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COVER STORY

The Role of Nutraceuticals: What Pharmacists Need to Know in 2020

BY LUMA MUNJY, PHARMD

LUMA MUNJY, PHARMD

WHAT ARE NUTRACEUTICALS?

Nutraceuticals are commonly defined as any substance that is a food or part of a food which provides medicinal or health benefits, including the prevention and treatment of disease.[1] This term includes a broad array of agents such as dietary supplements, isolated nutrients, herbal supplements, and specific food products.[2] It is estimated that 77% of Americans use dietary supplements, including more than 70% of adults who are aged more than 60 years.[3,4] With an increase in use and variety of nutraceuticals, it is essential that pharmacists are made aware of the potential benefits and risks of the products that are available for consumer use.

MONITORING OF NUTRACEUTICAL PRODUCTS IN THE UNITED STATES

Monitoring of nutraceutical products differs from that of prescription drugs. Nutraceuticals are broadly regulated under the Federal Food, Drug and Cosmetic Act, with more specific regulation for dietary supplements, vitamins, and minerals, falling under the Dietary Supplement Health and Education Act of 1994 (DSHEA). Although the FDA oversees the manufacturing and distributing process of supplements, rigorous clinical trials and investigations of safety and efficacy are not required to market such products. Nutraceuticals are not intended, according to FDA standards, to prevent, treat, or cure disease.[5-7]

According to the DSHEA, manufacturers and distributors of dietary and herbal supplements must ensure the safety and accurate labeling of their products, to guarantee that they are not adulterated or misbranded.[7] If adulteration or misbranding is identified, the FDA is responsible for taking action to ensure safety and remove products from consumer use. For example, in March 2019, the FDA took action against foreign and domestic companies stating false claims for more than 50 supplement products alleging to prevent, cure, or treat Alzheimer disease.[8,9] To learn about the latest warnings and alerts regarding the safety of such products, pharmacists can refer to the FDA Dietary Supplement and Advisory List available on the FDA's website.[10]

In addition to FDA oversight, the official United States Pharmacopeia (USP) and the official National Formulary are considered national compendia in the United States, accepted as sources to provide official guidance. The USP sets quality standards for drug substances, drug products, excipients, and dietary supplements under federal law in the United States, and USP standards are considered binding under the Federal Food, Drug, and Cosmetic Act for any manufacturer claiming USP approval.[11-13] The 4 P's of quality that the USP provides are: **P**ositive identity, **P**otency, **P**urity, and **P**erformance of ingredients in a product.[14] Positive identity ensures the listed ingredients are present in the supplement and that

rigorous testing and auditing have been conducted for verification. Assessment of potency guarantees the listed ingredients are present in the stated amounts. Purity safeguards against harmful excipients and/or contaminants such as pesticides, mold, and active pharmaceutical agents, to name a few. Performance ensures the formulation will break down and release the appropriate ingredients, allowing absorption via the labeled route of administration.[14]

USP also provides standards for food ingredients under the umbrella of nutraceutical products. Pharmacists can refer to the Food Chemicals Codex monographs for references regarding assessment of food chemicals and additives.[12]

UNDERSTANDING NUTRACEUTICAL LABELS

Because the term *nutraceuticals* refers to both dietary supplements and food products, understanding label information is essential for providing appropriate consultations and prevention of potential harm to patients. Supplement labels provide information regarding suggested use, serving size, percent daily value of the active ingredients, and a list of inactive ingredients, as well as cautions and warnings. The manufacturer's address, lot number, and notice of potential allergens should also be present. It is important to note that only the potency of the active ingredients is listed on the product label. Inactive ingredients are not tested for strength or potency in the supplement but are verified only as being present in the product.[15]

Food product labels that fall under the category of nutraceuticals must abide by labeling requirements under the FDA's Nutrition Facts Labeling Guidance as well. These are also regulated under the Federal Food, Drug and Cosmetic Act. Labeling for food products requires Nutrition Facts labeling, whereas dietary supplements require Supplement Facts labeling. A notable difference in Nutrition Facts compared with Supplement Facts includes the requirement to list "zero" amounts of nutrients in the Nutrition Facts label. Additionally, sources of dietary ingredients and ingredients without a daily reference intake or daily recommended value cannot be listed in the Nutrition Facts panel for foods.[16]

The images in the FIGURE depict the differences between a Nutrition Facts and a Supplement Facts label.[16]

USE OF NUTRACEUTICALS IN THE UNITED STATES

As previously stated, the Council on Responsible Nutrition reported that dietary supplement usage has been at an all-time high in recent years, with approximately 77% of Americans reporting using supplements in 2017, and rates have been steadily rising.[3] It is estimated that 9 of 10 Americans have some form of nutritional deficiency and 8 of 10 physicians recommend supplements for patient use.[3] Additionally, an increased number of millennials adhere to specialized eating plans, such as gluten-free, vegan, vegetarian, and dairy-free diets; this makes their need for nutritional supplementation potentially higher, to ensure that they consume essential nutrients.[14,17]

Overall, nutraceuticals are used for numerous health purposes. An overview of some common nutraceutical products and their use follows.

FIGURE. NUTRITION FACTS VERSUS SUPPLEMENT FACTS LABEL[16]

Nutrition Facts

8 servings per container
Serving size **2/3 cup (55g)**

Amount per serving **Calories**	**230**
	% Daily Value*
Total Fat 8g	**10%**
Saturated Fat 1g	**5%**
Trans Fat 0g	
Cholesterol 0mg	**0%**
Sodium 160mg	**7%**
Total Carbohydrate 37g	**13%**
Dietary Fiber 4g	**14%**
Total Sugars 12g	
Includes 10g Added Sugars	**20%**
Protein 3g	
Vitamin D 2mcg	10%
Calcium 260mg	20%
Iron 8mg	45%
Potassium 235mg	6%

* The % Daily Value (DV) tells you how much a nutrient in a serving of food contributes to a daily diet. 2,000 calories a day is used for general nutrition advice.

Supplement Facts

Serving Size 1 Capsule
Servings Per Container 100

Amount Per Capsule	**% Daily Value**
Calories 20	
Total Fat 2 g	3%*
Saturated Fat 0.5 g	3%*
Polyunsaturated Fat 1 g	†
Monounsaturated Fat 0.5 g	†
Vitamin A 765 mcg	85%
Vitamin D 21 mcg	105%
Omega-3 fatty acids 0.5 g	†

*Percent Daily Values are based on a 2,000 calorie diet.
†Daily Value not established.

Ingredients: Cod liver oil, gelatin, water, and glycerin.

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DIETARY SUPPLEMENTS AND THE COMMON COLD

Zinc, *Echinacea purpurea*, nasal saline, honey (buckwheat), geranium extract, and garlic have all been marketed as dietary supplements used for the common cold. Meta-analyses assessing the effectiveness of zinc for reducing symptoms of the common cold have concluded that zinc lozenges shortened the duration of nasal discharge, nasal congestion, sneezing, sore throat, cough, and muscle aches, with minimal adverse effects (AEs) noted.[18] Evidence has demonstrated that the use of buckwheat honey showed improvement over placebo for decreasing the frequency of cough and improving the quality of sleep in pediatric patients.[19] *Echinacea purpurea*, nasal saline, geranium extract, and garlic have provided inconsistent results and require improved trials to demonstrate their effectiveness for use in the common cold. [20]

DIETARY SUPPLEMENTS AND DEPRESSION

Marketing for the use of dietary supplements in the management of depression is widespread; the most common supplements include omega-3 fatty acids, St John's wort, SAMe, and inositol. Of these therapies, meta-analyses have provided evidence that St John's wort may have effectiveness in the treatment of mild to moderate depression in comparison with placebo; however, well-controlled trials are needed to confirm its place in therapy.[21] It should also be noted that several drug–drug interactions exist with the use of St John's wort, and pharmacists should be diligent in assessing all medications for interactions before recommending use of the product. Omega-3 fatty acids, SAMe, and inositol have inconclusive evidence and require further assessment before recommendations can be made.[22]

DIETARY SUPPLEMENTS AND SPECIAL POPULATIONS

Special populations—eg, those who are pregnant and/or nursing; older adults—may be at greater risk for AEs, and caution should be taken when recommending nutraceutical products in these populations. During pregnancy, for example, levels of essential vitamins and minerals such as iron, calcium, and folic acid may decline, but they are required for proper growth and development of the fetus.[23] Although prenatal vitamins are readily available without prescription, pharmacists should recommend that patients who are pregnant be assessed by their obstetrician prior to the use of supplements or nutritional products.[24] In geriatric populations, the use of nutraceuticals should be monitored because of the increased risk for drug, supplement, and food interactions that may lead to AEs.[4] The National Institute on Aging recommends a balanced diet including a variety of healthy foods and fortified food products to maintain adequate nutrition in geriatric patients; however, individuals with malabsorption of nutrients due to disease- or drug-induced nutrient depletions should be assessed by a health care provider to determine need for supplementation.[25] For further information, pharmacists can access the US Department of Agriculture Dietary Reference Intake calculator to assess specific nutrient needs in various populations.[26]

