RESEARCH
Review

Drug–Nutrient Interactions: A Broad View with Implications for Practice

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ABSTRACT

The relevance of drug–nutrient interactions in daily practice continues to grow with the widespread use of medication. Interactions can involve a single nutrient, multiple nutrients, food in general, or nutrition status. Mechanistically, drug–nutrient interactions occur because of altered intestinal transport and metabolism, or systemic distribution, metabolism and excretion, as well as additive or antagonistic effects. Optimal patient care includes identifying, evaluating, and managing these interactions. This task can be supported by a systematic approach for categorizing interactions and rating their clinical significance. This review provides such a broad framework using recent examples, as well as some classic drug–nutrient interactions. Pertinent definitions are presented, as is a suggested approach for clinicians. This important and expanding subject will benefit tremendously from further clinician involvement.
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THE WIDESPREAD USE OF PATENT MEDICINES ALONG with the broad variability in nutrition status, dietary habits, food composition, and dietary supplement use, set the stage for an infinite number of potential drug–nutrient interactions (DNIs). Although the number of interactions and permutations may seem overwhelming, and the proportion that is clinically significant is not clear, clinicians should not discount the relevance of DNIs to their practice.

For many years, the potential for interaction between drug therapy and nutrition was scarcely mentioned in topical publications (1,2). This began to shift with isolated reports—now considered classic findings—such as the influence of vitamin C deficiency on barbiturate action (3), the influence of isoniazid on vitamin B-6 metabolism (4), and the influence of iron on tetracycline absorption (5). There were also classic reviews on the impact of malnutrition on drug metabolism (6), the effect of food on drug absorption (7), and the influence of drugs on nutrient disposition (8). By then, the most clinically recognized DNIs were the result of intraluminal interactions between drugs (eg, levodopa, tetracycline) and food (7). For a time, DNIs were synonymous with drug–food interactions. It took a few more years to broaden the perception of DNIs among clinicians (9-12). Updates often repeated the same lists of examples without always putting them into clinical or mechanistic perspective. Much of this historic view has been described elsewhere (13). More contemporary reviews and compilations of DNIs have reframed the subject, allowing for a more systematic approach to identifying and evaluating them (14-17). Despite some advances in recognizing DNIs and understanding some of the mechanisms, data on how best to manage individual DNIs still remain inadequate at this time.

This article provides the contemporary framework for viewing and evaluating DNIs. Illustrative of the need for such a model of DNIs is the difficulty in easily locating the literature on the topic. A quick Medline search of the term *drug–nutrient interaction* yields only about 20 articles (compared with approximately 1,000 articles for the term *drug–drug interaction*); search results that do not reflect the broad nature of the subject. A more deliberate search requires that dozens of additional terms be used in an attempt to gather relevant DNI articles. Each individual nutrient, food, food group, nutrition status term, nutrient biomarker, drug, and drug biomarker, among other terms need to be sought with a keen eye toward potential DNIs in studies, case reports, laboratory findings, animal studies, or in vitro tissue or cellular findings. Such a search was conducted for this article and yielded several hundred papers when limited to the previous year. As this is not intended to be a systematic review of the available literature, the article includes select recent examples that represent each class of DNI that will be introduced to the reader in subsequent sections. Most of the examples included are human data, with passing reference to in vitro/animal data. As becomes apparent from a search for *drug–nutrient interaction*, one of the limitations is in the definition of the term.

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Bioavailability—the extent to which an administered drug becomes biologically available in the systemic circulation

Clearance—a pharmacokinetic expression to define the elimination of a substance (due to metabolism and/or excretion) from the body as a volume of a compartment per unit of time (mL/min or L/h)

Cytochrome P450—an enzyme system responsible for metabolizing a wide range of substances; often abbreviated as CYP and followed by a description of the isoenzyme family, subfamily, and number (eg, CYP3A4)

Disposition (of a drug or nutrient)—the physiologic absorption, distribution, and elimination (ie, metabolism and/or excretion)

Effect (of a drug or nutrient)—the physiologic action of a substance at a cellular or subcellular target

Enzyme—complex proteins that catalyze chemical reactions, biotransforming the ligand into one or more metabolites which may be physiologically active; drug metabolizing reactions are classified as Phase I (oxidation) or Phase II (conjugation)

Gene Polymorphism—the presence of alternate nucleotide sequences for a gene in a population subset, thereby coding for an alternate expression of the protein

