-week oral thiamin period.

7.3. Potassium-Sparing Diuretics

Foods that are high in potassium content and salt substitutes that contain potassium may increase the risk of hyperkalemia in patients receiving potassium-sparing diuretics.

A study in nine healthy subjects evaluated the effect of food (standardized breakfast) on the absorption of spironolactone and its metabolites *(160)*. The results indicate that food increases absorption of spironolactone with a 95.4 ± 66.9% mean increase in AUC when compared to a fasting state ($p<0.001$).

A report describes several studies that were conducted to evaluate the effects of food on the absorption of combination hydrochlorothiazide/triamterene tablets or capsules and combination hydrochlorothiazide/amiloride tablets *(161)*. The authors concluded that food, particularly food high in fat content, increases the absorption of triamterene; however, this increase occurred only with the capsule formulation and not with the tablet formulation. Food decreased the absorption of amiloride by approximately 25%.

7.4. Thiazide/Thiazide-Like Diuretics

A study found that hydrochlorothiazide absorption was increased when administered with a high-fat meal, but this occurred only with administration of hydrochlorothiazide/triamterene capsules and not with the tablets *(161)*. An earlier study also found that food enhanced the absorption of hydrochlorothiazide *(162)*.

In contrast, the manufacturer recommendations for Microzide® (hydrochlorothiazide capsules) state that administration of hydrochlorothiazide with food decreases bioavailability by 10% and the maximum plasma concentration decreases by 20% *(163)*. The data to support this recommendation are no longer available, but perhaps it is the formulation of hydrochlorothiazide that influences absorption and effects that food have on absorption.

A review article describing the effects of low-dose diuretics summarized several studies and concluded that hydrochlorothiazide can increase serum total cholesterol, LDL cholesterol, and triglyceride levels *(164)*. The author concluded that, although there is controversy surrounding the issue, the available data suggest that these adverse effects on lipid profile are dose related and low doses (<25 mg) have minimal effects on lipids. This article also summarized the effect of hydrochlorothiazide (12.5 mg) on glucose and insulin metabolism. Based on the nine trials evaluated, the author concluded that hydrochlorothiazide at doses <12.5 mg per day have minimal effect on plasma glucose and insulin levels and that only doses > 25 mg have the potential to cause significant insulin resistance and glucose intolerance *(164)*. A study designed to evaluate the frequency and severity of ventricular arrhythmias in patients receiving diuretic therapy for hypertension also evaluated the effect of diuretic therapy on glucose and insulin in hypertensive men *(165)*. This study randomized 232 men to one of six regimens: (1) 50 mg/day hydrochlorothiazide, (2) 50 mg/day hydrochlorothiazide + 40 mmol KCl per day, (3) 50 mg hydrochlorothiazide + 40 mmol KCl per day + 400 mg magnesium oxide per day, (4) 50 mg hydrochlorothiazide + 100 mg triamterene per day, (5) 50 mg chlorthalidone per day, or (6) placebo (10 mg/day thiamin). There was no significant change in mean fasting glucose or insulin levels in any of the hydrochlorothiazide regimens; however, the chlorthalidone group experienced significant increases in serum glucose (mean change 12 mg/dL, $p<0.01$).

Hydrochlorothiazide has been shown to increase zinc excretion *(166)*. One study evaluated the effects of combination hydrochlorothiazide/amiloride (50 mg/5 mg daily; $n=15$) compared to hydrochlorothiazide alone (25 mg daily; $n=8$) and control subjects ($n=8$) and found that the 24-h urinary excretion of zinc was significantly greater for both patient groups as compared to control subjects (1103±103 μg/24 h for hydrochlorothiazide/amiloride vs 1225±120 μg/24 h for hydrochlorothiazide vs 473±48 μg/24 h for control, $p<0.0001$ compared to controls) *(167)*.

8. RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM (RAAS) AGENTS

8.1. Angiotensin-Converting Enzyme Inhibitors

8.1.1. General

Angiotensin-converting enzyme inhibitiors (ACE-I) interfere with the conversion of angiotensin I to the potent vasoconstrictor angiotensin II. These agents are widely used in reducing clinical events from ischemic heart disease and decreasing the progression of renal dysfunction. Hyperkalemia is a common adverse event for which the risk is increased in patients with renal insufficiency, patients taking potassium-sparing diuretics, or patients with dietary intake high in potassium.

Recently, a study described a drug–natural product interaction with ACE-I. Licorice-induced pseudoaldosteronism has been described since 1968. Glycyrrhizin, which is the active component of licorice, was being taken by a 77-year-old man for allergic rhinitis for several years; however, the pseudoaldosteronism caused by glycyrrhizin was masked by concurrent ACE-I use. Once the ACE-I dose was reduced, hypokalemia became evident. This is the first case where masking effect of ACE-I on the development of pseudoaldosteronism has been described *(168)*.

Again, hyperkalemia is a common side effect of ACE-I. Patients with a history of hypertension are routinely advised to follow a low-sodium diet and they may try to achieve this through the use of available salt substitutes which usually contain potassium salts. Two cases of severe hyperkalemia from concomitant use of salt substitute and ACE-I have been reported. In the first case, the patient was on lisinopril 20 mg daily and in the second case the patient was on enalapril 2.5 mg twice daily. Both patients had some degree of renal dysfunction and were taking excessive amount of “Lo Salt” substitute. Serum potassium levels were reported to be 7.6 and 7.0 mmol/L, respectively, on admission. In each case the serum potassium returned to normal range after cessation of the salt substitute *(169)*. Fatal hyperkalemia due to combined therapy with a cyclooxygenase-2 inhibitor, an ACE-I, and potassium-rich diet was described in a 77-year-old mildly hypertensive and hypothyroid woman with no underlying renal disease. Her diet included eating one banana a day “to keep a good potassium level” and significant medications included enalapril 2.5 mg daily and rofecoxib 25 mg daily *(170)*.

Captopril at high doses has been associated with taste disturbance because the thiol radical (-SH) within the compound can chelate with serum zinc and the depletion of zinc subsequently leads to taste disturbance *(171)*. However, a comparative study of taste disturbance by losartan and perindopril showed that both drugs altered taste sensitivity in six Japanese men without influencing zinc concentrations in plasma and saliva *(172)*.

Several case–control studies have shown an association between hypoglycemia and ACE-I *(173–175)*. Increase in insulin sensitivity due to enhanced insulin-mediated peripheral glucose disposal from muscular tissue may be the mechanism through which hypoglycemia occurs. The adverse event was usually but not always reported in diabetic patients treated with antidiabetic agents. ACE-I have several advantages over other antihypertensive medications in diabetic patients (i.e., preventing nephropathy and preventing cardiovascular events) and, therefore, any potential increase in risk of hypoglycemia is greatly outweighed by the other benefits of ACE-I therapy *(176)*.

8.1.2. Specific Agents

Absorption of *benazepril* is not affected by the presence of food *(177)*. Food decreases absorption by about 30–40% and, therefore, *captopril* should be given 1 h before meals *(178)*. Food does not affect the absorption of *enalapril (179)*. The rate of *fosinopril* absorption may be slowed by the presence of food in the GI tract; however, the extent of absorption of fosinopril is not affected *(180)*. *Lisinopril* absorption is not influenced by the presence of food in the GI tract *(181)*. Food does not significantly lower the rate or extent of *perindopril* absorption. In clinical trials, perindopril was generally administered in a non-fasting state *(182)*. Although the rate of absorption is reduced, the overall absorption of *ramipril* is not significantly affected by the presence of food in the GI tract *(183)*. Food slows absorption of *trandolapril*, but does not affect AUC or $C_{\max}$ of trandolaprilat or $C_{\max}$ of trandolapril *(184)*.

8.2. Angiotensin Receptor Blockers

8.2.1. GENERAL

The angiotensin receptor blockers (ARBs) inhibit the binding of angiotensin II to the AT_1receptor. ARBs are similar in clinical effect to the ACE-I; however, this relatively new class has fewer side effects including cough. Little information is available with regard to ARBs and drug-nutrient interactions.

8.2.2. SPECIFIC AGENTS

Food with a high fat content does not affect the bioavailability of *candesartan* after candesartan administration *(185)*. Subclinical reduction in taste sensitivity was reported with candesartan and valsartan in eight healthy nonsmoking men. The mechanism of ARB-induced taste disturbance is not clear since serum and saliva zinc concentrations did not change *(186)*. Food does not affect the bioavailability of *irbesartan (187)*. *Losartan* may be administered with other antihypertensive agents, and with or without food *(188)*. Food does not appear to affect the bioavailability of *olmesartan (189)*. Food slightly reduces the bioavailability of *telmisartan*, with a reduction in the AUC of about 6% with the 40 mg tablet and about 20% after a 160 mg dose *(190)*. Food decreases the exposure (as measured by AUC) to *valsartan* by about 40% and $C_{\max}$ by about 50% *(191)*.

8.3. Others

8.3.1. ALDOSTERONE BLOCKERS

Spirinolactone and *eplerenone* are two agents that are used commonly in this class. Specific food–nutrient–drug interactions are discussed for each drug (see Section 7.3.). Because these agents affect the renin–angiotensin–aldosterone system, the risk of hyperkalemia exists. Patients can become hyperkalemic if combined with other risk factors such as renal dysfunction and diets rich in potassium. Spirinolactone was discussed previously in the section on diuretics. The manufacturer states that eplerenone absorption is not affected by food *(192)*.

8.3.2. RENIN INHIBITORS

Aliskiren is an agent that inhibits angiotensin I production. Relatively little information is available with regard to drug-nutrient interactions. When taken with a high-fat meal, the mean AUC and $C_{\max}$ of aliskiren are decreased by 71 and 85%, respectively. In the clinical trials of aliskiren, it was administered without requiring a fixed relation of administration to meals *(193)*.

9. LIPID MODULATING AGENTS

9.1. HMG-CoA Reductase Inhibitors

9.1.1. GENERAL

The so-called “statins” competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting step in de novo cholesterol biosynthesis, which causes a decrease in serum cholesterol and increase in low-density lipoprotein (LDL) receptor number and activity. Grapefruit juice inhibits the metabolism of certain HMG-CoA inhibitors leading to elevated drug levels (see Chapter 10).

9.1.2. ATORVASTATIN

Although food decreases the $C_{\max}$ by approximately 25% and the AUC by 9%, LDL cholesterol reduction is similar whether atorvastatin is given with or without food *(194, 195)*.

9.1.3. ROSUVASTATIN

Administration of rosuvastatin with food decreased the rate of drug absorption by 20% as assessed by $C_{\max}$, but there was no effect on the extent of absorption as assessed by AUC. Significant LDL cholesterol reductions are seen when rosuvastatin is given with or without food *(196)*.

9.1.4. SIMVASTATIN

Low concentrations of high-density lipoprotein (HDL) is associated with cardiovascular disease risk. One strategy for treating low HDL is to combine lifestyle changes with niacin plus a statin. Antioxidants have also been advocated in CAD patients for inhibiting LDL oxidation and atherogenesis. A recent study enrolled 160 subjects with CAD and low HDL to determine the effects of simvastatin/niacin and/or antioxidant therapy (vitamin E and C, β-carotene, and selenium) on progression and regression of CAD. The results of the study surprisingly showed that when the simvastatin/niacin combination is administered with antioxidants, the potentially beneficial response to HDL was attenuated compared to subjects who took simvastatin/niacin alone *(197)*.

Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before an American Heart Association-recommended low-fat meal *(198)*.

9.1.5. LOVASTATIN

The plasma concentrations of lovastatin when given on an empty stomach were reduced by an average of one-third as compared to when lovastatin was administered immediately after a standard test meal and, therefore, lovastatin should be administered with meals *(199)*.

9.1.6. FLUVASTATIN

Administration of fluvastatin with food increases the rate (twofold increase in $C_{\max}$ as compared to administration 4 h after meal) but not the extent of absorption. No differences in the lipid-lowering effects were observed between the two administrations (with or without food) *(200)*.

9.1.7. PRAVASTATIN

While the presence of food in the GI tract reduces systemic bioavailability, the lipid-lowering effects of the drug are similar whether taken with or 1 h prior to meals *(201)*.

9.2. Niacin

Certain foods may exacerbate the flushing that is common when starting niacin therapy. Alcohol, spicy foods, and hot beverages may need to be timed sufficiently before or after niacin dosing *(202)*. To maximize bioavailability and reduce the risk of gastrointestinal upset, administration of niacin with a low-fat meal or snack is recommended *(203)*.

The effect of niacin on glucose is not well understood. After acute administration of nicotinic acid, studies have reported glucose concentrations as falling, rising, or not changing. Glucose tolerance testing studies have shown inconsistent results from no effect to decreased glucose tolerance. However, chronic administration of nicotinic acid has consistently shown deterioration of glucose tolerance and rise in fasting blood glucose concentration in normal and diabetic patients. Minor increases (4–5% on average) in glucose levels result from niacin-induced insulin resistance, but these increases are often clinically insignificant or readily treated. Glycemic control in diabetes should be monitored following niacin initiation or dosage increase *(202,204)*.

9.3. Fibric Acids

9.3.1. GENERAL

Gemfibrozil and fenofibrate are the two agents available in the United States. Drug–nutrient interactions mainly relate to absorption of drug when given with or without food (see Chapter 11).

9.3.2. FENOFIBRATE

Several studies have examined the bioavailability of fenofibrate. Fenofibrate has low bioavailability when taken on an empty stomach and is highly lipophilic and, therefore, is practically insoluble in water *(205)*. In the presence of food fenofibrate absorption increases ~35%. Since high-fat meals are to be limited in treatment of hypertriglyceridemia for which fenofibrate is often prescribed, studies of newer formulations of fenofibrate have looked at whether it can be taken with or without food. In 113 healthy adult subjects three different formulations of fenofibrate, micronized or microcoated or insoluble drug delivery microparticle (IDD-P), were evaluated. The study concluded IDD-P fenofibrate formulation had an equivalent extent of absorption under fed or fasting conditions, suggesting that dosage regimens could include administration of the product without food providing greater convenience and simplicity for patients *(205)*. A randomized, double-blind, placebo-controlled trial evaluated food-related efficacy of micronized fenofibrate coated on inert microgranules (FF-uG) for treatment of hypertriglyceridemia. The study mainly looked at lipid parameters and found no inequivalence in triglyceride-lowering effects of the fenofibrate given with or without food and thus can be administered without regard to meals *(206)*. In two other clinical trials, the bioavailability of various fenofibrate formulations was evaluated. The first study evaluated a fenofibrate sustained-release formulation and concluded that administering after a meal increased bioavailability, and the second study looked at a nanoparticle formulation and found that they can be given without regard to food since pharmacokinetics were not significantly altered by food *(207,208)*.

9.3.3. GEMFIBROZIL

The absorption of gemfibrozil is affected by the presence of food. One study found that both the rate and the extent of absorption of the drug were significantly increased when administered 0.5 h before meals. Average AUC was reduced by 14–44% when gemfibrozil was administered after meals compared with administration 0.5 h before meals. A subsequent study found that the rate of absorption of gemfibrozil was increased ($C_{\max}$ was 50–60% greater) when administered 0.5 h before meals as compared to administration either with meals or fasting. In this study, there were no significant effects on AUC with regard to administration with meals. Gemfibrozil is recommended to be given before a morning and evening meal *(209)*.

9.4. Bile Acid Resins

9.4.1. CHOLESTYRAMINE, COLESTIPOL, AND COLESEVELAM

Bile acid resins bind to and reduce enterohepatic circulation of bile acid, leading to production of more bile acids from cholesterol. Bile acid resins in high doses, cholestyramine and colestipol in particular, can reduce the absorption of fat-soluble vitamins (A, D, E, or K) though the effect is negligible in healthy patients consuming a well-balanced diet *(210)*. These agents are not absorbed systemically and thus do not cause serious systemic side effects; however, they can cause GI side effects such as bloating and constipation and very rarely intestinal obstruction. Colesevelam, the newer agent in this class, has greater specificity for bile acids and in comparison to older agents it causes less constipation and clinically significant reduction in the absorption of vitamins A, D, E, or K during clinical trials of up to 1 year *(211,212)*. Cholestyramine, colestipol, and colesevelam are recommended to be given with meals *(212)*.

9.5. Cholesterol Absorption Inhibitors

9.5.1. EZETIMIBE

Concomitant food administration (high-fat or non-fat meals) had no effect on the extent of absorption of ezetimibe; however, the $C_{\max}$ of ezetimibe was increased by 38% with consumption of high-fat meals. Ezetimibe can be administered with or without food *(213)*.

9.6. Omega-3 Fatty Acids

Patients with diabetes are advised to be cautious when taking omega-3 fatty acids because increases have been reported in plasma glucose requiring increased doses of insulin or hypoglycemic agents. However, several reports show that omega-3 fatty acids do not impair glycemic control in diabetic patients. A recent multicenter, randomized, double-blind, placebo-controlled study evaluated the possible worsening of glycemic control after 2–3 g of omega-3 fatty acids per day in patients with hypertriglyceridemia with and without glucose intolerance or diabetes. The study did not find major alterations in glycemic indexes (fasting glucose, HbA1c, insulinemia, and oral glucose tolerance) in patients with impaired glucose tolerance or diabetes *(214)*. In clinical trials the only prescription omega-3 fatty acid product (Lovaza®) was administered with meals *(215)*.

10. ORGANIC NITRATES

The organic nitrates exert their effect by increasing nitric oxide availability to vascular smooth muscle which results in vasodilation. They are used primarily for the treatment and prevention of myocardial ischemia.

10.1. Isosorbide Mononitrate

The influence of food on the bioavailability of isosorbide mononitrate after single-dose administration, 60 mg tablet, was evaluated in three different studies involving either a "light" breakfast or a high-calorie, high-fat breakfast. Results of these studies indicate that concomitant food intake may decrease the rate but not the extent of absorption of isosorbide mononitrate *(216)*.

11. VASOACTIVE AGENTS

The agents included in this section are those which affect the vasculature and/or cardiac contractility. They are utilized for several different disease states such as heart failure (dobutamine), sepsis (epinephrine), pulmonary hypertension (bosentan), and hypertension (hydralazine).

11.1. Dobutamine, Amrinone, and Norepinphrine

Two studies have evaluated the effect of dobutamine on serum potassium levels *(217,218)*. In 13 patients with severe idiopathic of ischemic dilated cardiomyopathy, dobutamine (10±1 μg/kg/min) was administered. A significant decrease in plasma potassium occurred at peak infusion (4.6±0.1 to 4.2±0.2 mmol/L, $p<0.0001$) and lasted for at least 45 min following discontinuation of the infusion *(217)*. A second study evaluated plasma potassium levels in 198 patients undergoing a dobutamine stress test and found that at peak dose of dobutamine (mean peak dose = 20 μg/kg/min) a small, yet statistically significant, decrease in plasma potassium occurred (4.22 ± 4.8 to 3.86 ± 0.35 mmol/L, $p<0.00001$) *(218)*.

To evaluate whether calcium inhibits the effect of dobutamine or amrinone, a study of 46 patients was performed 1 day following elective aortocoronary bypass surgery *(219)*. Patients were given either dobutamine 2.5 μg/kg/min for 6 min increased to 5 μg/kg/min for 6 min ($n=22$) or amrinone 10 μg/kg/min ($n=12$) or 20 μg/kg/min ($n=12$) for 20 min and then an infusion of calcium chloride 1 mg/kg/min for 20 min (reduced to 0.25 mg/kg/min for 5 min in the dobutamine groups) or saline (control). The patients served as their own controls and hemodynamic parameters were measured at baseline and at 5 min intervals. The hemodynamic parameters that were increased with dobutamine alone (cardiac output and heart rate) were not increased as much when calcium was infused (30% less increase in

CO). The calcium infusion did not alter the amrinone-induced hemodynamic changes. The authors conclude that calcium may inhibit the cardiotonic actions of β-adrenergic agonists.

In order to determine whether a redox environment contributes to cardiac function in humans, two studies evaluated the effect of vitamin C on left ventricular function *(220,221)*. The first study included 19 patients who were referred for elective diagnostic heart catheterization and had no valvular disease or ventricular dysfunction. A dobutamine infusion (2.5, 5, or 7.5 μg/kg/min) was administered alone and was then administered with vitamin C (500 mg) infused into the left main coronary artery for 10 min. Left ventricular (LV) pressure and LV peak positive dP/dt (LV + dP/dt) were directly measured. Vitamin C was also administered alone and had no effect on hemodynamic parameters measured. Infusion of the vitamin C with dobutamine resulted in a 22% increase in inotropic response to dobutamine (474 ± 60 mmHg/s increase in LV + dP/dt with dobutamine alone vs 581 ± 76 mmHg/s increase in LV + dP/dt with dobutamine + vitamin C, $p<0.01$). A similar study in heart failure patients did not produce the same findings which lead to the hypothesis that increased endogenous nitric oxide (NO) in heart failure patients opposes the positive effect of vitamin C on contractility. To examine this the authors performed a study in 11 male heart failure patients testing the hypothesis that in the setting of NO synthase inhibition vitamin C will augment the response to dobutamine in patients with heart failure *(221)*. Patients were given dobutamine (2.5, 5, or 7.5 μg/kg/min) alone and then with both vitamin C (500 mg) and N^G-monomethyl-L-arginine (500 mg) infused intracoronary. The results indicate that the addition of L-NMMA allows vitamin C to produce a significant, albeit modest, increase in LV + dP/d*t* (25 ± 5% increase with dobutamine alone, 27 ± 6% increase with dobutamine and L-NMMA, 37 ± 5% increase with dobutamine, L-NMMA, and vitamin C).

The metabolic effects of dobutamine and norepinephrine were evaluated in 16 healthy male volunteers. Patients were administered norepinephrine (0.1 μg/kg/min, $n=9$), dobutamine (5 μg/kg/min, $n=7$), or placebo (0.9% NaCl, $n=9$) in addition to infusions of [$^{15}N_2$]-urea (7 μg/kg bolus, then 0.0112 mg/kg/min infusion), [6,6-D_2]-glucose (4 mg/kg/min plus 0.05 mg/kg/min), and [1-^{13}C]L-leucine (0.27 mg/kg/min plus 0.005 mg/kg/min). Blood samples were taken during regular intervals over an 8-h study period to determine plasma concentrations of glucose, lactate, insulin, glucagon, norepinephrine, and epinephrine. Metabolic parameters were determined and results demonstrate that dobutamine causes a slight decrease in glucose production, leucine flux, and ketoisocaproate flux; however, no change was observed in plasma glucose, insulin, glucagon, or lactate concentrations. Norepinephrine resulted in an increase in glucose production; however, no change in leucine and ketoisocaproate flux was observed *(222)*.

11.2. Epinephrine

Several studies have evaluated the effects of epinephrine infusions on metabolic parameters *(223–229)*. These studies have demonstrated that epinephrine causes glycogenolysis, suppression of glucose uptake in splanchnic and peripheral tissue, and stimulation of endogenous glucose production *(224,226,227,229)*. In addition, it has been shown to increase proteolysis and VO_2 *(224, 225)*.

11.3. Bosentan

The effect of food on the bioavailability of bosentan (125 mg tablet and 62.5 mg tablet) was studied in 16 healthy male volunteers *(230)*. Despite earlier studies with a 500 mg tablet which demonstrated a twofold increase in bioavailability when administered with food, this study found only a slight increase (10% increase in AUC with the 125 mg tablet).

11.4. Hydralazine

The effect of food on hydralazine absorption was evaluated in eight subjects who were given oral hydralazine under four conditions: (1) fasting, (2) with a standard breakfast (500 kcal, 17.4 g fat, 68.2 g carbohydrate, 17.4–17.6 g protein), (3) with a bolus of enteral nutrients (470 mL containing 500 kcal, 17.5 g fat, 68.2 g carbohydrate, 17.5 g protein) given over 20 min, and (4) with a slow infusion of the same enteral nutrients administered via nasogastric tube over 6 h *(231)*. The study found that hydralazine absorption was decreased by the standard breakfast and enteral nutrition bolus and was increased by the enteral infusion as compared to the fasted state.

12. CLINICAL RELEVANCE

The data presented here are based largely on small studies, case reports, and data on file with drug manufacturers. The significance of these drug–nutrient interactions and effects on nutritional status should be taken into consideration on an individual patient basis and large-scale recommendations cannot be made until larger studies have been performed. The information attained from the studies presented can be used to influence therapy decisions and monitoring parameters on an individual patient basis.

13. LIMITATIONS OF THE DATA

The information included in this chapter results from an extensive literature search. Articles were identified via MEDLINE using the following search terms in combination with the drug classes and individual drugs: nutrition disorders, obesity, malnutrition, nutritional status, protein–energy malnutrition, protein deficiency, food, absorption, bioavailability, food–drug interactions, fatty meal, enteral nutrition, dietary proteins, diet, vitamin, mineral, herbal, drug–nutrient interactions, dietary supplement, weight loss, weight gain, hyperglycemia, hypoglycemia, lipids, electrolytes, and glucose. Search findings were limited to English language and humans. Article references were also used to identify additional literature. The limitations of the presented data are largely based on the size of the studies identified. The majority of them are small studies or observational in design. Larger, prospective studies are necessary to truly examine the influence of drugs on nutritional status and vice versa.

14. RESEARCH NEEDS

Although there are many drug–nutrient interactions that have been identified, there are many more that have yet to be evaluated. Areas of particular interest include the influence of obesity on drug effects and how dietary supplements affect drug absorption and efficacy.

15. CLINICAL RECOMMENDATIONS

The information included in this chapter should be used to help guide decisions with regard to patient therapy for the treatment of cardiovascular disease and the influence that nutritional status and food/dietary supplements may have on these decisions. It is recommended to interpret and apply the data presented in this chapter to patient care on an individual patient basis.

DISCUSSION POINTS

- The absorption of several agents used in the treatment of cardiovascular diseases is affected by administration with food.
- Several agents used for the treatment of cardiovascular diseases have been shown to affect glucose regulation and these effects should be considered when administering these agents to patients being treated for or at risk of developing diabetes mellitus.
- There are limited studies evaluating the effects of dietary supplements or obesity on the efficacy and safety of cardiovascular medications and, therefore, a need for more research in this area exists.

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17

Influence of Neurological Medication on Nutritional Status

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Objectives

- Define the potential nutritional risks associated with chronic antiepileptic drug therapy.
- Understand the possible nutrition interactions in critically ill patients requiring aggressive pharmacologic therapy in the acute management of neurologic insults, including traumatic brain injury, stroke, and intracranial hemorrhage.
- Recognize the potential treatment strategies to prevent negative health outcomes related to specific drug–nutrient interactions in neurologically impaired patient populations.

Key Words: Antiepileptic; carnitine; enteral nutrition; neurologic; osteopenia

1. INTRODUCTION

The treatment of neurologic illness frequently requires chronic, long-term therapy with medication that may cause significant interactions with nutritional status. Clinical impact of these drug–nutrient interactions may include altered vitamin nutriture, increased or decreased metabolism of drugs or nutrients, and alterations in gastrointestinal motility. The combined effects of these interactions place patients receiving chronic medical therapy at risk for various degrees of malnutrition. A review of the scientific background of these adverse interactions, as well as possible therapeutic interactions, follows; the intent is to allow clinicians to optimize the medical and nutrition therapy of this patient population.

2. ANTIEPILEPTIC DRUGS

Antiepileptic drugs (AEDs) are used to achieve seizure control in patients with epilepsy. Patients frequently require long-term therapy with one or more medications. Due to the influence of AEDs, alterations in bone metabolism and status of B vitamins have been documented. Absorption of some AEDs may be negatively

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impacted by co-administration with certain vitamins and enteral nutrition products. Reviews of significant drug–nutrient interactions with the use of AEDs are available *(1)* and several aspects will be discussed in the following sections.

2.1. Bone Mineral Status

2.1.1. REVIEW OF MECHANISMS/SCIENTIFIC BASIS

The use of AEDs has been shown to have a significant impact on bone mass and bone mineral density (BMD) in various populations. Consequently, AED use has been associated with an increased risk of bone fractures. In a case–control study of more than 200,000 adult patients, use of AEDs had the highest odds ratio (OR) for fracture risk when compared to any other independent risk factor (OR 2.1, 95% confidence interval [CI] 2.0–2.2) *(2)*.

Many theories have been suggested for alterations in BMD in epileptic patients and have included evaluation of the role of AED-associated enzyme induction. The enzyme-inducing AEDs include carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and primidone, while the non-enzyme-inducing AEDs include clonazepam, ethosuximide, gabapentin, lamotrigine, levetiracetam, topiramate, valproic acid, and zonisamide (Table 1). Enzyme-inducing AEDs cause hepatic induction of the cytochrome P450 (CYP) enzyme system including CYP27A1, CYP27B1, and CYP24A1 responsible for vitamin D metabolism *(3,4)*. With increased catabolism of vitamin D via the CYP, the result is decreased levels of active vitamin D and inadequate intestinal calcium absorption, hypocalcemia, increased levels of parathyroid hormone, and increased bone turnover *(3,5)*. Conflicting reports related to the significance of vitamin D levels, as well as the role of enzyme-inducing AED in the development of bone disease, have made the mechanism of AED-associated bone disease more complex. The effect of vitamin D deficiency on BMD, the impact of long-term AED use, and the impact of AED enzyme inducers were examined in a cross-sectional study of ambulatory patients *(6)*. AED therapy was shown to decrease BMD in adult patients, regardless of

Table 1
Metabolism of Antiepileptic Drugs

Antiepileptic Drug	*Metabolized by*	*Induces*
Carbamazepine	CYP1A2, -2C8, -2C9, -3A4	CYP2C9, -3A, UGT
Lamotrigine	UGT	UGT
Oxcarbazepine	UGT	CYP3A4/5, UGT
Phenobarbital	CYP2C9/19	CYP2C, -3A, UGT
Primidone	CYP2C9/19	CYP2C, -3A, UGT
Phenytoin	CYP2C9/19	CYP2C, -3A, UGT
Topiramate	–	–
Valproic acid	CYP2C9/19, UGT	–
Zonisamide	CYP3A4, UGT	–

vitamin D status as evaluated by 25(OH)-vitamin D. Enzyme-inducing medications were associated with lower BMD, although this was not statistically significant. It should be noted that all patients receiving enzyme-inducing AEDs had serum 25(OH)-vitamin D levels below what is considered normal by current standards. BMD was negatively correlated with duration of AED therapy and multiple drug therapy *(6)*.

Subjects taking valproic acid also suffer from bone disease, although the mechanism with this AED is not clear. A recent study compared 40 adult patients on long-term valproic acid to age- and sex-matched patients taking phenytoin ($n = 40$) and age- and sex-matched healthy controls ($n = 40$). All patients on valproic acid and phenytoin had significant bone loss. BMD was 14% below controls in patients treated with valproic acid and was 13% below controls in patients treated with phenytoin. Two-thirds of patients treated with valproic acid had *T*-scores that were diagnostic of osteopenia or osteoporosis (37 and 23%, respectively) *(7)*. The mechanism of bone loss appears to be related to increased bone resorption as patients on valproic acid had higher levels of serum calcium, parathyroid hormone, and telopeptide of Type I collagen (a marker of bone resorption). A longitudinal study of patients on AED monotherapy compared BMD in Korean patients on carbamazepine, valproic acid, and lamotrigine, evaluated at baseline and after 6 months of AED therapy using dual-energy X-ray absorptiometry (DEXA) of the right calcaneus and biochemical markers of bone metabolism. Carbamazepine was associated with significantly lower *Z*-scores and decreased levels of vitamin D *(8)*. Conversely, a twofold increase in osteocalcin (a marker of bone formation) levels was seen in patients on valproic acid and lamotrigine, possibly suggesting a compensatory mechanism to maintain bone homeostasis in the two agents without enzyme-inducing properties *(8)*. Unfortunately, no allowance was made for the seasonal impact of vitamin D.

2.1.2. Reported Cases/Descriptions

A prospective study of ambulatory male veterans examined alterations in BMD at the femoral neck in patients on chronic AED therapy (phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, and phenobarbital). Younger males (age 25–44 years) in this study were shown to have more than a 2.5-fold increased prevalence of femoral bone loss (annual loss of 1.8% of femoral neck BMD) *(9)* compared to a healthy male population *(10,11)*. In a population of older women, there was a 1.6-fold increased rate of annual bone loss at the calcaneus and the total hip when continuous users of AEDs were compared to nonusers, translating to a 29% increased risk of hip fracture over 5 years in this cohort of patients *(12)*. Enzyme-inducing AEDs are thought to present the greatest risk for bone loss. Ambulatory adult patients taking enzyme-inducing AEDs for >3 years were evaluated retrospectively to assess degree of bone loss *(13)*. Patients on AEDs had a statistically significant increased risk of both osteopenia and osteoporosis across all age and gender groups. When compared to a medically normal population based on World Health Organization guidelines, 40% of the patients receiving AEDs were osteopenic compared to an expected rate of 15.3%, while 18% were osteoporotic compared to an expected rate of 0.6% in healthy individuals. In addition, based on decreases in *T*-scores across all age and gender groups, fracture risk was doubled in this population *(13)*.

Case reports of osteopenia and hypocalcemia further highlight the implications of alterations in bone homeostasis in patients on AEDs. Valproic acid-induced osteopenia has been suggested in a 28-year-old mentally retarded man being treated with divalproate. Serum levels of 25(OH)-vitamin D and 1,25$(OH)_2$-vitamin D were within normal limits. Osteopenia was diagnosed via DEXA with low *T*-scores in the neck, Ward triangle, and trochanter. Other risk factors commonly associated with osteopenia in these patients such as low vitamin D levels, small body size, and Down syndrome were not present; lifestyle factors associated with bone loss such as tobacco use, steroid use, and immobility were also not associated with osteopenia in this case *(14)*.

Hypocalcemia reduced seizure control in a 32-year-old mentally retarded, institutionalized patient who began having seizures despite therapeutic drug levels *(15)*. He had previously been seizure-free for 5 years. His AED regimen included phenytoin and phenobarbital and serum levels of AED were within the therapeutic range. Additional blood work demonstrated the following: hypocalcemia (total calcium 5.9 mg/dL) with an albumin of 37.7 g/L, hyperparathyroidemia (PTH 160 pg/mL), and vitamin D deficiency (25(OH)-vitamin D 5.7 ng/mL with a 1,25$(OH)_2$-vitamin D 53 ng/L). Intravenous calcium supplementation was instituted until the calcium level approached normal. Supplementation was then converted to 1 g oral calcium and 0.25 μg calcitriol daily. Calcium levels normalized after 2 months of supplementation, and the patient subsequently became seizure-free. Loss of seizure control due to hypocalcemia may be an uncommon clinical presentation that can be successfully treated with calcium and vitamin D supplementation.

2.1.3. Clinical Relevance

Risk of fracture is significantly higher in patients with epilepsy when compared to a healthy population. In a population study of more than 40,000 patients with epilepsy, fracture rates were almost twofold higher than the reference cohort. In particular, the risk of hip fracture was three times higher in both men and women >50 years of age *(16)*. Whether fractures are traumatic as a result of seizure activity or pathologic in nature is poorly defined. Due to the possible effects of AEDs on BMD, it is suggested that AED use is an independent risk factor for bone loss and subsequent fractures. A recent retrospective analysis of AED-treated patients with a history of fractures demonstrated that pathologic fractures are experienced throughout the life cycle at much higher rates than in the general population; of note, more than half of the pathologic fractures in this group occurred in patients less than 50 years of age *(16)*. The effects of AEDs may cause osteopenic/osteoporotic fractures to occur at a much younger age than would be expected in a healthy population *(17)*. Although the exact mechanism of AEDs on bone health is yet to be defined, the clinical impact of metabolic bone disease in this population suggests a need for intervention. Few neurologists routinely screen their patients for bone disease *(18)*, which increases the risk for considerable bone loss and fractures in this population prior to diagnosis.

In patients treated with phenytoin, carbamazepine, and valproic acid, supplementation with vitamin D has been shown to increase levels of 25(OH)-vitamin D_3 and parathyroid hormone and improve ultrasound measures of bone mineralization 1 month after receiving supplementation with 100,000 IU of 25(OH)D_3 *(19)*. Inadequate intake of calcium or vitamin D may place patients on AEDs at increased risk for deficiencies or loss of BMD. Several studies evaluating BMD in epileptic patients have documented average calcium intakes of 541–1026 mg/day *(6,8,12,20)*, which are below recommended intake guidelines *(21)*. Estimated annual health-care costs related to the treatment of osteoporotic fractures in the United States exceed 13 billion dollars *(22)*. Intervention in this population of high-risk patients may help to decrease the morbidity and health-care costs associated with decreased BMD and increased fracture risk.

2.1.4. Limitations of Data

Much of the research evaluating the impact of AED use on BMD is retrospective in design. Retrospective and cross-sectional studies may be unable to control for lifestyle factors such as physical activity, tobacco use, alcohol use, and calcium and vitamin D intake or to control for other medical conditions that may confound the association between AED use and bone loss.

2.1.5. Research Needs

Prospective longitudinal studies to define the mechanism of bone loss in patients on AED are needed in order to determine appropriate preventative or treatment strategies in individuals affected by metabolic bone disease. Newer AED regimens should be evaluated to determine their role in development of bone disease. The impact of calcium and vitamin supplementation on rates of bone loss should also be evaluated prospectively to identify specific supplementation guidelines for implementation in this at-risk population.

2.1.6. Clinical Recommendations

Supplementation with vitamin D and calcium may have significant impact on the rate of bone loss. Therapeutic options in the management of AED-related bone loss vary for prophylactic treatment of bone disease versus management of existing disease. Disease prophylaxis should include vitamin D and calcium supplementation, although the exact amount is unclear. Vitamin D supplementation at a dose of 400 IU (10 μg) may be adequate to prevent bone loss *(23)*. Individuals on multiple- or high-dose AED therapy or who have limited outdoor exposure may require prophylactic doses of vitamin D up to 2000 IU (50 μg) daily *(24)*. Evaluation of bone disease should be undertaken in individuals on long-term AED therapy who have not received prophylactic treatment. Biochemical markers may be suggestive of bone loss, such as hypocalcemia, hypophosphatemia, elevated alkaline phosphatase and parathyroid hormone levels, and decreased serum 25(OH)-vitamin D levels; however, in some cases, biochemical markers will be normal. Individuals with documented bone loss may benefit from treatment with vitamin D at doses of 2000–4000 IU (50–100 μg) while monitoring for response to therapy, namely

Table 2
Management of Bone Loss from Antiepileptic Drug Therapy *(23,24)*

Degree of Bone Disease	*Calcium*	*Vitamin D*	*Monitoring*	*Clinical Considerations*
Prophylaxis: (monotherapy)	1000 mg	400 IU (10 µg)	Biochemical markers: serum calcium, phosphorus, alkaline phosphatase, 25(OH)-vitamin D, parathyroid hormone (PTH) DEXA	Adjust therapy in setting of decreased bone density
Prophylaxis (multi-drug regimen or high-dose therapy, or monotherapy with risk factors, i.e., limited sun exposure, immobility)	1000 mg	400–2000 IU (10–50 µg)	Biochemical markers DEXA	Adjust therapy in setting of decreased bone density
Osteopenia or osteoporosis	1000 mg	2000–4000 IU (50–100 µg) (dose titrated to improvement in biochemical markers or DEXA)	Biochemical markers Urinary calcium excretion Serial DEXA	Consider bisphosphonate therapy with lack of improvement on vitamin D supplementation
Osteomalacia	1000 mg	5000–15,000 IU (125–375 µg) × 3–4 weeks (titrate dose to normalization of 25(OH)-vitamin D, calcium, and phosphorus levels)	Biochemical markers Urinary calcium excretion Serial DEXA Bone biopsy (may be necessary to diagnose)	Ongoing monitoring to prevent morbidity associated with bone disease

normalization of biochemical abnormalities or improvement in bone density. In persons who have progressed to osteomalacia, evidenced by significant hypocalcemia, increased parathyroid hormone levels and alkaline phosphatase, and low levels of 25(OH)-vitamin D, treatment should include higher doses of vitamin D. Supplementation with vitamin D at doses of 5000–15,000 IU (125–375 μg) continued over 3–4 weeks should aim to raise 25(OH)-vitamin D levels above 30 ng/mL. Inadequate data exist to routinely recommend the use of bisphosphonates in patients on long-term AED *(23)*. A summary of calcium and vitamin D supplementation and monitoring guidelines is available in Table 2.

2.2. *B-Vitamin Status*

2.2.1. Review of Mechanisms/Scientific Basis

Folate (FA) and vitamin B_{12} are important cofactors needed for the remethylation of homocysteine to methionine (Fig. 1). FA, in the form of 5-methyltetrahydrofolate, donates a methyl group and vitamin B_{12} is the coenzyme that allows the conversion of homocysteine to methionine. Vitamin B_6 is necessary for the metabolism of homocysteine to cystathionine *(25)*. An inverse relationship between plasma homocysteine and folate levels exists in patients on AED therapy; folate levels are decreased in patients on AEDs *(26,27)* (see Chapter 18). The low folate levels seen in individuals receiving AEDs are attributable to several different mechanisms: alteration in intestinal pH causing impaired intestinal absorption; inhibition of intestinal conjugases to hydrolyze the polyglutamates of dietary folate into an absorbable form; interference with transport of folate into tissues; and depletion of folate due to its role as a cofactor in phenytoin metabolism *(28)*. Deficiencies of the B vitamins may result in hyperhomocysteinemia with a subsequent increase in cardiovascular risk in individuals treated with AEDs. The mechanism for vitamin B_6 or vitamin B_{12} alterations in AED therapy is unclear.

Pregnant women on chronic AED therapy may also be at risk for impaired B-vitamin status associated with AED. It is estimated that 1 in 200 pregnancies is exposed to one or more AED, with a significant increase in the risk of congenital malformations in the offspring of women with epilepsy. Treatment with more than one agent appears to carry an even higher risk of fetal complications in comparison to women on monotherapy *(29)*. The increased risk of congenital malformations is attributed to the teratogenic effects of AED, and women with epilepsy have double the risk of having a child with a congenital malformation when compared to women not receiving AED *(30)*. Teratogenicity appears increased in women treated with carbamazepine and valproic acid. Neural tube defects (NTD) occur at rates of 0.5–1% for carbamazepine and 1–5% for valproic acid *(31,32,33)*. Altogether major congenital malformations with carbamazepine are estimated at 2.2–8% *(34)*. More recent research has demonstrated that valproate (adjusted OR 4.1, CI 1.6–11), carbamazepine (OR 2.5, CI 1.0–6.0), and oxcarbazepine (OR 10.8, CI 1.8–106) were independent risk factors for development of congenital malformations; low serum folate (<4.4 mmol/L; OR 5.8, CI 1.3–27) was also an independent risk factor *(35)*.

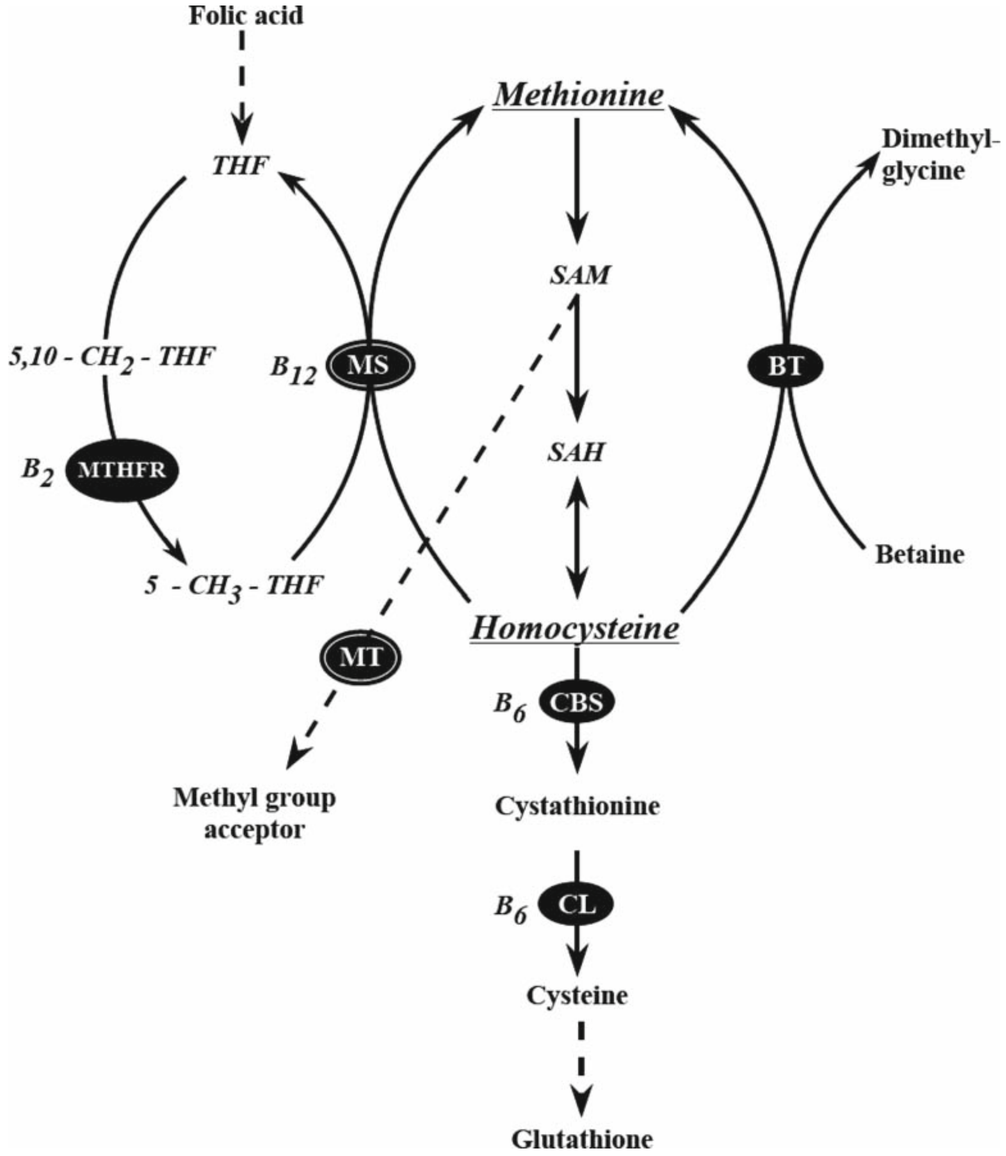
Folic acid
THF
Methionine
Dimethyl-glycine
SAM
5,10 - CH_2 - THF
B_{12}
MS
BT
B_2
MTHFR
SAH
Betaine
5 - CH_3 - THF
Homocysteine
MT
B_6
CBS
Methyl group acceptor
Cystathionine
B_6
CL
Cysteine
Glutathione

Fig. 1. Summary of homocysteine metabolism.
Legend: $\mathbf{B_2}$, Riboflavin; $\mathbf{B_6}$, Pyridoxal-5-phosphate; $\mathbf{B_{12}}$, Cobalamin; **BT**, Betaine homocysteine methyltransferase; **CBS**, Cystathionine-β-synthase; **CL**, Cystathioninelyase; **MTHFR**, Methylenetetrahydrofolate reductase; **MS**, Methionine synthase; **MT**, a variety of methyltranferases; **SAH**, *S*-Adenosylhomocysteine; **SAM**, *S*-Adenosylmethionine; **THF**, Tetrahydrofolate; $\mathbf{5\text{-}CH_3\text{-}THF}$, 5-Methyltetrahydrofolate; $\mathbf{5{,}10\text{-}CH_2\text{-}THF}$, 5,10-Methylenetetrahydrofolate *(25)*.

The primary theory in the development of congenital malformations is related to alterations in folate metabolism due to AEDs. Enzyme-inducing AEDs stimulate the CYP system, causing significantly decreased levels of folate *(36)*. As a result, women with epilepsy are at higher risk for folate deficiency. Deficient folate status has been closely linked to the development of NTD during the period of organogenesis which occurs in the first several weeks after conception; consequently, routine FA supplementation is recommended for all women of childbearing age *(37)*. Women with a prior pregnancy affected by a NTD carry an increased risk of a recurrent NTD-affected pregnancy *(38)*. Multiple trials have demonstrated significant risk reduction for recurrent NTD when periconceptual FA supplementation is administered in doses of 0.4 –4 mg/day *(30)*. In particular, the Medical Research Council demonstrated that risk of NTD was decreased by 72% when high-risk individuals were supplemented with 4 mg FA daily *(38)*. The American College of Obstetricians and Gynecologists recommends that women treated with AEDs receive periconceptual doses of FA similar to women with a history of NTD *(39)*. Another set of recommendations suggests supplementation of 5 mg of folic acid beginning 3 months prior to conception and continuing through the end of the first trimester in women receiving AEDs *(34)*. Regardless of the specific folic acid dose administered the patient's vitamin B_{12} status should be assessed as well.

2.2.2. Reported Cases/Descriptions

Plasma total homocysteine (tHcy) and FA levels were measured in 130 epileptic patients on AED *(25)*. An inverse correlation was found between FA and tHcy concentrations in both young patients (1–14 years) and older patients (15–35 years) ($r = -0.289, p < 0.05$; $r = -0.465, p < 0.001$, respectively). FA deficiency was found in 8–18% of patients. Deficient patients were on long-term therapy (>5 years) and required multiple AED for seizure control. Levels of vitamin B_{12} were within normal limits while methionine levels were low, suggesting that FA deficiency was responsible for the induction of elevated homocysteine levels. Supplementation with FA resulted in normalized homocysteine levels *(25)*.

Tamura and colleagues *(40)* demonstrated that few patients on AED monotherapy displayed elevated homocysteine levels (11% of patients: three on phenytoin, three on carbamazepine, one on lamotrigine); however, low plasma folate status was found in 85% of patients on phenytoin, 65% on carbamazepine, 54% on valproic acid, while this trend was only seen in 11% of patients on lamotrigine; mean erythrocyte folate levels were normal in all groups. While plasma folate levels reflect recent dietary intake, erythrocyte folate reflects long-term folate consumption. In this report, decreased levels of the coenzyme form of vitamin B_6, pyridoxal-5′-phosphate (PLP), were seen in more than half of the patients on phenytoin, carbamazepine, and valproic acid, but in only 22% of patients on lamotrigine *(40)*. A significant inverse relationship between tHcy and folate and vitamin B_{12} levels was found in patients on carbamazepine, but no significant relationship existed with the other AED in this population. Based on these results, it is suggested that hyperhomocysteinemia may not be a significant clinical issue in patients with adequate folate nutriture *(40)*. More recent work evaluating homocysteine levels in patients on lamotrigine and valproic acid has reinforced this view. Homocysteine, FA, and vitamin B_{12} concentrations in newly diagnosed epileptic patients treated with lamotrigine or valproic acid were assessed at baseline prior to initiation of AED therapy and after 32 weeks of AED treatment. No significant differences were found in tHcy, erythrocyte FA, and vitamin

B_{12} levels between baseline and after treatment in patients on lamotrigine. Patients on valproic acid had a decline in tHcy levels and increase in vitamin B_{12} concentration after 32 weeks of treatment *(41)*. Due to the short time on AED therapy, the study period may have been inadequate to effectively evaluate the impact of AED on plasma homocysteine levels or B-vitamin status.

FA and vitamin B_6 levels were significantly lower in patients compared to controls (13.5 ± 1.0 nmol/L versus 17.4± 0.8 nmol/L, $p < 0.002$, and 39.7 ± 3.4 nmol/L versus 66.2 ± 7.5 nmol/L, $p < 0.001$, respectively) and tHcy levels were significantly higher (14.7 ± 3.0 μmol/Lversus 9.5 ± 0.5 μmol/L, $p < 0.05$) in a population of 51 adult patients on long-term AED compared to age- and sex-matched controls *(27)*. A significant inverse relationship between elevated homocysteine levels (>14.9 μmol/L) and low FA levels was noted ($p < 0.01$), while no significant correlations between vitamin B_6 and tHcy levels were demonstrated *(27)*.

Concentrations of tHcy before and after methionine loading were evaluated in patients receiving enzyme-inducing AEDs or non-enzyme-inducing AEDs *(42)*. Higher levels of fasting tHcy ($p = 0.01$) and postmethionine load tHcy levels ($p < 0.001$) were seen in individuals receiving enzyme inducers compared to controls, while patients on non-enzyme-inducing AED had lower postmethionine load tHcy levels ($p = 0.01$) *(42)*. Vitamin B_{12} levels were normal in all groups. An inverse relationship between plasma tHcy and erythrocyte FA was demonstrated ($p < 0.0001$) *(42)*. Additional work by Apeland and colleagues demonstrated that individuals receiving AEDs with documented hyperhomocysteinemia, supplemented with folic acid (0.4 mg), pyridoxine (120 mg), and riboflavin (75 mg) for 30 days, had significant reductions in fasting (36%) and postmethionine loading (29%) tHcy levels with concurrent increases in serum FA and plasma PLP levels. Total cholesterol and LDL cholesterol decreased significantly although markers of endothelial activation such as P-selectin and von Willebrand factor were unchanged, suggesting a possible increased risk of cardiovascular disease *(26)*.

In comparisons of epileptic patients on AED to epileptic patients not on AED with a group of age- and sex-matched healthy controls, 64% of epileptic patients on AED had hyperhomocysteinemia versus 20% of epileptics not on AED and 27% of controls *(43)*. In epileptic patients treated with phenytoin, significantly lower FA levels were found compared to non-AED patients and controls ($p < 0.05$), while patients on carbamazepine tended to have lower levels of PLP *(43)*. Significant negative correlations were found between tHcy and FA levels in all study subjects. In addition, an inverse relationship was found between duration of phenytoin treatment and FA status *(43)*.

Several case reports of pregnant women treated with AED who had pregnancies affected by NTD bring into question the effectiveness of folic acid or B-vitamin supplementation as a preventative tool. Many of these cases are associated with valproic acid therapy which does not induce the CYP system. Craig et al. *(44)* described a 26-year-old woman on long-term valproic acid who was treated with high-dose folic acid supplementation (4 mg/day) for 18 months prior to conception. Supplementation was discontinued after the first trimester. The infant was born with a

NTD as well as other features consistent with fetal valproate syndrome (ventricular and atrial septal defects, cleft palate, and bilateral talipes). Another case study of biochemical abnormalities during pregnancy in a patient treated with valproic acid supplementation suggested that high-dose multivitamin supplementation can offer a protective effect to the teratogenesis associated with valproic acid *(45)*. The teratogenic effects of valproate have been attributed to various vitamin deficiency states beyond folic acid, including pantothenate, vitamin B_6, vitamin B_{12}, riboflavin, and niacin *(45)*. Urinary metabolites were measured routinely throughout the pregnancy and compared to six pregnant historical control patients in order to assess the role of high-dose multivitamin supplementation in normalization of metabolite levels. This supplementation was reduced and then discontinued after the occurrence of several seizures. During the time period that supplementation was decreased, fetal brain growth slowed, which may suggest that the high-dose multivitamins have a protective effect against the teratogenic properties of valproic acid *(45)*. Additional studies are needed to determine the role for high-dose B-vitamin supplementation in conjunction with valproic acid.

A more recent case of altered vitamin status associated with valproic acid therapy compared 4 women with NTD-affected pregnancies to 2 pregnant controls on valproic acid not affected by NTD and 40 pregnant women with normal pregnancies who were not receiving AED *(46)*. Women treated with valproic acid were taking high-dose periconceptual folic acid (5 mg/day). Low levels of PLP were seen in two of the NTD-affected women and in one of the non-NTD-affected women. Despite folic acid supplementation, levels of plasma and red cell folate were decreased in the NTD-affected women compared to the non-NTD-affected women, which may suggest an alteration in folate metabolism. In a subsequent pregnancy, one of the women with low vitamin B_6 levels added vitamin B_6 supplementation to high-dose periconceptual folic acid and delivered a healthy infant. The role of vitamin B_6 supplementation may offer some benefit in prevention of NTD, but it must be used cautiously as high doses of vitamin B_6 may alter the therapeutic effectiveness of valproic acid by increasing the activation of GABA transaminase; the therapeutic effect of valproic acid is related to an increase in the amount of cerebral GABA activity *(46)*.

Lamotrigine may also impact B-vitamin levels and increase the risk of NTD. Candito *(47)* describes a case study of a multiple gestation pregnancy affected by a double fetal neural tube defect despite high-dose periconceptual folate supplementation (5 mg/day). PLP and vitamin B_{12} levels were decreased when compared to a control pregnancy (also multiple gestation), and 58 healthy pregnant controls who were not supplemented with folic acid *(47)*. The results of this case suggest that supplementation with vitamins B_6 and B_{12} may offer an additional protection against NTD.

2.2.3. CLINICAL RELEVANCE

Inconsistent results are seen in studies evaluating homocysteine levels and AED use. It appears that individuals on long-term therapy, particularly with enzyme-inducing drugs, may be at risk for FA deficiency and possibly alterations in vitamin B_6 and B_{12} levels. A consistent inverse relationship between folate status and tHcy levels suggests that intervention may be possible. Mortality risk from a cardiovascular event in epileptic patients is significant, as high as three times compared to other populations *(48,49)*. Measurement of FA and tHcy levels in patients on long-term AED or in patients requiring multiple AED agents may prevent the deleterious health effects related to hyperhomocysteinemia. Supplementation with folic acid, vitamin B_6, and riboflavin was shown to normalize tHcy levels and to increase FA and vitamin B_6 status. Hyperhomocysteinemia may also increase risk of fetal malformations or delay fetal growth *(26)*.

Given the significant increased risk of NTD in women treated with AED, appropriate vitamin supplementation must be considered in an effort to decrease the potentially devastating consequences of NTD and malformations in the offspring of epileptic women. Women with epilepsy should be counseled prior to pregnancy about the importance of adequate intake of FA and possibly other B vitamins.

2.2.4. Limitations of Data

Much of the available data include small subsets of patients on various AED. The effects of therapeutic interventions with FA, vitamin B_6, and vitamin B_{12} to normalize homocysteine levels or to reduce risk of NTD in women treated with AED have not been studied adequately to make strong supplementation recommendations. In particular, much of the data on NTD on AED treatment come from case studies or retrospective analyses of small groups of affected women.

2.2.5. Research Needs

Additional research is needed to further delineate the appropriate dosages of B vitamins in individuals at risk for deficiency. The clinical impact of elevated homocysteine levels in epileptic patients, as well as the outcomes of interventions to modify hyperhomocysteinemia, should be evaluated prospectively.

With regard to pregnancy complications, research is needed to determine all the mechanisms of NTD in women receiving AED therapy. Folic acid supplementation decreases the risk, but case reports of infants exposed to AED developing NTD in the setting of high-dose folic acid supplementation suggest that other causative factors are at play. Other published cases suggest alterations in other B vitamins, particularly vitamin B_6 and vitamin B_{12}, may play a role. Prospective, randomized studies are needed to determine the efficacy and safety of additional B-vitamin supplementation at doses that will be unlikely to impact the therapeutic affect of AED therapy.

2.2.6. Clinical Recommendations

Individuals on long-term AED therapy should be screened for hyperhomocysteinemia and FA deficiency. Inadequate data are available to recommend routine supplementation of individual B vitamins; however, a multivitamin supplement and possibly folic acid supplementation may be beneficial in prevention of inadequate B-vitamin nutriture. Individuals on carbamazepine with elevated homocysteine levels should also be screened for vitamin B_{12} deficiency and supplemented accordingly.

FA supplementation should be considered in all women of childbearing age on AED. In the absence of negative outcomes associated with high-dose FA supplementation and its potential protective role, FA supplementation at a dose of 4 mg/day may provide benefit. To date, inadequate data are available to suggest a routine level of supplementation of other B vitamins in epileptic women on AED who are planning pregnancy.

2.3. Hyperammonemia

2.3.1. REVIEW OF MECHANISMS/SCIENTIFIC BASIS

Valproic acid is routinely used to treat seizures and mood disorders. The anticonvulsant effect is thought to be due to increased levels of GABA with inhibition of *N*-methyl-D-aspartate (NMDA) receptors and blockade of neuronal sodium and calcium channels *(50)*. A rare side effect of treatment with valproic acid is hyperammonemic encephalopathy (VHE), a severe condition that can be lethal if left untreated.

The mechanism of VHE development is not clearly understood, but several theories have been postulated. Valproic acid has been shown to deplete carnitine stores in several ways including decreased endogenous carnitine synthesis due to enzyme inhibition (butyrobetaine hydroxylase); inhibited intracellular carnitine transport; competitive binding with mitochondrial enzymes that interrupt β-oxidation; and decreased renal reabsorption of free carnitine and acylcarnitine *(51)*. Carnitine deficiency in patients on valproic acid has been associated with an increased risk of VHE. In the setting of carnitine deficiency, long-chain fatty acids are inhibited from transport into the mitochondria. Lack of long-chain fatty acids decreases the rate of β-oxidation and the production of acetyl-CoA and adenosine triphosphate (ATP). A lack of β-oxidation results in a shift to ω-oxidation. Metabolic by-products of valproic acid ω-oxidation are 2-propyl-4-pentenoic acid (4-en-VPA) and propionate. The 4-en-VPA metabolite has been associated with hepatotoxic effects of valproic acid. Carnitine is essential for the conversion of acyl-CoA to acylcarnitine; with suboptimal carnitine levels, toxic levels of acyl-CoA accumulate resulting in impaired energy metabolism in the mitochondria. A final consequence of carnitine deficiency is disruption of the urea cycle possibly by decreased levels of the enzyme needed to initiate the urea cycle, carbamoyl phosphate synthase I (CPS I), or decreased synthesis of *N*-acetylglutamate (NAG) *(51)*. It has been postulated that propionate, a metabolite of valproic acid, results in a decreased level of NAG. Suboptimal levels of NAG inhibit CPS I which prevents ammonia from entering the urea cycle. The urea cycle removes two ammonia ions with each cycle; failure of the urea cycle results in increased ammonia levels. The metabolite 4-en-VPA results in decreased availability of acetyl-CoA. Adequate amounts of acetyl-CoA are needed to bind with glutamate to form NAG *(52)*. The end result of elevated ammonia levels is an increased cerebral glutamate concentration which can cause astrocyte swelling and cerebral edema *(52)*.

Increased risk for VHE has been suggested in carnitine-deficient individuals, although not all studies have confirmed this correlation *(51)*. Risk factors for carnitine deficiency include cirrhosis and chronic renal failure due to decreased endogenous carnitine biosynthesis; critical illness associated with hypercatabolism such as sepsis, multi-system organ dysfunction, and trauma.

2.3.2. Reported Cases/Descriptions

Development of hyperammonemic encephalopathy is a rare side effect of valproic acid. Cases have been reported in the pediatric population, in patients treated for psychiatric disorders, and in epileptic patients on long-term valproic acid therapy. Low carnitine levels have been documented in psychiatric patients receiving valproic acid. Thirty patients receiving valproic acid for an average of 2.5 years (range 6 months to 9 years) had low levels of free and total carnitine, although these patients did not have elevated ammonia levels or encephalopathy *(53)*. A recent evaluation of valproic acid-induced encephalopathy in a group of seven adult patients demonstrated that all patients had elevated ammonia levels, while only one patient had low carnitine levels. The patients in this observation were on valproic acid for relatively short periods of time (range 3 days to 3 years). Normalization of ammonia levels occurred after discontinuation of valproic acid. Carnitine supplementation was administered to the patient with a documented deficiency, but no difference was seen in recovery time or EEG findings *(54)*. Acute hyperammonemic coma was documented in an adult woman receiving long-term valproic acid (6 years). Intermittent episodes of confusion and lethargy followed by periods of lucidity were described over several months culminating in periods of unresponsiveness and subsequent coma with a serum ammonia level of 921 μg/dL (normal range 22–78 μg/dL). Carnitine levels were within normal limits. Treatment involved discontinuation of valproic acid, lactulose therapy, and carnitine supplementation. Ammonia levels normalized over the next 48 h and the patient regained consciousness *(55)*.

2.3.3. Clinical Relevance

There are insufficient data at the present time to make clinical recommendations related to dietary protein in patients with VHE. The impact of protein on ammonia levels was examined in a small group of young patients treated with valproic acid. After a protein load of 1 g/kg body weight, ammonia levels were significantly higher than after fasting or after an oral fat load *(56)*.

2.3.4. Limitations of Data

VHE is a rare complication of valproic acid therapy. Much of the information published is based on case studies or small case series. Few studies address the impact of treatment options to lower ammonia levels. Inadequate information is available to determine what subset of patients are at highest risk for this rare and serious complication.

2.3.5. Research Needs

Protein metabolism increases production of ammonia. Current research has not adequately addressed the impact of dietary protein load on hyperammonemia related to valproic acid. Additional studies in this population should evaluate the role of dietary protein restriction in patients with VHE, the appropriate level of protein restriction if any, and the length of time that the protein restriction should be continued. Other therapeutic options, such as carnitine supplementation should be studied in prospective, randomized controlled trials in the adult population to determine appropriate dosage recommendations. Investigators should aim to better define the population of patients who should receive routine screening for this complication in order to prevent this clinical scenario.

2.3.6. Clinical Recommendations

It may be prudent to limit protein initially and monitor for fluctuations in the serum ammonia level. If ammonia levels do not respond to modifications in the protein load, clinicians need to assess utility of ongoing protein restriction based on the clinical scenario. Long-term over-restriction of protein may lead to worsened outcomes in critically ill patients. Supplementation with L-carnitine may provide some benefit in individuals with documented carnitine deficiency or at risk for carnitine deficiency. In the pediatric population, for individuals with valproic acid toxicity carnitine dosage recommendations are 100 mg/kg/day in divided doses every 6 h with a maximum dose of 3 g. In the setting of severe hepatotoxicity, intravenous L-carnitine may have a higher likelihood of hepatic recovery *(57,58)*. Inadequate data are available to make recommendations related to the appropriate dose of L-carnitine in adult patients with VHE.

2.4. Enteral Nutrition and Antiepileptic Drugs

2.4.1. Review of Mechanisms/Scientific Basis

Historically, phenytoin has been the most prominent AED studied for its proposed interaction with enteral nutrition (see Chapter 13). Carbamazepine has also been evaluated for its potential interaction with enteral feeds. Carbamazepine is an insoluble drug that is stable in an acid environment. Thus, slower gastric clearance may improve bioavailability.

2.4.2. Reported Cases/Descriptions

The interaction between phenytoin and enteral nutrition has long been theorized and proposed solutions exist based on the current literature *(59)*. Four prospective, randomized, controlled trials of phenytoin and enteral nutrition in healthy volunteers have been reviewed *(60,61)*. Only one of those studies investigated the effect of the enteral nutrition formulation delivered via a feeding tube, while the others studied the effect on oral supplementation and phenytoin *(59)*. None of these studies found an interaction between phenytoin and enteral nutrition formulations *(59)*. Ironically, there were 25 documented reports and studies that were not randomized or placebo-controlled, that did support an interaction in patients *(60)*. The various theories of interaction range from the impact of local pH *(62–64)*, the tubing itself *(65)*, or to a particular component of the enteral nutrition formulation *(66)*. Relative bioavailability of 90% was reported in a randomized, crossover study comparing administration of carbamazepine suspension through a nasogastric tube with continuous enteral feeds and oral intake after an overnight fast in seven healthy adult males *(67)*. The serum carbamazepine concentrations with enteral nutrition were significantly lower after 8 h *(59)*. Likely because of the small study group, statistical significance was not achieved when evaluating the lower maximum concentration of carbamazepine *(67)*. Kassam et al. *(68)* evaluated carbamazepine recovery and intact protein of an enteral nutrition product in vitro. An increase in recovery (79%) was shown when simulated gastric secretions versus intestinal secretions (59%) were mixed with carbamazepine *(68)*.

2.4.3. CLINICAL RELEVANCE

Frequently, high or multiple doses of phenytoin may be required to achieve therapeutic levels in some patients *(59)*. Perhaps, the bioavailability of carbamazepine is impacted more so with postpyloric continuous enteral feeding infusion versus gastric feedings.

2.4.4. LIMITATIONS OF DATA

The lack of prospective, randomized, controlled studies compared with numerous published case reports remains a limiting factor when reviewing the literature of enteral nutrition and phenytoin. The small study sample sizes and the in vitro studies limit the ability to draw complete conclusions regarding if and when to hold enteral nutrition when administering carbamazepine.

2.4.5. RESEARCH NEEDS

Concise prospective, randomized, placebo-controlled studies evaluating the exact mechanism of the enteral formulation that interacts, or does not interact, with phenytoin and carbamazepine are suggested.

2.4.6. CLINICAL RECOMMENDATIONS

Of the various proposed methods optimizing the management of the phenytoin–enteral nutrition interaction, none is completely reliable, and monitoring of serum phenytoin concentrations is highly recommended *(59)*. Separating the administration of enteral nutrition and phenytoin dosing by 1 h, possibly 2 h, before and after each phenytoin dose seems to produce the most consistent results *(69,70)*. Clinically, if the patient can attain therapeutic serum phenytoin levels while receiving higher doses of phenytoin less frequently throughout the day, enteral nutrition administration may be less impacted. Regardless of the method used to achieve therapeutic serum concentration of phenytoin, consistency of drug administration and goal enteral nutrition provision is the main objective *(59)*. The existing recommendation for concurrent administration of carbamazepine and postpyloric enteral nutrition infusion suggests holding the enteral nutrition 2 h before and after the drug dose *(59)*.

3. DOPAMINERGIC DRUGS/ANTI-PARKINSONIAN AGENTS

3.1. Levodopa

3.1.1. REVIEW OF MECHANISMS/SCIENTIFIC BASIS

Parkinson's disease is a chronic, progressive, irreversible neurodegenerative disease, characterized by the loss of neurons in the substantia nigra *(71)*. The nigral neurons project to large, deep gray matter structures in the cerebral hemispheres known as the corpus striatum. The nigral neurons are responsible for producing the neurotransmitter dopamine. The nigrostriatal pathway in short provides the background control of smooth and balanced motor movements. Parkinson's disease causes these neurons to die, thus overall motor movements are affected *(71)*. The actual cause of Parkinson's disease remains unknown; however, both genetics and environment may play a role in its development. Treatment has long included the use of levodopa, a dopamine precursor.

The absorption of orally ingested levodopa depends upon the gastrointestinal transit rates, as absorption occurs mainly in the proximal third of the small intestine (duodenum/jejunum) *(72)*. Although levodopa is not absorbed in the stomach, delayed gastric emptying can affect overall absorption of levodopa. The bioavailability of levodopa is approximately 30% due to prior decarboxylation to dopamine by the enzymes dopa decarboxylase and to a lesser extent to 3-*O*-methyldopa by catechol-*O*-methyltransferase (COMT) that is found in the gut mucosa and the liver *(73)*. Therefore, the longer levodopa remains in the stomach, or is delayed by gastric emptying, the more it is subject to presystemic clearance. Parkinson's disease induces a greater variability of gastric emptying due to disturbed gastric motor function *(74)*. Meals and the makeup of those meals may possibly interfere with the absorption of levodopa. The drug–nutrient interactions between levodopa and dietary protein, and levodopa and pyridoxine (vitamin B_6) and aspartame, are a major nutritional focus when treating patients with Parkinson's disease. It has been presumed that certain peptides/amino acids (i.e., valine, leucine, isoleucine, tryptophan, tyrosine, and phenylalanine) compete for transport at the gastrointestinal level. Neutral amino acids are carried across cell membranes by system L-type amino acid transporters (e.g., LAT1), which are heterodimeric and part of the solute carrier transporter super family (SLC3, SLC7). Levodopa is at least in major part carried by this transporter as well *(75)*. The affinity for these high capacity transporters appears considerable. An interaction at this level although poorly characterized can vary the rate of absorption of levodopa into the circulation and possibly into the brain *(76–78)*. Thus, limiting dietary protein during the day has been thought to enhance the uptake of levodopa during the day *(77,79)*. Decreasing protein throughout the day has been thought to possibly decrease levodopa fluctuations which may reduce some symptoms of Parkinson's disease. This nutritional practice continues to remain controversial, especially given the use of sustained-release products and normal fluctuations.

