American Society for Parenteral and Enteral Nutrition

Drug – Nutrient Interaction Section

Newsletter

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What constitutes functional foods?
(Le Trinh Thuy Tien - MD, MPH)

The term "functional foods" was coined in Japan in the early 1980s. Today, other definitions could overlap with functional foods such as medical foods, nutraceuticals, probiotics, designer foods, pharmafoods, and vitafoods. Although there is no internationally accepted definition of what constitutes functional foods, according to the International Food Information Council (IFIC) "functional foods" can be described as "foods or dietary components that may provide a health benefit beyond basic nutrition."[1] The development of functional foods has increasingly focused on the role of certain foods and food ingredients in helping to prevent and reduce the risk of diseases.[2]

In 1991, the Ministry of Health, Labour and Welfare (MHLW) in Japan was the first to use a more precise terminology for functional foods as Food for Specified Health Use (FOSHU). These were referred to as "foods containing ingredients with functions for health and officially approved to claim its physiological effects on the human body."[3] In Japan, to sell food as FOSHU, the assessment of the safety of the food and effectiveness of the "functions for health" is required and the MHLW must approve the claim.[3]

In 1998, the European Commission Concerted Action on Functional Food Science in Europe (FUFOSE) also stated the definition of functional foods as "foods satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either an improved state of health and well-being and/or reduction of risk of disease."[4] Following that outcome of the consortium, the FUFOSE classed functional foods as "not pills or capsules, must remain foods, and demonstrate effects in amounts that can normally be expected to be consumed in the diet".[4] In contrast, the FOSHU classification does not make a distinction in this way and therefore functional foods were also presented in the form of capsules and tablets.[3]

The American Dietetic Association published a statement in 2009 stating "all foods are defined as functional at some physiological level because they provide nutrients or other substances that furnish energy, sustain growth, or maintain/repair vital processes. However functional foods move beyond necessity to provide additional health benefits that may reduce disease risk and/or promote optimal health."[5] In addition, the State Food and Drugs Administration (SFDA) in China extended the old definition as "Health (functional) foods means that a food has special health functions or is able to supply vitamins or minerals. It is suitable for consumption by special groups of people and has the function of regulating human body functions, but it is not used for therapeutic purposes. And it will not cause any harm whether acute or subacute or chronic."[6]

In conclusion, functional foods typically must have some proven health benefits beyond basic nutritive value. From the wide range and varied definitions, the types of foods that may be considered as functional foods can be classified into three broad categories:[7]

- Whole foods or unmodified or conventional foods – the simplest forms of functional foods that naturally contain bioactive components
    - Many fruits and vegetables, grains, dairy products, fish, and meats will contain bioactive components that supply health benefits in addition to basic nutrition
    - For example: lycopene in tomatoes, ellagic acid in raspberries, beta-glucans in oat bran cereal, omega-3 fatty acids in oily fish, and calcium in dairy products

- Enhanced, enriched levels or fortified foods with bioactive components
    - For example: bread made with flour enriched with folate, calcium-fortified orange juice, tomatoes with a high level of lycopene
- Purified or isolated food ingredients
    - For example: omega-3 fatty acids extracted from oily fish, isoflavones isolated from soy

Health benefits of functional foods can range from effects of nutrient content to relationships between components in the diet and reduced risk of disease, supported by the scientifically evidence-based weight.[7]

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Drug Induced Nutrient Deficiency of the Month (Deficiency *du jour*)
Anti-Epileptic Medications and Nutrient Deficiencies

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According to the Centers for Disease Control and Prevention (CDC), there are more than 3.4 million people in the United States and 50 million people worldwide with epilepsy.[1,2] In the U.S., over 90% of patients with epilepsy are taking medication for this disease.[3] There are a plethora of agents that providers can choose from when treating an epileptic patient; however, many epileptic agents can cause depletion of critical nutrients. Are you aware of which anti-epileptic agents can cause nutrient depletions?

