



Helping Patients Navigate the Claims of Complementary and Alternative Medicine

Despite a boatload of claims, there's little data to strongly support most supplements and non-traditional interventions. Neurologists can help their patients be safe and save money.

If only you knew what Kevin Trudeau knows. There are cures for cancer. There are cures for diabetes. There are cures—natural cures—for neurological diseases you might know about if you weren't too busy trying to stuff the pharmaceutical industry's pockets with cash. Trudeau, a convicted felon for charges of fraud and larceny, defendant in numerous lawsuits by the Federal Trade Commission, and subject to millions dollars in fines, is perhaps the dominating face of complimentary and alternative medicines.

The charlatan businessman has made fortunes off of misfortune, storming into the medical community sans lab coat or medical degrees with a “step right up folks” approach to shill his books, most notably, *Natural Cures 'They' Don't Want You to Know About*. “They” are you, and unfortunately for you there are enough people desperate for any semblance of relief that Trudeau's books have sold millions of copies and line shelves at reputable dealers like Barnes & Noble and WalMart.

Unbeknownst to those readers, or perhaps just unrecognized, is the reality that Kevin Trudeau and others like him simultaneously highlight two conflicting theories of complimentary and alternative medicines: That somewhere out there, there is an all-natural, magical pill to cure their suffering; or that all knowledge of alternative medicine comes from guys who claim to have been a “secret covert operative”¹ (as opposed to the yellow-pages-listed covert operative), who has been to Area 51 in Nevada.²

And with that competing against you, it's your job to help patients navigate through CAM, letting them know when and to what extent an alternative medicine might help them. Here, we take a look at what works, what doesn't, and how to set patients on the right course when you feel a CAM could be beneficial or at least not harmful.

General Approaches

“Complimentary and alternative medicine” or CAM is the term widely used by researchers, physicians, and the public to



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describe the spectrum of therapies from acupuncture and yoga to herbal supplements and medicinal alcohol consumption. While scientists are interested in quantifying and qualifying the effect of these various approaches, often the companies that promote and manufacture them are not.

And for good reason. If a company proved once and for all that ginkgo biloba, for example, had a measurable medicinal effect, the FDA would likely step in to monitor the product as a pharmacologic agent. This would in turn mean the manufacturers—who now simply produce, bottle, and market ginkgo—would have to undertake costly and time-consuming dose-finding studies and clinical trials. Their consumer base would shrink, too. While just about every American is a potential customer now, under FDA supervision, only those with prescription sheet in hand could purchase the product.

When one of those customers or would-be customers approaches you about CAM, it's important to find balance. "I think it is difficult to take hope away from patients," says Martin Farlow, MD, Professor of Neurology at Indiana

University School of Medicine, Vice Chair for Research in the Department of Neurology, and Associate Director of the Indiana University Alzheimer Center. "I think the neurologists should assure themselves that a CAM approach a patient and/or family wants to try is not dangerous to health nor costing inappropriate sums. Be neutral about the treatment, but remain supportive of managing their overall illness," Dr. Farlow says. He adds that in his experience about 70 percent of patients have a negative view of CAM and are dismissive.

The approach and attitude you take on the subject of CAM can influence your patients' willingness to discuss their use of alternative therapies with you. Brushing aside your patients' CAM use completely can appear close-minded and isn't likely to change their view of CAM. Instead they're likely to simply withhold their supplement use from your patient interviews. Neurologists shouldn't be "condescending or rude, but still firm in acknowledging that the evidence is uniformly either nonexistent or negative," says

Table 1: Selected Food Sources of Vitamin E

FOOD	Milligrams (mg) Alpha-tocopherol per serving	% DV*
Wheat germ oil, 1 tablespoon	20.3	100
Almonds, dry roasted, 1 ounce	7.4	40
Sunflower seed kernels, dry roasted, 1 ounce	6.0	30
Sunflower oil, over 60% linoleic, 1 tablespoon	5.6	30
Safflower oil, over 70% oleic, 1 tablespoon	4.6	25
Hazelnuts, dry roasted, 1 ounce	4.3	20
Peanut butter, smooth style, vitamin and mineral fortified, 2 Tablespoons	4.2	20
Peanuts, dry roasted, 1 oz	2.2	10
Corn oil (salad or vegetable oil), 1 tablespoon	1.9	10
Spinach, frozen, chopped, boiled, 1/2 cup	1.6	6
Broccoli, frozen, chopped, boiled, 1/2 cup	1.2	6
Soybean oil, 1 tablespoon	1.3	6
Kiwi, 1 medium fruit without skin	1.1	6
Mango, raw, without refuse, 1/2 cup sliced	0.9	6
Spinach, raw, 1 cup	0.6	4

*DV = Daily Value. The DV for vitamin E is 30 International Units (or about 20 mg alpha-tocopherol). Most food labels do not list a food's vitamin E content. A food providing 5 percent of the DV or less is a low source while a food that provides 10 to 19 percent of the DV is a good source. A food that provides 20 percent or more of the DV is high in that nutrient.