Malnutrition—general term for "poor nutrition status," which refers to nutrient intake out of balance with requirements; it can refer to underweight, overweight or obesity, and altered states of metabolism, as well as specific nutrient imbalances; best identified by a thorough nutrition assessment

Object (of interaction)—the influenced party or "victim" of an interaction

Pharmaceutic—the term relating to physical and chemical properties of drug molecules, as well as the design and evaluation of drug delivery systems/dosage forms, and the monitoring of drug disposition following administration

Pharmacodynamic—the term relating to the influence of the administered drug on the body, organ, or tissue

Pharmacokinetic—the term relating to the influence of the body on an administered drug

Precipitating Factor (of interaction)—the initiating factor or "perpetrator" of an interaction

Physicochemical—pertaining to physical and chemical properties of a substance (eg, drug or nutrient)

Receptor—a protein that serves as a reactive site of attachment with some degree of affinity for a ligand (eg, drug or nutrient)

Transporter—a membrane-embedded protein responsible for moving a substrate (drug or nutrient) from one side of the membrane to the other; can be "active" requiring energy as adenosine triphosphate (ATP) (ie, ATP-binding cassette [ABC] superfamily; for example, P-glycoprotein) or not (ie, solute carrier [SLC] superfamily; for example, organic anion transporting polypeptides [OATP] and peptide transporters [PepT])

Volume of Distribution—a pharmacokinetic expression to define the theoretical body volume that a drug distributes to after absorption; this is based on a substance's unique distribution and binding throughout the body as determined by both physiologic factors and substance-related factors and described as a volume per unit of body weight (L/kg)

Figure 1. Glossary of terms relevant to drug−nutrient interactions.

Definitions and Framework

The working definition of a DNI used here is broader than often described. 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 nutrition status (15). An interaction is considered to be clinically significant if it alters therapeutic drug response or compromises nutrition status resulting in some degree of malnutrition. The clinical consequences of an interaction are related to alterations in the disposition and effect of the drug or nutrient. As used here, 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 cellular level. Nutrition status is considered optimal when nutrient requirements are balanced by nutrient intake to maintain a healthy body composition and function (see Figure 1 for a glossary of the terms presented in italics throughout this section).

Based on the definition provided, DNIs can be classified into one of five distinct groups (Figure 2) (15). The many known DNIs can then be categorized, with each having an identified *precipitating factor* ("perpetrator") and an *object of the interaction* ("victim"). In some cases the drug is the precipitating factor (eg, causing changes to nutrition status); while in others the drug is the object of the interaction (ie, changes in drug disposition result from a nutrient, food, or nutrition status). DNIs are clinically important if the precipitating factor produces significant change to the object of the interaction based on some measureable physiologic criteria. Therefore, significant interactions that need to be totally avoided are not that common, instead, close monitoring with modification to the regimens are often all that is necessary. A list of DNIs should generate a question about the mechanism behind each one.

Precipitating Factor	Object of the Interaction	Potential Consequence	Examples (3-7,18-39)
Nutrition status	Drug	Treatment failure or drug toxicity	**Obesity** causes lower ertapenem concentration following a standard dose, but toxicity of acyclovir following a usual dose **Vitamin C** deficiency prolongs pentobarbital action
Food or food component	Drug	Treatment failure or drug toxicity	**Enteral nutrition** formula impairs absorption of ciprofloxacin **Food** can interfere with levodopa and alendronate absorption, but improves absorption of deferasirox and of gabapentin-enacarbil **Grapefruit juice** increases nilotinib bioavailability and simvastatin toxicity
Specific nutrient or other dietary supplement ingredient	Drug	Treatment failure or drug toxicity	**Iron** sulfate reduces doxycycline concentration when taken together **Vitamin C** may reduce fluconazole activity **Vitamin D** reduces atorvastatin concentration **Daidzein** increases bioavailability and reduces clearance of theophylline
Drug	Nutrition status	Altered nutrition status	**Capecitabine** may cause hypertriglyceridemia Low dose **quetiapine** causes significant weight gain **Sorafenib** is associated with sarcopenia
Drug	Specific nutrient	Altered nutrient status	**Carbamazepine** lowers vitamin D and biotin status **Ezetimibe** reduces vitamin E absorption **Isoniazid** impairs vitamin B-6 status **Ribavirin** plus **peginterferon-α2b** impairs vitamin B-12 status

Figure 2. Classification of drug−nutrient interactions (15).

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

Figure 3. Location and mechanisms of drug−nutrient interactions (14). [a]Consequence to the drug and/or nutrient.