HERBAL SUPPLEMENTS

Herbal supplements are a subset of dietary supplements that contain 1 or more herbs. They are also referred to as botanicals and are made from plants, fungi and/or algae, or a combination of these substances. Herbal products are often sold as teas, extracts, tablets, capsules, or powders.[27] Common herbal supplements include green tea, valerian root, cinnamon, *Ginkgo biloba*, evening primrose oil, black cohosh, and chamomile, to name a few. An ample number of herbal supplements exist, and pharmacists can consult the National Institute of Health's National Center for Complementary and Integrative Health for current research and recommendations regarding their use.[28]

PROBIOTICS

Probiotics are also under the umbrella of nutraceutical products. Probiotics generally consist of live microorganisms that can be placed in dietary supplements and fermented foods and in topically applied products including cosmetics. Probiotics may contain a variety of diverse bacteria; the most common include *Lactobacillus* and *Bifidobacterium* Yeast, too, such as *Saccharomyces boulardii,* may be included in probiotic supplements. Probiotics have demonstrated some effectiveness in specific health conditions, such as preventing antibiotic-associated diarrhea, preventing necrotizing enterocolitis in premature infants, treating periodontal disease, and supporting remission of ulcerative colitis. Probiotic use shows promising results; however, studies with consistent formulations and amounts of each culture are needed to establish guidance regarding products. Probiotics are generally safe but should be used cautiously in patients who are immunocompromised and/or critically ill to prevent new infections or worsen current ones.[29]

DRUG-INDUCED NUTRIENT DEPLETIONS

Drug-induced nutrient depletions pose an additional area for pharmacist consultation regarding use of nutraceutical products. Drug-induced depletions may be mild to moderate in nature and can be corrected through use of nonprescription products. For example, use of histamine-2 receptor blockers has been associated with calcium depletion; therefore, calcium supplementation may be needed, especially in older adults who are at a higher risk of bone fractures and osteoporosis. More severe depletions require

TABLE. COMMON NUTRIENT–DRUG INTERACTIONS[30]

Nutrient Depleted	Associated Drugs/Drug Classes
Calcium	Corticosteroids, loop diuretics, H_2RAs, benzodiazepines, digoxin, SSRIs
Vitamin D	Corticosteroids, bile acid sequestrants, H_2RAs, SSRIs
Folic acid	Oral contraceptives, pancreatic enzymes, hormone replacement therapy
Vitamin B_{12}	Metformin, H_2RAs, PPIs, hormone replacement therapy
Vitamins A and K	Bile acid sequestrants
Potassium	Loop diuretics, thiazide diuretics, corticosteroids, digoxin
Magnesium	Oral contraceptives, loop diuretics, thiazide diuretics, PPIs, H_2RAs, digoxin, hormone replacement therapy

H_2RA indicates histamine-2 receptor antagonist; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor.

evaluation by a health care professional to establish replacement needs, as in the case of the depletion of such electrolytes as potassium and magnesium in the presence of thiazide and loop diuretics. Pharmacists should be aware of common drug-induced nutrient depletions and educate patients regarding the need for nutrient replacement and/or referral for evaluation. The TABLE highlights some common nutrient–drug interactions.[30]

CONCLUSIONS

Nutraceutical use across the United States is increasing, and this provides an opportunity for pharmacists to counsel patients on the appropriate use of available products. As the number of nutraceuticals increases, it is essential for pharmacists to remain informed on the latest recommendations for their use and safety. Pharmacists can refer to the FDA website for current information regarding the purity, safety, efficacy, and use of nutraceutical products. Product selection should be based on verification of authenticity through national compendia such as the official USP. Only products with a USP label ensure the purity, potency, performance, and presence of the listed ingredients on the label. The need for supplementation is highly patient-specific: It ranges from broad use of multivitamins to specific replacement of nutrients due to drug-induced nutrient depletions and conditional replacement during pregnancy and lactation. A detailed patient history, assessment of current medications, and determination of risk and benefit should guide pharmacists' recommendations of nutraceutical products. ◆

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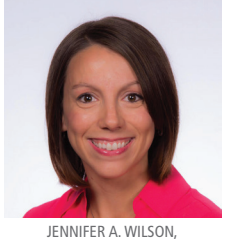
FEATURE

Melatonin: Considerations for Use in Patients With Sleep Disorders

BY RASHI C. WAGHEL, PHARMD, BCACP; AND JENNIFER A. WILSON, PHARMD, BCACP

RASHI C. WAGHEL, PHARMD, BCACP



JENNIFER A. WILSON, PHARMD, BCACP

Melatonin, an endogenous, or natural, hormone mainly produced by the pineal gland in the brain, regulates several body processes, including circadian rhythm and sleep patterns.[1,2] Darkness stimulates melatonin release, whereas light, especially blue light emitted by screens, suppresses release.[2] Secretion of melatonin varies by age, with highest secretion in those aged approximately 1 to 3 years and lowest secretion in young infants (<1 year) and elderly adults aged at least 65 years.[3,4]

Melatonin can be given exogenously, such as in the form of a synthetically produced supplement, and has been investigated for various medical conditions, most commonly sleep disorders, including jet lag, insomnia, shift-work disorder, and other circadian rhythm disorders (eg, delayed sleep phase syndrome or non–24-hour sleep–wake disorder).[1,2]

When given exogenously, melatonin is proposed to improve sleep onset latency (time to fall asleep) rather than cause drowsiness to induce sleep.[2,3] Doses of 1 mg to 5 mg of melatonin taken at night can produce 10 to 100 times higher nighttime peaks within an hour when compared with endogenous peaks.[3] Metabolism of melatonin occurs in the liver, resulting in a relatively short half-life of 30 minutes to 60 minutes.[3] Most exogenous melatonin is synthetically produced.[2] Less often, it is produced from animal pineal gland; bovine derivations should be avoided because of possible bacterial contamination.[2]

SAFETY OF MELATONIN SUPPLEMENTS

Melatonin appears to be safe for short-term use in the general population as an 8-mg dose per day for up to 6 months. Even with larger doses (up to 10 mg, which is safe to use for up to 2 months), only mild adverse effects (AEs) such as dizziness, headache, nausea, and drowsiness were generally reported. Some patients may be able to take melatonin safely for up to 2 years.[1] Long-term studies of the use of melatonin for up to 2 years in children have shown similar AEs as those in short-term studies; however, because these studies are limited, long-term use of melatonin should occur under health care provider supervision, regardless of age.[1,5]

There is a lack of evidence in pregnant women regarding safety, and so melatonin should be avoided in this population. Higher doses (75-300 mg/day) have been associated with inhibition of ovulation, and so patients desiring to become pregnant should avoid high or frequent doses.[1,5] Few data are available regarding use in lactation, and so women who are breastfeeding should be counseled to avoid use.[1,5]

In children, melatonin may be safe when used short term in low doses. Dosing should be limited to 3 mg daily for infants (aged >6 months) and children. Melatonin use in adolescents may potentially affect sexual hormones and development, so doses should not exceed 5 mg daily if medically needed. Otherwise, it should be avoided for healthy children.[1,5] Elderly patients may be more susceptible to AEs such as daytime drowsiness because of decreased clearance of the drug in this population.[5] Melatonin is specifically not recommended in elderly patients with dementia who have irregular sleep–wake rhythm disorder.[6]

EFFICACY OF MELATONIN SUPPLEMENTS

Melatonin has been studied in a variety of sleep disorders, but evidence is often weak or conflicting because of smaller or lower-quality studies. Most evidence supports its use in delayed sleep phase syndrome, non–24-hour sleep–wake disorder in the blind, and primary insomnia.[1,6] It is often used for occasional insomnia, although evidence and dosage is less certain.[2] In chronic insomnia, there is evidence of a slight reduction

TABLE. MELATONIN USE FOR SLEEP DISORDERS SUMMARY[1,2,6-14]

