Interactions between nutritional supplements and drugs are an important frontier in nutritional medicine. If nutritionally-oriented health practitioners do not establish their authority over that frontier, control of it will be taken by those intent on discrediting the use of nutritional therapies. An authoritative voice requires access to detailed, critical and objective information about the results of clinical and experimental studies of drug-nutrient and drug-supplement interactions.

**Media Coverage: Distorted and Incomplete**

Nutritional supplements have been hard hit in the press lately. Large meta-analyses have shown that supplements of beta-carotene and vitamin E increase mortality. Of course, these reports failed to reveal the whole story. The increase in cancer mortality associated with beta-carotene is limited to smokers and heavy drinkers; for others, beta-carotene supplements decrease the risk of colon cancer. The form of vitamin E used in most of the clinical trials with negative outcomes was synthetic D,L-alpha-tocopherol. Conclusions derived from studies of D,L-alpha tocopherol may have no relevance to the effects of natural D-alpha-tocopherol, and studies utilizing alpha-tocopherol as the only vitamin E isomer may have no relevance to supplementation with mixed tocopherols. In fact, high dose supplementation with alpha-tocopherol lowers plasma levels of gamma-tocopherol (which is a more potent antioxidant, anti-inflammatory and inhibitor of platelet activation) than alpha-tocopherol.

Many cardiologists turned against vitamin E supplements when they were shown to reverse the benefits of simvastatin-niacin therapy and halt the progression of coronary artery disease in this specific group of patients. There is scant evidence that vitamin E interacts with statin therapy of hyperlipidemic patients. Also ignored by the press was the evidence that selenium, 100 mcg/day, enhances the ability of statins to raise HDL2-C, and that fish oil, 4000 mg/day, raises HDL2-C by 40% even without statin therapy.

Beneficial drug-supplement interactions receive almost no attention in the public or medical press, despite the fact that several hundred separate beneficial interactions have been reported in the peer-reviewed scientific literature. Potentially hazardous interactions, in contrast, are being waved at doctors and patients like "falling rock zone" signs, even when no evidence for an interaction exists. Earlier this year, the Harvard Medical Letter warned its readers that combining chondroitin sulfate and aspirin might increase their risk of hemorrhage. Aspirin is well-known as an inhibitor of platelet function. Highly sulfated preparations derived from chondroitin sulfate have anticoagulant effects following parenteral administration. There is not a shred of evidence that oral chondroitin sulfate at the doses used to treat osteoarthritis has any antithrombotic effects. Obviously it has become more respectable to warn against the dangers of dietary supplements than to advocate their use.

**Supplements and Cancer**

A world-renowned specialist in the treatment of breast cancer has been publicly warning women that immune-boosting supplements increase the risk of breast cancer, citing as evidence the relatively low rate of breast cancer among women with AIDS and the fact that certain TH-2 related cytokines may enhance tumor progression. This type of warning ignores the large body of research that enhancement of natural killer cell activity or of TH-1 driven cellular immunity is of benefit for cancer treatment and prevention both. Extracts of the fungus *Coriolus versicolor* have been widely used and extensively researched in Asia as an aid to cancer chemotherapy, with benefits established in human clinical trials. *Coriolus* extracts enhance TH-1 activity.

In creating an electronic database of interactions between drugs, nutrients and dietary supplements (The Drug-Nutrient Workshop, www.Nutrition Workshop.com), I discovered that 21 separate natural products have been documented to enhance anti-cancer therapies in vivo by decreasing the toxicity of anti-neoplastic drugs. Some of these substances, like glutamine, melatonin, vitamin B6, and N-acetylcysteine, have been studied in human clinical trials. Other substances, like theanine and silymarin, have only been studied in laboratory animals. Still others, like coenzyme Q10, L-carnitine and magnesium, prevent toxicity by inhibiting the depletion of specific nutrients by specific agents, like adriamycin and cisplatin.

**Drug-Induced Nutrient Depletion**

Among the 878 drugs and fixed-drug combinations I studied, over 400 had specific nutrient-depleting effects. The substance depleted by the greatest number of drugs is coenzyme Q10. The effect of statins in inhibiting co-Q synthesis is well known. This effect is actually increased by co-administration of vitamin E (700 IU/day) along with statins, possibly because co-Q is consumed in the recycling of the oxidative metabolites of vitamin E (tocopheryl quinones) back to tocopherols.

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potential effects of the drugs being used in increasing the requirement for specific nutrients, perhaps necessitating corrective nutritional supplementation.