The character of any interaction and its mechanism may be further classified to help in predicting and preventing their occurrence (Figure 3) (14). Mechanisms of an interaction relate to the *physicochemical* attributes of the medication and of the food or nutrient, within the environmental matrix (eg, gastrointestinal lumen, systemic tissue). The consequence of an interaction (ie, altered disposition of a drug or nutrient) is linked to its location. For example, at the gastrointestinal epithelia, an influence on membrane transporters and/or metabolizing enzymes can alter the *bioavailability* of a drug or nutrient.

DNIs can be mechanistically viewed in *pharmaceutic*, *pharmacodynamic*, and *pharmacokinetic* terms (Figure 4). Pharmaceutical interactions involve physicochemical reactions that take place in a delivery device (eg, enteral feeding tube) or within the gastrointestinal lumen. These can influence the bioavailability of a drug or nutrient. For example, ciprofloxacin bioavailability can be significantly reduced as a result of chelation in the presence of enteral nutrition formula (20).

Pharmacodynamic interactions involve the clinical effect of a drug or the physiologic effect of a nutrient. Qualitative or quantitative biomarker measures of drug action or of nutrition status help to define pharmacodynamic interactions. These interactions can be antagonistic (eg, warfarin with vitamin K, reduces international normalized ratio) or additive in effect (eg, warfarin with vitamin E, increases bleeding risk) (40).

Pharmacokinetic interactions are best defined by changes in relevant parameters (eg, bioavailability, *volume of distribution*, *clearance*). A substantial increase or decrease in bioavailability or clearance is likely to be clinically relevant. These interactions can involve *transporters* and *enzymes* that are important for drug absorption, distribution, or elimination. Nutrients can also serve as substrates for many of these same