Condition Studied[a]	Doses Studied	Results
DSPS - *likely effective*[1,5,6]	0.3-5.0 mg daily up to 4 weeks	Improves sleep onset latency; improves QOL (eg, mental health, vitality, bodily pain) in young adults with DSPS
Non–24-hour sleep–wake disorder - *likely effective*[1,5,6]	0.5-10 mg daily in adults and 0.5-4.0 mg daily in children for up to 6 years	Improves circadian rhythm sleep disorders in adults and children who are blind
Beta blocker–induced insomnia - *possibly effective*[1]	2.5-5.0 mg at night (eg, 1 hour before bed and after taking the beta blocker)	May improve sleep latency, total wake time, wakefulness after sleep onset, and/or increase total sleep time to counter proposed decrease in endogenous melatonin with beta blocker use
Insomnia - *possibly effective*[1,2,6,7,8,9]	0.3-5.0 mg in adults nightly typically for ≥ 21 days 5 mg in children for 28 days (0.05-0.15 mg/kg for 7 days in 1 trial)	Short-term use may improve sleep-onset latency, increase total sleep time, and improve sleep quality; more benefit may be seen in elderly individuals (due to melatonin deficiency); more benefit seen with insomnia with certain comorbidities (depression, schizophrenia, bipolar disorder, epilepsy, asthma, cystic fibrosis, tuberous sclerosis, autism spectrum disorders, and developmental disabilities), whereas conflicting results have been seen with other conditions (Alzheimer disease, dementia, Parkinson disease, traumatic brain injury, substance use disorder, and dialysis)
Jet lag - *possibly effective*[1,2,10,11]	0.5-5.0 mg (preferably 2.0-3.0 mg) at local bedtime on day of arrival and for 2-5 nights thereafter	May improve alertness, jet lag, psychomotor performance, daytime sleepiness, and fatigue; may be most effective when traveling eastward through ≥5 time zones
Preoperative anxiety and sedation - *possibly effective*[1,12]	3.0-14.0 mg orally or 0.05-0.2 mg/kg sublingually in adults 0.05-0.4 mg/kg in children	Studies show conflicting efficacy; may improve sedation and reduce preoperative anxiety similar to taking midazolam, clonidine, or gabapentin as a preanesthetic agent
Shift-work disorder - *possibly ineffective*[1,2,11,13]	1.0-10.0 mg after night shift	Does not significantly improve sleep latency, sleep efficiency, or adjustment to rotating shift work; may slightly increase total sleep time and/or overall sleep quality
REM sleep behavior disorder - *insufficient evidence* [1,6]	3.0 mg nightly for 4 weeks	May increase likelihood of appropriate muscle paralysis during REM sleep

DSPS indicates delayed sleep phase syndrome; QOL, quality of life; REM, rapid eye movement.

[a]Ratings (*likely effective, possibly effective, possibly ineffective, insufficient evidence*) based on the Natural Medicines Comprehensive Database rating system.[1]

in sleep onset latency (about 7-12 minutes) compared with placebo and a small improvement in subjective sleep quality.[1,7,8] However, the American Academy of Sleep Medicine and the American College of Pharmacy both state that sufficient evidence is lacking to recommend use of melatonin in the general population for chronic insomnia.[7,8] Despite the lack of evidence, guidelines recognize that an informed patient would be more likely to use melatonin over no treatment.[8] An overview of melatonin efficacy in insomnia, along with other sleep disorders, can be found in the TABLE.[1,2,6-14]

COUNSELING POINTS

Pharmacists can counsel patients on selecting products to ensure that they choose the intended product strength (eg, melatonin

can be dosed in both milligrams and micrograms: 0.3 mg or equivalently, 300 mcg). A 300-mcg dose of exogenous melatonin produces higher-than-normal physiologic concentrations, and so high doses are not usually necessary.[2] Lower doses may also minimize potential AEs such as dizziness, headache, nausea, and sleepiness, but no study results support this.[5] Patients should be counseled on appropriate timing of dose and length of use depending on indication (eg, 30-60 minutes before bedtime for insomnia).[2] Additional details can be found in the Table.[1,2,6-14] Regardless of whether a patient chooses to use melatonin for sleep disorders, patients should be counseled on appropriate sleep hygiene, such as establishing a regular sleep pattern, avoiding daytime naps, and avoiding use of electronics before bed.[15]

CONCLUSIONS

Strong evidence from long-term clinical trials evaluating the use of melatonin for sleep disorders is lacking. Although some evidence shows modest benefit in reducing sleep onset latency and improving sleep quality, the overall clinical impact may be limited. However, melatonin is generally regarded as safe in the general population, with only mild AEs reported. As such, despite the lack of strong evidence, patients may opt to try melatonin to help with sleep disorders such as insomnia or jet lag. ◆

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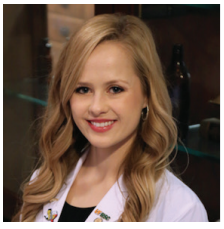
FEATURE

To D or Not to D: That Is the Question

BY CHELSEA RENFRO, PHARMD, CHSE; AND ALEX STANLEY, PHARMD CANDIDATE

CHELSEA RENFRO, PHARMD, CHSE



ALEX STANLEY, PHARMD CANDIDATE

Vitamin D encompasses a group of fat-soluble secosterols that are found in certain foods and supplements and can also be produced when synthesis of vitamin D is triggered after the sun's ultraviolet rays touch skin. It is required for bone growth and remodeling,and when paired with calcium, it can help to prevent osteoporosis. Low levels of vitamin D have been linked with poorer health and with disease.[1] Although the importance of vitamin D in regard to bone health has been established, its importance in other areas, such as skin pigmentation, pregnancy, cancer, and immune function, is unclear and not supported by clinical evidence.[1,2]

WHO NEEDS VITAMIN D

Because few foods naturally contain vitamin D, supplementation is commonly used to avoid risk of vitamin D deficiency (TABLE).[1] Herein are described 4 populations of patients who may benefit from vitamin D supplementation.

Breastfed Infants

The American Academy of Pediatrics (AAP) recommends that infants who are breastfed receive vitamin D supplementation. Although most infant formulas contain vitamin D, the AAP still recommends that infants who are receiving less than 1 L of formula per day also receive supplementation, in addition to those who are exclusively breastfed.[3] The results of a 2010 study of data from the Infant Feeding Practices Study II, in which mothers of both breastfed and formula-fed infants responded to mailed questionnaires on a variety of topics, including dietary intake, found that 44% to 58% of infants met the 2003 recommended amount of 5 mcg per day of vitamin D. When the AAP recommendation increased to 10 mcg per day in 2008, less than a quarter of infants would have met the recommendation.[4] Mothers who responded to the question gave a variety of reasons for not supplementing their infants with vitamin D, including lack of knowledge about supplementation, misinformation about vitamins in formula and breast milk, inconvenience of administering supplements, and infant's dislike of them. Common phrases repeated by the mothers were, "I didn't know I should," "Baby formula has all that is needed and recommended," and "It causes [the baby] to spit up."[5]

Of the mothers who responded to the questionnaire who were breastfeeding, most (88.4%) preferred to take a vitamin D supplement themselves rather than directly administer it to their infant. The benefits of maternal supplementation with vitamin D include ease of administration, both mother and infant receiving vitamin D, and decreased risk of infant toxicity due to dosing errors. Maternal supplementation at 100 mcg to 162.5 mcg per day, or a single monthly dose of 3750 mcg, can sufficiently enrich breast milk with enough vitamin D to meet an infant's needs without causing toxicity. If mothers choose to give their infants vitamin D supplementation directly, the infant should receive 10 mcg per day through drops administered by mouth or in the bottle.[5]

Older Adults

The results of a study conducted between 2011 and 2014 found that vitamin D supplementation use has increased in the United States, with 26% of older adults (≥60 years) taking a vitamin D supplement.[6] As people grow older, their skin becomes thinner and they cannot absorb and process vitamin D as efficiently.[1] Further, renal decline can occur in older adults. This affects vitamin D levels because the kidneys are needed to convert vitamin D in the body.[1]

When levels of vitamin D in the body are inadequate, bones can become thin, fragile, and misshapen, and the risk of osteoporosis is increased.[2] Therefore, the National Osteoporosis Foundation recommends that women and men aged under 50 years receive 10 mcg to 20 mcg of vitamin D per day, and that those 50 years and older receive

TABLE. RECOMMENDED DIETARY ALLOWANCES OF VITAMIN D[1a]

Age	Male	Female	Pregnancy	Lactation
0-12 months	10 mcg	10 mcg	-	-
1-13 years	15 mcg	15 mcg	-	-
14-18 years	15 mcg	15 mcg	15 mcg	15 mcg
19-50 years	15 mcg	15 mcg	15 mcg	15 mcg
51-70 years	15 mcg	15 mcg	-	-
>70 years	20 mcg	20 mcg	-	-

[a]Adequate intake.
Adapted with permission: *Dietary Reference Intakes for Calcium and Vitamin D.* Washington, DC: National Academies Press; 2011.

