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Advances In Pharmacology

An Evidence-Based Update On Vitamins

K. Kelly Orr, PharmD, and Anne L. Hume, PharmD, FCCP, BCPS

In the United States, dietary supplements include vitamins, minerals, amino acids, herbal and nonbotanical products such as melatonin, as well as certain types of foods. Vitamins remain the most common type of dietary supplement used by otherwise healthy adults. Vitamins are available as single entity products, mixtures such as B complex or antioxidant products, **multivitamins** (MV) which frequently contain 10 or more vitamins, and **multivitamin multiminerals** (MVMM) which may include over 20 different vitamins and minerals. This article summarizes the evidence on the use of multivitamin and single vitamin products among healthy individuals without documented deficiencies.

Multivitamin Products

An estimated 35% to 50% of Americans regularly take MVMM products,[1,2] even though vitamin and mineral deficiencies are uncommon among otherwise healthy adults, with the exception of vitamin D and iron. Use is most common among women, older adults, and nonhispanic whites and frequently for the purpose of preventing chronic diseases. Other predictors of use include having higher levels of education, physical activity, and overall healthier diets. In fact, studies demonstrating modest health benefits may actually represent unmeasured healthy behaviors.

Many studies have evaluated the potential benefits of MV or MVMM products. One recent study, using data from the clinical and observational trials of the Women's Health Initiative, identified vitamin use at baseline and at follow-up visits over 8 years. Use of MV, MVMM, or high-dose multivitamin supplements was not associated with reduced risk of eight common cancers, **cardiovascular disease** (CVD), or total mortality.[3] Although other clinical trials, such as the Physicians' Health Study II, are evaluating the effects of MV use on cancer, CVD, eye disease, and cognitive status, little evidence supports the use of MV or MVMM products in otherwise healthy adults.

Vitamin A

The best evidence for the use of vitamin A, as beta-carotene, is for the prevention of age-related macular degeneration. The **Age-Related Eye Disease Study** (AREDS) Research Group has recommended an antioxidant combination including 15 mg beta-carotene in individuals over 55 years of age who are at risk of developing macular degeneration. Other components in the AREDS formulation include vitamin C, vitamin E, zinc, and copper.[4]

Although a diet of fruits and vegetables rich in vitamin A has been associated with a reduction in cancer risk, two earlier cancer prevention trials identified safety concerns with beta-carotene supplements. **The Alpha-Tocopherol, Beta-Carotene** (ATBC) Cancer Prevention Study Group **and Beta-Carotene and Retinol Efficacy Trial** (CARET) found an increase in lung cancer and overall mortality in current or former smokers taking beta-carotene and/or vitamin A (retinyl palmitate).[5,6] Several "eye health" formulations omit vitamin A and are marketed specifically towards current and former smokers.

Consumers should be aware of the potential adverse effects from excess vitamin A consumption. In doses over 50,000 IU, acute toxicity may manifest as headaches, blindness, increased intracranial pressure, nausea, vomiting, and lack of muscular coordination. Because vitamin A exposure may result in craniofacial, cardiovascular, and central nervous system malformations, pregnant women should not consume more than 5,000 IU per day. In addition, other evidence in adults suggests higher retinol concentrations may be associated with reduced bone mineral density and an increased risk of hip fracture by impairing the effect of vitamin D on calcium absorption.[7]

Vitamin A is in many **over-the-counter** (OTC) products not commonly associated with vitamins. Original Airborne Zesty Orange contains 2,000 IU vitamin A (retinyl palmitate) to be taken up to three times daily as needed. Airborne Triple Pack Zesty Orange, has 5,000 IU vitamin A (retinyl acetate) in each tablet, to be taken every 3 hours as needed with no daily maximum dose stated. This could result in ingestion of 40,000 IU of vitamin A in a 24 hour period, approaching levels of acute toxicity. Neither formulation warns about the risk of vitamin A toxicity, nor that current and former smokers should avoid its use, although pregnant and breastfeeding women are cautioned not to use the product.

Vitamin C

Vitamin C, in high dosages, continues to be promoted for its role in immune function and the common cold. The **Food and Drug Administration** (FDA) has warned manufacturers against making unlawful marketing claims for OTC products in combination with vitamin C, citing insufficient substantiating data. Vitamin C may be legally marketed to "support a healthy immune system" or other structure-function claims. The prevention and treatment of cold symptoms at 200 mg or more daily has been observed only in people experiencing extreme climates or in athletes, such as skiers, marathon runners, and soldiers in subarctic temperatures.[8] As for a way to prevent, or treat, cancer, a recent review of 38 trials of vitamin C (or vitamin E) for cancer prevention or treatment found little evidence to support its use for this purpose.[9]