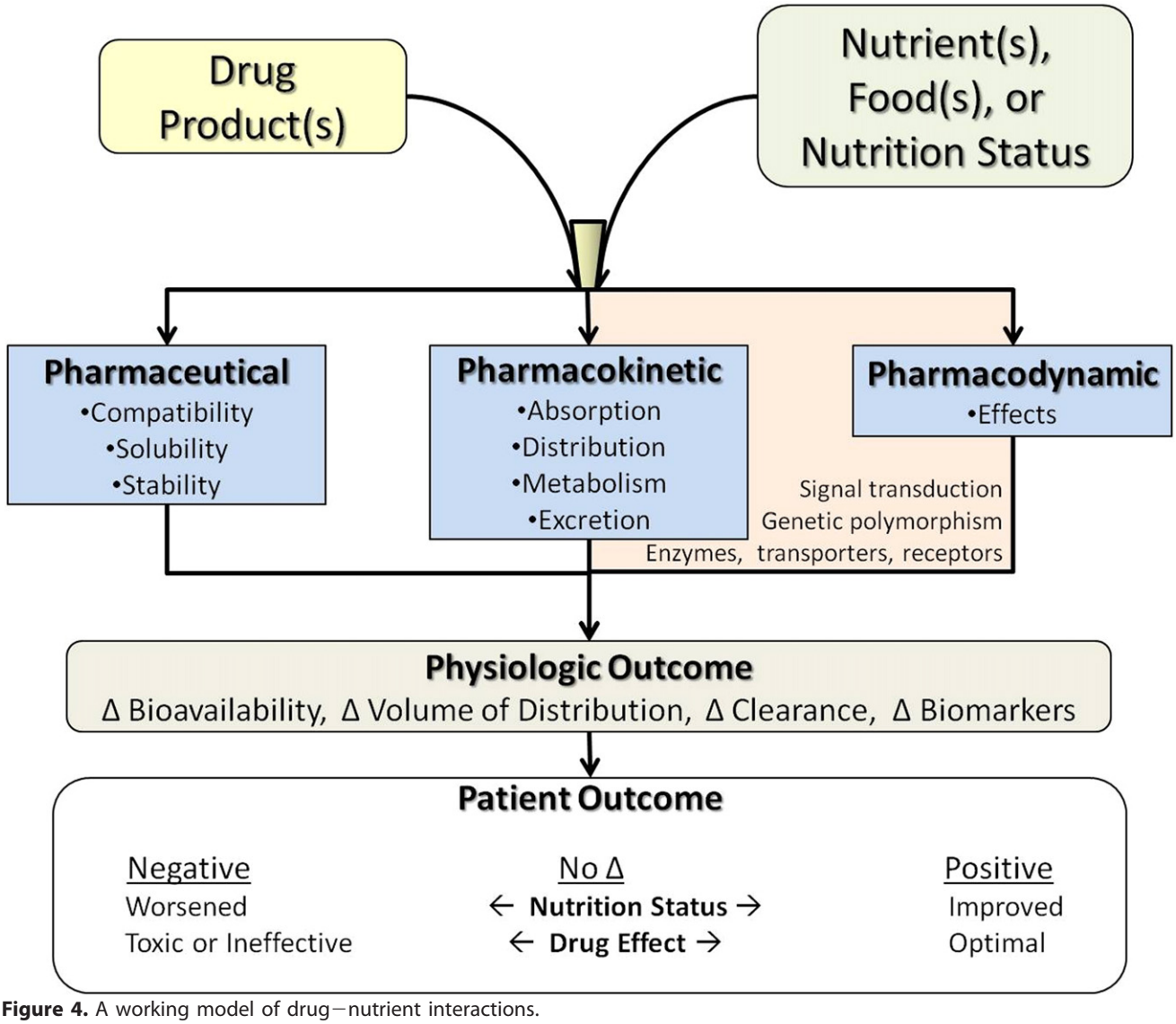

Figure 4. A working model of drug–nutrient interactions.

enzymes and transporters setting up the potential for interaction. Each physiologic transporter and enzyme is a protein coded for by a gene; some of which are polymorphic. Transporters include those proteins responsible for influx to or efflux from cells; they are embedded in cell membranes with differing tissue localization throughout the body (40-42). There is currently a greater awareness of the gastrointestinal distribution of transporters influenced by nutrients and disease states (43,44).

Enzymes include those responsible for "phase I" oxidation reactions, such as the *cytochrome P450* (CYP) group of enzymes, and "phase II" conjugation reactions, such as UDP-glucuronosyl transferases. Drugs and nutrients can influence signal transduction pathways that ultimately impact on drug transporters and metabolizing enzymes through receptor-mediated gene expression (45,46). The genetic expression of many metabolizing enzymes and some transporters is under the regulation of transcription factors such as pregnane X receptor (PXR). A number of drugs (eg, amlodipine, beclomethasone, megestrol, testosterone) can activate PXR, which induces several CYP isoenzymes responsible for metabolizing many drugs and some nutrients (47,48). Other substances (eg, bergamottin found in grapefruit juice) may also influence PXR (47). As more of the substances that can activate PXR are identified, their potential involvement in drug interactions, including DNIs, can be better predicted and prevented (47). As more is learned generally about specific drugs that serve as substrate, inducer, or inhibitor of various transporters and enzymes in different tissues, the more likely that direct or indirect interaction with nutrients that influence these same proteins can be determined or predicted (49).

Although the term *DNI* often carries a negative connotation, some interactions can be considered positive in effect (50-57). Positive or negative, DNIs have erroneously been considered less relevant than drug–drug interactions; a comparison of views is interesting. Although not the case initially, interactions between one drug and another have

long been recognized as influencing patient outcomes through altered drug disposition and effect. Drug interactions contribute to adverse drug effects, leading to hospitalizations and even to withdrawal of approved drugs from the market (58,59). An evaluation of a proprietary database (MarketScan Database, Thomson Medstat, Ann Arbor, MI) containing almost 20 million patients suggests that nearly 250,000 adverse drug reactions occurred during a 4-year period (60). Although nutritional disease ranked in the top five comorbid conditions among hospitalized patients in this cohort, the proportion of these adverse reactions that can be defined as DNIs has not yet been determined. The science of describing drug–drug interactions has evolved considerably, to the point where they are widely recognized, identified, and managed in practice (61). In part, this is supported by the drug development and approval process. Conversely, the recognition of DNIs' importance to practice has grown much slower. The US Food and Drug Administration (FDA) does not include an evaluation of DNIs in its guidance process for drug development (62,63). This guidance document (62) does provide criteria on determining the significance of an interaction (ie, degree of change in biomarker or parameter) so it could be applied to DNIs. The magnitude of change in a given parameter will reflect the severity or clinical relevance of an interaction after taking any confounding patient and drug factors into consideration. For example, the influence of a nutrient on strength of an interaction could be based on the degree to which drug exposure (ie, bioavailability) and/or clearance is influenced. It is not easy to predict the clinical relevance of drug interactions that are identified from in vitro, in vivo, or in silico models (64). However, in the meantime, the role of clinical observation and documentation is vital. The responsible clinician is at the forefront of elevating the prominence of DNIs, as was the case early on with drug–drug interactions. What follows is a description of each class of DNI as a means to further lay out the framework for the clinician. Thereafter, a description of clinicians' roles is provided.