20 mcg to 25 mcg of vitamin D per day.[7]

Increasing vitamin D levels is also a modifiable risk factor to potentially reduce falls and fractures in older adults if taken daily. Sanders and colleagues sought to determine whether a high annual dose of vitamin D, instead of daily doses, would reduce the risk of falls and fractures. They conducted a study in 2010 on community-dwelling women 70 years and older and found that annual administration of 12,500 mcg of vitamin D increased the risk of falls and fractures, with the highest risk being within the first 3 months after administration.[8] Based on these findings, daily dosing for older adults is preferred. It is recommended that adults younger than 70 years receive 15 mcg of vitamin D per day, and those 70 years and older receive 20 mcg per day.[2]

Individuals Who Have Undergone Bariatric Surgery

Obesity, which is prevalent in the United States, poses many health risks, and an increasing number of adults are undergoing weight loss (bariatric) surgery.[9] Although bariatric surgery decreases the risk of disease and other complications related to obesity, it also decreases the body's ability to absorb vitamins and other nutrients.[10] According to the American Society for Metabolic and Bariatric Surgery, vitamin D deficiency occurs in up to 100% of patients who have undergone surgery for weight loss. To this end, they recommend vitamin D_3 supplementation for these patients at daily doses of 75 mcg.[11]

Individuals With Diabetes

Vitamin D deficiency also has been linked with hypertension, kidney disease, and diabetes.[12] Beta cells in the pancreas, where insulin is secreted, have vitamin D receptors, and it is speculated that vitamin D may improve insulin sensitivity and secretion, as well as glomerular filtration rate.[13] Study results related to this effect have been inconclusive, however, and research on the effect of vitamin D supplementation in patients with diabetes continues.[14] Regardless, supplementing with 15 mcg of vitamin D per day in people younger than 70 years, and 20 mcg per day in those 70 years and older, to ensure that each patient meets the recommended daily value, has many health benefits and may later prove to be beneficial in patients with type 1 and type 2 diabetes.[2]

WHAT PHARMACISTS AND THEIR PATIENTS NEED TO KNOW

Although in some instances quantities that are higher than the recommended dietary allowance are indicated, overaggressive supplementation of vitamin D, or any nutrient, may result in adverse reactions.[1] Inform patients that evidence supports the benefit of vitamin D to bone health but that its use is unclear in areas previously discussed, such as skin pigmentation, pregnancy, cancer, and immune function. For the average, healthy adult patient, the recommended dietary allowance of 15 mcg per day—and 20 mcg per day for those aged over 70 years—is appropriate. ◆

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FEATURE

Omega-3 Recommendations: Counseling Points for Pharmacists

BY BRADY COLE, RPH

BRADY COLE, RPH

Omega-3 fatty acids (omega-3s) have received much publicity and advertising attention over the last few years stating that they are an essential supplement many people should consider taking. As a pharmacist, it is important to know which patients may benefit from omega-3 supplements the most, the supplements' proper dosage, and the benefits that can be expected. It is also important to know which health claims about omega-3s have the most validity.

OMEGA-3 COMPONENTS AND SOURCES

Omega-3 fatty acids have 2 main components that are beneficial in humans: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). DHA levels are highest in the retina and brain. Omega-3s can also be used to form eicosanoids, which have activity in the cardiovascular, pulmonary, immune, and endocrine systems. A third component of omega-3s, alpha-linolenic acid (ALA), is not active in the body, but it can be converted to EPA and DHA.[1,2]

The primary vehicle for EPA and DHA to enter the body is through the consumption of fish and other seafood, so the American Heart Association recommends consuming 2 servings of fish per week, particularly fatty fish such as tuna, salmon, herring, or sardines, which have high levels of omega-3s.[1,3] For patients who do not get enough omega-3s through their diet or who require a higher level than what their diet provides, OTC and prescription dietary supplements of omega-3s may help to meet their daily needs.

FISH OIL SUPPLEMENTS

Fish oil supplements are a common source of DHA and EPA. For individuals who cannot tolerate fish oil, or do not wish to take it, omega-3s are also contained in krill, cod liver, and algal oil supplements.

Fish oil supplements come in various dosage forms or combinations. A target dose of around 1 g of omega-3s is a good place to start.[4] When taking fish oil supplements, patients may experience an unpleasant "fishy" taste; however, the use of higher-quality products with a United States Pharmacopeia seal may alleviate this problem, as these products may be less likely to have the unpleasant taste or smell.[5] Patients may also be advised to store the capsules in the refrigerator or to take them at bedtime to avoid the unpleasant taste.

Krill oil, sourced from tiny crustaceans called krill, can be an alternative for patients who cannot tolerate the fishy smell or taste that can be associated with fish oil supplements. Krill oil is more stable than fish oil, which may mean it is absorbed better, and because it is not sourced from fish, it may be less likely to cause a fishy aftertaste. The use of krill oil has not been studied as extensively as that of fish oil, however, and probably should remain as a secondary recommendation until further research reinforces its safety and effectiveness. The recommended dosage from the manufacturer will be included on the krill oil product that is selected.[6]

For those patients who follow a vegetarian or vegan diet, pharmacists may recommend an algal oil supplement to add omega-3s to their diet. Algal oil is derived from algae and may be a good source of EPA and DHA; however, studies on algal oil have not been extensive.[7,8] Recommendations of these products may need to be limited to only those patients who cannot tolerate fish oil or those patients who do not consume any fish products because of dietary preferences or needs.

Pharmaceutical-grade omega-3 products are also available and are prescribed in dosages as high as 4 g per day. These products are indicated for patients with very high triglyceride levels.[9] Patients should be advised to not take dosages

TABLE. ADEQUATE INTAKES FOR OMEGA-3s[2]

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months[a]	0.5 g	0.5 g	-	-
7-12 months[a]	0.5 g	0.5 g	-	-
1-3 years[b]	0.7 g	0.7 g	-	-
4-8 years[b]	0.9 g	0.9 g	-	-
9-13 years[b]	1.2 g	1.0 g	-	-
14-18 years[b]	1.6 g	1.1 g	1.4 g	1.3 g
19-50 years[b]	1.6 g	1.1 g	1.4 g	1.3 g
51+ years[b]	1.6 g	1.1 g	-	-

[a]As total omega-3s.

[b]As alpha-linolenic acid.

Reprinted with permission from: Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids.* Washington, DC: The National Academies Press; 2005.

in this range through OTC products without the advice of their physician.

BENEFITS OF OMEGA-3s

The efficacy of omega-3s in various conditions has been researched extensively, sometimes with conflicting results. Several trials have been conducted researching the link between a diet rich in omega-3s and a decreased risk of cardiovascular disease.[9] Although these data vary across studies, the FDA states that there is supportive (but not conclusive) research indicating that consumption of EPA and DHA may reduce the risk of coronary heart disease.[9]

DHA is important for fetal growth and is found in high concentrations in the cellular membranes of the brain and the retina, and so many prenatal vitamins and infant formulas are fortified with DHA. Omega-3s have anti-inflammatory properties, and their use may provide some relief from mild inflammation or joint pain as well as help to reduce patients' reliance on nonsteroidal anti-inflammatory drugs for inflammation.[10]

Many other benefits claimed for omega-3s have been studied but have been proved inconclusive. These include potential benefits studied in patients with dementia, depression, and attention deficit/hyperactivity disorder, as well as cancer prevention.[9] Continued research is needed to try to uncover additional benefits or to confirm the validity of other perceived advantages of a diet rich in omega-3s.

RECOMMENDED DOSES

According to Dietary Guidelines for Americans 2015-2020, the goal for most Americans should be to consume 8 oz of seafood per week, which is about 250 mg of EPA and DHA per day.[11] For those patients who are looking for more advanced benefits from omega-3s, pharmacists may recommend a total dose of 1 g per day via supplements.[4] Patients with very high levels of triglycerides can be prescribed doses as high as 4 g per day while under supervision of a physician.[9]

The Institute of Medicine published a guideline in 2005 for intake of total omega-3s for infants and of ALA for children and adults, which is still used by the National Institutes of Health today (see TABLE).[2]

CONCLUSIONS

The use of omega-3 supplements may be beneficial for some patients; however, the most effective way to add omega-3s to the diet is by consuming them through food. Pharmacists may recommend 2 servings of fatty fish per week to patients as a starting point, which will not only introduce the beneficial EPA and DHA components into the diet but may also replace foods or meals that are not as healthy. For patients who are unwilling or unable to eat fish every week, other foods that are rich in omega-3s, such as flaxseeds, walnuts, Brussels sprouts, soybeans, or seaweed, can be recommended. Omega-3 supplements such as fish oil, krill oil, or algal oil are the next alternative for patients who cannot consume enough omega-3s from their diet. Pharmacists should be prepared to answer questions about omega-3 supplementation and know which types of patients could benefit from them the most. Educating patients on the reasoning for a recommendation and encouraging them to discuss recommendations with their physician will go a long way in ensuring positive outcomes. ◆

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FEATURE

Prenatal and Postnatal Supplementation: What Do Pharmacists Need to Know?

BY CORTNEY MOSPAN, PHARMD, BCACP, BCGP

CORTNEY MOSPAN, PHARMD, BCACP, BCGP

Prenatal vitamins are designed to support both the health of the mother and the development of the baby during pregnancy. Pregnancy is difficult to predict; it may take a woman 1 month, 1 year, or longer of trying to conceive before she becomes pregnant. Additionally, many critical fetal developments occur before a woman even knows that she is pregnant.[1] The results of a 2016 study found that in 2011, nearly half (45%) of pregnancies were unplanned, with a rate of unintended pregnancy among women of reproductive age of 4.5%.[2]

WHEN SHOULD A PRENATAL VITAMIN BE STARTED?