3.1.2. REPORTED CASES/DESCRIPTIONS

Traditionally, previous studies have shown that dietary protein redistribution is an effective treatment for some patients *(76,80,81)*. Frankel and colleagues *(81)* have suggested that levodopa absorption is hindered by a high-protein diet and vitamin B_6-rich foods (legumes, potato, spinach, and whole grain, especially wheat). More recently, researchers have been recommending a balanced diet (dietary protein 0.8 g/kg) with a 5:1–7:1 carbohydrate to protein ratio for all meals *(77,82,83)*. With respect to the genetic component of Parkinson's disease, a study of twins showed that Parkinson's disease before the age of 50 years is strongly genetic *(84)*. However, Tanner and colleagues did not find a genetic contribution to Parkinson's disease after the age of 50 years *(84)*. It remains unknown whether there exists a protective mechanism of coffee and smoking on the development of Parkinson's disease. Some researchers believe that there is a protective substance in cigarettes and coffee *(85–90)*, whereas others suggest that the substances themselves are not the relevant component, but it may be that individuals with addictive behaviors have a brain chemistry that makes them more resistant to developing Parkinson's disease *(85)*. Despite these claims, it is not recommended that individuals begin or continue using tobacco or coffee in order to prevent Parkinson's disease.

3.1.3. Clinical Relevance

As stated earlier, protein restriction remains controversial as an adjunct component for the treatment of Parkinson's disease. As the disease continues to progress and motor function continues to decline, medication adjustment may be examined more closely. Timing of medication administration and/or meal times may need to be re-evaluated.

3.1.4. Limitations of Data

Most of the research available related to Parkinson's disease and nutrition include only a small sample size. Many studies examining dietary protein intake and medication effects require that subjects maintain dietary records. This type of data collection may be extremely time consuming and not accurate. Another limitation in Parkinson's disease research may be the decreased ability to perform double-blinded trials when using actual foods *(91)*. For example, low-protein foods versus high-protein foods are easily distinguishable to many subjects.

3.1.5. Research Needs

The exact mechanism of why protein-controlled diets work remains a mystery. The specific function of the heterodimeric amino acid transporters, as well as the affinity of various substrates including levodopa, requires further research that may prove beneficial in the ongoing treatment of Parkinson's disease. Additional pharmacokinetic data would be useful to establish if this carrier competition occurs mainly in the intestinal mucosa, the blood–brain barrier, or both *(91)*.

3.1.6. Clinical Recommendations

The consumption of low-protein foods appears to be safe and effective in improving certain symptoms in fluctuating Parkinson's disease patients *(91)*. However, additional studies on the long-term safety of low-protein diets, the impact on quality of life, and again, the mechanism of action are needed to establish whether or not this should be routinely introduced in patients with advanced Parkinson's disease *(91)*.

3.2. Other Dopamine Agonists

Dopamine agonists, COMT inhibitors, and anticholinergics have also been used in managing neurodegenerative disorders such as Parkinson's disease. Dopamine agonists are associated with many short-term side effects such as nausea, vomiting dizziness, confusion, and hallucinations *(85)*. COMT inhibitors block the metabolism of dopamine and thereby enhance the effectiveness of levodopa, thus possibly reducing the incidence of Parkinson's symptoms. Anticholinergics are used to restore the balance between brain dopamine and acetylcholine in the corpus striatum. The reduction in acetylcholine can reduce muscle stiffness and possibly tremor *(71)*.

Anticholinergics can impair memory and thinking, especially in older individuals; thus, caution should be used when recommending these medications to patients with Parkinson's disease *(71)*. Anticholinergics may reduce the production of oropharyngeal secretions. However, a common side effect with anticholinergic use is increased thickening of the secretions. Another common side effect of anticholinergic medications is constipation. Adequate hydration may help to improve both of these side effects if seen in patients with Parkinson's disease.

4. CEREBROVASCULAR ACCIDENT

4.1. Warfarin

Anticoagulant therapy is often a component of the medical management of nonhemorrhagic stroke. Individuals with a history of cardioembolic stroke or with risk factors for cardioembolic stroke may be initiated on oral warfarin therapy. It is well known that a drug–nutrient interaction exists between vitamin K and warfarin (see Chapter 16). With excessive or inconsistent intakes of vitamin K, the therapeutic effect of warfarin may be altered *(92)*. Dysphagia after stroke is a frequent indication for enteral nutrition therapy either via a temporary or more permanent enteral access. Enteral nutrition formulations have been associated with significantly reduced bioavailability of warfarin *(93–95)* (see Chapter 13).

4.1.1. Review of Mechanisms/Scientific Basis

In the early 1980s, enteral nutrition products were reformulated to decrease the vitamin K content due to concerns for the impact on prothrombin time. Despite enteral formulations with lower vitamin K content, case studies of warfarin resistance in patients receiving concurrent enteral nutrition continue to appear. An in vitro analysis investigated the possibility that other components of enteral nutrition rather than vitamin K are responsible for diminished warfarin effect. Three enteral solutions (Isocal HC, Sustacal, and Vital HN) were compared to water using reversed-phase HPLC to assay warfarin. Selection of enteral formulas was based on case reports of warfarin resistance with Isocal and Sustacal, both of which contain intact protein; Vital HN, a partially hydrolyzed formulation containing protein as peptides and amino acids, was added as a comparison to evaluate protein binding as a mechanism for warfarin resistance. Significant decreases in warfarin concentration were seen in all three preparations of enteral formula, whereas there was no significant difference in the warfarin concentration in the water solution *(94)*.

4.1.2. Reported Cases/Descriptions

Despite decreased vitamin K content of enteral nutrition formulations, case reports demonstrate a decreased warfarin effect in patients on enteral nutrition. Martin described a case of a patient on continuous enteral feeding using Osmolite at 50–100 mL/h plus a full liquid diet (average vitamin K intake, approximately 100 μg/day). Minimal change in prothrombin time (PT) was seen despite increasing doses of warfarin (10–25 mg/day). Improvement in PT was seen after a parenteral dose of warfarin. Additionally, PT continued to improve after withdrawal of enteral feeding *(93)*.

More recently, Penrod has described case reports of warfarin resistance in two patients *(94)*. In the first observation, the patient was being fed with Isocal via continuous infusion into a percutaneous endoscopically placed gastrostomy (PEG) tube. PT was subtherapeutic until the warfarin dose was increased to 20 mg/day. When enteral feeds were discontinued, PT rapidly increased within 3 days and the warfarin dose was decreased to 7.5 mg/day. Penrod's second observation involved a patient on a previously therapeutic dose of warfarin of 5 mg/day *(94)*. Continuous enteral feeding with Sustacal was initiated after episodes of aspiration and subsequent decreases in PT were noted. Despite doubling the dose of warfarin, PT remained subtherapeutic until enteral nutrition was discontinued. On discharge, the patient was stable on an oral diet with a warfarin dose of 5 mg/day *(94)*.

A retrospective crossover case series in six ICU patients revealed that the change in INR during a pair of 3-day observation periods was significantly improved when feedings were held for 1 h before and after warfarin administration compared to co-administration despite similar drug doses *(95)*.

4.1.3. CLINICAL RELEVANCE

Fluctuations in the therapeutic effects of warfarin can increase the risk of negative outcomes in patients requiring oral anticoagulation. Numerous factors are involved in the clinical effect of warfarin including the genetic influence on pharmacokinetics (e.g., *CYP2C9* expression) and pharmacodynamics (e.g., *VKOR1* expression). Increased drug dosing in individuals on enteral feedings may be indicated; however, there may be significant risk to these patients when feedings are held temporarily or permanently. Alternating the timing of warfarin administration and enteral nutrition may mitigate the interaction seen with concurrent administration *(95,96)*. Close clinical observation and INR monitoring of warfarin are warranted in patients receiving the drug concurrently with enteral nutrition.

4.1.4. LIMITATIONS OF DATA

Inadequate data are available to describe the mechanism of reduced bioavailability of warfarin in patients receiving enteral feedings. Case study and retrospective reports as well as in vitro analysis suggest that binding can occur between warfarin and some component of enteral formulations. Some in vitro analysis suggests that protein binding is the causative factor, but the data are insufficient at this time to make this determination.

4.1.5. RESEARCH NEEDS

Further analysis of a potential interaction between warfarin and components of enteral nutrition formulations would be useful. Understanding the interaction would allow clinicians to determine a need for warfarin dosing adjustments or modifications to the enteral feeding schedule to prevent negative consequences from subtherapeutic or supertherapeutic anticoagulation.

4.1.6. CLINICAL RECOMMENDATIONS

Although limited, the available data suggest holding continuous enteral nutrition for 1 h during administration of oral warfarin therapy. As the vitamin K content of enteral nutrition products is similar to the amount of vitamin K typically consumed in an average oral diet *(59)*, the choice of enteral formula should be based on the patient's nutritional requirements and not the vitamin K content. In the setting of warfarin resistance in patients on enteral feedings, adjusting the feeding schedule may enhance the therapeutic effect of warfarin without a need for increased medication dosage *(95,96)*. In general, holding the enteral formula for 1 h before and after the dose of warfarin should be adequate to prevent competition for absorption *(59)*. For patients on continuous enteral nutrition, the infusion rate may need to be increased in order to meet daily nutritional requirements. In patients on warfarin in whom enteral nutrition will be discontinued, it may be necessary to decrease the warfarin dose to prevent a supertherapeutic effect.

5. MANAGEMENT OF TRAUMATIC BRAIN INJURY

5.1. Mannitol

5.1.1. REVIEW OF MECHANISMS/SCIENTIFIC BASIS

Chemically, mannitol is a sugar alcohol that has a tendency to lose one hydrogen ion in aqueous solutions, which causes the solution to become acidic *(97)*. Mannitol is also an osomotic diuretic that is believed to reduce intracranial pressure after head injury and may improve patient outcome *(98)*. Mannitol is administered intravenously and is filtered by the glomerulus of the kidney, but is not capable of being reabsorbed from the renal tubule, resulting in decreased water and sodium reabsorption due to its osmotic effect *(97)*. Thus, mannitol can increase water and sodium excretion, resulting in decreased extracellular fluid volume *(97)*. This diuretic effect of mannitol needs to be closely monitored when nutrition therapy is initiated to assure adequate electrolyte repletion and/or stabilization. Hypernatremia may prevail with high-dose mannitol for the treatment of elevated intracranial pressures. Mannitol can also be used to open the blood–brain barrier by temporarily shrinking the closely coupled endothelial cells which make up the barrier *(97)*. This allows mannitol to be virtually indispensable for delivering various drugs to the brain directly (e.g., in the treatment of Alzheimer's disease) *(97)*.

5.1.2. REPORTED CASES/DESCRIPTIONS

The administration of high-dose mannitol in the treatment for head injury has been under close scrutiny recently. Cruz and colleagues reported results showing that high-dose mannitol greatly reduced death and disability 6 months after the head injury *(99–101)*. A Cochrane systematic review that included these trials concluded that "high-dose mannitol seems to be preferable to conventional dose mannitol in the acute management of comatose patients with severe head injury" *(98,102)*. However, one of the trials was accompanied by an editorial that questioned the reliability and validity of the results, calling for further multicenter studies *(98,103)*. A follow-up investigation by the Cochrane Collaboration was unable to verify that the study actually took place *(98)*.

5.1.3. RESEARCH NEEDS

Reliable and valid randomized, prospective longitudinal studies examining the mechanism of high-dose mannitol administration are needed in order to determine appropriate treatment strategies in head injury. The impact of high-dose mannitol administration should be evaluated prospectively to identify guidelines for implementation in this at-risk population.

5.1.4. CLINICAL RECOMMENDATIONS

Due to the discovery that recommendations are based on questionable data, high-dose mannitol administration should be done with caution if at all. The osmotic diuretic properties of the drug still exist, making mannitol therapy a major contributing factor to electrolyte and fluid abnormalities. This may be more detrimental when patients are also receiving parenteral nutrition admixtures. Routine monitoring and correction of serum electrolytes, serum osmolality, and fluid disturbances are recommended.

5.2. Propofol

5.2.1. REVIEW OF MECHANISMS/SCIENTIFIC BASIS

Propofol is a short-acting intravenous anesthetic agent used for the induction of general anesthesia in adult and pediatric (>3 years old) patients; maintenance of general anesthesia in adult and pediatric (>2 months old) patients; and sedation in intubated, mechanically ventilated adults and for patients undergoing procedures such as colonoscopy or endoscopic feeding tube placement *(104)*. Propofol is formulated in an oil-in-water emulsion making it appear as a highly opaque white fluid *(105)*. Propofol provides no apparent analgesia. Propofol is highly protein bound in vivo and is metabolized by conjugation in the liver *(105)*. Its rate of clearance exceeds hepatic blood flow, thus suggesting extrahepatic excretion *(105)*. Propofol's mechanism of action remains uncertain although its primary effect may be potentiation of the GABA_A receptor, possibly by slowing the channel closing time *(105)*. More recent research has also postulated the endocannabinoid system may also contribute significantly to propofol's anesthetic action and to its unique properties *(106)*.

5.2.2. REPORTED CASES/DESCRIPTIONS

Cases have examined the incidence of propofol and postoperative pancreatitis *(107)*. Leisure et al. describe the possibility of pancreatitis induced by propofol infusion as seen by markedly elevated serum amylase, lipase levels, and CT scans examining the pancreas.

5.2.3. Clinical Relevance

Individuals with hypersensitivity to eggs, egg products, soybeans, or soy products may not receive propofol. Caution should be used with regard to patients with underlying hyperlipidemia as evidenced by increased serum triglyceride levels or serum turbidity *(107)*.

5.2.4. Research Needs

Further research is required to assist clinicians in optimizing the management of critically ill patients receiving propofol infusions. Additionally, further investigation on the long-term impact of extended propofol infusion in the critically ill population would possibly help to guide more efficient clinical practice in the intensive care setting.

5.2.5. Clinical Recommendations

Some formulations of propofol contain ethylenediamine tetraacetic acid (EDTA) which may lead to decreased zinc levels in patients with prolonged therapy (>5 days) or patients with a predisposition to zinc deficiency (e.g., burns, diarrhea, sepsis). Serum triglyceride levels should be monitored routinely with propofol infusion to assure adequate lipid clearance and possible avoidance of pancreatitis *(107)*.

5.3. Hypertonic Saline Therapy

5.3.1. Review of Mechanisms/Scientific Basis

Hypertonic saline (3 and 5% sodium chloride injection) therapy may be used in the treatment of intracranial hypertension (ICP = 20 mmHg) in severely brain-injured patients in whom mannitol has failed or is contraindicated. Hypertonic saline therapy may also be utilized in patients with significant hyponatremia (serum sodium <135 mmol/L) from cerebral salt wasting.

5.3.2. Clinical Relevance

Hypertonic saline therapy has the potential to cause great harm if administered inappropriately. Too rapid correction of hyponatremia can lead to profound permanent neurologic impairment. Central pontine myelinolysis or extrapontine myelinolysis can be seen in the early phases of hyponatremia correction *(108)*. If the serum sodium continues to rise too quickly, osmotic demyelination syndrome may ensue. This can be defined as a neurological disorder that can cause ailments of central neurons, spastic quadriparesis and pseudobulbar palsy, coma, and death *(108)*. To ensure the proper practice of hypertonic saline therapy, safeguards should be put into place to minimize the likelihood of a medication error or harm to a patient.

5.3.3. Limitations of Data

To date no studies have been conducted to evaluate drug–nutrient interactions with 3 and 5% sodium chloride injection.

5.3.4. RESEARCH NEEDS

Investigational research of hypertonic saline therapy and nutrition support would be beneficial for the traumatic brain-injured patient population. Studies examining the close monitoring of serum electrolytes and osmolality, along with adequate nutrition support, would possibly provide optimal treatment and care for the critically ill brain-injured patient.

5.3.5. CLINICAL RECOMMENDATIONS

Caution is warranted when patients are receiving both hypertonic saline therapy and nutrition support containing sodium.

6. SUMMARY

Patients with neurological illnesses often require long-term pharmacologic management in order to maintain disease control. Additionally, acute neurological events such as traumatic brain injury, stroke, and intracranial hemorrhage are frequently treated with medications that impact nutrient utilization and electrolyte status. The combined effect of neurologic medications places patients at risk for long-term health consequences throughout the life cycle. Failure to monitor patients requiring long-term antiepileptic drug therapy may increase the risk of metabolic bone disease, heart disease, and negative pregnancy outcomes. Acute complications of antiepileptic drugs may result in hepatic damage possibly complicated by nutritional deficiencies. Administration of neurologic medications may be complicated by co-administration with enteral nutrition. Failure to recognize these interactions may result in therapeutic failure.

Provision of adequate nutrient substrates may impact the overall therapeutic effects of ceratin drugs. In individuals requiring levodopa, modifying the protein content of the diet may be necessary to potentially suppress undesired symptoms of Parkinson's disease. Similarly, patients treated with propofol may require caloric restrictions to prevent the negative consequences associated with overfeeding and excessive lipid infusions. Modifications to the electrolyte content of nutrition regimens may be necessary in patients treated for traumatic brain injury. A thorough understanding of the potential drug–nutrient interactions associated with neurologic medications will aid the clinician in optimizing patient care and minimizing health complications.

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18 Drug–Nutrient Interactions Involving Folate

Patricia Worthington and Leslie Schechter

Objectives

- Review folate requirements in health and disease.
- Describe the biochemical alterations that occur as a result of folate deficiency.
- Identify risk factors for folate deficiency.
- Delineate practice guidelines for managing potential drug–folate interactions.

Key Words: Anemia; folate; folic acid; homocysteine; methionine; polymorphism

1. INTRODUCTION

The importance of maintaining optimal folate status throughout all phases of the life cycle has grown increasingly apparent in recent years. Studies have produced convincing evidence linking folate deficiency to health risks that extend well beyond the classic association with macrocytic anemia. The strongest evidence exists for the relationship between folate deficiency and neural tube birth defects *(1)*. Research also indicates that inadequate folate levels may increase risks for other types of birth defects, early miscarriage, atherosclerotic cardiovascular disease, some types of cancer, and neurological and neuropsychiatric disorders *(2,3)*. Among the many factors that influence folate status, drug–nutrient interactions stand out as a significant, and largely avoidable, cause of folate deficiency *(4)*.

2. BASIC REVIEW OF FOLATE

2.1. Description

Folate and folic acid are synonyms for the water-soluble B-complex vitamin, once referred to as B_9. Folate consists of a group of structurally similar compounds known as pteroylglutamates that occur naturally in food, whereas folic acid refers to a stable, synthetic form of folate (pteroylmonoglutamic acid) that is used in

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dietary supplements and fortified foods *(5)*. Folate coenzymes participate in a variety of complex metabolic pathways that involve the transfer of one-carbon units in methylation reactions that take place during synthesis of proteins, neurotransmitters, phospholipids, and nucleotides, which gives folate an essential role in DNA synthesis and repair. Folate also acts in conjunction with vitamin B_{12} as an essential cofactor in the remethylation cycle that converts homocysteine to methionine *(5)*. For this reason, a deficiency of either folate or vitamin B_{12} can lead to hyperhomocysteinemia, which has been identified as an independent risk factor in a number of medical conditions including occlusive cardiovascular disease, stroke, and dementia *(6,7)*. Because folate plays a role in so many critical metabolic functions, it is an attractive target for pharmaceutical agents that influence cell replication, neurotransmitter function, and cell membrane integrity.

Folate is naturally present in a wide range of foods including fresh green leafy vegetables (e.g., spinach, turnip greens), yeast, dry beans and peas, and citrus fruits. However, modern methods of cooking, processing, and distributing food can substantially reduce the amount of the dietary folate available. Since fortification of the food supply went into effect, breakfast cereal has become one of the best dietary sources of folic acid. No clinically significant interactions between folate and other nutrients have been identified *(5)*.

In the past, population surveys routinely revealed a high incidence of suboptimal folate levels among otherwise well-nourished individuals. Therefore, folate deficiency was once considered the most common vitamin deficiency found in developed nations *(8)*. To address this problem, the US Food and Drug Administration mandated that food manufacturers fortify breakfast cereals and other grain products with folic acid beginning in 1998, an action that initially led to substantial improvements in the folate status of the US population *(9)*. Subsequent data show an approximately 10% decline in folate levels, which researchers attribute to the relatively low folate content of the currently popular low-carbohydrate diets *(10)*. Much of this decline occurred at the high end of the distribution curves and, therefore, does not yet raise concerns about a re-emergence of widespread folate deficiency.

2.2. Folate Deficiency

2.2.1. RISK FACTORS

Although low consumption of dietary folate ranks as the leading cause of folate deficiency, inadequate levels can develop through a variety of mechanisms. Conditions that impair absorption or utilization, elevate nutrient requirements, or increase excretion of folate can also lead to a deficiency state. The risk for folate deficiency is especially high during periods of rapid growth or hypermetabolic activity *(5)*. Suboptimal folate status is often found in pregnant women, chronic alcoholics, the elderly, and individuals with sickle cell disease. As the folate status of the US population has improved, research has shifted away from dietary causes of folate deficiency to focus on the role of independent traits that may act as additional risk factors for diseases associated with folate deficiency. An area of increasing interest focuses on genetic variations in folate metabolism and the influence of these factors in determining nutrient status, disease risk, and response to drug therapy *(11)*.

Table 1
Risk Factors for Folate Deficiency *(2,5)*

Poor eating habits – Low intake of folate-rich foods, preference for cooked or processed foods over raw vegetables and fresh fruit
Restricted diets – Low-carbohydrate weight-reduction diets, phenylketonuria diet
Elevated requirements – Periods of rapid growth including pregnancy, lactation, and preterm infants; sickle cell disease; tumor growth, hemodialysis, hypermetabolic states
Malabsorption – Celiac disease, inflammatory bowel disease, short bowel syndrome, atrophic gastritis, lymphoma, or amyloidosis of the small intestine, intestinal bypass, drug effects
Impaired utilization – Chronic alcoholism, smoking, liver disease, drug effects, age-related changes, B_{12} deficiency, congenital enzyme deficiency
Increased excretion – Renal dialysis, biliary diversion, B_{12} deficiency

Certain lifestyle factors can influence folate levels. Ethanol abuse contributes to folate deficiency by combining poor diet with factors that interfere with absorption and metabolism of the vitamin. In addition, population surveys have revealed elevated homocysteine levels and low folate levels among smokers and coffee drinkers, but whether this effect is due to poor intake of the vitamin, altered folate metabolism, or a combination of the two is unclear *(12,13)*. Assays of pregnant women with a history of substance abuse have also revealed suboptimal folate levels, but again, researchers attributed this problem to poor eating habits rather than a direct effect by the substances in question *(14)*. Table 1 provides additional information concerning risk factors for folate deficiency *(2,5)*.

One prospective community-based controlled study showed an association between low folate levels and abuse of cough-suppressant mixtures containing codeine and/or dextromethorphan *(15)*. The same authors have also reported cases of megaloblastic anemia *(16)* and a neural tube defect *(17)*, which they also ascribed to cough-suppressant drug abuse, although no mechanism of action for this interaction was proposed. Poly-substance abuse, poor dietary habits, and concomitant nutrient deficiencies (such as cobalamin) may have contributed to these findings, but the authors, nevertheless, recommend that cough products carry warnings concerning the potential impact on folate levels and further suggest folate supplementation for individuals suspected of abusing cough suppressing preparations.

2.2.2. Identifying Folate Deficiency

Laboratory tests used to assess folate status include serum folate levels, erythrocyte folate concentrations, and serum homocysteine concentrations. The instability of folate and methodological differences among laboratories creates variation in folate results that makes comparison difficult *(5)*. Serum folate levels fluctuate with changes in dietary folate intake, serving primarily as an indication of current folate balance. Because low serum folate levels do not discriminate between a transient deficit in folate intake and a chronic state of tissue depletion, this laboratory test alone is a not a reliable indicator of folate status. Erythrocyte folate concentrations, on the other hand, are not affected by transient events and therefore do reflect tissue supplies of the vitamin. However, this value does not detect recent changes in folate status and may miss a developing deficiency *(5)*. Finally, plasma homocysteine levels, which increase as folate stores become depleted, can serve as an early, indirect measure of folate status. Elevated homocysteine levels that occur in conjunction with low erythrocyte folate levels strongly suggest the presence of a subclinical folate deficiency. However, vitamin B_{12} deficiency must also be excluded as an additional cause of elevated homocysteine levels *(5)*. Homocysteine levels may also serve as the best method for evaluating response to folic acid supplementation.

Folate deficiency develops slowly, over a period of several months to years. In a classic experiment conducted with himself as the only subject, Herbert delineated four stages of folate deficiency, in which metabolic abnormalities occur before clinical signs of deficiency appear *(18)*. The initial stage of folate deficiency involves negative folate balance characterized by low serum folate levels, while erythrocyte folate concentrations remain within the normal range. In stage 2, erythrocyte folate concentrations fall below 160 ng/mL, indicating a condition of folate depletion. Stage 3 is marked by a further drop in erythrocyte folate (below 120 ng/mL), elevated homocysteine levels, and evidence of metabolic dysfunction. In the final stage, clinical folate deficiency becomes apparent.

The clinical picture of folate deficiency bears many similarities to vitamin B_{12} deficiency, although folate deficiency does not cause the neurological damage associated with vitamin B_{12} deficiency. Patients with folate deficiency typically present with non-specific, often subtle complaints such as diarrhea, anorexia, and weight loss. Additional symptoms include cheilosis, glossitis, forgetfulness, irritability, and behavioral disorders *(18)*. Megaloblastic anemia with elevated mean corpuscular volume (MCV) is characteristic of the fourth, most advanced phase of folate deficiency. Because some metabolic activities require both cobalamin and folate, a B_{12} deficiency can lead to a functional folate deficiency, creating a hematological picture resembling folate deficiency despite normal concentrations of the vitamin.

2.3. Folate Requirements

The recommended intakes for folate appear in Table 2*(8)*. These values are expressed as dietary folate equivalents (DFE) to account for differences in bioavailability between naturally occurring dietary folate and synthetic folic acid *(8)*. Overall, the bioavailability of folic acid is substantially greater than that of natural folate, although data on bioavailability are quite limited. Naturally occurring dietary folate has a bioavailability of approximately 50%. Synthetic folic acid is nearly 100% bioavailable when taken on an empty stomach but adding folic acid to food reduces the bioavailability by approximately 15%. Despite these differences in bioavailability, both the natural and synthetic forms of folate perform identically after entering the blood stream *(2,3)*.

Table 2
Recommended Folate Intakes for Individuals *(8)*

Age	*RDA(μg/day, DFE)*
Infants (months)	
0–6	65[†]
7–12	80[†]
Children (years)	
1–3	150
4–8	200
9–13	300
14–18	400
Adults	
>18 years	400
Pregnancy	600
Lactation	500

† Adequate intake levels, all others are Recommended Dietary Allowance levels *(8)*

According to the calculation for DFEs, one DFE is equal to 1 μg of naturally occurring dietary folate. If folic acid is taken on an empty stomach, 1 μg folic acid is equivalent to 2 μg DFE. However, when folic acid is taken with meals or in fortified food, 1 μg folic acid equals 1.7 μg DFE *(8)*. Thus, 200 μg of synthetic folic acid taken on an empty stomach would provide 100% of the 400 μg of DFE recommended for adults. Of particular importance are the current guidelines for the prevention of neural tube defects. Current guidelines recommend folic acid supplementation for 1–3 months prior to conception with at least 400 μg/day of synthetic folic acid for women at low risk and up to 4 mg for those at high risk for neural tube defects *(19,19a)*. Because unplanned pregnancies are common other guidelines state that all fertile women, regardless of age, should receive 400 μg from fortified foods or as a supplement in addition to natural dietary folate. This level of supplementation would provide approximately 1000 μg of DFE *(8)*.

2.4. Safety of Folic Acid Supplementation

Folic acid toxicity is rare. Studies have demonstrated the safety of folic acid supplementation at daily doses of 15 mg over a period of 5 years *(20)*. Yet because high doses of folic acid can mask the hematological signs of vitamin B_{12} deficiency, the upper limit for folic acid consumption has been set at 1 mg/day. This amount of folic acid is considered unlikely to mask vitamin B_{12} deficiency. However, higher doses of folic acid can prevent macrocytic anemia but will not prevent the potentially irreversible neurological damage associated with vitamin B_{12} deficiency. This upper limit does not apply to situations in which higher doses of folic acid are used therapeutically under medical supervision *(8)*. Guidelines for patients with conditions that increase folate demands, including those receiving drugs with antifolate properties, typically recommend folic acid supplementation in the range of 1–5 mg daily. However, the potential exists for patients to exceed the 1 mg/day limit with a combination of fortified food and vitamin supplementation, underscoring the importance of monitoring vitamin B_{12} status *(21,22)*. Whether other deleterious health effects may result from long-term folic acid intake at or above the upper intake level remains largely unknown. Some concern has been raised regarding the potential role for chronically high folic acid levels to have harmful effects related to carcinogenesis, immune activity, and cognitive function, but these issues require further study *(23,24)*.

Sporadic reports of presumed – yet unconfirmed – allergic reactions to folic acid have appeared in the literature *(25,26,27)*. More recently, two published reports describe anaphylactic reactions to oral folic acid that were verified by oral provocational testing using folic acid as a single entity *(28)* and through positive intradermal testing *(29)*. In both cases, the patients' histories suggested the allergy involved only synthetic folic acid and not naturally occurring folates. Still another report outlines the case of an 80-year-old woman who developed a rash and profound hypotension after receiving intravenous folinic acid that required intravenous epinephrine *(30)*.

2.5. Folate Disposition

2.5.1. OVERVIEW

Dietary folate is ingested in a chemically inactive polyglutamate form, whereas the folic acid used in nutritional supplements and to fortify food is the monoglutamate form. Before absorption, folate polyglutamates must first undergo deconjugation by folate conjugases, found in saliva and in the small intestine, to form monoglutamate folate. Absorption of monoglutamate folate then takes place in the proximal small intestine, primarily in the duodenum and jejunum *(2,3)*. Monoglutamates undergo reduction by the enzyme dihydrofolate reductase to form the biochemically active tetrahydrofolate (THF) form of the vitamin, which then enters the portal circulation. Much of the folate in the portal circulation is taken up by the liver, the primary storage site for the vitamin. Some free folate is present in plasma, but approximately 60% is bound to proteins such as albumin or transferrin. High oral doses of folic acid bypass normal folate absorption mechanisms, resulting in unmodified folic acid entering the bloodstream along with the vitamin's normal circulating form, 5-methyltetrahydrofolate (5-methyl THF) *(22)*. Supplemental folate enters as DHF and requires dihydrofolate reductase (DHFR) action to be converted to THF. Folate excretion occurs primarily in urine and in bile, although enterohepatic circulation appears to play a role in maintaining serum folate levels *(2,5)*.

Although some folate enters the cell by diffusion, active transport by the system known as "reduced folate carrier" (RFC) maintains adequate intracellular folate concentrations *(31)*. The role played by the proton-coupled folate transporter is being explored. Fully reduced THFs can exist in several derivatives that serve as cofactors in a number of complex metabolic pathways. The predominant circulating folate, 5-methyl THF, is formed through the catalytic action of methylenetetrahydrofolate reductase (MTHFR) on 5,10-methylenetetrahydrofolate (MTHF). Within the cell, 5-methyl THF donates a methyl group in the multi-step conversion of homocysteine to methionine. In another metabolic cycle, the enzyme thymidylate synthase (TS) acts on the same substrate (MTHF) in a step critical to DNA synthesis and cell reproduction. Another fully reduced folate derivative, 5-formyl tetrahydrofolic acid or folinic acid, exists in a state that may represent a storage form of the vitamin. This folate is used therapeutically in cases where DHFR activity is blocked by antifolate drugs *(5)*.

2.5.2. Polymorphisms of Enzymes Involved in Folate Metabolism

Information gleaned from the Human Genome Project has identified numerous genetic variants in enzymes involved in folate metabolism, including mutations of key enzymes such as TS, DHFR, MHTFR, as well as the RFC transporter. This research has provided intriguing insights into the interaction of genes, nutrients, and the environment and has led to further investigation of the potential for polymorphisms involving folate-metabolizing enzymes to influence drug response and treatment outcomes. In particular, polymorphisms of the MTHFR gene have received the most scientific scrutiny.

Two relatively common variants of the MTHFR gene have been identified; both result in a functional impairment of the enzyme and varying levels of hyperhomocysteinemia *(32)*. The most common polymorphism, MTHFR C677T, involves a mutation at nucleotide position 677 on the MTHFR gene, with a change from cytosine (C) to thymine (T). Another common mutation, referred to as MTHFR A1298C, is distinguished by a substitution of adenine to cytosine at the 1298 nucleotide base pair. Estimates of the population frequency of these polymorphisms vary widely according to ethnic background, but may be as high as 20–30% for the C677T variant and up to 30% for the A1298C mutation in some populations *(32,33,34)*. Individuals who are homozygous for the MTHFR C677T polymorphism produce a heat-sensitive (thermolabile) enzyme that exhibits, in vitro, only 30–60% of the activity of the normal enzyme. The MTHFR A1298C enzyme does not exhibit thermolability, but has only 35% of the activity of the normal enzyme *(34,35,36)*.

MTHFR mutations, especially the C677T polymorphism, have been linked to health risks, including neural tube defects, poor pregnancy outcomes, and cardiovascular disease, while perhaps having a protective effect for certain cancers, such as lymphocytic leukemia and colon cancer *(32)*. However, folate status exerts a strong influence on the degree of risk associated with these polymorphisms. Research has shown, for example, that individuals with the MTHFR C677T polymorphism tend to have elevated serum concentrations of homocysteine that respond favorably to high folate intake. A DHFR mutation may be associated with an increased risk of breast cancer in multivitamin users *(37)*. The optimal dose, timing, and form of folate supplementation appropriate for individuals with this and other polymorphisms have not been determined *(38,39)*.

3. DRUG–FOLATE INTERACTIONS

A well-known association exists between long-term use of certain drugs and the development of megaloblastic anemia due to folate depletion. In some instances, the antifolate properties of the drug represent the intended mechanism of action;

in other cases, the interaction is an unwanted side effect of the drug. Until recently, drugs that depleted folate stores were thought to pose a hazard only to individuals in high-risk categories. However, drug–nutrient interactions involving folate have received increased scrutiny with the recognition that even subclinical folate deficiency can have serious and far-reaching health consequences. Specifically, studies that have shown an association between the use of antifolate drugs and elevated homocysteine levels have raised concerns regarding the safety of long-term use of these agents in patients at increased risk for cardiovascular disease *(40,41)*. However, the clinical significance of this adverse effect requires further study before definitive guidelines can be developed *(42)*. Other studies indicate that homocysteine levels may play a role in predicting the potential for toxicity with certain antifolate drugs *(43)*. Furthermore, evidence linking folate depletion to a broad range of congenital defects in infants of women who took DHFR inhibitors during pregnancy requires that the clinical significance of these interactions be re-assessed *(44)*.

Folate antagonists can disrupt folate activity through a variety of mechanisms. For example, drugs can impair intestinal absorption, alter protein binding of folate in the circulation, interfere with enzymes essential to folate metabolism, enhance liver metabolism of the vitamin, or block the release of folate from cells *(45)*. A large number of folate antagonists act by inhibiting the enzyme DHFR, thus blocking the conversion of dietary folate or supplemental folic acid to the active THF derivative. DHFR inhibition depletes the pool of THFs, which in turn, limits the availability of substrates for other folate-dependent enzymes. A better understanding of the numerous metabolic processes that depend on folate has led to the development of a class of antineoplastic agents that target other folate-dependent enzymes such as TS and glycinamide ribonucleotide transformylase, both of which play a critical role in cell proliferation *(46)*. Still newer antifolate agents – multi-targeted antifolates – work by inhibiting several enzymes involved in folate metabolism *(47,48)*. Administering folic acid or the reduced derivative, folinic acid, during treatment with antifolate drugs has the potential to alter both the therapeutic and the toxic effects associated with the drug *(49)*.

Although no current drug therapy targets the MTHFR enzyme, studies have examined the pharmacogenetic implications of MTHFR polymorphisms on plasma homocysteine levels, therapeutic folic acid supplementation, and the efficacy and toxicity of antifolate therapy. This growing body of scientific evidence suggests that gene–nutrient interactions play a role in overall health risks, treatment failures, and adverse drug reactions. However, further research is needed to elucidate ways this information can lead to therapies tailored according to genotype *(11,49,50)*. Strategies that consider drug–nutrient interactions in combination with these gene interactions hold much potential for the development of truly individualized treatment plans.

4. LIMITATIONS OF THE DATA AND FURTHER RESEARCH NEEDS

Overall, information concerning drug–nutrient interactions that impact folate status is incomplete. An important limitation to the available data concerning drug–folate interactions is that much of the early research relied on the development of megaloblastic anemia as the clinical end point for defining an interaction. In addition, relatively few studies have explored the clinical impact of antifolate drugs on homocysteine levels. This issue requires longitudinal trials that track the influence of antifolate drugs on homocysteine levels and long-term health risks, including the incidence of birth defects.

Theoretically, the improved folate status of the US population may lower the risk for drug-related folate deficiency by reducing the number of individuals who begin antifolate drug therapy with marginal folate stores. However, data supporting this premise are not yet available. Many questions remain unanswered concerning the need for folic acid supplementation in patients receiving folate antagonists. Further studies that compare folic acid to folinic acid supplementation will help clarify the indications for both agents. Of great concern is the potential for folic acid supplementation to alter the therapeutic activity of drugs. However, few guidelines are available regarding the optimal dosing regimen for folic acid supplementation or the need to adjust the dose of antifolate drugs. This significant issue requires further investigation that correlates vitamin status and drug concentrations with therapeutic efficacy and drug side effects. In addition, studies must address the extent and frequency of monitoring that is appropriate for patients receiving antifolate drugs.

In the years to come, prospective observational research is likely to produce drug-specific clinical practice guidelines concerning appropriate levels of folate intake during antifolate therapy. Further study of polymorphisms involving folate-metabolizing enzymes may lead to individualized strategies for enhancing the therapeutic effectiveness or reducing the toxicity of antifolate agents based on the patient's genotype. Ultimately, the objective for all research related to drugs that impact folate status is to delineate evidence-based clinical practice guidelines for maintaining optimal folate status without compromising therapeutic goals.

5. RECOMMENDATIONS

Despite the lack of evidence-based recommendations, basic measures designed to improve clinical outcomes related to the use of antifolate drugs are appropriate. For example, all fertile women should receive folic acid supplementation as recommended by the Institute of Medicine *(8)*, the Centers for Disease Control and Prevention (CDC) *(1)*, and the US Preventive Services Task Force *(19a)*. In addition, documentation of vitamin B_{12} status should be routine for all patients who are initiating folic acid supplementation. A comprehensive approach for addressing drug–nutrient interactions that involve folate should include strategies for monitoring patients at risk for drug–folate interactions, patient education, and appropriate intervention.

Monitoring for patients receiving drugs with antifolate properties aims to ensure that therapeutic goals are met without compromising folate status. Current information makes clear that monitoring must not depend on the development of macrocytic anemia as the sole criteria for identifying a deficiency state. To accurately evaluate folate status, monitoring must include homocysteine levels and erythrocyte folate concentrations. Although homocysteine levels can provide an early indication of declining folate stores, individual variation occurs in response to folate depletion and supplementation, suggesting that repeat testing may be necessary to ensure the validity of the marker *(51)*. At a minimum, baseline folate status should be evaluated when drug therapy is initiated, whenever the drug dose is changed, and at regular intervals in stable patients. No consensus exists regarding the appropriate interval for routine monitoring in stable individuals, however.

The risk assessment for folate–drug interactions should also include a dietary evaluation to determine the level of folate intake, through both fortified food and nutritional supplements. With the current level of food fortification and the widespread use of vitamin products containing folic acid, the potential exists for patients to achieve excessively high intakes of folic acid. The ramifications of chronically high folic acid intake, with regard not only to drug–nutrient interactions but also to other health risks, remain unknown *(24)*.

Increasingly, guidelines recommend supplementation with folic acid for patients receiving antifolate drug therapy. Considerable variation exists in the dose and timing of folic acid supplementation, however. As noted earlier, pharmacologic dosing regimens range from 1 mg to 5 mg per day, although evidence from studies of some antifolate drugs suggests that lower doses of folic acid may be appropriate *(46)*. The ability to use lower doses of folic acid would reduce the potential to obscure evidence of vitamin B_{12} deficiency. However, further studies are needed to determine the optimal level of folic acid supplementation for patients undergoing treatment with antifolate drugs, while taking into account relevant polymorphisms.

For patients receiving folic acid supplementation in conjunction with antifolate drug therapy, monitoring the therapeutic efficacy of the drug takes on great importance. Depending on the drug in question, monitoring may include regular measurement of drug levels, assessing for clinical evidence of efficacy, or observing for toxic side effects. For example, studies indicating that folic acid supplementation may induce a rapid drop in serum phenytoin levels demand that phenytoin levels be monitored closely in the early phase of folic acid supplementation until a new steady state of each is established *(52–54)*. On the other hand, disease activity and evidence of toxicity guide decisions regarding the need to adjust the dose of methotrexate in patients being treated for rheumatoid arthritis or psoriasis *(55–57)*. Table 3 provides more information regarding interactions between folic acid and specific drugs *(58–113)*.

Finally, patient education plays a fundamental role in the management of drug–nutrient interactions that impact folate status. Patients require information regarding the harmful effects of folate deficiency as well as the ability of folate consumption to alter drug activity. Awareness of the potential for an interaction can help patients avoid circumstances that could lead to unfavorable outcomes. A simple handout can be used to provide patients with the facts they need concerning interactions involving folate (see Fig. 1 for an example). In addition, as part of an ongoing campaign to reduce the incidence of neural tube defects, the CDC urge health-care professionals to act as advocates by routinely encouraging daily folic acid consumption among women of childbearing age in face-to-face encounters and through a variety of educational strategies within both the community and the health-care system *(114)*.

Table 3
Recommendations for Managing Potential Drug–Folate Interactions *(57–113)*

Drug	*Proposed Mechanism*	*Recommendations/Precautions*
Antiepileptics		Appropriate folic acid supplementation is especially important for women of childbearing age who have epilepsy. Some guidelines recommend supplementation beginning 1–3 months prior to pregnancy, but because of the high percentage of unplanned pregnancies, the most prudent approach is to provide folic acid supplementation for all women capable of becoming pregnant The goal is to maintain folate levels above 4 mg/mL. Recommended doses range from 400 μg/day to 5 mg/day. Other authors suggest 1 mg/day for all patients with controlled epilepsy, including pregnant women Further research is needed to confirm the appropriate level of folic acid supplementation for women with epilepsy
Phenytoin	An interdependent reaction exists between phenytoin and folate. Phenytoin may deplete folate by (1) raising intestinal pH, causing folate malabsorption, (2) inhibiting intestinal conjugases, (3) impairing folate transport, or (4) inducing hepatic microsomal enzymes.	When possible, initiate phenytoin and folate supplementation (1 mg/day) together after documenting normal vitamin B_{12} status. Further study is needed to determine the efficacy of lower doses (400 μg/day). When initiating folic acid supplementation in patients stabilized on phenytoin therapy, monitor phenytoin levels closely for the first

(*Continued*)

Table 3
(Continued)

Drug	*Proposed Mechanism*	*Recommendations/Precautions*
	Folate serves as a cofactor for phenytoin metabolism, potentially lowering phenytoin levels in patients receiving folic acid	10–15 days of folic acid therapy, until a new steady state is achieved. Greatest declines occur in patients with high phenytoin levels at the start of folic acid supplementation. Increases in phenytoin dose may be required
Valproic acid	Inhibits glutamate formyl transferase, altering the distribution of folate derivatives. May inhibit the synthesis of homocysteine to methionine	Guidelines generally recommend administering preconceptual folic acid with 4 mg daily. However, conflicting data exist concerning the effect of valproic acid on folate status. Further research is needed
Carbamazapine	Induction of hepatic microsomal enzymes, accelerating folate degradation	Guidelines recommend preconceptual folic acid supplementation with 4 mg/day
Phenobarbital primidone	Induction of hepatic microsomal enzymes, accelerating folate degradation	Studies have demonstrated low-serum folate concentrations with prolonged use. The clinical significance of the interaction is not clear
Antimetabolites		
Methotrexate (MTX)	Dihydrofolate reductase inhibitor	
High-dose antineoplastic therapy		Folinic acid is used for rescue therapy following high-dose methotrexate administration. Dosing guidelines for folinic acid are based on serum methotrexate levels at 24–72 h after MTX dose.

		The usual recommended dose for folinic acid is 15 mg/m^2 every 6 h beginning 24 h before MTX administration and continuing until signs of MTX toxicity have resolved. Folic acid supplementation during MTX treatment does not effect toxicity, risk of graft versus host disease, or relapse in bone marrow transplant recipients
Low-dose therapy for rheumatoid arthritis and psoriasis		Methotrexate treatment leads to increased levels of homocysteine that respond favorably to folic acid supplementation.Both folic acid and folinic acid reduce methotrexate toxicity. Dosing guidelines for folic acid recommend 1 mg/day folic acid, or 2.5 mg to 5 mg/week for folinic acid. Evidence suggests that continued folic acid supplementation reduces toxicity even in patients established on long-term MTX therapy The timing of folinic acid supplementation with respect to methotrexate administration may be important with folinic acid but not with folic acid. However, the potential for MTX–folate interactions may be avoided by administering the folic acid dose 24 h before and after the MTX dose weekly. Other factors such as previous GI symptoms, BMI, age, and NSAID use may also influence toxicity.

(*Continued*)

Table 3
(Continued)

Drug	*Proposed Mechanism*	*Recommendations/Precautions*
		Folic acid is significantly less expensive than folinic acid
Fluorouracil (5-FU)	The presence of excessive reduced folates increases trapping of 5FU anabolites within cells, possibly delaying elimination	Co-administration of folinic acid with fluorouracil or capecitabine may improve therapeutic efficacy in certain cancers, but fluorouracil toxicity may be enhanced. Monitor for signs of fluorouracil toxicity
Capecitabine		Lethal capecitabine toxicity has been linked to excessively high folic acid intake (15 mg/day), underscoring the importance of maintaining accurate medication profiles, including prescription and nonprescription drugs
Pemetrexed	Multitargeted antifolate activity: Disrupts activity of multiple folate-metabolizing enzymes: thymidylate synthase, glycinamide ribonucleotide formyltransferase, 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase, and dihydrofolate reductase	In conjunction with monthly vitamin B_{12} supplementation, administer 350–1000 μg folic acid beginning 5 days before treatment is initiated and continue throughout treatment
Antimicrobials		
Pyrimethamine	Dihydrofolate reductase inhibitor	Folinic acid (10–20 mg/day) may be used to reduce toxicity during treatment for toxoplasmosis without effecting pyrimethamine efficacy. In leukemic patients being treated for toxoplasmosis, folinic acid may worsen leukemia or induce a relapse

		Folic acid should not be used during pyrimethamine treatment for toxoplasmosis because a pharmacodynamic antagonism results, impairing the antiparasitic effects of pyrimethamine Either folic acid or folinic acid can be used in conjunction with pyrimethamine during treatment of malaria
Sulfadoxine/pyrimethamine		High doses of folic acid (5 mg/day) impair the efficacy of sulfadoxine/pyrimethamine used as intermittent preventive treatment of malaria in pregnancy, but 400 µg/day may be optimal in preventing neural tube defects while maintaining drug efficacy
Trimethoprim	Dihydrofolate reductase inhibitor	Studies suggest that trimethoprim use during early pregnancy increases risk of congenital defects. Folic acid supplementation appears to reduce the risk of birth defects associated with trimethoprim Long-term use of trimethoprim may increase homocysteine levels, raising concern regarding the safety of long-term use for patients with high cardiac risk. However, the role of folic acid supplementation has not been adequately studied in this patient population

(*Continued*)

Table 3
(Continued)

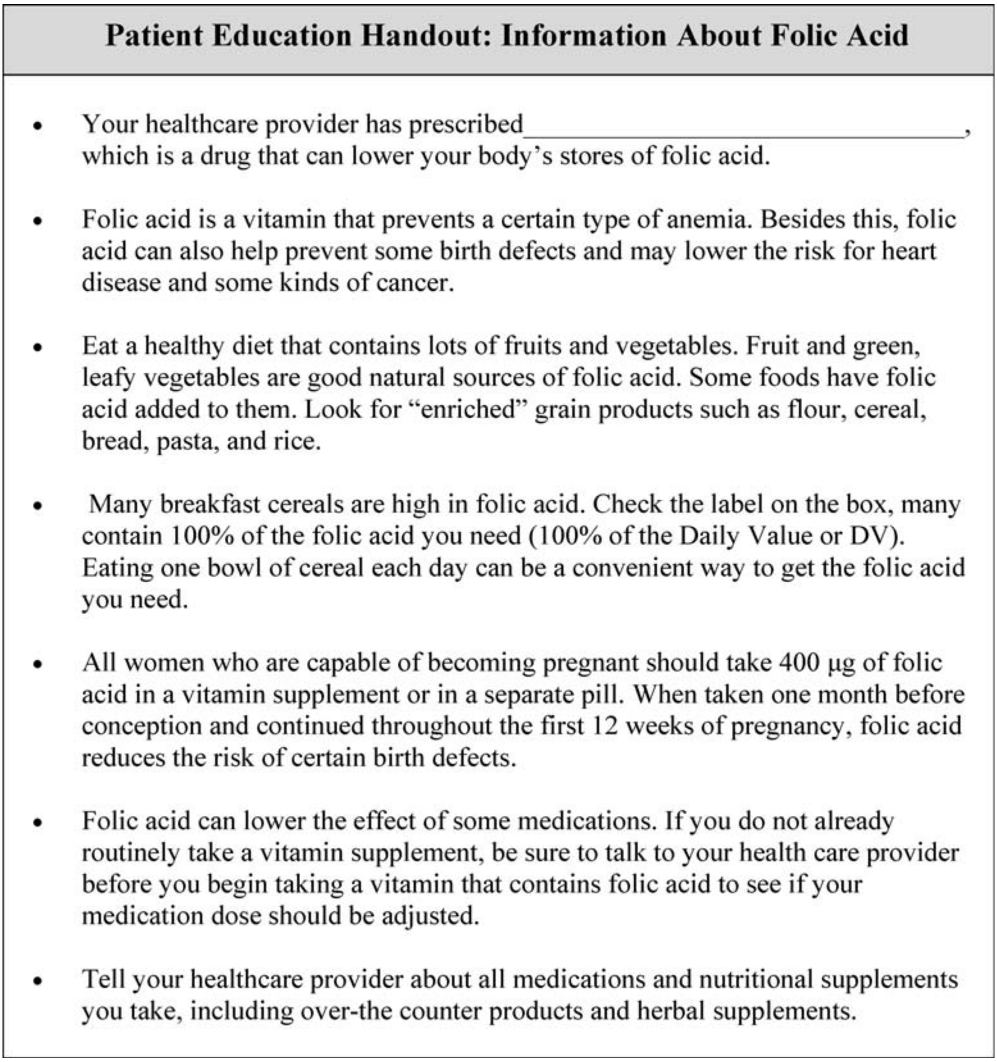
Drug	*Proposed Mechanism*	*Recommendations/Precautions*
		Use of folinic acid in conjunction with trimethoprim–sulfamethoxazole for treatment of pneumocystitis carinii has been linked to an increased risk for therapeutic failure and death
Psychotropic drugs	Suboptimal folate status may impair synthesis of 5-hydroxytryptamine and noradrenaline. A deficiency of one or both of these monoamines is thought to play a role in the pathogenesis of depression	Low folate levels are linked to poor response to treatment for depression. Supplementation with folic acid in daily doses ranging from 800 μg to 2 mg is recommended to improve treatment outcome in depression. Use of folic acid in combination with daily doses of 1 mg vitamin B_{12} is also recommended
Lithium		Low serum folate levels have been found in patients treated with lithium for mood disorders
Fluoxetine		Low serum folate levels places patients at risk for depressive relapse during treatment with fluoxetine. Women receiving 500 μg of folic acid with fluoxetine demonstrated improved antidepressant action. Further study is required to determine if folic acid supplementation at higher doses will have a similar effect in men receiving fluoxetine
Diuretics		
Loop diuretics Thiazide diuretics	Long-term diuretic use increases elimination of folate and has been linked to elevated homocysteine levels; triamterene is a weak	Supplementation with folic acid may be beneficial, particularly in patients with other

	inhibitor of dihydrofolate reductase. Animal models have also demonstrated that folic acid inhibits triamterene absorption	risk factors for folate deficiency. Further research is needed to determine clinical significance
Anti-inflammatory agents		
Sulfasalazine (SSZ)	SSZ acts as a potent inhibitor of reduced folate carrier (RFC). It also raises requirements through chronic hemolysis	Administer folic acid supplements; monitor for hematologic and hepatic toxicity. Pregnant women are advised to take 2 mg of supplemental folic acid daily. In some cases, folinic acid appears more effective in restoring folate stores than folic acid. The RFC–SSZ interaction leads to folate deficiency and may also explain the lack of synergism with combined SSZ/MTX treatment in rheumatoid arthritis. Consideration should be given to spacing SSZ administration apart from MTX; pharmacokinetic studies are needed to determine optimal timing
NSAIDs	In vitro, NSAIDs inhibit transformylase- and folate-mediated synthesis of serine from glycine and formate	The antifolate properties of NSAIDs are important factors in producing the anti-inflammatory activity of these drugs. The clinical significance of this drug–nutrient interaction and the impact of folic acid supplementation remain unknown

(*Continued*)

Table 3
(Continued)

Drug	*Proposed Mechanism*	*Recommendations/Precautions*
Miscellaneous		
Pancreatin	Pancreatic extract impairs folate absorption by forming an insoluble complex with folic acid	Folate status should be monitored for patients receiving treatment for pancreatic insufficiency. Folic acid supplementation may be indicated
Cholestyramine, colestipol	Binds folic acid, increasing elimination of the vitamin	Administer folic acid supplements 1 h before or 4–6 h after cholestyramine/colestipol dose
Metformin	Elevations in homocysteine levels have been linked to reductions in both vitamin B_{12} and folate, possibly due to impaired absorption	Monitoring of vitamin B_{12} and folate levels is indicated. Supplementation with folate reduces homocysteine levels. Clinical significance of this drug–nutrient interaction is unknown



Patient Education Handout: Information About Folic Acid

- Your healthcare provider has prescribed________________________________, which is a drug that can lower your body's stores of folic acid.
- Folic acid is a vitamin that prevents a certain type of anemia. Besides this, folic acid can also help prevent some birth defects and may lower the risk for heart disease and some kinds of cancer.
- Eat a healthy diet that contains lots of fruits and vegetables. Fruit and green, leafy vegetables are good natural sources of folic acid. Some foods have folic acid added to them. Look for "enriched" grain products such as flour, cereal, bread, pasta, and rice.
- Many breakfast cereals are high in folic acid. Check the label on the box, many contain 100% of the folic acid you need (100% of the Daily Value or DV). Eating one bowl of cereal each day can be a convenient way to get the folic acid you need.
- All women who are capable of becoming pregnant should take 400 μg of folic acid in a vitamin supplement or in a separate pill. When taken one month before conception and continued throughout the first 12 weeks of pregnancy, folic acid reduces the risk of certain birth defects.
- Folic acid can lower the effect of some medications. If you do not already routinely take a vitamin supplement, be sure to talk to your health care provider before you begin taking a vitamin that contains folic acid to see if your medication dose should be adjusted.
- Tell your healthcare provider about all medications and nutritional supplements you take, including over-the counter products and herbal supplements.

Fig. 1. Patient education handout: information about folic acid.

6. SUMMARY

Drug–nutrient interactions between therapeutic drugs and folate can impact both drug levels and vitamin status. Clinicians have long recognized the potential for drug–nutrient interactions to impact folate status, but the full clinical significance of these interactions has only recently begun to emerge. A tremendous need exists for research aimed at developing recommendations for the management of interactions involving folate. Areas that require further study include measures to promote optimal folate status without compromising therapeutic goals, appropriate dosing regimens for folic acid supplementation, monitoring guidelines, and the long-term health risks associated with drug-induced alterations in folate status including hyperhomocysteinemia. The potential for developing targeted drug therapy based on patients' genotype represents a promising opportunity for improving treatment outcomes.

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19 Drug–Nutrient Interactions That Impact on Mineral Status

Sue A. Shapses, Yvette R. Schlussel, and Mariana Cifuentes

Objectives

- Identify the macro- and microminerals and recall dietary sources of minerals and their normal regulation.
- Define how mineral status may be altered by certain medications.
- Identify certain minerals that may alter the activity of medication.
- Recognize how other drug substances (i.e., ethanol, caffeine, nicotine, and illicit drugs) may alter mineral status.

Key Words: Assessment; bioavailability; mineral; trace element; ultratrace element

1. INTRODUCTION

Concurrent administration of medication with nutrients can bring about interactions that change the absorption or metabolism of the medication or nutrient *(1,2)*. There are many more dietary supplements and drugs that are now taken simultaneously and some are known to interact with each other *(3)*. Certain drugs may exhibit decreased bioavailability or activity due to chelation and adsorption. Mineral status may be altered due to decreased absorption, increased excretion, or an altered mineral metabolism (Fig. 1). The results of such interactions may be clinically insignificant or severe. This chapter discusses mineral bioavailability and absorption and reviews mineral requirements, their sources, manifestations of deficiency and toxicity, and normal levels in the serum (Tables 1 and 2). Drugs that will affect mineral status (Table 3) in contrast to those minerals expected to interfere with drug absorption or activity (Table 4) are reviewed. The tables in this chapter have been designed to provide a simple and practical guide for practitioners.

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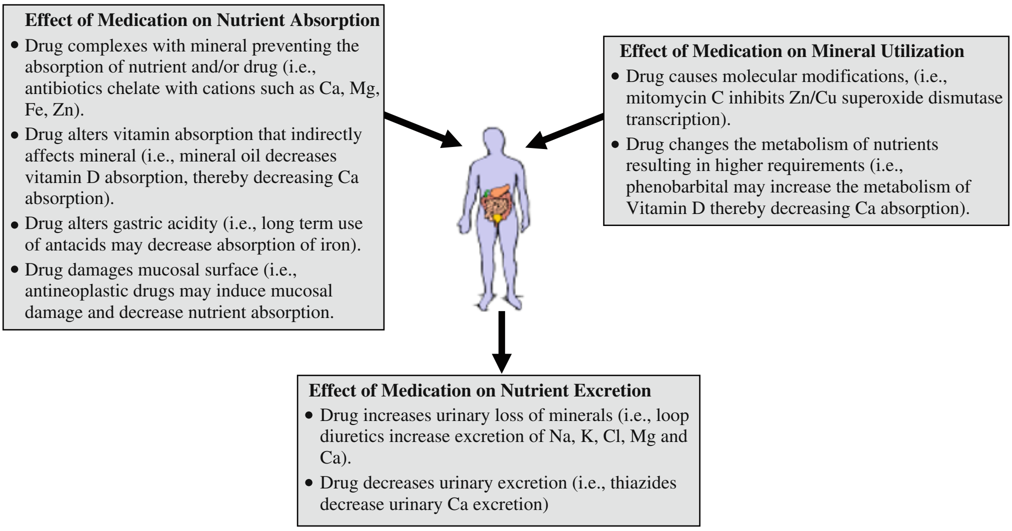

Effect of Medication on Nutrient Absorption

- Drug complexes with mineral preventing the absorption of nutrient and/or drug (i.e., antibiotics chelate with cations such as Ca, Mg, Fe, Zn).
- Drug alters vitamin absorption that indirectly affects mineral (i.e., mineral oil decreases vitamin D absorption, thereby decreasing Ca absorption).
- Drug alters gastric acidity (i.e., long term use of antacids may decrease absorption of iron).
- Drug damages mucosal surface (i.e., antineoplastic drugs may induce mucosal damage and decrease nutrient absorption.

Effect of Medication on Mineral Utilization

- Drug causes molecular modifications, (i.e., mitomycin C inhibits Zn/Cu superoxide dismutase transcription).
- Drug changes the metabolism of nutrients resulting in higher requirements (i.e., phenobarbital may increase the metabolism of Vitamin D thereby decreasing Ca absorption).

Effect of Medication on Nutrient Excretion

- Drug increases urinary loss of minerals (i.e., loop diuretics increase excretion of Na, K, Cl, Mg and Ca).
- Drug decreases urinary excretion (i.e., thiazides decrease urinary Ca excretion)

Fig. 1. Effect of medication on mineral kinetics.
Ca, calcium; Cl, chloride; Cu, copper; Fe, iron; K, potassium; Mg, magnesium; Na, sodium; Zn, zinc.

2. OVERVIEW OF MINERAL ABSORPTION AND BIOAVAILABILITY

Absorptive efficiency for many minerals is governed by homeostatic feedback regulation. When the body is in a depleted state, the intestine upregulates absorption of the nutrient. At a biochemical level, this regulation can be expressed by the control of intraluminal binding ligands, cell surface receptors, intracellular carrier proteins, intracellular storage proteins, or the energetics of transmembrane transport.

Mineral bioavailability is defined as the efficiency with which a natural or a manufactured source of an element delivers the element to storage or supplies it to a metabolically active tissue or to a protein. To assess for bioavailability, several factors must be determined. This includes the following: (a) whether the intake is below or above the physiologic requirement, (b) tissue mineral contents, if possible, as dependent variables, (c) range of linearity between mineral dose and response, and (d) the results of a *slope ratio analysis*. In general, mineral bioavailability may decrease due to many drugs, decrease with age, and in the presence of malnutrition-associated poorer integrity of the small intestine. Therefore, older individuals who are often taking numerous medications and eating more poorly than the young are at greater risk of mineral deficiencies.

The chemical form of a mineral is an important factor in its absorption and bioavailability. Although few studies have been done comparing absorption differences among mineral supplements, there is evidence that the form in which minerals are ingested affects absorption *(4)*. For example, the particle size, the surface area, and the solubility of a substance affect its dissolution rate *(5,6)*. Other manufacturing variables that may affect the release characteristics of minerals in a tablet include the tablet compression force and the type and amount of coating materials.

The absorbability and bioavailability of minerals in foods is as similarly complicated as minerals in solid dosage form. The composition of foods and beverages determines the chemical form of a mineral component. In many solid foods, elements are not free but are firmly bound in the food matrix. They can be in covalent association with a protein, as in metalloenzymes, or in electrochemical chelation arrangements to a nonspecific binder. Chelated forms of minerals may interact with other minerals or drugs to reduce absorbability *(7)*. Food fortification may affect mineral absorption *(8)*. The recommended US Food and Drug Administration meal used in drug–food interaction studies is a high-fat, high-calorie meal with minimal micronutrient content. With changing patterns in food preferences, fortification, and dietary supplementation, revision of current regulatory guidelines should take into account potential new drug–nutrient interactions.

Factors that enhance mineral absorption include the form of the mineral ingested, maintenance of chemical stability, presence of a specific transporter, small particle size, solubility, ascorbic acid, and low intestinal motility. Although certain fibers inhibit absorption of minerals, soluble fibers including nondigestible oligosaccharides (prebiotics) such as oligofructose, inulin, or lactulose stimulate absorption and retention of several minerals, particularly magnesium, calcium,and iron *(9)*. The mechanism underlying these positive effects is most likely related to increased solubility of these minerals in the cecum and the colon as a consequence of increased microbial fermentation and lower luminal pH. Clinical trials show evidence that prebiotics will enhance calcium absorption *(10,11)*. However, not all studies show positive effects *(12)*. For potential malabsorption with any mineral, it is best to approach treatment and prevention based on whether the evidence is definitive. For example, in those drugs whose effect is "questionable," routine monitoring and treatment is time consuming and therefore is not recommended.

Factors that inhibit absorption of minerals include oxalic acid, phytic acid *(13)*, fiber *(14)*, sodium, tannins *(15)*, caffeine, protein, fat, antacids, rapid transit time, malabsorption syndromes, precipitation by alkalinization, other minerals *(16)*, hormones, and nutritional status *(17)*. In addition, excess mineral excretion can occur due to a common side effect of many antibiotics (i.e., diarrhea), which may be caused by the alteration of the normal colonic flora. In this case, yogurt containing probiotic microorganisms can protect against other antibiotic-induced diarrhea.

Finally, genetics may also influence the absorption of minerals *(18)*. This is likely to be an important mechanism for individual absorptive responses to a specific drug, but currently there is limited information about how genes influence mineral and/or drug absorption and metabolism. A goal should be to identify pharmacogenomic biomarkers that stratify individuals based on a likely response to a particular medication, positive response, efficacy, negative response, and development of side effect or toxicity *(19)*.

3. MACROMINERALS

The macrominerals are discussed below with respect to absorption and bioavailability, assessment of status, and drug interactions. Status is typically measured in the serum (and sometimes in the urine). In general, hair mineral testing has been found to be an unreliable and crude estimate of mineral status due to contamination from the environment (i.e., shampoos and emissions) *(20)*. Remarkable progress is being made in understanding the molecular basis of disorders of human mineral metabolism, but this topic is tangential to our focus and therefore will not be discussed.

3.1. Sodium

Sodium is the most abundant (93%) of the cations in the blood. Its primary location is on the surface of bone crystals, and the rest is in the extracellular fluid, nerves, and muscles. Ingested sodium is almost completely absorbed in the intestine, with only 5% unabsorbed and excreted in the feces. Intestinal absorption may occur via the sodium/glucose cotransport system (distributed throughout the small intestine), the sodium chloride cotransport system (located in the small intestine and proximal colon), and a colon-located, electrogenic sodium absorption mechanism. A basolateral sodium pump maintains the inward gradient necessary for sodium absorption in all the described processes. With this very high absorption capacity, more than necessary will enter the system and excess sodium absorbed is excreted by the kidneys, a process that is in large part controlled by aldosterone. Low-sodium concentrations signal the release of the hormone and this promotes renal sodium reabsorption. Sodium is also lost through the sweat; however, the amount excreted is variable (i.e., exercise, temperature conditions, etc.). Normal serum concentrations of sodium range between 135 and 148 mmol/L (Table 1) and are measured routinely in the laboratory to determine electrolyte balance.

Sodium homeostasis is maintained by mechanisms that involve thirst, arginine vasopressin (antidiuretic hormone), and renal control of water excretion. In individuals with an altered sense of thirst (adipsia) or among electrolyte disorders, dysnatremias occur very frequently, especially among hospitalized patients and the elderly. Dysnatremias cause alterations in almost all body systems. Hyponatremia (which is more common than hypernatremia) can lead to edema and cause dehydration, both of which may lead to neuropathological damage and even death. Inappropriate management of these disorders (particularly the speed of correction) may in itself lead to severe damage *(21,22,23)*.

3.1.1. DRUG INTERACTIONS

Excess use of sodium bicarbonate to relieve acid indigestion may cause hypernatremia, and consumption of a high-sodium diet, especially in the elderly with heart disease, may pose an elevated risk for metabolic derangements *(24,25,26)* (Table 3). Sodium retention may also occur with other drugs, such as nonsteroidal anti-inflammatory drugs *(27)*, estrogens *(28)* and corticosteroids *(29)*, or with prolonged saline infusion *(30)*.

Increased excretion of sodium occurs with diuretic use and angiotensin-converting enzyme (ACE) inhibitors (Table 3). Dietary sodium restriction improves the antihypertensive action of diuretics and other blood pressure-lowering drugs. In patients taking lithium, both sodium and potassium excretion are increased *(31)*. In individuals predisposed to form kidney stones, hypercalciuria may be associated with a high-sodium intake *(32)*, and sodium restriction alone or with thiazide

Table 1
Clinical and Serum Assessment of Macromineral and Trace Mineral Status

	Symptoms		
Mineral *Food Sources and Daily Adult RDA or AI*	*Deficiency*	*Toxicity*	*Normal Serum Levels and Diseases Altering Status*
Sodium Salt, soy sauce, processed foods AI: 1.2–1.5 g	Muscle cramps, mental fatigue, anorexia, weight loss, poor growth, nausea	Hypertension in salt-sensitive individuals	**135–148 mmol/L (mEq/L)** ↓ Renal dis., diarrhea, profuse sweating, excess ADH, overhydration, HF, cirrhosis ↑ Renal disease, dehydration
Potassium Meat, milk, vegetables, fruits, grains, legumes AI: 4.7 g	Muscular weakness, paralysis, confusion, possible death Cardiac arrhythmias, paralysis, weight loss	Muscular weakness Vomiting	**3.5–5.3 mmol/L (mEq/L)** ↓ GI loss (vomiting, diarrhea), urine loss (Cushing's disease, drug-induced), alkalosis, sweating, dehydration ↑ Acidosis, renal disease, hypoaldosteronism
Calcium Dairy products, small fish with bones, broccoli, kale, tofu, Ca-enriched products AI: 1–1.2 g	Stunted growth Osteoporosis Rickets, osteomalacia, tetany, parathyroid hyperplasia	Constipation Thirst, nausea, vomiting, loss of appetite	**2.2–2.6 mmol/L (8.5–10.5 mg/dL)** Free ionized 4.4–5.4 mg/dL Tight regulation of serum levels ↓ Hypoparathyroidism diseases (liver, renal, critical illness) ↑ Hyperparathyroidism, excess vit D, renal failure, immobilization
Phosphorus Animal protein (all meats) RDA: 700 mg	Rare Neurological, skeletal, hematological, renal manifestations, rickets, osteomalacia, anorexia	Occurs with low Ca intake –> secondary hyperparathyroidism Results in reduced growth or bone loss	**0.7–1.4 mmol/L (2.3–4.3 mg/dL)** ↓ Alkalosis, gastrointestinal, malnutrition recovery, renal dis. ↑ Renal, malignancy, sarcoidosis, immobilization, Mg deficiency, bone malignancy, Cushing's dis.

(*Continued*)

Table 1
(continued)

Mineral *Food Sources and Daily Adult RDA or AI*	*Symptoms* *Deficiency*	 *Toxicity*	*Normal Serum Levels and Diseases Altering Status*
Magnesium Nuts, legumes, grains, seafood, dark green vegetables, chocolate RDA: 420 mg (M), 320 mg (F)	Weakness, confusion, hypertension, tingling, muscle weakness, poor growth, convulsions, neurological signs	Diarrhea (as with large doses of epsom salts), hypotension, hypothermia	**0.7–1.0 mmol/L (1.8–2.3 mg/dL)** ↓ Surgery, alcoholism, malabsorption, some renal diseases, diabetes, acidosis ↑ Sepsis, cardiac arrest, burns
Iron Meat, fish, shellfish, eggs, legumes, leafy green vegetables, enriched cereal/bread RDA: 8 mg (18 mg for women <50 yr)	Anemia, weakness, pallor, reduced ability to concentrate, lowered cold tolerance	Infections, liver injury, possible heart attack, acidosis, bloody stools, shock, colorectal cancer	**80–150 μg/dL (14–24 μmol/L)** ↓ Renal dis., malnutrition ↑ Hemochromatosis
Copper Liver, shellfish, water grains, nuts, seeds RDA: 900 μg	Rarely occurs; bone abnormalities, anemia, neutro- and leukopenia	Vomiting, diarrhea, liver and renal damage	**85–150 μg/dL (13–24 μmol/L)** ↓ Diarrhea, malnutrition, Menkes disease (kinky hair) ↑ Wilson's disease
Zinc Meat, fish, shellfish, grains, vegetables RDA: 11 mg (M) 8 mg (F)	Anorexia, growth and sexual retardation, anemia, poor taste, smell and wound healing, hair, nails, skin changes	Nausea, vomiting, diarrhea, dizziness, atherosclerosis, renal failure	**60–130 μg/dL (9–20 μmol/L)** ↓ Liver disease, stress, malnutrition, infection, burns ↑ Industrial exposure

ADH (antidiuretic hormone); AI (adequate intake level for nonpregnant adults); HF (heart failure); d (day); dis. (disease); F (female); GI (gastrointestinal); M (male); RDA (recommended dietary allowance for non-pregnant adults); vit (vitamin); yr (years)

diuretics helps to reduce urinary calcium *(33,34)*. Although immunosuppressive agents, such as cyclosporine, may not alter sodium levels in the body, subtle renal injury induced by cyclosporine could lead to salt sensitivity *(35)*. There can also be negative consequences of sodium restriction, especially in cases where the mechanisms to conserve sodium are impaired. Sodium restriction in combination with ACE inhibitors or amphotericin B can precipitate acute renal failure, and sodium repletion improves renal function *(36,37)*.

A number of drugs may cause inappropriate antidiuretic hormone (arginine vasopressin) secretion, where patients continue to drink water/fluids despite having hypotonic hyponatremia *(38)*. Drugs that may cause hyponatremia include tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, conventional and atypical antipsychotics, opioid analgesics, ACE inhibitors, sulfonylureas, thiazide diuretics, as well as clofibrate, the recreational drug known as "ecstasy" (3,4-methylenedioxy-*N*-methylamphetamine), the antiepileptic carbamazepine, nicotine, antineoplastic agents (cisplatin, cyclophosphamide and vinca alkaloids), vasopressin, and oxytocin *(23,38)*.