Several dietary supplements may also deplete nutrients. Calcium supplements, for example, impair absorption of iron and zinc from food. The effect of 600 mg of calcium on zinc status can be overcome by administration of 7.8 mg of supplemental zinc. Trimehtylglycine (betaine), a component of many products designed to lower homocysteine, may reduce carnitine levels by increasing carnitine excretion through the kidneys. A printed list of all the identified adverse nutritional effects of drugs and supplements would be awkward to use in clinical practice. A computer-based clinical tool allows the health practitioner to automatically identify the relevant depletions for each patient, depending upon the specific drugs and/or supplements being taken by the individual.

Adverse Drug-Supplement Interactions

When I surveyed the many reviews on adverse drug-supplement interactions which have appeared in the mainstream medical literature over the past few years, I was struck by the high degree of speculation and the low level of documentation.

The same is true for most of the books and compilations on the subject. The best documented drug-supplement interactions are pharmacokinetic.

They are caused by the effect of the supplement on drug absorption, metabolism or excretion. Most of the potential interactions described in reviews and compilations are pharmacodynamic. These are warnings based upon the ways in which known or suspected physiological effects of a supplement might impact on the pharmacological effect of a drug. These possible effects are interesting, but they may never occur, or they may be beneficial rather than harmful, depending upon the circumstances of the individual case.

There are, for example, 35 different dietary supplements with demonstrated ability to inhibit platelet function in vico following oral administration. (Some substances, like flaxseed oil, borage oil, and primrose oil, which are often classified as having platelet inhibiting effects, have been shown to not alter platelet function when fed to human volunteers.) It is possible that natural platelet inhibitors will show additive effects with each other or with aspirin or other antithrombotic drugs. Whether these effects occur at all and whether they are beneficial or hazardous is likely to depend upon the clinical circumstances. The aspirin-vitamin E interaction has been the most studied in this regard. Aspirin inhibits platelet aggregation; vitamin E inhibits platelet adhesion to the lining of blood vessels. Potential anti-platelet synergism exists. Use of low doses of vitamin E as alphatocopherol (50 IU/day) increased the risk of gingival bleeding by about 25% among men taking aspirin, according to an often-cited study. However, the addition of 400 IU/day of alphatocopherol to 325 mg aspirin/day significantly reduced the incidence of transient ischemic attacks (TIAs) in patients with previous TIAs, when compared to aspirin alone. To properly assess the risks and benefits of potential pharmacodynamic interactions, nutritional practitioners need to understand the results of clinical trials as they apply to their patients. In hypertensive male smokers, vitamin E supplementation, 50 IU/day, decreased the risk of ischemic stroke by 30% but increased the risk of hemorrhagic stroke by 145%. If the men also had diabetes, vitamin E decreased the risk of ischemic stroke by 77% without increasing the risk of hemorrhagic stroke.

The leader in provoking adverse pharmacokinetic interactions with drugs is St. John's wort, which has shown clinically significant adverse interactions with 24 different medications. What makes St. John's wort so problematic is its unusual ability to stimulate enzymes of drug metabolism and detoxification: the cytochrome P450 isozyme CYP3A4, which metabolizes about 50% of all drugs commonly used in the United States, and the P-glycoprotein (P-gp) transport protein. P-gp ejects a variety of xenobiotics from cells. It is part of a mechanism sometimes referred to as Phase 3 Detoxification. Drugs that are slowly absorbed and also are substrates for P-gp may have their plasma levels significantly reduced by St. John's wort. Zinc supplements induce the synthesis of another transport protein, metallothionein, which chelates minerals. Zinc-induced increase in tumor metallothionein inhibits the effectiveness of platinum-derived anti-neoplastic drugs. Supplemental zinc should be avoided by patients receiving cisplatin and related drugs.

The formation of an insoluble complex between minerals and drugs may significantly impair the absorption of quinoline or tetracycline antibiotics, thyroid preparations and L-DOPA, when these drugs are taken within a few hours of a mineral-containing preparation. Even some herbs, like dandelion and fennel, can be so rich in minerals that they inhibit absorption of these same drugs.

The mechanism involved in some adverse drug-supplement interactions has not been identified. Silymarin, a group of flavonoids found in milk thistle, was shown to reduce the bioavailability and blood levels of metronidazole (Flagyl) by 30% among healthy volunteers, an effect that could lead to therapeutic failure. None of the suspected mechanisms for this interaction are consistent with other known effects of milk thistle. Vitamin C (250 mg twice a day) plus vitamin E (200 IU twice a day), impaired the effectiveness of metronidazole in the treatment of H. pylori infection, again through an unidentified mechanism.