Influence of Nutrition Status on Drugs

Differences in drug disposition in special patient populations usually focus on those with renal impairment, hepatic dysfunction, or unique life-stage attributes. Pharmacokinetic and pharmacodynamic data are much less frequently assessed based on nutrition status (eg, protein-calorie malnutrition, obesity, micronutrient deficits), although the influence on drug metabolism has been recognized previously (6,65-67). Drug distribution and drug clearance are the two parameters most likely to be influenced by malnutrition, with the potential—if not recognized and addressed by modifying the initial dose or maintenance dose, respectively—to alter clinical response (68,69).

Drug manufacturer product labeling is rarely adequate in guidance for dosing medication in obese or underweight patients (70). The appropriate dosing regimen for even commonly used drugs (eg, heparin) is not always clear (71,72). Much attention has been given to antimicrobials in obesity, given the morbidity/mortality risk from infection if not accounting for altered drug distribution or drug clearance (73). A recent study of 839 hospital admissions identified that obese patients are at substantially greater risk for errors with weight-based drug dosing, although clinical outcomes were not described (74). One unfortunate aspect of weight-based dosing in practice is the use of empiric "ideal" body weight equations (75,76), or the incorporation of these tenuous values into an "adjusted" body weight equation. In the latter equation, the correction factor used is rarely drug-specific (69). An evidence-based estimate of lean body weight is suggested as a more appropriate metric in determining dosing weight for obese patients (69,77,78). The direction and magnitude of change in volume of distribution or clearance of a drug is unique to the drug and cannot be generalized across all drugs based simply on the presence of obesity or protein-calorie malnutrition. It is recognized that additional data are still needed to recommend more optimal drug dosing schemes for patients with poor nutrition status (69).

Food Effect on Drugs

Food in General. Oral drug administration concurrent with a meal alters the physicochemical conditions within the gastrointestinal tract, and may influence the rate and/or extent of drug absorption. A change in the extent of absorption is more clinically significant than a change in the rate of absorption because it influences bioavailability and varies with drug properties and meal characteristics (79). The FDA-recommended test meal contains about 800 to 1,000 kcal, with about 50% of calories as fat (eg, two eggs fried in butter, two strips of bacon, two slices of buttered toast, 4 oz hash brown potatoes, and 8 oz whole milk) (80). The rationale is that such a meal will create the greatest perturbation on gastrointestinal physiology and be reflected in a meal's influence on drug bioavailability. However, this FDA test meal is not always used in food-effect bioavailability studies. This can create some confusion in the literature if one study using a less extreme meal results in no marked change, while another study using the FDA test meal finds a substantial change in drug bioavailability. Therefore, it is important to note the test meal conditions used in a study before making a clinical recommendation.

In the time since the FDA provided their guidance, the ability to predict the influence of food on drug disposition has become more grounded in science (81). Data generated in vitro can often predict drug disposition and food effects using the Biopharmaceutics Classification System (81-84). There are four Biopharmaceutics Classification System classes based on drug solubility and intestinal permeability. Class II drugs have low solubility but high permeability and are expected—more than drugs in the other three classes—to have an enhanced extent of absorption when administered with food. When examined in a clinical study, the magnitude of change in bioavailability will determine how clinically significant the difference is between the fed and fasted states. On the other hand, food will impair the absorption of drugs with poor permeability, despite adequate solubility (ie, Biopharmaceutics Classification System Class III).

Specific Foods or Food Components. Specific foods can also have a unique influence on drug disposition. In vitro and in vivo studies help to tease apart possible mechanisms of

these interactions. Dietary proteins as well as protein supplements have been known to increase drug metabolism (85). Protein sources (eg, soy protein isolate, casein) may have differential effects on drug disposition through induction of enzymes and transporters (86). Several juices can interact with medication by altering transporters and metabolizing enzymes to a wider degree than initially described (87,88). Grapefruit juice was the first identified, but others have also been shown to interact with medication based on furanocoumarin and flavonoid content (24,89). Furanocoumarins appear to inhibit intestinal CYP3A isoenzymes, thereby increasing oral drug bioavailability, but can also interfere with transporters. The influence on drug transporters and metabolizing enzymes from consuming juices from pureed fruits and vegetables remains unknown, despite recognition of the many phytochemicals they contain. Among the many different constituents of common berries, the anthocyanins and anthocyanidins interact with a CYP isoenzyme and transporter in vitro (90-92). The higher concentrations of isolated flavonoids and other phytochemicals found in dietary supplement products may be more cause for concern in terms of DNIs as well as toxicity (93). Their potential to interact with drug substrate of these enzymes and transporters may be greater.