3.2. Potassium

Potassium is the major intracellular fluid cation, and extracellular fluid potassium constitutes approximately 2% of total body potassium. It plays a crucial role in muscle contractility (smooth, skeletal, and cardiac) and in the excitability of nerve tissue. In addition, it is relevant in the maintenance of electrolyte and pH balance. As opposed to the case of sodium, intestinal absorption of potassium is not so well understood. The cation is largely (90%) absorbed, and it has been suggested that the colon is the main site. Among the proposed mechanisms are a potassium/proton ATPase pump, at the apical membrane and potassium channels. Potassium balance is regulated in the kidney, with aldosterone promoting its excretion. Normal serum potassium is strictly controlled within a narrow range, 3.5–5.3 mmol/L, and is commonly assayed to identify renal disease and monitor electrolyte balance (Table 1).

Elevated serum potassium concentrations (hyperkalemia) may result in severe cardiac arrhythmias and cardiac arrest. However, this situation is not likely to occur by dietary means in an individual with normal circulation, intestinal, and renal function. Since the renal system is the primary (~90%) excretion route, lowered renal function predisposes the patient to hyperkalemia. Another well-known condition that increases the risk of hyperkalemia is diabetes mellitus. Extracellular potassium is taken up intracellularly by insulin action, and deficient insulin activation in diabetes leads to an increase in serum potassium *(39)*. Hypokalemia, on the other hand, is common among hospitalized patients and may occur with severe vomiting and diarrhea. It is common that hypokalemia coexists with hyponatremia and hypomagnesemia *(40)*. Hypokalemia is associated with muscular weakness, nervous irritability, and mental disorientation and in severe cases may result in cardiac arrhythmias and paralysis.

3.2.1. DRUG INTERACTIONS

Common drugs that cause potassium deficiency include thiazide and loop-type diuretics and laxatives (Table 3). Potassium and magnesium deficiencies due to diuretics are often not detectable using the standard methods of serum analysis and may occur in spite of potassium supplements *(41)*. Increased serum potassium levels have been reported with use of β-blocking drugs in conjunction with potassium-sparing diuretics *(42)*. Hyperkalemia may also occur with drugs like ACE inhibitors, angiotensin receptor blockers, salt substitutes, β-blockers, potassium-sparing diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), and heparin, among others. The development of hyperkalemia following hypokalemia is not uncommon and may be prompted by potassium supplementation, potassium iodide, potassium-sparing diuretics, parenteral nutrition (source of potassium), and magnesium supplementation (which may reduce kaliuresis) *(40)*. The presence of two or more of these medications is associated with an even faster development of hyperkalemia. Particular care must be taken in prescribing these to the elderly and patients with diabetes or renal impairment *(39)*.

3.3. Calcium

Calcium is the most abundant divalent cation in the human body, averaging about 1.5% of total body weight. Approximately 99% of the body's calcium is in bones and teeth, and the remaining 1% is in both the intracellular and extracellular fluids. Normal serum calcium concentrations range from 2.2 to 2.6 mmol/L (8.5–10.5 mg/dL) in adults (Table 1). Because total serum calcium concentrations are tightly regulated, its measurement tells little about calcium status. Serum *ionized* calcium better reflects alterations in calcium metabolism.

About 30% of dietary calcium is absorbed in the intestine via two main transport processes. In the duodenum and the proximal jejunum, a saturable, energy-dependent process occurs, which is regulated by calcitriol (1,25-dihydroxyvitamin D) and involves a calcium-binding protein that transports the cation through the cell *(43)*. The other process occurs throughout the small intestine and is nonsaturable and does not require energy. In this process, calcium is absorbed between the cells (rather than through them). The large intestine contributes to approximately 4% of dietary calcium absorption. Calcium is absorbed in its ionized form; therefore, it must be released from the insoluble salts in which it is presented in food and dietary supplements. Even though most calcium salts are dissolved in the acidic pH of the stomach, absorption is not guaranteed since calcium may form insoluble complexes with other dietary components within the more alkaline pH found in the small intestine, limiting its bioavailability. One such component is fiber. Magnesium and calcium compete for intestinal absorption when an excess of either is present in the intestinal tract.

Excessive oxalate consumption in situations where calcium or magnesium is unavailable (e.g., with consumption of aluminum hydroxide gels that bind calcium and magnesium) may lead to formation of kidney stones and interstitial renal failure. In addition, kidney stones have been associated with excessive dietary salt and protein intakes rather than excessive dietary calcium *(32)*.

3.3.1. DRUG INTERACTIONS

Furosemide, ethacrynic acid, triamterene, and other diuretics produce significant hypercalciuria. Furosemide has been utilized to control symptoms of hypercalcemia and has been observed to increase parathyroid hormone levels as it increases urinary calcium excretion *(44,45)* and this has been associated with renal calcification *(46)*. Thiazide diuretics (e.g., hydrochlorothiazide), on the other hand, cause renal calcium retention by stimulating calcium transport across the epithelial cells of the distal tubule and can cause hypercalcemia, although this side effect may only be transient. However, thiazide users do have a greater bone mineral content than do age- and sex-matched nonusers *(47)*. It has been suggested that thiazide drugs might have a therapeutic role in the management of osteoporosis *(48)*.

Indirectly, calcium status may be affected by long-term intake of antiepileptic drugs (Table 2). These medications, particularly phenobarbital and phenytoin, may induce vitamin D deficiency *(49)*, which in turn is expected to impair intestinal calcium absorption. More recently, it has been reported that epileptic patients under treatment have low bone mass in the absence of vitamin D deficiency *(50)*. Vitamin D deficiency, and therefore decreased calcium absorption, can also occur with medications that impair fat absorption such as antiobesity medications (e.g., orlistat) and hypolipidemic agents (e.g., cholestyramine). Gentamicin has been associated with hypocalcemia in humans *(51)*. Nevertheless, excess oral calcium supplementation may reduce gentamicin-induced kidney damage *(52)*. Prednisone and other glucocorticoids cause calcium malabsorption and increased renal excretion that may lead to bone loss and secondary hyperparathyroidism *(53)*. The immunosuppressant drug cyclosporine has metal-binding properties, with a high affinity for calcium and a somewhat lower affinity for magnesium and potassium *(54)*, which may reduce serum levels. Calcium carbonate has been shown to attenuate the absorption of certain medications, including ciprofloxacin *(55)* as well as other antibiotics, NSAIDs, and some β-blockers (Table 4). Proton pump inhibitors (e.g., lansoprazole, omeprazole, rabeprazole), which are used to treat ulcers, when taken concomitantly with calcium carbonate or calcium phosphate, can cause decreased absorption of these calcium salts and is associated with increased risk of hip fracture *(56)*.

3.4. Phosphorus

Phosphorus is second only to calcium in abundance among the inorganic elements in the human body. Approximately 85% is in the skeleton and the remainder is associated with organic substances of soft tissue. Approximately 55–70% of dietary phosphorus is absorbed with normal dietary intakes, and this may increase to 90% when intake is low or in infants and children *(57)*. Phosphorus absorption occurs in its inorganic form throughout the small intestine by a saturable, carrier-mediated active transport system or a linear, concentration-dependent diffusion process. Maintenance of phosphorus balance is achieved mainly through renal excretion. Magnesium, aluminum, and calcium impair phosphorus absorption. In adults, plasma inorganic phosphate ranges between 0.7 and 1.4 mmol/L (2.3 and 4.3 mg/dL) (Table 2); however, this varies largely with dietary phosphate content, age, growth, time of day, hormones, and renal function. Because of the widespread availability of phosphorus in food, deficiencies are rare and therefore status assessment is not a major consideration. In addition, evaluation of serum phosphorus concentrations lacks sensitivity and specificity and may be affected by several confounding factors unrelated to phosphorus status.

3.4.1. Drug Interactions

Aluminum hydroxide and sevelamer combine with phosphates in the intestine to form nonabsorbable products that are then excreted in the feces. The prolonged use of antacids containing nonabsorbable aluminum and magnesium hydroxide may result in hypophosphatemia *(58)* (Table 3). Phosphate depletion with the use of antacids has been described to cause bone demineralization and osteomalacia and rickets and symptoms of malaise and bone pain associated with hypophosphatemia and hypercalciuria *(59,60)*. These products are actually used to correct

Table 2
Clinical Assessment of Ultratrace Minerals

Mineral *Daily Adult RDA or AI*	*Symptoms* *Deficiency*	 *Toxicity*
Chromium Meat, unrefined foods, Brewer's yeast, beer RDA: 20–35 μg	Diabetes-like condition, reduced glucose control	Rare
Selenium Seafood, organ meat, meat, grains, certain vegetables RDA: 55 μg	Higher risk for heart disease, cardiomyopathy, increased red blood cell fragility, poor growth, muscle pain	Nausea, abdominal pain, nail and hair changes, nerve damage
Fluorine (fluoride) Drinking water, tea, seafood, toothpaste AI: 4 mg (M); 3 mg (F)	Dental caries, osteoporosis	Fluorosis (pitting and discoloration of teeth, skeletal osteosclerosis), nausea, diarrhea, itching, vomiting
Iodine (I) Iodized salt, seafood, plants grown in high I soil, and animals fed with high I plants RDA: 150 μg	Goiter, cretinism, myxedema, increased blood lipids, liver gluconeogenesis, retention of NaCl and water	Decreased thyroid activity, goiter-like enlargement
Manganese Most foods AI: 1.8 mg (M), 2.3 mg (F)	None reported in humans, possibly impaired growth, skeletal abnormalities, impaired central nervous system, defects in lipid and carbohydrate metabolism	Rare; nervous system disorders
Molybdenum Legumes, grains, dark green leafy vegetables, organ meat RDA: 45 μg	Rare; induces increased uric acid and xanthine excretion, mental disturbances, coma, hypermethioninemia	None reported

AI (adequate intake level for nonpregnant adults); F (female); M (male); NaCl (sodium chloride); RDA (recommended dietary allowance for nonpregnant adults)

hyperphosphatemia associated with chronic kidney disease. Calcium acetate or calcium carbonate are less frequently used as phosphate-binding agents in people receiving hemodialysis with hyperphosphatemia.

3.5. Magnesium

Magnesium is the second most abundant intracellular cation after potassium. A total of 21–28 g of magnesium is distributed between bone (60%) and extracellular fluids and soft tissues (40%). Magnesium absorption occurs throughout the entire small intestine. Absorption in the ileum appears to be saturable. Typical ingested amounts via the diet are absorbed by a saturable, carrier-mediated, facilitative transport system, with an efficiency of approximately 30–60%, which is expected to increase when magnesium status is poor and/or intake is low. Magnesium absorption is influenced by a variety of dietary factors (phytate, fiber, fatty acids).

Even though the homeostatic mechanisms are unclear, concentrations of magnesium are maintained by the kidney and the small intestine. Under conditions of magnesium deprivation, both organs increase retention of the mineral. Intestinal absorption, renal excretion, and transmembranous cation flux rather than hormonal regulation seem to be involved. Vitamin D increases magnesium absorption, but it is less relevant than its role in regulating calcium absorption. If magnesium depletion continues, the bone store contributes by exchanging part of its content with extracellular fluid. Serum magnesium can be normal in the presence of intracellular depletion of the mineral, but low serum levels usually indicate significant magnesium deficiency *(61)*.

Magnesium status is difficult to assess because only about 1% of total body magnesium is located extracellularly, and since it is homeostatically regulated, normal serum levels of 0.7–1.0 mmol/L (1.8–2.3 mg/dL) (Table 2) may occur in the presence of intracellular deficit. Magnesium status may be assessed by renal magnesium excretion after an intravenous magnesium load, where deficiency is revealed by a decreased excretion over two 24-h periods following the magnesium load.

3.5.1. Drug Interactions

Magnesium and potassium deficiency may coexist with some diuretic drug therapies. Many drugs such as loop and thiazide diuretics, aminoglycosides, cisplatin, pentamidine, and foscarnet can cause increased urinary loss of magnesium and subsequent deficiency *(61,62)* (Table 3). Magnesium deficiency is also seen with other drugs (see Table 3). When drugs classified as inducing "significant" hypomagnesemia (i.e., cisplatin, amphotericin B, cyclosporine) are administered, routine magnesium monitoring is warranted and routine magnesium supplementation should be initiated *(63)*. There are other drugs that may induce hypomagnesemia (i.e., aminoglycosides, laxatives, pentamidine, tacrolimus, carboplatin), where magnesium monitoring is justified but not routine magnesium supplementation.

High serum magnesium may occur in response to drugs (Table 3). A case was reported *(64)* where repetitive doses of the antacid aluminum magnesia for epigastric pain following bone marrow transplantation lead to hypermagnesemia with hypotension, hypothermia, and coma. It is noted that magnesium imbalance may be exacerbated in the posttransplant period with poor nutritional intake and other concomitant health problems. In a randomized trial with eight healthy people, 850 mg magnesium hydroxide increased glipizide absorption and activity *(65)* (Table 4). In theory, such changes could be therapeutic or detrimental under varying circumstances, and people taking glipizide should consult with their health-care provider before taking magnesium supplements.

Table 3
Potential Mineral Interactions due to Medications or Ethanol

Mineral	*Malabsorption*	*Risk of Tissue and/or Serum Mineral Depletion*	*Increased Risk of Mineral Retention*
Sodium	Colchicine, laxative overuse	Hydrochlorothiazide, loop diuretics (bumetanide, ethacrynic acid, furosemide), ACE inhibitors (captopril, enalapril, quinapril), lithium, tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, opioids, conventional and atypical antipsychotics, sulfonylureas, clofibrate, carbamazepine, nicotine, antineoplastic agents (i.e., cisplatin), vasopressin, oxytocin	Antacids with sodium bicarbonate, NSAIDs (ibuprofen, celecoxib, etodolac, indomethacin), estrogens, corticosteroids
Potassium	Colchicine, laxatives (mineral oil, bisacodyl, docusate, senna) neomycin	Thiazide and loop diuretics, amphotericin B, bronchodilators (terbutaline, albuterol), aminoglycosides (gentamicin, tobramycin), felodipine, corticosteroids, chemotherapy (cisplatin), digoxin, haloperidol, laxatives, thioridazine, ipecac abuse, licorice, lithium, aspirin, ethanol	Potassium-sparing diuretics (triamterene, amiloride, spironolactone), β-blockers (atenolol, betaxolol, labetalol, metoprolol, propranolol), ACE inhibitors, losartan, heparin, NSAIDs, haloperidol, sulfamethoxazole

Table 3
(continued)

Calcium	Bile acid sequestrants (colestyramine, colestipol), primidone, corticosteroids (prednisone), diphosphates, methotrexate, antibiotics (neomycin, cycloserine, erythromycin, minocycline), glutethimide, sulfonamides (trimethoprim, sulfamethoxazole), mineral oil, orlistat[a], antiepileptics (phenobarbital, phenytoin)	Loop diuretics, triamterene, aminoglycosides, corticosteroids, felodipine, albuterol, indomethacin, cisplatin, isoniazid, thyroid hormones, cyclosporine, Al-containing antacids	Bisphosphonates[b] calcium acetate, NSAID (diclofenac[b]), estrogens,[b] hydrochlorothiazide,[b]oral contraceptive,[b]sucralfate
Phosphorus	Mineral oil	Antacids (aluminum- or magnesium hydroxide and calcium carbonate), albuterol, phosphate binders, cisplatin, indomethacin, sucralfate	
Magnesium	Antibiotics (gentamicin, amikacin, tobramycin, amphotericin B), cisplatin, carboplatin, sulfonamides, bisphosphonates, mycophenolate agents, potassium phosphate, sodium phosphate, laxatives, pentamidine, tacrolimus, ateviridine	Thiazide and loop diuretics, nitrofurantoin,** albuterol, amphotericin B, cyclosporine, isoniazid, pentamidine, foscarnet, corticosteroids, cisplatin, digoxin,* felodipine, sotalol,[a] quinidine, aminoglycosides, metformin, ethanol, oral contraceptives	Laxative overuse (epsom salts, aluminum magnesia), potassium-sparing diuretics,[a] estrogens,[a] medroxyprogesterone,[a] mixed amphetamines
Iron	Magnesium hydroxide-containing antacids, cholestyramine, H_2 blockers (cimetidine famotidine, ranitidine), tetracyclines, neomycin, penicillamine, haloperidol, zinc	Aspirin, NSAIDs, haloperidol, deferoxamine, stanozolol	Oral contraceptives

(*Continued*)

Table 3
(continued)

Mineral	*Malabsorption*	*Risk of Tissue and/or Serum Mineral Depletion*	*Increased Risk of Mineral Retention*
	salts, ACE inhibitors, anti-Parkinson's disease treatments, levothyroxine		
Copper	Zinc salts, H_2 blockers, ACE inhibitors, ciprofloxacin	Penicillamine, zidovudine, valproic acid, allopurinol[a]	Oral contraceptives
Zinc	Cholestyramine	Thiazide and loop diuretics, penicillamine, tetracycline, zidovudine, ACE inhibitors, corticosteroids, aspirin, ethanol, oral contraceptives, valproic acid, *N*-acetyl cysteine, calcium acetate[a]	Zinc lozenge overuse, estrogens,[a] medroxyprogesterone, methyltestosterone[a]

Mineral deficiency (*) or mineral excess (**) influences drug effectiveness.

[a] Evidence is considered preliminary; clinical significance remains questionable.

[b] May help maintain a positive calcium (and bone) balance; evidence for bisphosphonates is preliminary.

Examples are given in parentheses; clinician should check mineral levels, and supplementation can be advised. Since most antibiotics are usually given for 2 weeks or less, deficiency of minerals is not usually a problem

Table 4
Medication with Absorption/Activity Affected by Minerals

	Ca	*Mg*	*Fe*	*Cu*	*Zn*
Antibiotics					
Azithromycin		↓			
Nitrofurantoin		↓			
Tetracycline, minocycline, doxycycline	↓	↓	↓		↓
Fluroquinolones (ciprofloxacin)	↓	↓	↓	↓	↓
Antihypertensive Therapy					
ACE inhibitors			**	↓	
β-blocker (nadalol, sotalol)	↓				
Diuretics	+	↓			
Centrally acting (methyldopa)		↓	↓		
Analgesic and/or anti-inflammatory					
NSAIDS (ibuprofen)			*	+	
NSAID–COX2 (rofecoxib)	↓				
Opioids (fentanyl)		+			
Chlorhexidine					+
H_2blockers					
Cimetidine		↓	↓		
Famotidine		↓			
Estrogens	+				
Miscellaneous used in rheumatoid arthritis					
Penicillamine			↓	↓	↓
Sulfasalazine			↓		
Hydroxychloroquine		↓			
Anticoagulant (warfarin)		↓	↓		↓
Antidiabetic (glipizide)		↓			
Bile acid sequestrants (cholestyramine)	↓		↓		
Bisphosphonates (alendronate, risedronate).	↓	↓	↓		↓
Thyroxine (levothyroxine)	↓				
Antiepileptics	↓				
Glucocorticoids	↓				↓
Other: digoxin	+				

↓: Reduces absorption or activity
+: Increases activity of drug
*: Iron should not be used concurrently with NSAIDs due to GI irritation
**: Iron inhibits cough associated with ACE inhibitors
There are many drug interactions and not every drug within a class is listed

The long list of drug interactions with magnesium and calcium makes these minerals (Tables 3 and 4) particularly susceptible to deficiency and/or interacting with the efficacy of a particular drug *(66,67)*. Hence, for patients on multiple drugs, careful monitoring and/or timing of supplementation should be considered.

4. TRACE AND ULTRATRACE MINERALS

Trace minerals are those that occur in microgram amounts per gram of tissue and are required in the diet in milligram doses per day. The trace minerals include copper, iron, and zinc. Ultratrace minerals are typically required in the diet in microgram amounts per day and include arsenic, boron, cadmium, chromium, cobalt, fluorine, iodine, lead, lithium, manganese, molybdenum, nickel, silicon, selenium, and vanadium. Some of the ultratrace minerals have been studied more than others and are considered essential in the diet (chromium, manganese, molybdenum, selenium, fluorine, iodine), while the functions of others are less clear and toxicity is a greater concern. Included here is a discussion of iron, copper, zinc, chromium, selenium, fluoride, and iodine, and Tables 1 and 2 include information about these minerals as well as manganese and molybdenum.

4.1. Iron

The most common form of anemia is iron-deficiency anemia, resulting from an inadequate iron supply for erythropoiesis *(68)*. The number of red cells in the blood stream is related to iron levels, and the red cell's function of carrying oxygen depends on its hemoglobin content. Body iron is contained primarily in hemoglobin, which is the most abundant and easily sampled of the heme proteins *(69)*. Iron is found mainly in a trivalent form as ferric oxide or hydroxide or its polymers. Iron absorption is very limited unless these salts can be solubilized and ionized by the intestinal contents to ferrous salts. The amount of iron absorbed from food can vary from 1% to more than 50%. Iron absorption depends on the constituents of the diet, on the type of iron compound present, and on the body's physiological need for iron, which is regulated by the intestinal mucosa. Under conditions of iron depletion, which exist for many women and children, the intestinal mucosa increases iron uptake efficiency, especially that of the nonheme iron *(70)*. If the body is iron replete, the percentage of iron absorbed will be low. Iron overload is thus prevented.

The availability of iron from food depends on its source (Table 2). For example, Asian diets contain a soybean inhibitor that adversely affects iron absorption *(71)*. Tannins, phytates, certain fibers (not cellulose), carbonates, phosphates, zinc, manganese, and low-protein diets also negatively impact iron absorption. In contrast, ascorbic acid, fructose, citric acid, stearic acid, high-protein foods, lysine, histidine, cysteine, methionine, and natural chelates (e.g., heme) all enhance the apparent absorption of iron. In addition, iron overload can result from a genetic disorder, hemochromatosis, which is associated with increased absorption of iron *(72)*. Iron stores are best evaluated with serum ferritin concentration *(73)*, but are also assessed with serum transferrin, red blood cell count, hemoglobin and by red blood cell size and color *(74)*.

4.1.1. DRUG INTERACTIONS

Drugs that interact with iron include the dopa drugs (methyldopa, levodopa, carbidopa), ciprofloxacin, penicillamine, and trientine. Thyroxine and ACE inhibitors form stable complexes with iron *(75)* (Table 3). Iron-dependent oxidative stress, elevated levels of iron and of monoamine oxidase (MAO)-B activity, and depletion of antioxidants in the brain may be major pathogenic factors in Parkinson's disease, Alzheimer's disease, and related neurodegenerative disease *(76)*.

Aspirin use has been associated with lower serum ferritin in subjects with inflammation, infection, or liver disease *(77)*. In addition, high pH induced by antacids may form iron aggregates and convert iron to its ferric form, decreasing absorption *(78)*. Aluminum hydroxide gels bind iron, also decreasing its absorption; however, certain antacids may not reduce the efficacy of iron absorption. Bile acid sequestrant drugs (e.g., cholestyramine, colestipol) may reduce the absorption of iron. Medications used to treat ulcers or other stomach problems, including histamine (H_2-receptor) blockers (e.g., cimetidine, ranitidine, famotidine, nizatidine), change the pH in the stomach and subsequently alter the absorption of iron. It is possible that this effect could also occur with other antiulcer medications including antacids and proton pump inhibitors (e.g., omeprazole, lansoprazole). Iron levels may be increased by oral contraceptive medications. Body iron stores as well as its bioavailability in tissue may be important independent predictors of risk of cardiotoxicity in man *(79)*. Iron ion preparations administered concomitantly with mycophenolate mofetil, an immunosuppressive agent, may decrease its absorption *(80)* but more recently, this has been refuted *(81)*.

4.2. Copper

Copper is absorbed by the small intestine and is typically in the range of 30–40%. A small fraction of dietary copper is solubilized in the stomach, but its absorption at that site is not considered to be nutritionally significant. The absorption of copper varies inversely with copper intake and can be as low as 12% with very high copper intakes *(82)* to a theoretical maximum absorptive capacity of 67%. In developed societies, these extremes in absorption would be rare. Copper absorption is believed to be equally distributed along the small intestine and occurs through a rate-limiting active transport and diffusion component. The enterohepatic circulation is important for copper balance. Approximately 50% of the copper reaching the small intestine reappears in the bile and is lost in the stool. After absorption, copper is primarily bound to albumin and transported to the liver. Once copper reaches the liver, it is distributed throughout the body primarily by the copper transport protein, ceruloplasmin, with smaller amounts bound to albumin and other minor copper binders.

Copper salts including chloride, acetate, sulfate, and carbonate are highly bioavailable, with the exception of copper oxide. In general, the macronutrients and foods that will increase copper intestinal absorption include protein and polybasic amino acids, whereas a decrease in copper absorption has been shown with hemicellulose, fructose long-chain fatty acids, and a vegetarian diet *(83,84)*. Copper absorption and bioavailability are reduced in the presence of divalent cations including zinc, iron, tin, and molybdenum. Copper and these minerals are antagonistic, following classical pharmacologic responses *(85)*. Age is an important determinant of copper absorption. A steady increase in serum copper levels has been reported from childhood to old age *(86)*, but this increase is not likely due to an increased copper absorption *(83)*. Although normally bound to proteins, copper may be released and become free to catalyze the formation of highly reactive hydroxyl radicals in environmental exposure and cause oxidative damage associated with neurodegenerative changes. Interestingly, a deficiency in dietary copper also increases cellular susceptibility to oxidative damage *(87)*. Copper status is measured in the serum with normal adult levels ranging from 65 to 150 μg/dL (10–24 μmol/L).

4.2.1. DRUG INTERACTIONS

Copper absorption is blocked by zinc salts (see Section 4.3). Penicillamine, zidovudine, and valproic acid have been shown to deplete serum copper levels (Table 3) *(88)*. Copper supplementation may enhance the anti-inflammatory effects of NSAIDs, while reducing their ulcerogenic effects *(89)*. Both iron and copper decrease the absorption of ACE inhibitors, though the binding sites may differ *(90)*. Allopurinol, a medication used to treat gout, may reduce copper levels. The H_2-receptor blockers lower copper absorption. There is evidence that stomach acid is needed for optimal absorption of copper. Long-term use of H_2-receptor blockers may therefore promote a deficiency of these nutrients *(91)*. Oral contraceptives and estrogen replacement for postmenopausal women can increase blood levels of copper. Therefore, copper supplements are not appropriate in women taking either of these.

Copper should be avoided when taking the antibiotic ciprofloxacin, since it may decrease absorption of this fluoroquinolone *(92)*. The interaction occurs due to other minerals too (Table 4) and can be reduced by taking ciprofloxacin 2 h after consuming mineral-containing supplements *(93)*.

4.3. Zinc

The low pH of the stomach results in the release of bound zinc into its free form but none is absorbed in the stomach. In man, zinc absorption occurs from the duodenum to the ileum, with the greatest absorptive capacity in the jejunum. Zinc is typically absorbed at a rate of 15–30%. At high zinc intakes, zinc absorption may be inhibited by the production of intestinal cell metallothionein, a zinc-binding protein. Zinc salts are regularly used for the treatment of Wilson's disease, an inherited disease of copper accumulation and toxicity in brain and liver. Zinc's mechanism of action in blocking copper absorption is due to metallothionein. Although metallothionein also blocks zinc absorption, it is believed that copper has a higher affinity for metallothionein than zinc. After absorption, copper and zinc are bound to albumin in the serum and transported to the liver. Zinc is repackaged and released into circulation bound to α2-macroglobulin. In circulation, zinc is bound to albumin (57%), α2-macroglobulin (40%), and low-molecular-weight ligands such as amino acids (3%). Zinc uptake into cells is carrier mediated and energy independent, but the specific mechanisms are not known *(94)*. In tissues, zinc is often bound to metalloenzymes involved in the degradation of the extracellular matrix and possibly involved in the process of tumor growth *(95)*.

Zinc is normally consumed in the form of organic complexes with protein and its content correlates with protein level. It is well known that the bioavailability of zinc from plant sources is poor compared to animal sources. Dietary supplements are typically in the form of zinc sulfate, acetate, or gluconate, which are better absorbed than zinc phosphate, citrate, or carbonate. Fibers and phytates (found in grains, cereals, and vegetables) will decrease zinc bioavailability. Other metals will also interfere with Zn absorption, such as aluminum salts (widely used as an antacid), phosphorus, and tin. Zinc deficiency may contribute to anemia, which has been shown to be correctible by combined iron and zinc supplementation, although iron or zinc supplementation alone was only marginally effective *(96)*. Zinc interferes with calcium, magnesium *(97)*, copper, iron *(98)*, and selenium bioavailability *(99)*. Since copper deficiency may influence anemia, lower levels of HDL cholesterol, or cardiac arrhythmias, copper intake should be increased if zinc is taken for more than a few days (except for patients with Wilson's disease) *(100)*. Serum zinc levels do not normally change in most healthy people except under conditions of extreme deficiency (Table 2). Urinary zinc levels can be confounded due to contamination and disease states that increase its excretion *(101)*. A zinc tolerance test requires the subject to ingest 200 mg zinc sulfate (45 mg elemental zinc) after an overnight fast with blood draws at 2, 4, and 6 h after ingestion.

4.3.1. Drug Interactions

Cholestyramine reduces plasma cholesterol because of its ability to sequester intestinal bile acids. Metabolic alterations, including diminished intestinal absorption of vitamin D, have been reported with long-term use of cholestyramine and may negatively affect magnesium balance, as well as calcium, iron, and zinc balance *(102)*. Zinc status is also altered by many other drugs including aspirin, diuretics, and corticosteroids (Table 3).

Zinc interferes with the gastrointestinal absorption of a number of drugs. Taking zinc at the same time as tetracyclines inhibits the absorption of the antibiotic *(103)* (Table 4). Benzamycin, a topical combination of benzoyl peroxide and erythromycin, is used to treat acne. Using topical erythromycin with a zinc solution increases the efficacy of the antibiotic in the treatment of inflammatory acne *(104)*. People taking penicillamine should not supplement with zinc since the supplement may decrease the absorption and/or the activity of the medication in the body *(105)*. Similar to the effect of iron and copper, individuals taking ACE inhibitors for hypertension may also experience decreased zinc absorption. It is prudent for people taking these inhibitors long term to consider taking a multimineral tablet preemptively. To guard against a zinc-induced copper deficiency, supplements containing zinc should also contain copper *(106)*. Calcium acetate is used to prevent high phosphorus blood levels in people with kidney failure. However, taking this drug together with zinc may reduce absorption of zinc *(107,108)* and therefore zinc supplements are recommended. *N*-acetyl cysteine (NAC) may increase urinary excretion of zinc. Long-term users of NAC may consider adding supplements of zinc and copper *(109)*.

There is some evidence that zinc supplementation enhances the response to certain drugs, including interferon therapy in patients with chronic hepatitis C *(110)* (Table 4). In addition, zinc enhances the effects of zidovudine, used to treat

HIV infection. A study found that adding 200 mg zinc per day of treatment in AIDS patients decreased the number of *Pneumocystis carinii* pneumonia and *Candida* infections compared with people treated with zidovudine alone *(111)*.

Chlorhexidine is an antimicrobial used to prevent and treat gingivitis. Using a zinc solution at the same time as chlorhexidine may increase the antiplaque activity of the drug *(112)* and may reduce the possibility of staining *(113)*. Whether taking a zinc supplement at the same time as chlorhexidine produces the same beneficial effects is unknown. Zinc supplementation may be protective against taste alterations caused or exacerbated by irradiation, especially of head and neck cancers *(114)*. However, using zinc nasal spray has been associated with severe or complete loss of smell *(115)*. During menopause, women are at risk of nutritional disturbances, but women on hormone-replacement therapy have been shown to have improved serum copper, zinc, magnesium, and calcium levels *(116)*. A study showed that taking methyltestosterone increased the amount of zinc in the blood and hair of boys with short stature or growth retardation *(117)*. Methyltestosterone is also used in men to treat testosterone deficiency and in women to treat breast cancer and swelling following pregnancy and menopause.

4.4. Chromium

Dietary chromium primarily exists as trivalent chromium [chromium(III)] in the food supply *(118)*. Chromium salts differ substantially in solubility, which in turn determines the absorption and utilization of this mineral. Similar to other minerals, its absorption is increased by vitamin C *(119)*. It is widely available in a variety of foods; the RDA for chromium has been set at 20–35 μg/day (Table 2). Chromium is needed for optimal action of insulin at target tissues. Chromium, in a form called chromium picolinate, has been studied for its potential role in altering body composition with inconclusive results, thus far. One clinical trial in type 2 diabetics found, however, that chromium picolinate helps to normalize glycosylated hemoglobin, blood glucose, and serum cholesterol levels *(120)*. Importantly, a meta-analysis shows that there is no effect of chromium on glucose or insulin concentrations in nondiabetic subjects. The data for persons with diabetes are inconclusive *(121)*. Excessive chromium picolinate should be avoided since it can be altered by antioxidants or hydrogen peroxide in the body and cause free radical damage *(122)*. Several cases of toxicity have been reported from megadoses of chromium picolinate (>600 μg per day) *(123)*.Taking more than 300 μg per day of chromium without the supervision of a doctor is ill advised.

4.4.1. DRUG INTERACTIONS

Chromium tablets taken together with hypoglycemic agents require monitoring, since supplements can reduce the need for insulin and oral agents. Therefore, hypoglycemia can result if a patient's drug dosage is not adjusted *(124)*. The administration of 16,16-dimethyl prostaglandin E_2 may decrease chromium absorption *(125)*. Preliminary data suggest that corticosteroid treatment increases chromium loss *(126)*. Finally, there is also preliminary evidence that chromium enhances mood in people taking sertraline *(127)*, which is typically used for depression.

4.5. Selenium

Selenium has both essential and toxic properties with a narrow range of intake between the two. Selenium is instrumental in the detoxification of peroxides and free radicals. The absorptive efficiency of selenium is high. Selenium is transported on the very-low- and low-density lipoproteins. Normal blood values for adults range from 55 to 72 μg/L. People with disorders that are manifested by increased oxidative stress to the red cell (i.e., β-thalassemia, diabetes, and/or smoking) tend to have slightly lower blood selenium levels. Toxicity is rare unless the individual has excess intake or is exposed to environmental sources of selenium. Selenium deficiency is rare in the United States. This is not the case in China (Keshan disease) and other parts of the world where food choice is restricted to locally grown items from soils deficient in selenium. Both selenium and iodine deficiency are associated with impaired thyroid function, which in turn results in poor growth, reduced mental capacity, and decreased longevity. Selenium deficiency has been demonstrated in premature infants *(128)* and in persons using long-term selenium-free enteral or parenteral nutrient solutions *(129)*. Selenium enhances the antioxidant effect of vitamin E. Although most research suggests that selenium prevents cancer, one study found an increased risk of squamous cell carcinoma in people taking selenium supplements *(130)*. The National Academy of Sciences recommends that selenium intake should not exceed 400 μg per day, unless the higher intake is monitored by a health-care professional *(131)*.

4.5.1. Drug Interactions

Clozapine is a neuroleptic used to control symptoms of schizophrenia when other treatments are ineffective. One controlled study showed that taking clozapine can decrease blood levels of selenium *(132)*. More research is needed to determine whether people taking clozapine require selenium supplementation. Valproic acid, which is used to manage epilepsy, is thought to decrease selenium levels *(133)*, yet a recent study in epileptic children shows no alterations of serum selenium with valproic acid *(134)*. Oral corticosteroids have been found to increase urinary loss of selenium *(135)*, but its clinical importance is not clear.

Selenium may reduce drug- or nutrient-induced oxidative stress *(136)*. In one study, administration of a selenium product (Seleno-Kappacarrageenan) reduced the kidney damage and white blood cell-lowering effects of cisplatin *(137)*.Others found that selenium supplementation prevents cisplatin resistance in patients with ovarian tumors *(138)*. The amount of selenium used in these studies may be toxic and should be used only under the supervision of a physician. Simvastatin and niacin have been shown to lower LDL cholesterol and raise HDL cholesterol yet may be less effective in raising HDL cholesterol when taken with antioxidants (including selenium) *(139)*.

4.6. Fluoride

Fifty percent of fluoride is absorbed within 30 min after ingestion. Without simultaneous ingestion of calcium and other cations that may form insoluble compounds with fluoride, 80% may be absorbed *(140)*. Body fluid and tissue levels of fluoride concentrations are proportional to long-term intakes rather than homeostatic regulation. Fluoride is largely (~99%) bound to calcified tissues in the body. About 50% of absorbed fluoride is eliminated by the kidneys in the urine, whereas in young children, only 20% may be excreted, while the rest is retained for the developing bone and teeth *(141,142)*. Fluoride deficiency has been prevented with water fluoridation, mineral supplementation, and topical fluoride products. In general, fluoride has a high bioavailability from water and toothpaste but if consumed with other divalent or trivalent cations, absorption may be reduced up to 25% *(143)*. However, fluoride ingestion from toothpaste may result in intakes equaling those ingested from food sources in young children, thus possibly reaching recommended upper limits *(144,145)*. The primary adverse effect of chronic excess fluoride intake is fluorosis *(146)*. At a water fluoride level of 1 part per million (or 1 mg/L), roughly 13% will have enamel fluorosis. Enamel fluorosis is considered only a cosmetic concern, as it causes the teeth to be a brownish color with surface irregularities and may be more resistant to dental caries. In children, this occurs due to high fluoride intakes before the teeth erupt (<8 years of age).

In skeletal fluorosis, early signs may be an increased bone mass, stiffness, or pain in joints, leading to osteosclerosis, muscle wasting, neurological defects *(98)*, and osteoarthritis *(147)*. Although much research has been done concerning the safety of water fluoridation, early studies showed some evidence of an increased fracture risk. However, more recently a pooled analysis of 29 studies found no increased risk of fracture in areas of water fluoridation and concluded that the earlier studies were low in quality *(148,149)*.

4.6.1. Drug Interactions

Fluoride (in the form of monofluorophosphate) taken in combination with estrogens produces a beneficial synergistic effect on bone mass *(150)*. In addition, sodium benzoate and many compounds in tea, such as tannin, catechin, and caffeine in combination with fluoride, may reduce dental caries but these studies need to be confirmed in human trials *(151)*.In general, drugs do not interfere with fluoride absorption.

4.7. Iodine

Dietary iodide is rapidly and completely absorbed in the stomach and the intestinal tract, with minor amounts appearing in the feces *(152)*. Free iodide appears in the blood and is distributed in the extracellular fluid, concentrating in the thyroid, salivary, and gastric glands. The thyroid concentrates iodide, amounting to 70–80% of the total body iodide. Since there is no mechanism in the kidneys to conserve iodide, urinary output is up to 90% of total excretion of the mineral. Urinary iodide closely correlates with its plasma concentrations and has been used to monitor iodide status in populations. Iodide deficiency and depletion of thyroid iodine stores cause a reduction in thyroid hormone release and ultimately goiter. Several substances, called goitrogens, have been identified as capable of interfering with iodide metabolism and inhibiting thyroid hormonogenesis. Some examples of such compounds are halide ions (bromide and astatide), thiocyanate, perrhenate, pertechnetate, and perchlorate. Nutritional assessment of iodide is accomplished with physical examination (i.e., presence of goiter), quantification of urinary iodide excretion, and determination of serum thyroxine. Radioactive iodide uptake by the thyroid gland may be measured. A high and quick overall iodide uptake suggests iodide deficiency.

4.7.1. DRUG INTERACTIONS

The antiarrhythmic amiodarone induces thyrotoxicosis, partly because of its rich iodine content *(153)*. These patients may have altered thyroid hormone profile without thyroid dysfunction, hypothyroidism, or thyrotoxicosis*(154)*. Interestingly, although considered generally very safe, cases of thyroid dysfunction have been reported with long-term treatment with the antiseptic povidone-iodine. Careful monitoring of thyroid dysfunction is recommended in patients treated with long-term povidone-iodine *(155)*. Lithium, used to treat psychiatric disorders, inhibits thyroid hormone release from the gland. Lithium blocks the release of iodine and thyroid hormones from the thyroid, thus enhancing the effectiveness of radioiodine therapy *(156)*. Additive hypothyroid effects may occur with the use of iodine products in combination with antithyroid drugs (i.e., methimazole, propylthiouracil).

4.8. Other Minerals

A number of other minerals have been shown to be essential, such as *manganese* and *molybdenum*, which are included in Table 2. Information about drug interactions for these two minerals is limited, but there is evidence that redox-active drugs, such as antibiotics, enhance manganese–superoxide dismutase activity *(157)*. *Arsenic*, a known poison, has been shown to be essential to chickens, rats, pigs, and goats, but its function in humans is unclear. It is thought to have a role in bone metabolism. Animals with arsenic deficiency display depressed growth, myocardial degeneration, and premature death. *Boron* is essential for rats, but its biological function is unknown. *Strontium* is not an essential mineral but has been shown to increase bone density when taken in the form of strontium ranelate *(158)*. However, excessive intakes will compete with calcium for absorption and may cause rachitic-like bone *(159)*. *Silicon* has been found essential to chickens and rats and seems to be involved in bone formation. Skeletal abnormalities typify silicon deficiency in these species. *Lithium* is a mineral that may be present in some supplements and is used to treat mood disorders. Taking celecoxib, ibuprofen, indomethacin together with lithium can result in significant increases in lithium blood levels *(160)*. Hence, NSAIDs should be used with caution in individuals taking lithium-containing drugs or supplements, and they should consult their health-care practitioner about having their lithium blood levels checked regularly.

Mercury is toxic, and exposure to this metal causes cutaneous and neurological symptoms. In 1997, the Food and Drug Administration Modernization Act identified food and drug products that contain intentionally introduced mercury compounds. Drug products with mercury include dandruff/seborrheic dermatitis/psoriasis products (mercury oleate); external analgesic products; poison ivy products (merbromin, mercurochrome); and stimulant laxatives (calomel or mercurous chloride). Many mercury compounds used in over-the-counter drug products have been found to be *not* generally recognized as safe and effective and are classified as new drugs. In 1999, the American Academy of Pediatrics and the US Public Health Service alerted clinicians and the public about thimerosal, a mercury-containing preservative used in some vaccines for children *(161,162)*. Mercury in dental fillings has also been implicated as potentially causing long-term toxic effects *(163)*. Chelating agents (i.e., dimercaprol) should be used for a symptomatic patient.

5. OTHER SUBSTANCES AFFECTING MINERAL STATUS

5.1. Ethanol

Excess alcohol consumption has been associated with malnutrition in general and studies have found alterations in several minerals. Higher hair zinc or copper values were found in 43 male alcoholics than in 39 controls; however, in that study, no relation was observed between hair zinc or copper and nutritional status *(164)*. Lower selenium status is found in heavy alcohol drinkers *(165)* and is associated with impaired liver function in cirrhotic alcoholics, which may be corrected by selenium supplementation *(166)*. Alcoholics also commonly present with magnesium deficiency, and short-term oral magnesium therapy has been observed to improve liver cell function, muscle strength, and electrolyte status (serum sodium, calcium, phosphorus, potassium, and magnesium) in these patients *(167)*. Chronic ethanol consumption also affects calcium status. Lower serum vitamin D metabolites and calcium levels below the reference limits have been observed in alcoholics without differences in serum PTH, phosphorus, or magnesium *(168)*. However, others have found that excessive ethanol consumption may lead to decreased magnesium levels *(169)*, by inhibiting intestinal absorption or by increasing the rate of excretion *(170)*. Overall, ethanol can lead to a number of nutritional deficiencies due to both direct and indirect (poor nutritional intake) causes.

5.2. Caffeine

Caffeine is found in coffee, tea, soft drinks, chocolate, guaraná (*Paullinia cupana*), nonprescription drug products, and many supplement products. Excess caffeine consumption is a concern in calcium nutrition since it not only increases urinary excretion but also impairs intestinal calcium absorption, both leading to a negative net calcium balance. It has been calculated that for each 6 fl oz serving of coffee (~100 mg caffeine), calcium balance is more negative by 4.6 mg/day. It has been observed that the harmful effects of caffeine on bone mass do not occur unless the person is drinking more than three cups of coffee per day with a calcium intake less than 800 mg/day *(171)*. Adding milk to coffee may be an easy way to offset this imbalance *(172)*. Ciprofloxacin may decrease the elimination of caffeine from the body, causing increased caffeine blood levels and unwanted actions *(173)*.

5.3. Smoking

There are few studies on the effect of cigarette smoking on mineral or other nutrient status in general, even though impaired nutrient status may contribute to the development of smoking-related diseases. Many oxidants and pro-oxidants contained in tobacco smoke are capable of producing free radicals and enhance lipid peroxidation in biological membranes. Therefore, nutrients involved in cellular antioxidant processes would be affected, such as vitamin C, β-carotene and vitamin E, and vitamins of the B complex.

Regarding mineral nutrition status, cadmium, which is present in tobacco, decreases the bioavailability of selenium and acts antagonistically to zinc, a cofactor for the antioxidant enzyme superoxide dismutase *(174)*. Smoking has been found to be a significant predictor of poor selenium status *(175)*. Additionally, circulating selenium may be influenced by smoking-associated elevated levels of inflammatory mediators such as interleukin (IL)-1, IL-2, IL-6, and IL-8.

The effect of cigarette smoking on calcium balance and bone has been studied more than other minerals and is associated with reduced bone mass and a higher rate of bone loss *(176)*. It is estimated that lifetime hip fracture risk is increased by 31% in women and 40% in men who smoke *(177,178)*. A decreased intestinal calcium absorption in smokers may be a contributing factor *(179)*. Serum ceruloplasmin concentrations and erythrocyte copper/zinc–superoxide dismutase activity are indices of copper status and are found to be elevated in smokers *(176)*, probably as the body's anti-inflammatory response to smoking. Although there is evidence of low hemoglobin in smokers, reduced serum iron levels are not consistently observed.

An inadequate diet may compromise nutritional status in smokers. Data from the Second National Health and Nutrition Examination Survey *(180)* indicate that smokers are less likely to consume fruits and vegetables, high-fiber grains, low-fat milk, and vitamin and mineral supplements than do nonsmokers. The high cancer risk associated with smoking may be compounded by a lower intake of cancer-protective nutrients. It is also possible that smokers have increased mineral and nutrient requirements. Interestingly, an epidemiological study *(181)* found that use of vitamin and mineral supplements may reduce fetal death risk associated with maternal smoking.

5.4. Illicit Substances

Consumption of addictive drugs such as cocaine and marijuana affects food and liquid intake, taste preference, and body weight. Also, there may be changes in specific nutrient metabolism due to malnutrition. For example, heroin addiction can cause hyperkalemia *(182,183)* and hypernatremia, possibly due to partial dehydration *(184)*. Others have found that heroin addicts show lower levels of serum potassium and selenium levels than do control subjects, whereas sodium, magnesium, phosphorus, and copper–zinc ratios were higher *(185)*. Poor dietary habits and low zinc status have been observed among marijuana abusers *(185)*. It has been shown that multiple illicit drug-dependent subjects have elevated serum copper and zinc concentrations, as well as reduced iron levels as compared with nondrug-dependent control subjects *(186)*.

Both poor nutritional status and high-risk behavior lifestyles commonly observed in illicit drug users influence mineral status. In this scenario, and given the relevance of mineral status in immunity and antioxidant defense, immunodeficiency may be induced, which may increase susceptibility to infections such as HIV. Illicit drug abusers may thus greatly benefit from micronutrient intervention.

6. LIMITATIONS OF CURRENT DATA AND FUTURE RESEARCH NEEDS

Multiple drug use is common in the elderly, making them especially vulnerable to an altered nutrient status. Studies to improve our understanding of polypharmacy and its effects on nutrient status are essential. In addition, with more foods being fortified, the effect on drug absorption and bioavailability should be examined. Investigations into drug–mineral interactions with the wide variety of nutritional and herbal supplements currently being consumed are also necessary in order to understand possible alterations, optimize the effectiveness, and minimize the toxicities of these little-studied substances. In addition, there is limited information about genetic influences on mineral and/or drug absorption and metabolism and this should also be a goal of future studies. Finally, with the ever-present danger of bioterrorism, investigations into how nutrient status is affected by potential biological agents and prophylactic antibiotics that would be distributed to prevent biological warfare should be encouraged.

Given the relatively recent discoveries of beneficial effects of some trace and ultratrace elements, further studies of drug interactions with these minerals, about which little is currently known, are warranted. The use of stable isotopes to study minerals rather than radioisotopes should be encouraged. And although the costs of stable isotopes are high and require sophisticated laboratories with mass spectrometry, as technology is refined *(187)*, these techniques will become more standard.

7. CLINICAL RECOMMENDATIONS

In general, drugs that induce malabsorption should be taken 1–2 h before a meal. Drugs that interfere with metabolism will cause problems if taken on a long-term basis and supplementation of the affected mineral would be recommended. Other methods to maintain mineral status should also be implemented, such as use of probiotics (i.e., yogurt with live cultures) for drug-induced diarrhea (i.e., antibiotics) causing excessive mineral loss.

The major drugs that influence sodium and potassium are the diuretics and these need to be monitored in most hypertensive and/or cardiac patients. Many other drugs may result in retention of sodium and potassium (Table 2). Adequate hydration is important to balance the electrolytes, as well as to recommend the appropriate foods (Table 1) to either restrict or replace these minerals.

There are many drugs that may deplete body stores of calcium that affect a wide range of patients. For example, corticosteroids, antibiotics, sulfonamides, mineral oil, and bile acid sequestrants will all result in malabsorption of calcium, whereas loop diuretics, aminoglycosides, corticosteroids, antiepileptics, isoniazid, and thyroid hormones will deplete calcium stores (Table 2) and increase the risk of osteoporosis. The beneficial effects of estrogens and thiazides on maintaining calcium balance should be considered when recommending these drugs to patients.

Phosphorus is affected by fewer drugs, but its importance in maintaining bone health should not be underestimated. The number of patients at risk of an imbalance of these minerals essential for bone health is alarming and supplementation of calcium (about 1 g/day) should be considered.

Magnesium status, like calcium, can be depleted by many drugs although there are fewer that affect the absorption of magnesium (Table 2). Many patients are at risk of magnesium deficiency including those with asthma, hypertension, emphysema, heart conditions, tuberculosis, and diabetes. In addition, young women taking oral contraceptives are also at risk of magnesium deficiency, and alcoholics often present with deficiency signs associated with magnesium. Magnesium-rich foods or supplements (~400 mg/day) can be recommended.

The trace minerals iron, copper, and zinc are also affected by many drugs (Table 2) and the appropriate mineral-rich foods should be recommended. Alternatively, clinicians can suggest supplements of these minerals in amounts equal to or less than their daily recommended levels (Table 1). The ultratrace minerals are important for health and many (i.e., chromium, selenium, iodine) also have interactions with drugs. For others, however, an excess rather than deficiency can be a problem.

As the use of a variety of nutritional supplements, including megadoses of vitamins and minerals, increases, the need to assess for potential interactions between vitamin and mineral supplements and medications becomes more and more important. Older adults whose mineral status is already compromised due to aging and who generally take a number of different medications daily *(188)* must be questioned about all the medications and food supplements (e.g., herbs, vitamins, minerals) and any major dietary changes with their prescribing practitioner. Furthermore, health education about medications should include warnings and information about potential interactions between food supplements and drugs. This could help improve the prognosis for drug interactions affecting mineral status and minerals that affect drug absorption and activity.

DISCUSSION POINTS

- Many minerals interact with drugs and may result in deficiencies. Malabsorption is especially common with calcium, magnesium, and iron. Name some of the medications that are influencing these minerals.
- Mineral excess is less common than deficiencies, yet there are many drugs that could potentially increase retention. Name a few of these drug–mineral interactions.
- Discuss the primary disease states of patients who would be most at risk of mineral deficiencies.
- Understanding how minerals or other foods may increase or decrease the activity of a drug can prevent unwanted side effects. Name the primary minerals that may interfere with the activity of drugs and the types of patients who would be most at risk.
- Illicit drug users have multiple reasons for mineral deficiencies. Discuss how you would approach the nutritional care of these patients.

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V

DRUG–NUTRIENT INTERACTIONS BY LIFE STAGE

20 Drug–Nutrient Interactions in Infancy and Childhood

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Objectives

- Understand the impact of nutritional status on the growth and development of pediatric patients.
- Identify common interactions between drugs and nutrients and dietary supplements and nutrients, including vitamins.
- Discuss ways to manage medications to avoid interactions.

Key Words: Childhood; development; growth; infancy; pediatric

1. INTRODUCTION

Medical care is becoming increasingly complex, especially for the pediatric population as children with certain chronic diseases are living longer due to novel treatments. Nutrition is exceedingly important in infants, children, and adolescents. Inadequate nutrition will directly affect growth, development, and puberty. Chronic medication use can result in a depletion of certain nutrients which in the growing infant, child, and adolescent can have long-term consequences. Drug–nutrient interactions occur between medications (prescription and nonprescription) and certain foods, fluids, and vitamin and mineral supplements. Although not all of these interactions are significant, some are serious. Health-care professionals need to be aware of these interactions and prevent their occurrence by educating themselves and their patients. It is through knowledge of these drug–nutrient interactions that one can help optimize therapeutic effects, prevent therapeutic failures, and minimize adverse drug events and drug–nutrient interactions *(1)*.

Unfortunately there are no epidemiologic studies describing drug–nutrient interaction in pediatrics. However, drug–nutrient interactions may be more frequent in children and infants because of the difficulty in taking medications, especially those in

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a solid oral dosage form. Crushing a tablet, opening a capsule, or making a liquid preparation from a solid dosage form may result in changes in drug efficacy. Mixing these forms with food to improve palatability may lead to a drug–nutrient interaction. Children with chronic illness receive multiple medications, thus increasing the likelihood of drug–drug and drug–nutrient interactions. These children receive certain medications for long periods of time that can affect growth and development. Parents are also treating their children with "nontraditional pharmacological" agents and using "natural products," some of which are not tested and can increase the likelihood of drug–nutrient interactions.

Although there are a large number of medications used in pediatrics, there are certain drugs that are more routinely prescribed. Table 1 lists medications routinely used in pediatric practice and their drug–nutrient interactions *(1–3)*. There is a global lack of information regarding medication use in pediatrics,

Table 1
Common Pediatric Conditions, Medications, and Selected Drug–Nutrient Interactions

Medical Condition	*Medication*	*Comments*
Asthma	Albuterol	Caffeine administration increases albuterol's adverse drug reactions
	Theophylline	Food may induce sudden release of sustained release preparations
Cardiac disease	Digoxin	Digoxin absorption decreased with foods high in fiber or pectin
	Hydralazine	Chronic hydralazine use may cause a pyridoxine deficiency
Epilepsy	Phenobarbital	High doses of pyridoxine may decrease phenobarbital's effect Increased requirements of folate may be required with chronic use
	Phenytoin	Bioavailability is decreased with tube feedings; consider holding feedings for 2 h prior to and 2 h after phenytoin administration; high doses of folate may decrease phenytoin bioavailability; high doses of phenytoin may increase folate clearance
	Valproic acid	Carnitine requirements may be increased
Infectious diseases	Ciprofloxacin	Suspension may adhere to feeding tubes and divalent cations
Inflammatory bowel disease	Sulfasalazine	Folate absorption is impaired
Organ transplantation	Cyclosporine	Grapefruit juice increases and St. John's wort decreases cyclosporine concentrations
	Tacrolimus	Grapefruit juice increases tacrolimus concentrations

and the area of drug–nutrient interactions cannot be limited to pediatric patients. Drug–nutrient interactions may be divided into several categories including (1) effect of food on drug absorption (increased, decreased, or delayed), (2) alterations of drug metabolism, (3) effects of medications on nutrient absorption or use, and (4) pharmacologic interactions of medications with nutrients. These are among those included in a broader definition of drug–nutrient interactions *(4)*.

The majority of the available literature focuses on the effect of food on the absorption and bioavailability of medications (see Chapter 8). We now know that food and nutritional components can have effects on the metabolism of medication, as is the case with grapefruit juice's effect on the cytochrome P450 enzyme system (see Chapter 10). There is, however, less information regarding the effects of other nutrients on drug metabolism. Another area that needs further investigation is the site of absorption of medications. Chronically ill and critically ill patients often receive medications via an enteral feeding tube. It is necessary to know where the drug is absorbed to be able to know its extent of absorption when administered into a certain portion of the gastrointestinal tract. For example, a medication absorbed in the stomach will not be effective if administered postpylorically. In this chapter we will discuss the requirements for growth and development in pediatric patients and the impact of nutritional status. We will describe common drug–nutrient interactions in this age group, the limitations of current data, issues related to natural health products (NHP), provide recommendations for the management of drug–nutrient interactions, and suggestions for future directions related to drug–nutrient interactions in infancy and childhood.

2. GROWTH AND DEVELOPMENT

Growth and development starts from conception and needs to be closely monitored in infancy, throughout childhood, and into adulthood. Due to physiological changes that occur after birth, an infant will lose about 10% body weight in the first week of life and typically regain the weight by 8–10 days after birth. In the first year of life, the weight of an infant doubles by about 5 months and triples in 1 year; body length increases by 55% and head circumference by 40% *(5)*. Growth then slows through childhood and another growth spurt occurs during adolescence. During these periods of accelerated growth, many changes occur in the body (e.g., puberty), and nutrient needs change as well. There are a variety of medical conditions that can affect growth and development. Some of these conditions are treated with drugs that may alter growth and development by a variety of mechanisms. These may include a direct effect of the drug on the body or a secondary effect (i.e., drug–nutrient interaction). Further discussion of specific conditions is beyond the scope of this section but factors related to growth, development, and nutritional status will be reviewed.

3. NUTRITIONAL ASSESSMENT

Nutritional status is closely related to growth and development and may be complicated by numerous medical conditions. Pediatric patients with complex medical conditions will benefit from an assessment of nutritional status from a dietitian and other clinicians who specialize in pediatric nutrition. Pediatric conditions which may be high risk for drug–nutrient or drug–drug interactions include childhood cancers, cystic fibrosis, congenital heart disease, bronchopulmonary dysplasia, inflammatory bowel disease, gastrointestinal disorders, end-organ failure requiring organ transplant, renal disease, seizure, and other neurologic disorders. Table 2 provides a list of components to evaluate in the nutritional assessment of an

Table 2
Components of a Nutritional Assessment

Components	*Key Questions*
Medical history	What are the acute and chronic illnesses? Are there nutrition and growth implications? What diagnostic procedures, surgeries, medications, psychosocial issues (e.g., socioeconomic status), or other therapies (e.g., chemotherapy, radiation, immunosuppression) that may have an impact on nutrition?
Diet history	Is the diet age appropriate? Texture or foods, frequency, and amount of foods? Is there any oral feeding difficulty? Is there a history of food allergies (hypersensitivities) or intolerances? If so what is the reaction(s)? Any foods which are avoided and why? Any recent changes in appetite or intake? How is the diet taken (by mouth, enteral feedings, supplements, parenteral nutrition)? Any issues with limited access to food? What is the assessment of the diet history? Adequate or Inadequate?
Gastrointestinal history	Any problems with nausea, vomiting, diarrhea, constipation, or reflux?
Medications	Do any of the medications have potential drug–nutrient interactions, drug–drug interactions, or side effects affecting nutritional status? Is there a recent use of steroids, immunosuppressants, chemotherapy, anticonvulsants, anticoagulants, or gastrointestinal medications? What is the timing and dosing of the medications? Who administers the medications? Are there side effects from the medications which may effect dietary intake?

Vitamin/mineral supplements	Are there additional supplements being taken and how much and how often? Are these appropriate, given the diet history, medical history, and medication list?
Herbal supplements	Any herbal supplements, which may interact with medications taken, contribute to gastrointestinal history, or have negative impact?
Available labs	Are there abnormal lab values that can be attributed to the diet and a modification to the diet or the supplement can be added? Any vitamin and mineral labs drawn due to possibility of deficiency?
Growth parameters	What is the growth history? What is the current growth evaluation? Has there been recent weight loss or rapid weight gain? Is there stunting or wasting? Is the patient overweight?
Physical assessment	Does physical assessment verify growth parameter assessment? Are there any signs of a vitamin or a mineral deficiency? Is there skin breakdown? How is dental health?
Nutritional needs	Does the diet provide all of the needed, calories, proteins, fluid, vitamins, and minerals? (see Tables 6–10 for guidelines) Are there specific nutritional needs based on medical history? Based on growth parameters and diet history is there a need for a change in the current diet?
Assessment	What is the assessment of the patients' nutritional status taking all of the above into consideration?
Recommendations	Are any modifications needed to promote normal growth and development? If the diet is found to be inadequate, what can be done to make the diet adequate? Any changes or additions needed for vitamin and mineral supplementation? What monitoring methods are recommended (e.g. growth assessments, food records, laboratory values, compliance)? Are the recommendations, age appropriate, feasible, and how will the outcome be measured and in what time frame? Are appropriate referrals made (e.g., social work, speech therapy, occupational therapy, early intervention, Women, Infants, and Children (WIC) program, Registered Dietitian, behavioral psychologist, or other specialty physicians)?
Education	Is education needed? Verbal and written? Is it age and culturally appropriate? Have all caregivers been educated?

infant or a child. If a child does not have appropriate nutrition, his/her growth will be adversely affected, resulting in wasting, stunting, or obesity. All components need to be taken into consideration in order to have a comprehensive nutritional assessment to make the appropriate recommendations. Nutritional assessments including growth assessments need to be reassessed often due to changing physiologic status of a child. Body composition and nutritional requirements change with growth and development. These changes need to be accounted for in the evaluation of a patient's nutritional status since they will impact on drug action, metabolism, and excretion.

It is important that regular growth measurements are taken at regular intervals after birth and plotted on growth charts, which provide a visual picture of overall growth. The National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and HealthPromotion in 2000 revised the previous NCHS growth charts and are available on the Internet, www.cdc.gov/growthcharts, for boys and girls for birth-to-36 months and 2-to-20 years. The measurements needed for birth-to-36 months are weight, length, and head circumference. Standing height and weight are needed for the 2-to-20 year growth charts. Between 1997 and 2003, the World Health Organization conducted the Multicenter Growth Reference Study to develop new growth standards for infants and young children from ages birth to 5. The WHO growth charts are designed to promote the worldwide standard of growth and development based on the breastfed infant. These charts are available at www.who.int/childgrowth/en. Incremental growth can be calculated from weight and length measurements obtained over a given period of time (e.g., 1 month) and can be compared to recommended growth velocity values (Table 3) *(6)*. Stunting is an indicator of chronic malnutrition, whereas wasting alone is an indicator of acute malnutrition. Table 4 shows the criteria and classification for wasting and stunting as defined by the Waterlow Criteria *(7)*. Body mass index (BMI) is a measure of relative weight to height in an individual. BMI is calculated by dividing weight in kilograms by standing height in meters squared (kg/m^2). In children and adolescents ages 2–20, the BMI is plotted on the growth chart, whereas children 0–24 months are plotted on the weight-for-length chart. The BMI percentile value can be used to classify weight status (Table 5) *(8,9)*. The specific number value of the BMI is not as

Table 3
Growth Velocity *(6)*

Age (cm/month)	*Weight (g/day)*	*Length*
<3 months	25–35	2.6–3.5
3–6 months	15–21	1.6–2.5
6–12 months	10–13	1.2–1.7
1–3 years	4–10	0.7–1.1
4–6 years	5–8	0.5–0.8
7–10 years	5–112	0.4–0.6

Table 4
Waterlow Criteria for Grading Malnutrition *(7)*

Weight Assessment		*Length/Height Assessment*	
% Median Weight-for-Height	Wasting Class	% Median Height-for-Age	Stunting Class
90–110%	Within normal	≥95%	Within normal
80–89%	Mild	90–94%	Mild
70–79%	Moderate	85–89%	Moderate
<70%	Severe	<85%	Severe

Table 5
Body Mass Index Interpretation *(8,9)*

Weight Status Category	*BMI Percentile*
Underweight	<5th
Healthy weight	5th to <85th
Overweight	85th to <95th
Obese	≥95th

significant as assessing the percentile trend over time. BMI-for-age growth curves for children 5–19 years old are also available *(10)*. Growth measurements are only one component of the nutritional assessment. Another component of the nutritional assessment is a review of medications.

4. NUTRITIONAL REQUIREMENTS

The Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board, Institute of Medicine of the National Academies is the committee responsible for developing and maintaining the dietary reference intakes (DRIs). These DRIs include Recommended Dietary Allowances (RDAs) as well as three additional reference values, Adequate Intakes (AIs), Estimated Average Requirements (EARs), and Upper Levels (ULs). Table 6 provides selected DRIs for infants, children, and adolescents *(11)*. Energy requirements can also be estimated by using prediction equations to determine basal energy needs (Table 7) *(12)*. This value must then be multiplied by an activity/disease severity factor (1.1–1.3 for mild illness, bed rest, 1.3–1.5 for moderate illness, average activity, 1.5–1.7 for severe illness and above average activity) to determine total energy needs. Tables 8 and 9 provide the equations to determine estimated energy requirements. For children $>$ 3 years of age, height, weight, and a determination of a physical activity coefficient are needed to use the equations. Note that these equations provide only a guideline for the initial estimation of energy needs. The patient's response (e.g., weight and length) to the energy intake should be used

Table 6
Selected DRIs for Protein, Fiber, Iron, Calcium, and Vitamin D *(11)*

Life Stage Category	*Age (year)*	*Protein (g/kg/d)*	*Fiber (g/d)*	*Iron (mg/d)*	*Calcium (mg/d)*	*Vitamin D (μg/d)*
Infants	0–0.5	1.52*	ND	0.27*	210*	5*
	0.5–1	1.2	ND	11	270*	5*
Children	1–3	1.05	19*	7	500*	5*
	4–8	0.95	25*	10	800*	5*
Males	9–13	0.95	31*	8	1300*	5*
	14–18	0.85	38*	11	1300*	5*
Females	9–13	0.95	26*	8	1300*	5*
	14–18	0.85	26*	15	1300*	5*

* = Adequate Intake levels, all others are Recommended Dietary Allowances
ND = Not Determined

Table 7
WHO Equations for Predicting Energy Expenditure from Body Weight *(12)*

Age	*Equation to Determine Energy Expenditure at Rest (kcal/d)*	
(years)	*Males*	*Females*
0–3	(60.9 × wt (kg)) – 54	(6.1× wt (kg)) – 51
3–10	(22.7 × wt (kg)) + 495	(22.5 × wt (kg)) + 499
10–18	(17.5 × wt (kg)) + 671	(12.2 × wt (kg)) + 746

Table 8
Estimated Energy Requirements (EER) for Infants and Young Children *(11)*

Age (months)	*EER Equation (kcal/d)*
0–3	(89 × wt (kg) –100) + 175 (kcal for energy deposition)
4–6	(89 × wt (kg) –100) + 56 (kcal for energy deposition)
7–12	(89 × wt (kg) –100) + 22 (kcal for energy deposition)
13–36	(89 × wt (kg) –100) + 20 (kcal for energy deposition)

to determine whether an adjustment to this caloric estimate should be made. Reports on the DRIs can be found at www.nap.edu *(11)*. For fluid requirements, see Table 10*(13)*.

5. MEDICATION ADMINISTRATION AND DRUG ABSORPTION

Pediatric patients use many of the same medications as the adult population; however, the specific method of drug administration may be different. Pediatric patients often cannot swallow a tablet or a capsule intact. In addition, since most

Table 9
Estimated Energy Requirements (EER) for Boys and Girls *(11)*

Life Stage	EER Equation (kcal/d)
Boys	
3–8 years	88.5 − (61.9 × age [years]) + PA × (26.7 × wt [kg] + 903 × height [m]) + 20
9–18 years	88.5 − (61.9 × age [years]) + PA × (26.7 × wt [kg] + 903 × height [m]) + 25
	PA 1.00 if PAL is estimated to be $\geq 1.0 < 1.4$ (sedentary) 1.13 if PAL is estimated to be $\geq 1.4 < 1.6$ (low active) 1.26 if PAL is estimated to be $\geq 1.6 < 1.9$ (active) 1.42 if PAL is estimated to be $\geq 1.9 < 2.5$ (very active)
Girls	
3–8 years	135.3 − (30.8 × age [years]) + PA × (10.0 × wt [kg] + 934 × height [m]) + 20
9–18 years	135.3 − (30.8 × age [years]) + PA × (10.0 × wt [kg] + 934 × height [m]) + 25
	PA 1.00 if PAL is estimated to be $\geq 1.0 < 1.4$ (sedentary) 1.16 if PAL is estimated to be $\geq 1.4 < 1.6$ (low active) 1.31 if PAL is estimated to be $\geq 1.6 < 1.9$ (active) 1.56 if PAL is estimated to be $\geq 1.9 < 2.5$ (very active)

PA = physical activity coefficient; PAL = physical activity level or the ratio of total energy expenditure divided by basal energy expenditure

Table 10
Fluid Requirements in Pediatric Patients *(13)*

Body Weight	*Baseline Fluid Requirements*
1–10 kg	100 mL/kg
11–20 kg	1000 mL + 50 mL/kg for each kilogram over 10 kg
> 20 kg	1500 mL + 20 mL/kg for each kilogram over 20 kg

doses are individualized based on the child's weight, a dose that is appropriate may not be available in a preformulated tablet or capsule. This requires parents or caregivers to crush tablets or open capsules and mix them with a small quantity of liquid or food if a commercially liquid preparation is unavailable *(1)*. Little data are available on these potential drug–nutrient interactions.

5.1. pH Effects

By altering the integrity of the commercially available formulation, the medication may be adversely effected by the pH in the stomach. One classic example is omeprazole, a highly acid-labile medication *(14)*. Omeprazole is formulated as a capsule containing enteric-coated granules designed to protect the drug from stomach acid until it can dissolve in the more alkalotic environment of the intestine where the drug is absorbed. Crushing the granules or dissolving them in an alkalotic liquid will impair the integrity of the enteric coating and result in drug degradation in the stomach acid. There are two options for patients who cannot swallow an intact capsule. The first is to open the capsule and mix the granules with fruit juice. The second option is to prepare a suspension in a sodium bicarbonate base that buffers the stomach contents long enough for the medication to pass through to the intestine.

5.2. *Phenytoin and Enteral Feeds*

Phenytoin presents multiple challenges secondary to its nonlinear pharmacokinetics (absorption and elimination). Phenytoin suspension adheres to polyvinylchloride found in feeding tubes. Also, the concomitant administration of phenytoin suspension and enteral formulas can decrease phenytoin bioavailability, resulting in decreased serum concentrations *(15,16)* (see Chapter 13).

Marvel and Bertino *(15)* conducted a study evaluating a single dose of phenytoin suspension administered with Ensure (intact protein) and Vivonex (hydrolyzed protein) and found no significant effect on the overall absorption of the suspension. Despite these and similar findings, much of the remaining literature suggests that absorption can be impaired. If clinically feasible, the feedings should be interrupted for 2 h before and after the dose although the outcome benefit of this procedure is not clear. It is also important to flush the feeding tube to remove any enteral feeds that may remain in the tube prior to medication administration.

5.3. *Ciprofloxacin and Enteral Feeds*

There are several problems with administering ciprofloxacin via feeding tubes. The commercial suspension is oil based and adheres to feeding tubes. In addition, the suspension has been found to clog the smaller bore feeding tubes used in pediatric patients. To administer ciprofloxacin via feeding tube, an immediate-release tablet should be crushed and mixed with water. The feeding tube should be flushed before and after the dose is administered *(3)*. Separation by at least 1 h is also necessary to avoid complexation of drug with divalent cations in the feeds. Additionally, ciprofloxacin should not be given via jejunal tube as absorption from the jejunum is limited *(17)*.

5.4. *Effect of Food on Drug Absorption*

Palatability of liquid medications is another issue that is continually addressed in the pediatric population. To mask the taste of medications, they are often mixed with a liquid or a soft food. As a result, the effect of food on drug absorption must be considered (see Chapter 8). Table 11 lists medications whose absorption is known to be affected by food *(18–25)*.