The drug that is most subject to adverse interactions with nutritional supplements is the anticoagulant, warfarin (Coumadin), which stops the cycle of vitamin K regeneration in the liver. I identified 49 natural products that could interfere with warfarin therapy; 21 of these were confirmed adverse interactions and 28 were possible but had never been actually demonstrated. Many of the possible...
interactions are linked to the presence of coumarins, chemicals with a structural similarity to warfarin, in herbs. It is possible that coumarins could displace warfarin from its binding to plasma protein, increasing the concentration of free drug in plasma, but this has never been confirmed. Some highly publicized supplement interactions with warfarin have failed confirmation in controlled studies. Coenzyme Q10 is structurally similar to vitamin K and has been reported to interfere with response to warfarin, based upon uncontrolled case reports; however, no effect of coenzyme Q10, 100 mg/day for 4 weeks, on warfarin was seen in a placebo-controlled trial. Similarly, early reports indicated increased bleeding in patients receiving warfarin and vitamin E together, but a controlled study showed no effect of vitamin E on the anticoagulant response to warfarin, as measured by INR, at doses up to 1200 IU/day.

Beneficial Drug-Supplement Interactions

The large numbers of beneficial drug-supplement interactions reported in the peer-reviewed scientific literature allow nutritional practitioners to employ innovative therapies demonstrated to enhance the effects of conventional medical therapy. Most such interactions reflect additive or complementary effects of supplements and drugs, or the ability of supplements to compensate for toxic drug effects that are not directly related to therapeutic effects. The supplements with the greatest number of well-researched beneficial drug interactions are fish oils. Controlled clinical trials have demonstrated that fish oil supplements can enhance the response to anti-inflammatory drugs, antiarrhythmic agents, anti-depressants, neuroleptics, beta-blockers, anti-lipemic drugs, insulin and lithium. The specific fatty acid distribution of the fish oil (EPA vs. DHA), the form (triglyceride, esterified fatty acid, or free fatty acid) and the dose needed to produce the desired effect vary considerably, depending upon the class of drug being studied. In general, high EPA preparations interact more favorably with psychiatric medications and high DHA preparations offer better support to cardiovascular medications. Omega-3 fatty acid esters appear to have a more profound anti-inflammatory effect, whereas free fatty acids derived from triglycerides are responsible for the antiarrhythmic effect and prevention of sudden cardiac death.

Even when dietary supplements do not enhance drug actions, they may offer protection against drug toxicity. Among the hundreds of beneficial drug-supplement interactions, there are 6 products demonstrated to prevent acetaminophen liver toxicity in experimental animals, 8 that decrease side effects of antipsychotic medications in humans, 6 that diminish the gastrointestinal toxicity of aspirin and NSAIDs, 9 that have been shown to prevent cisplatin toxicity, 4 that counteract corticosteroid side effects, 4 that protect against anticonvulsant toxicities.

The ability of nutritional therapies to significantly enhance responses to conventional medication will be an important factor in the growth and acceptability of integrative health care.

Conclusion

Almost half the drugs commonly used in the United States have the ability to deplete specific nutrients, creating a need for nutritional supplementation. Dietary supplements, in turn, may significantly affect the absorption, metabolism, pharmacologic actions, and toxicity of many drugs. Although adverse interactions between supplements and drugs have received extensive coverage in the medical and the public press, beneficial drug-supplement interactions are at least as important. I developed the Drug-Nutrient Workshop as a clinical tool that allows health practitioners to create individual patient files containing all the drugs and supplements each patient is taking. The software automatically generates a summary of all the potential interactions, beneficial or adverse, between drugs and supplements being taken, including the effect of drugs and supplements in depleting nutrients and the interaction between food or dietary components and drug or supplement absorption. One part of the summary lists supplements that are not being taken that have the potential to enhance the effects of drugs or supplements that are being taken. A mouse click on any section in the summary opens a window containing a description of the interaction selected and references, most of them to primary research in the peer-reviewed medical literature.

The effective practice of nutritional medicine demands that practitioners understand how nutritional therapies affect and are affected by, the drugs their patients are taking. Avoidance of potential adverse interactions is important for responsible care, but makes only limited use of the extensive data that are available. Applying knowledge of the proven ways in which dietary supplements can enhance treatment response to conventional drugs is the strongest counter-offensive to the current anti-supplement political climate.

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References

Drugs & Supplements


45. Huang et al, Vitamin C and E supplements to lansoprazole-amoxicillin-metronidazole triple therapy may result in reduced eradication rate of metronidazole-sensitive Helicobacter pylori infection. Helicobacter 2002; 7: 310-16.