Although safe, diarrhea, nausea, vomiting, heartburn, gastrointestinal cramping, flushing, headache, or insomnia can occur with acute administration of several grams vitamin C. Frequent high dosages of 2 grams daily may cause urinary oxalate stones; urate and cysteine stones have also occurred with long-term use.[10]

Vitamin D

Research on vitamin D has demonstrated potential benefits beyond the prevention of osteoporosis. Better considered a hormone, vitamin D consists of ergosterol and 7-dehydrocholesterol (provitamin D3). Multiple cells express vitamin D receptors, including osteoblasts, muscle cells, ovarian and prostate cells, circulating monocytes, pancreatic islet cells, and many others. Vitamin D deficiency may be present among adults of all ages, not only frail older adults living in nursing homes. Among healthy older adults living independently, the incidence of unrecognized vitamin D deficiency may reach 40% to 50%.

Small clinical trials and many observational studies have identified a range of potential health benefits with vitamin D, although few are supported by evidence from large clinical trials. Several meta-analyses have reported that supplemental vitamin D in dosages between 700 IU and 1000 IU are associated with a reduction of about 20% in the risk of falling in older adults. The administration of dosages less than 700 IU of vitamin D have not been associated with this potential benefit. In addition, individuals with vitamin D concentrations of 82 nmol/L or higher had a 50% lower incidence of colorectal cancer than those with concentrations of 30 nmol/L or less in one meta-analysis. A case-control study from the Women's Health Initiative reported that concentrations of vitamin D below 31 nmol/L were associated with a significantly increased risk for invasive colorectal cancer.

The optimal intake of vitamin D remains controversial. New dietary recommendations for vitamin D in adults are expected in 2010 from the Institute of Medicine. Although vitamin D toxicity is quite rare, clinicians should recognize that many different OTC products now contain vitamin D. For example, some glucosamine products include vitamin D in their formulations. A consumer who consumes many different types of OTC products may be getting 1000 IU of vitamin D daily from each product.

In October 2008, the American Academy of Pediatrics and the Institute of Medicine recommended doubling the adequate intake of vitamin D 200 IU to a minimum of 400 IU per day for infants, children, and adolescents. The changes reflected the growing evidence that vitamin D intake will have lifelong benefits in maintaining bone health as well as playing a potential role in the prevention of chronic diseases, such as cancer. Although rare, cases of rickets are reported in the United States, especially with the re-emergence of breastfeeding, and can be both prevented and treated by supplemental vitamin D.[11]

Vitamin E

At least 10% of adults use 400 IU or more of vitamin E as alpha-tocopherol daily, although evidence for the prevention of cancer, CVD, and cognitive decline is lacking. Major randomized, controlled trials do not demonstrate favorable clinical outcomes with vitamin E. The ATBC trial, Women's Health Study, **Heart Outcomes Prevention Evaluation** (**HOPE**) study, and Physician's Health Study II found no difference in cardiovascular events or mortality. In the HOPE-TOO study, patients taking vitamin E had an unexpected 13% increase in heart failure.[12] Data regarding vitamin E and the prevention of cancer is inconsistent, with most trials showing no benefit. Both HOPE-TOO and Women's Health Study did not demonstrate a reduction in the risk of cancer. The **Selenium and Vitamin E Cancer Prevention Trial** (SELECT) also report no reduction in prostate cancer in relatively healthy men. The DATATOP study showed that vitamin E had no effect on progression of Parkinson's Disease. Two high quality trials of vitamin E reported no benefit in patients with Alzheimer's disease or mild cognitive impairment.[13]

Although dosages of 100 mg to 800 mg vitamin E (approximately 150 to 1,200 IU) are taken without adverse effects, both the ABTC study and the Physician's Health Study II reported hemorrhagic stroke. The use of high dosages of vitamin E should be discouraged in patients taking antiplatelet or anticoagulant therapies, as well as other dietary supplements with antiplatelet properties.

Vitamin K

Vitamin K is now frequently a component in MV and MVMM formulations, especially those promoted as "senior formulas" or for "bone health." Combination calcium and vitamin D products also commonly include vitamin K 20 mcg to 80 mcg per tablet. Vitamin K has been added because observational studies suggested a decreased risk of fractures associated with higher dietary intake. Clinical trials from Japan have also reported reductions in fracture risk using pharmacologic dosages of menaquinone-4. The activity of osteocalcin depends on the gamma-carboxylation of three glutamate residues by vitamin K. Vitamin K may also affect osteoprotegerin, a cytokine that binds RANKL, potentially inhibiting the maturation of osteoclasts and decreasing bone resorption. Despite the evidence with vitamin K and osteoporosis, patients taking warfarin should recognize the potential for an interaction, especially if multiple products containing larger amounts of vitamin K are being taken.