Drug Name(s)	**Fosphenytoin, Phenytoin**	**Valproic acid**	**Carbamazepine, Oxcarbazepine**	**Phenobarbital, Primidone**
Nutrient(s) Depleted	↑/↓ phosphate, vitamin D, calcium, biotin, folic acid, vitamin K, vitamin B12, thiamine, pyridoxine, selenium	Carnitine, folic acid, selenium,	Sodium, biotin, folic acid, pyridoxine, vitamin D, calcium	Biotin, calcium, folic acid, vitamin D, vitamin K, pyridoxine
Laboratory Test(s)	CMP, serum phosphorus, serum 25-hydroxy vitamin D, RBC folate, serum biotin, serum vitamin K, serum B_{12} or MMA, whole blood thiamine, serum pyridoxine, serum selenium,	Serum total and free carnitine, RBC folate, serum selenium	CMP, serum biotin, RBC folate, serum pyridoxine, serum 25-hydroxy vitamin D	CMP, serum biotin, RBC folate, serum 25-hydroxy vitamin D, serum vitamin K, serum pyridoxine
Reported Mechanism(s)/ Interaction(s)	• Fosphenytoin provides 0.0037 mMol phosphate/mg phenytoin sodium equivalents (PE)[4] • Chronic phenytoin therapy has been associated with decreased bone mineral density; it is hypothesized that phenytoin enhances the metabolism of vitamin D causing deficiency. Hypocalcemia and hypophosphatemia may also be seen.[5,6] • Fosphenytoin/Phenytoin may deplete biotin through competitive inhibition or inhibition of its transport in the intestine.[7-9] • Phenytoin may reduce the absorption of folic acid in the intestine, and/or accelerate its metabolism.[9-11]	• Long term administration of valproic acid has been associated with decreased carnitine levels. The exact mechanism has not been identified.[22-24] • Valproic acid inhibits glutamate formyltransferase resulting in a decrease in the formation of the active metabolite of folic acid.[23-25] • It is thought that valproic acid metabolism creates reactive metabolites which are dependent on selenium for neutralization and excretion.[14, 26]	• Hyponatremia associated with carbamazepine and oxcarbazepine therapy is frequently caused by syndrome of inappropriate antidiuretic hormone (SIADH). The risk of SIADH seems to be dose related.[30-32] • Carbamazepine reduces serum biotin levels and increases excretion of biotin metabolites. It is hypothesized that carbamazepine is a competitive inhibitor of biotin transportation in the intestine.[7-8, 14, 30] • Carbamazepine decreases the function of folate conjugate	• Phenobarbital reduces serum biotin levels and increases excretion of biotin metabolites.[7, 14, 30] • Phenobarbital decreases the function of folate conjugase through its induction of CYP450 enzymes leading to reduced folate absorption from food sources.[11, 38-39] • It is hypothesized that phenobarbital induction of CYP450 enzymes increases the metabolism of vitamin D into its inactive form leading to a reduction in calcium absorption from the GI tract.[11] • It is hypothesized that phenobarbital interferes with vitamin K metabolism. A correlation has also been found

	• Phenytoin interferes with vitamin K metabolism. A correlation has been found between vitamin K deficiency and neonates whose mother was on anticonvulsant therapy.[12-15] • Phenytoin may impair the uptake of Vitamin B_{12} by the hematopoietic and neural cells.[16-18] • There is an increased prevalence of thiamine deficiency in some patients taking phenytoin; however, the exact mechanism has not been identified.[14, 19-21] • Phenytoin/fosphenytoin may increase the breakdown of pyridoxine through induction of the metabolizing enzyme in the liver.[14, 21] • Phenytoin may increase the production of reactive oxygen species that deplete the stores of selenium.[14]		through its induction of CYP450 enzymes leading to reduced folate absorption from food sources.[11, 14, 31] • Carbamazepine increases the breakdown of pyridoxine by induction of the metabolizing enzyme.[14, 32] • It is hypothesized that carbamazepine induction of CYP450 enzymes increases the metabolism of vitamin D into its inactive form leading to a reduction in calcium absorption from the GI tract. [14, 33-37]	between vitamin K deficiency and neonates whose mother was on anticonvulsant therapy.[13, 15, 39] • Phenobarbital increases the breakdown of pyridoxine due to its induction of metabolizing enzymes.[11, 32] • Long term primidone has been associated with low serum biotin levels and increased excretion of organic acids. It is hypothesized that primidone may inhibit intestinal absorption, decrease renal reabsorption and increase biotin catabolism.[7-8] • Primidone might increase the metabolism of Vitamin D and decrease serum 25-hydroxy vitamin D. Decreased vitamin D levels can lead to impaired absorption of calcium.[14] • Though the mechanism is unknown, decreased folate levels have been observed in patients taking primidone.[11, 38-40]
Management	Monitor nutrient(s) levels especially in those at increased risk and consider supplementations as appropriate in deficient patients.			