Because of the prevalence of unintended pregnancy as well as the uncertainty of how quickly or slowly conception will occur, prenatal vitamins should be started 3 months prior to attempted conception.[1] This is to ensure that any potential nutritional deficiencies have been corrected, or increased needs supplied, prior to conception.[1] If prenatal vitamins cannot be started 3 months in advance, folic acid supplementation should be initiated at least 1 month before trying to get pregnant. This is crucial because folic acid aids in growth and development and because the neural tube, which later develops into the baby's spinal cord, spine, brain, and skull, forms between week 4 and week 6 of gestation, before most women know they are pregnant. This can help reduce the risk of neural tube defects.[3,4] Prenatal vitamins should be continued throughout the entire pregnancy.[4]

The results of a 2017 survey by the March of Dimes found that only 34% of women aged 18 to 45 years who took a prenatal vitamin during their current or last pregnancy started the prenatal vitamin before they knew that they were pregnant. Although 97% took a prenatal vitamin, these may have not been started by the optimal time to prevent birth defects, which have an annual prevalence in the United States of 120,000, or 3% of births per year. Use of prenatal vitamins prior to the knowledge of pregnancy was lower in minority populations, with just 10% of African American and 27% of Hispanic patients taking them before they knew they were pregnant.[5]

WHAT VITAMINS SHOULD PREGNANT PATIENTS TAKE?

The American College of Obstetricians and Gynecologists (ACOG) recommends that all female patients of childbearing potential "be screened regarding their diet and vitamin supplements to ensure they are meeting recommended daily allowances for calcium, iron, vitamin A, vitamin B_6 [pyridoxine], vitamin B_{12} [cobalamin], vitamin D, and other nutrients."[6] Folic acid supplementation should be encouraged for these patients as well regardless of dietary intake of folic acid, to reduce the risk of neural tube defects.[7]

Despite being recommended in 1998 by the National Academy of Medicine as an essential nutrient,[8] the role of choline in maternal and fetal development remains underrecognized. Of the top 25 prenatal vitamins, none contained the 450-mg recommended daily allowance, often providing only 0 mg to 55 mg per day.[9-11] Lack of sufficient levels provided in prenatal vitamins could be of consequence because only 25% of women of childbearing potential from high-income countries such as the United States obtain enough choline from their diets.[10-13] Choline is emerging as a nutrient of important consequence during pregnancy because it plays an important role in neural tube development, memory development, stem cell proliferation, and apoptosis.[9] Choline is thought to have an impact on

TABLE. RECOMMENDED DAILY INTAKE OF VITAMINS AND MINERALS DURING PREGNANCY[7,14-19]

	ACOG	CDC	FDA[a]	WHO
Calcium (elemental)	≥19 years: 1000 mg 14-18 years: 1300 mg	N/A	1300 mg	1500-2000 mg[b]
Choline	N/A	N/A	550 mg	N/A
DHA	N/A	N/A	N/A	N/A
Folic acid (vitamin B_3)	400 mcg before pregnancy 600 mcg during pregnancy	400 mcg	600 mcg	400 mcg
Iodine	200 mcg	220 mcg	290 mcg	N/A
Iron (elemental)	27 mg	N/A	27 mg	30-60 mg
Vitamin A	≥19 years: 770 mcg 14-18 years: 750 mcg	10,000 IU	1300 mcg	Only recommended in areas with severe vitamin A deficiency
Vitamin B_6	1.9 mg	N/A	2 mg	Not recommended
Vitamin B_{12}	2.6 mcg	N/A	2.8 mcg	N/A
Vitamin C	≥19 years: 85 mg 14-18 years: 80 mg	N/A	120 mg	Not recommended
Vitamin D	15 mcg	N/A	15 mcg	Not recommended
Vitamin E	Not recommended unless needed to prevent deficiency	N/A	19 mg	Not recommended

ACOG indicates American College of Obstetricians and Gynecologists; DHA, docosahexaenoic acid; N/A, no recommendation available; WHO, World Health Organization.

[a]Recommended intake during pregnancy.

[b]Recommended intake during pregnancy with low dietary intake of calcium.

Reprinted and updated with permission from Segal K, Cieri-Hutcherson NE, Lampkin S. Recommending prenatal vitamins: a pharmacist's guide. *Pharmacy Times*® website. pharmacytimes.com/resource-centers/omega-3/recommending-prenatal-vitamins-a-pharmacists-guide. Published October 4, 2018. Accessed March 20, 2020.

the risk of development of neural tube defects independent of folic acid intake.

The TABLE includes information from ACOG, CDC, FDA, and the World Health Organization (WHO) regarding the recommended vitamins and minerals a woman should take during pregnancy.[7,14-19]

WHEN CAN A PRENATAL VITAMIN BE STOPPED?

Patients who are pregnant may struggle with long-term adherence to their prenatal vitamin because of undesirable effects such as a fishy aftertaste[20] due to docosahexaenoic acid (DHA), constipation from iron or calcium, or general nausea from taking the prenatal vitamin on an empty stomach. Thus, there is a delicate balance between advising women of proper duration of use for health benefits for the mother and baby and preventing unnecessary supplementation due to adverse effects that can affect patients' quality of life.[21]

Breastfeeding is well established as the best nutrition option for infants if mothers are able to breastfeed. One of the values of breastfeeding is provision of essential vitamins and nutrients in breast milk. However, it is debated whether simply following a well-balanced diet may be sufficient to provide these valuable nutrients to infants.[22,23] The CDC recommends continuation of nutrient supplementation in mothers who breastfeed only if they follow restrictive diets (eg, vegetarian diets). They do state that nutritional supplementation may also offer benefit in women who breastfeed who consume balanced diets.[22,23] Supplementation likely provides the greatest benefit to meet increased iodine needs.[22] No leading organization provides any clear or specific vitamin or nutrition supplement recommendations in lactation.

Most women will continue the same prenatal vitamin used throughout pregnancy during lactation, but there are different and unique nutritional needs during pregnancy.[23] ACOG makes no definitive recommendation on how long prenatal supplements should be continued during the postnatal period or which vitamins should be supplemented and at what dose.[24] Supplementation with DHA, vitamin D, folic acid, or iodine has been shown to improve the infant's visual acuity, hand/eye coordination, attention, problem solving, and information processing.[25] The WHO recommends continuation of prenatal vita-

mins for at least 3 months in the postpartum period in geographic regions with a high incidence (≥40%) of anemia in pregnancy.[26] It is recommended to increase choline intake to 550 mg daily during lactation.[12] Continuation of prenatal supplements until the mother has completed breastfeeding may be worthwhile if the supplement is tolerable and affordable for the mother in light of these data.

KEY POINTS FOR PHARMACISTS

Pharmacists can play a key role in ensuring that patients are taking appropriate prenatal and postnatal supplements—including ensuring that patients are taking formulations that include the vitamins and nutrients recommended by leading organizations at appropriate dosages. Pharmacists can screen both women using contraception and women who are actively planning to try to get pregnant for potential supplementation needs by asking, "Are you planning to become pregnant in the next 12 months?" This allows prepregnancy planning to occur to ensure that patients can try to prevent adverse health outcomes associated with pregnancy and potential birth defects before they occur. At a minimum, all female patients of reproductive potential should be advised to take folic acid, even if adherent to contraception, to reduce the risk of neural tube defects.

Selecting a prenatal vitamin can be an overwhelming task for patients, as nutrient contents vary greatly from one prenatal vitamin to the next and especially because there are no nutrient standards or requirements that must be adhered to for a product to be labeled a *prenatal vitamin*. Prenatal vitamins that contain appropriate appointments of folic acid, iron, and iodine should be targeted, and these will often contain adequate amounts of other important nutrients such as B vitamins, calcium, copper, DHA, vitamin A, vitamin D, vitamin E, and zinc.[27] In their 2018 study, DeSalvo and colleagues found that of the 163 OTC and 88 prescription prenatal vitamins included in the study, more than 80% were able to correct vitamin and mineral deficiencies in the average pregnant woman who could not get those vitamins and minerals from dietary intake alone.[28] Generally, these vitamins contained recommended daily allowances for most vitamins and minerals; however, choline, magnesium, and vitamin D were often not provided in sufficient levels.[28] Pharmacists should pay attention to the selection of prenatal vitamins and ensure that they include the recommended daily allowance for these vitamins and minerals. Alternatively, they may need to recommend supplementation with an additional supplement to meet these levels. ◆

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FEATURE

Identification and Communication Approaches to Drug and Dietary Supplement Interactions

BY JAY HIGHLAND, PHARMD

JAY HIGHLAND, PHARMD

Dietary supplement use is common among adults in the United States. According to the results of the 2019 Council for Responsible Nutrition Consumer Survey on Dietary Supplements, 77% of Americans reported consuming dietary supplements.[1] Data on prescription drug use from the National Center for Health Statistics (2013-2016) indicated that about 48% of Americans have used at least 1 prescription medication in the past 30 days, and research has shown that approximately one-third of American adults have reported taking dietary supplements while using prescription medications.[2,3] Although drug interactions exist among many prescription medications and dietary supplements, certain nutrients may be beneficial for patients, particularly while taking certain medications, and as frontline providers, pharmacists are ideally positioned to educate patients on which supplements to take with their medications.[1,4]

The following patient cases provide examples of potential dietary supplement and medication interactions along with counseling approaches and suggested supplements that could be used in such scenarios.