Pyridoxine, Folic acid and Cyanocobalamin

Pyridoxine, folic acid, and cyanocobalamin frequently are used in combination to prevent or self-treat CVD. While studies have evaluated the effect of these vitamins on reducing homocysteine concentrations, the evidence does not support a reduction of cardiovascular disease or mortality in otherwise healthy adults. The American Heart Association does not recommend B vitamin supplementation beyond that obtained from a balanced diet for reduction of risk in heart disease and stroke.[14]

For cancer prevention, findings are mixed. Folic acid supplementation in a multivitamin and dietary consumption both show a reduction in colon cancer, however studies evaluating risk with other cancers find no relationship. A recent study from Norway, where there is no fortification of food, has raised concerns about folic and vitamin B12 in patients with underlying ischemic heart disease. A significant increase risk of cancer and overall mortality was related to supplementation.[15]

The strongest evidence for supplemental folic acid 400 to 800 mcg daily is in prevention of neural tube defects as part of preconception planning. Those at high risk, such as women taking anticonvulsant medications, are recommended to take 4 mg daily. The US Preventive Services Task Force advises providers to recommend folic acid to all women of childbearing age since dosages of 400 to 800 mcg daily are not harmful.[16]

Pyridoxine in dosages of 10mg to 25mg every 8 hours has provided relief of nausea and vomiting during the first trimester, particularly in women with severe symptoms. The American College of Obstetrics and Gynecology continues to recommend pyridoxine, with or without doxylamine, as a first-line option.[17]

Riboflavin

Riboflavin is used as a method of migraine prophylaxis at dosages up to 400 mg per day. A placebo-controlled double blind study in adults found riboflavin significantly reduces frequency and duration of migraines, while another small trial found it equal to beta-blockers in preventing attacks. More studies are needed to fully understand the extent of its efficacy, although its safety profile is quite favorable. At this dosage, patients may experience frequent urination, change in urine color to yellow or orange, or diarrhea. It may be used as a second-line agent for migraine prevention.[18, 19]

Niacin

Consumers use niacin, or nicotinic acid, to treat elevated lipid levels. Older, large clinical trials have shown that niacin may reduce cardiovascular events and overall mortality when used in pharmacologic dosages between 1000mg and 4000 mg daily. At these dosages, **low density lipoprotein (LDL)** cholesterol levels are decreased by 5% to 25%, while triglycerides are reduced by 20% to 50%. Unlike statins, niacin also increases **high density lipoprotein (HDL)** cholesterol by 15% to 35%.

A review of OTC niacin preparations found "no flush" products contain inosotil hexaniacinate, a prodrug of nicotinic acid, that gradually hydrolyzes therefore reducing flush. Its peak concentration of nicotinic acid is low compared with other formulations and no clinical studies have demonstrated its effectiveness for the treatment of dyslipidemias. OTC extended-release formulations of niacin offer ease of dosing and less flushing, although simple self-care measures can be applied to the less expensive immediate-release products to help reduce this. These include slowly titrating dose, administration after meals, avoiding hot drinks or alcohol, or incorporating aspirin 81 mg 30 minutes prior to niacin.

Niacin is inappropriate for the self-treatment of dyslipidemia. Hepatotoxicity is more common with extended-release preparations which require close monitoring. Other adverse effects include headache, nausea, vomiting, peptic ulcer disease, and diarrhea. Patients with diabetes who take 4.5 grams daily for 5 weeks had an average increase of plasma glucose by 16% and hemoglobin A1 C by 21%. Daily dosages of 2.5 grams or less increase plasma glucose by 4% to 5% and hemoglobin A1 C by 0.3% or less. Effects are dose-dependent and patients with diabetes should be monitored carefully. The risk of hyperuricemia occurs at dosages greater than 2 grams daily, and individuals with a history of severe gout should avoid niacin completely.[20]

Product Quality

Dietary supplement content is dependent upon the product and is not regulated by the FDA. If a supplement is warranted, consumers should look for products with US Pharmacopeia Verification or Consumer Labs Quality Seal. These independent agencies test for labeled ingredients and lack of contaminants within the product. Note: these seals do not indicate efficacy or safety of that particular supplement.

Summary

American adults take many types of vitamin supplements, despite limited evidence of their efficacy, especially in preventing chronic diseases such as cardiovascular disease and cancer. Supplements contain significant amounts of vitamins when consumed from multiple sources. Excess consumption of some vitamins may have detrimental health effects. Use of MMVM products appears to be safe; however, clinical outcomes have not been established. Although vitamin D and preconception folic acid may be appropriate for self care, a health care provider should monitor other vitamin supplements for disease prevention, such as niacin. Beyond supplementation as treatment for vitamin deficiencies, evidence is lacking.

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The authors and spouses/significant others have no financial interests to disclose.

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