Table 11
Drugs Effected by Food for Absorption *(18–25)*

Drug	*Comments*
• Erythromycin base (e.g., E-mycin®, EryTabs®, EYRC®)	• Administer on an empty stomach
• Erythromycin stearate (e.g., Erythrocin®)	• Administer on an empty stomach
• Fluorquinolones (i.e., ciprofloxacin)	• Drug chelates with divalent cations and becomes inactive; separate administration
• Penicillins (i.e., penicillin V potassium, amoxicillin)	• Administer 1 hour before or 2 hours after a meal
• Nitrofurantoin (e.g., Macrodantin®)	• Administer with food (increases absorption and minimizes GI upset)
• Itraconazole (e.g., Sporanox®)	• Administer capsules with food, administer solution on empty stomach
• Griseofulvin (e.g., Fulvicin®, Grifulvin V®)	• Administer with high-fat meal
• Theophylline (sustained release products)	• "Dose dumping" possible with high-fat meal

5.4.1. CONTRADICTORY AND ADDITIVE EFFECTS

Some clinical or adverse effects of medication may be enhanced by administration with food. The classic example has been consumption of vitamin K-rich foods while taking warfarin. Warfarin interferes with hepatic recycling of vitamin K. Inconsistent consumption of foods high in vitamin K may decrease the effectiveness of warfarin and potentially place the patient at risk for a clot, while sudden elimination of dietary vitamin K may place a patient at risk for bleeding episodes. Patients should be instructed to eat a consistent diet to avoid rapid changes in INR or prothrombin time *(26)*.

Stimulant drugs such as methamphetamine derivatives and ephedrine derivatives should not be taken with caffeine as this combination may result in jitteriness, nervousness, or insomnia *(27)*. Likewise alcohol (including drug products containing alcohol) should be avoided when taking medications known to cause drowsiness, such as antihistamines (e.g., diphenhydramine). To further confuse matters, it should be noted that pediatric patients often have paradoxical CNS stimulant effects with antihistamines *(28)*. Thus in these patients it may be especially important to avoid caffeine and other stimulants.

6. NATURAL HEALTH PRODUCTS

The use of NHP is widespread in both adult and pediatric populations and still increasing. One in six parents surveyed in one report admitted given dietary supplements to their children *(29)*. Another study evaluated adult patients who commonly took prescription medications. The authors noted that over 18% of those surveyed reported using at least one herbal product or high-dose vitamin therapy. More concerning is that over 60% of those patients did not report that use to their physicians *(30)*.

A variety of reasons have been identified for the lack of patient's disclosure of NHP to physicians. For example, some patients do not believe NHP to be related to their medical care or do not think of them as medications. Others do not disclose NHP usage to avoid scorn from their health-care providers *(29)*.

Although NHP may have some utility, they are not without toxicities and interactions seen with more conventional medications (see Chapter 12). Tables 12 and 13 list some of the commonly used NHP and their interactions *(25,26,29–41)*.

Table 12
Natural Health Product–Drug Interactions *(29–32)*

Natural Health Product	*Conventional Drug*	*Result of Interaction*
Chromium	• Calcium carbonate and other antacids	• Decreased chromium absorption
Garlic	• Warfarin, NSAIDS, ticlopidine, dipyridamole, and other antiplatelet drugs • Protease inhibitors	• Garlic inhibits platelet aggregation and prolongs bleeding and clotting times • CYP450 interaction
Ginger	• Anticoagulants • Antidiabetic medications	• Platelet dysfunction • Effects blood sugar levels
Ginseng	• Anticoagulants • Alcohol	• Increases INR • Increases alcohol clearance
Licorice	• Digitalis and cardiac glycosides • Corticosteroids and thiazide diuretics • Spironolactone	• Effects potentiated by increased potassium loss • Increased sodium retention, hypertension, and hypokalemia • Most licorice candies sold in the United States do not contain licorice
Ma Huang	• Monoamine oxidase inhibitors • Methylxanthines (i.e., caffeine), cardiac glycosides, anesthetics	• Increased toxicity • Potentiates effects

7. MANAGEMENT OF DRUG–NUTRIENT INTERACTIONS

The management of drug–nutrient interactions includes identification, prevention, and management.

7.1. Identification

During the medical interview, all patients need to be asked what medications (prescription and nonprescription), oral supplements, and NHP they are taking

Table 13
Vitamin–Drug Interactions *(25,26,33–41)*

Vitamin	*Drug*	*Comments*
Vitamin A	• Cholestyramine	Decreases vitamin A absorption
	• Mineral oil	
	• Neomycin	
	• Warfarin	• Increases hypoprothrombinemic effects
Vitamin B	• Aminoglycosides	Decreases vitamin B_{12} absorption
	• Aspirin	
	• Phenobarbital	• Antagonizes the response to vitamin B_{12}
	• Phenytoin	• Destroys dietary vitamin B_{12} in vitro
	• Chloramphenicol	
	• Vitamin C	
Vitamin K	• Warfarin	• Decreases the effectiveness
Calcium	• Digoxin	• Potentiates digoxin toxicity
	• Calcium	Decreases drug absorption
	• Iron	
	• Quinolones	• Calcium absorption impaired by bran, oxalate-containing foods, and whole-grain cereals
	• Tetracyclines	
Folic acid	• Chloramphenicol	• Decreases response to folic acid
	• Phenytoin	• Increases phenytoin metabolism
	• Sulfasalazine	• Decreased folic acid absorption
Iron	• Antacids	• Binds to iron, decreasing its absorption
	• Chloramphenicol	• Decreases the response to iron therapy
	• Quinolones	• Decreases quinolone absorption
	• Tetracyclines	• Decreases tetracycline absorption
Magnesium	• Benzodiazepines	Decreases drug absorption
	• Ciprofloxacin	
	• H_2-blockers	
	• Iron	
	• Phenytoin	
	• Steroids	
	• Tetracyclines	
Zinc	• Calcium	Decreases zinc absorption
	• H_2-blockers	
	• Iron	Decreases drug absorption
	• Quinolones	
	• Tetracyclines	
		• Zinc absorption impaired by coffee, brans, and whole-grain cereals and legumes

including the method of administration. This is especially true if the patient is complaining of an unexpected side effect or experiencing a lack of therapeutic effect. The health-care professional needs to have an open attitude so that patients feel comfortable and will disclose all medications they are using as well as share their health beliefs. In addition, pharmacies dispensing medications should have software and appropriate upgrades to identify potential drug–nutrient interaction and procedures for addressing those identified.

7.2. Prevention

The best way to prevent drug–nutrient interactions is the education of all staff and patients and their caretakers. Parents should be encouraged to get all their medications through one pharmacy so that the pharmacist is able to identify all potential interactions including drug–nutrient interactions. Pharmacies and health-care facilities should ensure that drug–nutrient interaction software is current to help identify and prevent potential interactions. Health-care professionals should ask the patients about all medication and supplement administration. Hospitals and pharmacies need to set up systems so that cross-check mechanisms exist to identify drug–nutrient interaction (e.g., use of labels, computer alerts, and educational materials) *(42)*. Protocols should be developed for medication administration in those patients with chronic disease. Those patients who are receiving several medications can benefit from an interview with a pharmacist who can help them develop a schedule for medication administration. The involvement of dietitians and other health-care professionals is essential in the management of and education on drug-nutrient interactions. Dietitians need to be aware of the patient's diet and drug therapy and can help prevent and identify drug–nutrient interactions. They can educate patients about the intake of certain foods as well as monitor the patient's daily intake of these foods *(43)*.

7.3. Management

Once the drug–nutrient interaction has been identified, the specific problem needs to be corrected. It may require changing the timing of medication administration or checking a drug level. Another option is to select an alternate medication, if appropriate. One mechanism to manage issues with medication absorption is to adequately separate feedings from medication administration. Some of the literature states that feedings should be held 2 h prior to and 2 h after medication administration. In pediatric patients, continuous enteral feeding is not uncommon which makes medication administration difficult in cases where feedings must be held. One recommendation is to change the feeding regimen to bolus feedings or increase the infusion rate, if appropriate, to eliminate nutritional losses resulting from holding the feedings. If the patient has a GJ tube, it is possible to continue giving the feedings postpylorically, but administer the medication into the stomach if the site of absorption is unknown. Some patients will benefit from a schedule for medication administration for patients and their caretakers in an outpatient setting. In an inpatient setting, systems change and alerts need to be put into place to prevent the drug–nutrient interaction from occurring.

8. FUTURE DIRECTIONS

To fully understand the extent of drug–nutrient interactions, we need to have a better understanding of the nutrient effects on drug metabolism and clearance and vice versa. With a larger portion of patients receiving medications via feeding tubes, it is important that the site of absorption of medications be more clearly defined. There is still a lack of information regarding the interactions between NHP with conventional medications. Given the widespread use of NHP, it is important that these interactions are identified and health-care providers and patients are adequately educated about the potential risks of taking the medications concomitantly. Many drugs used in pediatric patients have not been adequately studied, especially in neonates. In addition, drugs approved for adults are often used "off-label" to treat pediatric patients with disorders such as hypertension and type 2 diabetes, which are rapidly becoming prevalent in pediatric patients. Much research still needs to be done to evaluate drug–nutrient interactions in pediatric patients with chronic diseases who take multiple medications. While we do know about the effects of chronic disease on the nutritional status of the patients, we know much less about the long-term effects of medications in pediatric patients with chronic illness who now have longer life expectancies. Research also needs to be done on the prevention of drug–nutrient interactions in pediatric patients.

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21

Drug–Nutrient Interaction Considerations in Pregnancy and Lactation

Myla E. Moretti and Danela L. Caprara

Objectives

- Describe the physiologic changes that occur with pregnancy and how they may impact on drug disposition.
- Identify nutrient requirements in pregnancy and medication that may influence nutrient status.
- Describe the physiologic changes and nutrient requirements of lactation and influences with drug disposition.

Key Words: Human milk; lactation; placental transfer; pregnancy; risk assessment

1. INTRODUCTION

The use of drugs in pregnancy and lactation has long presented a clinical dilemma for health-care practitioners and an ethical dilemma for the researcher. Formulating a risk–benefit assessment becomes complicated by the fact that a fetus or an infant may unnecessarily be exposed to potentially harmful drugs. History has taught us that drugs used by the mother can have disastrous effects on the offspring. The ironic dichotomy, however, is that lack of treatment itself may pose a risk to maternal life, and subsequently to the fetus. In truth, relatively few drugs to date have been proven human teratogens *(1)* and even fewer are known to cause harm to the infant exposed via breast milk *(2,3)*. The situation becomes further complicated when one considers the unique nutritional challenges in this population. Pregnancy and lactation is a time of increased caloric, macronutrient, vitamin, and mineral requirements. While these requirements are clearly warranted for the overall health and well-being of the mother, these increased needs also offer protection to the offspring. Each year there is growing evidence that maternal nutritional status and nutrient intake play a significant role in

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malformation rates and other pregnancy outcomes. Since drugs may impair or interfere with such critical pathways, it is quite probable that drug–nutrient interactions may provide the key to mechanisms of teratogenicity or drug toxicity in pregnancy and lactation.

2. MATERNAL PHYSIOLOGICAL CHANGES IN PREGNANCY: THEIR IMPACT ON DRUG PHARMACOKINETICS AND DISPOSITION

In any normal pregnancy there are several physiological changes that the maternal body experiences in response to stimuli provided by the fetus. These adaptations are essential to accommodate the growth and development of the fetus and the supporting placental unit. They can also significantly alter disease course and treatment. In this section we will focus on how physiological adaptations of cardiovascular, respiratory, renal, gastrointestinal, and hepatic function in pregnancy can have important implications on drug absorption, distribution, metabolism, and elimination.

The process of assessing drug effects and safety relies heavily on understanding their mode of action and the physiologic processes affected by this action. In this respect, a drug's pharmacokinetic properties play a tremendous role. Pregnancy, however, presents a unique situation because the maternal–fetal unit undergoes significant physiologic changes. This in turn results in an alteration of the pharmacokinetic properties that have otherwise been established in the nonpregnant patient.

2.1. Drug Absorption

In pregnancy, drug absorption can be affected in a variety of ways. Symptoms of nausea and vomiting frequent in pregnancy may affect drug absorption. Modifying the dosing schedule so that drugs are taken when the patient is least likely to vomit may be of benefit in ensuring that drugs are more readily absorbed. The hormonal changes of pregnancy, notably increases in progesterone, are thought to act on smooth muscle, causing a decrease in intestinal motility and leading to delayed gastric emptying *(4)* and prolonging bowel transit times *(5)*. This potentially delays onset of drug action and time to peak drug concentration, which is of particular importance for drugs which require quick onset of action. In the first and second trimester, gastric mucus secretion increases and acid secretion decreases, changing gastric pH *(6)*. Depending on an agent's pK_a, these gastric changes will affect ionization of the drug, in turn modifying absorption, since only nonionized drugs freely diffuse across the lipid bilayer. To date, both motility and acid changes have not translated into clinical effect and appear to have little impact on overall absorption. In clinical studies, changes in gastric transit time during each trimester were not noted *(7,8)*.

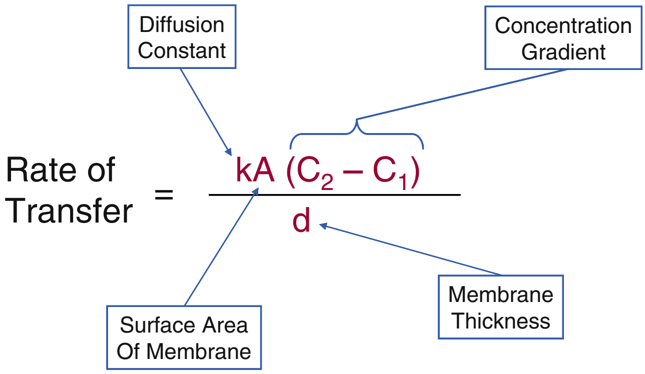
Increased cardiac output *(9,10)* and tidal volume *(11)* are observed early on in pregnancy, resulting in increased pulmonary blood flow and hyperventilation. This is likely to increase alveolar uptake of drugs administered by the inhalational route. Certain anesthetics, namely halothane, isoflurane, and methoxyflurane, were shown to have reduced dose requirements in pregnancy *(12)*. The skin and mucosal membranes also experience increased perfusion *(13)* potentially resulting in increased absorption of topically administered drugs.

2.2. *Distribution*

By the third trimester, plasma volume expands significantly, as much as 50% *(14,15)* increasing the apparent volume of distribution for most drugs. It can be expected then that drugs which are highly distributed to water compartments in the body will exhibit a decrease in peak concentration achieved. This has been reported for a number of drugs *(16–18)* and clinically, higher doses may be required *(19)*. Along with an increase in cardiac output, uterine *(20,21)* and renal perfusion *(22,23)* are also significantly increased in the pregnant patient. The resulting enhanced clearance has translated to decreased steady-state drug concentrations for several drugs *(16–18,24–26)*. Once again these changes indicate that in order to achieve an appropriate therapeutic response, many drugs may have increased dosage requirements as pregnancy progresses.

2.3. *Placental Transfer*

Most drugs easily gain access to the fetal compartment by moving across the placenta. The placenta, really a lipid bilayer, is not a barrier to drugs as was once believed and most drugs are likely to be found on the fetal side. Generally, for most drugs which are small molecules, passage across the placenta is thought to occur by passive diffusion. Active transport, facilitated diffusion, phagocytosis, and pinocytosis have also been described *(27)*; therefore, even larger molecules can be transported across the placenta (Fig. 1). These transport mechanisms also play a critical role in nutrient transport across the placenta.



Transfer is greatest for
lipophilic, non-ionized, and low molecular weight drugs.

Fig. 1. Drug placental transfer during pregnancy.

2.4. Protein Binding

As plasma volume expands in pregnancy, it is not accompanied by a proportional increase in albumin production, resulting in decreased plasma protein concentrations *(28,29)*. In addition, albumin is more occupied by hormones during pregnancy, leading to a diminished capacity of the protein to bind drugs and a subsequent increase in free drug concentration. Although this would theoretically result in an increase in available active drug, the effects of increased biotransformation and clearance seem to offset the consequences of decreased albumin, with no resultant net effect.

Another serum protein α_1-acid glycoprotein maintains constant levels in maternal plasma throughout pregnancy. On the other hand, the fetus displays significant decreases in this protein and although fetal data are not available, evidence in newborns suggests that they have increased free fractions of some weak base drugs which normally bind to α_1-acid glycoprotein *(30)*.

2.5. Metabolism

The dramatic changes in estrogen and progesterone in normal pregnancies have multiple effects on hepatic metabolism. Progesterone stimulates microsomal enzyme activity, increasing metabolism of drugs such as phenytoin *(26)*. In contrast, progesterone and estradiol inhibit microsomal oxidases *(31,32)*, thereby reducing hepatic elimination of other drugs such as theophylline and caffeine. Interestingly, Wadelius and colleagues *(33)* found that changes in CYP2D6 activity during pregnancy were varied depending on whether patients were inherently poor or extensive metabolizers. The specific role of changes in enzyme activity and its alteration in drug metabolism have not yet been elucidated for many drugs.

2.6. Elimination

As early as the 6th week of gestation, glomerular filtration is increased *(23,34)*, though renal tubular reabsorption does not appear to be changed in pregnancy *(35)*. The resulting effect from the increased glomerular filtration is enhanced elimination of drugs that are normally cleared by the kidney and a lowering of steady-state concentrations.

2.7. Adherence

The patient's perception of teratogenic risks of drugs is well documented *(36–39)* and it is not surprising then that adherence with dosing regimens may be diminished in the pregnant patient *(40)*. Although this is not necessarily a direct pharmacokinetic effect attributable to physiologic changes of pregnancy, compliance needs to be considered into the equation when evaluating therapeutic effect and outcomes in pregnancy.

2.8. Clinical Relevance

The clinical relevance of these pharmacokinetic changes remains very much understudied *(7,18)*. As a result, few pregnancy-specific dosing guidelines exist. Most clinicians continue to use the doses recommended for the nonpregnant patient, which could have detrimental effects on the mother and will likely have an impact on pregnancy outcome. The difficulty of course is that performing drug studies on pregnant women presents significant ethical and therapeutic challenges. Moreover, sequential studies need to be conducted at all stages of pregnancy because the pharmacokinetics evolve as pregnancy does.

3. NUTRIENT REQUIREMENTS IN PREGNANCY

A woman's nutritional status preconceptionally and during pregnancy can profoundly affect maternal, fetal, and infant health. Ensuring proper nutrition during pregnancy includes assessing maternal weight gain, caloric intake, and dietary intake throughout pregnancy. Recommended nutrients from dietary sources have been described (Table 1). A normal pregnancy and a well-balanced diet generally provide the requirements of all nutrients except iron and folate where supplementation is recommended. The Institute of Medicine recommends multivitamin supplementation for pregnant women who do not consume an adequate diet *(41)*. Women who may be at a higher risk of nutrient deficiencies include women carrying multiple gestations, heavy smokers, adolescents, complete vegetarians, substance abusers, and women with other dietary restrictions including lactose intolerance *(42)*. In these subgroups, daily multivitamin supplementation has definite benefit and is part of the standard of prenatal care. The specific nutrient requirements [Recommended Dietary Allowances (RDA) or Adequate Intake (AI) levels] as set forth in the Institute of Medicine's Dietary Reference Intakes are listed in Table 2 *(43–48)*. These dosing standard values are based on dietary intakes for Americans and Canadians, and although they take population variability into account, they are not intended for use in persons with acute or chronic disease. Intake at or above the RDA/AI has a low probability of inadequacy *(48)*.

3.1. Folic Acid

Several studies have documented the benefit of folate fortification in a gestational diet in the prevention of neural tube defects (NTDs) *(49,50)*. During the last decade, there have been studies suggesting that supplementation with folic acid fortified multivitamins may decrease the risk of defects beyond NTDs, such as orofacial clefts, limb deficiencies, and cardiovascular abnormalities *(51)*. Multivitamin supplementation has also been associated with a reduction in the number of low-birth-weight and small-for-gestational-age babies and maternal anemia *(42)*. Although studies may have included women with inadequate daily nutrient intake from diet alone, they do suggest a benefit for the recommendation of multivitamin supplementation preconceptionally and throughout pregnancy in all expectant mothers.

Folate is a water-soluble B-complex vitamin important in the synthesis of DNA and cell replication (see Chapter 18). Deficiencies during pregnancy have long been associated with pregnancy-induced megaloblastic anemia and supplementation has been proven a successful treatment strategy. Inadequate folate intake in early pregnancy has also been associated with an increased risk for NTD *(52)*. The preconceptional supplementation of folic acid in women planning pregnancy has been shown to reduce both the occurrence and the recurrence of NTDs *(52,53)*. Cereal fortification of folate in 1996 has resulted in a 32% decrease in the prevalence

Table 1
Micronutrients of Concern in Pregnancy and Lactation

Nutrient	*Function*	*Common Sources*	*Additional Concerns in Pregnancy*
Vitamin A (retinol)	Fat-soluble vitamin, main importance for visual function	Green leafy vegetables, yellow-orange vegetables	Associated with increased risk of neonatal cranial–neural–crest defects* at increased supplementation levels *(119)*
Vitamin B_1 (thiamin)	Water soluble, involved in the release of energy from cells	Milk, raw grains	Acute deficiencies in women with severe nausea and vomiting lead to Wernicke’s encephalopathy
Vitamin B_2 (riboflavin)	Water soluble, involved in the release of energy from cells	Green vegetables, milk, eggs, cheese, fish	Deficiencies may increase risk of preeclampsia by nearly fivefold in high-risk women *(120)*
Vitamin B_6 (pyridoxine)	Water soluble, involved in lipid, carbohydrate, protein metabolism and heme synthesis	Vegetables	Used to treat nausea and vomiting in pregnancy; Low levels associated with decreased APGAR scores *(121)*
Vitamin B_{12}	Water soluble, involved in DNA synthesis and cell division	Animal proteins	Dietary deficiency may be seen in vegan diets; Low vitamin B_{12} status may be a risk factor for NTDs *(122)*
Vitamin C (ascorbic acid)	Water soluble, reduces free radicals. Involved in collagen formation. Essential for optimal iron absorption	Fruits and vegetables	Deficiencies associated with increased risk for PROM and preeclampsia *(123,124)*
Vitamin D (calciferol)	Fat soluble, involved in bone formation and mineralization; Needed for calcium absorption	Fortified milk; UV light required for vitamin conversion to active form	Deficiency associated with negative effects on calcium homeostasis and skeletal mineralization of the neonate (congenital rickets, craniotabes, lower bone mineral content) *(125)*

Vitamin E (tocopherols)	Fat soluble, antioxidant	Animal protein and fats	Deficiency associated with preeclampsia *(126)*
Vitamin K_1 (phylloquinone)	Fat soluble, required for the synthesis of clotting factors II, VII, IX, X	Green leafy vegetables, tomatoes, dairy, and eggs	Deficiency associated with neonatal bleeding tendencies
Folic Acid	Water soluble, important for DNA synthesis and cell replication	Fortified grains, dried beans and leafy greens	Subclinical folate deficiency in early pregnancy associated with increased incidence of cleft lip/palate and NTDs *(52)*
Iron	Production of hemoglobin	Animal protein, fortified grains, dried beans	Maternal iron deficiency anemia increases risk for low birth weight, preterm labor, perinatal mortality *(127)*
Calcium	Building block of bone and tissue	Dairy and green leafy vegetables	Essential for fetal bone and tissue development
Zinc	Involved in nucleic acid and protein metabolism; Essential in early gestation	Oysters, animal protein, beans, and nuts	Deficiency associated with IUGR, congenital malformations, perinatal death, impaired immunological and cognitive development *(121)*

* Include craniofacial, CNS, thymic, and heart defects

Table 2
Nutrient Requirements in Pregnancy and Lactation *(43–48, 55a)**

	Nonpregnant	*Pregnancy*	*Lactation*
Energy	Based on age, weight, height, and level of physical activity	+ 0 kcal (1st trim) + 340 kcal (2nd trim) + 352 kcal (3rd trim)	+ 330 kcal (1st 6 mo) + 400 kcal (2nd 6 mo)
Protein	0.8 g/kg	+ 25 g	+ 25 g
Fat-soluble vitamins			
Vitamin A (retinol)	700 μg	770 μg	1300 μg
Vitamin D† (calciferol)	5 μg	5 μg	5 μg
Vitamin E (α-tocopherol)	15 mg	15 mg	19 mg
Vitamin K† (phylloquinone)	90 μg	90 μg	90 μg
Water-soluble vitamins			
Vitamin C	75 mg	85 mg	120 mg
Thiamin (B_1)	1.1 mg	1.4 mg	1.4 mg
Riboflavin (B_2)	1.1 mg	1.4 mg	1.6 mg
Niacin	14 mg	18 mg	17 mg
Pyridoxine (B_6)	1.3 mg	1.9 mg	2 mg
Folate	400 μg	600 μg	500 μg
Vitamin B_{12}	2.4 μg	2.6 μg	2.8 μg
Pantothenic acid†	5 mg	6 mg	7 mg
Biotin†	30 μg	30 μg	35 μg
Choline†	425 mg	450 mg	550 mg
Minerals			
Calcium†	1000 mg	1000 mg	1000 mg
Chromium†	25 μg	30 μg	45 μg
Copper	0.9 mg	1 mg	1.3 mg
Iodine	150 μg	220 μg	290 μg
Iron	18 mg	27 mg	9 mg
Magnesium	310 mg	350 mg	31 mg
Manganese†	1.8 mg	2 mg	2.6 mg
Molybdenum	45 μg	50 μg	50 μg
Phosphorus	700 mg	700 mg	700 mg
Selenium	55 μg	60 μg	70 μg
Zinc	8 mg	11 mg	12 mg

* Compared with requirements for nonpregnant women 19–30 years of age

† Adequate intake (AI) level, all others represent Recommended Dietary Allowances (RDA)

of elevated maternal serum α-fetoprotein values, a marker used to screen for open NTDs *(54)* along with a 25% decline in the prevalence of open NTDs *(55)*. Thus folate is not only a nutrient needed to prevent megaloblastic anemia in pregnancy but also a vitamin essential for reproductive health.

Folate supplements should be administered 3 months prior to conception and throughout the first trimester. Since the preconceptional period is the optimal time for ensuring adequate folate consumption, the RDA is for all fertile women to take at least 400–800 μg/day *(55a)*. If the mother has had a prior child affected by a neural tube defect, supplementation in subsequent pregnancies should be increased to 4 mg/day *(56)*.

3.2. Iron

Iron is essential for the production of maternal hemoglobin and for fetal–placental development. In normal pregnancy, the RDA is 30 mg/day. The absorption of iron is very inefficient and only 10% of this will be absorbed. The amount of iron absorbed from diet together with that mobilized from maternal stores is insufficient to meet maternal demands in pregnancy *(57)*. As such, supplementation is recommended throughout pregnancy. Of note, iron competes with both copper and zinc at intestinal absorption sites and cosupplementation of these compounds is recommended via prenatal vitamins when iron supplementation is required.

Studies have shown up to a twofold increase in risk for preterm labor in women with iron deficiency anemia (IDA) in the first or second trimester, with the risk depending on the degree of hemoglobin deficiency *(58)*. Severe anemia (Hb <6 g/dL) has been associated with reduced amniotic fluid volume, fetal cerebral vasodilatation, and nonreassuring fetal heart rate patterns *(59)*. For expectant mothers with IDA in the second or third trimester, it is recommended that an additional iron supplementation of 30–120 mg/day be given until the IDA is corrected. Due to the implications of severe IDA, it is critical to treat aggressively with RBC transfusions, especially if there are signs of fetal hypoxemia.

3.3. Vitamin A

Vitamin A (retinol) is a fat-soluble vitamin (a retinoid) important for the maintenance of visual function. The RDA for pregnant women is 770 μg (700 μg in nonpregnant women), which corresponds to approximately 2600 IU of vitamin A per day using the previous dosing units. Beta-carotene is one of several plant-synthesized carotenoids that are partially converted to retinol during or after absorption *(60)*. These are often referred to as pro-vitamin A carotenoids (e.g., β-carotene, α-carotene, β-cryptoxanthin). Although animal studies have identified the teratogenic potential of retinoids, carotenoids have not been shown to be teratogenic *(60)*. In humans, doses exceeding 15,000 IU (4500 μg)/d are often used to treat acne (i.e., isotretinoin). Research has shown that these levels of synthetic retinoids can cause a 25% increase in congenital fetal anomalies *(61)*. This "retinoic acid embryopathy" is characterized by craniofacial, cardiac, thymic, and central nervous system structure abnormalities (cranial–neural–crest defects). Consumption of dietary vitamin A at levels above 10,000 IU (3000 μg)/

day has also been associated with these congenital defects *(62)*, although not in all studies *(63)*. Since well-balanced diets provide the RDA for vitamin A in pregnant and lactating women, a risk– benefit approach would suggest not recommending daily supplementation in normal pregnancies.

4. SPECIAL MATERNAL CONSIDERATIONS: DRUGS AND DISEASE WHICH AFFECT NUTRIENT STATUS

4.1. Antiepileptics and Vitamin K

Epilepsy is a common major neurological complication affecting approximately 0.5% of all pregnancies *(64)*. Antiepileptic medications, such as phenobarbital, phenytoin, and carbamazepine, have been shown to cross the placenta and induce hepatic microsomal enzymes in the fetal liver, potentially inducing the degradation of vitamin K. Several studies suggest that these enzyme-inducing antiepileptic drugs (AEDs) may result in neonatal bleeding due to fetal vitamin K deficiency *(65)*. As such, it came into common practice to provide prenatal administration of oral vitamin K to pregnant epileptic women taking AEDs in addition to the recommended prophylactic dose given to neonates shortly after birth to help prevent hemorrhagic disease in newborns. It is estimated that 24–40% of women with epilepsy receive vitamin K prophylaxis during the last month of pregnancy *(66)*.

Recent evidence does not support the notion that newborns of women treated with AEDs are at increased risk of hemorrhagic disease. Antenatal vitamin K can be prescribed on an individualized basis in certain circumstances, such as imminent premature delivery *(67)*; however, prophylaxis is not considered routine practice for all epileptic pregnant women on AED *(67)*.

4.2. Folic Acid Antagonists

There are two groups of folate antagonists. Dihydrofolate reductase (DHFR) inhibitors displace folate from the enzyme, blocking the conversion of folate to its more active reduced metabolites *(68)*. Aminopterin, methotrexate, sulfasalazine, pyrimethamine, triamterene, and trimethoprim are included in this group. The second group of folate antagonists may affect other enzymes of folate metabolism, impair the absorption of folate, or increase the degradation of folate *(69)*. These include primarily AEDs such as carbamazepine, phenytoin, primidone, and phenobarbital (see Chapters 17 and 18).

The concern with folic acid antagonists in pregnancy involves their ability to interfere with the metabolism of folate and thus theoretically placing the fetus at risk of defects associated with folate deficiency (i.e., NTDs). Epidemiological studies have shown that folic acid antagonists may increase the risk not only of NTDs but also of cardiovascular defects, oral clefts, and urinary tract defects *(69)*. The folic acid component of multivitamins may reduce the risks of defects associated with DHFR inhibitors; however, evidence suggests that supplementation may not protect the fetus from the risks associated with AEDs *(69)*. This is not surprising since there has been a direct fetal toxic effect proposed for drugs such as phenytoin and phenobarbital that extend beyond their ability to affect maternal and fetal folate levels *(70)*.

4.3. Hyperemesis Gravidarum

Nausea and vomiting in pregnancy (NVP) is the most common medical condition in pregnancy affecting 50–90% of women *(71)*. Hyperemesis gravidarum is defined as persistent vomiting leading to a 5% weight loss of prepregnancy weight along with electrolyte imbalance and ketonuria and occurs in 1% of pregnancies *(71)*. The pathogenesis of NVP is poorly understood and the etiology is likely multifactorial *(72)*.

Following the thalidomide scare and the voluntary withdrawal of Bendectin® in the United States in 1983, the use of pharmacological antiemetic therapy has been used with great caution by pregnant women due to misconceptions of contraindication in pregnancy *(73)*. However, the Society of Obstetrics and Gynaecology of Canada (SOGC) has clearly outlined recommendations in the treatment of NVP since early treatment can improve quality of life, decrease hospitalizations and additional office visits, and reduce time lost from work *(72)*. Recommendations include beginning with dietary and lifestyle changes, including eating small, frequent meals consisting of bland food. Alternate remedies such as ginger supplementation, acupuncture, and acupressure may also be useful. When conservative measures are not sufficient to provide relief, doxylamine/pyridoxine combination (Diclectin®) should be the standard of care since it has the greatest body of evidence to support its efficacy and safety *(72)*. The use of other histamine receptor (H_1) antagonists (i.e., dimenhydrinate, diphenhydramine, hydroxyzine) is considered safe in pregnancy and may be considered in the management of acute or breakthrough episodes of NVP. Metoclopramide is safe in the management of NVP; however, evidence for its efficacy is limited *(72)*. When NVP is refractory to initial recommended pharmacotherapy, investigations of other potential causes should be undertaken *(72)*.

5. PHYSIOLOGIC CHANGES AND NUTRIENT REQUIREMENTS IN LACTATION

During lactation and in the postnatal period, the physiologic changes which had occurred during pregnancy begin to revert to their prepregnancy state. The number and size of uterine vessels which had increased during pregnancy will diminish. Extracellular volume lessens with a diuresis and increased blood volume will return to normal within 1 week *(57)*. It may take days or weeks for cardiac output and other cardiac parameters to return to prepregnancy values *(74,75)*, while the hemostatic changes, such as increased coagulability, also normalize in the 4–6 weeks after delivery *(76)*.

Postnatally, human milk production is divided into three distinct stages. The breasts begin to secret colostrum within 24 h after delivery, a yellowish secretion that persists for several days. Following colostrum is transitional milk, which has a composition that can be highly variable between mothers and even over time within the same mother *(77)*. The transition to mature milk can take several weeks after which time the composition of human milk is relatively stable *(77)*. Colostrum contains higher proportions of minerals, vitamins, and proteins than transitional or mature milk but is lower in fat content and energy value *(78)*. Colostrum also contains relatively high concentrations of immunoglobulins.

Breastfeeding is certainly the optimal form of human infant nutrition, recommended for nearly all women and their infants. Human milk will meet all the nutritional requirements of a suckling infant. The benefits of breastfeeding transcend cultural, environmental, and geographic barriers *(79)*. While its advantages are striking in the developing world, even in industrialized nations such as the United States and Canada, the benefits are still very apparent *(79,80)*. Exclusive breastfeeding is associated with reductions in a number childhood illnesses including otitis media *(81,82)*, sudden infant death syndrome *(83)*, diarrhea *(84)*, necrotizing enterocolitis *(85)*, and respiratory infections *(81)*. A number of studies have also shown improvements in the child's cognitive and neurobehavioral outcomes *(79,86)*. Benefits to the mother include decreased risks of breast cancer *(87,88)*, ovarian cancer *(89)*, and osteoporosis *(90)*.

The increased nutritional requirements of pregnancy do not end at delivery. In fact during lactation, the mother may notice an increase in appetite and thirst. Breastfeeding women are encouraged to continue eating well-balanced diets; however, routine supplementation is not necessarily required *(91)*. Lactation creates energy requirement for the mother and although some energy stores will be present from pregnancy, women may require additional intakes of approximately 500 kcal per day during lactation compared to prepregnancy intakes. Generally, lactating women require greater vitamin and mineral intake as compared to the nonpregnant or lactating patients. A summary of the nutrient requirements in lactation is shown in Table 2.

Despite the incredible demands that lactation makes on the maternal system, it is interesting to note that even when the maternal diet is suboptimal, and lacking in nutrients, milk production remains relatively unchanged *(78)*. Only in instances of severe maternal malnutrition or dehydration, such as those observed during famine, is there an impact seen on maternal milk and subsequent infant health *(92)*.

6. DRUG DISTRIBUTION INTO HUMAN MILK

The process of selecting the appropriate pharmacological treatment for a lactating woman is a complicated one. Any risk–benefit assessment must consider both the mother and the infant who may potentially be exposed to drug but who is also experiencing the benefits of mother's milk. Almost all drugs will gain access to the milk. When we consider the physicochemical properties of drugs, and the biological properties of breast milk and the mammary duct, it becomes apparent that drugs gain access to the mammary compartment as to any other bodily fluid or tissue. When measurements have been performed in humans, nearly all drugs have been detected in milk. Since most drugs are believed to passively diffuse into breast milk, transport across the mammary barrier is governed by standard pharmacokinetic and pharmacodynamic principles, whereby drugs diffuse down the concentration gradient. A drug's lipid solubility, protein binding, acid/base characteristics, molecular weight, maternal systemic bioavailability, and its half-life all influence transport into milk *(93)*. Additionally, transport proteins may play a role in active secretion of drugs into milk *(93a)*. An infant's subsequent "dose" depends on the drug concentration in breast milk and the milk volume consumed. To further quantify the amount of drug that the infant will be systemically exposed to, one must also consider the gastrointestinal absorption or oral bioavailability *(94)* as well as the metabolism, elimination, and half-life of the drug in the infant *(94)*.

Human milk can be considered a compartment just as any other tissue. The reason most drugs passively diffuse into milk relates to their inherent physicochemical properties. That is, they are frequently small in molecular weight, usually less than 100–200 Da *(95)* and they are frequently weak acids or bases *(96)* Their small molecular weight allows for easy diffusion across the lipid bilayers of the mammary epithelia (alveolar cells) into mature milk. However, in the early stages of lactation, there are gaps between alveolar cells of the mammary glands *(93)*, allowing for greater permeability of drugs in the first few days of lactation; larger molecules may have easier access across these cells during this early period. Since human milk is also slightly more acidic than blood *(97)*, basic molecules will tend to become ionized, depending on their pKa and become "ion trapped" in the milk. Breast milk is relatively high in fat, about 3–4% *(98)*, such that drugs which are highly lipid soluble will tend to diffuse into breast milk to a greater extent. The protein binding of a drug also influences the diffusion into breast milk since it is only the free fraction of drug that is able to diffuse across the lipid bilayer. So, highly protein-bound drugs are less likely to diffuse into human milk.

The mother's plasma concentration of a drug will also influence the amount of drug in milk. This is because the concentrations in milk tend to correlate with concentrations in maternal plasma *(99)* and the two follow similar concentration–time profiles. In fact, when sampled over time, the concentration of drug in milk will display an initial peak followed by a more gradual decline in concentration. As maternal plasma concentrations of drug fall, so will the drug concentrations in breast milk, although there will be a lag in the breast milk concentrations to allow for distribution. Maternal plasma half-life of a drug, therefore, will also influence the amount of drug in milk. Drugs with very short half-lives may be present in the maternal systemic circulation only for brief periods. They may peak rapidly in plasma and dissipate just as rapidly, which may not allow for significant transfer into milk

6.1. Expressing and Quantifying Infant Exposure

Infant exposure to drugs in milk can be expressed in a number of ways. The milk-to-maternal plasma concentration ratio (M:P) is an expression used to represent the amount of drug reaching milk relative to maternal plasma concentrations. Obtaining an accurate M:P value (C_M/C_P) would involve measurement of drug concentration in maternal blood (C_P) and in milk (C_M) at precisely the same time. Practically speaking, however, this simultaneous sampling is rarely feasible. Another method to calculate this M:P value is to calculate the area under the curve (AUC) of the concentration–time profile of the drug in plasma and milk and then express M:P as a ratio of AUCs. Nevertheless, the M:P ratio can still fluctuate as milk composition is not homogenous from the fore milk to the hind milk and can even vary by time of day.

Despite these fluctuations, by steady state and with appropriate sampling, most drugs will display a relatively constant M:P value *(93,99)*, stabilizing once the drug has achieved steady-state concentrations in the mother and subsequently in the milk. Still, this is not an ideal method of estimating infant risk since it does not necessarily give information about infant dose. It is merely an indication of relative drug disposition, which could probably have been predicted from its physicochemical characteristics as described above. When the M:P value = 1, the milk and the plasma levels are similar; however, there is no indication of what those levels are. In fact, this could mean that levels are low in both milk and plasma.

A more appropriate method of quantifying infant exposure is the relative infant dose (RID), as a percentage of a weight-adjusted dose. This value is calculated by direct measurement of the drug in milk. For a fully breastfed infant, average milk intakes are assumed to be approximately 150 mL/kg/day *(100)*. Therefore the dose to the infant (D_{INF}) can be calculated as follows:

$$D_{\mathrm{INF}}\,(\text{per kg}) = C_{\mathrm{M}} \times 150\,\text{mL/kg/d}$$

Expressing this as a percentage of the maternal dose (D_{MOM}) provides information about the relative infant exposure:

$$\text{RID} = \left[\frac{D_{\mathrm{INF}}\,(\text{per kg})}{D_{\mathrm{MOM}}/\text{Mom's Wt}}\right] \times 100\%$$

The resulting percentage is the amount of drug the infant would be expected to be exposed to relative to the mother's weight-adjusted dose. This expression is complicated by the fact that a single-point concentration measurement would only give an idea of infant exposure if drug concentrations in milk stayed constant over time, which they do not. Therefore, some have suggested that milk be sampled repeatedly over a dosing interval and the AUC of the drug in milk be calculated. From the AUC, both the maximum and the average milk concentrations can be determined *(101)*. These can then be used in the above equation to represent maximum and average relative infant exposures. When available, actual therapeutic infant doses can also be used in this equation to express relative dose. This would be ideal and it allows the clinician and the patient to understand the amount that the suckling infant would ingest relative to how much an infant would be exposed to if the child required this treatment therapeutically. Generally, a cutoff of 10% has been considered acceptable as far as dose-related effects are concerned *(101)* and drugs whose relative dose is less than 10% are usually compatible with breastfeeding. Typically, this relative infant exposure is an easier concept to grasp for both health-care practitioners and lactating women who are making treatment choices and is preferred in counseling.

6.2. *Infant Issues*

Once a drug has entered into the breast milk compartment, estimating the exposure to the infant must still account for the disposition of the drug in the infant. That is, even if the drug is ingested by the infant, oral bioavailability and infant half-life play important roles in determining systemic exposure to the infant. Many drugs which enter the infant's gastrointestinal tract become unstable in the acidic environment of the stomach and are rapidly inactivated *(102)*. Other drugs, due to their physicochemical properties, are simply poorly absorbed from the gut, such as drugs which are not lipophilic or those which are very large *(95)*. Moreover, even after absorption, many drugs undergo significant metabolism in the liver before reaching the systemic circulation (first-pass effect). These barriers to absorption decrease the likelihood that significant drug concentrations will be found in the systemic circulation of the infant and hence the likelihood of dose-related adverse reactions. In short, although drugs may gain access to the milk, if they cannot be absorbed by the infant to any appreciable degree, they are not likely to pose significant risks of exposure.

Several investigators have suggested that breast milk concentrations of a drug can be predicted solely based on these physicochemical characteristics of the drug *(103–105)*. The models which have been proposed take into account the drug's pK_a, its lipid solubility, acid–base characteristics, protein binding, along with breast milk characteristics such as fat and protein content and pH. Ito and Koren *(106)* have also extrapolated this prediction of milk concentrations to estimate the exposure to an infant by considering the clearance in infants and the normal daily dose to infants.

Generally speaking, most drugs will gain access to the breast milk in very low concentrations, usually less than 10% of the maternal dose on a per kg basis (maternal weight-adjusted dose) and frequently less than 1% *(101)*. Because of these subclinical concentrations that will be delivered to the infant, most drugs pose little risk for use in the lactating patient. However, the possibility of local reactions within the gastrointestinal tract cannot be ruled out. Furthermore, nondose-related or idiosyncratic reactions, which may result from even extremely low concentrations in milk, cannot be predicted based on the concentrations of drug ingested by the infant. For most agents, however, clinicians can encourage women to continue breastfeeding. In cases where information is sparse or conflicting, infants should be observed for changes.

Information about specific drugs, their excretion into human milk, and their relative compatibility with breastfeeding has been reviewed extensively. There are a number of excellent resources for clinicians and patients who require specific information about the risks of drugs in lactation (Table 3).

7. SPECIAL CONSIDERATIONS: DRUGS THAT INFLUENCE MILK PRODUCTION OR INFANT INTAKE

7.1. *Drugs that Increase Milk Production*

Human milk production is highly regulated by prolactin and oxytocin. Both hormones are involved in milk production and milk ejection, although the precise

Table 3
Information Sources for Evaluating Risks of Drug use in Pregnancy or Lactation

Resource Type	*Resource Name*	*Pregnancy, Lactation, or Both*	*Additional Comments*
Website + telephone services	The Organization of Teratology Information Specialists http://www.otispregnancy.org	Both	Located throughout North America, service hours and topics covered vary
Website + textbook	TERIS – Teratogen Information System and online version of Shepard's Catalog of Teratogenic Agents http://depts.washington.edu/~terisweb/teris/index.html	Pregnancy	Subscription required, alone or as part of ReproRisk subscription within Micromedex
Website + textbook	Catalog of Teratogenic Agents, 11th ed. Shepard TH. Baltimore, MD: Johns Hopkins University Press, 2004	Pregnancy	Subscription required, alone or as part of ReproRisk subscription within Micromedex
Website	Reprotox: An Information System on Environmental Hazards to Human Reproduction and Development www.reprotox.org	Both	Subscription required, alone or as part of ReproRisk subscription within Micromedex
Website	Developmental and Reproductive Toxicology Database (DART): National Library of Medicine http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?DARTETIC.htm	Both	Free database of reproductive and developmental toxicology literature
Website	LactMed, National Library of Medicine http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT	Lactation	Free database, regularly reviewed by editorial board

Textbook	Drugs During Pregnancy and Lactation, 2nd ed. Schaefer C, Peters P, Miller RK. London, UK: Elsevier, 2007	Both	
Textbook	Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, 7th ed. Briggs, Freeman & Yaffe. Baltimore, MD: Lippincott, Williams & Wilkins, 2005	Both	Subscription for quarterly updates also available
Textbook	Drugs and Human Lactation, PN Bennett and AA Jensen, Amsterdam: Elsevier, 1996 *(95)*	Lactation	Not recently updated
Textbook	Medications and Mothers' Milk, T. Hale, Amarillo, TX: Pharmasoft Publishing, 2006	Lactation	Published frequently
Article	Transfer of drugs and other chemicals into human milk. American Academy of Pediatrics Committee on Drugs. Pediatrics (2001);108:776–789	Lactation	Consensus guideline from the AAP, updated periodically
Article	Drugs that affect the fetus and newborn infant via the placenta or breast milk. Pediatr Clin North Am 2004;51:539–579	Both	Recent review

mechanism of milk production are complex and do involve several hormones *(78)*. The regulation by these hormones can be disturbed by drugs particularly those which either stimulate or suppress prolactin release. Dopamine, for example, acts on the pituitary to decrease prolactin, thereby decreasing milk production.

Drugs which have an antidopaminergic effect such as domperidone and metoclopramide can stimulate milk production (galactogogues) and are used clinically to do so *(107,108)*. Neither has been shown to cause serious adverse effects in infants. Chlorpromazine, an antipsychotic, blocks the dopamine receptor, which would increase prolactin and subsequently breast milk. It was shown to be clinically effective in doing so *(109)*; however, its unfavorable side effect profile (e.g., extrapyramidal effects) would make it less attractive as a galactogogue. Human growth hormone was also shown to increase milk production *(110,111)* though little is known about its safety or mechanism of action and at this time, growth hormone is principally used to increase milk production in cows. One human trial investigated the use of thyrotropin-releasing hormone (TRH) for increasing milk production *(112)* as it will increase prolactin release. Though effective, use of TRH has been limited, possibly due to its unknown effects on maternal thyroid function when used for this indication.

7.2. Drugs that May Decrease Milk Yield

As part of family planning, many women will need to consider their contraceptive choices during lactation. Hormonal contraceptives are a mainstay in this regard; however, because they modify the normal hormonal milieu of the woman, they are likely to have an impact on lactation and milk production. Current recommendations suggest that women should consider progestin-only agents medroxyprogesterone or levonorgestrel implants as they do not impair milk volume *(113)*. In contrast, the estrogen–progestin combination contraceptives are not recommended since they may decrease milk yield. The literature suggesting this is predominantly based on earlier data with higher dose estrogen-containing products which are no longer available on the market. A systematic review of the issue could not establish sufficient evidence that hormonal contraceptives affected milk quality or quantity *(114)*. Nevertheless, most authorities recommend using the previously mentioned products as first-line hormonal contraceptives in lactating women *(113)*.

Studies have shown that alcohol disrupts the hormonal milieu in the lactating woman and may impair milk ejection *(115,116)*. In addition, infants seem to respond to alcohol-induced flavor changes by consuming less milk *(117,118)*. Though occasional use of small amounts of alcohol in a lactating women is unlikely to pose significant risk, based on these data, it would be prudent to avoid high-dose or chronic alcohol consumption in lactating women.

8. SUMMARY AND RECOMMENDATIONS

In an ideal world, randomized controlled studies would be conducted to precisely document and investigate this unique population. However, it remains ethically difficult to justify clinical trials in pregnant or lactating women. Withholding treatment from such patients for research purposes would not be reasonable and as evidence for the benefits of particular nutrients becomes more prevalent, clinicians are obligated to encourage supplementation, even in the absence of clinical trials. Practically speaking, these studies are difficult to perform and as a result data have often been limited to observational trials, retrospective studies, or case reports and case series. In the case of observational data, studies are therefore limited by the number of patients who actually require a specific medication and from whom appropriate data can be collected. Investigating the mechanisms of harm, and in particular the interactions with nutritional components, adds a level of complexity to such research *(119–127)*. For example, the clinical consequence of drug competition for a transporter known to secrete vitamins into milk is not yet known *(128)*. As a result, the medical community remains cautious, acknowledging that questions linger and research into the efficacy and safety of drugs in pregnancy and in lactation needs to continue.

In a common sense approach, pregnant and lactating patients should be offered treatment that would be most clinically effective for them and which still takes into account the fetal and infant safety data. Close monitoring of the mother and the infant and drug measurements may help to provide an accurate picture of exposure. Strong evidence has emerged about the tremendous benefits of adequate maternal nutrition in preventing birth defects and promoting the well-being in their children. The prevention of specific birth defects with nutrient supplementation may provide the key to the mechanisms by which some drugs cause specific malformations and, more importantly, may lead to advances in prevention.

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22 Drug–Nutrient Interactions in the Elderly

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Objectives

- Provide a description of who makes up the elderly population.
- Identify risk factors for drug–nutrient interactions in the elderly.
- Describe examples of drug–nutrient interactions in the elderly.

Key Words: Geriatric; health care; malnutrition; polypharmacy

1. INTRODUCTION

The goal of geriatric pharmacotherapy is to promote successful aging by maintaining functional independence, preventing disability and iatrogenic disease, and increasing health-related quality of life. The prevalence of drug use in the elderly is widely recognized, as are many of the consequences. These include a higher incidence of adverse drug events and drug–nutrient interactions *(1)*. The elderly are more prone to experience drug–nutrient interactions, given their higher use of medication, chronic and cumulative disorders, and the likelihood of marginal nutritional state.

1.1. The Elderly

Numbering well over 37 million, the elderly, arbitrarily defined as those 65 years of age and older, constitute approximately 12.4% of the population of the United States. This segment of the population is expected to increase to 55 million by 2020. By the year 2050 the elderly cohort will grow to approximately 21% of the nation's population, with the "old-old" cohort, aged 85 years and older, being the most rapidly growing segment of the population *(2)*. Demographics aside, elder adults are the most heterogeneous population with respect to physical, social, and health status *(3)*. So the degree of frailty or disability is more clinically meaningful than an individual's chronological age. Frailty refers to a loss of physiologic reserve that

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makes a person susceptible to disability from minor stresses *(4)*. Any definition of frailty must include multisystem impairment, instability, change over time, an association with aging, and an associated increased risk of adverse outcome *(5)*. Although several definitions exist for disability (e.g., impairment of a specific function in activities of daily living), the prevalence rate is declining among the elderly *(6)*. This is in part explained by younger cohorts of elderly living in better health for longer periods of time with implications for reduced health-care expenditures *(7,8)*. Successful aging has been described as a process by which deleterious effects are minimized and function is preserved *(9)*. One 75-year-old man may be viewed as being a frail elder if he is suffering from chronic disease and disability, whereas another 75-year-old man may be viewed as having aged "successfully" if he has limited disease and disability *(9,10)*. Unfortunately the elderly have the highest rate of acute illness, as well as chronic illness and disability *(11,12)*. The presentation of chronic disease increases with age as 80% of the elderly population has at least one chronic condition *(13,14)*. As a result, the elderly use a disproportionate amount of medication.

1.2. Medication Use

Older adults account for at least one-third of the prescription and nonprescription medication use even though they only comprise about 12.4% of the US population *(15,16)*. Data on drug use in the elderly vary by cohort age and clinical setting. The average number of agents used increases with age, with an average of 4.4 drugs for those 80 years old and above. Drug use is significant in institutionalized elderly, with 9% taking 10 or more drugs daily *(17)*. Patients in long-term care facilities can be at considerable risk for drug–nutrient interactions, where drug use averages five agents per patient per month, placing them at risk for about two potential interactions in that time *(18)*. Although no simultaneous assessment of nutritional status was performed in a group of patients surveyed, the most frequently used medications were those associated with nutritional alterations *(17)*. Many of the interactions identified relate to the gastrointestinal tract or those that impact on electrolyte status. Available data indicate that 91–94% of ambulatory adults aged 65 and older use medications, 44–57% using five or more, and 12% using ten or more medications *(19)*. Of rural elderly, 10% use five or more prescription drugs at a given point in time *(12)*.

Community-dwelling elders use analgesics, diuretics, cardiovascular medications, and sedatives often, whereas nursing home residents use psychoactive medications most often, followed by diuretics, antihypertensives, analgesics, cardiovascular medications, and antibiotics *(12,13,20–22)*. One well-known study sought to examine the pharmacoepidemiology of prescription medication use in community-dwelling elderly living in rural Pennsylvania *(12)*. The authors found that among more than 900 participants, over 71% reported taking at least one prescription medication. The old-old participants reported taking more cardiovascular agents, anticoagulants, vasodilating agents, potassium supplements, and diuretics than did the younger elderly *(12)*. Self-treatment with over-the-counter medications is common, especially for chronic disease states whose prevalence increases with age, such as arthritis and constipation. The most frequently used over-the-counter medications are analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDS), insulin, and gastrointestinal products such as laxatives.

In addition to high utilization of prescription and over-the-counter medications, the use of dietary supplements (i.e., nutrients, herbal medicine, and other natural health products) is also increasing. Surveys suggest that 25–59% of elderly use at least one dietary supplement product *(19,23–27)*. Common supplements used in the elderly include multivitamin–multimineral products, vitamin E, vitamin C, calcium, gingko, ginseng, garlic, saw palmetto, and St. John's wort *(23,24,28,29)*. The rising popularity and utilization of supplements is explained by the high price of medication and patient dissatisfaction with conventional medical treatment *(30,31)*. Vitamin and mineral supplement intake is often highest in those with the best dietary intakes of those nutrients, setting the stage for drug–nutrient interactions and potentially deleterious effects of excessive dosing. For example, while pharmacologic doses of vitamin E may play a role in modulating insulin action in the elderly, it may increase the risk of bleeding with warfarin and may also increase the risk or severity of infection in older individuals *(32–34)*. One report identified that 54% of elderly patients using nonnutrient dietary supplements (three products on average) with their medication regimen (six on average) were taking at least one drug–supplement combination that could cause a recognized interaction *(25)*. It bears keeping in mind that many interactions involving dietary supplements are based on case reports or on theoretical grounds and that no prospective evaluation exists to identify the true prevalence or clinical relevance of many of these interactions (see Chapter 12).

1.3. Appropriateness of Medication Use

Assuring medication appropriateness in the elderly is a concept popular with the provision of pharmaceutical care *(35–41)*. The elderly are at risk of specific drug-related problems. These can include adverse drug reactions, withdrawal events, cognitive impairment, medication error, overdose, therapeutic failure, nonadherence and inappropriate medication use, and drug interactions that may encompass drug–nutrient interactions *(42,43)*. The screening and evaluation of drug interactions is one component in ensuring medication appropriateness and should encompass screening for drug–nutrient interactions *(44,45)*. Because drug interactions are common, it is important for the clinician to be knowledgeable about an interaction, to recognize an interaction, to understand its potential implication, and to determine an appropriate course of action in the management of a potential interaction (see Chapter 1).

The geriatric population is at particularly high risk of developing adverse drug events, including drug–nutrient interactions, for several reasons, with the most consistently reported risk factor being polypharmacy. The risk of adverse drug events increases exponentially as the number of medications increases *(46–50)*. Other associated or suspected risk factors include comorbidity, history of a previous event, changes in pharmacokinetics and pharmacodynamics, nonadherence, and fragmented health care *(46,51,52)*. Although controversial, it is unlikely that age, in and of itself, is a risk factor for adverse drug events *(53,54)*.

Because the elderly utilize a disproportionate percentage of medications and are at risk of developing a host of drug-related problems, a list of medications best avoided in the elderly was developed by Beers and colleagues *(55)*. Using the Beers' criteria, nearly 25% of community-dwelling elderly patients received potentially inappropriate medications *(56–59)*. Based on an evaluation of a national database, it is estimated that the elderly are prescribed at least one potentially inappropriate medication at 4.5% of the over 10 million outpatient visits they make *(60)*. The influence of many of these drugs has not been as well documented vis-à-vis nutritional implications. The prevalence rates of adverse drug events in the community have been shown to range from 2.5% to as high as 50.6%, in long-term care 9.5–67.4%, and in the hospital setting 1.5–44% *(46–50,52,61–65)*. In nursing home residents, adverse drug events occur in 22%, with as many as 20,000 life-threatening or fatal events annually in the United States, many of which are preventable *(66)*. Often the drugs themselves are not so much the problem as is the way in which they are used *(67)*.

Analysis of self-reported adverse drug events in community veterans showed that cardiovascular (33.3%), central nervous system (27.8%), musculoskeletal (9.7%), respiratory (5.6%), endocrine (4.2%), and gastrointestinal (2.8%) medications were most likely to cause an adverse drug event *(61)*. Analysis of those associated with hospital admissions in patients 50 years and above showed that corticosteroid, digoxin, NSAID, antihypertensive, and benzodiazepine use were common *(50)*. The number of medications and the number of diseases on admission were also associated with the risk of an adverse drug event, leading to hospitalization *(50)*.

It has been estimated that for every dollar spent on medication in a nursing facility, $1.33 is spent treating a drug-related problem *(68)*. In the ambulatory setting, the cost of these adverse drug events was approximated to be $76.6 billion *(69)*. This does not include problems of underutilization. The literature (e.g., cardiovascular) suggests that some effective medications are actually underused in the elderly (e.g., β-blockers, angiotensin-converting enzyme inhibitors, warfarin) despite evidence supporting their efficacy in these patients and consensus statements advocating their use *(70–78)*. Many adverse drug events are thought to be preventable with a study of hospitalized patients, indicating that, compared to their younger counterparts, the elderly had a higher rate of preventable events (5.3% vs 2.8%, $P = 0.001$) *(53)*. The authors suggest that this was due to more complex medical issues in the elderly rather than to less aggressive or less appropriate care *(53)*. Clearly, drug-related problems are common in the elderly, costly to the health-care system, and oftentimes preventable *(56)*. Unfortunately, the proportion that may be related to drug–nutrient interactions is not yet quantified.

2. A DESCRIPTION OF PHYSIOLOGIC ALTERATIONS IN THE ELDERLY

Age-related physiologic changes result in a functional decline of organ systems and homeostatic mechanisms, but at variable rates in different patients *(3,79–81)*. The resultant decline in reserve capacity can impair an individual's ability to respond to physiologic stress and to "bounce back" from illness. Functional decline

Table 1
Age- Related Physiologic Changes

Organ System	*Physiologic Change*
Body composition	↓ Total body water
	↓ Lean body mass
	↑ Body fat
	↓ Albumin
	↑ α_1-Acid glycoprotein
Integument	↓ Collagen and elastin leading to epithelial and dermal thinning and wrinkling
	Changes in pigmentation due to loss of melanocytes
	↓ Number of melanocytes in the hair bulbs
	↓ Number of hair follicles
Skeletal system	Osteopenia
Sensory changes	↓ Accommodation of the eye lens, causing presbyopia
	↓ Peripheral vision from glaucoma and night-time vision
	Macular degeneration leading to loss of central vision
	Cataracts
	Presbycusis (high-frequency hearing loss)
	↑ Threshold for smell, taste, pain, and temperature
Central nervous system	↓ Brain mass and increase in neuronal apoptosis
	↓ Neurotransmitters (some)
	↓ Cognitive abilities (some)
Cardiovascular system	↓ Cardiac mass
	Loss of myocytes and subsequent hypertrophy
	↓ Myocardial sensitivity to β-adrenergic stimulation
	↓ Baroreceptor function
	↓ Maximal cardiac output with exercise
	↑ Total peripheral resistance
	Delayed diastolic relaxation
Pulmonary system	↓ Lung mass
	↓ Respiratory muscle strength
	↓ Chest wall compliance
	↓ Functional alveolar surface area
	↓ Tidal volume leading to decreased response to hypercapnia and hypoxia
	↓ Forced expiratory flow rates
Oral changes	Altered dentition
	↓ Ability to taste sweet, sour, and bitter
Gastrointestinal system	↓ Lower esophageal sphincter pressure
	Potential ↑ in gastric pH
	Delay in gastric emptying
	↓ Gastrointestinal blood flow
	↓ Intestinal mucosal surface area

(*Continued*)

Table 1
(Continued)

Organ System	*Physiologic Change*
Liver	↓ Liver mass ↓ Blood flow leading to decreased presystemic metabolism of medications with high extraction ratios
Renal system	↓ Renal mass and blood flow ↓ Renal tubular function (secretion) ↓Glomerular filtration ↑ Filtration fraction
Genitourinary system	Atrophy of the vagina Hyperplasia of the prostate Potential predisposition to urinary incontinence
Endocrine system	Atrophy of the thyroid gland and ↑ incidence of thyroid disease ↑ Incidence of diabetes mellitus
Immune system	↓ Cell-mediated immunity

ensues and progresses and independence is jeopardized. Table 1 provides a summary of age-related physiologic changes by organ system. The clinical implication for some of these physiologic changes on drug therapy and nutritional status is more readily apparent than others. Several of these are highlighted further.

2.1. Body Composition

Body composition changes with age, resulting in an increase in total body fat and a decrease in total body water and lean mass in the elderly. This change in composition affects the distribution of medications in the elderly. Although there are exceptions, in general the volume of distribution of water-soluble medications, such as digoxin *(82)*, ethanol *(82)* cimetidine, and lithium *(83)*, is decreased due to the decrease in total body water *(84)*. This leads to higher plasma concentrations of these medications and the potential need for lower initial doses. Sproule and colleagues reviewed the differential pharmacokinetics of lithium in elderly patients *(83)*. Their study suggests that lithium pharmacokinetics are influenced by age, with the elderly requiring approximately 30% less of a dose to achieve similar concentrations as those observed in the young *(83)*. This observation is likely due to an increase in body fat and a decrease in body water, resulting in a smaller volume of distribution of this water-soluble medication. The opposite is generally true of lipid-soluble medications. Since there is a relative increase in total body fat in the aged, the distribution of these medications can be increased and the plasma concentrations decreased, and if distributed to adipose tissue, they are slower to leave the fat compartment for excretion. Thus the half-life of these medications can sometimes be increased (depending upon other variables, such as blood flow) and accumulation can occur. Examples of such lipid-soluble medications are diazepam and chlordiazepoxide.

Changes in protein binding also affect the distribution of medications in the elderly. A decrease in albumin concentration, due to age itself or more commonly chronic disease, can result in higher free concentrations and increased clearance of otherwise highly protein-bound (>90%), acidic medications. Often times, this is of little clinical significance. However, there are a few acidic, highly bound medications in which the increase in free concentration is noteworthy, including that of naproxen, phenytoin, valproate, and warfarin *(84)*. Highly bound medications have the potential to interact with other medications via competitive protein binding and they often possess other physicochemical properties, such as low extraction by the liver, and small volumes of distribution that together create a profile of a medication known as a narrow therapeutic index. Medications with narrow therapeutic indices are those in which the difference between blood levels needed to achieve efficacy and to cause toxicity is small. Phenytoin, valproate, and warfarin are classic examples of such medications with a narrow therapeutic index. Thus, vigilant monitoring of patients on these medications is the standard of care. Any interactions with these drugs, including drug–nutrient interactions, would be expected to be significant.

2.2. Gastrointestinal Function

Oral ulcers and poor dentition often occur in the elderly although they are probably secondary to poor hygiene and other diseases rather than to aging itself *(10)*. Nonetheless, 50% of elderly patients have an ulcerative, a hyperplastic, or an atrophic oral lesion *(10)*. The occurrence of these can have an impact on pharmacotherapy because some medications (e.g., phenytoin, corticosteroids, immunosuppressants, and certain antibiotics) can contribute to oral disease. Oral ulcers and poor dentition may also affect nutritional status due to decreased oral intake.

Xerostomia, or dry mouth, is also common in the elderly and can be exacerbated by any medication exhibiting anticholinergic properties such as the antihistamines, decongestants, ipratropium, antipsychotics, certain antidepressants, and urinary anticholinergic/antispasmodic agents, among others (see Chapter 15). Xerostomia is particularly disturbing to patients, because it can contribute to dental caries and it can cause difficulty in swallowing medication and food *(85)*.

Other changes in the gastrointestinal tract include achlorhydria, delayed gastric emptying, and a modest decrease in the intestinal mucosal surface area *(10,86)*. Theoretically these changes may affect the extent or the rate of absorption of certain medications. However, in most instances, this is not of clinical relevance. Moreover, one study by Hurwitz and colleagues suggest that basal gastric hypoacidity in healthy elderly may not be as common as previously thought *(87)*. The effects that these changes have on drug absorption are thought to be minimal in most instances, as few drugs have been demonstrated to have a significantly decreased rate or extent of absorption *(88)*. There is also little evidence to suggest that such changes in absorption have a clinically significant effect on pharmacological efficacy or safety. An exception to this are medications absorbed by active transport (e.g., calcium) whose decrease in absorption may be significant *(86,89,90)*. Some researchers suggest that the decreased absorption of calcium is associated with decreased production and activation of vitamin D or resistance to its effects *(91,92)*. Water-soluble vitamins are probably absorbed normally, including the absorption of vitamin B_{12} in patients without gastric atrophy *(86)*.

Little is known about the transdermal absorption of medications in the elderly. One small study analyzed the pharmacokinetics of a transdermal fentanyl patch in elderly patients vs young patients and found that the elderly required early patch removal due to side effects that were not observed in their younger counterparts. The study also found that higher serum concentrations accompanied the side effects observed in the elderly patients *(93)*. Lastly, the absorption of medications with high first-pass metabolism may be increased.

2.3. Liver Function

Hepatic mass declines by approximately 40% by age 80 *(3)*. This decrease in mass and in hepatic blood flow has the potential to decrease the metabolism of certain medications *(86,94)*. Medications that are most affected include those that undergo a large first-pass metabolism (e.g., fentanyl, propranolol) *(95)*, whereby the medication is in large part metabolized by the liver prior to systemic availability. Medications with a large first-pass metabolism rely primarily upon (hepatic mass and) blood flow for systemic clearance. In the case of decreased hepatic blood flow and decreased first-pass metabolism, the extent of absorption of these medications may be increased. Conversely, medications with a low hepatic extraction *(95)* (e.g., phenytoin, warfarin, valproic acid) rely primarily upon hepatic size and enzymatic activity for systemic clearance. Changes in hepatic physiology due to aging itself are difficult to quantify as diet, ethanol, tobacco use, and other medication also contribute to changes in drug metabolism *(84)*.

The metabolism of some medications in the elderly is decreased, whereas that of others is largely unaffected. Hepatic metabolism is affected by changes in hepatic mass, hepatic blood flow, and hepatic enzyme activity. In general, the metabolism of medications that undergo Phase I reactions (i.e., oxidation, reduction, dealkylation, hydroxylation) is decreased (e.g., diazepam, chlordiazepoxide), whereas medications that undergo Phase II reactions (i.e., glucuronidation, sulfation, acetylation) are unaffected (e.g., lorazepam, oxazepam) *(84,95,96)*. So from a pharmacokinetic standpoint, lorazepam or oxazepam would be preferred benzodiazepines in the elderly – although it is important to note that the elderly are particularly sensitive to the anxiolytic and sedative effects of all benzodiazepines due to changes in pharmacodynamics *(84)*.

Some medications when administered orally undergo first-pass metabolism by the intestine and liver before they are able to reach the bloodstream for distribution and effect. In the elderly, however, a decrease in metabolic capacity and hepatic blood flow leads to an increase in bioavailability of these medications with high extraction ratios (e.g., fentanyl, propranolol, verapamil) *(84)*. Because these medications are highly extracted from the liver, clearance is primarily dependent upon (hepatic mass and) blood flow. Medications that have a low extraction rate from the liver rely upon liver mass and functional activity of hepatic enzymes for clearance. Medications with intermediate hepatic clearance rely upon hepatic enzyme activity, hepatic mass, and blood flow for hepatic clearance *(95)*. CYP3A4 is the most prevalent isozyme responsible for metabolizing the largest percentage of medications. The clinician could check for other factors that are known to affect the metabolism of certain medications, such as diet, tobacco, and ethanol use.

2.4. Renal Function

The physiologic decline of the kidney and its implications are probably the most evident of organ systems with respect to altered medication handling. With age, there is a decrease in renal blood flow, kidney mass, and number of functioning glomeruli *(97,98)*. There are also renal tubular and vascular changes that lead to declining renal function *(97,98)*. In general, the creatinine clearance starts to decline in the fourth decade of life at a rate of approximately 1 mL/min/year *(99)*. The serum creatinine concentration may appear normal or unchanged in the aged despite true renal dysfunction *(100)*. This is observed because a decrease in the clearance of creatinine is offset by a decrease in creatinine production, due to a decline in muscle mass with age *(98)*.

The age-related decline in renal function, and therefore the renal elimination of medications, is of great clinical importance. Glomerular filtration is decreased in the elderly and its decline can be estimated by measuring the creatinine clearance *(84,101–103)*. An actual measurement of creatinine clearance via the 24-h collection of urine is often not feasible and may produce inaccurate results in patients with urinary incontinence and urinary retention. Therefore, the decline in glomerular filtration is often estimated using a creatinine clearance equation *(104)*. A decrease in the clearance of renally eliminated medications in the elderly may lead to increases in the area under the concentration–time curve (AUC), in half-life, and in steady-state concentrations, which may lead to toxicity. Therefore, many medications need to be dose-adjusted based on the extent of decline in the creatinine clearance (e.g., allopurinol, gabapentin, many antibiotics, histamine$_2$ receptor antagonists, digoxin, amantadine, pramipexole, ropinirole) *(84,101–103)*.

2.5. Pharmacokinetics and Pharmacodynamics

The changes in physiology described above are, in part, responsible for alterations in the absorption, distribution, metabolism, and excretion of medications. Study of the influence of aging on pharmacokinetics began in earnest in the early 1970s *(94)*. This information may also be utilized to identify risk factors for drug–nutrient interactions in the elderly. A summary of the known age-related changes in pharmacokinetic parameters seen in the elderly is given in Table 2.

The participation of elderly patients in early clinical and pharmacokinetic trials was very limited – often including only healthy elderly in single-dose pharmacokinetic studies, thereby not reflecting the clinical use of the medication. Presently, the US Food and Drug Administration (FDA) mandates that the elderly be

Table 2
Summary of Pharmacokinetic Changes in the Elderly *(84,95,101–103,108)*

Pharmacokinetic Parameter	*Pharmacokinetic Change*
Absorption	Rate of absorption affected more than extent of absorption
	Passive absorption unaffected
	Active absorption may be affected
	↑ Bioavailability of medications with high first-pass effect
	Little evidence to suggest that absorption changes result in clinically meaningful changes in outcome. Rarely is the dose adjusted prospectively
Distribution	↓ Albumin leading to increased free concentration of acidic medications that are highly protein bound (≥ 90%)
	↑ α1-Acid glycoprotein leading to decreased free concentrations of basic medications
	↑ Distribution of lipid-soluble medications potentially leading to lower blood concentrations and longer half-lives
	↓ Distribution of water-soluble medications potentially leading to higher blood concentrations
	Changes in volume of distribution primarily impact upon the loading dose of a medication with a dose-related response
	Rarely is the dose adjusted prospectively
Metabolism	Medications with high extraction rates are most affected in the elderly; a decrease in extraction occurs, leading to higher bioavailability (e.g. fentanyl, propranolol, verapamil)
	Rarely is the dose adjusted prospectively
Excretion	Pharmacokinetic parameter most clinically affected
	Decline in estimated creatinine clearance despite potentially "normal" serum creatinine value; "normal" serum creatinine reflects decrease in production of creatinine rather than normal renal function
	Dose is commonly adjusted prospectively for decreased estimated creatinine clearance

represented in clinical trials so that more can be learned about the differing pharmacokinetic effects of a particular medication in the young and the old. It mandates that pharmacokinetic and pharmacodynamic information derived from studies (formal studies or pharmacokinetic screens) in the elderly be described in the product labeling under a specific section devoted to geriatric use of the medication *(105)*. In 1997, the FDA established that prescription drug labeling includes information on "geriatric use" *(106)*. Although studying a new drug in the elderly is not required, clinical trials are expected to report data in populations for whom the drug will be marketed. Despite this, the numbers of elderly included remain small, with rare subjects 75 years and older. This is important to recognize, given the known heterogeneity of the population. Moreover, clinical recommendations made on the basis of limited pharmacokinetic data are difficult. Sproule and colleagues highlight this disconnect in their review of lithium pharmacokinetics in the elderly *(83)*. They highlight that even though there are some pharmacokinetic data on lithium in the aged, there have been no placebo-controlled studies of lithium in the aged, so clinical recommendations are based on extrapolation of small pharmacokinetic studies and anecdotal reports of lithium use in the aged *(83)*.