Case Study #1

An Adult Woman Picks Up Birth Control Medication and Would Like to Purchase a St John's Wort Supplement

A 35-year-old woman arrived at the pharmacy window to pick up her birth control medication (norethindrone acetate + ethinyl estradiol + ferrous fumarate). She also brought a bottle of St John's wort to the window to add to her purchase. After prompting from the pharmacist, the patient stated she was taking the St John's wort for mild depression and stress support.

What concerns might exist regarding her current birth control medication and this supplement?

PHARMACY PROCEDURES

The pharmacy technician who helped the woman with her medication pickup knew to notify the pharmacist of any other medications or supplements the patient was taking. The pharmacist then confirmed with the patient that she was not taking any other dietary supplements. He then completed an updated drug utilization review (DUR) with the new information provided.

The pharmacist was then able to counsel the patient on the potential for drug–supplement interactions. He explained that St John's wort can interact with the birth control medication the patient is currently prescribed, decreasing the birth control medication's effectiveness by increasing its breakdown. The patient stated that she previously received a diagnosis of mild depression but had not followed up with her regular primary care doctor after the initial diagnosis and had not used any medications or other therapy.

The pharmacist then recommended that she not initiate the St John's wort until speaking with her primary care provider or psychiatrist because of the potential interaction.[5] The pharmacist advised the patient that alternative prescription options, as well as other therapies, could treat depression while not decreasing the effectiveness of her birth control. He offered to provide recommendations to her health care provider if it was determined that a medication option was warranted. The pharmacist also recommended several supplements to ensure that she receives the nutritive support she may need while taking birth control therapy.[6]

After the pharmacist provided the information, the patient appreciated that he took the time to alert her to the potential interaction and offered to speak with her health care provider about alternative options, if necessary. The patient was receptive to following up with her primary care provider. The pharmacist contacted the patient by phone a few days after their discussion; she had seen her primary care provider, and they had determined she would try counseling to help her cope with her mild depression and stress, without initiating prescription medication at this time. Because of the recommendations made by her pharmacist and the subsequent discussion with her prescriber, she also initiated supplements to reach the total recommended daily value of folic acid, magnesium, and vitamin B_6, as these nutrients may be depleted after chronic use of birth control.[7,8]

Case Study #2

An Elderly Patient Prescribed Digoxin Inquires About Hawthorn Supplements

A 75-year-old man approached the pharmacy drop-off window with a prescription for digoxin and requested to speak with the pharmacist about a hawthorn supplement he also brought to the counter.

What concerns might exist regarding digoxin and this supplement?

PHARMACY PROCEDURES

The patient explained to the pharmacist that his wife had read an article online saying that hawthorn could be helpful for patients with heart failure like himself. Because the pharmacist was not familiar with the hawthorn supplement, she consulted an online medication profile and drug interaction checker. She also reviewed the patient's comprehensive medication list in his patient profile in the pharmacy fulfilment system (TABLE) and confirmed with the patient that the list was current.

The online medication profile and drug interaction checker confirmed that hawthorn may enhance the activity of digoxin, which is a medication with an already-narrow therapeutic index. The pharmacist explained to the patient that hawthorn use could potentially cause digoxin to reach toxic levels in his body, and so hawthorn would be emphatically not recommended. Further, the pharmacist told him that his chronic digoxin therapy could possibly deplete his nutritional stores of calcium, magnesium, and potassium. She suggested supplement dosing to be sure he got the total daily recommended values.[7,8]

The patient was surprised by this information. He was unaware that supplements could interact with his prescription medications, and he thanked the pharmacist for alerting him. The pharmacist advised the patient to always inform health care providers of any herbal or other supplements he takes, or might be interested in taking, to help prevent future drug interactions.

CASE STUDIES DISCUSSION

Pharmacists can meaningfully impact the prevention of drug–supplement interactions and the complications that interactions may cause. As frontline health care providers, pharmacists are ideally positioned to provide guidance and education when

TABLE. CASE STUDY #2: PATIENT'S CURRENT MEDICATION LIST

Drug	Dose	Directions
Losartan	50 mg	Take 1 tablet by mouth daily in the evening.
Metoprolol succinate	100 mg	Take 1 tablet by mouth daily.
Spironolactone	25 mg	Take 1 tablet by mouth daily.
Furosemide	20 mg	Take 1 tablet by mouth daily in the morning.
Digoxin	0.125 mg	Take 1 tablet by mouth daily.
Potassium chloride	20 mEq	Take 1 tablet by mouth twice daily with food.
Atorvastatin	40 mg	Take 1 tablet by mouth daily.

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situations like the ones described above occur. They can remind patients and/or their caregivers about the importance of alerting their health care providers to any supplements they take.

Proper education of the entire pharmacy staff to check for missing information or missing medications in a patient profile can help to provide comprehensive care and ensure the best patient outcomes. This can be achieved through systematic approaches—for instance, during all medication pickups, inquiring about allergies and about medications and herbal supplements that may not be on file. Documenting this information will make the patient's profile more complete and will make future DURs more efficient. ◆

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NOTES

NOTES

Common Drug Classes, Drug-Nutrient Depletions, & Drug-Nutrient Interactions

Pharmavite LLC

Purpose: For educational use by healthcare professionals only.

Disclaimer: People taking prescription drugs may be more likely to have reduced levels of certain nutrients. Low nutrient levels may lead to other problems. Prescriptions are important to the consumer's health and will function without the recommended dietary supplements. The dietary supplements mentioned here are not intended to replace prescription drugs. It is important to advise consumers to consult with their healthcare provider before beginning a dietary supplement regimen.

DND = Drug Nutrient Depletion

General Recommendation for all Categories: Daily Multivitamin

DRUG CATEGORY	Drug Category Brief Description	Drug-Induced Nutrient Depletions	Additional Suggested Supplements for Nutritional Support*	Dietary Supplements that have Potential for Interactions with Drug (or Drug Class)**
1. ACID-SUPPRESSING DRUGS and ANTACIDS[1–5] Ex: Nexium®, Pepcid®, Prevacid®, Prilosec®, Tagamet® and others	1. H2 antagonists block histamine (H2) receptors on gastric mucosal cells and decrease the production and secretion of acid. 2. Proton-Pump Inhibitors block the acid transporter pump on the luminal surface preventing acid from entering the gastric lumen. 3. Antacids directly neutralize existing acid in the stomach.	**DND:** **H2 antagonists deplete calcium, folic acid, iron, vitamin B_{12}, and vitamin D.** **Proton-pump inhibitors deplete magnesium and vitamin B_{12}.** **RECOMMENDED SUPPLEMENTATION:** • **H2 antagonists and proton-pump inhibitors:** * **Vitamin B_{12}: 25–1000 mcg/day** * **Magnesium: 250–400 mg/day**	Calcium: 500 mg daily Iron[a]: discuss with healthcare provider. Vitamin D[b]: 25-50 mcg (1000-2000 IU) daily Vitamin C - with *H. pylori* [c]: 250-500 mg/day Zinc[d]: 15 mg daily	**Goldenseal and Ginger:** These supplements may increase stomach acid and thus might interfere with antacids, H2 antagonists, and proton pump inhibitors. **Green Tea:** Tagamet® (cimetidine) can inhibit the metabolism of caffeine in green tea and significantly reduce its clearance.
2. ANTIBIOTICS[1–4,6] Ex: Amoxil®, Bactrim®, Ceclor®, Cipro®, Levaquin® and others	Antibiotics are used to treat bacterial infections.	**DND:** **Antibiotics deplete calcium, magnesium, potassium as well as certain B vitamins (B_1-thiamin, B_2-riboflavin, B_3-niacin, B_5-pantothenic acid, B_6, B_9-folic acid, B_{12}) and vitamin K.** **RECOMMENDED SUPPLEMENTATION:** • **Calcium: 500–1000 mg daily in divided doses** • **Magnesium: 250–400 mg daily**		**Calcium, Iron, Magnesium, and Zinc:** When taken concurrently with antibiotics, absorption of both can be affected due to formation of insoluble complexes. **Green Tea Catechins:** Certain antibiotics (fluoroquinolones) reduce clearance of some green tea constituents (caffeine and theophylline) and may increase the risk of their side effects: nervousness, palpitations, and insomia. **St. John's wort:** It causes photosensitivity and may exacerbate the photosensitizing effects of certain antibiotics.
3. ANTIDEPRESSANTS[1–3, 6–7] *(continued page 2)* Ex: Cymbalta®, Lexapro®, Paxil®, Prozac®, Zoloft® and others	This class of medications increases the levels of one or more of the biogenic amines (e.g. norepinephrine, serotonin, dopamine) in the central nervous system. Clinical improvement from antidepressant therapy generally takes 3–6 weeks.		Calcium[e]: 500-100 mg/day Vitamin D[e]: 25-50 mcg (1000-2000 IU) daily Folic acid[f]: 240 mcg daily	**Melatonin:** Melatonin may interact with medications that inhibit serotonin reuptake including a number of antidepressant medications. Endogenous melatonin levels are reduced by SSRI medications.

