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## Commentary

# Drug and nutrition interactions: not just *food* for thought

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## SUMMARY

***What is known and objective:*** **The management of drug-drug interactions – from recognition of the interaction potential, to addressing the negative consequences – are well-recognized and avoided, or rapidly addressed when identified clinically. Drug-nutrition interactions are no less important than drug-drug interactions in patient care. Unfortunately, beyond those caused by food, these interactions are less commonly recognized or identified and managed. This article will re-introduce the topic of drug-nutrition interactions to clinicians.**
***Comment:*** **Although many clinicians are acutely aware of and vigilant for potential drug-drug interactions, most are less aware of the possibility of drug-nutrition interactions beyond classic food-drug interactions. Interaction can occur between a drug and a nutrient, multiple nutrients, food in general, specific foods or components, or nutrition status. An interaction is considered clinically significant if it alters therapeutic drug response and/or compromises nutrition status. Mechanistically the interactions may be physicochemical reactions, actions at membrane transporters or metabolizing enzymes, or an influence on physiologic function. Appreciating the many types of drug-nutrition interactions will aid the clinician and have the potential to influence patient outcome.**
***What is new and conclusion:*** **Ongoing advances in knowledge about drug and nutrition interactions have potential to improve patient care. Drug-nutrition interactions need to be better recognized, understood on a mechanistic basis, predicted, and managed as necessary.**

## WHAT IS KNOWN AND OBJECTIVE

The quote 'let food be thy medicine' as ascribed to Hippocrates is no less true today than it was when first spoken over 2 millennia ago. Although many observe this entreaty to limit their drug intake while selecting healthful foods, it bears appreciating that this practice does not negate the potential for interaction. This potential for interaction between food and medication (i.e. food–drug interactions) has been recognized for quite some time. However, although many clinicians have focused on food–drug interactions, the much wider concern for patients at risk of the more expansive sphere of drug and nutrition interactions is less well recognized. These drug–nutrition interactions are no less concerning than drug–drug interactions, in their ability to influence patient outcome. As such, they need to be better recognized, understood, predicted and then managed as necessary. This article will begin this process of reintroducing the topic of drug and nutrition interactions.

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## COMMENT

Drug–nutrition interactions result from physical, chemical, physiological or pathophysiological relationships not only between a drug and a nutrient but also between a drug and multiple nutrients, food in general, specific foods or components, or nutrition status.[1,2] The combined or reciprocal action of a drug with any of these other elements requires that one is a *precipitating factor to* and the other an *object of* the interaction. The precipitant may be any of these (i.e. drug, nutrient, multiple nutrients, food, food component or nutrition status). While some could therefore be subclassified as 'food–drug' interactions and others as 'drug–nutrition status' interactions, the common overarching term is drug and nutrition (drug–nutrition) interactions (see Table 1).[3–9]

Regardless of the precipitant or object, a drug–nutrition interaction is considered clinically significant if it alters therapeutic drug response and/or compromises nutrition status.[10] The severity of drug–nutrition interactions can vary in the same manner as do drug–drug interactions. Mechanistically, the interactions may be physicochemical reactions (i.e. pharmaceutical) or actions at membrane transporters or metabolizing enzymes (i.e. pharmacokinetic) or antagonistic, additive or synergistic on physiological function (i.e. pharmacodynamic). Alterations in drug (or nutrient) disposition and effect are the clinical consequence of the interaction. This drug–nutrition interaction framework has been described in further detail elsewhere.[10]

Some of the interactions described decades ago are often recognized in isolation rather than within the context of a drug–nutrition interaction classification scheme. Examples include the influence of isoniazid on vitamin $B_6$ metabolism[11] and the influence of iron on tetracycline absorption.[12] Additionally described have been the impact of malnutrition on drug metabolism[13] and the influence of drugs on nutrient disposition.[14] As mentioned earlier, the effects of food on drug absorption as a result of intraluminal interactions are often the most clinically recognized of the drug–nutrition interactions.[3] However, contemporary reviews have reframed the subject, allowing for a more systematic approach to identifying and evaluating all types of drug and nutrition interactions.[1,10,15,16] With ongoing advances in recognizing interactions, understanding their mechanisms and learning how best to manage individual interactions, patient care can be further improved.