The in-depth study of pharmacodynamics in the elderly is limited to only a few medications or medication classes, most notably the benzodiazepines, β-adrenergic agents, calcium channel blockers, opioid analgesics, and warfarin *(84,107)*. However, many clinically relevant drug–nutrient interactions involve changes in pharmacodynamics. The pharmacodynamic changes that are observed with these medications in the aged are thought to be due to changes in the intrinsic sensitivity of the elderly to these agents, rather than to changes in pharmacokinetics. Such changes in intrinsic sensitivity are thought to occur at the level of the drug–receptor complex or from alterations in postreceptor events. It is here that interactions, including drug–nutrient interactions, may take place mechanistically *(81,108)*. The clinical effect of these changes is either an increased response or a decreased response to the above agents or classes.

Elderly patients are thought to exhibit an increased response to benzodiazepines, opioid analgesics, and warfarin *(81,84,96,109,110)*. They have been shown to inhibit more vitamin K-dependent clotting factor synthesis at similar plasma warfarin levels than their younger counterparts and are often able to achieve a therapeutic international normalized ratio (INR) at lower doses than younger patients *(111)*. The clinician should routinely check for drug–drug interactions and drug–nutrient interactions as many medications and foods are known to inhibit the metabolism of warfarin and increase the risk of bleeding.

Conversely, the elderly tend to exert an attenuated response to β-adrenergic agonism and antagonism and are therefore less responsive to β-agonist and β-antagonist medications *(81,96,108,112)*. Lastly, the effects of calcium channel blockers are also altered in the elderly. While the elderly possess a heightened response to the antihypertensive effects of calcium channel blockers, they also exhibit an attenuated response to the effects of calcium channel blockers on cardiac conduction *(81,84,107)*.

The FDA states, in a guidance document, that the number of pharmacodynamic differences to date is too small to warrant separate pharmacodynamic studies in the elderly as a routine requirement. Yet, one can argue that the reason why there is little known difference in pharmacodynamics between the young and old is because there has been little incentive to investigate potential differences. The FDA does recommend separate studies in sedative/ hypnotics, psychoactive medications, and in instances in which Phase II/III studies suggest large differences in safety or efficacy in elderly vs younger patients *(113)*.

2.6. Nutritional Status

Nutritional status is central to all the pieces of a traditional history and physical patient assessment and needs to be included for each individual patient. All health-care professionals involved in the care of geriatric patients should at least screen them for poor nutritional status when a clinical nutrition expert is unavailable.

Malnutrition is evident in many older persons for a variety of reasons – some physiologic and others pathologic *(114)*. Poor nutritional status may be defined by protein-calorie undernutrition, overnutrition, dehydration, or imbalances of specific nutrients determined by clinical history, physical examination, and laboratory findings. Addressing malnutrition can prevent morbidity including the increased risk of infection, pressure ulcers, poor wound healing, weakness, falls, osteopenia, macular degeneration, disturbed drug metabolism, cognitive deficits, as well as the mortality that is associated with poor nutritional status. The ability to identify those with malnutrition or at risk for malnutrition is therefore important. Serum albumin levels, an independent risk factor for all-cause mortality, likely reflect frailty and disease severity more than they reflect nutritional status in the elderly *(115)*.

A number of screening tests are available to help identify poor nutritional status in the elderly. These range from the simple SCALES evaluation (Table 3) to slightly longer screening tools. The DETERMINE checklist, using a 10-item form, can be used easily even by a nonhealth-care provider. The Level I screen that follows that checklist, while still easy, does require a health-care provider *(116)*. The Mini-Nutritional Assessment (MNA) is another rapid yet more sophisticated tool useful for identifying elderly patients with poor nutritional status *(117)*. The MNA has excellent sensitivity and specificity while being both reproducible and easy to administer *(118)*. Furthermore, it may be applied to healthy, frail, and sick elderly. A comparison of several screening tools is available *(118)*, any of which can be used to quickly identify those at risk for poor nutritional status. Most screening tools include “medication use” as a vital portion of the overall score. Given the relationship between malnutrition and poor outcome, all efforts at assessing nutritional status in the elderly are necessary and must include evaluation of drug–nutrient interactions.

The nonphysiologic causes of malnutrition, identified through weight loss, can be due to social, psychological, and/or medical causes. A popular

Table 3
Screen for Malnutrition *(114)*

S – Sadness
C – Cholesterol <4.14 mmol/L (160 mg/dL)
A – Albumin <40 g/L (4 g/dL)
L – Loss of weight
E – Eating problems (cognitive or physical)
S – Shopping problems or inability to prepare a meal

Table 4
Etiology of Weight Loss *(114,119,120,125)*

M – Medication(s)
E – Emotional problems (depression)
A – Alcoholism, anorexia, or abuse of elders
L – Late-life paranoia
S – Swallowing problems (dysphagia)

O – Oral problems
N – No money for food, counseling, or care (poverty); nosocomial infections

W – Wandering and other dementia-related behavior
H – Hyperthyroidism, hyperparathyroidism, hypoadrenalism
E – Enteric problems, including malabsorption
E – Eating problems, including inability to feed oneself
L – Low-salt, low-cholesterol and other therapeutic diets
S – Social problems, including ethnic preferences, isolation, etc.
Shopping and meal preparation problems

mnemonic for identifying the major treatable causes of malnutrition in the elderly, MEALS ON WHEELS (Table 4), begins with "Medication" *(119)*. At the most basic level, those drugs implicated in weight loss in the elderly can be identified among virtually all pharmacological classes. They include drugs that induce anorexia, malabsorption, or hypermetabolism (Table 5).

Both institutionalized elderly and those dwelling in the community are at risk for malnutrition, global or nutrient-specific. It has been estimated that malnutrition, defined predominantly as protein-calorie undernutrition, occurs in about 15% to as high as 25% of community-dwelling elderly, in as many as 65% of hospitalized elderly, and in 85% of those in long-term care institutions *(114,120,121)*. This does not include those with micronutrient (electrolyte, vitamin, and mineral) deficits or excesses. With age there may be decreased nutrient absorption, distribution, metabolism, and excretion. Deficits in dietary intake of micronutrients are more likely than macronutrients in elderly subjects living in institutions *(122)*. More than 90% of these subjects did not meet the recommended dietary allowance (RDA) for vitamin E, calcium, and folate, while additionally more than 80% of the men did not meet the RDA for pyridoxine and zinc. Rates of poor vitamin A or zinc status in the elderly may approach 20% and 25%, respectively *(121)*. Together these alterations in nutritional status can impact negatively on immune function, contributing to the risk of infection in this population *(121)*. For example, a study of community-acquired pneumonia in the elderly suggests that as many as 85% of the patients were malnourished *(123)*. A prospective follow-up study of elderly patients admitted emergently to a hospital for noncancer medical reasons revealed not only that 20% were malnourished but also that the mortality rate at 9 months in the malnourished group was 44% compared to 18% in the nonmalnourished patients ($P<0.001$) *(124)*.

Table 5
Medications that May Produce Weight Loss in the Elderly *(114,231–234)*

Mechanism of Weight Loss	*Medication*
Dysphagia	Alendronate, anticholinergics, antineoplastics and immunosuppressants, corticosteroids, iron, nonsteroidal anti-inflammatory drugs (NSAIDs), potassium, quinidine
Nausea, vomiting, diarrhea or anorexia	Amantadine, amiodarone, anesthetics, antibiotics (most), antineoplastics, cimetidine, colchicine, digoxin, erythromycin, iron salts, levodopa, lithium, metformin, metronidazole, NSAIDs, nutritional supplements, opioids, phenothiazines, potassium salts, selective serotonin reuptake inhibitors, spironolactone, theophylline, tricyclic antidepressants, vitamin D
Delayed gastric emptying	Anticholinergics, caffeine, calcium channel blockers, clonidine, dicyclomine, iron, meperidine, nitrates, opiates, oxybutynin, theophylline, tricyclic antidepressants, verapamil
Increased gastric emptying	Bethanachol, erythromycin, laxatives, metoclopramide, misoprostol
Altered taste or smell	Albuterol, allopurinol, amiloride, angiotensin-converting enzyme inhibitors, antihistamines, aspirin, bismuth, captopril, carbamazepine, chloral hydrate, chlorpropamine, digoxin, diltiazem, dipyridamole/aspirin, enalapril, flurazepam, iron, levodopa, lithium, metformin, metronidazole, nifedipine, opioids, penicillin, phenytoin, propranolol, thioridazine
Drowsiness (missed meals)	Antidepressants, antiemetics, antihistamines, antipsychotics, benzodiazepines, skeletal muscle relaxants
Depression	Anticonvulsants, barbiturates, benzodiazepines, β-blockers, clonidine, digoxin, levodopa, neuroleptic
Dry mouth	Antihistamines, anticholinergics, antipsychotics, benzodiazepines,diuretics, decongestants, tricyclic antidepressants
Malabsorption	Cholestyramine, colchicine, ganglionic blockers, laxatives (including sorbitol), methotrexate, neomycin
Hypermetabolism	Pseudoephedrine, theophylline, thyroxine, thyroid extracts, triiodothyronine

While protein-calorie and micronutrient deficits are associated with increased morbidity and mortality, the obese elderly are also at risk for morbidity and diminished quality of life. Data suggest the presence of a dysregulation of the feeding response with age *(125)*. There is also a decrease in lean body mass (sarcopenia) with aging. This may be accounted for in part by the physiologic anorexia of aging with central and peripheral mechanisms including inflammation *(125)*.

Micronutrient deficiencies include the vitamins pyridoxine, cobalamin, calciferol, and folic acid, and the minerals calcium, magnesium, and zinc. These nutrient deficits can result from reduced food intake or altered nutrient absorption, metabolism and excretion, or both. In one study of homebound elderly, the intake of several nutrients (magnesium, vitamins E and C, zinc, vitamin B_6, folate, vitamin B_{12}) was inadequate relative to the estimated average requirement in at least 25% of subjects *(126)*. Most concerning was that 95% of women did not meet the adequate intake level for calcium, and all but one subject had vitamin D intakes below the adequate intake level. Vitamin D deficits are associated with declines in muscle function, which impacts upon mobility and increases the risk of falls in the elderly *(127)*.

Risk factors for poor nutritional status in the elderly are numerous, with some data suggesting that two-thirds of independently living elderly are at significant risk *(128)*. Given that over 9.5 million elderly live alone in the United States, and their risk of being found helpless or worse in the home is 3.2% per year, there is clearly more to be done in terms of more seriously assessing this population *(129)*. The risk of malnutrition in the elderly occurs with depression, oral disorders, dementia, concurrent illnesses, and the medications used to manage them. Poor micronutrient status in turn may be responsible for some of the cognitive dysfunction seen in the elderly *(130,131)*. Given the fortification of the American food supply with folic acid in recent years, concerns have arisen about potentially irreversible neurologic dysfunction in elderly with marginal vitamin B_{12} status without apparent hematologic signs *(132)*.

While knowledge about optimal nutrition for the elderly is far from complete, differences between the young and the old are seen. More attention has been directed at specific nutrient dosing standards for the elderly *(133)*, which have for the most part been reflected in the most recent dietary reference intake volumes *(134)*. Coming to a consensus on requirements in the elderly necessitates reviewing and interpreting the available data. Interpreting biochemical indices of nutritional status in the elderly may be difficult due to the confounding by disease and by medications that are being used *(135)*. Many nursing home residents are reported to have low vitamin blood levels, which may be accounted for by poor intake as well as drug-induced alterations *(136)*. The clinical consequence of low circulating levels is likely less important than low levels of functional indices of vitamin status. For example, despite serum vitamin B_{12} levels in the normal range, many elderly may have clinically manifest, functional cobalamin deficits based on serum methylmalonic acid and homocysteine levels *(137,138)*. While pyridoxine status is reported to decline with aging, the data suggest that decreased intake, bioavailability, or total body clearance are unlikely to explain the alteration *(139,140)*. Depending on the assay method used, the prevalence of vitamin B_6 deficits in the elderly may be as high as 86% *(141)*. There exist age-dependent differences not only in nutrient requirements per se but also in the established ratio of one nutrient to another.

For example, the dose of vitamin B_6 required per gram of protein intake is lower for the elderly than for younger individuals *(142)*. Whether this relationship changes when consuming medications that alter pyridoxine status is not known.

Drug-induced nutritional problems can occur as a result of decreased food intake (inability to shop and prepare food due to altered mental status, as well as drug-induced oral problems and anorexia), malabsorption, altered metabolism, and excretion. These are more likely to occur in individuals with marginal nutritional status to begin with. The elderly are at high risk for many reasons including prolonged and chronic illnesses, the regimens used to manage them, and reduced dietary intake with age. Adverse drug reactions could include altered taste and smell, which would impact on food selection and intake. Drug reactions that include lightheadedness, breathlessness, joint pain, or impaired visual acuity could restrict food shopping or preparation, while loss of appetite and adverse drug effects on the gastrointestinal tract can limit food intake and absorption *(143)*.

Energy expenditure decreases with advancing age due to less physical activity and a lower metabolic rate. Energy requirements can be met at intakes of about 25 kcal/kg daily on average, while protein requirements remain at about 1 g/kg daily for the elderly. Fluid (water) needs of about 30 mL/kg per day remain important for the elderly to prevent significant consequences of dehydration. Compared with younger adults, the elderly have different requirements for a number of micronutrients (e.g., higher calcium, vitamin D, vitamin B_6, and vitamin B_{12} requirements, lower chromium and vitamin A requirements) based on altered absorption, circulating levels, physiologic measures, metabolism, or excretion.

The influence of food/nutrients on drug disposition and the specific effect in the elderly were extensively summarized at an international conference on nutrients, medications, and aging *(88)*. In that conference, the authors described the effects of food on absorption, diet components on enzyme induction, protein on metabolism, and malnutrition on metabolism *(144)*.

Drug-induced malnutrition is concerning, given the findings of marginal nutritional status in many elderly. What follows is a review of some medication consumed by the elderly that can affect food intake, nutrient absorption, metabolism, and excretion, as well as food influences on drug disposition.

3. CLINICAL EVIDENCE

3.1. Overview of Drug–Nutrient Interactions in the Elderly

The elderly are at risk for drug–nutrient interactions because they use a disproportionate amount of prescription and over-the-counter medications, often have poor nutritional status, and often are instructed to take their medication with meals to increase adherence. The presence of food may alter the rate and/or extent of drug absorption. A delayed rate of absorption is important only if it is necessary to achieve a rapid effect or a high peak concentration – taking the drug 1 h before or 2 h after food avoids the interaction. For most chronic therapies, the rate of absorption is less important since a steady-state blood level is likely attained and maintained. The effects of food that alter drug metabolism or excretion can also serve as the mechanism of drug–nutrient interactions *(145–152)*. The mechanism of drug–nutrient interaction may be through food acting as a physical barrier to drug absorption, by altering gastric emptying rate, or by reacting physicochemically with the drug (chelation, precipitation). In general, fatty meals decrease motility and gastric emptying rate, increasing the time the medication spends in the stomach. This may be important if the drug is unstable in an acidic environment or if rapid absorption is required. Conversely, small meals and liquid meals empty rapidly and may decrease time available for absorption.

Drug–nutrient interactions in elderly diabetics *(153)* and elderly cardiac patients have been reviewed and guidelines provided *(154)*. The risks vary not only depending on the medications used but also with dietary patterns and organ function. The consequence of these interactions in the diabetic, for example, includes hyperglycemia, hyperosmolar hyperglycemic state, neuropathies, and hypoglycemia with risk of pseudostroke *(153)*. In patients with cardiovascular disease, multiple risks for an interaction exist that involve reduced drug absorption, as well as drug-induced edema, anorexia, and micronutrient deficits *(154)*.

3.2. The Effect of Food on Drug Disposition in the Elderly

3.2.1. ENTERAL FORMULAS

Strategies to improve adherence with drug regimens in community-dwelling elderly may include recommendations to take all their medication with their morning or evening meal. Strategies to improve nutritional status of the elderly particularly in transitional care settings may increase the risk for drug–nutrient interactions. For example, the use of liquid meal substitute formulas in place of water or juice with each medication administration may increase the total nutrient intake but can alter the bioavailability of some drugs. Likewise, frequent feedings throughout the day may not allow for an appropriate environment to administer drugs that should be administered on an empty stomach. The mixing of some medications in various beverages to increase drug regimen adherence should not be undertaken without evaluating the potential for pharmaceutical interaction between the drug and the beverage. Many elderly patients with cerebrovascular disease, dementia, aspiration, gastrointestinal disorders, and failure to thrive receive enteral feeding. Many interactions exist between enteral formulas and medication (see Chapter 13).

3.2.2. DIETARY SUPPLEMENTS

The indiscriminant use of dietary supplements does not necessarily improve outcomes in the elderly and has the potential to interact with other medication (see Chapter 12). For example, the impact of vitamin A or vitamin E supplementation on the immune response of the elderly can be deleterious and potentially counterproductive in the face of vaccination or antimicrobial regimens *(155,156)*.

An examination of the literature on herbal supplements used by the elderly for dementia identified a series of papers describing the potential drug–supplement interactions that would place the elderly at risk for an adverse drug event *(157)*. In total, 28 were identified, which examined five herbals – St. John's wort (11 articles), ginseng *(7)*, kava *(5)*, ginkgo *(4)*, and valerian *(1)*. These herbals are marketed in the United States as dietary supplements. St. John's wort is reported to interact with theophylline, cyclosporin, warfarin, indinavir, digoxin, and the selective serotonin-reuptake inhibitors. Digoxin, warfarin, and phenelzine interact with ginseng. Aspirin, warfarin, and trazodone may interact with ginkgo. Both kava and valerian may interact with sedatives including benzodiazepines and barbiturates. A study was conducted that specifically evaluated the interactions between dietary supplement use and prescription medications used in a cohort of 285 patients in a Veterans Affairs geriatric clinic *(25)*. The mean age of patients in this study was 78 years. Patients were taking a mean of six prescription medications, excluding vitamins and minerals, and a mean of three dietary supplements (vitamins, minerals, herbals). The investigators found that 54% of patients were taking at least one dietary supplement and prescription medication that could potentially interact. Forty-five potential and possible interactions were found; these mainly involved the interaction of an antiplatelet or an anticoagulant with garlic, gingko, and ginseng, leading to increased risk of bleeding; the interaction of garlic with an antihypertensive, leading to excessive blood pressure lowering effect; or decreased absorption of medication with flaxseed or psyllium *(25)*.

3.2.3. Substances in the Diet Used Habitually

3.2.3.1. Caffeine. Caffeine is probably the most frequently and widely consumed drug *(158)*, but it is often thought of as a dietary constituent rather than a drug and considered as being generally safe. Yet, caffeine (1,3,7-trimethylxanthine) is a central nervous system stimulant that has been implicated in various diseases and can be associated with toxicity when taken in excessive amounts. Effects of caffeine taken in excess include gastrointestinal effects, headache, palpitations, angina, nervousness, insomnia, delirium and seizures, and decreased appetite, all of which could lead to decreased nutritional intake. Caffeine is present not only in many foods and drinks but also in some dietary supplements and over-the-counter medications. Not only is caffeine a common substance in foods and medication, making cumulative intake easy, but it can interact pharmacokinetically and pharmacodynamically with other medication. Caffeine is metabolized primarily by CYP1A2. It therefore has the potential to interact with medication also metabolized by the same isozyme *(158)*. Pharmacodynamic caffeine interactions include increased risk of hypokalemia with other medications known to cause hypokalemia, such as diuretics and corticosteroids; increased gastrointestinal side effects of medications such as the

NSAIDs, corticosteroids, and ethanol, which may lead to changes in appetite; and increased central nervous stimulation with other stimulants such as theophylline, β-agonists, and decongestants, which may also affect appetite *(159)*.

3.2.3.2. Ethanol. The use of ethanol is a problem that is underrecognized in the elderly population *(160)*, when in fact, widowers over 75 years of age have the highest rate of alcoholism in the country *(161)*. Prevalence rates of alcohol-related problems in the aged vary depending on the definition and method of measurement. Estimates range from 1 to 6% for community-dwelling elderly, 7 to 22% for hospitalized elderly, from 28 to 44% in patients admitted to psychiatric units *(162)*. Detecting alcohol-related problems in the elderly is often difficult because symptoms may be confused with other medical conditions and using changes in social and work functioning as an indicator of alcohol abuse is often not applicable in the aged *(162)*. Several scales and questionnaires have been developed to detect alcohol abuse and have been assessed specifically in the elderly *(163–165)*.

Reid and colleagues suggest that theoretically there are many mechanisms in which alcohol can cause functional impairment in the elderly including trauma, osteoporosis, malnutrition, lack of control of chronic disease states, and drug–alcohol interactions *(166)*. Alcohol is related to a myriad of health problems including liver disease, alcoholic dementia, neuropathy, depression, insomnia, loss of libido, late-onset seizure disorder, incontinence, diarrhea, myopathy, heart failure, poor self-care, hypertension, and falls/fractures. Alcohol can also cause poor nutrition as a result of poor oral intake, as well as the depletion of micronutrients such as folate, thiamin, pyridoxine, zinc, magnesium, and selenium. Alcohol also affects lipid metabolism and can lead to the development of adverse reactions due to alcohol–drug interactions *(162,166)*.

Functional impairment due to alcoholism can lead to drug–nutrient interactions by way of decreased self-care abilities that lead to decreased food acquisition, preparation, and intake. Alcohol and drug–nutrient interactions can impair physical, cognitive, and functional abilities in the elderly. The relationship between alcohol use and functional disability in cognitively impaired patients (MMSE $\leq$ 24, normal 27–30) was examined *(166)*. The authors retrospectively investigated the use of alcohol in 242 patients in a hospital-based geriatric center and found that heavy drinkers (>14 drinks/ wk) had higher basic activities of daily living scores and lower instrumental activities of daily living scores. Of note is that only 6% of the patients were heavy drinkers. Moderate drinkers (>1 and <14) had higher basic and instrumental activities of daily living scores. Their study suggests that the effect of alcohol in elderly patients with cognitive impairment is complex. The authors recorded concomitant medications but did not comment on potential drug–alcohol interactions. Since these patients were cognitively impaired, it is likely that some of the patients would have been on psychoactive medications, which would presumably interact with alcohol *(166)*. Such ethanol–drug interactions can in turn contribute to the development of drug–nutrient interactions. For example, a psychoactive medication has the potential of interacting with alcohol by augmenting its central nervous system effects, such as sedation and confusion, which could lead to inadequate food preparation and intake and altered nutritional status.

3.2.4. GRAPEFRUIT JUICE INTERACTIONS

Grapefruit juice, a common beverage consumed by many people over the age of 50, contains compounds that may both reduce atherosclerotic plaque formation and inhibit cancer cell proliferation *(167,168)*. In recent years, grapefruit has been shown to interact with many medications *(167–171)*. Because grapefruit juice is often consumed with breakfast when many medications are given, a scenario is set for many potential or actual drug–nutrient interactions to occur. The most notable drug interactions with grapefruit are its effects on cyclosporine, some dihydropyridine calcium channel blockers, and most HMG-CoA reductase inhibitors (see Chapter 10).

Although the majority of grapefruit juice studies have been conducted in healthy, young patients, the interaction between felodipine and grapefruit juice has been evaluated in the elderly *(171)*. Twelve healthy elderly subjects (70–83 years of age) were evaluated in an unblinded, single-dose, crossover study. Subjects were administered 5 mg felodipine with grapefruit juice or water. Subsequently, six of these subjects then received 2.5 mg felodipine for 2 days followed by 5 mg felodipine for 6 days with 250 mL grapefruit juice or water. Steady-state concentrations of felodipine and concentrations of the felodipine metabolite (dehydrofelodipine) were measured as were blood pressure and heart rate for 24 h after single dosing and after repeated dosing. Mean AUC were 2.9-fold ($P<0.001$) and fourfold ($P<0.05$) greater with grapefruit juice in both single-dose and multiple-dose studies. Interindividual variability in the extent of the interaction was high. Half-life was not altered. Systolic and diastolic blood pressures were lower with grapefruit juice in the single-dose study ($P<0.1$ for systolic blood pressure and $P<0.001$ for diastolic blood pressure), whereas they were not different between groups at steady state in the multiple-dose study. Heart rates were higher with grapefruit juice in both studies but this effect was greater and more prolonged at steady state ($P<0.01$). This study demonstrates an instance in which a pharmacokinetic and a pharmacodynamic drug–nutrient interaction with grapefruit juice occurred even in healthy elderly. The authors concluded that normal dietary amounts of grapefruit juice produced a pronounced, unpredictable sustained interaction with felodipine by reducing its presystemic metabolism in the elderly *(171)*. This suggests that the elderly should be cautioned about concomitant grapefruit juice and felodipine ingestion. Because the elderly were more susceptible to hypotensive events, the authors state it is particularly important to caution against periodic consumption of grapefruit juice with felodipine. This warning would apply to any time of day during drug therapy as an interaction can still occur with a normal amount of grapefruit juice consumed as much as 24 h before felodipine *(171)*.

3.3. The Effect of Medication on Nutritional Status in the Elderly

3.3.1. ANTICOAGULANTS

3.3.1.1. Warfarin. Warfarin is an anticoagulant used to prevent thromboembolic events. Elders are widely thought to be at increased risk for warfarin-related bleeding and are often less likely to be treated with warfarin, in part because of concern regarding adherence with monitoring and bleeding risk *(172–174)*. Pharmacodynamic studies in the elderly suggest that geriatric patients are intrinsically more sensitive to the anticoagulant effects of warfarin than are their younger counterparts *(81,84,96)*. Thus, elderly patients often require a lower dose of warfarin than do younger patients to achieve the same INR goal *(173)*. The elderly patient who is at risk for falls or with a history of falls is often not perceived to be a good candidate for warfarin because of a resultant bleed that can occur after a fall *(71)*.

Elderly patients may also be nonadherent with either warfarin administration or blood testing needed for INR monitoring. Warfarin interacts with numerous medication and some foods. Thus, it is important to identify patients who may not comply with warfarin therapy or other drug therapies, because sporadic use of medication or foods that interact with warfarin can lead to clinically important changes in the INR, resulting in bleeding or a thromboembolic event. Warfarin inhibits activation of vitamin K-dependent clotting factors, which is the basis of its interaction with foods containing vitamin K, such as green leafy vegetables, vegetable broths, and vegetable oil-based salad dressings. Food interactions may be harder to manage than drug–drug interactions because the astute clinician is able to anticipate drug–drug interactions with warfarin and is knowledgeable in managing drug interactions with warfarin. The issue is made more complex by the polymorphism in enzymes that either metabolize warfarin or serve as the drug's target.

Food interactions may be harder to manage because less may be known about the amount and timing of intake of the interacting food. Therefore, rather than counsel patients to decrease their intake of vitamin K-containing foods, which may lead to micronutrient deficiencies, it is wise to counsel patients to maintain a consistent intake of vitamin K. It is the drastic change in vitamin K intake, as opposed to the absolute vitamin K intake, that can lead to variability in maintaining a goal INR.

Wells reviewed the literature on warfarin–drug and food interactions and rated the evidence behind the proposed interaction using two independent raters *(175)*. Of 120 original articles reporting a drug or food interaction with warfarin, the authors suggest that 43 foods or drugs were highly probable in causing a clinically important interaction with warfarin *(175)*. Among the reports possessing strong evidence for a clinically relevant interaction with warfarin were foods high in vitamin K, large amounts of avocado and enteral feeds, which likely contained high amounts of vitamin K. *(175,176)*. New formulations of enteral feeds usually contain no more than the RDA for healthy elderly, so vitamin K is rarely the cause of warfarin insensitivity *(169)*. However, the protein content of enteral formulations may play a role in warfarin resistance and as such the feedings should be held at least 1 h before and after administering the warfarin *(177)*. When educating patients about warfarin–food interactions, it is important to relay to patients that they need not avoid foods high in vitamin K, rather they should attempt to remain consistent in their intake of foods with vitamin K. Warfarin has also been known to interact with vitamin E, gingko, ginseng, and garlic, resulting in an increase in INR *(25,146,178,179)*. Beyth and colleagues developed a multicomponent comprehensive program for management of warfarin therapy aimed at improving control of warfarin's effects and reducing events that may precipitate bleeding. They randomized 325 patients 65 years and older to usual care or intervention, consisting of, among other things, education about drug–drug and drug–nutrient interactions in which patients were trained about changes in lifestyle and diet. At 6 months, major bleeding was more common in the control group, whereas more time was spent at goal range INR in the intervention group. Mortality was similar in both groups *(172)*.

3.3.2. ANTIEPILEPTICS

3.3.2.1. Phenytoin. Phenytoin is a common antiepileptic agent used in the elderly. It is considered to be a narrow therapeutic index medication, meaning the concentration difference between that which produces a therapeutic effect and that which produces toxicity is small. Phenytoin also has a saturable absorption and metabolism. At low levels, it possesses linear pharmacokinetics such that an increase in dose produces a proportional increase in plasma concentration of phenytoin. However, at higher concentrations, the same increase in dose will produce a disproportionately greater increase in plasma concentration *(180)*. Owing to phenytoin's narrow therapeutic index and nonlinear pharmacokinetics, phenytoin–food interactions can markedly influence plasma concentrations and therefore drug safety and effectiveness *(181)*.

Wilder studied potential food-associated differences in absorption between 100 mg of Mylan's ER phenytoin sodium capsules and Parke-Davis' 100 mg Dilantin Kapseals® *(181)*. A single-dose, two-way crossover study was conducted in 24 healthy subjects (18–70 years old) to determine the influence of a high-fat meal on the pharmacokinetics of these two formulations. The impact of switching products at steady-state levels was investigated using a simulation method of pharmacokinetic data previously obtained from 30 epileptic patients. Based on AUC, the bioavailability of the Mylan product administered with food was 13% lower than that of Dilantin Kapseals®. Simulations of substituting the Mylan product with Dilantin Kapseals® suggested that the 13% decrease in bioavailability would result in a median 37% decrease in phenytoin concentrations when given with food; in 46% of patients, concentrations would likely fall below the normal range. Simulations of substituting Dilantin Kapseals® for the Mylan product suggested an increase of 15% in bioavailability would occur and result in a median 102% increase in phenytoin concentrations, with 84% of patients having concentrations above the therapeutic range. Results suggest that when taking phenytoin sodium with food, product switches may result in either side effects or loss of seizure control *(181)*.

Yet another study by Cook et al., examining the effect of food on the bioavailability of Dilantin Kapseals® in a nonblinded, single-dose, randomized, crossover studyin healthy patients 29–69 years old after a fast and a high-fat meal,suggested that there were no clinically relevant changes in bioavailability and that patients may take Dilantin Kapseals without respect to meals *(182)*.

Based on the results of these two studies, it seems prudent to avoid switching phenytoin products in patients stabilized on a particular formulation and to recommend taking phenytoin consistently with respect to food. It is important to pay particular attention to elderly patients and those requiring high concentrations of phenytoin to maintain seizure control.

Phenytoin may interact with tube feedings and several mechanisms have been proposed, including binding of phenytoin suspension to the tube or binding of phenytoin to the nutrient formula. The type of formula may affect the extent of this interaction *(183,184)*. However, a study of the effects of elemental formula (Vivonex TEN®) and lactose-free formula (Ensure®) on the absorption of phenytoin suspension was conducted in 10 normal volunteers. No difference in AUC, peak concentrations, or time to peak was observed with either formula *(184)*. Likewise, the bioavailabilities of phenytoin sodium solution and acid suspension were not found to be affected by continuous nasogastric administration of Isocal® *(185)*. Phenytoin is primarily absorbed in the duodenum. Using a jejunal feeding tube for administration may impair absorption of phenytoin, since the primary site of absorption is bypassed *(186)*. Despite the frequent use of phenytoin and nutritional supplements, there appears to be little information regarding outcomes relating to phenytoin–enteral feed interactions in the elderly population who would be likely to encounter such a potential interaction.

Phenytoin and folic acid also interact with one another; phenytoin can decrease folic acid levels and folic acid can, in turn, decrease phenytoin concentrations. While the exact mechanism of the interaction is unknown, phenytoin may induce metabolism that uses folate as a cofactor *(187)* and folic acid may affect the affinity of phenytoin to the enzymes responsible for metabolizing the drug *(188,189)*. Thus, long-term phenytoin use can decrease folic acid levels. But subsequent supplementation with folic acid is controversial because folic acid supplementation can decrease phenytoin levels to the point of seizure breakthrough *(187)*, and a dose increase in phenytoin may be needed.

Older studies examining the interaction were small *(190,191)* and administered large doses of folate (10 mg/day) daily. The smaller quantities of folic acid found in typical multivitamins are not likely to cause a clinically significant interaction with phenytoin. Yet one case report describes a 79-year-old man with severe folate deficiency who developed aplastic anemia while on phenytoin therapy *(192)*. The authors suggest that the aplastic anemia was due to phenytoin and folate deficiency, because of the existence of a temporal relationship, discontinuation of phenytoin and folate replacement, which corrected hematological values, and absence of other recognizable causes of anemia *(192)*.

3.3.3. ANTIDEPRESSANTS

3.3.3.1. Monoamine Oxidase Inhibitors. Nonselective monoamine oxidase inhibitors (MAOI) represent the prototypical medication class known to interact significantly with food. Although they are infrequently used in the current management of depression in the elderly, it is still noteworthy to briefly discuss their interaction with food. Nonselective MAOIs, such as tranylcypromine, phenelzine, and isocarboxazid, inhibit the activity of monoamine oxidase A and B in a sustained and unpredictable manner, thereby decreasing the metabolism of amines such as epinephrine, norepinephrine, and dopamine for a period of time, from several days to several weeks after discontinuation of the drug *(193)*.

There are numerous foods that contain tyramine, a monoamine, which is also metabolized by MAO. Ingesting these foods concomitantly with an MAOI can lead to the accumulation of these amines and consequential blood pressure elevation, potentially resulting in fatal hypertensive crisis, with severe headache and stiff neck, palpitations, nausea, and vomiting *(193,194)*. Patients therefore need to avoid the myriad of foods that contain tyramine. Examples of foods that contain tyramine include aged cheeses and wines, processed and cured meats, and chocolate, to name a few.

Selegiline is a selective monoamine oxidase B inhibitor used in elderly patients with Parkinson's disease and has also been used to manage depression with a transdermal preparation. At recommended doses for Parkinson's disease, selegiline does not interact with tyramine *(195)*. However, when taken above the recommended dose of 5 mg orally twice daily, selegiline loses its selectivity and may interact with tyramine-containing foods to cause a hypertensive crisis. It is important to counsel patients to adhere to selegiline dosing to avoid this potentially significant drug–nutrient interaction.

3.3.4. ANTIMICROBIALS

3.3.4.1. Tetracyclines and Fluoroquinolones. Tetracyclines and some fluoroquinolones classically interact with antacids and other products containing calcium, aluminum, magnesium, and iron by chelating with these polyvalent cations, resulting in a decrease in the absorption of the tetracycline or fluoroquinolone *(151,196)*. Food, especially that containing dairy products, can decrease the absorption of tetracycline and to a lesser extent, doxycycline. The effects of an enteral feeding product, Ensure®, on ciprofloxacin and ofloxacin were studied in healthy volunteers *(197)*. The authors found that it decreased the absorption of both ciprofloxacin and ofloxacin when compared to water ($P<0.01$), but also suggested that ciprofloxacin was significantly more affected than ofloxacin ($P<0.005$). The relative bioavailability of ciprofloxacin was $72\pm14\%$ ($P<0.005$) of that when given with water *(197)*.

3.3.5. ENDOCRINE AGENTS

3.3.5.1. Metformin. Metformin, a biguanide used for the management of type 2 diabetes mellitus, may cause vitamin B_{12} malabsorption, especially in the presence of atrophic gastritis *(145)* and with long-term therapy. Reports of metformin-induced vitamin B_{12} deficiency in Europe date back to the 1970s when it was predicted that approximately 10–30% of patients on metformin therapy would develop vitamin B_{12} deficiency *(198)*. The incidence of clinically significant vitamin B_{12} deficiency is not known. It has been estimated that it takes less than 9 years to up to15 years on metformin therapy to develop associated vitamin B_{12} deficiency *(199,200)*.

Several mechanisms have been proposed by which metformin causes vitamin B_{12} deficiency. These include alterations in the motility of the small intestines, a direct effect on the absorption of vitamin B_{12}, bacterial overgrowth, and alteration in the calcium-dependent uptake of B_{12}–intrinsic factor complex at the ileum *(199–201)*. Based on this hypothesis, administration of calcium may decrease the severity of vitamin B_{12} deficiency associated with metformin. This was tested by Bauman and colleagues in a small study of 21 patients originally on sulfonylurea therapy without vitamin B_{12} deficiency. They switched half of the patients to metformin therapy on study entry (in a 2:1 ratio based upon study entry date). They measured baseline and serial vitamin B_{12} levels and holotranscobalamin levels, which measures early, subclinical negative vitamin B_{12} balance even before serum vitamin B_{12} levels decrease. Patients were given calcium carbonate 1200 mg/day 3 months into metformin therapy. The authors concluded that calcium supplementation reversed the decline in holotranscobalamin levels and had no impact on serum vitamin B_{12} levels *(201)*.

A case report in the United States describes a 63-year-old man on metformin (dose unknown) for 5 years who developed a probable metformin-induced vitamin B_{12} deficiency *(200)*. The patient had no history of bowel surgery and had a balanced nonvegetarian diet. No glossitis, parasthesias, or other neurological abnormalities were found on examination. Laboratory findings included a mean corpuscular volume of 114 fl, a hematocrit of 33.6%, a vitamin B_{12} level of 109.7 pg/mL (normal 187–1059 pg/mL), and a folate level of 750 ng/mL (normal >190 ng/mL) and intrinsic factor antibody findings were negative. A Schilling test was suggestive of intestinal malabsorption of vitamin B_{12} (recovery of radiolabeled vitamin B_{12} of 2.5% and 3.4%). The patient's metformin therapy was stopped and oral vitamin B_{12} was instituted at 1000 μg daily for 2 months. A repeat Schilling test was suggestive of normal vitamin B_{12} absorption, with and without intrinsic factor (17.5% and 17.7%) *(200)*.

Andres and colleagues share their experience with metformin and vitamin B_{12} deficiency *(199)*. They describe 10 European patients with documented metformin-induced vitamin B_{12} deficiency. The mean age of these patients was 69 (range 52–84). Patients were using metformin for an average of 9 years (range 3–10) at an average dose of 2015 mg (range 1400–2550 mg). Clinical symptoms were present in a few patients and included asthenia, peripheral neuropathy, and edema. One patient required blood transfusions. Average serum vitamin B_{12} levels were 148 pg/mL and serum homocysteine was also abnormal. Patients had normal creatinine and folate levels, and no patient had antibodies to intrinsic factor. The average hemoglobin level was 11 g/dL. Nine of ten patients had normal Schilling tests. One patient had atrophic gastritis and one patient had chronic diarrhea. All patients were treated with a maximum of 1000 μg of oral or intramuscular vitamin B_{12} and vitamin B_{12} levels and blood counts normalized within 3 months of treatment *(202,203)*.

These case reports suggest that long-term metformin therapy can cause vitamin B_{12} deficiency, but in most cases, it is asymptomatic. In some instances, metformin therapy was continued and in other instances, it was not. Whether metformin therapy should be discontinued or not remains to be determined but treatment with oral vitamin B_{12} appears to reverse the deficiency within 2–3 months.

3.3.5.2. Levothyroxine. Antacids, ferrous sulfate, high-fiber diets, and calcium have all been shown to decrease the absorption of levothyroxine *(204–208)*. A case report of a 63-year-old woman with long-standing hypothyroidism clinically euthyroid on levothyroxine revealed that chronic use of aluminum and magnesium containing antacids decreased absorption of levothyroxine, resulting in elevated thyroid-stimulating hormone levels despite levothyroxine 2000 μg daily *(209)*. Discontinuation of the antacids resulted in normalization of thyroid-stimulating hormone and return to the previous dose of levothyroxine, 50 μg/day *(209)*. Singh and colleagues further investigated the effects of calcium carbonate on the absorption of chronic levothyroxine in veterans aged 27–78 and found that calcium carbonate reduced thyroxine absorption and increased TSH from 1.6 to 2.7 mIU/L ($P = 0.008$) *(208)*. The proposed mechanism of this interaction is the adsorption of levothyroxine to calcium carbonate.

3.3.5.3. Bisphosphonates. The oral bioavailability of the bisphosphonates (e.g., alendronate, ibandronate, risedronate) used for the prevention and treatment of osteoporosis is poor (<1%) and is further decreased in the presence of food. Small studies of alendronate and risedronate revealed their bioavailabilities were reduced by 40% and 55%, respectively, when administered shortly before a meal as opposed to in the fasting state *(210,211)*. Even orange juice and coffee were found to reduce the bioavailability of alendronate by 60% *(210,211)*. The bisphosphonates can also cause a local irritation of the gastrointestinal tract, leading to esophagitis, esophageal ulcers, and esophageal strictures in rare instances, especially when taken inappropriately *(210–212)*. Therefore they are contraindicated in patients with esophageal disease. Clinical studies suggest that the incidence of gastrointestinal events, including dysphagia and esophagitis, is similar to placebo *(213–216)*, but these studies were efficacy studies in which safety and tolerability were not primary endpoints and clinical experience suggests that many patients do not tolerate the oral bisphosphonates well. One study evaluating early case reports of alendronate and adverse event reporting to the manufacturer suggests that about 16% (199/1213) of reported events were related to the esophagus and 26% of those were considered serious. Alendronate was taken inappropriately in 61% of cases in which administration technique was known. Most patients were elderly and symptoms developed within 2 months of starting alendronate *(212)*.

Because of their poor oral bioavailability and their risk of esophagitis, very specific administration instructions are necessary to maximize bioavailability and decrease the risk of esophagitis. The oral bisphosphonates should be taken with 6–8 ounces of plain water only, first thing in the morning at least one-half hour before any food, drink (besides plain water), or medication has been consumed, and patients must remain upright for one-half hour after taking the bisphosphonate and until food is consumed to decrease the risk of reflux and esophageal irritation. These complicated administration instructions can be difficult for elderly patients to follow, especially if they have cognitive impairment, functional immobility, or are taking many medications. Moreover, calcium and vitamin D supplementation is recommended in patients taking bisphosphonates to maximize their effectiveness. But like all other medications, the administration of calcium/vitamin D with the bisphosphonates needs to be staggered *(210,211)*.

3.3.6. GASTROINTESTINAL AGENTS

3.3.6.1. Proton Pump Inhibitors. Proton pump inhibitors (PPIs) are commonly used in the elderly to manage gastritis, gastroesophageal reflux disease and to prevent NSAID-induced ulcers. The available PPIs include omeprazole, lansoprazole, esomeprazole, rabeprazole, and pantoprazole. The PPIs are acid-labile medications formulated orally as enteric-coated granules that traverse the stomach intact and the medication is released in the less-acidic medium of the duodenum. The administration of PPIs with nonacidic juices may impair their absorption. Thus it is recommended that these agents be administered with an acidic juice like apple juice or orange juice and not with milk *(217)*. Rabeprazole and pantoprazole tablets should be swallowed whole and unaltered. They should not be chewed or crushed. The same goes for the orally disintegrating tablets as they also contain enteric-coated granules. Lansoprazole, omeprazole, and esomeprazole capsules can be opened and their granules given with acidic juices. There is little data regarding the PPI in the elderly *(217)*. Among the data that are available in the elderly, there is no information to suggest that the absorption of PPIs is impaired to any clinical extent due to achlorhydria or impaired gastric acid secretion *(217,218)*. Food may decrease the maximum plasma concentration of the PPI but the AUC is not significantly affected. Still, it is best to counsel patients to administer their PPI about one-half hour prior to meals if practical. If this is not possible, counsel patients to take their PPI at the start of the meal *(217)*.

The acidic medium of the stomach is required for vitamin B_{12} to be released from dietary sources. Thus, long-term use of histamine-2 receptor antagonists (H_2RAs) and PPIs may contribute to vitamin B_{12} deficiency *(219)*, particularly in the elderly who tend to be at higher risk *(220)*. Force and colleagues conducted a retrospective, case–control study in middle-aged and elderly patients (mean age 71.2±20.8) and found that the need for vitamin B_{12} supplementation was preceded by at least 10–12 months of chronic acid suppression therapy with H_2RAs and PPIs in more cases than controls (18.4% vs 11%, OR 1.82, $P = 0.025$) *(221)*.

3.3.6.2. Bile Acid Sequestrants. Cholestyramine, colestipol, and colesevelam are lipid-lowering agents that decrease gastrointestinal pH and bind bile salts to prevent their reabsorption in the ileum. They are then excreted and may cause steatorrhea and fat malabsorption *(145)*. Malabsorption of fat-soluble vitamins A, D, E, and K can occur because the absorption of these vitamins is usually facilitated by bile acids *(150,196,222)*.

3.3.6.3. Laxatives. The elderly use many laxatives, which may lead to fluid and electrolyte imbalances and nutrient depletion *(174)*. Mineral oil is well-known by the elderly as an old remedy for constipation. When used as a laxative long term, it may deplete fat-soluble vitamins by forming micelles and acting as a vehicle for lipid-soluble moieties *(145,150,151,223)*.

3.3.7. Parkinson Agents

3.3.7.1. Levodopa. The interaction between levodopa and food – especially dietary protein – has been evaluated in several small studies *(224,225)*. Levodopa is absorbed in the small intestine by the neutral amino acid transporter and is extensively metabolized in the periphery prior to uptake in the basal ganglia, where it is needed to exert its effect. Two mechanisms have been proposed for these interactions. One proposed mechanism is that food delays and decreases the absorption of levodopa from the small intestines, by delaying gastric emptying and increasing exposure of levodopa to degradative enzymes in the stomach and intestines. Another proposed mechanism involves the ability of levodopa, an amino acid, to compete with large neutral amino acids in the diet for transport across membranes. Whatever the mechanism, this interaction is likely to be more significant in patients with progressive Parkinson's disease who experience motor fluctuations like "on–off" phenomena, as opposed to patients without existing motor fluctuations *(224)*. It is also more likely to occur with clinically significant consequences in patients receiving enteral nutrition by continuous administration *(226)*. Switching to intermittent feedings can resolve the interaction in this case. While the redistribution of dietary protein is cited as a management option for patients experiencing motor fluctuations *(227)*, this interaction is not likely to be clinically significant in early staged Parkinson's disease patients because large amounts of protein are needed (2 g/kg) to cause a significant interaction *(224,228)*. Vitamin B_6 may also decrease the effects of levodopa; it is a codecarboxylase, which may decrease blood levels of levodopa by increasing the peripheral metabolism of levodopa before it can cross the blood–brain barrier for uptake into the basal ganglia *(149–151)*. However, levodopa is almost always coadministered with a dopa decarboxylase inhibitor (carbidopa) and this likely minimizes the significance of this interaction.

3.3.8. Weight-Influencing Medication

3.3.8.1. Unintentional Weight Loss. In the long-term care setting, there is a growing regulatory focus on unintentional weight loss, as a marker of poor nutritional status. The impact of substantial weight loss on quality of life and overall health status can be significant. Pressure ulcers, falls, fractures, decreased resistance to infection, impaired wound healing, increased skin friability, osteopenia, anemia, and cognitive problems can occur. Studies show that undernutrition is associated with increased morbidity and mortality *(229,230)*.

The Center for Medicare and Medicaid Services (CMS) has identified nine additional quality indicators in nursing homes, one of which is unintentional weight loss *(231)*. Thus, nursing homes and surveyors are paying more attention to pressure ulcers, malnutrition, and dehydration, all potentially linked with consequences of unintentional weight loss. The nutrition section of the CMS surveyor guidance document has been revised and expanded *(232)*. Numerous preventable causes of weight loss in the elderly can be explained with medications foremost among them (Table 5). Duration of use should be considered in the evaluation of a potentially offending agent. It is unlikely that a 10-day course of antibiotic therapy will have a substantial impact on weight. On the other hand, chronic use of a taste-altering medication could have a major impact.

Medication regimens may cause cognitive disturbances (e.g., psychotropics, clonidine, metoclopramide), anorexia (e.g., digoxin, antidepressants, theophylline), gastrointestinal irritation (e.g., aspirin, erythromycin, NSAIDs), constipation (e.g., opioid agonists, calcium channel blockers), diarrhea (e.g., sorbitol-containing medications), and altered metabolism (e.g., theophylline, levothyroxine). Medications can cause weight loss indirectly by causing dysphagia, gastrointestinal side effects, delayed gastric emptying, early satiety, altered taste or smell, sedative effects leading to lack of desire to eat or napping and missed meals, or they may cause depression *(231,233)*.

3.3.8.2. Unintentional Weight Gain. Many psychoactive medications can cause significant weight gain. The mechanism involved is complex and probably multifactorial, involving the metabolic, endocrine, and neuronal systems *(234)*. Reports of weight gain associated with antipsychotics date back to the 1960s *(235)*. Many of the first-generation antipsychotics and the newer atypical antipsychotics (clozapine, olanzapine, quetiapine, risperidone, ziprasidone) all have the potential to cause weight gain that can potentially be significant *(236)*. Olanzapine and clozapine may have the potential to cause more weight gain than other atypicals, as evidenced by direct comparative trials *(237,238)*. Most studies evaluating weight gain with psychoactive agents employed younger patients with schizophrenia. But because these agents are widely used in elderly patients for neuropsychiatric symptoms, it is important to research their weight-gaining properties in elders who likely have concomitant cardiovascular disease and diabetes, which may make weight gain more problematic. Allison and colleagues conducted a meta-analysis in studies utilizing patients with a wide range of ages and found that mean weight change at 10 weeks was +1.08 kg with haloperidol, +4.45 kg with clozapine, +2.1 kg with risperidone, +4.15 kg with olanzapine, +2.18 with quetiapine (at 6 weeks), and +0.04 with ziprasidone *(238)*. In general, the weight gain that occurs with psychoactive agents is usually centrally distributed, occurs early in the course of therapy, and has been associated with altered adherence to therapy *(228,234,235,238)*.

Antidepressants can also cause a significant weight gain. Tricyclic antidepressants (TCAs) can stimulate appetite and cause carbohydrate cravings *(235)*. Amitriptyline, typically avoided in the elderly, may cause the most side effects. The weight gain associated with TCAs is dose dependent and duration dependent. The SSRIs are less likely to affect weight significantly. In fact, there is often an initial weight loss associated with the SSRIs, which may be followed by a return to baseline weight. Therefore the overall weight change associated with them tends to be negligible. Mirtazapine is also a well-known inducer of weight gain *(239,240)*. In short-term studies employing a large range of patient ages, it has been shown to cause a >7% weight gain in 7.5% of patients *(241)*. Long-term studies are underway to further investigate weight gain associated with mirtazapine. Lithium can also cause significant weight gain. Patients on lithium can gain up to 10 kg in their first several years of therapy *(242,243)*. Other psychoactive medications that can cause weight gain include some anticonvulsants, such as valproic acid and carbamazepine. Other medications that can cause weight gain include antidiabetic medications, particularly sulfonylureas, repaglanide, netaglinide, and insulin and corticosteroids. Antihistamines and NSAIDS can cause some fluid retention, but clinically significant weight changes are rare *(235)*.

3.3.9. Other Medication-Induced Micronutrient Abnormalities

3.3.9.1. Diuretics. The elderly are prone to fluid and electrolyte imbalances due to changes in the renin–angiotensin–aldosterone system and antidiuretic hormone. They also possess altered thermoregulatory function, baroreceptor function, and have an altered thirst drive. Therefore the aged may be prone to interactions between diuretics and electrolytes. It is widely known that potential effects of thiazide diuretics include hyponatremia and hypokalemia, hyperlipidemia, hyperglycemia and hypercalcemia, although these metabolic disturbances are not always as clinically relevant at doses used today. A retrospective review of elderly patients, 65–99 years old, investigated the need for lipid-lowering therapy following the initiation of thiazide diuretics compared with other antihypertensives. The use of low-dose thiazides was not associated with an increased need for lipid-lowering therapy *(244)*. The effects of diuretics on serum sodium and potassium are described below.

3.3.9.2. Hyponatremia and Hypernatremia. Many medications can cause hyponatremia, including carbamazepine, valproic acid, TCAs, trazodone, venlafaxine, antipsychotics, SSRIs, and thiazide diuretics *(245–251)*. Booker describes the cases of six elderly patients with severe symptomatic hyponatremia (112±5.5 mmol/L) in which a thiazide diuretic was suspected of causing the electrolyte abnormality *(246)*. The patients were 65–87 years of age and had serum sodium concentrations ranging from 105 to 121 mmol/L. Symptoms developed within 4 days of thiazide initiation in the majority of instances. In two patients, hyponatremia was corrected and recurred upon thiazide rechallenge and in another two patients, hyponatremia recurred without rechallenge, perhaps suggesting that elderly patients with concomitant conditions are at risk of hyponatremia from various causes, including stress. Proposed mechanisms of thiazide-induced hyponatremia include volume contraction and decreased glomerular filtration rate and increased reabsorption of sodium and water *(246)*.

The SSRIs (e.g., fluoxetine, paroxetine, sertraline) can also cause hyponatremia by causing a syndrome of inappropriate antidiuretic hormone (SIADH). The incidence is rare, but because these medications are widely used in the management of depression in the elderly, the prevalence of SIADH increases *(245)*. Guay reviewed a series of SSRI-induced SIADH in elderly patients (mean age 75 years). The majority of patients developed hyponatremia within 14 days of SSRI therapy, although hyponatremia with SSRI therapy can occur at any time. Only 20% of patients were symptomatic (mean sodium level 120 mmol/L). Serum sodium normalized within several days of discontinuing the SSRI. Christe and Vogt described eight cases of SSRI-induced SIADH in elderly patients with a mean age of 86 (range 78–89) *(248)*. The development of SIADH occurred within the first 3 months of SSRI therapy and as quickly as 3 days. Three patients were also on concomitant diuretic therapy. Three-quarters of the patients were symptomatic (nausea, diarrhea, dizziness, confusion). The hyponatremia resolved within 17 days after discontinuation of the SSRI in five cases. No rechallenge was offered, but despite this, one patient developed recurrent hyponatremia, suggesting that concomitant conditions can place elderly patients at risk of electrolyte abnormalities *(248)*. A survey of spontaneous reporting of adverse events associated with antidepressant therapy found that hyponatremia occurred primarily in elderly women, in the summer and during the first few weeks of antidepressant use *(249)*.

Other case reports of SIADH caused by citalopram, valproic acid, lisinopril, and amiloride/hydrochlorothiazide have been described in elderly patients *(250–253)*.

Stress, hypothyroidism, and hypoadrenalism can also impair diuresis, leading to hyponatremia. The elderly are susceptible to these disease states and are on many medications that can alter sodium levels. Additionally, signs and symptoms of hyponatremia in the elderly are often subtle and nonspecific (including somnolence, headache) and do not occur until the serum sodium falls below 125 or 130 mmol/L or lower. Progression to coma and seizures can occur, so it is important that clinicians recognize this important interaction *(245,247,254)*. Medications that can cause hypernatremia include those that can induce diabetes insipidus, including lithium, amphotericin, and demeclocycline.

3.3.9.3. Hypokalemia and Hyperkalemia. Many prescription medications can interact with potassium status, leading to hypokalemia or hyperkalemia. Loop diuretics (e.g., furosemide), thiazide diuretics (e.g., hydrochlorothiazide), and corticosteroids can all cause hypokalemia (<3.5 mmol/L). Diuretic-induced hypokalemia can be significant enough to warrant potassium supplementation. Unlike the diuretics listed above, potassium-sparing diuretics (e.g., spironolactone, amiloride) can cause hyperkalemia, as can many other medications.

Medications can cause hyperkalemia (>5 mmol/L) by three main mechanisms: increase in potassium intake, decrease in potassium excretion, or a shift of potassium from the intracellular fluid to the extracellular fluid *(255)*. Medications that increase potassium intake include enteral nutrient formulas and oral nutrient supplements, oral potassium supplements, and penicillin G. Salt substitutes, often used in the elderly cardiac patient trying to avoid a large sodium intake, can also contribute to hyperkalemia, so it is important to inquire about the use of salt substitutes in patients on other medications that can increase potassium levels.

Medications commonly used in the elderly that decrease potassium output include angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor antagonists, heparin, and NSAIDs. Medications that shift potassium extracellularly include β-blockers and digoxin. In addition to the elderly using combination medications that contribute to hyperkalemia, they also suffer from diseases that can increase hyperkalemia, including diabetes, metabolic acidosis, and renal insufficiency. Reardon and Macpherson conducted a case–control study to analyze hyperkalemia in patients on ACEI. They found that 11% of 1818 patients (mean age 67) developed hyperkalemia on ACEI and that concomitant risk factors included renal insufficiency and heart failure *(256)*. Therefore, it is important to know which medications and disease states can alter potassium levels, to inquire about enteral supplements, salt substitutes, and other over-the-counter medications that can cause hyperkalemia (such as NSAIDS), to monitor potassium levels in patients on chronic medications that can alter potassium levels, and to educate patients on the signs and symptoms of hyperkalemia (paresthesias and muscle weakness) *(255,257)*.

3.3.9.4. Other. Many medications can affect the absorption of vitamin B_{12}, often by interfering with intrinsic factor, which is necessary for vitamin B_{12} absorption. Examples include metformin and the PPIs, cholestyramine, ethanol, cimetidine, allopurinol, and potassium *(233)*.

Particular care needs to be exercised with the use of corticosteroids chronically or in high doses. Corticosteroids can cause hyperglycemia or glycosuria that may affect diabetic control and can lead to dehydration, sodium retention, and potassium wasting. Corticosteroids can also cause calcium depletion, enhancing the risk of osteoporosis and fractures *(145)*.

Case reports have suggested that antipsychotics may impair glucose tolerance and predispose patients to the development of diabetes mellitus. However, it is difficult to determine whether this is due to the disease state for which the antipsychotic is being used (schizophrenia, bipolar disorder), to the antipsychotic therapy itself, to confounding factors such as obesity, or concomitant cardiovascular disorders. Despite antipsychotics being commonly used in the elderly for agitation associated with dementia, case reports that exist are primarily in younger patients being treated for schizophrenia. Therefore it is premature to determine whether antipsychotics are associated with clinically important changes in glucose tolerance in the elderly *(258–263)*. Anticonvulsants may decrease the activation of vitamin D_3 to 1,25-dihydroxy-cholecalciferol *(196)*. Antacids reduce the absorption of selenium, chromium, iron, calcium, zinc, folate, magnesium, and vitamin B_{12} *(196)*. Thiazide diuretics can cause angina-like effects that are precipitated by foods containing monosodium glutamate *(151)*.

4. LIMITATIONS OF THE DATA

How well do the existing data describe drug–nutrient interactions in the elderly? In 1994, the FDA issued a guidance document regarding studies in support of special populations including the geriatric population *(105,113)*. The guidance states that drugs that are to be used substantially in the elderly should be adequately studied in the elderly. The guideline further encourages the inclusion of patients 75 years and older in clinical studies and recommends that geriatric patients with concomitant disease not be excluded from studies unnecessarily. However, this was only a recommendation, not a requirement. Furthermore, no stipulation was made to identify drug–nutrient interactions.

In 1997, the FDA established the geriatric use subsection of product labeling to inform clinicians about the use of medication in the elderly *(105,113)*. Under the geriatric-labeling regulation, most prescription products need to include recommendations for use in the geriatric population and the data supporting the recommendation also need to be included. Specific information that is supplied includes information about the use of a medication in the elderly and relevant data supporting it, a statement declaring whether a sufficient number of geriatric patients were included in studies or not, difference in safety or effectiveness and supportive data, pharmacokinetic and pharmacodynamic data in the elderly, determination if the medication is substantially renally excreted, and information describing potential hazards with use in the elderly. Evidence is required that supports a recommended dose and dosing interval and modification of the dose or the interval in the elderly. Lastly, if there are no geriatric data pertinent to product labeling, the sponsor must provide reasons for omission. Drug–nutrient interactions are still not included.

Over-the-counter medications need not submit geriatric use information *(264–266)*. Although the FDA mandates a geriatric use section of the product information, it requires little with respect to the actual data analysis of information included in this section. Specifically, the FDA merely recommends that an adequate number of geriatric patients be included in clinical trials, with no actual percent inclusion mandated. It offers suggestions for pharmacokinetic analyses, including the option to perform pharmacokinetic screening involving trough blood level determinations at steady state from geriatric and younger patients to detect a difference, or from formal pharmacokinetic analyses, which can be done in either healthy geriatric patients or volunteers. It does not recommend formal pharmacodynamic studies be conducted unless other phase II/III studies suggest large differences in efficacy or safety between geriatric and other adult patients. The FDA recommends drug–drug interaction studies be completed in the elderly if an interaction is likely and for certain medications, including digoxin, oral anticoagulants, medication extensively metabolized hepatically but again, it makes no mention of drug–nutrient interactions. In 1998, the FDA issued its “final rule” requiring sponsors to tabulate the number of elderly patients they include in trials. It does not address requirements for the conduct of clinical studies nor does it require sponsors to perform additional studies to include more geriatric patients. It merely requires sponsors to submit existing data that had already been collected *(288)*. More recently the FDA developed a guidance document addressing drug interactions, yet there is no specific mention of drug–nutrient interactions *(267)*.

5. FUTURE RESEARCH NEEDS

The elderly comprise the fastest growing segment of the population and they use a disproportionately higher percentage of medication. As clinicians, it is important to be aware of the changes in physiology that accompany aging and the effects that these changes have on drug disposition in the elderly patient. Health-care providers need to keep in mind that advancing by chronological age is not a clinical disease. While much is made of the demographics of the elderly focusing on alterations based on chronological age, the variability in physiologic function with age is more important to determine. Physiologic function will relate more directly to nutrient and drug disposition. This may help us to better understand, predict, or address the clinical relevance of the interactions between nutrients and drugs. It is essential to evaluate the nutritional implications of each of the most frequently used medications for chronic conditions in the elderly. While it is unlikely to become a requirement of the drug approval process, it should be considered critical in the drug usage process. It is also important to identify the alterations in drug disposition in physiologic subgroups of the elderly with the use of oral meal replacements, vitamin and mineral supplements, soy protein and amino acid supplements, as well as herbal and other nonnutrient dietary supplements.

Crome and Flanagan address the future needs of pharmacokinetic studies in the elderly. They state that the elderly should be included in more Phase I and Phase II studies so that pharmacokinetic and pharmacodynamics can be collected early on. They advocate conducting pharmacokinetic dose-ranging studies in elderly patients to better determine appropriate doses for later clinical trials (Phase III and IV). They also recommend using a parallel, placebo arm to collect controlled information about pharmacodynamics and to be able to directly compare the groups *(94)*.

Since the majority of studies, including drug–nutrient interaction studies, are conducted in younger individuals, little data exist about drug–nutrient interactions in the elderly per se. However, a few studies evaluating the implementation and outcome of drug–nutrient interaction-tracking programs have been conducted *(268,269)*. These studies suggest that drug–nutrient interactions are common and identifiable and preliminarily suggest that intervention programs can decrease the incidence of drug–nutrient interactions. More of these studies are needed.

6. CLINICAL RECOMMENDATIONS TO PREVENT OR MANAGE INTERACTIONS IN THE ELDERLY

Changes in geriatric physiology, pharmacokinetics, pharmacodynamics, and nutritional status, in addition to other factors such as polypharmacy, nonadherence, and suboptimal prescribing, can lead to atypical disease state presentation and increased susceptibility to adverse drug events, including drug–drug and drug–nutrient interactions *(238)*. The goals of geriatric pharmacotherapy are to maintain functional independence, to prevent disability and iatrogenic disease, and to increase health-related quality of life *(270)* by promoting the use of rational drug therapy when drug therapy is indicated. Hanlon and colleagues developed the Medication Appropriateness Index, an instrument with demonstrated reliability and validity that should be used by clinicians in the routine evaluation of drug therapy, including drug–nutrient interactions *(44,45)*.

A comprehensive geriatric assessment is the standard of care in geriatric medicine *(11,238,271)* and is often conducted using a team approach. Components of the comprehensive geriatric assessment include a functional assessment, a cognitive assessment, and a social and nutritional assessment, in addition to the standard history and physical. An organized assessment of nutritional status, comprehensive medication use, and drug–nutrient interactions should be performed routinely *(270,272)*. Meal supplements and dietary supplements should be used cautiously in the elderly as they have the potential to adversely influence drug disposition and nutritional status.

Routinely educating oneself, patients, other clinicians, health professional students, and federal agencies about changes in the elderly and drug–nutrient interactions should occur. Specifically, one should become knowledgeable about changes in physiology and drug disposition that occur in the elderly and the mechanism, likelihood, severity, and the management of specific drug–nutrient interactions. Periodic review of the literature, contribution to the literature, development of continuing education programs, inclusion of geriatric and drug–nutrient interaction topics in health professional curricula, and patient health fairs and educational programs should serve to increase recognition and knowledge of geriatric issues and drug–nutrient interactions.

Research has shown education to be effective in preventing drug–nutrient interactions. For example, Byeth and colleagues demonstrated that patient education about warfarin, including drug–nutrient interactions, was effective in preventing bleeding complications in the elderly *(172)*. Strategies reported by Byeth were successful and can and should be replicated in practice. These included assessment of warfarin indication and risks, as well as the provision of patient education. The patient education intervention used a workbook formatted for older adults and used coaching techniques to teach the elderly to take an active role in their care and to communicate necessary health information to their health-care providers *(172)*.

Likewise, strategies to address drug–nutrient interactions in long-term care facilities have been identified in the literature and should be replicated *(18)*. They include educating health-care providers (particularly about timing of food with drug regimens), establishing administrative policies and protocols based on limiting the occurrence of preventable drug–nutrient interactions, and regular monitoring of nutritional status, medication profiles, and laboratory data to evaluate the potential for interactions. Clinicians can utilize some of the successful strategies outlined in the few studies available.

Promotion of geriatric patient inclusion in clinical trials and research incentives may also increase our recognition and knowledge about geriatric pharmacotherapy and drug–nutrient interactions. Once we have become proficient in the understanding of geriatric drug–nutrient interactions, we need to translate that knowledge into implementable skills that can be used in clinical practice, with vigilant monitoring conducted to prevent adverse drug–nutrient interactions in the elderly.

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VI

DRUG–NUTRIENT INTERACTIONS IN SPECIFIC CONDITIONS

23

Drug–Nutrient Interactions and Immune Function

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Objectives

- Synthesize the data concerning nutritional status, immune function, immune-related disease, nutritional consequences of infections, or autoimmune disease.
- Describe the dietary components that can affect immune function.
- Identify drug–nutrient interactions that can occur during infections and autoimmune diseases.

Key Words: Antioxidants; autoimmune disease; children; elderly; HIV; infection; inflammation; tuberculosis

1. INTRODUCTION

The complex function of the immune system is dependent upon nutritional status. The same can describe disorders of the immune system including infection and autoimmune diseases. The medications used to manage these diseases have the potential to interact with the intricate immune–nutrient axis. Each of these areas is complex and this chapter builds upon the more general information before proceeding into the interactions. There are brief overviews of the immune system and the major global infectious agents. Up-to-date information concerning the numbers of individuals affected by infections and immune-related diseases and their nutritional status, with emphasis on at-risk populations in developing countries, is included. There is an extensive discussion of gut immunity and the role of prebiotics and probiotics. An in-depth look at the major autoimmune diseases that afflict adults and the nutritional consequences of these diseases is included as well. An extensive review of the effects of major drug classes used to treat infection and autoimmune disease on nutritional status is provided. Finally, we include data on certain essential nutrients that enhance immune responses in clinical studies of infection and autoimmune disease, usually during drug therapy. Our goal is to help the reader better understand the complexity of these interactions and how nutritional status serves as the keystone to optimizing drug therapies for immune-related diseases.

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Nutritional status greatly affects the ability to mount an effective immune response. However, the effects of nutrients differ with the age of the individual, as well as with lifestyle factors. Since seniors are the greatest consumers of prescription drugs, often using multiple agents, we review the data from clinical studies that examine the effects of nutrients and/or drugs on immune responses in this age group. Immune-mediated diseases and immune responses can also affect nutritional status and are affected by dietary habits. In this area, we examine the effects of acute infection and the importance of vaccines especially in childhood and in the elderly. The use of antimicrobials to treat chronic infections such as tuberculosis (TB) and human immunodeficiency virus (HIV) infection and anti-inflammatory drugs for treatment of autoimmune diseases including diabetes, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) is also included.

For the majority of chronic diseases, whether immune-related or not, there are cardinal features of disease that impact nutritional status. Usually, during the course of disease, there is an increase in metabolic rate that is often associated with fever and pain. Additionally, gastrointestinal (GI) tract impairment results in decreased intake and/or absorption and increased excretion. Often, prolonged drug therapy adversely affects the liver and its capacity to enhance fat absorption (and fat-soluble vitamin absorption) and produce nutrient carrier proteins. Similarly, many drugs affect pancreatic function, causing alterations in protein breakdown and glucose utilization. Drugs can also influence gastric emptying and intestinal motility. Many chronic diseases (and a number of drugs used to treat them) result in tissue destruction, possibly due to increases in oxidative damage; it is often difficult to determine which is the first event and which is the consequence *(1)*.

In the United States, immune-related conditions altogether are the third leading cause of death, surpassed only by heart disease and cancer. Of the ten leading individual causes of death, five have links to the immune system directly: chronic lower respiratory disease, pneumonia/influenza, diabetes, nephritis, and septicemia *(2)*. It is estimated that in 2004, the United States spent about \$1.9 trillion, or 16% of its gross domestic product, on health care *(3)*. Chronic diseases such as heart disease, cancer, and diabetes are the leading causes of death and disability in the United States, accounting for 70% of all deaths (1.7 million) each year. Chronic diseases are among the most common and costly health problems; these are also among the most preventable. In fact, the Centers for Disease Control and Prevention (CDC) affirms that eating nutritious foods combined with being physically active and avoiding tobacco use can help prevent or control the devastating effects of these diseases *(4)*.

It has been reported that chronic illnesses, such as diabetes, arthritis, and other immune-related diseases, as well as cardiovascular disease affect about 45% of the adult US population *(5)*. It must also be noted that certain lifestyle habits, such as cigarette smoking and alcohol consumption, may also affect dietary intake, immune function, and drug disposition. In 2005, tobacco caused 5.4 million deaths worldwide, which is an average of one death every 6 s *(6)*. In 2006, about 15% of men and 8% of women were cigarette smokers in the United States *(7)*.

Based on 2005 data, the percentage of individuals in the United States reporting fair-to-poor health is about 12% in those 45–54 years of age and gradually increases to over 30% in those 75 years of age or older *(8)*. Patients with multiple chronic conditions cost up to seven times as much as patients with only one chronic condition. Health-care expenditure by the elderly (age >65 years) is about three times their percent in the population, and as life expectancy is increasing, so would the percent elderly in the population. Furthermore, a much higher proportion of the elderly than the non-elderly have expensive chronic conditions *(3)*. Multiple interactions add to the complexity of predicting the effects of nutritional status and concomitant drug use on the immune responses of individuals, especially in the very young and the very old.