DRUG CATEGORY	Drug Category Brief Description	Drug-Induced Nutrient Depletions	Additional Suggested Supplements for Nutritional Support*	Dietary Supplements that have Potential for Interactions with Drug (or Drug Class)**
3. ANTIDEPRESSANTS[1–3, 6–7] *(continued from page 1)*				**SAM-e:** Studies suggest SAM-e may augment the actions of anti-depressant drugs in individuals who are refractory to, or do not get full remission from their anti-depressants. **St. John's wort and 5-HTP:** St. John's wort and other supplements such as 5-HTP, in combination with drugs that increase CNS serotonin levels, can increase the risk of serotonergic side effects, including serotonin syndrome.
4. ANTIEPILEPTICS[1–3] **(Anticonvulsants)** Ex: Dilantin®, Lyrica®, Mysoline®, Tegertol®, Trileptal® and others	These drugs work by decreasing the firing of aberrant neurons in the brain and/or decreasing the spread of abnormal activity to the surrounding regions of the brain.		Calcium[g]: 500 mg daily Vitamin D[g]: 25–50 mcg (1000–2000 IU) daily Vitamin B_{12}[h]: 25–1000 mcg daily	Use caution with the following supplements since they may interfere with the effectiveness of antiepileptic drugs. **Folic acid** **Gingko biloba** **Niacin** **St. John's wort**
5. ANTIPSYCHOTICS[1–3] *(continued page 3)* Ex: Abilify®, Haldol®, Seroquel®, Risperdal®, Zyprexa® and others	Antipsychotics block receptors for neurotransmitters (i.e. dopamine, serotonin). They can reduce the symptoms of schizophrenia, decrease agitation and/or aggression associated with other psychiatric conditions and may stabilize mood in bipolar disease.	**DND:** **Vitamin B_2 (Riboflavin)** **RECOMMENDED SUPPLEMENTATION:** • **Daily Multivitamin** • **B Vitamins**	Vitamin C[i]: 250–500 mg daily	**Echinacea:** Echinacea may inhibit the human drug metabolizing enzyme CYP1A2 leading to decreased clearance (increased blood levels) of Zyprexa®, and this increases potential for side effects. **Evening Primrose Oil:** Seizures have been reported in people with schizophrenia treated concomitantly with phenothiazine drugs and evening primrose oil. **Ginkgo biloba:** Ginkgo has been report to cause seizures or lower seizure threshold. Thus, in combination with drugs that lower seizure threshold (including antipsychotics), there may be a significant increase in risk of seizures. **Ginseng:** Ginseng may exacerbate some psychiatric conditions including hysteria, mania, and schizophrenia and thus compromise the therapeutic benefit of antipsychotics. It may also inhibit some of the drug metabolizing enzymes responsible for clearance of antipsychotic drugs.

DRUG CATEGORY	Drug Category Brief Description	Drug-Induced Nutrient Depletions	Additional Suggested Supplements for Nutritional Support*	Dietary Supplements that have Potential for Interactions with Drug (or Drug Class)**
5. ANTIPSYCHOTICS[1–3] *(continued from 3)*				**Goldenseal:** Goldenseal can inhibit cytochrome P450 2D6 (CYP2D6) and might affect effectiveness of several antipsychotics as well as impact potential for side effects. **St. John's wort:** St. John's wort in combination with antipsychotic drugs may lead to unpredictable effects. It is also known to cause photosensitivity and this risk may be increased in combination with certain antipsychotics (phenothiazines), which also can cause photosensitivity.
6. ANXIETY MEDICATION[1–3] **(Benzodiapezines)** Ex: Ativan®, Prosom®, Restoril® Valium®, Xanax® and others	Benzodiazepines are a class of drugs primarily used to treat anxiety.	**DND:** **Calcium** **These medications decrease calcium absorption by increasing metabolism of vitamin D, which is needed for calcium absorption.** **RECOMMENDED SUPPLEMENTATION:** • **Calcium: 500–1000 mg daily in divided doses**	Melatonin[j]: 1–3 mg daily	**Kava:** The combination of kava and benzodiazepines is not recommended due to their similar effects.
7. BIRTH CONTROL[1–3] **(Oral Contraceptives)**	Synthetic and semi-synthetic analogs of estrogen and/or progesterone are used to prevent pregnancy by (1) inhibiting ovulation, (2) thickening cervical mucus and/or (3) diminishing endometrial integrity.	**DND:** **Folic acid** **Magnesium** **Vitamin B_6** **RECOMMENDED SUPPLEMENTATION:** • **Folic acid: 240 mcg daily** • **Magnesium: 250–400 mg daily** • **Vitamin B_6: 2-5 mg daily**	Calcium[k]: 500 mg daily Vitamin B12[l]: 25–1000 mcg/day	**Copper and Iron:** Oral contraceptives may increase serum copper and iron levels. **Garlic and St. John's wort:** Garlic and St. John's wort supplements may decrease effectiveness of oral contraceptives. St. John's wort also causes photosensitivity which may be exacerbated by oral contraceptives. **Green Tea:** Use caution with green tea and oral contraceptives. Oral contraceptives can decrease caffeine clearance by 40–65% and may increase adverse effects of caffeine in green tea. Adjust dose or discontinue if necessary.

DRUG CATEGORY	Drug Category Brief Description	Drug-Induced Nutrient Depletions	Additional Suggested Supplements for Nutritional Support*	Dietary Supplements that have Potential for Interactions with Drug (or Drug Class)**
8. BLOOD PRESSURE MEDICATION[1–3,8] (Anti-hypertensives) Ex: ACE Inhibitors, Angiotensin Receptor Blockers (ARBs), Beta Blockers, Calcium Channel Blockers.	The major classes of anti-hypertensive drugs include: ACE inhibitors, ARBs, beta blockers, and calcium channel blockets. These drugs help reduce blood pressure by either decreasing total peripheral resistance, or cardiac output or both.	**DND:** **ACE inhibitors deplete zinc.** **Calcium channel blockers deplete potassium.** **RECOMMENDED SUPPLEMENTATION:** • **ACE inhibitors- Zinc: 15 mg daily** • **Calcium channel blockers-Potassium: ≤ 100 mg daily**	CoQ10[m]: 100–200 mg daily Iron[n]: Take as directed by healthcare provider	**Calcium** (with calcium channel blockers only)**:** Calcium supplements may interfere with the blood pressure lowering activity of these drugs. **CoQ10 and Fish Oil:** These supplements may decrease blood pressure in combination with anti-hypertensive drugs. Monitor blood pressure regularly. **Garlic, Ginkgo biloba & St. John's wort:** These supplements have the potential to interfere with the cytochrome P450 system and therefore affect the metabolism and/or clearance of drugs. **Green Tea and Goldenseal:** These supplements may affect therapeutic benefits of anti-hypertensive drugs. **Melatonin:** Melatonin may impair the efficacy of some calcium channel blockers. Monitor for changes in therapeutic efficacy and adjust doses as necessary and/or avoid use of melatonin with this drug class. **Potassium** (with ACE inhibitors and ARBs only)**:** Taking these drugs along with potassium supplements increases risk for hyperkalemia due to a decrease in renal potassium excretion. **Vitamin D:** Vitamin D supplements interfere with the activity of a calcium channel blocker (verapamil).
9. BLOOD THINNING MEDICATION[1–3] (Anticoagulants/Antiplatelets) *(continued page 5)* Ex: Aspirin, Coumadin® (Warfarin), Plavix®, Ticlid® and others.	1. Anticoagulants decrease the potential for clotting via the Prothrombin-Thrombin-Fibrinogen cascade. 2. Antiplatelets decrease potential for clots as a result of impacting platelet aggregation.			Use caution with the following supplements as they may increase effectiveness of medication and potentially increased risk of bleeding. **Bilberry** **Cod Liver Oil** **Dong Qual** **Evening Primrose Oil** **Feverfew** **Fish Oil** **Flaxseed Oil** **Garlic** **Ginger Root** **Ginkgo biloba** **Ginseng** **Glucosamine** **Goldenseal** **Grape Seed Extract** **Green Tea** **Horse Chestnut** **Milk Thistle** **Saw Palmetto** **Vitamin C** **Vitamin E**