**Table 1.** Categorizing drug and nutrition interactions[3–9]

| Precipitant | Object | Example |
|---|---|---|
| Food | Drug | Meals can interfere with levodopa absorption |
| Food component | Drug | Calcium reduces ciprofloxacin bioavailability |
| Specific nutrient | Drug | Vitamin D reduces atorvastatin concentrations |
| Nutrition status | Drug | Obesity results in lower ertapenem concentrations |
| Drug | Specific nutrient | Carbamazepine lowers biotin status |
| Drug | Nutrition status | Quetiapine causes significant weight gain |
| Drug | Metabolic status | Capecitabine may cause hypertriglyceridaemia |

### *Types of drug and nutrition interactions*

*Food* in general has been well established as influencing absorption and bioavailability of certain drugs.[3,17] Well-designed food-effect studies are especially valuable to the evaluation of each new oral medication. Although complex physicochemical mechanisms are in play, the low-solubility, high-permeability (i.e. BCS class II) drugs have an increased extent of absorption with food (e.g. carbamazepine), whereas the absorption of drugs with low permeability is often impaired by food (e.g. indinavir). Thus, knowing a drug's solubility and permeability characteristics may help predict its interaction with food.

Specific *food components* can also prompt changes in drug disposition, often through specific mechanisms. But in many cases, these too may be predicted based on known properties of each drug and mechanism of interaction. This can alleviate the need to memorize long lists of interactions. For example, fruit juices have the capacity to serve as the precipitating factor in interactions.[18] The end result, for example, with grapefruit juice, may be increased oral bioavailability (e.g. atorvastatin, sildenafil) or decreased bioavailability (e.g. etoposide, L-thyroxine).[19–22] This seeming dichotomy is explained by differential effects on metabolizing enzymes (i.e. CYP3A) and transporters (i.e. OATP1A2), respectively. In fact, the fruit juice effect through alterations in OATPs is a rapidly developing research area that will allow increased recognition and prediction of interactions in clinical practice.[23]

Beyond specific foods, certain individual *nutrients*, often found in supplemental doses, can also influence drug disposition. Up to 45% of patients using dietary supplements with prescription drugs are at risk of interaction, with as many as 29% considered clinically serious.[24–27] Non-nutrient supplements (e.g. dietary polyphenols, herbals) have also been implicated.[27–30] These compounds interact with drugs at the level of transporters and/or metabolizing enzymes.

The *nutrition status* of an individual, much like renal or hepatic function, is also a factor in drug disposition and effect. Drug distribution and clearance are the elements most influenced by poor nutrition status (e.g. protein–calorie malnutrition, obesity), with product labelling rarely adequate enough to guide dosing regimens in these patients.[31,32] Weight-based drug dosing regimens are not reflective of drug disposition in malnourished and obese patients.[31,33] This is further complicated when relying on body surface area or 'ideal' body weight rather than on more appropriate metrics for dosing medication.[31,34]

The precipitating factor of an interaction may also be the *drug* itself. The influence of medication on overall nutrition status (e.g. weight gain, weight loss), on metabolic status (e.g. hyperglycaemia, hypertriglyceridaemia) or on the status of specific nutrients (e.g. hypokalemia, zinc deficiency) can be multifactorial.[35,36] Through an effect on the gastrointestinal tract (i.e. taste disorders, stomatitis, nausea, vomiting, diarrhoea and malabsorption), many medications can impair a patient's overall nutrition status. Some medications may indirectly influence food intake by altering a patient's capacity to gather, prepare or ingest food. These may include drugs that cause severe cognitive disturbances, visual changes, movement disorders or gait abnormalities. Many of these are at play in the elderly in particular given their generally high use of medication.[37]

The absorption, distribution, metabolism and excretion of specific nutrients can also be influenced by *drugs*. When the detrimental effects on specific nutrients are acknowledged as significant, they may be addressed by supplementation (e.g. pyridoxine administered with isoniazid). Although overt classic nutrient deficiency syndromes are rarely seen, lesser degrees of deficit are still associated with clinical manifestations. In some cases, these nutrient deficits are already appreciated as adverse drug effects. For example, drug-induced osteomalacia (e.g. antiepileptic drugs) can be caused by drug influence on vitamin D metabolism.[38–40] Likewise, drug-induced hepatotoxicity and hyperammonaemia (e.g. valproic acid) may result from carnitine deficits.[41,42] Adverse drug effects explained by drug-induced nutrient deficits continue to be explored.

## WHAT IS NEW AND CONCLUSION

Drug and nutrition interactions, in the broadest sense, are starting to become better recognized and understood in clinical practice. In cases where enough data are available, they may be predicted and then appropriately managed. With ongoing advances, the expectation is that patient care can be further improved. Readers can look for review articles that will cover specific drug–nutrition interactions by medication category or clinical population in the months ahead.

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