2. THE HUMAN IMMUNE SYSTEM

The human immune system is comprised of cells, tissues, and organs that interact with each other for the primary purpose of maintaining the internal integrity of the body. In order to protect against external pathogens, immune cells are located at all orifices as well as in the lungs, along the GI tract and in the liver. Immune cells are also found in the central nervous system, in the walls of blood vessels, and they can move to any area within the body that is the site of a challenge. The primary organs of the immune system include the thymus, bone marrow and the spleen; lymph nodes and mucosal-associated lymphoid tissues comprise the secondary organs.

The GI tract represents the largest surface area in the body in contact with the external environment *(9)*. Despite constant exposure to pathogens, defense mechanisms assure that the mobility and proliferation of both internal and external microorganisms is closely monitored and appropriate responses are coordinated for the continuous protection of mucosal epithelial cells *(10)*. In the past decade, significant research has focused on understanding the mechanisms by which the gut mucosal-associated lymphoid tissue (GALT) functions and its critical role.

2.1. Functions of Immune Organs

The primary function of the thymus is the maturation of certain lymphocytes. Within the bone marrow, there are pluripotential cells or stem cells. The bone marrow stem cell-derived white blood cells include granulocytes (most numerous of which are the neutrophils), lymphocytes, and macrophages that circulate in the blood and lymph and can move throughout the body *(11)*.

There are two major categories of lymphocytes, T cells and B cells. T cells, associated with immunosurveillance and cell-mediated immunity, are involved in the killing of pathogens that live within human cells, such as viruses and intracellular pathogenic organisms. The two major types of T cells include T helper cells that help to generate most of the body's immune responses and T cytotoxic cells that modulate the helper response to maintain immune balance. B cells produce antibodies, in response to T helper cell signals. Antibodies adhere to extracellular pathogens such as bacteria and contribute to their demise. The cells of the immune system synthesize and secrete numerous cytokines that can bind to receptors on cells of the immune system or other cells to initiate responses. The cytokines include interleukins, interferons, and tumor necrosis factors; prostaglandins, formed from long-chain fatty acids, also modulate immune responses and are synthesized by cells of the immune system. T and B cells are unique in that they have memory functions and are rapidly activated when exposed to a pathogen for the second or subsequent times. The memory function is the basis of vaccination responses. Under normal circumstances, during the development of the immune system in the early months of life, the immune system "learns" to recognize the antigens on its own cells and develops tolerance for self-antigens.

The major chronic diseases of the immune system are caused by an inappropriate response of the immune system to self-antigens resulting in autoimmune diseases. Autoimmune diseases are noncontagious, although these may be triggered by an infectious agent. On the cellular level, the T cells no longer recognize self-antigens; either they stimulate the production of antibodies to the self-antigens, autoantibodies, or there is otherwise destruction of self-cells by the immune system. There is a strong genetic predisposition to autoimmune diseases; however, the triggering event is considered to be environmental. Pathogens, pollutants, drugs, and even nutritional factors have been implicated as initiating factors in autoimmune diseases. Certain autoimmune diseases are organ specific such as Hashimoto's disease, which affects the thyroid, diabetes, which affects the pancreas, and inflammatory bowel diseases (IBD), which affect the GI tract. Other diseases such as SLE and RA are systemic. In the majority of autoimmune diseases, there is a much greater incidence in women relative to men. For example, the incidence of SLE is 10-fold higher and the incidence of Hashimoto's thyroiditis about 20 times higher in women.

Pregnancy is a time of change for the maternal immune system. The pregnant woman's immune responses must be modulated so that the developing embryo is not destroyed when it is recognized by the immune system as "nonself." Tolerance is particularly important during the entire pregnancy, as the growing fetus' immune system is forming and maternal cells circulate within the amniotic fluid. Likewise, the developing fetal immune system cannot be vigorous enough to destroy the immune or other maternal cells and tissues. This one example provides a glimpse into the flexibility as well as the complexity of the immune system. The neonatal immune system is not fully developed at birth and exposure to external antigens is critical for the "education" of immune cells. Many childhood infections occur only once because the immune system remembers and destroys these pathogens if challenged for a second time.

Although it may appear that the immune system has the capacity to defend against pathogens, this is obviously not the case in many instances as there have been epidemics throughout human history. A critical factor in host defense is nutritional status. Millions of white blood cells are formed each day and usually a corresponding number are destroyed. Significant nutritional resources are expended to maintain the immune system at its optimum and if the required nutrients are not consumed, the result is a less than optimal immune response to infection. As discussed below, we still have many examples of undernutrition associated with childhood pathogens such as measles and diarrheal disease. Conversely, acute infections can also affect nutritional status. High fever is often accompanied by a lack of appetite, nausea, and/or diarrhea. Chronic inflammation from infection or autoimmune diseases also often adversely impacts nutritional status.

2.2. Gut Microflora and Immunity

Nonpathogenic bacteria that normally live in the GI tract, also called commensal bacteria, play an important role in nutrition and in immunity. Specifically, there are physiologic interactions between the bacteria at the interface in the GI tract and both the adaptive and the innate immune responses. The gut bacteria stimulate human gene expression and there is cross talk between the organisms that colonize the intestine and in particular the intestine wall. The gut microflora provide appropriate stimulation such that immune tolerance is established. Mechanisms by which beneficial gut bacteria contribute are related to stimulation of a low-grade upregulation of T cells that ultimately contributes to reduction of proinflammatory processes that may be linked to invasion by pathogenic microorganisms and also the maintenance of tolerance *(12)*. Interplay between commensal microbes in the gut lumen leads to both direct and indirect modes of protection from pathogens. Disruption of these interactions may not only affect the integrity of the mucosal barrier but may also allow certain pathogens to overwhelm or avoid mucosal immune responses *(9)*.

2.3. Nutrients and Nutritional Status and Immunity

Observations in the fields of nutrition, immunology, and epidemiology combined with well-controlled clinical trials have demonstrated that various nutrients are essential in the development, maintenance, and expression of the immune response. Among essential nutrients, vitamin A has been most extensively studied as reviewed by Semba *(13)*. Specifically vitamin A deficiency has been directly linked to depressed immunity *(14,15)*. Children with no responses to recall antigens (anergy) have significantly increased risk of diarrheal disease. Vitamin A deficiency is predictive of diarrheal disease and the disease also reduces vitamin A status, leading to a vicious cycle of sickness. Zinc deficiency is also associated with diarrheal disease and supplementation in children has been shown to reduce the incidence in underdeveloped countries *(16)*. The involvement of vitamins A and D in gene expression that controls growth and immune development has also been extensively studied *(17)*.

2.4. Aging of the Immune System

The aging of the immune system results in greater occurrence of infection in seniors *(11)*. Bogden et al. *(18)* documented a significant decline in delayed-type hypersensitivity responses (DTH) to previously encountered antigens (a clinically relevant in vivo measure of immune function) in individuals 60 years old and older. They found about 40% of this apparently healthy population were anergic and thus did not have a skin test response to the seven common test antigens; another 30% had partial responses. Similarly, Marrie et al. *(19)* have documented the progressive decline in both number and diameter of skin test responses to seven test antigens in individuals aged 66–82 compared to those aged 25–40; thirty five percent of those aged 25–40 had positive responses to five of seven antigens, whereas none of the matched group aged 66–82 had five responses. At the same time, only 1.5% of the younger group was anergic, as evidenced by the lack of responses to the seven antigens, while 18% of the older group had no responses. In addition to responding to fewer antigens, the older group also had approximately half the induration response as seen in the younger group. The decline in immune function combined with the loss of appetite, reduced mobility, and increased use of several drugs to treat the multiple chronic conditions that affect the aging population also contributes to the rise in respiratory infections.

Clinical studies have shown that DTH can be used as a predictor of morbidity and mortality in the elderly – elderly with anergy had twice the risk of death from all causes as elderly that responded to the antigens *(20)*. Moreover, in hospitalized elderly who had undergone surgery for any reason, anergy was associated with a greater than 10-fold increased risk of mortality and a fivefold increased risk of sepsis *(21)*. DTH responses are also indicative of morbidity within an age-matched elderly population; those who lived at home and were self-sufficient averaged positive responses to two antigens and indurations of about 8 mm compared to those in nursing homes who were self-sufficient (1.1 responses and 4 mm induration) and nursing home residents that were not self-sufficient (0.5 responses and 4 mm induration) *(19)*. Thus, if micronutrient supplements could improve DTH responses in the elderly, the health effects could be very great *(22)*.

In addition to declines in responses to antigens that the body has already seen, the aging immune system also has declines in response to new antigens, often presented in the form of vaccines. Vaccines are important drugs used to “educate” the immune system to very small quantities of an antigen from a pathogen so that it can respond vigorously when challenged directly by the environmental pathogen. Several vaccinations are important in preventing infection-related morbidity and mortality, especially in seniors. However, even when seniors are vaccinated, there is not a 100% response rate to the vaccines, and this may be in part due to the nutritional status of the senior.

Two infections are associated with high rates of morbidity and mortality in the aging population, influenza (flu) and pneumonia. The flu caused over 35,000 deaths per year in US seniors during the 1990–1999 influenza seasons *(23)*, and currently the flu burden in the United States is still estimated to be between 25,000 and 50,000 cases per year, leading to 150,000 hospitalization and 30–40,000 deaths *(24)*, and reported by age *(25)*. The CDC data from 2006 indicate that immunization coverage for seniors (>65 years) has been almost flat in the past 5 years, at about 65% *(23)*. Interestingly, the CDC also estimated that 132 million doses of flu vaccine will be distributed for the 2007–2008 flu season *(26)*, higher than previous years. The effectiveness of the vaccination has been debated but recent meta-analysis of the data suggests that vaccination of the elderly was associated with a significant 27% reduction in the risk of hospitalization for pneumonia or influenza and a 48% reduction in the risk of death *(27)*.

Pneumococcal disease is defined as infections that are caused by the bacteria *Streptococcus pneumoniae*, also known as pneumococcus. The most common types of infections caused by these bacteria include middle ear infections, pneumonia, bacteremia, sinus infections, and meningitis *(28)*. Pneumococcal diseases are a worldwide public health problem, causing more than one million deaths each year in children under 5 years of age, mainly in developing countries *(29)*. In contrast, in industrial countries, most pneumococcal diseases including bronchopneumonia occur in the elderly. The worldwide mortality rate average is between 10 and 20 per 100,000 people who are infected each year. This rate can reach 50 per 100,000 among the high-risk groups (those who suffer from chronic conditions and immune deficiencies). In the United States, over 65% of seniors took the pneumococcal vaccine in 2004–2005 *(23)*. Traditionally, most seniors who took one of these vaccines took both vaccines *(30)*. Both influenza and pneumococcal vaccination levels among adults aged >65 years remain below the Healthy People 2010 objective of 90% coverage nationwide *(23)*. Importantly, aside from improving vaccination rates, optimization of immune responses to vaccines can significantly reduce the risk of disease in the elderly.

Infections and other diseases are often diagnosed in midlife; these illnesses may not occur independent of other chronic conditions such as allergies and immune-related diseases *(31–33)*. Both the prevalence and the number of conditions increase with age, as reported in a study of US Medicare beneficiaries. While 82% of those who were 65 years old suffered from one chronic condition, 65% had multiple chronic conditions. The number of conditions increased from 74% in those aged 65–69 – with an average of 2.3 conditions – to 88% in individuals aged 85 and older – with 2.7 conditions *(34)*. In this population, the most prevalent cause of hospitalization was for bronchopneumonia; 48% of hospitalizations had this diagnosis. Another cause of serious illness in the elderly is postoperative infection, which was found to be the cause of 13% of hospitalizations in the Medicare population. About 85% of adults over age 65 were taking some prescription drug prior to the diagnosis of a new disease such as diabetes *(35)*.

Dietary practices affect pathogenesis and are able to alter the courses of several diseases. With regard to the effect of diseases on nutritional status, it is known that in many diseases and particularly in GI diseases, the disease itself has a significant effect on the nutritional status *(36)*. As mentioned earlier, the target population of many of the diseases is the elderly. It must also be noted that about 30% of the US population over 65 years of age have experienced total tooth loss *(37)*. Tooth loss is often associated with decreased total food consumption and especially decreased consumption of nutrient-rich foods such as meats and raw fruits and vegetables that are hard to chew.

3. OVERVIEW OF INFECTIOUS DISEASES AND VACCINES

Infectious diseases with global consequences, their mode of transfer, incidence rates, and availability of vaccines are summarized in Table 1. The majority of the infections are the result of viruses including measles, rubella, respiratory syncytial virus (RSV), yellow fever, and smallpox. There are several new infectious agents, such as Ebola virus and rotavirus, which have been seen in human populations in the past decades. Bacterial infections with cholera and/or meningococcal meningitis are still the cause of widespread morbidity and mortality, especially during wars and famines. Malaria, an intracellular parasitic infection, remains a major disease in sub-Saharan Africa. Over 30% of all deaths worldwide can be attributed to infectious diseases *(38)*. Data published late in 2007 show that in the United States, death from methicillin-resistant *Staphylococcus aureus* (MRSA) has surpassed

Table 1
Infections with Global Consequences

Disease	*Transmission*	*Incidence*	*Vaccine Availability*	*Reference*
Anthrax	Humans generally acquire the disease directly or indirectly from infected animals. The causative agent of anthrax is the bacterium *Bacillus anthracis*, the spores of which can survive in the environment for years or decades, awaiting uptake by the next host There are three types of anthrax in humans: cutaneous anthrax, acquired when a spore enters the skin through a cut or an abrasion; gastrointestinal tract anthrax, contracted from eating contaminated food, primarily meat from an animal that died of the disease; and pulmonary (inhalation) anthrax, from breathing in airborne anthrax spores Cutaneous anthrax, acquired when a spore enters the skin through a cut or an abrasion, is responsible for 95% of human cases	Number of cases is low and in data for 1995–1999, there were 236 cases reported in the United States *(272)*	Vaccines are available for animals and humans. However, in humans their use should be confined to high-risk groups, such as those occupationally exposed and in some military settings. Antibiotic therapy usually results in dramatic recovery of the individual or animal infected with anthrax if given before onset or immediately after onset of illness. Antibiotic therapy may also be used for prophylaxis in asymptomatic patients believed to have been exposed to anthrax spores	*(273)*

Chicken pox	Case–fatality ratios (deaths per 100,000 cases) in healthy adults are 30–40 times higher than that among children 5–9 years of age	Each year from 1990 to 1994, prior to availability of varicella vaccine, about 4 million cases of varicella occurred in the United States. Of these cases, approximately 10,000 required hospitalization and 100 died	Most developing countries have other vaccine-preventable diseases that cause significantly greater morbidity and mortality, and varicella vaccine is not a high priority for routine introduction into their national immunization programs	*(274)*
Cholera	Cholera is an acute intestinal infection caused by ingestion of food or water contaminated with the bacterium *Vibrio cholerae*	Most persons infected with *V. cholerae* do not become ill, although the bacterium is present in their feces for 7–14 days. When illness does occur, about 80–90% of episodes are of mild or moderate severity and are difficult to distinguish clinically from other types of acute diarrhea. Less than 20% of ill persons develop typical cholera with signs of moderate or severe dehydration	It has a short incubation period and produces an enterotoxin that causes a copious, painless, watery diarrhea that can quickly lead to severe dehydration and death if treatment is not promptly given. Vomiting also occurs in most patients	*(275)*
Ebola hemorrhagic fever	The Ebola virus is transmitted by direct contact with the blood, secretions, organs, or other bodily fluids of infected persons Burial ceremonies where mourners have direct contact	Approximately 1850 cases with over 1200 deaths have been documented since the Ebola virus was discovered	No specific treatment or vaccine is yet available for Ebola hemorrhagic fever. Several vaccine candidates are being tested but it could be several years before any are available.	*(276)*

(*Continued*)

Table 1
(Continued)

Disease	*Transmission*	*Incidence*	*Vaccine Availability*	*Reference*
	with the body of the deceased person can play a significant role in the transmission of Ebola		A new drug therapy has shown early promise in laboratory studies and is currently being evaluated further. However, this too will take several years	
	The infection of human cases with Ebola virus has been documented through the handling of infected chimpanzees, gorillas, and forest antelopes – both dead and alive – as was documented in Côte d'Ivoire, the Republic of Congo and Gabon. The transmission of the Ebola Reston strain through the handling of cynomolgus monkeys has also been reported			
	Health-care workers have frequently been infected while treating Ebola patients, through close contact without the use of correct infection control precautions and adequate barrier nursing procedures			

Malaria	Malaria is caused by a parasite called Plasmodium, which is transmitted via the bites of infected mosquitoes	A child dies of malaria every 30 s. More than one million people die of malaria every year, mostly infants, young children, and pregnant women and most of them in Africa	The combination of artemisinin derivatives with another effective antimalarial medicine (artemisinin-based combination therapies or ACTs) is currently the most effective treatment for falciparum malaria – the most lethal form of the disease	*(277)*
Measles	The highly contagious measles virus is spread by coughing and sneezing, close personal contact or direct contact with infected nasal or throat secretions	In 2006, it was estimated that there were 242,000 measles deaths globally	Vaccination has been available for 40 years and had a major impact on measles deaths. Overall, global measles mortality decreased by 68% between 2000 and 2006	*(278)*
Meningo-coccal meningitis	The bacteria are transmitted from person to person through droplets of respiratory or throat secretions	It is estimated that between 10 and 25% of the population carry *Neisseria meningitidis* at any given time. Attack rates range from 100 to 800 per 100,000 population, but individual communities have reported rates as high as 1000 per 100,000 In 1996, Africa experienced the largest recorded outbreak of epidemic meningitis in history,	Several vaccines are available to prevent the disease. Polysaccharide vaccines, which have been available for over 30 years, exist against serogroups A, C, Y, W135 in various combinations. A monovalent conjugate vaccine against serogroup C has recently been licensed in developed countries for use in children and adolescents. This vaccine is	*(279)*

(*Continued*)

Table 1
(Continued)

Disease	*Transmission*	*Incidence*	*Vaccine Availability*	*Reference*
		with over 250,000 cases and 25,000 deaths registered. Between that crisis and 2002, 223,000 new cases of meningococcal meningitis were reported to the World Health Organization. In 2002, the Great Lakes region was affected by outbreaks in villages and refugee camps which caused more than 2200 cases, including 200 deaths	immunogenic, particularly for children under 2 years of age, whereas polysaccharide vaccines are not. All these vaccines have been proven to be safe and effective with infrequent and mild side effects. The vaccines may not provide adequate protection for 10–14 days following injection	
Respiratory syncytial virus (RSV)	Spread of the virus from contaminated nasal secretions occurs via large respiratory droplets, so close contact with an infected individual or contaminated surface is required for transmission	RSV is the single most important cause of severe lower respiratory infections in infants and young children. RSV includes among other diseases pneumonia and bronchiolitis, diseases being associated with substantial morbidity and mortality. The global annual infection and mortality figures	Development of vaccines to prevent RSV infection has been complicated by the fact that host immune responses appear to play a role in the pathogenesis of the disease. A combination of a live-attenuated vaccine with a subunit vaccine is also being considered for protecting adults against RSV illness,	*(280)*

		for RSV are estimated to be 64 million and 160,000, respectively	although a preliminary test of this strategy in healthy young and elderly adults was inconclusive	
Rotavirus (RV)	Person-to-person contacts, airborne droplets, or contact with contaminated items	Worldwide, RV is estimated to account for almost 40% of all cases of severe diarrhea, which translates into 600,000 deaths each year, mostly in children under age 2. Up to 85% of these deaths occur in countries defined as "low income"	RV vaccine became available recently and financial support for vaccination in Latin America and several Eastern European countries was gained *(281)*	*(282)*
Rubella	Rubella is an infection caused by a virus. Congenital rubella syndrome (CRS) is an important cause of severe birth defects. Rubella is spread in airborne droplets when infected people sneeze or cough	It is estimated that there are 700,000 deaths due to CRS each year	Rubella vaccines are safe and effective and for infant immunization are usually given in combination with measles/mumps vaccine as MMR. In some countries, mostly in the industrialized world, rubella has been nearly eliminated through childhood immunization programs. However, it is important to ensure that coverage in infants is sustained at over 80% to avoid shifting of rubella transmission to older age	*(283)*

(*Continued*)

Table 1
(Continued)

Disease	*Transmission*	*Incidence*	*Vaccine Availability*	*Reference*
			groups. For prevention of CRS, women of childbearing age are the primary target group for rubella immunization. Immunizing women between the ages of 15 and 40 will rapidly reduce the incidence of CRS without affecting childhood transmission of the rubella virus	
Smallpox	An acute, highly contagious, often fatal infectious disease caused by an orthopoxvirus characterized by a biphasic febrile course and distinctive progressive skin eruptions. Smallpox is transmitted from person to person by infected aerosols and air droplets spread in face-to-face contact with an infected person after fever has begun, especially if symptoms include coughing. The disease can also be transmitted by contaminated clothes and bedding, though the risk of infection from this source is much lower	Vaccination has succeeded in eradicating smallpox worldwide	Smallpox vaccine contains live vaccinia virus, a virus in the orthopoxvirus family and closely related to variola virus, the agent that causes smallpox. Immunity resulting from immunization with vaccinia virus (vaccination) protects against smallpox	*(284)*

Tuberculosis (TB)	An infectious bacterial disease caused by *M. tuberculosis*, which most commonly affects the lungs. TB is transmitted from person to person via droplets from the throat and lungs of people with the active respiratory disease. Tuberculosis is an airborne infectious disease that is preventable and curable.	Worldwide incidence with the clinical disease is about 8 million and death over 1.5 million	Vaccine is available but booster may be needed	*(285,285, 286,286)*
Yellow fever	Humans and monkeys are the principal animals to be infected. The virus is carried from one animal to another (horizontal transmission) by a biting mosquito (the vector). The mosquito can also pass the virus via infected eggs to its offspring (vertical transmission). The eggs produced are resistant to drying and lie dormant through dry conditions, hatching when the rainy season begins. Therefore, the mosquito is the true reservoir of the virus, ensuring transmission from one year to the next	There are 200,000 estimated cases of yellow fever (with 30,000 deaths) per year	Vaccination is the single most important measure for preventing yellow fever. In populations where vaccination coverage is low, vigilant surveillance is critical for prompt recognition and rapid control of outbreaks. Mosquito control measures can be used to prevent virus transmission until vaccination has taken effect	*(287)*

(*Continued*)

Table 1
(Continued)

Disease	*Transmission*	*Incidence*	*Vaccine Availability*	*Reference*
	Several different species of the *Aedes* and *Haemogogus* (S. America only) mosquitoes transmit the yellow fever virus. These mosquitoes are either domestic (i.e. they breed around houses), wild (they breed in the jungle), or semidomestic types (they display a mixture of habits). Any region populated with these mosquitoes can potentially harbor the disease. Control programmers successfully eradicated mosquito habitats in the past, especially in South America. However, these programmers have lapsed over the last 30 years and mosquito populations have increased. This favors epidemics of yellow fever			

death from AIDS *(39)*. There has also been a progressive and significant increase in antibiotic-resistant strains of bacteria and other pathogens. For example, as reported by the National Antimicrobial Resistance Monitoring System, 19% of *Campylobacter* isolates were resistant to the fluoroquinolone ciprofloxacin in 2004 relative to 12.9% in 1997 *(40)*. Most recently, there have been outbreaks of MRSA in the United States. MRSA is resistant to most antibiotics including all penicillins and cephalosporins. MRSA is most frequently found among persons in hospitals and health-care facilities and in individuals who have weakened immune systems *(41)*.

Vaccines against childhood and adult infections have been responsible for saving millions of lives annually throughout the world (Table 1). In developing countries, the World Health Organization (WHO) has an active program of immunization and developed nations also immunize their children against diseases that were common in the 20th Century and now have been almost eradicated *(42)*. Common vaccines used throughout the world include tetanus, diphtheria, pertussis, polio, measles, mumps, rubella, hepatitis B, and chicken pox. Analysis based on 2005 data for the United States shows that this strategy has been very successful and for diphtheria, mumps, pertussis, and tetanus, there has been a greater than 92% decline in cases and a 99% or greater decline in deaths *(43)*. However, in developing countries, the at-risk populations may not have access to certain vaccines. The WHO estimated that in 2002, 1.4 million deaths among children under 5 years were due to diseases that could have been prevented by routine vaccination *(44)*. This represents 14% of global total mortality in children under 5 years of age *(45)*. It is important to note that nutritional status affects the efficacy of the vaccination and that childhood malnutrition can compromise the protection conferred by the vaccinations.

3.1. Infectious Diseases Prevalence and Evaluation of Risk Factors

3.1.1. RESPIRATORY INFECTION

Respiratory infections are major killers of infants and young children in developing countries, accounting for about 4 million deaths worldwide, the largest infectious disease death toll *(38)*. Over 30% of all deaths in young children in underdeveloped countries can be attributed to respiratory infections. Influenza and pneumonia, as well as acute respiratory infection following measles and HIV infections, are the major causes of morbidity and mortality in children. Respiratory infections are also the major killers of frail elderly. As indicated above, bronchopneumonia is the most prevalent cause of hospitalizations in the US Medicare population *(46)* (Table 2).

Malnutrition is a serious risk factor for susceptibility to respiratory infection as well as for the progression of respiratory infections. Prior viral infections, especially RSV-associated pneumonia, often linked to malnutrition, also appears to reduce immune responses to bacterial pathogens that infect the airways. Aside from malnutrition that may be present prior to respiratory infection, the infections can cause a further 10–20% reduction in food intake. Thus, nutritional intervention is critical especially in the care of infected children.

Table 2
Major Global Diseases: Prevalence and Mortality *(38,49,288–290)*

Disease	*Prevalence/Mortality*
Respiratory infections	3.9 million deaths/year *(38)*; cause of 30% of all childhood deaths in underdeveloped countries
HIV	Globally, 33.2 million people living with HIV, 2.5 million people became newly infected, and 2.1 million people died of AIDS in 2007. Twenty-five million have died from AIDS since 1981. In North America, there are about 1.3 million people living with HIV/AIDS, with about 50,000 newly infected and about 21,000 death associated with the disease in 2007 *(288)*
Diarrheal diseases	Two million deaths/year globally *(289)*
Tuberculosis	Overall, one-third of the world's population is currently infected with the TB. Estimated, 1.6 million deaths resulted from TB in 2005 *(49)*

3.1.2. HIV INFECTION AND AIDS

The human immunodeficiency virus was first identified in 1984 following the recognition in 1981 of an unusually high number of infections caused by the pathogenic microorganism *Pneumocystis carinii* and the appearance of a rare form of cancer, Kaposi's sarcoma, in homosexual men in San Francisco and New York *(47)*. HIV infection was shown to be caused by one of two retroviral species designated HIV-1 and HIV-2. The virus infects cells of the immune system, resulting in severe immunosuppression that has been termed acquired immunodeficiency syndrome (AIDS) *(48)*.

Since its discovery, HIV infection has spread throughout the world and has become a major threat to populations especially in underdeveloped nations. Currently, the WHO estimates that about 33.2 million people worldwide are infected with the HIV virus; half of those infected are women *(49)*. It is estimated that more than 25 million people worldwide have died as a consequence of this epidemic. During 2007, more than 2.5 million people worldwide were newly infected with the virus, and the death toll is estimated to be about 2.1 million *(49)*, decreased from 2.7 million in 2002 *(38)*.

During the last 25 years, HIV disease has been extensively studied, including the relationship between HIV infection and nutrition. Nutritional status has been demonstrated to affect the course of the infection from the onset, during latency and progression to AIDS, as well as throughout the course of opportunistic infections *(50–60)*. Nutritional therapy is especially important in sub-Saharan Africa and other underdeveloped countries where more than 60% of HIV-infected people live *(61)* and where antiretroviral drugs are often not available *(62)*. Of great concern are the children under 5 years of age who are infected, are also malnourished, and not receiving drug therapies; mortality rates are significantly increased in malnourished, infected children *(61)*.

3.1.3. DIARRHEAL DISEASES

Diarrheal diseases are the third most common cause of mortality from infectious disease worldwide and the leading cause of childhood morbidity and mortality in underdeveloped countries. About 1.7 million people die annually worldwide from diarrheal diseases *(38)*. The major causes are pathogenic viruses, bacteria, or gut parasites that infect undernourished children. Associated with diarrheal disease are dehydration, fever, anorexia, convulsions, measles, micronutrient deficiencies, and severe protein–energy malnutrition *(63)*.

Recently, it has been suggested that certain diarrheal diseases may be associated with the modification of the gut environment due to the overuse of antibiotics. Although antibiotics are beneficial for treating illness caused by certain enteric pathogens, they may also contribute to disease by eliminating certain commensal microbes that inhibit or suppress the growth of pathogenic microbes in the gut.

3.1.4. TUBERCULOSIS

TB is the fourth leading cause of death from infectious diseases worldwide *(38)*. About one-third of the world's population (almost 2 billion people) is infected with the causative organism (*Mycobacterium tuberculosis*); in 2005, 8.8 million people fell ill with TB and 1.6 million people died *(49)* (Table 2). In the developed world, TB is often seen in individuals infected with HIV or other chronic diseases that reduce immune responses to bacterial infections. The most common type of TB is pulmonary and infants, children, the elderly, those with diabetes or other immunodeficiency diseases, or immune depression as a result of cancer chemotherapy, or organ transplant medications are most at risk. The pulmonary form is spread via contact with infected sputum. Malnutrition is a major risk factor for TB infection; specifically, protein and calorie malnutrition are well-documented risk factors. Recently, it has been suggested that loss of appetite may independently contribute to the malnutrition in TB *(64)*. Low intakes of vitamin A and C as well as reduced exposure to the sun and/or low vitamin D intake have all been seen in individuals infected with TB *(65)*.

3.2. Nutritional Status and Infectious Diseases

Poor nutritional status is strongly associated with an increased risk of contracting new infections and/or overcoming the disease. Scientific studies of undernutrition have focused on the most at-risk populations (pregnant women, neonates, and toddlers) and on single nutrients that have consistently been shown to be associated with severe, observable adverse effects.

3.2.1. VITAMIN A IN DEFICIENT POPULATIONS

The most well-studied micronutrient deficiency is vitamin A; supplementation has been shown to significantly reduce the risk of xerophthalmia, the major cause of childhood blindness in developing countries even today *(66)*. In addition to preventing blindness, vitamin A has been acknowledged as the "anti-infective vitamin" for almost a century. However, vitamin A deficiency and its dire consequences still affect over 250 million preschool children worldwide *(67)*. Vitamin A deficiency consequences also include growth failure, depressed immunity, and a higher risk of anemia *(68)*. Decades of clinical studies have shown that vitamin A status is significantly associated with morbidity and mortality from some infectious diseases including measles and diarrheal infections *(13,14)*. Vitamin A supplementation studies have also shown that supplemented children have better outcomes, especially if their vitamin A status was low at the time of infection/hospitalization *(69,70)*. These data were confirmed and extended to show that vitamin A supplementation also reduced the number of children with measles-related pneumonia and reduced the time to recovery *(71)*. Recently, well-controlled studies in Mexican children have shown that supplementation reduced diarrhea and respiratory infections *(72)*. The mechanism of action of vitamin A includes decreasing the prevalence of diarrheal-related viral infections even though viral shedding was prolonged *(73)*. Another study demonstrated a pathogen-specific mucosal immune response in the vitamin A-supplemented children as measured by the reduced fecal concentration of monocyte chemoattractant protein-1 after infection with *Escherichia coli (74)*. In a separate study, Long et al. *(75)* reported that vitamin A supplementation reduced certain gastrointestinal parasites in infected Mexican children and concomitant zinc supplementation added to the beneficial effects of vitamin A although not all parasites responded favorably.

3.2.2. Zinc in Deficient Populations

Zinc is a critical nutrient for immune function. This mineral is a component of the thymic hormone thymulin required for the maturation of T lymphocytes. Zinc is required for the functioning of over 200 enzymes necessary for virtually all cell functions including cellular proliferation that is critical to the production of the millions of new white blood cells daily. Zinc deficiency is associated with severe immune dysfunctions. Zinc deficiency also results in a loss of appetite and thus may further promote nutrient deficiencies due to decreased food intake.

In many underdeveloped countries worldwide, toddlers, young children, and pregnant women are at a high risk for vitamin A, zinc, and iron deficiency *(15)*. Zinc deficiency, as with iron deficiency, is associated with diets low in meat protein sources *(46,63)*. Iron deficiency is a major problem among preschool children worldwide, and consequences of iron deficiency include retarded psychomotor development, impaired cognitive function, and anemia *(76,77)*. The link between iron deficiency and increased risk of infection is not as clear as it is for vitamin A and zinc. However, vitamin A supplementation often also concomitantly increases iron status and therefore it is difficult to separate the effects of any single nutrient from the effects of others that change during a single nutrient supplementation program.

Zinc deficiency is common in underdeveloped countries and infant and toddler morbidity and mortality has been directly associated with zinc intake and status *(78)*. Osendarp et al. *(79)* completed a well-controlled study in infants (about 1 month old) in Bangladesh. The infants were given 5 mg/d zinc or placebo for about 2 years. In the infants with low initial zinc serum levels, the supplementation resulted in significantly enhanced growth and significant reduction in acute respiratory tract infections. These researchers have also reported that zinc supplementation during pregnancy significantly reduced infant diarrheal disease morbidity *(79)*. Tielsch et al. *(80)* examined the potential for zinc supplementation at twice the dose used in the Osendarp study (10 mg/d) in zinc-deficient Nepalese children 1–35 months of age. They did not find an effect of zinc supplementation on frequency and duration of either diarrhea or acute respiratory tract infections; there was no effect on mortality.

Intervention studies have examined the effects of zinc supplementation on infection outcomes in adults and children in developing countries. Range et al. *(81)* examined the potential for daily supplementation with 45 mg of zinc or a multivitamin–mineral supplement (containing vitamins A, B, C, D, E, selenium, and copper), or both supplements compared to placebo to affect mortality rates in 499 Tanzanian patients with tuberculosis, 43% also had HIV. Following 7 months of supplementation, there was a significant reduction in deaths in those given both supplements who were infected with both diseases. Some studies have examined the effect of antiretroviral therapy on micronutrient status and have found that the drug therapy may enhance nutritional status by reducing the viral load. Other studies have not confirmed this finding and it appears that the drugs may enhance certain nutrient levels, but not all. Short-term zinc supplementation in Bangladeshi children suffering from persistent diarrhea resulted in a significant reduction in episodes and duration of diarrhea and improved linear growth in the underweight children *(82)*. A 6-month supplementation study in children 6–48 months of age in India found a significant 25% reduction in diarrheal incidence with 25 mg/week of zinc supplementation plus B vitamins compared to B vitamins alone. Moreover, there was a 14% reduction in diarrhea during the subsequent 6 months *(83)*. Hoque and Binder *(84)* reviewed the beneficial effects of oral rehydration and zinc supplementation on diarrheal disease morbidity and mortality and indicated that there is a biological plausibility for zinc's effects on the GI tract. Drain et al. *(85)* reviewed both the observational and intervention studies and determined that further research is required to clearly understand the effects of drugs on nutritional status and also to determine when and if micronutrient supplementation, including zinc, should be implemented. A similar recommendation for high-quality studies was made in an extensive meta-analysis of intervention studies using zinc for 3 months or longer in children less than 5 years of age. This review found significant beneficial effects of zinc on both diarrhea and lower respiratory tract infections and pneumonia *(86)*.

3.2.2.1. Zinc Status, Immune Function, and the Elderly. Both zinc and vitamin A deficiencies have been associated with increased risk of respiratory infection. Numerous studies have shown that zinc supplementation reduces the incidence of infection in poor children, and a recent meta-analysis concluded that zinc supplementation reduced significantly the frequency and severity of respiratory infections *(86)*. Since low zinc status has been associated with reduced immune function, there is interest in whether enhanced zinc status might improve immune function in the elderly. Some studies in senior men and women have found that zinc supplementation in populations with initially low zinc status resulted in increased serum thymulin levels, enhanced appetite, improved antibody responses to influenza vaccine, improved delayed hypersensitivity responses, and decreased respiratory infections *(87)*. In contrast, 6 months of zinc supplementation (at 15 or 30 mg/d) in healthy seniors (55–70 year old) affected some immune cell ratios positively at 15 mg/d, but not at 30 mg/d *(88)*. Elderly are also at increased risk of respiratory infections including colds. Several zinc-containing products are marketed with the claim that these reduce cold symptoms. Caruso et al. *(89)* published a meta-analysis of the data from intervention studies with zinc lozenges, nasal spray, or nasal gel and reported that the quality of the studies permitted only 4 of 14 studies to be included in their analysis. Three of the four studies found no significant effect of the zinc lozenges or nasal spray. There was one positive study for the nasal gel. Thus there does not appear to be a consistent finding of benefit with these products even though the dose of zinc is often well above current recommended intake levels.

3.2.3. BETA-CAROTENE

β-Carotene is the major carotenoid precursor of vitamin A and it too has immunoenhancing properties that may be additional to its role as a source of vitamin A *(90)*. β-Carotene, because of its structure, can absorb the high energy generated by UV light including sunlight. Long-term exposure to UV has been shown to decrease immune responses. β-Carotene supplementation in both young and senior men reduced the immunosuppressive effects of UV light in well-controlled studies. Since many seniors relocate to sunnier environments where exposure to UV is increased, these data suggest that β-carotene may protect from any depressions in immune responses due to long-term sun exposure *(91)*. Although observational studies suggested that low serum β-carotene may influence HIV-1, randomized trials were not able to demonstrate benefits of supplementation. Recently, a cross-sectional study that looked at serum β-carotene relative to biologic markers of HIV-1 disease severity showed a significant association. Of importance, this research also suggests that the low serum β-carotene may be a consequence of a more active disease rather than a deficiency that is amenable to intervention *(92)*.

3.2.4. VITAMIN E

Low serum vitamin E levels have been seen in individuals with impaired immune responses associated with viral infection. Vitamin E supplementation at increasing doses up to 600 IU/day in healthy seniors has been shown to improve the function of immune cells and cytokines associated with enhanced immune responses. Vitamin E supplementation in healthy, well-nourished seniors resulted in enhanced delayed hypersensitivity responses, responses to the hepatitis B vaccine, lymphocyte proliferation, and reduction in the formation of immunosuppressive prostaglandins *(93)*. Vitamin E supplementation has also been shown to reduce the incidence of respiratory tract infections in seniors in a nursing home environment *(94)*. Von Herbay et al. *(95)* reported that serum vitamin E levels were significantly lower in patients with severe viral hepatitis compared to controls. Serum vitamin E levels returned to control levels when the hepatitis subsided, suggesting that hepatitis involved oxidative reactions that consumed vitamin E. Low vitamin E status has been associated with the conversion of an avirulent viral strain to a virulent one in an animal model *(96,97)*. However, not all intervention studies have found an immunoenhancing effect of vitamin E supplementation. Graat et al., *(98)* in a study involving over 650 individuals over age 60 gave one-fourth of the population a supplement of 200 mg of vitamin E for about 14 months. They found no decrease in the incidence of self-reported acute respiratory tract infection and an increase in the duration and symptoms compared to placebo. The same study included a multivitamin/mineral supplement arm and also showed no significant decreased risk of infection – however, there was no increase in duration or symptoms in this arm of the study. The group given both active treatments responded similarly to the individuals getting each active alone.

3.2.5. Other Relevant Essential Nutrients

3.2.5.1. Vitamin C. Vitamin C supplementation, following depletion in a controlled, metabolic ward study, restored the delayed hypersensitivity responses that were severely depressed following the depletion phase of the study. The level of supplementation required was several fold higher than the current recommended intake level. Vitamin C also regenerates the antioxidant form of vitamin E and therefore may be particularly important to see the full benefit of vitamin E supplementation. Vitamin C is also critically important in the killing of bacterial pathogens by neutrophils, the most abundant population of white blood cells. Neutrophils contain very high concentrations of vitamin C, and the vitamin protects these cells from self-destruction by the oxidants produced to kill the pathogens *(99)*.

3.2.5.2. Vitamin D. Vitamin D can be synthesized in the skin during short-term exposure to UV light. For light-skinned individuals, direct sunlight exposure beyond 15–20 min does not result in further synthesis of vitamin D and may be immunosuppressive. Many studies have shown that vitamin D in its active form (1,25-dihydroxyvitamin D_3) is an important immune system regulator *(100,101)*. Vitamin D deficiency is defined by most experts as a serum 25-hydroxyvitamin D level of less than 20 ng/mL with insufficiency at concentrations below 30 ng/mL. Using that definition, the prevalence estimation which has been recorded is that 1 billion people worldwide have vitamin D deficiency or insufficiency and between 40 and 100% of US and European elderly men and women still living in the community suffer from vitamin D deficiency *(102–106)*. Vitamin D deficiency has been linked to different immune system-mediated diseases including ulcerative colitis and Crohn's disease *(107,108)* because of malabsorption and decreased outdoor activities in climates that are not optimal for vitamin D synthesis in the skin *(108)*. Vitamin D has been reported to play a role in TB infection in some but not all studies. It has been suggested that destruction of *M. tuberculosis* results from upregulation of genes for vitamin D receptor and for the 1-α-hydroxylase enzyme. High levels of vitamin D result in the synthesis of cathelicidin which is a peptide capable of destroying some infectious agents. In a recent small Finnish study, Laaksi et al. found that subjects with serum 25(OH)D concentrations < 40 nmol/L (16 ng/mL) had significantly more days of absence due to respiratory infection than did control subjects *(109)*.

Several investigators have examined the effects of different combinations of vitamins and minerals on immune responses, mainly in healthy seniors *(110)*.

There are consistent findings of enhancement in delayed hypersensitivity responses, proliferative responses, and enhancement of responses to certain vaccines important for the health of the elderly. In some cases, there were also reductions in the rates of infections and decreased morbidity if infections did occur.

3.2.5.3. Arginine and Glutamine. It is well accepted that protein deprivation results in significant immune depression. In addition to nutritional deprivation, major trauma to the body results in a hypermetabolic and hypercatabolic state in which muscle tissue proteins are used to provide metabolic substrate for the traumatized body. In fact, major trauma can result in acute protein malnutrition that can cause serious, life-threatening effects on the heart, liver, and immune system. Recent research has focused on certain individual amino acids and nucleotides that have been shown to individually enhance immune responses, especially during stressful situations such as surgery and other trauma *(111)*. The two amino acids that have been studied most extensively are arginine and glutamine. Arginine supplementation restores lymphocyte proliferative responses and enhances delayed hypersensitivity responses; enhancement of T lymphocyte responses is thought to be the major mechanism involved in the immune enhancement *(112)*. In addition, arginine enhances the formation of collagen and is thus important in wound healing *(113)*. Glutamine serves as a major source of energy for lymphocytes, mucosal cells lining the GI tract, and for macrophages. This conditionally essential amino acid also plays a role in cell signaling through gene regulation. Glutamine is also the precursor of glutathione, a major water-soluble antioxidant. Nucleotides are required for the proliferation of all rapidly dividing cells including cells of the immune system and the lining of the GI tract. Nucleotide supplementation has been found to enhance immune responses to infectious agents in animal models (reviewed in *114,115*).

4. EFFECT OF DRUGS (USED TO MANAGE MAJOR INFECTIOUS DISEASES) ON NUTRITIONAL STATUS

Antibiotic use by humans in the United States is estimated at 4.5 million pounds annually *(116)*. As antibiotics are used to treat many acute and chronic infections, we have tabulated important information about the numerous classes of these drugs, their common names, the instructions for dosing and whether it should be taken with or without food, the nutritional effects of the different antibiotics, and any related adverse reactions on the GI tract (Table 3).

Antibiotic exposure, however, is considered to be much higher due to inadvertent exposure to foods that contain antibiotics, such as beef, chicken, and certain root vegetables. Estimates of antibiotic use in the veterinary industry and as growth promoters in the animal feed industry approach 50 million pounds/year based on 2004 data. Antibiotic-resistant strains of pathogens are a growing problem and result in the use of multiple antibiotics and stronger drugs that can further adversely affect nutritional status via nutrient absorption, elimination, and/or utilization.

In 2005, evidence-based guidelines that were issued by the European Respiratory Society in collaboration with the European Society of Clinical Microbiology and Infectious Diseases for the management of community-acquired pneumonia were

Table 3
Select Antibiotic Drug Classes and Drug–Nutrient Interactions

Drug Family	*Drug Name*	*Administration Instructions*	*Nutritional Effects*	*GI-Related Adverse Reactions*
Cephalosporin	Cefadroxil	Take at regular intervals and complete the prescribed course unless otherwise directed *(294)*		Diarrhea, nausea and vomiting, inflammation of the large intestine *(294)*
Penicillins	Amoxicillin	Can take with water, fruit juice, milk, or carbonated beverages *(295)*		Diarrhea *(292)*
	Ampicillin	Take with water on an empty stomach 1 h before or 2–3 h after meals *(296)*		
	Penicillin	Take with water on an empty stomach 1 h before or 2–3 h after meals *(296,297)*		
	Flucloxacillin	Take this medication an hour before food or on an empty stomach *(298)*		Diarrhea, nausea and vomiting, inflammation of the large intestine, and liver *(298)*
Tetracyclines	Tetracycline	Take with water on an empty stomach 1 h before or 2–3 h after meals *(295,297,299)*	Avoid calcium (milk and dairy products) and iron-containing foods, antacids, or supplements for 2–3 h after taking drug *(292,295,300)* Tetracyclines can interfere with the activity	Anorexia, nausea, vomiting, diarrhea *(291)*

(*Continued*)

Table 3
(Continued)

Drug Family	*Drug Name*	*Administration Instructions*	*Nutritional Effects*	*GI-Related Adverse Reactions*
			of folic acid, potassium, and vitamins B_2, B_6, B_{12}, C, and K *(295)*	
Macrolides	Erythromycin stearate	Take with water on an empty stomach 1 h before or 2–3 h after meals *(299,300)*	Erythromycin may interfere with the absorption and/or activity of calcium, folic acid, magnesium, and vitamins B_6 and B_{12} *(292)*	May upset stomach *(299)* GI side effects including nausea, vomiting, abdominal pain, diarrhea, and anorexia *(291)*
	Azithromycin	Take with water on an empty stomach 1 h before or 2–3 h after meals *(300)*. When taken with food its absorption is reduced by 50% *(301)*	Avoid aluminum- and magnesium-containing antacids *(292,299)*	GI side effects including dyspepsia, flatulence, vomiting *(291)*
	Dirithromycin	Take with food or within 1 hour of eating a meal *(299)*		
Rifampin	Rifampicin	Take with water on an empty stomach 1 h before or 2–3 h after meals *(296)*		
	Rifampin	Take on an empty stomach *(300)*	Cause vitamin D deficiency. Give vitamin D if patient cannot tolerate milk *(300)*	
Quinolones	Ciprofloxacin; norfloxacin	Can be taken with meals but best when taken 2–3 h after meals *(299)*	Avoid calcium (dairy products), aluminum, zinc, iron- and magnesium-	Nausea, diarrhea, vomiting *(291)*

			containing antacids or supplements *(252,292,299,301)* Give with increased fluids *(300)*	
Oxazolidinone	Linezolid		Large quantities of foods or beverages with high tyramine content should be avoided	Disturbances of the gut such as diarrhea, constipation, nausea, vomiting, or abdominal pain *(302)*
Other	Vancomycin	Injection		Nausea *(303)*
	Teicoplanin	Injection		Nausea and vomiting *(304)*

adapted by Switzerland. These guidelines take into consideration the increase in the prevalence of resistant bacteria combined with relevant clinical information to help determine an appropriate course of treatment. Treatment algorithms that carefully exclude other causes based on symptoms as well as the use of the appropriate antibiotic at a minimal dose were recommended. Since the use of antibiotics is estimated to be well above the expected prevalence of bacterial infections in North America, the optimal use of antibiotics in the context of respiratory infections still needs to be determined *(117)*. In addition to the increased risk related to antibiotic-resistant bacteria, there are multiple nutritional and food-related considerations related to antibiotic use, as illustrated for several common antibiotics in Table 3. The use of antibiotics may trigger autoimmune diseases *(118)*. The use of antibiotics is associated with significant temporary changes in the colonization of the large intestine and the microbiota balance (see below).

4.1. HIV

The primary objective of HIV drug therapy is to halt viral replication. Most drugs target the enzymes that either permit the virus to enter the host cell's DNA or decrease the potential for the virus to replicate within the host's cells. Drug treatment usually involves the simultaneous administration of at least two drugs; in developed countries, these are given to infected individuals from the onset of symptoms and continue indefinitely. Selected HIV-1 medications and their nutritional effects are summarized in Table 4. This table includes detailed information about the 18 most commonly used drugs, the effects of the drug on nutritional status, effects on appetite, fat absorption and the effect of dietary fat on drug absorption and other relevant information, and the detailed instructions for administration (see also Chapter 26). Resistance to HIV drugs is common and thus throughout the course of the disease there are multiple adjustments in drug combinations.

For HIV, even when patients are asymptomatic, there are many relevant nutritional consequences due to the advance of the disease *(47)*. Continuing production of proinflammatory cytokines and a general state of increased metabolic activity contribute to the weight loss seen as disease progresses. Reduced dietary intake and nutrient malabsorption also contribute to the deteriorating nutritional status. Finally, most drugs used to treat HIV and AIDS have similar adverse effects on the GI tract, resulting in nausea and diarrhea, loss of appetite, dyspepsia and anorexia, loss of sensation in the mouth, and changes in taste perception. Consequently, patients suffer from decreased food intake. There is also an acceleration of loss of nutrients because of the persistent diarrhea seen with the disease as well as in response to drug therapy. Both macro- and micronutrients are lost in diarrhea including proteins, fat, fat- and water-soluble vitamins, sodium, and potassium. More serious adverse effects to drugs include pancreatitis and liver dysfunction *(48,119)*.

There appears to be an increased requirement for macronutrients and several of the micronutrients in HIV-infected individuals. When clinical studies are undertaken, these patients are almost always treated with a multidrug regimen. HIV-infected patients often have elevated triglycerides and may have higher circulating fatty acids. Arginine and glutamine, amino acids that have been shown to be

Table 4
Drugs Used to Treat HIV and Possible Nutritional Effects *(47,251,251)*

Drug Class	*Specific Drug*	*General Effects Related to Nutritional Status*	*Administration Instruction/Specific Nutritional Effects*
Nucleoside analogs reverse transcriptase inhibitors (NRTIs)	Zidovudine	▪ Nausea ▪ Diarrhea ▪ Constipation ▪ Loss of sensation in the mouth ▪ Oral ulcers ▪ Changes in taste perception	The effect of food on the absorption from tablet is unknown *(291)* Reduction in copper and zinc blood levels. If low B_{12}, more likely to develop blood-related side effects (anemia) *(292)*
	Didanosine	▪ Loss of appetite ▪ Other GI tract reactions that result in decreased food intake	Should be taken on an empty stomach 30 min before or 2 h after eating food *(291,292)*
	Zalcitabine	▪ More serious adverse effects include pancreatitis and liver dysfunction *(48,119,291)*	Absorption is reduced when drug is administered with food *(291)*
	Stavidine		Zerit should be taken every 12 h without regard to meals *(291)*
	Lamivudine		Epivir (liquid or tablets) can be administered with or without food *(291)*
Protease inhibitors (PI)	Saquinavir (Fortovase)	▪ Dyspepsia and anorexia ▪ Redistribution and accumulation of body fat	Increased (about eight times higher) single-dose absorption under fasting conditions was reported *(291)*
	Saquinavir (Invirase)	▪ Increase in triglycerides ▪ Increase in cholesterol ▪ Onset of new diabetes and exacerbation of preexisting conditions ▪ Diarrhea ▪ Nausea*(291)*	Patients should be advised to take drug within 2 h of a full meal. When drug is taken without food, concentrations of drug in the blood are very low and may result in much reduced (~8 times less) antiviral activity *(291)*

(*Continued*)

Table 4
(Continued)

Drug Class	*Specific Drug*	*General Effects Related to Nutritional Status*	*Administration Instruction/Specific Nutritional Effects*
	Ritonavir		Drug should be taken with food if possible Drug may cause a reduction in copper and zinc blood levels. If patients have low B_{12}, they are more likely to develop blood-related side effects like anemia *(292)*
	Amprenavir		May be taken with or without food. Should not be taken with a high-fat meal (reduces its effectiveness) *(291)*
	Indinavir		Take each dose (every 8 h) without food but with water at least 1 h before or 2 h after a meal. May be taken with a light meal (that contains no fat). Can cause kidney stones and should be taken with water or other liquids *(291,293)*
Nonnucleoside reverse transcriptase inhibitor (NNRTI)*(291)*	Nevirapine		Drug is readily absorbed and the bioavailability is not affected by ingestion of foods including high-fat meals *(291)*
	Delaviridine		May be administered with or without food; however, there is a significant reduction in the amount of the drug in the plasma when taken with a high-fat meal. Drug should be taken apart from antacids (at least 1 h) *(291)*

	Efavirenz		It may be taken with or without food; however, high-fat meals should be avoided as it may increase absorption significantly *(291)*
Sulfonamides	Co-trimoxazole	Most common adverse effects are GI related including nausea, vomiting, and anorexia. Caution when given to patients with folate deficiency *(291)*	Should be taken with plenty of fluids. The incidence of hyperkalemia appears to be higher with AIDS patients receiving co-trimoxazole *(291)*
Macrolides	Clarithromycin	Most frequent effects were diarrhea, abnormal taste, and nausea *(291)*	Can be taken with or without food. The drug is rapidly absorbed, with about 50% bioavailability. Food slightly delays absorption with increased plasma concentration but without increased bioavailability *(291)*
Antiprotozoal	Atovaquone		Administration with food enhances drug's absorption (twofold). The bioavailability is highly dependent on the formulation and the diet *(291)*
Orexigenics	Megestrol		The effect of food on absorption has not been evaluated *(291)*
	Dronabinol	Effective against anorexia associated with AIDS *(291)*	Drug should be taken prior to lunch and dinner *(291)*

immunomodulatory, have been given to HIV-infected patients with consequent beneficial effects such as increases in lymphocyte counts and decreases in infections *(113)*.

With regard to micronutrients, there are consistent reports of significantly lower circulating levels of riboflavin, niacin, folate, and vitamins B_6 and B_{12}; vitamin B_6 and folate are important for optimal immune responses. Low serum vitamin A levels are predictive of poor long-term outcomes. Indicators of increased oxidative stress are well documented and circulating levels of selenium, vitamin C, and vitamin E are often reduced *(31,47,120–124)*.

4.2. TB

TB is normally treated with up to four antibiotics simultaneously in order to reduce the potential of forming drug-resistant strains of the bacteria. TB treatment is long term and the drugs have adverse effects on food consumption and may cause vomiting, diarrhea, and loss of appetite (Table 3). Following acute infection, there is often a latent period where the bacteria are not reproducing and infected patients recover their strength. There are few well-controlled studies that indicate that nutritional interventions can affect the progression of TB once contracted.

There are also a few studies that show success in reducing the progression from latent to reactivated disease with nutritional measures. However, there are very few studies and it is difficult to separate the influence of nutritional intervention from those of the antibiotic therapy. In summary, poor nutritional status increases the risk of contracting TB and continued malnutrition cannot improve prognosis. Long-term, beneficial nutritional interventions have yet to be identified for TB patients *(65)*.

5. AUTOIMMUNE DISEASES

5.1. Autoimmune Disease Prevalence and Evaluation of Risk Factors

The number of differentiated autoimmune diseases continues to grow and as of recently, eighty distinct autoimmune diseases have been identified. Examples of organ-specific autoimmune diseases include Type 1 diabetes (pancreas), Graves' and Hashimoto's diseases of the thyroid, and Meniere's disease of the ear. Systemic diseases include SLE, multiple sclerosis, RA, and other arthritides as well as numerous other less frequently studied diseases such as myasthenia gravis and scleroderma *(125)*. A 1997 epidemiological study identified 24 of the most commonly occurring autoimmune diseases in the United States and found that about 3% of the adult population has an autoimmune disease. For the 24 types of autoimmune disease, women were at 2.7 times greater risk than men *(126)*. More recently, it has been estimated that autoimmune diseases afflict 8–10% of the US population or about 24 million people. Importantly, 78% of the affected individuals were women *(127)*. Collectively, autoimmune disease is one of the top 10 leading causes of death of children and for women for every age group up to 64 years old *(125,128)*. Incidence rates vary among the autoimmune diseases, with estimates ranging from less than one newly diagnosed case of systemic sclerosis to more than 20 cases of adult-onset rheumatoid arthritis per 100,000 people. Prevalence rates range from less than 5 per 100,000 to more than 500 per 100,000 (Graves' disease, rheumatoid arthritis, thyroiditis) *(129)*. For comparison, the prevalence of Type 1 diabetes is 192 per 100,000 US adults, whereas lupus is seen in about 24 per 100,000 people (mainly women). Jacobson et al. *(126)* indicate that the incidence of rheumatoid arthritis and Type 1 diabetes and three other autoimmune diseases will increase over time, based upon past analyses. These authors also point out the need for better demographic information about the prevalence and incidence of autoimmune diseases. The economic impact is considerable because the majority is afflicted during their most productive years, and the conditions are chronic, with no cures currently available.

5.1.1. Rheumatoid Arthritis

RA is a chronic, progressive autoimmune disease of unknown origin that is associated with a genetic predisposition and an environmental trigger *(130)*. RA causes a deterioration of articular joints causing pain, stiffness, swelling, and deformity that over time results in severe disability. The autoantibodies in RA are sometimes referred to as rheumatoid factor and titers are used diagnostically. The autoantibodies are found in the joint fluids and are probably the initiators of the inflammation seen in peripheral joints. The age of onset may be in youth or young adulthood resulting in juvenile RA. About 1% of the population suffers from adult-onset RA; more than 2 million American adults are affected and 75% are women *(131)*. Oxidative damage to the joints and increased production of inflammatory cytokines are hallmarks of RA. Patients with RA may also have symptoms of anemia that is unrelated to a lack of dietary intake of iron. Anemia of chronic disease (ACD) is associated with a reduction in red blood cell (RBC) iron. There appears to be a redistribution of iron from inside the RBC to within the synovial fluid. The RBC have receptors for the rheumatoid factor. Binding of rheumatoid factor to the receptor on the RBC triggers autoimmune destruction of the erythrocyte and release of iron into the synovial fluid. RA-associated ACD causes an increase in oxidative damage in the joints exposed to free iron *(130,132)*. Low saliva output is also seen in about 25% of RA patients who may also be suffering from a second autoimmune disease, Sjogren's syndrome. Hyposalivation results in decreased buffering capacity, which can contribute to mucosal infections, dental caries, difficulties in tasting, eating, swallowing, and/or speaking *(133)*.

5.1.2. Systemic Lupus Erythematosus

SLE mainly affects women of childbearing age; only 10% of lupus patients are male. Worldwide, the incidence in white women is 1 in 1000, but it is 1 in 250 in black women. In the United States, the disease affects about 1.4 million women. About one-third of patients have more than one autoimmune disease; about half have a relative that is also affected by autoimmune disease, highlighting the genetic component of the disease. Broader health impact of SLE includes accelerated atherosclerosis, which increases the risk of heart attacks and other cardiovascular events like heart failure and strokes. This makes it crucial to try to prevent such complications by reducing other risk factors for heart disease such as smoking, high blood pressure, and high cholesterol. SLE may also cause kidney disease, which can progress to renal failure and require dialysis *(134)*. There are few data associating nutritional status and risk of lupus. A prospective epidemiological study noted that low vitamin E status preceded diagnosis of SLE and RA in a well-characterized population *(97)*. Another small study from Korea suggests that patients with SLE have lower intakes of antioxidant nutrients and carotenoids than age- and sex-matched controls *(135)*. There are suggestions from a limited number of studies that certain food components and nutrients, such as vitamin D, may affect the course of the disease. Most of the data, however, are from small studies over relatively short periods of time; however, a recent analysis from the Nurse's Health Study I and II of over 90,000 women who had been followed from 1980 to 2002 and did not have either RA or SLE at baseline showed no association of vitamin D intake with risk of developing these two autoimmune diseases *(136)*.

5.1.3. Inflammatory Bowel Disease

Ulcerative colitis (UC) and Crohn's disease (CD) are idiopathic, chronic, inflammatory disorders of the GI tract that are immunologically mediated. Collectively, these disorders are referred to as IBD. The chronic inflammation can develop via many mechanisms, suggesting these are heterogeneous diseases on many levels. IBD can present as bloody diarrhea, abdominal pain, malnutrition, and lifelong relapses. Most commonly, these disorders present in two peaks with regard to age. The first peak is between 15 and 30 years and the second peak is between 60 and 80 years. Both age peaks share common pathophysiology *(137)*. Although UC and CD share many aspects, there are few important differences related to the location of the inflammation and the depth of the inflammation. In CD, the inflammation location could be anywhere along the GI tract (from mouth to anus), whereas in UC, the inflammation is restricted to the colon and is confined to the mucosal layer of the large bowel. Finally although both diseases dispose the individuals affected to cancer, UC does so to a greater extent *(138)*.

The pathogenesis of IBD is very complex and only partly understood. Onset or reactivation of the disease is believed to be due to convergence of four separate components. These components are genetic susceptibility, environmental triggers, immune response combined with luminal antigens, and adjuvants. Genes that control mucosal barrier integrity and microbial clearance and/or homeostasis, as well as innate immune responses, have been implicated *(139,140)*. Although it is commonly believed that overaggressive T-cell immune responses to commensal (i.e., nonpathogenic) bacteria found in the GI tract are responsible, there is evidence that activated innate (macrophage) and acquired (T and B cells) immune responses and loss of tolerance to enteric commensal bacteria are involved. Further, recently it has been reported that there is no direct evidence of defective T-cell regulatory function *(139)*. Commensal gut bacteria play a major role in the development and relapses of IBD either as adjuvants (activation of innate immune response including dendritic cells and antigen-presenting cells) or as antigens (stimulation of T cell and activation via T-cell receptor) *(139)*. Human data suggest that in UC the commensal bacteria balance is tipped toward more proinflammatory types of bacteria, specifically, bifidobacteria and peptostreptococci *(141)*.

Although mortality rates are low, IBD is associated with high morbidity *(142)*. There are variable incidence rates of IBD across different countries. As many as 1.4 million people in the United States and 2.2 million in Europe suffer from these diseases *(142)*. The highest incidence rates and prevalence for both UC and CD have been reported from northern Europe *(143,144)*, the United Kingdom *(145)*, and North America *(137,146)*, which are the geographic regions that have been historically associated with IBD. However, reports of increasing incidence and prevalence from other areas of the world such as southern or central Europe *(144,147)* and Asia *(148–150)* show that occurrence of IBD is a dynamic process. The prevalence of IBD has increased in the past few decades and it is expected that more people will be affected by this disease as more populations are adopting the Western lifestyle. A 2008 analysis from the United Kingdom covering CD up to 2005 demonstrated that the incidence rate relative to previous decades is still on the rise and that the incidence in children under age 16 is also increasing *(151)*. It has been suggested that the recent dramatic increase in incidence, especially in the pediatric population, is related to modifiable environmental factors rather than genetic changes, specifically to increased omega (ω)-6 fatty acids and thus the relative decrease in ω-3 fatty acid consumption. Interestingly, the skewed consumption toward ω-6 relative to ω-3 starts in utero and continues during infancy when the GI system is still developing *(152)*. Proinflammatory by-products from linoleic acid metabolism such as prostaglandins (such as E_2) and leukotrienes are implicated.

The principal medical therapies used to induce disease remission in patients with UC depend on disease activity and extent. Drugs that are used as a function of the severity of the disease include aminosalicylates and antibiotics (for mild disease), corticosteroids (for moderate disease), and immunosuppressants such as cyclosporine (for severe disease). Therapies that are used to prevent disease relapse include aminosalicylates, azathioprine, and meracaptopurine *(140,153)*. Detailed review of therapy including conventional and unconventional therapies as well as newer approaches was reported by Ardizzone et al. and Domenech et al. *(138,140)*. Colectomy with creation of an ileal pouch, anal anastomosis (J pouch), has become the standard of care for patients with severe or refractory colitis and results in an improved quality of life in most patients *(138)*. Drug therapy for patients with CD is more complex and depends on the location (ileal vs. colonic vs. ileocolonic) as well as the behavior of the disease (inflammatory vs. penetrating vs. stenosing) and the extent of activity of the disease (mild, moderate, or severe) in a given patient. Drug therapy typically includes aminosalicylates and antibiotics (for mild mucosal disease), enteral nutritional therapy (including elemental or polymeric formulas), corticosteroids (for moderate disease), and immunomodulators such as infliximab (for corticosteroid-resistant or fistulizing disease). Aminosalicylates, mercaptopurine, azathioprine, methotrexate, and infliximab can be used as maintenance therapies *(138)*.

Two additional biologic agents with recent FDA drug approval are natalizumab and certolizumab. These drugs are for the induction and maintenance of remission in patients with moderate to severely active Crohn's disease. Natalizumab is a recombinant, humanized immunoglobulin (Ig) G4 monoclonal antibody against α4 integrins *(154,155)*. The approval contains highly restrictive conditions and other comedications should be discontinued before starting treatments and other comedications (steroids) should be tapered off *(156)*. Certolizumab pegol is a humanized anti-TNF monoclonal antibody fragment *(157)*. Data suggest that in a subpopulation of patients who responded to the initial induction therapy, there were also fewer relapses with maintenance therapy *(158)*.

Factors contributing to malnutrition in IBD may include reduced oral intake, malabsorption, and increased nutrient losses from the gut and drug–nutrient interactions. Specifically, people with CD often experience a decrease in appetite, which can affect their ability to consume food needed for good health and healing. Furthermore, in the case of CD there is often diarrhea and therefore increased risk of developing overall malnutrition in terms of calories combined with poor absorption of necessary nutrients. Of particular relevance is deficiency in calcium, vitamin D *(159,160)*, folate *(161)*, and zinc *(162)*. For example, folate deficiency may result from competitive inhibition with concomitant sulfasalazine therapy used to treat IBD *(140,163)*.

There are no consistent dietary rules or a special diet that has been proven effective in improving symptoms, preventing, or treating CD. However, it is very important that people who have CD follow a nutritious diet and avoid foods that seem to worsen their symptoms. In any case, dietary supplementation is an important aspect of the overall strategy for the treatment of IBD *(162,164,165)*, especially for children. Interestingly, incorporation of fiber into the diet has been controversial *(166)*. Anti-inflammatory drugs such as steroids and mesalamine induce GI side effects including nausea, vomiting, heartburn, and diarrhea, all of which may decrease food intake or reduce food absorption *(166)*.

5.1.4. Diabetes

There are two classes of diabetes: Type 1, an autoimmune disease, and Type 2, associated with metabolic syndrome and obesity. Regardless of the initial cause, the long-term consequences of these chronic conditions are similar. There are numerous and cumulative debilities to many tissues and organs of the body as the consequences of diabetes *(167–172)*; however, the major cause of death is atherosclerotic cardiovascular disease *(173)*. In addition, common secondary consequences of diabetes include bacterial and fungal infections.

5.1.4.1. Type 1 Diabetes. Type 1 diabetes, an autoimmune disease, is caused by the self-destruction of the majority of the insulin-secreting cells of the pancreas *(174,175)*. Genetic predisposition and a triggering factor that initiates the inappropriate recognition of the insulin-secreting pancreatic islet cell as nonself by T cells are two major factors that are thought to be essential in the development of Type 1 diabetes *(176)*. Inappropriate destruction of islet cells results in increased oxidative stress on the pancreas and furthermore, due to the lack of insulin, there is imminent increased oxidative damage and continued adverse effects *(177–179)*.

The difference between the two types of diabetes is the need for insulin immediately once there is a diagnosis of Type 1 diabetes as the autoimmune destruction of the islet cells of the pancreas that produce insulin has proceeded to the point of clinical recognition of the disease. The precipitous rise in circulating glucose levels is often the defining feature of the diagnosis; glucose is also excreted at high levels in the urine. Moreover, glucose does not enter the tissues appropriately, resulting in a lack of energy source in critical tissues and organs such as the brain and the retina *(170,171)*. Without the administration of insulin, the Type 1 diabetic would succumb in a few weeks or months. Thus, insulin is the drug that is administered daily to Type 1 diabetics. Type 1 diabetes often develops during childhood before the age of 10. Even with the use of insulin, the nutritional management of the patient (who is usually young) is critical for optimal long-term survival *(180,181)*.

There is also an increase in the procoagulant factors in the blood along with hypertriglyceridemia, increased LDL, and reduced HDL levels. Advanced glycation end products (AGEs) that result from glucose binding inappropriately with the body's proteins are triggers for many immune cells to produce inflammatory cytokines. AGE receptors are also found on endothelial and renal cells where the binding of AGE results in the production of inflammatory cytokines such as interleukin-1, tumor necrosis factor, and insulin-like growth factor-1. Consequently, there is an increase in inflammation in the blood vessels throughout the body and over time, a loss of renal function *(182)*.

As diabetes progresses, there is an overall decrease in antioxidant status with decreased levels of vitamin C, glutathione, superoxide dismutase, and other antioxidants in the blood of diabetics compared to nondiabetics that are age-, sex-, and dietary intake matched *(183)*. Reduced antioxidant status may be a major factor in the increased damage to both the micro- and the macrovasculature in diabetics. Hyperglycemia is associated with depressed cellular immune responses and that results in increased prevalence of bacterial and fungal infections; infections are often persistent, with the formation of ulcers and deep infections in soft tissue and bone *(184–186)*. Increased oxidative stress and free radical damage could be the cause of many of the pathologies seen in diabetes *(187)*. Important nutritional consequences of diabetes including elevated triglycerides, increased lipid oxidation, impaired function along the entire GI tract including dysphagia, nausea, and fecal incontinence and the formation of glycation products in the blood are summarized in Table 5.

The potential for beneficial effects of antioxidant supplementation in patients with type 1 diabetes was examined by Jain et al. *(177–179)*. They found a marked decrease in glycosylated hemoglobin and reduction in triglyceride levels following supplementation with vitamin E *(177)*. Recently, Holick summarized many of the adverse effects related to vitamin D deficiency including the effects on Type 1 diabetes *(188)*. Specifically, there are several studies that show reduced risk of Type 1 diabetes after vitamin D supplementation. Both reduced risk due to intervention and increased risk due to deficiency are documented (see below).

5.1.4.2. Type 2 Diabetes. Type 2 diabetes develops most frequently in midlife, although the incidence is increasing in the young in association with prevalence of overweight and obesity. Approximately 50% of individuals with Type 2 diabetes are 65 years old or older. The disease is characterized by a depressed response of target tissues to insulin, resulting in a higher than normal circulating level of glucose and a lower than normal level of glucose in tissues *(169,187)*. Additionally, Type 2 diabetics often have hyperlipidemia and hypertension and are also often obese.

Table 5
Nutritional Consequences of Diabetes *(167–172)*

Short-Term Consequences	*Long-Term Consequences*
▪ Low level of vitamin C in the blood ▪ Elevated triglycerides ▪ Hypertension, hypertriglyceridemia, decreased HDL, and increased risk of atherosclerosis and cardiovascular diseases ▪ Hypertriglyceridemia, probably due to a decrease in lipoprotein lipase activity. Consequently, the plasma levels of VLDL are elevated, and increased deposition of lipids possibly accelerates the atherosclerotic process. ▪ Injury to the endothelia cells as a result of hyperglycemia, insulin resistance, increased plasma LDL, decreased HDL, abnormal platelet aggregation, and coagulation ▪ Increased production of oxidants by the endothelial cells as a result of hyperglycemia via two mechanisms: nonenzymatic glycation of proteins and increased production of H_2O_2 ▪ Increased level of lipid peroxidation products as well as antioxidant enzymes	▪ Diabetic gastroenteropathy includes dysphagia, nausea, vomiting, diarrhea, constipation, and fecal incontinence ▪ The incidence of liver diseases is higher with frequent viral hepatitis ▪ Formation of advanced glycosylation products, activation of protein kinase C, increasing growth factor, and production of cytokines ▪ Once infected, the ability of diabetics to tolerate the infection is reduced ▪ Morbidity due to infection ▪ Cardiovascular diseases including acceleration of atherosclerosis of coronary and peripheral arteries, cardiomyopathy, and cardiac neuropathy ▪ Monckeberg's sclerosis due to calcification of the media of large arteries ▪ More frequent ischemic heart disease relative to general population ▪ More frequent myocardial infarction with an increased lethal ventricular arrhythmias possibly induced by more fibrosis complicated by reduced response to antiarrhythmic drugs ▪ Autonomic neuropathy causes the alteration in the vagus nerve function and sympathetic activity leading to cardiac arrhythmia ▪ Increased stiffness of diabetic ventricle may lead to congestive heart failure ▪ Peripheral neuropathy: increased incidence of peripheral vascular disease. Chronic foot ulcers involving both micro and macrovessels ▪ Blindness and vision disability that develops in both Type 1 & Type 2 diabetes (although the onset and the rate may be different in the two types of diabetes) ▪ Cataract is considered an important ocular manifestation of diabetes ▪ Increased levels of glaucoma ▪ Diabetic nephropathy in Type 1 (30–40%) and Type 2 (5–10%). Clinical signs include hypertension, renal insufficiency, heavy albuminurea, and edema ▪ Noninfectious complications of diabetes include several abnormalities including xanthomas, scleroderma, and necrobiosis

Elevated body mass index (BMI) is related to decreased insulin sensitivity in Type 2 diabetics *(167)*. There is an increased risk of Type 2 diabetes in both men and women with increased central or visceral obesity *(189)*. Long-term effects of Type 2 diabetes include nephropathy, neuropathy, retinopathy, impaired cellular immunity, osteoporosis, and multiple adverse effects on the cardiovascular system *(168,173,190–195)*. Diet changes are often the first line of defense against the insulin resistance seen in Type 2 diabetes. However, only about 10% of adults can control their circulating glucose levels with lifestyle changes alone *(196)*.