DRUG CATEGORY	Drug Category Brief Description	Drug-Induced Nutrient Depletions	Additional Suggested Supplements for Nutritional Support*	Dietary Supplements that have Potential for Interactions with Drug (or Drug Class)**
9. BLOOD THINNING MEDICATION[1–3] (Anticoagulants/Antiplatelets) *(continued from page 4)*				**Vitamin K:** People taking anticoagulant medications should maintain consistent amount of vitamin K from their diet and supplement regimen, while avoiding fluctuations in intake or large doses of vitamin K. **Coenzyme Q10 (CoQ10):** CoQ10 is structurally similar to vitamin K and my interfere with effectiveness of anticoagulants.
10. CHOLESTEROL LOWERING MEDICATION (Statins)[1–3] Ex: Crestor®, Lescol®, Lipitor®, Mevacor®, Zocor® and others	Statins inhibit the HMG CoA reductase enzyme–a key step in the hepatic synthesis of cholesterol. The reduction of cholesterol synthesis subsequently increases the liver's removal of circulating LDL cholesterol. Note: HMG CoA reductase is also a key enzyme in the synthesis of coenzyme Q10 (CoQ10)	**DND:** **CoQ10** **RECOMMENDED SUPPLEMENTATION:** • **CoQ10: 100–200 mg/day**	Vitamin D°: 25–50 mcg (1000-2000 IU) daily Fish Oil°: 500–1000 mg EPA + DHA daily	**Garlic (containing allicin) and St. John's wort:** These supplements may impact cytochrome P450 metabolism of some statins and affect their effectiveness. **Red Yeast Rice:** Red yeast rice contains lovastatin which also lowers blood cholesterol levels. This supplement should not be taken with cholesterol-lowering drugs unless under the supervision of healthcare professional. **Vitamin A:** Long term use of cholesterol lowering drugs may increase vitamin A levels in the blood. Vitamin A levels may need to be monitored in some individuals.
11. CORTICOSTEROIDS[2–3] Ex: Prednisone	Corticosteroids are synthetic compounds that mimic the effects of hormones naturally produced in the body by adrenal glands. They are known for relieving inflammation, pain and discomfort resulting from various health conditions	**DND:** **Calcium** **Vitamin D** **Magnesium** **RECOMMENDED SUPPLEMENTATION:** • **Calcium: 500 mg daily** • **Vitamin D: 25–50 mcg (1000–2000 IU) daily** • **Magnesium: 250–400 mg daily**		Use caution with the following supplements as they may interact with and/or affect effectiveness of medication. **Herbal Supplements** **Licorice** **St. John's wort**
12. DIABETES MEDICATION (Oral Hypoglycemics)[1–3,10–11] Ex: Avandia®, Diabeta®, Glucophage® (Metformin), Prandin®, and others		**DND:** **Folic acid** **Vitamin B_{12}** **RECOMMENDED SUPPLEMENTATION:** • **Folic acid: 120–240 mcg daily** • **Vitamin B_{12}: 25–1000 mcg daily**		Use caution with the following supplements as they may interfere with the effectiveness of oral hypoglycemic drugs and/or cause additive blood glucose lowering effects and increase risk of hypoglycemia when used in combination. **Alfalfa** **Aloe Vera** **Alpha Lipoic Acid** **Bilberry** **CoQ10** **Chromium** **Garlic** **Ginkgo biloba** **Ginseng** **Green Tea** **Melatonin** **Milk Thistle** **Niacin** **St. John's wort** **Vitamin K_1**

DRUG CATEGORY	Drug Category Brief Description	Drug-Induced Nutrient Depletions	Additional Suggested Supplements for Nutritional Support*	Dietary Supplements that have Potential for Interactions with Drug (or Drug Class)**
13. DIGIOXIN[1–3] Ex: Cardoxin®, Digitek®, Lanoxicaps®, Lanoxin® and others	Digoxin is derived from the leaves of the Digitalis lantata plant (a variety of foxglove). It is used to treat heart failure and atrial fibrillation.	**DND:** **Calcium** **Magnesium** **Phosphorus** **Potassium** **Vitamin B_1 (Thiamin)** **RECOMMENDED SUPPLEMENTATION:** • **Calcium: 500–1000 mg daily in divided doses** • **Magnesium: 250–400 mg daily** • **Potassium: ≤ 100 mg daily**		**Calcium:** High levels of calcium increase the likelihood of a toxic reaction to digoxin. Low levels of calcium interfere with the function of digoxin. Consistent intake of calcium and monitoring of calcium levels by a healthcare professional is recommended. **Hawthorn:** The activity of digoxin may be enhanced by hawthorn supplements. **St. John's wort:** St. John's wort supplements may reduce serum levels of digoxin.
14. DIURETICS[1–3,9] Ex: Aldactone®, Diamox®, Lasix®, Microzide® (HCTZ), Zaroxolyn® and others		**DND:** **Loop diuretics (especially furosemide) can increase calcium excretion and decrease calcium status. Thiazide diuretics deplete magnesium, potassium, and zinc.** **Potassium sparing diuretics deplete folic acid.** **RECOMMENDED SUPPLEMENTATION:** **Loop Diuretics** **Calcium: 500-1000 mg/day** **and Thiazide Diuretics** **Magnesium: 250-400 mg/daily** **Potassium: ≤100 mg daily** **Zinc: 15 mg daily** **Potassium-Sparing Diuretics** **Folic acid: 240 mcg daily**		**Calcium:** Thiazide diuretics reduce calcium excretion by the kidneys and may increase risk for hypercalcemia, metabolic alkalosis, and possible renal failure. **CoQ10 and Fish Oil:** When taken together with diuretics, these supplements may have additive blood pressure lowering effects and increase risk for hypotension. **Ginkgo biloba:** Ginkgo may reduce the effectiveness of some diuretics.
15. HORMONE REPLACEMENT THERAPY (Estrogens)[3] Ex: Estrace®, Premarin®, Prempro®	Hormone replacement therapy is used to replace female hormones that are no longer produced after menopause.	**DND:** **Folic acid** **Magnesium** **Vitamin B_6** **Vitamin B_{12}** **RECOMMENDED SUPPLEMENTATION:** • **Folic acid: 240 mcg daily** • **Magnesium: 250–400 mg daily** • **Vitamin B_6: 2-5 mg daily** • **Vitamin B_{12}: 25–1000 mcg daily**		**Caffeine:** The stimulating effects of caffeine may be increased due to inhibition of metabolism or clearance of caffeine by hormone replacement therapy. **Calcium and Vitamin D:** Calcium and vitamin D may increase absorption of hormone replacements. These supplements are recommended to improve bone mineral density during estrogen therapy. **Red Clover Extract and Soy Isoflavones:** These supplements may interfere with the activity or absorption of hormone replacement therapy. **St. John's wort:** St. John's wort may alter hormone metabolism including estrogen and progesterone. This supplement is not recommended during hormone replacement therapy. **Zinc and Magnesium:** Excretion of these minerals is reduced by hormone replacement therapy.

*Suggested supplements that may support overall health and are not at all intended to replace any prescription medications.

**These supplements listed may have the potential to interact with the drug or drug classes. Use caution or avoid these supplements unless approved by your physician or preferred healthcare provider.

a. Iron may be affected H2 antagonists in those with elevated risk/pre-existing iron deficiency. However, iron is not recommended to be routinely supplemented while taking H2 antagonists. High levels of iron can cause unnecessary oxidative stress and other undesirable effects. Iron supplementation is only recommended for those with the effects of iron depletion (i.e. anemia).

b. Vitamin D is important for calcium absorption.

c. PPI use may be associated with reduced serum /plasma levels of vitamin C in patients with H. pylori infection.

d. Zinc may be affected by H2 affected by H2 antagonists. However, zinc supplementation may not be recommended for all individuals. One should consult their health care provider on the best option for supplementation and consider health status, health history, and current medication use.

e. An association between SSRI use and risk for osteoporosis has been established. In addition, SSRI's may impact bone formation and resorption through serotonin receptors.

f. Observational data have shown lower folate status in patients with major depressive disorder (MDD), compared to healthy controls. Discuss supplementation with your physician or preferred health care professional, especially if on SSRI antidepressant therapy.

g. Dilantin, Phenobarbital, and Tegretol can increase the metabolism/clearance of vitamin D, leading to a subsequent decrease of calcium absorption. Individuals taking these medications for 6 months or more should consider calcium and vitamin D supplements.

h. Dilantin, Phenobarbital, and Mysoline have been reported to reduce vitamin B_{12} absorption as well as serum and cerebrospinal fluid vitamin B_{12} levels in some individuals. Megaloblastic anemia and neuropsychiatric side effects have been associated with these drugs.

i. Vitamin C taken in adjunct with atypical antipsychotics may reduce oxidative stress.

j. Endogenous melatonin is depleted by benzodiazepines.

k. Calcium supplementation may be warranted with oral contraceptive use to help support bone health if dietary calcium intake is inadequate.

l. Serum levels of vitamin B_{12} have shown to be lower in those using oral contraceptives compared to non-users. Supplementation may be a consideration for individuals already at risk for low vitamin B_{12} status or a deficiency, such as vegetarians.

m. Beta blockers can deplete CoQ10.

n. Low dose ferrous sulfate supplements may help alleviate ACE inhibitor-related cough.

o. Consider supplementing with vitamin D. Fat soluble vitamins (vitamins A, D, E, K) may be affected by medication use.

p. EPA and DHA omega-3 fatty acids help support heart health.

Sources:†

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†Additional references available upon request.

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