Effect of Specific Nutrients or Dietary Supplement Ingredients

In one of the few areas for which DNI prevalence data exist, an estimated 12% to 45% of individuals using dietary supplement products with prescription drugs are at risk for interaction, with 6% to 29% considered potentially serious or clinically significant (94-97). This is noteworthy, given that approximately 53% to 73% of adults use dietary supplements regularly, according to nationally representative surveys (98,99). Data are available and continually evolving on drug interactions associated with individual dietary supplement ingredients; nutrients and non-nutrients alike (40,96,100,101). The use of herbal medicine ingredients (eg, ginseng, Echinacea) in dietary supplement products can substantially alter the effects of a drug by influencing transporters and/or enzymes (102). A review of the interaction potential for herbals with cardiovascular agents reveals the paucity of data on product safety and suggests the need for clinical trials specifically designed to identify them (103).

Not much attention is given to the interactions that can occur between dietary supplements and therapeutic nutrient dosing. For example, the intestinal transport of zinc can be significantly reduced by thiamin, riboflavin, and pyridoxine, but improved by nicotinic acid, based on an in vitro study (104). Thiamin and folic acid transport can be reduced by polyphenols (105). As mentioned previously, many of the dietary polyphenols and other phytochemicals increasingly found in supplement products are substrates for—or influence expression and activity of—transporters and drug metabolizing enzymes (106-114). For example, soy isoflavones (eg, daidzein, genistein) can substantially upregulate two drug transporters and five enzymes (27,115). Even specific probiotic strains can play a role in altering transporter function responsible for drug and nutrient absorption (116). Cautious interpretation and extrapolation from in vitro and in vivo data are necessary until more human data become available.

Influence of Drugs on Global Nutrition Status

Food Intake and Absorption. The influence of medication on overall nutrition status can be multifactorial (117,118). Drugs can influence food intake, digestion, and absorption. Many drugs are responsible for influencing food intake through effects on the gastrointestinal tract and/or central mechanisms. The mechanism for the sensitivity of gastrointestinal function to drugs has received less attention (119). When substantial, disturbances to gastrointestinal function (eg, taste disorder, xerostomia, stomatitis, nausea, vomiting, diarrhea) can impair an individual's ability to maintain or improve their nutrition status (118). Even the odor of a dosage form can contribute to reduced intake (120). Alternatively, indirect effects on food intake (eg, impaired ability to gather, prepare, ingest) can occur as a result of drug-induced cognitive disturbances, visual changes, movement disorders, and gait abnormalities, when severe (121,122).

Macronutrient Metabolism. Medication may also be associated with altered metabolic function. Metabolic adverse effects (eg, weight gain, hyperglycemia, dyslipidemia) have been documented. The influence of some antipsychotic drugs on weight gain has been well-described (123,124). Weight gain, hyperglycemia, and dyslipidemia have been associated in particular with use of second-generation antipsychotics (eg, olanzapine, quetiapine, risperidone) (29,123,125). Pharmacoepidemiologic data suggest that there is no predictable difference between first- and second-generation antispychotics in resultant diabetes (126). Weight loss can also be attributed to medication, for example, those drugs with appetite-suppressant properties (122).

Influence of Drugs on Specific Nutrients

The influence of drugs on the status of a specific nutrient can also be multifactorial (117). Drugs can influence nutrient absorption, distribution, metabolism, and excretion. The clinical significance of changes in nutrient status as a result of drug use is based in part on the relevance of individual biomarkers. The magnitude of change in the biomarker will also be important; the clinical manifestations are as much patient-specific as drug-specific. Developing an overt classic nutrient deficiency syndrome is considered an extremely rare consequence of an interaction. Instead, some lesser degree of deficit may be associated with clinical manifestations. This highlights the value of routine nutritionally focused history-taking and physical examinations.