5.2. Nutritional Status and Autoimmune Diseases

Most autoimmune diseases have an ongoing inflammatory component and therefore it may be that the oxidative damage caused by the inflammation may reduce the overall antioxidant status of the patient with autoimmune disease. Comstock et al. *(97)* found that lower than average serum vitamin E levels preceded the diagnosis of two autoimmune diseases, RA and SLE. De Pablo et al. *(197)*, using data from NHANES III, found that individuals 60 years or older and who reported three or more of the criteria of RA had significantly lower serum levels of antioxidant carotenoids and also had increased serum level of C reactive protein, a marker of oxidative stress, compared to age-matched non-RA participants. As mentioned above, several studies have noted the beneficial effects of vitamin E in diabetes. Low sunlight exposure and/or vitamin D status has been associated with a greater risk of multiple sclerosis. Additionally, cigarette smoking, which would increase oxidative stress, is also linked to increased risk *(198)*.

Exposure to tobacco smoke during the first years of life as well as within 3 months of breast feeding following delivery has been associated with the presence of rheumatoid factor in healthy young children *(199)*. Two recent papers point to the potential for fetal exposures to increase the risk of developing autoimmune diseases *(200,201)*. Undernutrition in utero has been associated with decreased immune responses in the neonate and increased risk of atopy. Similarly, low birth weight has been shown to increase risk of autoimmune diseases in animal models and may have a similar effect in humans. As indicated above, the immune system can react to self-antigens and attack specific organs or multiple, systemic sites within the body, resulting in inflammation and cellular destruction. One clear example of how the immune system can influence one's nutritional status is seen in the autoimmune disease, pernicious anemia. In autoimmune-related pernicious anemia, the body synthesizes antibodies against gastric parietal cells responsible for the secretion of intrinsic factor that is required for the absorption of vitamin B_{12} (cobalamin). The autoimmune disease also results in a significant drop in the production of acid in the stomach, as parietal cells are also the source of gastric acid. Thus, both the intrinsic factor associated absorption and the acidic pH required for B_{12} release from foods are adversely affected *(202)*. Vitamin B_{12} is a cofactor in the synthesis of DNA and is required for the development of all new cells. Erythrocytes are one of the major cell types that are produced at high rates daily. A deficiency of vitamin B_{12} causes a malformation of the nucleus of the immature red blood cell. This larger than normal (i.e., megaloblastic) red cell is characteristic of the anemia seen with B_{12} deficiency. Other major targets for the adverse effects of vitamin B_{12} deficiency are epithelial cells and the myelin-producing cells lining nerves; these cells are actually of immune-cell origin. Injections of vitamin B_{12} overcome the requirement for both intrinsic factor and stomach acid. High oral doses of B_{12} (1000 times the recommended intake level) can also reduce the signs of B_{12} deficiency *(203)*.

5.2.1. IBD

In the case of IBD, elemental diets will produce symptomatic relief and objective remission in up to 90% of patients and may be considered as a first-line therapy for pediatric patients *(204)*. However, most patients relapse soon after resumption of a normal diet. Achievement of prolonged remission has been possible when these people are put onto diets that exclude specific foods that they are intolerant of such as cereal, dairy products, yeast, and certain types of fat *(205)*. Vitamin E in combination with vitamin C has been found to decrease oxidative stress in a clinical placebo-controlled trial, with individuals suffering from Crohn's disease that were in a state of high oxidative stress *(206)*.

5.2.2. FIBER (PREBIOTICS)

Prebiotics have been defined as nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or the activity of one or a limited number of commensal bacteria in the colon and thus improve host health *(207)*. It is well established that breast milk confers health benefits to feeding infants and although no one ingredient can be responsible alone, it is also recognized that human milk contains oligosaccharides that may serve as prebiotics *(208)*. Prebiotics such as inulin and oligofructose are present in a large number of plant species as storage carbohydrates and are naturally found in the diet in relatively low concentration. Prebiotics can act as substrate for selected commensal bacteria, thus helping promote and sustain beneficial species that are already present in the colon *(209)*. Microbial fermentation of dietary fibers and oligosaccharides results in the production of the short-chain fatty acids (SCFA) – acetate, propionate, and butyrate. Production of these SCFA is associated with a reduction in the pH of the large intestine and potentially several physiological benefits. Reduction of the pH due the production of SCFA has been linked to reduced production of putrefactive substances as well as reduction of blood markers related to fat metabolism in hypercholesterolemic patients *(210)*. In addition, stimulation of intestinal peristalsis is one benefit associated with the production of the SCFA *(211)*. Importantly, the SCFA profile changes as a function of the fiber *(212)*.

Several immune-modulating effects of fructooligosaccharides (FOS), including nonspecific immune enhancement, have been reported recently. Guigoz et al. reported the results of an intervention study where elderly nursing home patients received 8 g of FOS daily divided into two 4 g doses. Results showed that the beneficial bifidobacteria counts increased significantly during the 3 weeks of supplementation. Bacteroid [also found in IBD-inflamed regions of inflamed mucosa *(213)*] counts also increased, while others (Enterobacteriaceae, enterococci, and lactobacilli) were not significantly altered. Significant increase in peripheral T lymphocytes and CD4 + and CD8 + T cells, accompanied by a significant decrease in phagocytic activity of granulocytes and monocytes as well as a decrease in inflammatory cytokine RNA in peripheral blood mononuclear cells, indicated a decrease in the inflammatory process *(214)*. The increase in the numbers of leukocytes both in the gut mucosa and in the blood that coincided with a decrease in proinflammatory cytokines demonstrated the powerful effects that are associated with this prebiotic intake. Similar results were observed in a small clinical trial with CD patients with moderately active disease. Significant reduction in disease activity, as well as significant increase in fecal bifidobacteria combined with positive effects on dendritic cells, suggesting promotion of immunoregulatory response as a contributor to the overall improvements *(215)*. Importantly, the increase in mucosal bifidobacteria was associated with clinical remission; however, direct cause and effect was not ascertained. More recently an animal study demonstrated that a mixture of FOS:inulin enhanced immune function after administration of an oral vaccine. While not all measured clinical markers met expected changes, several important observations including increased survival rate in the FOS:inulin-treated animals suggested that FOS:inulin treatment offered an overall improved immune response, especially after the administration of the Salmonella vaccine *(216)*. Review of clinical trials with infants and with a combination of FOS and lactose-based oligosaccharides demonstrated increased bifidobacteria, reduction of pathogenic bacteria as well as reduction in stool pH, and improved consistency and frequency *(208)*. Importantly, despite differences in the basic sugar units and the structure of the oligosaccharides, their incorporation resulted in quantifiable positive impact, suggesting a promising potential to the class of prebiotic compounds.

It is well established that many bacteria capable of causing food poisoning reside within the gut flora of humans and animals and may even be consumed inadvertently *(217)*. Regardless of the safety and processing standards that the food undergoes, it is impossible to prevent exposure to pathogenic species that are an integral part of the food system. However, the individual's response to such challenges varies. It has been proposed that by preferential feeding, indirectly, prebiotics enhance resistance to colonization by undesired species, while promoting colonization by desired species *(209)*. Due to the effects of colonization, there is a modulation of the enteric and the systemic immune functions with a consequent decrease in overall inflammation and disease *(218)*. It has been suggested that the benefit of prebiotics in IBD is related to their production of butyrate as a result of fermentation and production of short-chain fatty acids in the colon. In vitro studies show that butyrate suppresses the activation of nuclear factor-κB (NF-κB), and butyrate-containing enemas of individuals suffering from UC decrease inflammation as measured by the reduction of macrophages that are positive for NF-κB *(219)*.

A combination of prebiotics and probiotics to enhance the potential of each alone is referred to as synbiotics. The combination assumes that it would encourage indigenous probiotic bacteria and provide them with prebiotics to promote their growth. The first data set from a randomized clinical trial with such a combination in patients with UC was encouraging and resulted in a short-term improvement based on various clinical measures *(220)*. It was concluded, however, that the direct effect of the probiotic bacteria is unknown and several possible mechanisms might be involved.

5.2.3. PROBIOTICS

Selected beneficial bacteria have been traditionally used in various human food products to modify the food format while extending the shelf life of the product. Currently, in addition to their functional effects on the food, their effects on the host are also being studied. MacFarlance defines probiotics as "live microbial additives that change the composition and or the metabolic activities of the microbiota or modulate host immune function in a way that benefits health" *(209)*. However, there might be a significant role for inactivated bacteria as well. The most common probiotics used are bifidobacteria and lactobacilli *(209)*. Importantly, bifidobacteria and lactobacilli are more predominant in breast-fed infants *(221)*. Specific mechanisms involved with probiotic bacteria include successful competition with other bacteria that are involved in disease etiology; removal of inflammatory stimuli; direct effect on the expression of inflammatory cytokines; direct influence on dendritic cells; and influence on both downregulation of proinflammatory response and stimulation of a more tolerant immune response *(220)*. Overall, probiotics bring in an additional remarkable opportunity to treat various GI diseases. Although only a small number of organisms have been evaluated to date, there are still tremendous and fertile grounds for future candidates. The long-term effects, especially for infants, of the manipulations of both prebiotics and probiotics need careful attention as these potentially can affect multiple diseases and can have long-term consequences. The mechanism by which intake of probiotics contributes to the delicate gut microbiota balance is important as there may be a concern related to overstimulation and a consequent inflammatory response. The benefits and risks associated with the use of live – relative to inactivated – bacteria to simulate response also needs to be carefully evaluated *(222)*. The use of specific strains as probiotics must be emphasized as even traditional probiotic strains have been shown to induce inflammation in susceptible host animal model systems *(139)*.

The role of probiotics in the treatment of intestinal infection and inflammation was reviewed by Vanderhoof *(223)*, who examined the clinical data in intestinal infections including viral, antibiotics, *C. difficile*, and traveler's diarrhea, as well as newer evidence related to inflammatory diseases.

Probiotic bacteria may offer benefits in cases of bowel-related autoimmune diseases, such as IBD. The therapeutic potential of probiotics has been investigated as an attractive alternative, one that may directly affect one of the causes of the disease. The therapy could potentially direct the gut's microbiota away from the proinflammatory bacterial species. The proposed mechanism of action claims that regular feeding with live probiotic microorganisms effectively dilutes pathogenic bacteria and beneficially affects gut health, thus stimulating immune responses *(220,224)*. In addition, this treatment option would be associated with low side effect burden *(213)*. Traditional therapies for mild UC have had only limited success as the disease tends to relapse; conventional therapies do not eliminate the root cause of the inflammation but offer temporary relief. Similarly in CD, despite manipulation of the gut's bacteria that has been associated with short-term efficacy due to antibiotic use, long-term efficacy has not been established, while major side effects exist. One successful intervention with probiotic therapy was reported in a placebo-controlled clinical trial with individuals with relapsing chronic pouchitis despite ileal pouch-anal anastomosis. It was concluded that the specific probiotic mixture (VSL#3, a mixture of eight different bacterial stains) is effective in preventing flare-ups *(225)*. Benefits were attributed to increase in concentration of protective bacteria due to the specific bacteria that were used. In a follow-up study with the same combination (VSL#3) but at a higher dose, Gionchetti et al. concluded that this treatment is effective for mild disease *(226)* and suggested that this has potential as an alternative treatment after further well-controlled clinical confirmatory trials.

5.3. Nutrients as Anti-inflammatory Agents

Various nutrients act to modulate the immune response and therefore act to suppress inflammation. Some nutrients (like zinc) are central to several processes and they participate via several mechanisms including their catalytic contribution in enzymatic activities, their role in DNA transcription that is related to immune response, and as a component of proteins that are involved in signal transductions. Other nutrients are not essential and rely on their biological effects. Vitamins and minerals such as copper, iron, selenium, and zinc and other nutrients such as the amino acids arginine and glutamine, the sulfur-containing amino acids cysteine or methionine have been reported beneficial *(227)*. Yet other nutrients such as polyphenols, specifically epigallocatechin, has also been shown to confer some anti-inflammatory effects as well *(228)*. Downregulation of COX-2 activity is considered protective, and several dietary components have been shown to inhibit COX-2 and/or reduce the formation of inflammatory prostaglandins – the products of COX-2 enzyme activity *(229,230)*. COXs are involved in the oxidation of arachidonic acid (ω-6), vitamin E and other essential antioxidant vitamins and minerals *(231,232)*.

5.3.1. Omega-3 Fatty Acids

Omega-3 (ω-3) fatty acids contain their first double bond between the third and fourth carbon atom from the methyl end of the molecule. The essential ω-3 fatty acid is linolenic acid and it contains 18 carbons. The longest ω-3 fatty acids are eicosapentaenoic acid and docosahexaenoic acid with 20 and 22 carbons, respectively. Omega-3 fatty acids have anti-inflammatory properties compared to ω-6 fatty acids and it is the dietary balance between ω-3 and ω-6 fatty acids that can impact inflammatory responses at the cellular and tissue levels *(233,234)*. The mechanisms by which ω-3 fatty acids reduce inflammation are related in part to their ability to act as an antagonist to the ω-6 fatty acid, arachidonic acid, by decreasing the amount of arachidonic acid that is available for production of inflammatory mediators *(228)*.

Simopoulos *(231)* and Belluzzi *(235,236)* have reviewed the clinical data on the anti-inflammatory properties of the longest chain ω-3 polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid. These oils, usually in the form of either algal or fish oil, have been shown to reduce the inflammation associated with several types of autoimmune diseases including RA, IBD, SLE, multiple sclerosis, and psoriasis. The fish oil-derived ω-3 polyunsaturated fatty acid inhibits leukotriene B4, a potent chemoattractant and proinflammatory eicosanoid implicated in the pathogenesis of inflammatory bowel disease *(237)*. Supplementation with a liquid formula containing antioxidant and ω-3 fatty acid significantly improved serum antioxidant status, reduced the proportion of arachidonic acid, and increased the proportion of eicosapentaenoic acid and docosahexaenoic acid in plasma phospholipids and adipose tissue, suggesting a shift to an anti-inflammatory phenotype *(238)*. Supplementation of nine capsules of an enteric-coated fish oil preparation (equals 2.7 g ω-3 polyunsaturated fatty acid) has been shown to be efficacious in maintaining remission in Crohn's disease when compared with placebo *(239)*. In addition to clinical benefits, supplementation appears to be safe at the levels given in most clinical studies. In many of the studies in patients with RA, there was also a decreased need for NSAID and/or corticosteroids. Anderson and Fritsche *(240)* in a comprehensive review examined the divergent database on the effects of ω-3 fatty acid supplementation during infectious disease. Since ω-3 fatty acids can reduce inflammatory responses in part by downregulating macrophage and lymphocyte functions, there is still a question about the efficacy of supplementation during infection. This extensive review concluded that ω-3 fatty acids can have beneficial effects in some instances, but not in all, and that further research is warranted.

5.3.2. RA AND OTHER ARTHRITIDES

As indicated above, the types of fats consumed can directly affect the concentration of inflammatory mediators in tissues in joints. Survey data suggest that consumption of olive oil as part of a Mediterranean diet is associated with lower risk of development of RA as well as decreased symptom severity. Olive oil contains monounsaturated (ω-9) fatty acids and is considered to be either neutral or reducing the proinflammatory responses seen with ω-6 fatty acid intakes. High fish consumption, which would increase the intake of ω-3 fatty acids, is also associated with decreased risk of incident RA *(241)*. In addition to survey data, an intervention study in patients with RA showed that a Mediterranean diet vs. a Western-type diet consumed for 12 weeks resulted in a significant decrease in a composite index of disease activity, an increase in physical activity, and an improved vitality *(242)*.

Supplementation with anti-inflammatory nutrients has resulted in pain reduction in some studies and reduction in pain medication use in others. In one study involving 49 RA patients, supplementation with λ-linolenic acid (ω-6) and eicosapentaenoic acid (ω-3) for 1 year resulted in decreased pain and tapering of NSAID use in 80% of patients compared to 33% in the placebo group. A number of studies have examined the effects of supplementation with ω-3 fatty acids and have shown consistent reductions in tender joints and morning stiffness *(232,235)*. A prospective case-control study, EPIC_NOAR, investigated the potential for fruits, vegetables, and vitamin C intakes to reduce the risk of incident inflammatory polyarthritis. Lower intakes of all these dietary components significantly increased the risk of disease. The adjusted odds ratio for disease comparing the lowest vitamin C intake to the highest was 3.3 and for fruits and vegetables, the odds ratio was 1.9 *(243)*. Recent data from the Nurse's Health Study examined the association of intake of nutrients that have been associated with increased risk of inflammation and risk of developing RA. Benito-Garcia et al. prospectively examined the association between intakes of protein (total, animal, and vegetable), iron (total, dietary, supplemental, and heme iron) and their food sources and the risk of RA. After adjusting for age, smoking, BMI, and reproductive factors, they found no clear association between either protein or iron intake and risk of incident RA *(244)*.

6. EFFECT OF DRUGS (USED TO MANAGE AUTOIMMUNE DISEASES) ON NUTRITIONAL STATUS

6.1. RA

Aspirin and other NSAIDS are usually the first medications given to reduce the inflammation in RA. However, their efficacy is often inadequate. Corticosteroids are potent anti-inflammatory drugs but do not stop the joint erosion and their efficacy decreases with use. Disease-modifying drugs, such as gold compounds, cause potential adverse reactions that include GI tract disturbances. Cytotoxic drugs (e.g., methotrexate) are the next group of drugs given when RA continues to cause pain and joint destruction. These drugs reduce pain but do not affect disease progression. The progressive nature of RA results in the successive use of more toxic drugs that have serious side effects on overall health and nutritional status *(122,245,246)*. Additionally, as discussed below, the potential for the development of drug-induced osteoporosis is significantly increased by both corticosteroids and cytotoxic drugs. Table 6 outlines the five major classes of drugs used in the treatment of autoimmune diseases. These include NSAIDs, corticosteroids, disease-modifying antirheumatic drugs (DMARDs), cytotoxic drugs, and novel drugs including tumor necrosis factor antagonists (TNF antagonists). The table also includes instructions on drug administration and the nutritional effects of the drugs.

Liver dysfunction and GI tract discomforts are common with NSAIDs, cytotoxic drugs, and corticosteroids. Newer NSAIDs that target only the COX-2 may not cause as many GI tract problems as older drugs that targeted both COX-1 and COX-2. Most of the cytotoxic drugs, such as methotrexate, are folate antagonists and therefore these will decrease folate status and increase homocysteine levels. Increasing folate intake can overcome some of these effects; however, there may be a decrease in drug efficacy *(247)*. Methotrexate can also cause mouth ulcers that can affect overall consumption of food. Cyclosporine, another cytotoxic drug, reduces the activity of T cells and is a potent immunosuppressive agent used for transplantation and RA therapy *(248)*. However, side effects include hyperglycemia, hypercholesterolemia, electrolyte disturbances, and renal insufficiency *(249)*. Some studies show that intravenous cyclosporine is also associated with hypomagnesemia. The TNF-targeted drugs can result in increased infections, as TNF is a normal immune cytokine involved in the destruction of pathogens *(130)*. Newer drugs that target TNF used to treat RA include etanercept and infliximab, which show indications of actually stopping the disease progression. The drugs bind to TNF before it can trigger inflammatory responses. Both drugs are not given orally; etanercept is given by injection and infliximab is given by intravenous infusion *(122,250)*.

6.2. SLE

As with most diseases, treatment is traditionally carried out in progressive fashion (Table 6). For patients with symptoms that are not life-threatening, with muscle or joint pain, fatigue, skin manifestations (such as rashes), options include NSAIDs and antimalarial medications.More aggressive therapy is required for life-threatening and more serious manifestations such as kidney inflammation, lung or heart involvement, and central nervous system symptoms. Treatment in these circumstances might involve high-dose corticosteroids and other immunosuppressive drugs such as azathioprine, cyclophosphamide, and cyclosporine. As with other immune-related diseases, sometimes several medications must be combined to control the disease and prevent tissue damage. Treatment depends upon an individual assessment of risks and benefits. Most immunosuppressive medications, for instance, may cause significant side effects including increased risk of infections, nausea, vomiting, hair loss, diarrhea, high blood pressure, and osteoporosis *(134)*.

6.3. Type 2 Diabetes

There are a number of distinctive oral drugs that are used alone or in combination for treatment of Type 2 diabetes. Table 7 includes the administration instructions and the nutritional effects of these noninsulin-containing drugs. However, many patients eventually also require insulin injections *(251–253)*. Metformin, which is frequently the first drug used in the treatment of Type 2 diabetes in overweight adults, is currently approved for the treatment of Type 2 diabetes in children. Combination therapies are frequently prescribed. These include the addition of α-glucosidase inhibitors or thiazolidinediones, meglitinides, and sulfonylurea agents *(253,254)*. Sulfonylureas have been associated with causing increased weight gain and hypoglycemia *(255)*. α-Glucosidase inhibitors compete with the native enzyme and slow the breakdown of starches, thereby slowing the rise in blood glucose following a meal. However, there are significant GI side effects such as diarrhea, cramping, abdominal pain, and flatulence that can affect compliance and also result in loss of fluids and micronutrients. Lowered serum levels of vitamins B_6, B_{12}, and folic acid are associated with increased serum homocysteine, a risk factor for cardiovascular and cerebrovascular diseases and diabetic neuropathy *(256–261)*. Although there has not been a clear association between serum homocysteine levels and drugs to treat diabetes, metformin may induce vitamin B_{12} malabsorption, and this may result in higher homocysteine levels *(262)*.

Insulin, which is the most commonly used drug for treatment of both types of diabetes, has a well-recognized side effect of inducing weight gain. Thus it is especially difficult for the overweight or obese patient to lose or even maintain weight during insulin therapy. Currently, obese diabetics are also often given antiobesity drugs including sibutramine or orlistat. The latter agent may reduce fat-soluble vitamin and carotenoid status and also reduce long-chain fatty acid levels that are important immunomodulators. The effects of weight reduction interventions on nutritional as well as immunological status can be numerous and particularly serious for the diabetic *(35,263)*

Oxidative stress is increased in diabetics *(183,264)* and antioxidant nutrient status is often lower than optimal *(265)*. Ascorbic acid and glucose enter cells

Table 6
Drugs Used to Treat Autoimmune Diseases and Possible Nutritional Effects *(118,247,248,250,251,305,306)*

Drug Class/Mode of Action	*Specific Drug*	*Administration Instructions*	*Nutritional Effects and Other Indications*	*Autoimmune Disease*
Nonsteroidal anti-inflammatory drugs (NSAIDs) *(291)*	Indomethacin	Should be taken with food to prevent stomach irritation; however, high-protein and high-fat food have been reported to interfere with the drug absorption *(292)*	Cause GI irritation, bleeding, and iron loss. Drug may increase potassium levels. It has been reported to decrease absorption of folic acid and vitamin C. Calcium and phosphate levels may be reduced *(292)* Sodium and water may be retained *(252,291)*	RA, SLE *(134)*
	Ibuprofen	Should be taken with food to prevent GI upset *(292)*	Cause GI irritation, bleeding, and iron loss. Drug may increase potassium levels. Sodium and water may be retained *(292)*	
	Naproxen	Should be taken with food to prevent upset stomach *(292)*	Cause GI irritation, bleeding, and iron loss. Drug may increase potassium levels. Sodium and water may be retained *(292)*	

(*Continued*)

Table 6
(Continued)

Drug Class/Mode of Action	*Specific Drug*	*Administration Instructions*	*Nutritional Effects and Other Indications*	*Autoimmune Disease*
Glucocorticosteroids and corticosteroids *(291)*	Cortisone Prednisolone Methylprednisolone Dexamethasone Betamethasone Budesonide	Drugs can cause stomach upset and should be taken after eating a meal, before 9:00 am/pm for best results. Drug cause protein wasting and for some diseases, high-protein diets should be recommended (perhaps not SLE) *(292)*	Drugs may increase loss of magnesium and increase loss of potassium in the urine. Drug may increase loss of vitamin B_6. Sodium retention may be problem. Drugs reduce the body's ability to activate vitamin D, increasing the risk of bone loss *(292)*	RA, IBD CD
Disease-modifying antirheumatic drugs (DMARDs) Anti-inflammatory effects as well as immunomodulatory properties	Gold compounds		Predominant action appears to be a suppressive effect on the synovitis of active rheumatoid disease*(291)* Reduce number of monocytes and cytokine production	RA
	Plaquenil	GI complaints (diarrhea, anorexia, nausea) may occur *(291)*		SLE *(134)*

	Penicillamine	Food decreases drug absorption, thus should be taken 1 h before or 2 h after any food to avoid this interaction. When taken with iron, its absorption is decreased *(292)*	This is a chelating agent; it chelated copper, iron, and zinc *(252,292)*. Therapy with this drug has been associated with sodium depletion *(292)*. It also reduces excess of cysteine. Drug may cause a vitamin B6 deficiency *(252,291)*.	
Cytotoxic immunosuppressant drugs Used based on the premise that the drugs downregulate immune functions; however, there is lack of evidence that the suppression of the immune system accounts for clinical effects.	Cyclophosphamide	Take on an empty stomach unless sever GI upset. May cause nausea, mouth sores, and food aversions *(292)*	Active alkylating metabolites interfere with the growth of rapidly dividing cells. The mechanism is though through cross-linking to DNA	SLE *(134)*
	Methotrexate	Food can interfere with the drug absorption, and it can cause stomach upset. May cause nausea, mouth sores, and food aversions *(292)*	Decrease leukocyte trafficking. Considered effective as an anti-inflammatory as well as an immune suppressive agent, thus decrease	

(*Continued*)

Table 6
(Continued)

Drug Class/Mode of Action	*Specific Drug*	*Administration Instructions*	*Nutritional Effects and Other Indications*	*Autoimmune Disease*
Cytotoxic drugs suppress both cellular and humoral host defenses			folate status and increase homocysteine *(291,292,295)* It is recommended that for RA people should supplement with folic acid *(292)* however, drug efficacy may be decreased *(247)*	
	Azathioprine	May cause nausea, mouth sores, and food aversions *(292)*	Immunosuppressive antimetabolite. Mechanism in which it affects autoimmune disease is unknown. Inhibit the proliferation	SLE *(134)*

			of T lymphocytes and antibody formation*(291)*	
	6-Mercaptopurine	May cause nausea, mouth sores, and food aversions *(292)*	Purine analog that interferes with nucleic acid biosynthesis *(291)*	
	Chlorambucil	May cause nausea, mouth sores, and food aversions *(292)*	Bifunctional alkylating agent has been found active against selected neoplastic diseases *(291)*	
	Cyclosporine	Original – mixed with any liquid Modified – mixed with orange or apple juice. NOT with milk Take in same intervals between doses and meals everyday *(60)* Avoid drinking grapefruit juice or eating grapefruit while taking cyclosporine	Inhibit T-cell activation; patients treated with intravenous cyclosporine might experience hypomagnesemia and hypocholesterolemia *(60,307)*	RA, SLE *(134)* Severe UC and CD

(*Continued*)

Table 6
(Continued)

Drug Class/Mode of Action	*Specific Drug*	*Administration Instructions*	*Nutritional Effects and Other Indications*	*Autoimmune Disease*
		Might need to limit amount of dietary potassium		
	Mycophenolate	Taking mycophenolate with food often helps to prevent side effects such as nausea or stomach pain Take antacids at least 1 h before mycophenolate or wait at least 2 h after taking mycophenolate before taking an antacid	Mycophenolate targets an enzyme in the body called inosine monophosphate dehydrogenase, which is important for the formation of deoxyribonucleic acid (DNA) in cells. By interfering with DNA, the medication impairs function of immune system cells that become overactive in autoimmune diseases such as lupus The most common side effects with mycophenolate include stomach upset, nausea, vomiting, or diarrhea.	CD, RA, SLE *(134)*

		Some vaccinations should be avoided while taking this medication	
Novel drugs Tumor necrosis factor (TNF) antagonist IL-1 receptor antagonist	Infliximab	This compound is a monoclonal antibody containing regions that bind to TNF- α	CD,UC, RA
	Adalimumab *(308)*	A fully human IgG1 anti-TNF-α monoclonal antibody	CD, RA
	Etanercept	Prevents the biological activity of TNF; binds to TNF and blocks interaction with cell surface *(250)*	RA
	Anakinra	Anakinra is a disease-modifying antirheumatic drug. Not approved to use with etanercept	RA
Aminosalicylate derivatives of salicylic acid (5ASA)	Mesalamine (various formulations) *(309–312)*	Could cause loss of appetite, vomiting, gas,	Mild to moderate UC and CD

(*Continued*)

Table 6
(Continued)

Drug Class/Mode of Action	*Specific Drug*	*Administration Instructions*	*Nutritional Effects and Other Indications*	*Autoimmune Disease*
Bowel-specific aminosalicylate, anti-inflammatory agent			and diarrhea. Mild abdominal pain and nausea	Some are approved to induce remission
Prodrug of aminosalicylate; designed to be broken down and thus release the active ASA in the colon; designed specifically to reduce absorption and allow topical colon application *(311)*	Sulfasalazine is broken down by bacteria in the colon into two products: 5-ASA (considered the active) and sulfapyridine		Reduced absorption of folic acid Nausea, vomiting, gastric distress, and anorexia (loss of appetite) occur in up to one of every three patients receiving the drug *(313)*	UC, CD, RA
	Olsalazine	Take this with food or after meals to prevent stomach upset	This medication may cause stomach upset, gas, bloating, nausea, and loss of appetite *(314)*	UC
	Balsalazide disodium		GI effects include abdominal pain, diarrhea, nausea, and vomiting *(315)*	Indicated for the treatment of mildly to moderately active UC

Table 7

Drugs Used to Treat Type 2 Diabetes and Possible Nutritional Effects *(253,254)*

Drug Class/Mode of Action	*Specific Drug*	*Administration Instructions*	*Nutritional Effects and Other Indications*
Sulfonylureas Insulinotropic, increases circulating insulin. Insulin secretion from the islet is stimulated perhaps by increasing β-cell sensitivity to glucose *(291)*	Glipizide	Drug should be administered 30 min before a meal *(291)*	Numerous drugs (niacin, thiazide diuretics, β-blockers, corticosteroids) reduce insulin sensitivity, thus decrease efficacy
	Glimepiride	Drug should be administrated with meals *(291)*	
	Glyburide	Drug should be administrated with breakfast or a main meal. One or two dozes are usually sufficient *(291)*	Newer drugs (glipizide) control of blood glucose w/o deleterious changes in the plasma lipoprotein levels. Some sulfonylureas cause adverse GI effects like diarrhea (5% for glipizide)
	Chlorpropamide	The drug is absorbed rapidly and within 2–4 h reaches maximum levels in the blood *(60,291)*	
Meglitinides Insulinotropic, stimulates the release of insulin from the pancreas; therefore, it requires functioning β cells *(291)*	Repaglinide	Drug should be taken before the meal (15 min)	GI effects like nausea (5%) or diarrhea (5%) *(291)* Effective with metformin; should not be taken with sulfonylureas
Biguanides Increases insulin-simulated glucose uptake, reduces hepatic glucose production and increase insulin-simulated glucose uptake at the periphery *(291)*	Metformin	Drug should be taken with meals	Adverse GI symptoms including diarrhea, nausea, and anorexia are approximately 30% higher than with a placebo, especially initially. Food decreases the extent and slightly delays the absorption. A decrease in B_{12} levels is observed in 7% of the patients, perhaps due to

(*Continued*)

Table 7
(Continued)

Drug Class/Mode of Action	*Specific Drug*	*Administration Instructions*	*Nutritional Effects and Other Indications*
			interference with B_{12} absorption. Stabilization or decreased body weight. Tendency to improve lipid profile, particularly when baseline is elevated *(291)* Used effectively with sulfonylureas Slightly anorectic. May reduce triglycerides
α-Glucosidase inhibitors Inhibition of α-glucosidases in the intestinal brush border, leading to delay in carbohydrate absorption	Acarbose, miglitol	Should be taken with the first bite of the meal, for every meal	GI symptoms of diarrhea in ~20% of cases over control. Low serum calcium and low plasma vitamin B_6 were associated with the drug May be used in combination with sulfonylurea; metformin; or insulin. Due to its different mechanism of action, the effects of the combined drugs are additive *(291)*

Thiazolidinediones Enhances insulin sensitivity. Lower blood glucose levels and decrease insulin level. Increased the insulin content of pancreatic islets	Rosiglitazone Pioglitazone	Maybe administered with or without food	Increase in weight has been observed when used as a single treatment. HDL increased over time while LDL increased only in the first couple of months of therapy *(291)* Has been approved to be used in combination with sulfonylureas or metformin Patients with known risks for heart disease or who are at high risk for heart attack are advised by the FDA to talk with their physician about the safe use of this class of diabetes drugs *(316)*

through a glucose transporter and elevated glucose levels competitively inhibit the movement of vitamin C into cells. Consequences of lower than optimal antioxidant status have been documented in the cardiovascular tissues and lipoproteins of diabetics *(266)*. Supplementation with vitamin E and vitamin C has been shown to have beneficial effects on several immune parameters in diabetics *(267)*. Vitamin E supplementation reduced protein glycosylation and platelet aggregation in Type 1 diabetics and improved glycemic control and insulin action in Type 2 diabetics *(268)*. Several studies have shown that vitamin E supplementation reduced the potential for LDL oxidation ex vivo. Recent data suggest that vitamin E reduces the synthesis and secretion of inflammatory cytokines from macrophages taken from diabetics *(182)*. The efficacy of vitamin E in diabetes may be influenced by genetic factors *(269)*.

Chromium supplementation in some studies in diabetics has been shown to decrease blood glucose by potentiating the action of insulin. However, there are data indicating that chromium absorption is decreased in diabetics *(270,271)*.

7. CONCLUSIONS

The immune system functions to ensure the internal integrity of the body by constant surveillance of the normal portals of entry to the body, responding to unanticipated breaks in the skin or other body parts, and by monitoring the cells of the body to recognize and destroy cells that have been altered in some way to make them recognizable as “nonself.” During fetal development and continuing through the first years of life, the cells of the immune system that are responsible for self-recognition are educated to tolerate, and not destroy, cells that have self-antigens on their surface. The immune system involves the formation of millions of new cells daily and thus there is a very high requirement for energy and essential nutrients to support this high cellular turnover. The immune system is not fully developed at birth and responses become more vigorous during adulthood and then, in general, become less strong during the sixth decade and thereafter.

Pathogenic organisms (e.g., viruses, bacteria, fungi, protozoans) can be destroyed by the immune system, but the immune system can also be overcome by these pathogens. Many of these infectious agents seriously affect nutrient absorption and/or inappropriately increase loss of nutrients. The double effects of infection and loss of nutrients can cause the pathogen to overwhelm the body’s capacity to fight off the infection. The availability of antibiotics has increased survival from infections. But all drugs have negative effects, and many involve the GI tract, resulting in lowered nutritional status. Moreover, there are new, highly virulent infectious agents and current antibiotics may not be effective against these new human pathogens. Multidrug therapies are often used, and these can have additive and/or synergistic negative effects on dietary intake/nutrient losses.

Vaccines are critical drugs that work only if there is an optimal immune response to the vaccine’s antigen. Responses to vaccines are also, in many cases, dependent upon the nutritional status of the individual being vaccinated. Moreover, in the very early years of life and in the elderly, immune responses are not as vigorous as these are in adulthood. Research has found that certain micronutrient supplementations can improve responses to certain vaccines.

Several serious infections, such as respiratory tract infections, diarrheal diseases, HIV, and tuberculosis, affect billions of lives globally and are responsible for millions of deaths annually. Numerous drugs are used in the treatment of these infections. Both the disease itself and the treatments can cause additional detriments to the immune system. These interactions are often overlooked and an examination of the detailed tables provided in this chapter documents the need for attention to the drug–nutrient effects as well as the potential nutrient–drug effects.

When the immune system is triggered by some unknown agent to recognize certain cells or tissues of the body as nonself, the result is autoimmune disease. There are about 80 characterized autoimmune diseases and virtually all of them are found in a much greater frequency in women compared to men. This chapter reviewed the major effects of RA, SLE, and diabetes and the drugs used to treat these diseases as well as the nutritional consequences of the disease, drugs, and their interactions. The limited data on the potential for certain nutrients to be of benefit in autoimmune disease treatment are also reviewed. Additional research is required in this area.

Finally, there are data that suggest that certain vitamins, minerals, multivitamins, ω-3 fatty acids, and certain amino acids may enhance immune responses to infections, reduce autoimmune responses, improve vaccine responses, and reduce secondary infections. Many of the studies have been done in young children and in the elderly, groups with compromised immune responses. These studies are particularly important in the elderly as it is this population group that has the greatest exposure to drugs, often multidrugs, daily. At present, most of the nutritional studies have included healthy elderly who do not consume drugs. It is critical for future studies to examine the role that nutritional interventions can play in improving immune responses in elderly taking commonly used drugs that could adversely influence their nutritional status. Drug–nutrient interactions can have serious effects on the ability of the body to mount an optimal immune response.

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24 Drug–Nutrient Interactions in Patients with Cancer

Todd W. Canada

Objectives

- Describe the nutritional status of patients with cancer.
- Identify drug-induced changes in the nutritional status of patients with cancer.
- Provide suggestions for further research in this area to better manage these patients.

Key Words: Antioxidants; cachexia; chemotherapy; electrolytes; oncology

1. INTRODUCTION

Patients with cancer are at risk for poor nutritional status. This poor nutritional status may be a result of treatment modalities or conversely it may influence the patient's response to therapeutic interventions. This drug–nutrient interaction interface is important to explore further.

1.1. Epidemiology

Nutrition plays a major role in cancer prevention and its therapy. Dietary choices and physical activity are the two major modifiable determinants of cancer risk. Evidence suggests that one-third of the more than 500,000 cancer deaths in the United States can be attributed to these each year *(1)*. The observation of improved 5-year survival rates for all cancers is encouraging because much of the research into early cancer detection and treatment appears to be invaluable *(2)*. Unfortunately, the increase in 5-year survival over time (1950–1990) had little relationship to changes in the mortality from cancer. There are several reasons that the 5-year survival rates have increased. These include improvements in the treatment of established cancer, earlier identification of patients in their disease course, and early effective treatment regimens. Naturally, if more effective treatments of existing disease and more cancers are found early and treated, then mortality rates should decrease. The major explanation for improved 5-year survival rates

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without improved mortality is simply changes in the diagnosis of cancer, including better detection of subclinical cancers. However, epidemiological studies of populations whose diets are high in vegetables and fruits and low in animal fat, meat, and total calories have shown reduced risks for some of the most common types of cancer *(3)*.

1.2. Nutritional Status in Patients with Cancer

One of the most important factors in the response to cancer treatment and mortality is the overall condition of the patient at the time of diagnosis. Approximately 50% of patients have experienced weight loss by the time of cancer diagnosis and this unfortunately conveys a poor prognosis. By the time of death, virtually all cancer patients will experience loss of their lean body mass although their weight may actually increase from fluid retention (e.g., anasarca) or underlying tumor burden. Additionally, cancer has one of the highest incidences of protein-calorie malnutrition among hospitalized patients. The protein-calorie malnutrition is often related to the underlying disease itself, treatments related to the cancer, or a combination of the two. The major causes of death in more than 800 cancer patients were infections and organ failure associated with the underlying malignancy *(4)*. Interestingly, 10% of these patients were characterized at autopsy to have had extreme degrees of debilitation, malnutrition, and electrolyte imbalance. Most of these cancer patients experienced greater than 25% loss of their body weight. This represented one of the earliest reports of the syndrome of cancer-related cachexia. It also emphasized the important role of malnutrition in the pathogenesis of cancer and how commonly nutrition therapy is overlooked in this patient population *(5)*.

The cancer anorexia–cachexia syndrome is characterized by progressive, unintentional loss of body cell mass or lean body mass and systemic inflammation *(6–8)*. Clinical features of cachexia include host tissue wasting with skeletal muscle atrophy, anorexia, anergy, fatigue, anemia, hypoalbuminemia, and ultimately debilitation. Reduced muscle strength may help diagnose cancer cachexia *(9)*. Patients with nearly identical primary cancers and disease stages may vary significantly in terms of the development of cachexia. Although cachexia is often seen in patients with advanced malignancies, it may already be present in the early stages of tumor growth. The development of cachexia may be related to variations in tumor phenotype, oxidative stress, and host response although several facets of this multifactorial etiology are still unclear *(10)*. The primary clinical determinants of weight loss in cancer represent a multifactorial process as depicted in Fig. 1.

The most common rationales for weight loss are typically decreased oral intake of nutrients, increased requirements either from the tumor or its associated treatments, and inefficient use of nutrients *(11)*. Tumors of the gastrointestinal (GI) tract may present a physical obstruction or induce a malabsorptive state, thereby reducing oral intake or its absorption. There are several reasons for decreased oral intake and the frequent observation of GI symptoms in cancer patients may influence weight loss. In a study to identify the primary symptoms responsible, the following were evaluated in approximately 250 cancer patients: constipation, diarrhea, nausea,

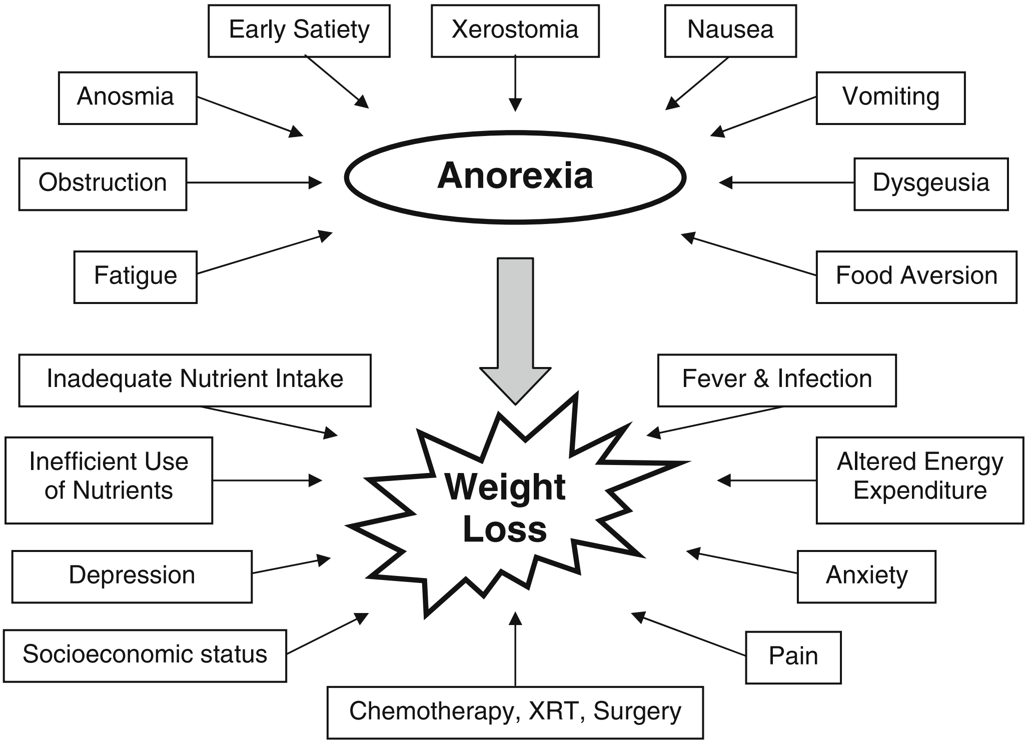
Early Satiety
Xerostomia
Nausea
Anosmia
Vomiting
Obstruction
Anorexia
Dysgeusia
Fatigue
Food Aversion
Inadequate Nutrient Intake
Fever & Infection
Inefficient Use of Nutrients
Weight Loss
Altered Energy Expenditure
Depression
Anxiety
Socioeconomic status
Pain
Chemotherapy, XRT, Surgery

Fig. 1. Factors associated with weight loss in cancer.

vomiting, abdominal fullness, abdominal pain, milk product intolerance, difficulty swallowing, mouth pain, mouth dryness, taste changes, denture problems, and difficulty chewing *(12)*. After obtaining a complete nutritional assessment including dietary and weight history, it was observed that the most common symptoms were abdominal fullness (61%), taste changes (dysgeusia) (46%), constipation (41%), mouth dryness (40%), nausea (39%), and vomiting (27%). The effects of these symptoms in patients with greater than 5% weight loss were compared to those with less than 5% weight loss. Interestingly, constipation and nausea were not statistically significant between the groups; however, they may have been clinically significant in terms of inducing weight loss, given the frequent use of opioid analgesics for cancer-related pain.

During simple starvation, the host is normally able to adapt by reducing energy expenditure, conserving protein, and utilizing fatty acids and ketone bodies derived from fat as an energy source. These adaptations are attenuated or absent in cancer-related cachexia, where energy expenditure may be increased and ongoing protein losses occur. Increased requirements may be a direct effect of increased energy expenditure. Resting energy expenditure (REE) measurements from indirect calorimetry in cancer patients represent wide variability. In an evaluation of 200 cancer patients, the mean measured REE was 98.6% of predicted using the anthropometric-based formula of Harris and Benedict *(13)*. However, it was noted that 33% were hypometabolic (measured REE $<$ 90% of predicted), 41% were normometabolic (measured REE 90–110% of predicted), and 26% were hypermetabolic (measured REE $>$ 110% of predicted). Patients who were characterized as hypermetabolic had a longer duration of disease than the normometabolic patients (32.8 vs. 12.8 months), indicating that duration of malignancy may have some impact on energy metabolism.

Several changes in nutrient metabolism have been described in patients with cancer-related cachexia. These changes have been ascribed to a number of tumor-derived, proteolysis-inducing factors and lipid-mobilizing factors (e.g., zinc–α2-glycoprotein) as well as proinflammatory cytokines derived from the immune system (e.g., tumor-necrosis factor-α, interleukin-1, and interleukin-6). These patients exhibit glucose intolerance and insulin resistance with increased rates of glucose production and recycling via lactate (from the Cori cycle) *(11)*. Lipolysis rates have not always been found to be significantly increased but lipogenesis appears to be reduced. Whole-body protein turnover and proteolysis has been observed to be increased in most advanced cancer patients compared to starved normal individuals and weight-losing noncancer patients *(11)*. As expected with progression of disease, protein turnover appears to increase further. Cancer patients with advanced disease and weight loss appear to exhibit an impaired adaptability to simple starvation, because fat mobilization is impaired and muscle proteolysis persists. All of these metabolic alterations observed in cancer have been referred to as an inefficient use of nutrients. Additionally, if surgery is required as part of the cancer treatment, it may cause further alterations in nutrient metabolism, such as an increased energy expenditure and protein requirements. It becomes apparent that reversing the metabolic defects observed in cancer patients is not a simple process.

2. EVALUATING NUTRITIONAL DERANGEMENTS IN PATIENTS WITH CANCER

2.1. *Nutritional Assessment*

Nutritional assessment of cancer patients is routinely accomplished by taking a medical and nutrition history while conducting a thorough physical exam guided by subjective global assessment *(14)*. The Mini-Nutritional Assessment and the Malnutrition Screening Tool can identify oncology patients who are nutritionally at risk *(15)*. Several factors that may place cancer patients at nutritional risk include other underlying acute or chronic diseases, inadequate food and nutrient intake patterns, multiple medications, and poor psychological or socioeconomic status. Whether patients have a new or recurrent cancer diagnosis, their current stage of cancer, and the presence of voluntary and involuntary weight loss are especially informative for nutritional assessment in the cancer population. Serum albumin may also be helpful, as it has been shown to be of prognostic significance *(16)*.

2.2. *Role of Therapeutic Modalities*

Chemotherapeutic agents may contribute to host malnutrition by a variety of direct and indirect mechanisms including nausea, vomiting, mucositis, GI dysfunction, and learned food aversions (Table 1). The adverse nutritional effects of

Table 1
Chemotherapy-Related Effects in Cancer

Head and Neck
Oropharyngeal ulcerations/stomatitis
Anosmia/dysgeusia
Anorexia
Learned food aversions
Esophagus
Esophagitis
Stomach
Nausea and vomiting
Small and large intestine
Enteritis/colitis
Typhilitis (*neutropenic enterocolitis*)
Diarrhea
Protein-losing enteropathy (*BMT regimens*)
Other
Depression/grief
Pain
Anemia/fatigue

chemotherapy may be compounded in the host who is already cachectic from the tumor or who has received prior or concurrent radiation therapy. Fortunately, the adverse effects of chemotherapy are relatively short lived, but repeated courses within 2–4-week intervals generally do not allow the host to recover fully. Most patients usually have 1–2 weeks of fatigue, GI symptoms, and poor oral intake after each course of chemotherapy followed by 1–2 weeks of suboptimal oral intake and slowly improved activities of daily living. These durations may be prolonged depending on the host's functional and socioeconomic status, depression, opioid use, and concurrent radiation therapy.

2.3. Drug–Nutrient Interaction Data

Drug–nutrient interactions can broadly be interpreted to include the influence of nutritional status on drug disposition and the influence of medication on nutritional status, as well as the influence of food or specific nutrients on drug disposition *(17)*.

Despite the wealth of information regarding malnutrition in cancer from reduced intake of nutrients, there are very few reports that have specifically focused on drug–nutrient interactions and their impact in this population *(18,19)*. The actual incidence and the clinical significance of drug–nutrient interactions in oncology are likely patient and cancer-dependent owing to the variations in age and treatment modalities. The combination of chemotherapy, radiation therapy, and/or surgery may induce specific nutrient deficiencies, appetite suppression, altered taste perception, and impaired nutrient absorption, metabolism, and excretion. One of the reasons for few reports of drug–nutrient interactions in cancer may be related to the route of administration, given the historically narrow focus on drug–food interactions. Most chemotherapeutic agents used clinically are administered parenterally; however, there are exceptions as some are taken orally (e.g., busulfan, melphalan, hydroxyurea, procarbazine, fludarabine, capecitabine, and temozolomide). The bioavailability of these oral drugs has generally been the major focus of the published drug–nutrient interactions where most have shown reduced absorption when administered with food *(18)*.

3. THE INFLUENCE OF NUTRITIONAL STATUS

Weight loss in cancer patients can be of prognostic significance. The effects of weight loss in cancer were originally described from the Eastern Cooperative Oncology Group in over 3000 patients *(20)*. The prognostic effect of weight loss on response to chemotherapy and survival along with the frequency of weight loss in a variety of tumor types was evaluated. Chemotherapy response rates were lower overall in the patients with weight loss. Within each tumor type evaluated, survival was shorter in the patients who had experienced weight loss compared to those patients who had not. The study noted that 46% of patients had experienced no weight loss in the previous 6 months and were comprised of non-Hodgkin's lymphoma, breast cancer, acute nonlymphocytic leukemia, and sarcoma tumor types. The remaining 54% of patients had lost between 0 and 5%, 5 and 10%, or greater than 10% of their body weight. Of the patients reporting greater than 10% weight loss, most had GI cancers primarily of pancreatic or gastric origin. These study findings emphasize the importance of pre-existing malnutrition in patients about to undergo chemotherapy and signify how early recognition and intervention to prevent worsening of cancer-related cachexia may afford the best opportunity to prevent its debilitating consequences *(16)*. It could be argued in a broad sense that the poor drug response in the malnourished patients is itself an adverse drug–nutrient (drug–nutritional status) interaction in these patients with cancer.

The role that weight-based dosing or body surface area-based dosing of chemotherapy plays in the adverse outcomes of patients with cancer remains unclear. Data suggest that dosing of chemotherapy agents might be better based on patient-specific variables (e.g., nutritional status, gene polymorphisms, total body clearance) *(21)*.

Alternatively, some data support specific nutrient deficits in improving patient response. The study of depriving malignant tumors of their copper supply as a potent antiangiogenesis strategy for stabilizing patients with advanced cancer is one of the true drug–nutrient interactions in oncology. The use of the investigational agent tetrathiomolybdate to purposefully lower total body copper content in patients with advanced stages of metastatic breast, kidney, colon, lung, skin, and pancreatic cancer did show that those able to achieve a mild copper deficiency had longer survival periods and stable disease *(22)*. Another impressive drug–nutrient interaction was observed when patients with gastric cancer received 5-fluorouracil (FU) and parenteral nutrition that was depleted of L-methionine *(23)*. This study evaluated the effects of 7 days of an L-methionine-depleted diet with 5-FU and found marked degeneration of the gastric cancer postoperatively. The depletion of L-methionine apparently enhanced the therapeutic effects of 5-FU in this gastric cancer study.

4. THE INFLUENCE OF MEDICATION

4.1. Gastrointestinal Function

Drug-induced GI disorders (nausea, vomiting, diarrhea, or constipation) may influence oral or enteral nutrition therapy tolerance and administration. Furthermore, most cancer patients with chronic pain often require maintenance bowel regimens to prevent obstipation from their opioid-based treatments. Clinicians should routinely monitor bowel function in the oncology patient as this is frequently problematic, given the adverse effects from chemotherapy (e.g., mucositis) and the other extreme of constipation from opioids and poor oral intake of fluids and/or food. Specific attention should be focused on the remaining GI tract integrity if prior surgery or radiation therapy has been part of the treatment regimen. This becomes a major consideration when selecting drug or nutrition therapy.

4.2. Macronutrient Status

Drug-induced alterations in nutrient substrate utilization (*protein, carbohydrate, or fat*) may alter the interpretation of response to any form of nutrition therapy (Table 2) *(24,25)*. Glucose intolerance or overt hyperglycemia is common in cancer patients who present with febrile neutropenia and deserves prompt treatment and consideration in feeding.

Table 2
Common Drug-Induced Alterations in Nutrient Substrate Utilization *(24,25)*

Nutrient Altered	*Interfering Drug(s)*
Glucose metabolism - *Hyperglycemia, altered insulin sensitivity*	Corticosteroids Catecholamines (*epinephrine, norepinephrine, dopamine*) Megesterol Fluoroquinolones Diuretics Octreotide Tacrolimus
Glucose metabolism - *Hypoglycemia*	Fluoroquinolones Pentamidine (*increased insulin secretion*) Octreotide (*reduced glucagon secretion*)
Protein metabolism* - *Elevated blood urea nitrogen and urinary nitrogen losses, peripheral muscle wasting*	Corticosteroids
Fat metabolism - *Hypertriglyceridemia*	Cyclosporine Tacrolimus Propofol

* Elevated BUN may occur from hypovolemia with diuretics and from renal vasoconstriction with amphotericin B or cyclosporine *(24,25)*

4.3. Fluid, Electrolyte, and Acid–Base Status

Common drug–electrolyte interactions in the cancer patient generally occur 1–3 days after initiation of the drug therapy; however, patients with pre-existing renal dysfunction may develop manifestations immediately (especially tumor lysis syndrome). Tables 3 and 4 list many of the common drug-induced electrolyte and

Table 3
Common Drug–Electrolyte Interactions in Cancer Patients *(26–30)*

Disorder	*Interfering Drug(s) and Mechanism of Action*
Hypernatremia	Amphotericin B – *Nephrogenic diabetes insipidus*
	Lactulose – *Fecal water loss from diarrhea*
Hyponatremia	Diuretics (*loop > thiazide*) – *Increased renal Na*$^+$ *losses*
	Cisplatin – *Renal tubular defect in Na*$^+$ *handling*
	Cyclophosphamide, vincristine, selective serotonin reuptake inhibitors (SSRIs) – *SIADH*
Hyperkalemia	Trimethoprim, triamterene, amiloride, pentamidine – *Inhibits renal K*$^+$ *secretion*
	Angiotensin-converting enzyme (*ACE*) inhibitors – *Inhibits ACE and aldosterone*
	Heparin, spironolactone, cyclosporine, tacrolimus – *Inhibits aldosterone*
	Nonsteroidal anti-inflammatory drugs (*NSAIDs*) – *Decreased renal blood flow*
	Antineoplastics – *Tumor lysis syndrome*
Hypokalemia	Diuretics (*loop > thiazide*), amphotericin B, ifosfamide - *Increased renal K*$^+$ *losses*
	Corticosteroids (*hydrocortisone*) – *aldosterone-induced K*$^+$ *losses*
	Insulin, dextrose, β-agonists, and sodium bicarbonate – *Intracellular shift of K*$^+$
	Foscarnet – *Unknown mechanism*
Hyperphosphatemia	Antineoplastics – *Tumor lysis syndrome*
	Phosphate-containing laxatives – *Increased PO*$_4$ *intake*
Hypophosphatemia	Aluminum-containing antacids, sucralfate, Ca^{++} supplements – *Increased binding of PO*$_4$
	Dextrose – *Intracellular shift of PO*$_4$
	Foscarnet – *Unknown mechanism*
	Corticosteroids, ifosfamide, cidofovir – *Increased renal PO*$_4$ *losses*
Hypermagnesemia	Magnesium-containing antacids and laxatives – *Increased Mg*$^{++}$*intake*
Hypomagnesemia	Diuretics (*loop > thiazide*), amphotericin B, cisplatin, carboplatin, cetuximab, cyclosporine, tacrolimus, aminoglycosides – *Increased renal Mg*$^{++}$ *losses*
	Foscarnet – *Chelation of Mg*$^{++}$
Hypercalcemia	Thiazide diuretics – *Decreased renal Ca*$^{++}$ *losses*
	Vitamin D – *Increased GI Ca*$^{++}$*absorption*
Hypocalcemia	Loop diuretics, corticosteroids – *Increased renal Ca*$^{++}$ *losses*
	Foscarnet – *Chelation of Ca*$^{++}$

SIADH, syndrome of inappropriate antidiuretic hormone *(26–29)*

Table 4
Common Drug-Induced Acid–Base Disorders in Cancer Patients *(26–29)*

Disorder	*Interfering Drug(s) and Mechanism of Action*
Metabolic alkalosis	Corticosteroids – *Increased renal hydrogen losses and bicarbonate reabsorption, hypokalemia* Diuretics (*loop > thiazide*) – *Same as above with hypovolemia* Sodium bicarbonate, acetate, and citrate, Lactated Ringer's – *Source of alkali or bicarbonate precursor*
Metabolic acidosis	Acetazolamide, ifosfamide – *Increased renal bicarbonate losses* Amphotericin B, ifosfamide, cidofovir – *Renal tubular acidosis (distal and proximal)*

acid/base disorders seen in cancer patients *(26–30)*. The clinician should attempt electrolyte replacement from a chronic perspective (weeks to months) more than the acute (hours to days) time frame, given the durations of treatment many cancer patients receive along with the residual drug effects that can remain for years (e.g., cisplatin).

4.4. Vitamin Status

One of the few trials to examine specific nutrients in the plasma of breast cancer patients prior to a diagnostic biopsy and then 3–4 months after diagnosis showed some interesting results *(31)*. Although this study was not designed to evaluate drug–nutrient interactions, it did show that women with breast cancer who received chemotherapy (agents not specified) had higher concentrations of retinol and α- and γ-tocopherol compared to those with benign breast disease. The changes observed in these patients were small and may have had statistical significance; however, it is not clear what physiologic or clinical effects this truly represents. It may reflect the common use of nutrient supplements or dietary alterations in the oncology population after diagnosis since this is one of the few interventions patients feel they have some control over in their disease.

Another study that evaluated the effects of vitamin and trace element supplementation in lung cancer patients was unfortunately unable to show any significant differences in the serum concentrations of the nutrients tested in survivors or those dying during or after their treatments, which included chemotherapy (cyclophosphamide, doxorubicin, vincristine) and irradiation *(32)*. Again, this trial was small and not designed to evaluate drug–nutrient interactions but did emphasize that nutrient concentrations changed only slightly with supplementation and did not appear to affect overall mortality.

4.5. Nutrient Antioxidant Status

The observation that chemotherapeutic agents induce cell damage and destruction intuitively leads clinicians to believe that nutrient supplementation is beneficial in cancer patients. One trial examined this phenomenon in patients with various tumor types from osteosarcoma to testicular cancer who underwent various plasma antioxidant testing prior to and 8–15 days after chemotherapy *(33)*. The chemotherapy consisted of either cisplatin and doxorubicin, cisplatin and etoposide ± bleomycin, or cisplatin with 5-FU or methotrexate. The plasma concentrations of vitamin C and vitamin E and copper decreased, whereas vitamin A and β-carotene concentrations increased from baseline to values at 8–15 days later. Interestingly, all of the mean values obtained throughout the study were within the normal ranges for the testing laboratory. As a clinician, it is difficult to interpret the results of this trial, given the lack of physiological or clinical relevance of the alterations in the antioxidant concentrations.

5. OTHER INFLUENCES

Several issues have gained greater importance to cancer patients and clinicians, including the older age now seen at diagnosis and lack of information on the benefits of current treatments with this aging population. The physiological and metabolic changes of aging have important implications for potential drug–nutrient interactions in the cancer patient. The elderly often exhibit subclinical or overt signs of malnutrition, including deficiencies of visceral proteins (e.g., albumin), minerals (e.g., calcium), and vitamins (e.g., vitamin D). Furthermore, many of the elderly will have altered organ function, chronic diseases, and a poorer socioeconomic status, which may influence their nutritional well-being. The potential impact of oncologic treatments on the worsening of nutritional status in the elderly is a major area of future research.

6. LIMITATIONS OF CURRENT DATA

The obvious major limitation of the current data is the lack of published studies to guide oncology clinicians and patients in their identification, prevention, and treatment of the many potential drug–nutrient interactions. Most clinicians are unaware of any clinically important interactions as few have been the subject of short- or long-term oncologic research. The development of new treatment regimens or combinations of chemotherapeutic agents to cure cancer has a greater precedent for reduction of mortality than the observance of decreased nutrients in various bodily fluids from a potential drug–nutrient interaction. Furthermore, most of the research devoted to studying the relationship between dietary habits and cancer has used case-control designs. These are often limited, given the potential for dietary interviews or questionnaires to misclassify patients based upon their nutrient intake, use of supplements, or other factors.

The biochemical measurement of circulating nutrients to identify toxicities or deficiencies has been a promising research potential for oncology. However, the interpretation of these measurements is often complicated by the underlying malignancy or its treatment in altering the concentrations *(31)*, not to mention the cellular control and interaction not captured by serum biomarkers. Many of the studies have enrolled cancer patients after surgery, during chemotherapy and radiation treatment, or shortly after these have ended. Consequently, this leaves clinicians to question the etiological relevance of the findings. Some study designs have collected blood samples of various nutrients at different times in a patient's disease course that may include hospital admission, months after treatment has ended or just begun. What is uncertain is the time required for these patients to return to their baseline concentrations of the nutrients tested after resumption of their normal dietary habits (if possible).

7. FUTURE RESEARCH

Research in the area of drug–nutrient interactions for the cancer population is vastly unexplored. The observation that cancer can occur at any age and many patients are now survivors of cancer greatly impacts researchers as this does not easily allow physiological comparisons with healthy controls. The following areas are suggested as potentially valuable research areas for drug–nutrient interactions:

- The influence of nutritional status on drug disposition
  - Influence of weight-based compared with body surface area-based dosing on drug disposition and effect
- The influence of food or specific nutrients on drug disposition
  - Use of dietary supplements particularly those with antioxidant properties
  - Amino acid (e.g., methionine) or trace element (e.g., copper) restriction diets in newly diagnosed and end-stage cancer patients as a potential treatment option
  - Impact of micronutrient supplementation (or other nonnutrient supplements) on clinical efficacy and toxicity of chemotherapy regimens
- The influence of chemotherapeutic medication on nutritional status
  - Pediatric/elderly populations and the impact of oncologic treatments on nutritional status
  - Acute and chronic vitamin and trace element toxicities or deficiencies with chemotherapy (including commonly used regimens), radiation therapy, surgical resections of the GI tract, or any combinations of the above
- Defining the time course for alterations in nutrients at diagnosis, prior to and after treatments, during unexpected hospital admissions, and when clinically cured or no other treatment options available.

8. CONCLUSION AND RECOMMENDATIONS

Despite the absence of published studies examining drug–nutrient interactions in oncology patients, there are some clinically important drug–nutrient interactions that deserve attention. Clinicians need to be familiar with the drugs listed in Table 2 as these often result in worsening malnutrition (propofol is the exception) if not considered in the nutritional care plan of the patient. The perceptive clinician can easily appreciate how the development of drug-induced nutritional deficiencies may occur more quickly in the oncology population secondary to their frequent underlying chronic malnutrition. The use of a multidisciplinary approach including a physician, nurse, dietitian, and pharmacist can greatly improve the overall care of the cancer patient when considering drug–nutrient interactions.

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25 Drug–Nutrient Interactions in Transplantation

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Objectives

- Update developments within the field of transplant drug–nutrient interactions.
- Describe the biology of immunosuppressive medications used for transplantation.
- Evaluate the nutritional impairments associated with solid organ transplantation.
- Offer recommendations to health-care providers caring for these medically complex patients.

Key Words: Antibodies; immunosuppression; nutritional status; transplant

1. INTRODUCTION

Achievements in solid organ transplantation have relied heavily on developments in immunosuppressive therapy. With the advent of modern immunosuppression, post-transplant patient survival rates have improved dramatically over the last quarter of a century. The goal of current therapy is to improve outcomes by achieving adequate immunomodulation to allow acceptance of the allograft while preventing the numerous adverse effects of these medications. Of relevance to this chapter, immunosuppressive drugs clearly interact with the nutritional status of patients *(1)*. Solid organ recipients are frequently already nutritionally deficient as a result of their chronic disease and in a catabolic state from end-organ failure *(2)*, emphasizing the need for providers to better understand the interplay of drug–nutrient interactions. The current chapter is an update and elaboration of the previous edition *(3)* and will emphasize the specific metabolic disturbances of lifelong immunosuppression that need to be treated to maximize graft and patient survival.

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2. REVIEW OF MECHANISMS

A non-pharmacologically treated immune system will recognize a transplanted organ as foreign and attempt to reject the allograft. Lifelong immunosuppression with drugs is required to prevent rejection. Transplantation centers currently employ lower doses of several immunosuppressive agents simultaneously to achieve a desired effect while reducing the toxicity and adverse effects of each individual agent. The choice of which agents to employ is still both center and organ specific. Therefore, any attempt to learn a single regimen and the nutritional sequelae would be futile and caretakers should be familiar with the drug–nutrient interactions of each medication. However, the choice of agent can generally be associated with two distinct post-transplant time periods: “induction” and “maintenance.”

2.1. Induction Agents

The induction phase is marked by a heightened response to the transplanted organ and many (but not all) centers are now using specific induction agents during this early postoperative period. The goal of induction therapy is to minimize the risk of rejection during this time of increased alloreactivity *(4)*. Agents used for the induction phase of transplantation are generally very potent inhibitors of specific areas of the immune system and are only used for a short period of time (days to weeks) because of the risks of infection and development of post-transplant lymphoproliferative disorders. They are frequently mono- and polyclonal antibodies to specific subsets of lymphocytes. Due to their potent immunosuppressive effects, these agents are frequently given to treat steroid-resistant rejection as well.

2.1.1. MONOCLONAL ANTIBODIES

Monoclonal antibodies consist of OKT-3 (Muromonab-CD3, Orthoclone®; Ortho Biotech, Bridgewater, NJ), daclizumab (Zenapax®; Roche Laboratories, Nutley, NJ), basiliximab (Simulect®; Novartis Pharmaceuticals, Inc; East Hanover, NJ), and alemtuzumab (Campath®; Bayer Healthcare Pharmaceuticals, Inc; Wayne, NJ). OKT-3 can be used for induction and treatment of rejection crisis and it works by binding the CD3 complex and depleting CD3+ T lymphocytes. The use of this agent results in the release of inflammatory cytokines and repetitive exposure can result in the development of human antimouse antibodies *(5)*. It has been reported to cause nausea, vomiting, diarrhea, and decreased appetite *(6)*. The use of antiemetics and nonsteroidal anti-inflammatory agents prior to administration can alleviate the gastrointestinal effects. Daclizumab and basiliximab are monoclonal antibodies against the IL-2 receptor and mediate their effects by blocking T-cell activation rather than depletion. The side effects of daclizumab and basiliximab are less than OKT-3, but their role in treating rejection crisis is limited *(5)*. Alemtuzumab depletes lymphocytes and monocytes by binding to the CD52 complex; its side effect profile is similar to that of OKT-3 and can be managed with the same agents *(5)*. The potential role of alemtuzumab for treating rejection crisis as well as the long-term effects of this drug still need further study *(7)*.

2.1.2. POLYCLONAL ANTIBODIES

Polyclonal antibody preparations include the more popular rabbit antithymocyte globulin (ATG; thymoglobulin; Genzyme, Cambridge, MA) and horse antithymocyte globulin (ATGAM; Pharmacia-Upjohn, Kalamazoo, MI). ATG contains antibodies to numerous T-cell antigens and results in depletion of T cells. As a result of the profound T-cell depletion, the administration of ATG is associated with cytokine release and resulting fevers, chills, and constitutional symptoms *(5)*. Antithymocyte preparations are associated with loss of appetite *(6)*. Another complication of OKT-3 and ATG is post-transplantation lymphoproliferative disorders (PTLD). PTLD include a number of disorders (e.g., malignant monoclonal lymphomas), the treatment of which can complicate maintenance of nutritional status.

2.2. Maintenance Agents

The “heightened” anti-donor response that exists during the induction phase is “heightened” relative to the persistent response that recipients will mount against their organ for the life of the allograft. Therefore, maintenance agents are begun at the time of transplantation and administered to recipients for the life of the transplanted organ. The drugs utilized for maintenance therapy act on numerous levels of the immune system and are often bundled together to limit toxicity and maximize immunosuppression *(8)*. Although every transplant center individualizes the maintenance regimen based on the individual patient and their own experience, most consist of (1) corticosteroids, (2) calcineurin inhibitors, or mTOR inhibitors, and (3) antiproliferative agents. Since numerous combinations exist, it is essential that caretakers be familiar with each of the agents’ side effect profiles and potential drug–nutrient interactions.

2.2.1. CORTICOSTEROIDS

Corticosteroids have been a seminal component of immunosuppression in transplantation for 50 years. Steroids inhibit prostaglandin synthesis and thus are powerful anti-inflammatory agents *(5,9)*, but other mechanisms are still not well known and adverse clinical effects are common. The ill effects of prolonged steroid therapy include cataracts, hyperlipidemia, hypertension, increased infectious risk, glucose intolerance, muscle wasting, osteopenia, peptic ulcer disease, delayed wound healing, sodium retention, and weight gain *(5,9)*. Steroids reduce lipoprotein lipase activity, increase very low-density lipoprotein synthesis in the liver, inhibit bile acid synthesis, and decrease low-density lipoprotein receptor activity *(10)*. Lipoprotein abnormalities have been demonstrated to increase the risk of cardiovascular-related death in the post-transplant period *(11)*.

