1 An Introduction to Drug–Nutrient Interactions

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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 (Vd) (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, Vd 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 $\mu mol \cdot h \cdot L^{-1}$), followed by a lower exposure when administered one-half hour before either meal (1340 $\mu mol \cdot h \cdot L^{-1}$and 1320 $\mu mol \cdot h \cdot L^{-1}$), and it was lowest in the fasted state (1060 $\mu mol \cdot h \cdot L^{-1}$). 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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