CMP: Complete Metabolic Panel; RBC: red blood cell; MMA: methylmalonic acid

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FDA Evaluation of oral drugs via feeding tube

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The Food and Drugs Administration (FDA) released a document in June 2021, "*Oral Drug Products Administered Via Enteral Feeding Tube: in Vitro Testing and Labeling Recommendations Guidance for Industry*"

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/oral-drug-products-administered-enteral-feeding-tube-in-vitro-testing-and-labeling-recommendations

The change in FDA perspective to acknowledge the feeding tube route as an allowable and potentially exclusively available enteral route is a significant deviation from the past. Up until this point, few drugs have been evaluated for the feeding-tube route. Each ASPEN lecture that discussed the enteral options had to note the discussion of feeding-tube medications as a non-approved use.

Unfortunately, this guidance only applies to new drugs pursuing approval for the feeding-tube route. This document is created to provide guidance for what *in-vitro* testing should be done when a manufacturer is pursuing an indication that specifies the enteral feeding tube route in their labeling directions. The FDA notes a few drugs have already noted feeding tube route, but the methods used were inconsistent. The ones I have encountered, discuss only gastric delivery, and mostly from nasal entry.

Much of the document discusses the potential for feeding tube occlusion and gives a free pass to liquid medications with the assumption that liquid medications do not cause feeding tube occlusion. The FDA did not read the Cutie/Altman paper[1] that acid liquid medications such as Iron Sulfate syrup will form clogs when in contact with intact protein of enteral nutrition. The FDA probably didn't read Edes[2] where the sorbitol content of liquid medications given through feeding tubes was the issue in 40% of tube-fed patients with diarrhea. I wrote to the FDA to alert them to this oversight during the comment period for this guidance.

The FDA document discusses issues of tube length and materials used, as well as the potential for drug adhesion to the feeding tube material. This concept is often overlooked, as in the case with warfarin[3] which adheres to feeding tube material, whereas some authors assumed warfarin adherence to nutrition was responsible for changes in INR[4]. There has been suggestions that this also occurs with phenytoin[5] and amiodarone[6], although neither issue has been corroborated.

This guidance specifically does not include physical characteristics of enteral tubes (e.g., connector design), which are covered in the guidance for industry *Safety Considerations to Mitigate the Risks of Misconnections with Small-bore Connectors Intended for Enteral Applications* (February 2015), also known as ENFit connections. So, while this document will evaluate the potential for medication to cause occlusion of the feeding tube, the tests will use legacy catheter-based administration sets which, according to the Global Enteral Device Supplier Association (GEDSA), will be phased out soon.

https://stayconnected.org/wp-content/uploads/2020/09/200914_REVISED_ENFit%C2%AE_Connector_Conversion_Schedule_U.S._Canada_Legacy_Connector_Production-Phase_Out_Dates-1-1.pdf

The document includes drugs which are labeled for modified release to ensure when they are given through a feeding tube that their bioavailability matches the oral administration. This is surprising, since it is a general notion never to crush medication that have modified release[7] as there is too much potential to release a bolus dose, and/or clog the feeding tube with excipients. Another inconsistency in the

guidance is evaluation of enteric coating. Again, it is a general notion not to administer drugs with enteric coatings through a feeding tube, as per the Institute for Safe Medication Practices (ISMP):

https://www.ismp.org/resources/preventing-errors-when-administering-drugs-enteral-feeding-tube

The coatings will adhere and clog the feeding, or the acid labile drug would be exposed to gastric fluid.

The guidance recommends evaluation of dissolution in water at pH values of 5.5, 7.0, and 8.5. This conflicts with the FDA dissolution guidance which is conducted using simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 6.8).

https://www.fda.gov/media/70936/download#:~:text=To%20simulate%20intestinal%20fluid%20(SIF,should%20not%20exceed%20pH%208.0.

While there is mention of both gastric and jejunal types of feeding tubes, there is no mention of the expected difference in drug delivery when the distal site is used despite the significant difference in drug delivery at those two points.

There is also guidance for products which require preparation prior to administration through feeding tubes. The preparation should be tested for stability over 4 hours at room temperature and 24 hours stored at controlled refrigerated temperatures.

There are several other nuances that show that the FDA did not read ASPEN Safe Practices for Enteral Nutrition Therapy[8]. In any case, this is an improvement as new drugs and generics will now have specific feeding tube instructions that are FDA approved.

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