The risk of hyperglycemia and post-transplantation diabetes mellitus (PTDM) is particularly significant because patients who develop PTDM have an increased risk of other comorbidities and mortality *(12)*. Patients who develop PTDM have worse long-term outcomes than those who do not *(13–25)*. The patient with new-onset PTDM is characterized by both impaired β-cell insulin secretion and increased insulin resistance *(26)*. Steroids can increase hepatic gluconeogenesis, which is associated with elevated protein and amino acid catabolism and decreased anabolism *(27)*. The result is insulin resistance whereas calcineurin inhibitors inhibit pancreatic islet cell function. For the nutritionist, identifying those at risk and then aggressively treating according to the International Diabetes Federation-endorsed consensus guidelines on new-onset diabetes after transplantation *(28)* is crucial. Risk factors for PTDM include obesity, age, family history of diabetes, abnormal glucose tolerance tests, and African-American, Native American, or Hispanic descent *(29,30)*.

We now know that the influence of steroids on the development of DM is dose-dependent *(29)* and that transplant recipients with DM have worse outcomes than recipients who do not *(13–25)*. Therefore, it is not surprising that steroid reduction or elimination is a goal of most transplant physicians *(31)* and patients *(32,33)*. Several centers have developed steroid avoidance protocols *(34–36)*. However, the extent that steroid avoidance prevents cardiovascular risk factors and osteopenia has been mixed thus far *(37–48)* and requires further study *(49)*. Moreover, some prospective randomized data exist which suggest that steroid use may actually prevent calcineurin nephrotoxicity *(50)*.

2.2.2. Calcineurin Inhibitors

Regardless of steroid usage, most solid organ transplant recipients also receive a calcineurin inhibitor for maintenance therapy. The calcineurin inhibitors frequently encountered when caring for a transplant recipient are cyclosporine (Neoral®, Novartis Pharmaceuticals, East Hanover, NJ; Sandimmune®, Novartis Pharmaceuticals; Gengraf®, Abbott, Abbott Park, IL) and tacrolimus (Prograf®; Astellas Pharma US, Deerfield, IL). Both calcineurin inhibitors act by interfering with T-cell activation and proliferation by preventing IL-2 synthesis *(5,9)*. The therapeutic ranges for cyclosporine and tacrolimus are quite narrow and therefore require drug level monitoring. In addition, both drugs are metabolized by the cytochrome P450 enzyme (CYP) pathway, so the use of other drugs or consumption of foods that affect this pathway can dramatically impact drug levels.

The side effect profiles of calcineurin inhibitors are quite broad. They can cause neurotoxicity and nephrotoxicity. Tremors or headaches are common when levels are too high, and nephrotoxicity usually requires a dose reduction or drug change to prevent kidney graft loss or renal failure. In addition, hypertension, diabetes, and electrolyte disturbances are common. Both calcineurin inhibitors are diabetogenic, although tacrolimus seems to cause a higher rate of DM than does cyclosporine. These drugs also appear to cause hypertension through the inhibition of calcineurin, which causes systemic hypertension and decreased renal blood flow *(51–54)*. Therefore, the hypertensive side effect of calcineurin inhibitors is inseparable from the therapeutic suppression of the immune system. Interestingly, although tacrolimus is a more potent immunosuppressive agent, the rate of hypertension is higher with patients receiving cyclosporine than those on tacrolimus *(55)*. Treatment options for post-transplant hypertension should include sodium restriction, weight control, and regular exercise. Since sodium retention and graft vasoconstriction are mechanisms of hypertension in this patient population, diuretics and calcium channel blockers are frequently beneficial. The use of angiotensin-converting enzyme inhibitors should be approached with trepidation because they may decrease renal function or instigate graft thrombosis or acute tubular necrosis *(56,57)*.

Tacrolimus in particular is associated with hypomagnesemia and hyperkalemia. Hypomagnesemia is usually treated with magnesium supplementation and hyperkalemia with a low-potassium diet. More severe hyperkalemia can be treated with mineralocorticoids such as fludrocortisone acetate (Florinef®; Bristol-Myers Squibb, New York, NY), but this may lead to peripheral edema.

2.2.3. mTOR INHIBITORS

An alternative to calcineurin inhibitors would be inhibitors of the mammalian target of rapamycin (mTOR). One potential advantage to using mTOR inhibitors over calcineurin inhibitors is the reduced risk of nephrotoxicity. Care must be taken in initiating mTOR inhibitors for the patient still receiving full dose calcineurin inhibitors, as this may exacerbate renal toxicity *(58)*. Sirolimus (rapamycin; Rapamune®; Wyeth Pharmaceuticals, Madison, NJ) is a macrolide antibiotic that blocks T-cell activation by forming a complex with FK-binding protein which then binds mTOR and arrests various cell types in the G1 to S phase *(59)*. Sirolimus has a long half-life and is metabolized by the CYP pathway. Therefore, drug monitoring is essential to ensure efficacy and avoid toxicity. The side effect profile of sirolimus includes hypertriglyceridemia, hypercholesterolemia, impaired wound healing, diarrhea, and bone marrow suppression *(60)*. Sirolimus reduces the catabolism of apoB-100-containing lipoproteins and increases lipid levels *(61)*. Wound healing can be improved by avoiding the drug around the time of surgical interventions *(35)*. Hypertriglyceridemia may be effectively treated by administration of marine omega-3 fatty acids or the use of HMG-CoA-reductase inhibitors (i.e., statins) *(62)*.

2.2.4. ANTIPROLIFERATIVE AGENTS

The antiproliferative agents used for transplantation are azathioprine (Imuran®), mycophenolate mofetil or MMF (CellCept®; Roche Laboratories, Nutley, NJ), and enteric-coated mycophenolate sodium (Myfortic®; Novartis Pharmaceuticals, Inc.). These agents inhibit purine metabolism and prevent lymphocyte proliferation after stimulation. Azathioprine frequently results in bone marrow suppression, leukopenia, and hepatotoxicity and thus is no longer commonly used. Instead, centers are now relying on MMF or the delayed-release mycophenolate sodium as antiproliferative agents. The major side effects of MMF are leukopenia, nausea, and diarrhea *(63)*. In most cases, the side effects of MMF can be treated with dose reduction *(1)*. Alternatively, switching to the enteric-coated mycophenolate sodium was designed to reduce the gastrointestinal complications, but the efficacy still requires further study *(5)*.

3. DESCRIPTIONS AND CLINICAL RELEVANCE OF NUTRITIONAL STATUS

3.1. Renal Transplantation

The most common causes of chronic kidney disease requiring transplantation are diabetes, hypertension, glomerulonephritis, systemic lupus erythematosus, interstitial nephritis, renal stones, chronic pyelonephritis, and polycystic kidney disease *(64)*. As a result of their underlying chronic disease, many patients will already be malnourished and have vitamin and mineral deficiencies. Malnutrition, altered protein and lipid metabolism, and obesity can all be altered by poor renal function *(65)*. Renal failure also disrupts calcium, phosphorous, vitamin D, and aluminum homeostasis, which require vigorous electrolyte monitoring. Many patients are on restricted diets because of dialysis needs and may suffer nausea or poor appetite secondary to uremia. Fortunately, the recovery of renal function following transplantation results in an overall improvement in nutritional status *(66)*.

In the postoperative setting, malnutrition increases the patient's risk of infection, inhibits wound healing, and prolongs rehabilitation. Although renal transplant recipients' diets are frequently advanced rapidly, nutrient requirements need to be considered on an individual basis. As in any surgical patient, the decision to start enteral nutrition is decided on a case-by-case basis. Kidney transplant recipients remain at risk for obesity, diabetes, hypertension, hyperlipidemia, and osteoporosis. The major cause of long-term morbidity and mortality is cardiovascular disease. There is evidence that lipoprotein abnormalities can cause graft failure and chronic vascular rejection *(67,68)*. The traditional causes of atherosclerotic disease occur in transplant recipients, including hypertension, hyperlipidemia, DM, and lack of exercise, which are modifiable. In addition, more recent data demonstrate that calcium and phosphate homeostasis, homocysteine, inflammation, and oxidative stress are associated with disease *(69)*. In addition, recent data collected from the United Network for Organ Sharing (UNOS) database documented that recipient morbid obesity (defined by BMI > 35 kg/m^2) conferred a statistically significantly increased risk of delayed graft function, prolonged hospitalization, and acute rejection as well as a decreased overall graft survival in a study sample of over 27,000 recipients compared to normal weight patients (BMI 18.5–24.9 kg/m^2) *(70)*. Other registry databases and single center studies also report a similar trend but suggest that poorer outcomes are dependent on type of organ transplanted and degree of obesity as well *(71–73)*.

Impaired homeostasis of calcium, phosphorous, and vitamin D can result in osteopenia. The key is prevention with supplements because no effective treatment exists once bone injury has occurred. Daily calcium (800–1500 mg), phosphorous (1200–1500 mg), and active vitamin D (1–2 μg daily) may all be indicated but should be adjusted according to serum levels. In addition, hypomagnesemia secondary to cyclosporine may exist which requires supplementation.

3.2. Liver Transplantation

The liver is an integral component to nutrition and metabolism. Therefore, it is not surprising that patients with end-stage liver disease (ESLD) awaiting transplantation often suffer from malnutrition. A worsening nutrition status is associated with poor outcomes of patients with ESLD secondary to cirrhosis *(74)*. The etiology of malnutrition in the liver transplant patient is clearly multifactorial but nutrient and caloric intake, decreased intestinal absorption, and metabolic disturbances are all important *(75)*. Patients often have poor appetites and insufficient caloric intake resulting in a metabolic state resembling prolonged starvation with depleted glycogen stores, increased lipid oxidation, and decreased carbohydrate utilization *(76)*. The increased oxidative stress on the liver becomes additionally important because antioxidant deficiencies frequently co-exist. The causes of inadequate nutrient intake and utilization in liver disease include altered taste from zinc deficiency, hyperglycemia, restricted food choices due to dietary restrictions, and early satiety from ascites leading to gastric compression and sensations of fullness.

Cholestatic liver disease can lead to nutrient malabsorption. In particular, patients often have poor absorption of the fat-soluble vitamins (A, D, E, and K) secondary to bile acid deficiency. Patients requiring frequent paracentesis usually develop some level of protein deficiency. Adequate pretransplant nutritional status correlates favorably with post-transplant outcomes *(77,78)*. Thus, every effort should be made to optimize nutrition prior to surgery. The main goals of pretransplant nutritional therapy are to prevent further muscle breakdown and replete vitamin and mineral deficiencies *(79)*.

In the immediate postoperative setting of a functioning graft, increased protein breakdown continues and repletion of this substrate is beneficial at promoting wound healing and preventing complications *(79)*. Protein breakdown slows after surgery but continues for up to 12 months. However, some nutrient abnormalities, such as zinc and vitamin A levels, will return to normal within days of surgery *(80,81)*. In order to maximize dietary intake, small frequent meals can be used with supplements.

Long term, patients may develop osteopenia, weight gain, DM, hypertension, or elevated cholesterol levels which all contribute to morbidity and mortality *(82)*. Maintenance immunosuppressive agents are usually the cause. Steroid minimization or avoidance is usually attempted to avoid cardiovascular risk factors. In addition, there are data that the use of tacrolimus has reduced the prevalence of cardiovascular factors over cyclosporine *(55)*. As in the general population, exercise and low-fat, calorie-controlled diet is recommended. The use of antihyperlipidemics, antihypertensives, and diabetic medications may be necessary. The use of alendronate may prevent bone loss after liver transplantation *(83)*. More research is needed to determine long-term micronutrient needs of these transplant recipients.

3.3. Pancreas Transplantation

Pancreas transplantation is performed for diabetes mellitus. The majority of pancreas transplants performed yearly are in conjunction with renal transplants for diabetic nephropathy. Outcomes have improved over the last three decades, but simultaneous pancreas kidney transplants (SPKs) still have increased graft survival over isolated pancreas transplants, and kidney after pancreas transplants *(84)*. SPKs were historically performed with exocrine drainage provided via the bladder, but this frequently led to urinary complications and bicarbonate losses. Currently, most centers utilize enteric exocrine drainage as a first choice to prevent the aforementioned complications.

As a result of their diabetes, patients awaiting pancreas transplantation frequently have some degree of renal failure, gastroparesis, cardiovascular disease, and retinopathy. Therefore, preoperative nutritional status should be evaluated. Hyperglycemia should return to normal with a well-functioning graft and glycosylated hemoglobin levels should reflect this change after 2 months. Fluid and electrolyte disturbances require close attention in the immediate postoperative setting. Patients are at increased risk of hyperglycemia, hypokalemia, hypocalcemia, and metabolic acidosis secondary to bicarbonate loss. If urinary exocrine drainage is employed, urinary bicarbonate losses must be repleted. Graft and native pancreatitis can occur which requires aggressive fluid resuscitation. If the patients have gastroparesis, prolonged nasogastric decompression may be beneficial with postpyloric enteric feeding.

Interestingly, pancreas transplant recipients with diabetes still have similar carbohydrate metabolism to non-diabetic subjects receiving the same immunosuppressive medications, despite systemic insulin secretion *(85)*. Lifelong immunosuppression puts pancreas recipients at risk for fluid and electrolyte abnormalities, fistulas, gastroparesis, pancreatitis, hyperglycemia, obesity, hyperlipidemia, hypertension, and osteoporosis *(86)*. These conditions should be treated as in other solid organ recipients with diet therapy, exercise, vitamin supplementation, and hydration. The use of motility agents may be beneficial in patients with gastroparesis and the placement of a feeding jejunostomy tube should be considered in severe states.

3.4. Heart and Lung Transplantation

Depending on the etiology and severity of their disease, patients may undergo transplantation of the heart, single lung, double lung, or heart and lung simultaneously. The common causes of heart failure requiring transplantation are ischemic heart disease and cardiomyopathy. Patients awaiting lung transplantation frequently suffer from chronic obstructive lung disease, cystic fibrosis (CF), bronchiectasis, or pulmonary hypertension *(87)*.

3.4.1. HEART TRANSPLANTATION

The nutritional status of the patient depends on the etiology of their underlying disease. Chronic heart failure patients frequently suffer from malnutrition *(88,89)*. As a result of decreased cardiac output and peripheral blood flow, the body responds by releasing catecholamines that vasoconstrict splanchnic arterioles resulting in decreased gut perfusion. In addition, right heart failure leading to venous congestion can result in renal and hepatic dysfunction, which can exacerbate gastrointestinal disturbances. The increased catecholamines can also increase the patient's metabolic rate and lead to increased nutritional demands *(90)*. The presence of cardiac cachexia is associated with poor outcomes following heart transplantation *(91)*.

3.4.2. LUNG TRANSPLANTATION

In chronic lung disease, the etiology of malnutrition is different. There is increased energy expenditure from the work of breathing and patients with hyperinflated lungs can have decreased oral intake secondary to feelings of fullness. Patients with CF and bronchiectasis frequently suffer from infections that result in production of cachectin and increased energy expenditure. Patients with CF may also suffer from malabsorption due to pancreatic insufficiency. Determination of the nutritional status is essential because preoperative nutritional support is effective at reducing postoperative morbidity and mortality in lung transplant recipients *(92)*. In those patients requiring a heart and lung transplant, there is a high prevalence of gastroparesis that is often severe and resistant to prokinetic agents *(93)*.

3.5. Small Bowel Transplantation

Small intestinal transplantation is reserved for patients with irreversible small intestinal failure that have a poor prognosis on parenteral nutrition (PN). The most common conditions resulting in the need for transplantation are short bowel syndrome, malabsorption syndrome, motility disorders, neoplastic disease, and primary or secondary transplant failure *(94)*. The intestines can be transplanted alone, with a liver, or with multiple viscera depending on the etiology of disease. Fortunately, outcomes have improved in this field and currently represent a viable surgical option for patients dependent on long-term PN *(95)*. Current 4-year survival rates are 50% (intestine alone), 50% (intestine and liver), and 62% (multivisceral) *(96)*.

The nutritional management of small bowel transplant recipients is complex and labor intensive. Because of their underlying disease, patients may be malnourished and depleted of vitamins and minerals despite being maintained on PN.

In the immediate postoperative setting, diarrhea is quite common and requires close attention to fluid and electrolytes. Patients may have high volumes of enteric fluid losses. The causes of diarrhea are multifactorial and include changes in the grafts neural modulatory pathway, malabsorption, loss of ileocecal valve, bacterial overgrowth, graft ischemia–reperfusion injury, chylous ascites from disrupted lymphatics, and immunosuppression *(97)*. Patients may suffer from hyponatremia, hypokalemia, and hypomagnesemia. PN is frequently utilized for several weeks after intestinal transplantation, and enteral nutrition (EN) can be considered when the graft and remnant recipient intestines appear to have motility (usually 5–7 days).

Most recipients are able to maintain adequate nutrition following intestinal transplantation and children maintain growth velocities. Some centers advocate low-fat enteral formula for 4–6 weeks after surgery to prevent chylous ascites from disrupted lymphatics *(98)*. Medium-chain triglycerides are preferred because normalizing the absorption of fats is believed to take 4–6 weeks *(99)*.

Studies of long-term health risks to recipients of intestinal transplants still need further follow-up. Hypertension can occur and should be treated pharmacologically to avoid sodium restriction, which may discourage oral intake. The complex immunobiological mechanisms that are inherent to the intestines are a source of great research. The amount of immunosuppression needed to avoid rejection is quite high and leads to higher infectious risks. The main cause of transplant-related death is currently infection because induction agents have reduced rejection rates *(100)*.

4. LIMITATIONS OF THE DATA

As with any rapidly advancing field, much of the data concerning immunosuppressive drug–nutrient interactions are observational and not from prospective randomized trials. In addition, many transplant centers rely on experience and intuition to develop protocols for their individualized patient populations. The wide variety of disease states leading to end-organ failure and their respective nutritional ramifications result in many distinct combinations of medications. In addition, recent improvements within the field result in reluctance by providers to change modalities without solid data. Those centers which have pioneered newer protocols often have done so in a prospective manner without randomization, which means other concurrent advancements in critical care and infectious diseases significantly alter the interpretation of the results.

5. RESEARCH NEEDS

It is evident that current immunosuppressive agents are not without risks. As a result, newer agents are currently under development and need further study in pre-clinical trials. Most of these agents are aimed at minimizing calcineurin toxicity. MR4, a modified release tacrolimus formulation, is currently undergoing phase III trials but similar levels for efficacy will be necessary, giving it the same side effect profile as tacrolimus. Some of the other agents on the horizon include FTY720 (a sphingosine 1-phosphate receptor modulator), FK778 (an inhibitor of pyrimidine synthase), CP-690550 (a JAK3 inhibitor), AEB-071 (a protein kinase C inhibitor), and costimulatory blocking agents *(101,102)*. Many of these agents appear promising but further pre-clinical and clinical data are needed. It remains to be seen whether an evaluation of drug–nutrient interactions will be included in the drug development and testing process. In any event, a more thorough understanding of immunobiology will be needed to design lifelong agents with the specificity necessary to avoid adverse effects. Some centers are now focusing on short courses of treatment to induce states of tolerance to the grafts that avoid lifelong immunosuppression altogether *(103)*. Transplantation tolerance can be defined as an acquired modification to the host immune system that leads to indefinite, drug-free, allograft survival with maintenance of full immunocompetence *(104)*. Significant pre-clinical data are necessary before protocols aimed at avoiding lifelong immunosuppression through tolerance induction will reach the clinics *(105)*.

6. CLINICAL RECOMMENDATIONS

The success of transplantation has resulted from developments in immunosuppressive therapy. With the advent of these agents, patients benefit from longer, disease-free lives. Unfortunately, many of the agents currently used still have adverse effects that can interact with patients' nutritional status requiring long-term close surveillance and management. As the number of transplants performed has increased and outcomes improved, the number of health-care providers caring for these complex patients across settings has also increased. It is essential that providers have a complete understanding of the interplay between the nutritional status and immunosuppressive medications employed to minimize adverse effects. A multidisciplinary team is essential in caring for these patients.

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26 Drug–Nutrient Interactions in Patients with Chronic Infections

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Objectives

- Describe the potential significance of the food effect on drugs used to treat chronic infection.
- Identify the various drug–nutrient interactions with medication used to treat HIV infection.
- Describe drug–nutrient interactions involved in the treatment of tuberculosis and chronic hepatitis

Key Words: Antimicrobial; HIV; tuberculosis; metabolic disorder; viral hepatitis

1. INTRODUCTION

Drug–nutrient interactions can result in significant inconvenience to patients that may subsequently cause an increase in patient non-adherence. Unless instructed otherwise, most patients will take their medication along with meals. They assume that this may minimize gastrointestinal (GI) adverse effects, as well as potentially provide them a trigger to remember to take their medications. A lack of knowledge about drug–nutrient interactions may therefore lead to poor clinical outcomes. The impact of these interactions may potentially be of greatest individual and public health consequence in the treatment of chronic infection. This chapter deals specifically with drug–nutrient interactions in patients infected with *Mycobacterium tuberculosis*, the human immunodeficiency virus (HIV), or the chronic viral hepatitis viruses. Much of the focus will be on interactions occurring between oral drug dosage regimens and food.

2. MECHANISMS OF DRUG–NUTRIENT INTERACTION

2.1. The Food Effect

Although it is often difficult to determine the exact mechanism by which food causes a change in the bioavailability of a drug, several mechanisms may be

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involved *(1)*. These include a delay in gastric emptying, stimulation of bile flow, a change in GI pH, an increase in splanchnic blood flow, a change in luminal or mucosal metabolism of the drug substance, and a physical or chemical interaction with the dosage form or drug substance that may each contribute to altered drug bioavailability (see Chapter 8).

Food intake will directly affect GI secretions and gastric pH. In general, GI secretions will increase in response to food intake, resulting in an increase in acid secretion in the stomach and a lowering of gastric pH *(2)*. The impact of this change is that in the presence of a more acidic environment, the dissolution and absorption of basic drugs will be accelerated, whereas acid-labile agents will be degraded more rapidly. The quantity and content of a meal will also affect drug absorption. The intake of a large solid food meal, particularly when fat-containing, will delay the stomach-emptying rate, potentially resulting in increased degradation of acid-labile agents, but may result in increased absorption of agents that have slower dissolution rates *(2)*. The intake of large fluid volumes tends to increase gastric-emptying rates and can have the opposite effect of a large solid meal *(1)*. The contents of a meal also may play an important role in drug–nutrient interactions. For example, meals containing polyvalent metal ions (aluminum, calcium, iron, magnesium, or zinc) may bind to or chelate drug substances, making the drug unavailable for absorption. Examples of this type of interaction include the potential chelation of tetracycline or fluoroquinolone derivatives when coadministered with food items that have high quantities of polyvalent ions *(1)*. The content of a meal may also be an important determinant of alterations in drug metabolism *(3)*. Important examples include dietary protein, cruciferous vegetables, grapefruit juice, and the intake of charcoal-broiled meats (see Chapter 9).

Ultimately, drug–nutrient interactions can have one of three outcomes with regard to oral drug absorption. Drug absorption may be increased, decreased, or not affected at all. With regard to decreased absorption, it is important to separate *delayed* absorption (an increase in the time to reach maximal absorption [$T_{\max}$] but no change in area under the concentration–time curve [AUC]) from *reduced* absorption (a decrease in the AUC). Depending on the magnitude of the latter, a reduction in AUC may be clinically important, whereas the former is generally not clinically important.

2.2. Studying and Evaluating Food Effect

The US Food and Drug Administration (FDA), through the Center for Drug Evaluation and Research's (CDER) Food Effect Working Group, published guidelines for food effect bioavailability and bioequivalence studies for immediate and modified-release drug products *(4)*. This document provides consideration for study design, subject selection, dosage strength, the contents of the test meal, drug administration, sample collection, and data analysis. A randomized, balanced, single-dose, two-treatment (fed versus fasting), two-period, two-sequence crossover design involving a minimum of 12 subjects receiving the highest strength of a drug intended to be marketed is recommended for the study of food effect. In particular, the meal conditions recommended are those that "are expected to provide the greatest effects on GI physiology so that systemic drug availability is maximally affected." Specifically, a high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800–1000 kcal) meal is recommended as a test meal for food effect bioavailability and fed bioequivalence studies. This meal should derive 150, 250, and 500–600 kcal from protein, carbohydrate, and fat, respectively. The specifics of the design and test meal should be clearly outlined in the study report and are of great importance in interpreting the results of any food effect study.

3. DRUG–NUTRIENT INTERACTIONS FOR MEDICATIONS USED TO TREAT HIV INFECTION

The treatment of HIV infection has continued to evolve and includes the use of multiple agents simultaneously *(5,6)*. Currently, no cure for this infection exists, and therefore patients receiving pharmacological treatments are currently committing to prolonged and potentially lifelong therapy. The complexity of taking multiple agents, multiple times per day, is made that much more troublesome when many of the antiretroviral agents' bioavailability can be significantly impacted by food (Tables 1–4). The added burden of needing to administer one or more agents with or without food can make an already difficult to manage regimen nearly impossible for a patient to adhere to over the long term. The clinical ramification of poor adherence in this setting is clinically significant. The virus is more able to mutate and treatment failure is more likely if a patient is not adherent to their prescribed antiretroviral regimen more than 90% of the time *(5,6)*.

Table 1
Nucleoside Reverse Transcriptase Inhibitors: Recommendations for Coadministration with Food

Generic name	*Brand name*	*Current recommendation*
Abacavir	Ziagen, Epzicom*, Trizivir*	Can be given without regard to food
Didanosine	Videx, Videx-EC	Take on an empty stomach, 30–60 min before or 2 h after a meal
Emtricitabine	Emtriva	Can be given without regard to food
Lamivudine	Epivir, Combivir*, Trizivir*	Can be given without regard to food
Stavudine	Zerit	Can be given without regard to food
Tenofovir	Viread	Administer with food
Zalcitabine	HIVID	Can be given without regard to food; avoid simultaneous Mg/Al-containing products
Zidovudine	Retrovir, Combivir*, Trizivir*	Can be given without regard to food; consider low-fat meal coadministration

* Combination products

3.1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

3.1.1. ABACAVIR

Abacavir is rapidly and extensively absorbed after oral administration. The mean absolute bioavailability of the tablet formulation is 83% *(7,8)*. The bioavailability of abacavir tablets was assessed in the fed and fasting states *(9)*. After single doses of abacavir were taken with food, the maximum drug concentration in blood ($C_{\max}$) was reduced by 35% and the AUC by 5%. No significant difference in systemic exposure (i.e., AUC) was noted in the fed and fasting states and the tablets may therefore be administered with or without food. No specific food effect studies have been conducted on the oral solution, but the oral solution provides comparable systemic exposure to the tablet formulation and these products have been deemed interchangeable *(7)*.

Abacavir is eliminated metabolically via alcohol dehydrogenase. Because of their common metabolic fate, the pharmacokinetic interaction between abacavir and ethanol was studied in 24 HIV-infected patients *(7)*. Each patient received the following treatments on separate occasions: a single 600 mg dose of abacavir, 0.7 g/kg of ethanol, and abacavir 600 mg plus 0.7 g/kg ethanol. Coadministration of abacavir and ethanol resulted in a 41% increase in abacavir AUC and a 26% increase in abacavir half-life ($t\frac{1}{2}$). No effect on ethanol was seen in men.

Abacavir is available in a combination product (abacavir and lamivudine, (Epzicom^{TM}) that may be administered with or without food. Administration of this product with a high-fat meal does not change the bioavailability of lamivudine. Food does not alter the extent of systemic exposure to abacavir, but the rate of absorption decreases by approximately 24% compared with fasted conditions *(10)*.

3.1.2. DIDANOSINE

Didanosine is currently available as enteric-coated beadlets in a capsule and as a buffered formulation. The enteric coating protects didanosine from degradation by gastric acid. Additionally, this formulation has been shown to provide an equivalent AUC to the buffered tablet formulation of didanosine, although the $C_{\max}$ is reduced by 40% and the $T_{\max}$ is increased by approximately 1.5 h when administered as the enteric-coated formulation *(11)*. The impact of food on the two formulations is quite different. Food reduces the absolute bioavailability of the buffered formulation by approximately 50% *(12)*. The presence of food reduces the AUC of the enteric-coated formulation by 19% *(11)*. The timing of food administration has been studied in 10 HIV-infected patients *(13)*. This study showed that the food effect could be minimized if one administers the buffered formulation 30–60 min before or 2 h after a meal. As a result it is recommended that the buffered formulation be administered 30–60 min before or 2 h after a meal and the enteric-coated formulation be administered on an empty stomach.

3.1.3. EMTRICITABINE

Emtricitabine is available as a capsule and a solution for oral administration. This drug may be administered with or without food. The AUC was unchanged and the C_{max} was decreased by 29% when the capsule form of the drug was administered with a 1000 kcal high-fat meal. AUC and C_{max} were unaffected when the oral solution was administered with either a high- or a low-fat meal *(14)*.

3.1.4. LAMIVUDINE

Lamivudine is rapidly absorbed after oral administration with an absolute bioavailability in HIV-infected patients of 86% for the 150-mg tablet and 87% for the oral solution *(15)*. Lamivudine was administered to 12 HIV-infected patients on two occasions, once in the fasted state and once with food (1099 kcal, 75 g fat, 72 g carbohydrate, 34 g protein) *(15,16)*. Absorption was slower in the fed state (T_{max} 3.2 h versus 0.9 h), C_{max} was 40% lower in the fed state than fasted state, but there was no difference in the systemic exposure between the fed and fasted states. Therefore, lamivudine (tablet or oral solution) may be administered with or without food.

3.1.5. STAVUDINE

Stavudine is rapidly absorbed after oral administration with achievement of the C_{max} within 1 h after dosing of the capsule or oral solution. The administration of stavudine is not affected by food and it can be taken with or without food *(17,18)*.

3.1.6. TENOFOVIR

Tenofovir disoproxil fumarate is a water-soluble diester prodrug of the active ingredient tenofovir. Following oral administration, the oral bioavailability of tenofovir from this formulation is approximately 25%. Administration of tenofovir following a high-fat meal (700–1000 kcal, 40–50% fat) increases the oral bioavailability as evidenced by an AUC increase of approximately 40%, an increase in the C_{max} of 14%, and an increase in the T_{max} by 1 h *(19)*. It is therefore recommended that tenofovir be administered with a meal to enhance its bioavailability.

3.1.7. ZALCITABINE

Zalcitabine, when administered orally to HIV-infected patients, has a mean absolute bioavailability of more than 80% *(20)*. Coadministration with food in 20 patients resulted in a reduced rate of absorption (T_{max} of 1.6 h versus 0.8 h in fasted state), a 39% decrease in the C_{max}, and a 14% reduction in the AUC *(21)*. This has been considered to be clinically insignificant and zalcitabine can therefore be administered with or without food.

Coadministration of Maalox® (30 mL) with a single dose of 1.5 mg of zalcitabine in 12 HIV-infected patients resulted in a decrease in the mean C_{max} by approximately 33% and a reduction in the AUC by approximately 25% *(20)*. Although the clinical significance of this is not known, it is recommended that zalcitabine not be ingested simultaneously with magnesium/aluminum-containing products.

3.1.8. ZIDOVUDINE

Zidovudine is well absorbed after oral administration with a bioavailability that averages between 60 and 70% *(22,23)*. Considerable variability between patients does exist, and the bioavailability can range from 40 to 100%. Several studies have evaluated the impact of food on the absorption of zidovudine *(24,25)*. In general, food consumption tends to decrease the rate but not the extent of absorption of zidovudine. This is especially true for high-fat meals. One study in 13 patients with acquired immunodeficiency syndrome (AIDS) was conducted in the fed (a standard breakfast) and fasting states *(26)*. The mean AUC in the fed state was 24% lower than fasted state and there was more interpatient variability. In general, zidovudine is recommended to be administered without regard to food. Based on the results in patients with AIDS, it may be advisable to administer zidovudine on an empty stomach. If GI adverse events preclude this, coadministration with a low-fat meal is recommended.

Zidovudine is commercially available as a combination dosage form with lamivudine (Combivir®) and with lamivudine and abacavir (Trizivir®). Combivir® has been studied in 24 healthy subjects in the fed and fasted states *(27)*. There was no difference in the AUC regardless of the coadministration with food. Trizivir® has been studied in 24 subjects in the fed and fasted states as well *(28)*. The $C_{\max}$ was 32, 18, and 28% lower for zidovudine, lamivudine, and abacavir, respectively, when administered with a high-fat meal compared to the fasting state. Food did not alter the extent of absorption (i.e., AUC) of any of the components of Trizivir®. It is therefore recommended that both available combination oral products be administered with or without food.

3.2. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (Table 2)

3.2.1. DELAVIRDINE

Delavirdine is rapidly absorbed after oral administration, with peak plasma concentrations occurring approximately 1 h after administration and a bioavailability of approximately 85% *(29)*. Single-dose bioavailability of 100-mg tablets of delavirdine was studied in 16 healthy subjects and has been shown to be increased by approximately 20% when the tablets are allowed to dissolve in water and form a slurry before administration *(30)*. The 200-mg tablet has not been evaluated as a slurry for administration as it is not readily dissolved in water.

Table 2
Non-nucleoside Reverse Transcriptase Inhibitors: Recommendations for Coadministration with Food

Generic name	*Brand name*	*Current recommendation*
Delavirdine	Rescriptor	Can be given without regard to food
Efavirenz	Sustiva	Avoid taking with high-fat meals
	Atripla*	Take on an empty stomach
Etravirine	Intelence	Take following a meal
Nevirapine	Viramune	Can be given without regard to food

* Combination product

The effect of food on delavirdine absorption was evaluated in 13 HIV-infected patients in a multiple-dose, crossover study *(29)*. Patients were maintained on their typical diet (meal content was not standardized) and delavirdine was administered every 8 h with food or 1 h before or 2 h after a meal. Although the C_{max} was reduced by 25% in the fed state, there was no effect on AUC or C_{min} of coadministering delavirdine with food. It is therefore recommended that delavirdine be administered with or without food.

The effect of an acidic beverage on the pharmacokinetics of delavirdine has been evaluated in HIV-infected patients. Matched subjects with ($n = 11$) and without ($n = 10$) gastric hypoacidity were given delavirdine 400 mg three times daily. The pharmacokinetics of delavirdine and its *N*-desalkyl metabolite was determined over 8 h after administration for 14 days. Delavirdine exposure (as measured by C_{max}, AUC, and C_{min}) was lower and the extent of metabolism greater in subjects with gastric hypoacidity. Orange juice increased the absorption of delavirdine by 50–70% in subjects with gastric hypoacidity, but had only a marginal impact on absorption in subjects without gastric hypoacidity *(31)*.

3.2.2. Efavirenz

The absolute bioavailability of efavirenz has not been determined after oral administration. In HIV-infected patients, the T_{max} is reached in 3–5 h and patients achieve steady-state concentrations in 6–10 days *(32)*. The administration of efavirenz 600-mg capsules with a high-fat/high-caloric meal (894 kcal, 54 g fat) or a reduced-fat/normal caloric meal (440 kcal, 2 g fat) was associated with a mean AUC increase of 22 and 17% and a mean increase of 39 and 51% in efavirenz C_{max}, respectively, relative to the exposures achieved when given under fasted conditions *(28)*.

Administration of efavirenz 600-mg tablets with a high-fat/high-caloric meal (approximately 1000 kcal, 50–60% fat) was associated with a 28% increase in mean AUC of efavirenz and a 79% increase in mean C_{max} of efavirenz relative to the exposures achieved in the fasted condition *(32)*. It is recommended that coadministration of efavirenz with a high-fat meal be avoided to minimize the likelihood of adverse events.

Efavirenz is available in a combination product with emtricitabine and tenofovir (Atripla®). This product should be taken on an empty stomach *(33)*. However, Atripla® has not been evaluated in the presence of food.

3.2.3. Etravirine

Following administration of a 200-mg dose of etravirine the T_{max} occurs in 2.5–4 h, although the absolute bioavailability of this drug is unknown *(34)*. The drug's AUC is approximately twofold greater when administered following a meal compared to the fasted state *(34)*. The food content of the meal (345–1160 kcal, 17–70 g fat) does not seem to influence the extent of etravirine exposure *(34)*. So the current recommendation is that this drug should be taken following a meal.

3.2.4. Nevirapine

Nevirapine is readily absorbed after oral administration with an absolute bioavailability of more than 90% in both healthy subjects and HIV-infected patients *(35)*. Nevirapine 200 mg was studied in 24 healthy adults (12 men, 12 women) with either a high-fat breakfast (857 kcal, 50 g fat) or an antacid (Maalox® 30 mL) *(35)*. The AUC of nevirapine absorption was comparable to that observed under fasting conditions. In a separate study of six HIV-infected patients, nevirapine was studied when coadministered with the buffered formulation of didanosine *(35)*. Again, the AUC of nevirapine was not significantly altered. It is recommended that nevirapine be administered with or without food, a magnesium/aluminum-containing antacid, or didanosine.

3.3. Protease Inhibitors (PIs) (Table 3)

3.3.1. AMPRENAVIR

Amprenavir capsules and oral solution are rapidly absorbed after oral administration in HIV-infected patients with a $T_{\max}$ of between 1–2 h *(36)*. The absolute oral bioavailability of amprenavir has not been established. It is important to note that the oral solution is 14% less bioavailable than the capsule and is therefore not interchangeable on a milligram-per-milligram basis.

Table 3
Protease Inhibitors: Recommendations for Coadministration with Food

Generic name	*Brand name*	*Current recommendation*
Amprenavir	Ziagen	Can be given without regard to food; avoid high-fat meals; avoid vitamin E-containing supplements
Atazanavir	Reyataz	Can be given without regard to food
Darunavir	Prezista	Take with a meal
Fosamprenavir	Agenerase	Can be given without regard to food
Indinavir	Crixivan	Administer 1 h before or 2 h after a meal with sufficient quantity of water
Lopinavir/ Ritonavir	Kaletra	Take with food
Nelfinavir	Viracept	Take with a meal
Ritonavir	Norvir	Can be given without regard to food; take with meals to prevent GI upset
Saquinavir	Invirase	Take with a high-fat meal
Saquinavir	Fortovase	Take with food
Tipranavir	Aptivus	Can be given without regard to food; avoid simultaneous Mg/Al-containing products

The relative bioavailability of amprenavir capsules has been assessed in the fed and fasting states in healthy subjects *(36)*. Subjects were given a single 1200-mg dose of amprenavir on an empty stomach or after ingestion of a standardized meal (967 kcal, 67 g fat, 58 g carbohydrate, 33 g protein). In the fed state, $C_{\max}$ and $T_{\max}$ were reduced by approximately 33%, while the AUC was reduced by approximately 27%. It is therefore recommended that amprenavir be administered with or without food, but that it should not be taken with a high-fat meal.

Each capsule of amprenavir contains 109 IU of vitamin E in the form of *d*-α tocopheryl polyethylene glycol 1000 succinate. The total amount of vitamin E in the recommended daily adult dose of amprenavir is 1744 IU (almost 1200 mg/day). It is therefore recommended that patients receiving amprenavir not take additional vitamin E supplements.

Fosamprenavir is the calcium phosphate ester prodrug of amprenavir, which is rapidly and almost completely hydrolyzed to amprenavir and inorganic phosphate by cellular phosphatases in the gut epithelium as it is absorbed. Fosamprenavir has been studied in both healthy adult volunteers and HIV-infected patients; no substantial differences in steady-state amprenavir concentrations were observed between the two populations. The $T_{\max}$ amprenavir concentration after administration of a single dose of fosamprenavir occurred between 1.5–4 h (median, 2.5 h). The absolute oral bioavailability of amprenavir after administration of fosamprenavir has not been established *(37)*.

In a fasted state, administration of single, 1400-mg doses using the fosamprenavir 50 mg/mL suspension and of the 700-mg tablet provided similar amprenavir AUC exposures, although the $C_{\max}$ of amprenavir increased 14.5% with administration of the suspension compared with the tablet *(37)*.

3.3.2. Atazanavir

Atazanavir is rapidly absorbed, with a median $T_{\max}$ of approximately 2.5 h in healthy people and 2 h in HIV-infected individuals. Administration with food enhances bioavailability and reduces pharmacokinetic variability. Administration of a single dose of 400-mg atazanavir with a light meal resulted in a 70% increase in the AUC and a 57% increase in $C_{\max}$ relative to the fasting state, while administration with a high-fat meal resulted in a mean increase in AUC of 35% and no change in $C_{\max}$ relative to the fasting state. Administration with either a light or high-fat meal decreases the coefficient of variation of AUC and $C_{\max}$ by approximately one-half, compared to the fasting state *(38)*.

3.3.3. Darunavir

The absolute oral bioavailability of a single 600-mg dose of darunavir alone and after coadministration with ritonavir 100 mg twice daily was 37 and 82%, respectively. Darunavir coadministered with ritonavir 100 mg twice daily was absorbed following oral administration with a $T_{\max}$ of approximately 2.5–4 h. When administered with food, the $C_{\max}$ and AUC of darunavir coadministered with ritonavir are approximately 30% greater than in the fasting state. Therefore, darunavir coadministered with ritonavir should always be taken with food. Within the range of meals studied, darunavir exposure is similar *(39)*. In a study of 119 HIV-infected patients, the mean 12-h AUC was 61,668 ng·h/mL with darunavir 600 mg and ritonavir 100 mg twice-daily dosing.

3.3.4. Indinavir

Indinavir is rapidly absorbed in the fasted state with a time to serum peak concentration of 0.8 h, with an oral bioavailability of approximately 65% *(40)*. Indinavir was administered to 10 subjects ingesting a high-fat/high-calorie (784 kcal, 48.6 g fat, 31.3 g protein) meal *(41)*. In the fed state, the AUC of indinavir was reduced by approximately 77% and the $C_{\max}$ was reduced by 84%. A similar study in 12 subjects was performed to investigate the impact of a "light meal" *(40)*.

Subjects ingested a meal including dry toast with jelly, apple juice, and coffee with skim milk and sugar, or a meal of corn flakes, skim milk, and sugar. This meal type had little or no change in the AUC, $C_{\max}$, or trough concentrations of indinavir. It is recommended that indinavir be taken 1 h before or 2 h after meals. If GI upset occurs, indinavir may be administered with skim milk or a light/low-fat meal as described earlier.

The impact of grapefruit juice on indinavir pharmacokinetics was also studied *(40)*. A single 400-mg dose of indinavir was administered with or without 8 oz of grapefruit juice. The addition of grapefruit juice resulted in a reduction of indinavir AUC by approximately 26%. It is recommended that patients avoid taking indinavir with grapefruit juice.

Indinavir was studied in eight HIV-negative volunteers to determine the impact of the dietary supplement St. John's wort (*Hypericum perforatum*, standardized to 0.3% hypericin) on indinavir levels *(42)*. Patients received 800 mg of indinavir every 8 h for four doses prior to and at the end of a 14-day course of St. John's wort 300 mg three times per day. Indinavir concentrations were determined following the fourth dose of indinavir prior to and following St. John's wort. Following the course of St. John's wort, the AUC of indinavir was decreased by 57% and the $C_{\min}$ was decreased by 81%. It is therefore recommended that indinavir not be administered concomitantly with St. John's wort.

A known adverse effect of indinavir is nephrolithiasis. The stones that form in the kidney consist of indinavir crystals which form because indinavir is poorly soluble *(40,41)*. To minimize this adverse effect, it is recommended that indinavir be taken with at least 32 oz of water daily.

3.3.5. LOPINAVIR/RITONAVIR

The oral bioavailability of the combination product Kaletra® in humans has not been determined. In HIV-infected patients with no meal restrictions, Kaletra® 400 mg/100 mg at steady state had a $T_{\max}$ of approximately 4 h *(43)*. Under nonfasting conditions (500 kcal, 25% fat), lopinavir concentrations were similar following administration of capsules or liquid. Under fasting conditions, the AUC and $C_{\max}$ of lopinavir were 22% lower for the liquid relative to the capsule formulation.

A single dose of 400 mg/100 mg of Kaletra® capsule was studied when given with a moderate fat meal (500–682 kcal, 23–25% fat) *(43)*. The AUC of lopinavir was increased by 48% and the $C_{\max}$ was increased by 23% relative to the fasting state. For the oral solution, the corresponding increases in lopinavir AUC and $C_{\max}$ were 80 and 54%, respectively. Relative to fasting, administration of Kaletra® with a high-fat meal (872 kcal, 56% fat) increased the lopinavir AUC and $C_{\max}$ by 97 and 43%, respectively, for capsules, and 130 and 56%, respectively, for the oral solution *(43)*. It is recommended that Kaletra® be administered with food to enhance bioavailability and minimize pharmacokinetic variability.

3.3.6. NELFINAVIR

After oral administration of 750 mg (three 250 mg tablets) three times daily in 11 HIV-infected patients for 28 days, or 1250 mg twice daily in 10 HIV-infected patients, oral bioavailability has ranged from 20 to 80% *(44)*. The effect of food was evaluated in two studies (14 subjects) *(44)*. The meals contained 517–759 kcal (153–313 kcal derived from fat). Maximal plasma concentrations and the AUC of nelfinavir were two to threefold higher under fed conditions compared to fasting.

In healthy volunteers, a newly approved 625 mg tablet was not bioequivalent to the 250 mg tablet. Under fasted conditions in 27 subjects, the AUC and $C_{\max}$ were 34 and 24% higher, respectively, for the 625 mg tablet. In a relative bioavailability study under fed conditions in 28 subjects, the AUC was 24% higher for the 625 mg tablet, whereas the $C_{\max}$ was comparable for both formulations *(44)*.

It is recommended that nelfinavir should be taken with food to maximize bioavailability. Patients unable to swallow the tablets may dissolve the tablets in a small amount of water. Once dissolved, patients should mix the cloudy liquid well and consume it immediately. The glass should be rinsed with water and swallowed to ensure that the entire dose has been consumed *(44)*.

3.3.7. RITONAVIR

The absolute oral bioavailability of ritonavir in humans has not been determined. After administration of a 600-mg dose of the oral solution under fed (514 kcal, 9% fat, 79% carbohydrate, 12% protein) and fasting conditions, the $T_{\max}$ was 4 and 2 h, respectively. When the oral solution was given under nonfasting conditions, peak ritonavir concentrations were reduced by 23% and the AUC was reduced by 7% relative to fasting. A single 600-mg dose of the soft gelatin capsule (57 patients) and oral solution (18 patients) under nonfasting conditions (615 kcal, 14.5% fat, 76% carbohydrate, 9% protein) was evaluated in two separate studies *(45)*. Relative to the fasting condition, the extent of absorption (i.e., AUC) of the soft gelatin capsule was 13% higher in the fed state, whereas it was slightly reduced with the oral solution. These changes have been considered clinically not significant and, therefore, it is recommended that ritonavir be administered with or without food.

It is important to note that GI adverse reactions are quite common following the administration of ritonavir and that patients can take ritonavir with food to minimize these effects. These adverse effects are particularly troublesome with the oral solution. To remedy this, ritonavir oral solution has been studied when diluted with 240 mL of chocolate milk, or the enteral nutrition products Advera® or Ensure® *(45)*. Dilution occurred within 1 h of administration and did not significantly effect the rate or extent of absorption.

3.3.8. SAQUINAVIR

Saquinavir was originally introduced as a hard gelatin capsule (Invirase®). This formulation had an absolute oral bioavailability of approximately 4% following a high-fat breakfast (1006 kcal, 57 g fat, 60 g carbohydrate, 48 g protein) *(46,47)*. Additionally, the administration of grapefruit juice in eight healthy subjects has been shown to increase the bioavailability up to twofold *(48)*. Invirase® is currently most commonly administered in combination with ritonavir. When done so, it can be administered without regard to food *(5,46)*. If Invirase® is administered as the sole PI, it is recommended that it be administered with a high-fat meal to enhance bioavailability.

More recently, a soft gelatin capsule formulation (Fortovase®) has been introduced to improve on the poor bioavailability of the Invirase® formulation. The absolute oral bioavailability of saquinavir administered as Fortovase® has not been assessed. However, following single 600-mg doses, the relative bioavailability of saquinavir as Fortovase® compared to Invirase® was estimated to be 331% *(49)*. The effect of food on Fortovase® was evaluated in 12 healthy subjects receiving a single 800-mg dose with breakfast (1006 kcal, 57 g fat, 60 g carbohydrate, 48 g protein) *(49)*. The AUC in the fed state was increased approximately 6.7-fold. It is recommended that Fortovase® be administered with food.

3.3.9. TIPRANAVIR

Absorption of tipranavir in humans is limited, although no absolute quantification of absorption is available *(50)*. To achieve effective plasma concentrations on a twice-daily dosing regimen, tipranavir must be coadministered with 200 mg of ritonavir. In a dose-ranging evaluation in 113 HIV-uninfected volunteers (men and women), there was a 29-fold increase in the geometric mean morning steady state trough plasma concentrations of tipranavir after coadministration with ritonavir twice daily as compared with administration of twice-daily tipranavir alone. Bioavailability of tipranavir is increased when taken with a high-fat meal.

Antacids reduce absorption of tipranavir, requiring timing adjustments of antacid use. When tipranavir (coadministered with ritonavir) was given with 20 mL of aluminum- and magnesium-based liquid antacid, tipranavir AUC, $C_{\max}$, and serum concentration at 12 h after dosing were reduced by 25–29%. Consideration should be given to separating tipranavir with ritonavir dosing from antacid administration to prevent reduced absorption of tipranavir *(50)*.

3.4. Newer Antiretroviral Agents (Table 4)

3.4.1. MARAVIROC

Maraviroc is a chemokine receptor antagonist that acts as an entry inhibitor. It is designed to prevent HIV infection of CD4 cells by blocking chemokine receptor 5 (CCR5), a co-receptor necessary for HIV entry, from binding the virus. Peak plasma concentrations of maraviroc are achieved between 0.5 and 4 h after single

Table 4
Other Antiretroviral Agents: Recommendations for Coadministration with Food

Generic name	*Brand name*	*Current recommendation*
Maraviroc	Selzentry	Can be given without regard to food; caution with high-fat meals
Raltegravir	Isentress	Can be given without regard to food

oral doses of maraviroc 1200 mg in healthy volunteers. Maraviroc pharmacokinetics are not dose proportional. The absolute bioavailability of a 100-mg dose is 23% and is predicted to be 33% after a 300-mg dose *(51)*.

In a small, Phase I study, 24 HIV-infected adults with CCR5-tropic HIV were randomized to receive maraviroc 25 mg once daily, 100 mg twice daily, or placebo. Steady-state drug levels were reached within 7 days, with more favorable drug levels achieved in the fasted state. Coadministration of a 300 mg maraviroc tablet and a high-fat meal resulted in reduced $C_{\max}$ and AUC by 33% each in healthy volunteers. However, because no food restrictions were enacted during clinical trials, maraviroc may be taken with or without food *(51)*.

3.4.2. Raltegravir

Raltegravir inhibits the catalytic activity of HIV-1 integrase, an HIV-1-encoded enzyme required for viral replication. Inhibition of integrase prevents covalent insertion of unintegrated, linear HIV-1 DNA into the host cell genome, therefore preventing the formation of HIV-1 provirus.

Administration of raltegravir following a high-fat meal increased the raltegravir AUC by approximately 19% *(52)*. A high-fat meal slowed the rate of absorption, resulting in an approximately 34% decrease in the $C_{\max}$, an 8.5-fold increase in the plasma concentration at 12 h, and a delay in the $T_{\max}$ following a single 400-mg dose. The effect of consumption of a range of food types on steady-state pharmacokinetics is not known. Raltegravir was administered without regard to food in pivotal safety and efficacy studies in HIV-1-infected patients. Raltegravir is absorbed with a $T_{\max}$ of approximately 3 h post-dose in the fasted state *(52)*.

3.5. Alternative Therapies

Complementary and alternative therapies are commonly used by patients with HIV infection. As mentioned previously, St. John's wort has been shown to decrease the AUC of indinavir by 57% and the $C_{\min}$ by 81% *(42)*. As these decreases are likely to be clinically significant, the use of St. John's wort should be avoided in patients receiving PI therapy *(5)*. Garlic ingestion in two patients on ritonavir has been reported to result in severe GI symptoms *(53)*. The mechanism has not been fully elucidated, and no evaluation of this interaction at steady state is currently available. The effect of coadministration of garlic with saquinavir has been evaluated more formally in 10 healthy subjects *(54)*. Volunteers received 1200 mg of Fortovase® three times daily with meals for three 4-day study periods. During the second 4-day period, subjects received garlic capsules twice daily. In the presence of garlic, the mean saquinavir AUC decreased by 51%, the trough level decreased by 49%, and the mean $C_{\max}$ decreased by 54%. After a 10 day washout, the AUC, trough, and $C_{\max}$ values returned to 60–70% of their baseline. The use of ethanol in combination with didanosine can increase the risk of pancreatitis and should be avoided *(5,11)*. Anecdotal reports of recreational drug use in HIV-infected patients and its impact on antiretroviral disease and/or HIV disease progression and adverse events continue to appear. Table 5 summarizes current reports *(55,56)*.

Table 5
Interactions of Antiretroviral Agents with Substances of Abuse

Agent	*Comments*
γ-Hydroxy-butyrate (GHB, liquid XTC)	May result in increased levels and prolonged effect; avoid use in patients on non-nucleoside reverse transcriptase or protease inhibitors
Amyl nitrate	Can cause glutathione depletion in the liver; associated with increased disease progression
Ketamine	Use with ritonavir has been associated with an increased incidence of hepatitis
Alcohol	Increased risk of pancreatitis in patients taking didanosine
Methylenedioxymethamphetamine (MDMA, Ecstasy)	Possible increased levels with protease inhibitors; one death reported (ritonavir)

Future studies are needed to address this growing area in much greater detail. In the meantime, clinicians must include alternative therapies and recreational drugs as part of the assessment of a patient's medication history.

3.6. Metabolic Impact of the Treatment of HIV Infection – Beyond the Food Effect

As new, more effective therapies have been developed for the treatment of HIV infection, patients are living longer lives. As patients' lives have been extended, the use of antiretroviral agents has been prolonged for many in significant numbers of patients. As a result of this improvement in the care for and outcomes in patients with HIV infection, a variety of new adverse effects associated with both HIV disease and its treatment have been documented. In particular and germane to this text, a variety of metabolic complications have been identified in patients taking long-term antiretroviral therapy. These include fat accumulation, lipoatrophy, disorders of lipid and glucose metabolism, hyperlactatemia and lactic acidosis, and bone disorders.

3.6.1. Fat Accumulation

A variety of syndromes of fat accumulation have been documented in patients with HIV infection *(5)*. These include obesity, enlarged dorsocervical fat pad (buffalo hump), and, less commonly, benign symmetric lipomatosis. In addition, breast enlargement has been reported in women, and gynecomastia in men. Syndromes of fat accumulation have been noted both in the presence and in the absence of lipoatrophy.

Because recognition of abnormal fat accumulation coincided with the widespread use of PIs, many people initially assumed that these changes were directly related to this class of drugs. It is now widely recognized that these changes occur in PI-naïve patients and terms such as "protease paunch" have been removed from the lexicon used to describe these conditions. The specific roles of PIs and

NNRTIs in the development of these syndromes have not been defined, and it is evident that host factors such as age, baseline fat content and body mass index, race, gender, and HIV-specific factors also affect the risk for developing these syndromes *(57)*.

Cross-sectional studies in HIV-infected subjects with increased abdominal girth have demonstrated marked accumulation of visceral or intra-abdominal fat tissue (VAT) *(57)*. This is of concern as excess VAT is associated with increased risk of coronary artery disease, type 2 diabetes mellitus, cerebrovascular disease, gallstones, and in women, breast cancer. Additionally, visceral adiposity can be a factor in the development of metabolic syndromes characterized by glucose intolerance, hyperinsulinemia with insulin resistance, dyslipidemia, and hypertension *(57)*. The degree to which these are associated with low levels of adiponectin is not clear.

Although no specific treatment is approved for fat accumulation in HIV-infected patients, the following modalities have been studied with varying degrees of success: antiretroviral therapy switching, diet and exercise, metformin, thiazolidinediones, growth hormone, and liposuction.

3.6.2. Lipoatrophy

Peripheral fat wasting in patients with HIV infection treated with antiretroviral therapy has emerged as a distressing complication that threatens long-term treatment of the virus. Cross-sectional studies have reported prevalence rates that range from 25 to 60% *(58)*.

The etiology of adipose tissue loss is unclear. Currently available information suggests that the development of lipoatrophy is influenced by both the use of antiretroviral therapy and a variety of host factors including age, race, and degree of immunosuppression *(58)*. Both PIs and NRTIs are likely to play a role in the pathogenesis of lipoatrophy. Interestingly, antiretroviral therapy consisting exclusively of PIs appears to have a minimal tendency toward the development of lipoatrophy *(58)*. The risk of development of lipoatrophy is, however, dramatically increased when NRTIs and PIs are used in combination.

Currently there are no proven therapies known to reverse or prevent peripheral lipoatrophy associated with HIV infection. Approaches that have been considered include antiretroviral switching, the use of thiazolidinediones, antioxidants, and cosmetic surgery.

3.6.3. Lipid Abnormalities

Elevations of serum triglycerides and low-density lipoprotein cholesterol (LDL-C) with decreases in high-density lipoprotein cholesterol (HDL-C) have been observed in patients with HIV infection receiving antiretroviral therapy *(5)*. Both HIV infection (low HDL-C and elevated triglycerides) and PIs (elevated total and LDL-C and triglycerides) are important underlying causes of dyslipidemia in HIV-infected patients *(45)*. The use of NNRTIs will increase total cholesterol and LDL-C, but this may be offset by increases in HDL-C *(59)*.

It is recommended that a fasting lipid profile be performed prior to initiating antiretroviral therapy. It should consist of total cholesterol, HDL-C, triglycerides, and a calculated LDL-C. A repeat fasting profile should be obtained approximately 3 months after initiating antiretroviral therapy. If this remains normal, yearly repeats are recommended.

The decision to intervene for lipid abnormalities is a complex one that must take into account the patient's general condition, prognosis, and the presence or absence of significant cardiovascular risk factors. The following interventions are recommended *(59)*: (a) evaluate for potential exacerbating factors such as hypogonadism, hypothyroidism, liver disease, or alcohol abuse; (b) perform a cardiovascular risk assessment per the Adult Treatment Panel III guidelines; (c) encourage therapeutic lifestyle modification; and for patients who continue to be at significantly increased risk of cardiovascular disease despite the above, clinicians should consider substituting a non-PI-containing regimen and/or instituting a lipid-lowering agent.

3.6.4. Disorders of Glucose Metabolism

Prior to the availability of potent antiretroviral therapy, insulin resistance and diabetes were relatively uncommon in HIV-infected patients. Although fasting glucose levels remain normal in most patients receiving potent antiretroviral therapy, up to 40% of patients on a PI-containing regimen will have impaired glucose tolerance due to significant insulin resistance *(5,60)*.

Indinavir may induce insulin resistance by inhibiting cellular glucose uptake through interfering with the cellular glucose transporter GLUT-4 and/or inhibiting peroxisome proliferator-activated receptor γ (PPAR-γ) expression *(60)*. Whether all drugs in this class induce such changes remains uncertain, and the relative tendency of the different PIs to induce insulin resistance is unknown.

Fasting glucose should be obtained prior to and during antiretroviral treatment (3–6 months after initiating therapy and annually thereafter) with a PI-containing regimen. Because of a paucity of data regarding the treatment of diabetes during HIV infection, established guidelines for treating diabetes mellitus in the general population should be followed. In specific, when drug therapy for diabetes is required, consideration should be given to using an insulin-sensitizing agent such as metformin or a thiazolidinedione as first-line therapy *(60)*. Careful monitoring for potential adverse effects such as liver dysfunction and lactic acidemia is recommended.

Consideration should be given to avoiding the use of a PI as initial therapy or to substitute alternatives to the PIs if possible in patients with preexisting abnormalities of glucose metabolism or who have risk factors for diabetes mellitus. Substitution of the PI component of a regimen with nevirapine, efavirenz, or abacavir has been associated with short-term improvements in insulin resistance and may be considered where virologically appropriate *(5)*.

3.6.5. Hyperlactatemia and Lactic Acidosis

Hyperlactatemia and lactic acidosis have been observed in HIV-infected patients receiving antiretroviral therapy *(5)*. The spectrum of disease ranges from mild to moderate asymptomatic (subclinical) hyperlacatatemia to fulminant and life-threatening lactic acidosis. Fortunately, symptomatic hyperlactatemia is uncommon and life-threatening lactic acidosis is even more rare.

Asymptomatic and subclinical hyperlactatemia has been observed in 10–36% of cohorts of HIV-infected patients examined *(61)*. Evidence suggests that exposure to one or more NRTIs plays a central role through toxic effects on mitochondrial function *(61)*. It remains unclear what other factors may be involved in the pathogenesis of this disorder.

Interventions that should be considered for symptomatic hyperlactatemia and lactic acidosis include *(61)* (a) discontinuation of current antiretroviral regimen or switching to a NRTI-sparing regimen and (b) addition of any or all of the following: thiamin, riboflavin, L-carnitine, coenzyme-Q-10, vitamin C, vitamin E, and/or vitamin A. It should be noted that the use of these nutrients is based on case reports rather than prospective intervention trials. More generally, the administration of micronutrient supplements along with antiretroviral therapy may have biochemical and clinical benefits although these have not been well studied and the risk for harm may exist *(62)*.

3.6.6. Bone Disorders

Alterations in bone mineralization and development of avascular necrosis (AVN) have been reported to be more prevalent in HIV-infected persons than in non-HIV-infected persons *(5)*. Although vitamin D status is poor in young adults with HIV infection, it does not seem to be an influence of the infection *(63)*. The specific contributions of antiretroviral agents and HIV infection to osteopenia, osteoporosis, and AVN are not well defined. Patients on potent antiretroviral therapy regardless of drug class have higher rates of osteopenia and osteoporosis than treatment-naïve patients *(64)*. The link between AVN and antiretroviral therapy is weaker. AVN has been frequently reported in HIV-infected patients not receiving antiretrovirals and has been associated with low CD4+ cell counts, duration of HIV infection, and prior corticosteroid treatment.

The safety and efficacy of standard therapies used to treat bone demineralization have not been evaluated in HIV-infected patients. The following are recommended based on results obtained in non-HIV-infected individuals *(65)*. Lifestyle modification including weight loss and exercise should be attempted prior to considering drug therapy. The use of specific drug therapy including calcium and vitamin D supplementation, bisphosphonates (once vitamin D status is normalized), estrogen or selective estrogen receptor modulators, calcitonin, and teriparatide may be considered. Currently, no specific recommendation exists regarding changing antiretroviral therapy as no drug or drug class has been specifically associated with alteration in bone metabolism.

4. DRUG–NUTRIENT INTERACTIONS FOR MEDICATIONS USED TO TREAT *M. TUBERCULOSIS* INFECTION

The management of tuberculosis has long been a difficult clinical problem, as the causative agent is a slow-growing organism and effective therapy requires the use of multiple agents for extended periods of time. As with the treatment of HIV infection, alterations in one's lifestyle to accommodate drug therapy for a prolonged period of time add to the complexity of achieving optimal patient adherence. Given that pulmonary tuberculosis is transmitted via droplet nuclei that are aerosolized when an infected patient coughs, the public health impact of treatment failure, especially owing to a modifiable risk such as a drug–nutrient interaction, is unacceptable. Clinicians and patients alike need to be keenly aware of the food effect on the bioavailability of these agents (Table 6).

Table 6
Medications for the Treatment of Tuberculosis: Recommendations for Coadministration with Food and Antacids

Generic name	*Brand name*	*Current recommendation*
Aminosalicylic acid	Paser	Administer with a mildly acidic beverage or food such as orange, apple, or tomato juice, yogurt, or apple sauce; avoid antacids if possible
Cycloserine	Seromycin	Do not administer with food
Ethambutol	Myambutol	May be administered with or without food; avoid administration with an antacid
Ethionamide	Trecator	May be administered with or without food or an antacid; avoid excessive ethanol intake
Isoniazid	Nydrazid	Administer on an empty stomach and avoid antacids
Pyrazinamide	Pyrazinamide	May be administered without regard to food
Rifabutin	Mycobutin	May be administered with food; avoid antacids
Rifampin	Rifadin	May be administered with food; avoid antacids
Rifapentine	Priftin	May be administered with food; if taking concomitant antacid therapy, take rifapentine 1 h before or 2 h after antacid ingestion

4.1. Aminosalicylic Acid Granules

Aminosalicylic acid is commercially available in a granule formulation. The granules are designed for gradual release so as to avoid high peak levels that may cause toxicity. Aminosalicylic acid is rapidly degraded in acid media. After 2 h in simulated gastric fluid, 10% of unprotected aminosalicylic acid is decarboxylated to form meta-aminophenol, a known hepatotoxin *(66)*. The small granules are designed to escape the usual restriction on gastric emptying of large particles. Under neutral conditions such as those found in the small intestine or in neutral foods, the acid-resistant coating is dissolved within 1 min. The protective acid-resistant outer coating is rapidly dissolved in a neutral media so a mildly acidic food such as orange, apple, or tomato juice, yogurt, or apple sauce should be used to enhance the oral bioavailability *(66,67)*. In a single-dose (4 g) pharmacokinetic study with food in healthy subjects, the median time to peak serum levels was 6 h (range 45 min to 24 h) *(66,67)*. Patients who have neutralized gastric acid with antacids will not need to protect the acid-resistant coating with an acidic food, but the administration of an antacid is not necessary to achieve good absorption. It is also important to note that the granules are made of a soft skeleton and these may appear in the stool of patients *(66)*.

4.2. *Cycloserine*

Cycloserine is well absorbed after oral administration, with a T_{max} of 2–4 h *(68)*. The coadministration of cycloserine with food results in a 16% reduction in the C_{max} but no change in the AUC *(67,69)*. Preliminary data suggest that administration with a high-fat meal reduces the C_{max} by 31%, whereas administration with orange juice reduces the C_{max} by 20% *(67)*. The impact of antacid administration on cycloserine is also minimal *(67)*. It is recommended that cycloserine administration be without food if possible.

4.3. *Ethambutol*

Ethambutol is rapidly absorbed following oral administration with a T_{max} of 2–3 h and an approximate bioavailability of 80% *(70)*. Two separate studies have evaluated the impact of food on ethambutol *(67,69)*. The impact of a "standardized breakfast" on the mean AUC in 11 healthy subjects was minimal *(71)*. The coadministration of a high-fat meal in 14 healthy subjects (men and women) showed a delay in the time to peak serum levels, a decrease in the C_{max} by 16%, but little effect on the extent of absorption (i.e., AUC) *(72)*. The administration of an antacid is associated with a 28% decrease in C_{max} and a 10% decrease in the AUC of ethambutol *(72)*. It is therefore recommended that ethambutol be administered with or without food, but that it should not be administered with an antacid.

4.4. *Ethionamide*

Ethionamide is essentially completely absorbed following oral administration (approximately 80%) *(68,73)*. There appears to be no affect of the administration of ethionamide with a high-fat meal or an antacid on C_{max} or AUC *(67)*. Ethionamide can be administered without regard to food or an antacid. Excessive ethanol intake should be avoided as psychotic reactions have been reported *(74)*.

4.5. *Isoniazid*

Isoniazid is well absorbed following oral dosing, with the T_{max} of 1–2 h *(68)*. There are conflicting data regarding the impact of food on the bioavailability of isoniazid. In one study, the C_{max} and AUC of isoniazid were decreased by 70 and 40%, respectively, in the presence of food *(75)*. A more recent study in 14 healthy volunteers evaluated the impact of a high-fat breakfast on the absorption of isoniazid *(76)*. The high-fat meal reduced the C_{max} by 51%, increased the T_{max} twofold, and reduced the AUC by 12%. Additionally, data conflict with regard to antacid administration. A decrease ranging from 0 to 19% in the AUC has been reported *(76)*. The current recommendation is that isoniazid be administered on an empty stomach and that whenever possible, coadministration with an antacid should be avoided.

4.6. Pyrazinamide

Pyrazinamide absorption takes place in 1–2 h and appears to be complete *(69)*. The effect of a high-fat meal or an antacid on the bioavailability of pyrazinamide has been evaluated in 14 healthy volunteers *(77)*. Neither the high-fat meal nor the antacid had a significant effect on the extent of absorption. As a result, pyrazinamide may be administered without regard to meals.

4.7. Rifabutin

Following a single dose of 300 mg to nine healthy subjects, the drug was readily absorbed, with a T_{max} of 3.3 h *(78)*. The bioavailability of the capsule formulation, relative to an oral solution, was 85% in 12 healthy subjects *(78)*.

The effect of a high-fat meal was studied in 12 healthy men *(79)*. Although the time to maximal peak levels was prolonged from 3 to 5.4 h, relative to the fasting condition, there was no significant impact on the extent of absorption. The effect of an antacid on rifabutin has not been studied. The impact of the buffered didanosine formulation has been evaluated and this has shown no effect on rifabutin absorption *(67)*. Rifabutin may be given with food, but coadministration with an antacid should be avoided until it is specifically studied.

4.8. Rifampin

Rifampin is well absorbed from the GI tract, with a T_{max} of approximately 2 h (range 2–4 h) *(68,80)*. Rifampin is better absorbed in an acidic environment than in a neutral or alkaline one. The administration of a high-fat meal with rifampin has been evaluated in 14 healthy subjects *(81)*. The addition of a high-fat meal reduced the C_{max} by 36% and the AUC by 6%. The administration of an aluminum/magnesium-containing antacid had no effect on the bioavailability of rifampin *(81)*. It is recommended that rifampin be taken on an empty stomach whenever possible to minimize any potential decrease in absorption.

4.9. Rifapentine

The absolute bioavailability of rifapentine has not been determined. The relative bioavailability (with an oral solution as a relevance of rifapentine) after a single 600-mg dose to healthy adult volunteers was 70% *(82)*. The maximum concentrations were achieved from 5 to 6 h after administration of the 600-mg rifapentine dose. Food (850 kcal, 55 g fat, 58 g carbohydrate, 33 g protein) increased $AUC_{0–24\ h}$ and C_{max} by 43 and 44%, respectively, over that observed when administered under fasting conditions.

5. DRUG–NUTRIENT INTERACTIONS FOR MEDICATIONS USED TO TREAT CHRONIC VIRAL HEPATITIS

Chronic viral hepatitis is commonly caused by the hepatitis C virus (most common) or by the hepatitis B virus. Major advances in the pharmacological management of these diseases continue to be introduced. For hepatitis B virus, the introduction of oral therapies including lamivudine (discussed in Section 3.1) and adefovir has enabled patients to achieve improved therapeutic outcomes as compared to using injectable interferon therapy. For hepatitis C virus, the use of combination therapy with interferon plus oral ribavirin has dramatically improved the responsiveness of this difficult to treat disease. Given that these advances in therapy are administered orally, the potential for drug–food interactions is discussed (Table 7).

Table 7
Medications for the Treatment of Chronic Hepatitis: Recommendations for Coadministration with Food

Generic name	*Brand name*	*Current recommendation*
Adefovir	Hespera	Administer without regard to food
Ribavirin	Virazole	Administer with food

5.1. Adefovir

Adefovir is available as a diester prodrug. Oral bioavailability is approximately 59%, with a $T_{\max}$ that ranges from 0.58 to 4 h. When coadministered with food (1000 kcal high-fat meal) there was no affect on the pharmacokinetics of adefovir *(83)*. It is therefore recommended that adefovir be administered without regard to food.

5.2. Ribavirin

Ribavirin when administered orally is quickly absorbed through the concentrative nucleoside transporter (CNT2; SLC28A2), with a $T_{\max}$ of approximately 2 h. When coadministered with a high-fat meal, the rate of absorption was slowed ($T_{\max}$ 4 h), but the AUC was increased by 42% and the $C_{\max}$ was increased by 66% *(84)*. As bioavailability is enhanced in the presence of food, it is recommended that ribavirin be administered consistently with food. A recent study suggests that a high purine-containing meal significantly reduces ribavirin bioavailability *(85)*.

6. CONCLUSION

The impact of food on the absorption of drugs significantly complicates the treatment of any chronic disease. Increases in absorption may result in adverse reactions. Importantly, the impact on those with chronic infections differs from conditions such as hypertension and diabetes. Obviously, infections can be transmitted from one individual to another. So a decrease in absorption in treating an infection can lead to the development of a resistant infection. Subsequent spread of a resistant infection has significant public health ramifications.

Although many unanswered questions regarding drug–food interactions still exist, the information provided in this chapter should be used to educate healthcare professionals and patients to optimize patient outcome and minimize the development of drug-resistant infections. Older agents still in use were not subject to the more current, rigorous requirements of labeling and should be further investigated for interactions with food. Future studies are also needed to answer remaining questions about interactions between drugs used for chronic infections and food, alternative therapies, or illicit drugs.

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