The concept that some adverse drug effects are directly related to their influence on nutrient status is not new. 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 (35-37). A number of the antiepileptic medications adversely affect vitamin D metabolism and bone health (127). This has been better described with the older agents (eg, carbamazepine, phenobarbital, phenytoin) than the newer ones (31-34). Valproic acid treatment is associated with carnitine deficiency and altered acylcarnitine subspecies that reflect impaired intermediary metabolism likely re-

sponsible for drug-induced hepatotoxicity and hyperammonemia (128,129). The influence on the status of a nutrient in these circumstances may or may not be adequately addressed by nutrient supplementation while the patient is taking the drug (51,130,131). This is an area requiring more investigation to support recommendations for prophylactic nutrient supplementation. Conversely, there are some medication regimens that are associated with improvements in nutrient status (132,133).

In order for clinicians to recognize, identify, prevent, or manage DNIs that have the potential to influence patient outcomes, a more systematic approach is necessary. Their efforts will benefit from the definitions, classification schemes, and examples presented here.

Clinician's Role

To optimize a patient's clinical outcomes, it is important to recognize DNIs systematically as part of the patient assessment process or the drug regimen review. This requires an overall level of awareness of the DNI framework beyond a handful of isolated examples. By broadening the understanding of the potential mechanisms of interaction, the clinician can become more proactive in anticipating potential interactions. Some clinicians may view specific interactions (eg, calcium-containing food products and ciprofloxacin; tyramine-containing foods with monoamine oxidase inhibitors) as individual pieces of information but not recognize how each fits into the larger classification system. Understanding the physiology of nutrient disposition and status, and the steps in drug disposition are important to gaining a more comprehensive appreciation of DNIs. For example, if a new class of drugs is discovered to cross membranes using one of the folic acid transporters, the potential for interaction is recognized. This will support the clinician in evaluating patients for potential interactions and in making the most appropriate clinical evaluation and intervention. The clinician will always be prepared to ask: Is the patient's presentation (change in nutrition status or unexpected drug effect) related to an interaction? This question should remain high on the differential.

Clinicians should have access to interaction information that allows for safe treatment approaches. DNI resources are varied and continually evolving in terms of depth, breadth, and accessibility. Generally, drug product information is not considered an optimal resource for information on DNIs (134). Because of limited clinical DNI data generated as part of the drug development process, much is explored in post-marketing observational studies, or from individual case reports generated by clinicians, with subsequent mechanistic investigations and descriptions when novel interactions are identified. Even some drug–drug interactions are only recognized with widespread use after marketing so clinicians should remain just as vigilant for DNIs. Despite limitations in available data, there is an expectation that clinicians in health care systems or organizations identify and address DNIs (135).

Institutional Approach. The Joint Commission standards for patient care and for medication management are broad-based, integrated, and less prescriptive than in the past (135). Although there are no longer specific standards that address DNIs, several standards relating to patient assessment, patient care plans, medication order review, safe medication administration, patient monitoring, and patient education in a collaborative fashion would be interpreted to include a system for DNI identification and management. An element of performance for standard MM.05.01.01 indicates that all medication orders are reviewed for "existing or potential interactions between the medication ordered and food and medications the patient is currently taking" (135). Although narrow in scope, it does suggest that an organization perform this evaluation. The National Patient Safety Goals include one goal to reduce the harm associated with the use of anticoagulation therapy (136). An associated element of performance describes the use of authoritative resources to manage potential food interactions for patients receiving warfarin, regardless of care setting, and another element stresses providing education that includes drug–food interactions.

A coordinated interdisciplinary team-based system that includes registered dietitians, nurses, pharmacists, and physicians is considered critical to managing patients with the potential for DNIs (137,138). One approach is for a subcommittee of the Pharmacy and Therapeutics committee to develop and maintain policies and procedures on DNIs. This interdisciplinary group would determine which high-risk medications or high-risk patients to target for DNI monitoring. Procedures for identifying patients with a potential DNI, complete with assigned responsibilities and documentation of each intervention, would be critical. Decision support systems integrated into an institution's rules-based informatics systems can also be valuable. Periodic review of the policy, procedure, and interventions by the Pharmacy and Therapeutics committee would allow any necessary feedback.

DNIs can influence health outcomes particularly in vulnerable populations (139). When they occur, adverse consequences of DNIs (eg, decreased efficacy, increased toxicity, altered nutrition status) do not discriminate by health care setting. Special attention is given to patients at greatest risk for interactions regardless of the practice setting. The prevalence of medication use in the elderly increases the risk for adverse drug effects and DNIs (140,141). In addition to the elderly, obese, critically ill, transplant recipients, patients receiving enteral or parenteral nutrition, and patients with chronic disease who use multiple medications can be considered high risk. Some of the high-risk medications include antiepileptics, antimicrobials, and warfarin. A focus on commonly used chronic medications, especially those with a narrow range between efficacy and toxicity (eg, phenytoin, warfarin) and those with active metabolites makes practical sense. Individuals with known genetic variants in drug transporters, enzymes, or receptors may also be at higher risk.

Patient Approach. In practice, DNIs can best be identified as part of a thorough assessment of a patient's history and physical examination. A nutritionally focused history and physical examination is important to allow for identification of potential nutrient deficits, which can still occur even in high-risk groups using nutrient supplementation (142). Patient management will be based on the severity of the presenting DNI or

the risk potential for an interaction. In some cases, close monitoring of the patient is all that is required, in others the regimen needs to be adjusted (ie, altering drug timing with respect to meals, change drug dose, or add a nutrient supplement).

If the therapeutic outcome of a drug regimen is different than expected, the clinician could consider within the context of their overall nutrition assessment whether this outcome is related to the patient's nutrition status, dietary habits, or specific nutrient or other dietary supplement intake. Similarly, if a change to a patient's overall nutrition status or to the status of a specific nutrient or biomarker occurs, the contribution of the drug regimen could be considered within their overall assessment. Clinicians are encouraged to identify, document, and report DNIs through institutional committees, professional publications, the Institute for Safe Medication Practices, and the FDA. As with drug–drug interactions, the clinical significance and severity of DNIs can vary. The ability to assign causation in the case of a DNI is important. The drug interaction probability scale (143) was designed to assess the probability of a causal relationship between a drug interaction and an adverse event. Quick "yes" or "no" replies to each of 10 questions are scored (−2 to +2) and the scores totaled; the larger the value the higher the probability of an interaction. This scale has been used successfully by clinicians to evaluate and report DNIs (89,144-147).

The Case of Warfarin. Warfarin is a widely used anticoagulant that works by interfering with the vitamin K cycle. With a narrow therapeutic index, prothrombin time and international normalized ratio are used to closely monitor patients receiving this drug. Much has been made about the interaction between certain food (eg, enteral nutrition) or specific nutrients (eg, vitamin K) and warfarin. The ability to predict or avoid these interactions still might not guarantee optimal patient anticoagulation, given the large number of factors and interindividual variability involved in the disposition and effect of this drug (148). Warfarin dose requirements are significantly affected by *CYP2C9* and *VKORC1* genotype and age (149). CYP4F2 plays a lesser role in warfarin metabolism in some patients, which is also a critical enzyme for the metabolism of both vitamin K and vitamin E. DNIs are still significant at the level of intraindividual variability in response. A recent report describing the potential for an interaction between a dietary supplement beverage and warfarin attributes alterations in drug effect to vitamin K content (16 to 25 μg daily), glucosamine content, and n-3 fatty acid content (150). This product also contains a number of different juices that are high in flavonoid content and would also have the potential to interact—although prospective evaluation is still necessary. The purported interaction between cranberry juice and warfarin initially based on anecdotal reports has not been supported by mechanistic and prospective clinical trials (151-153). Concentrated extracts of cranberry taken in pharmaceutical dosage forms that contain high doses of flavonoids may interact with warfarin, although this occurred without altering pharmacokinetics or plasma protein binding (154). Garlic and ginger can decrease platelet aggregation, which might theoretically increase warfarin's bleeding risk, but no cases have been reported in the literature. However, bee pollen has been reported to substantially increase international normalized ratio, requiring drug dose reduction in a patient otherwise on a stable warfarin regimen (147). As always, close patient monitoring is vital.

CONCLUSIONS

Although broad, the topic of DNIs remains relevant to clinicians in practice. Patient care often includes an evaluation for DNIs. As the patient assessment becomes more systematic, it will not only improve recognition and management of expected interactions, but may allow for identification and reporting of previously unrecognized DNIs. The definition and classification scheme presented here can be helpful in organizing the known interactions, as well as categorizing new interactions as they are identified and reported by clinicians. Much more research of DNIs needs to be conducted, which will take the lead from clinicians' findings. As mechanisms are better identified for each interaction, management approaches for widely recognized DNIs can be offered and evaluated prospectively. Until DNIs are more formally recognized as part of drug development and regulation, the vital work of all clinicians and researchers with an interest in improving patient care will continue.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST

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