Source: <http://nccam.nih.gov/>

David Knopman, MD, Professor of Neurology at the Mayo Clinic in Rochester, MN.

And the numbers back up the claims. Less than 40 percent of patients who use CAMs tell their doctor, making it imperative for neurologists to ask patients about their non-traditional medical therapies. To varying degrees, a person's cultural identity may play a deciding role in how likely he or she is to use alternative medicine. Their home country may also be a factor. In the United States, 42 percent use CAMs. In Germany, up to 65 percent may use alternative therapies. The number is approximately 20 percent in the United Kingdom.³

When determining what other non-pharmacologic and prescription drugs a patient is taking, also be sure to find out how much, where they purchase the products, and what they spend before discussing the pros and cons of each agent with them.

Vitamin E

Vitamin E is a dietary compound that works as an antioxidant, scavenging toxic free radicals. Evidence that free radicals may contribute to the pathological processes of cognitive impairment including Alzheimer's disease (AD) has led to interest in using vitamin E in the treatment of Alzheimer's disease and Mild Cognitive Impairment (MCI).⁴

However, studies examining the role of vitamin E supplements have not been favorable. One of the latest analyses reviewed⁴ two unconfounded, double-blind, randomized trials in which treatment with vitamin E at any dose was compared with placebo for patients with AD or MCI. They concluded "there was no significant difference in the probability of progression from MCI to AD between the Vitamin E group and the placebo group. There was no significant difference between the placebo group and the Vitamin E group in adverse events."

Another study published⁶ in February shot down hope for

vitamins E and C, alone and in combination, concluding that use of the supplements didn't reduce the risk of AD or overall dementia over 5.5 years of follow-up. One study on the other side of the fence did find evidence to suggest that among elderly individuals with an APOE epsilon4 allele, there was an association between using antioxidant supplements in combination with NSAIDs and less cognitive decline over time.⁶

Those who used a combination of vitamins E and C supplements and NSAIDs at baseline declined by an average 0.96 fewer points every three years than did nonusers ($P < .05$) on the Modified Mini-Mental State exams. "This apparent effect was attributable entirely to participants with the APOE epsilon4 allele, whose users declined by 2.25 fewer points than nonusers every three years ($P < .05$)," the authors write.

It should be noted, though, that some studies have found protection against the development of AD with high intake of vitamin E from food sources, and though "the correct dosages are not known, a diet rich in these vitamins could probably reduce the risk of dementia,"⁷ according to one study by Landmark.

Patients should know most studies of the safety of vitamin E supplementation have lasted for several months or less, so there is little evidence for the long-term safety of vitamin E supplementation. The Food and Nutrition Board of the Institute of Medicine has set an upper tolerable intake level (UL) for vitamin E at 1,000mg (1,500 IU) for any form of supplementary alpha-tocopherol per day. Based for the most part on the result of animal studies, the Board decided that because vitamin E can act as an anticoagulant and may increase the risk of bleeding problems, this UL is the highest dose unlikely to result in bleeding problems.

Ginkgo biloba

Ginkgo biloba is one of the most popular supplements and has been a staple in the CAM market. Extracted from the leaves of the maidenhair tree, Ginkgo biloba has long been used in China as a traditional medicine for various ailments.⁸

A standardized extract is widely prescribed for the treatment of a range of neurological conditions including memory and concentration problems, confusion, depression, anxiety, and headache. The mechanisms of action are thought to reflect the action of numerous components of the extract and include increasing the supply of blood by dilating blood vessels, reducing blood viscosity, modification of neurotransmitter systems, and dropping the density of oxygen free radicals.⁸

So far, there's no reliable scientific evidence that Ginkgo biloba boosts memory or delays onset or progression of AD and other types of dementia. And the findings that do support these notions are typically from short-term studies involving smaller groups of patients.

There is, however, recent interest in EGb761 and its role in Parkinsonism. EGb761 is described as "a patented and well-defined mixture of active compounds extracted from Ginkgo biloba leaves, with neuroprotective effects, exerted probably via its antioxidant or free radical scavenger action."⁹

One such study in mice showed that EGb761 improved MPTP-induced impairment of locomotion in a manner that correlated with enhancement of striatal dopamine levels in a behavioral analyses.⁹ "These findings suggest that, in mice, EGb761 attenuates MPTP-

induced neurodegeneration of the nigrostriatal pathway and that an inhibitory effect against oxidative stress may be partly responsible for its observed neuroprotective effects," the authors write.

For patients interested in the supplement, Ginkgo biloba appears to be safe with no significant side effects compared with placebo, but patients with vascular diseases should avoid the supplement.

Folic Acid

The human body requires folate—the naturally occurring B vitamin found in leafy green vegetables, dry beans, and some fruits and other vegetables—to synthesize DNA and RNA and to manufacture red blood cells. Folic acid, the synthetic version

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that acts in the same way, is frequently added to grain products in the US and is also available as a supplement.

Low levels of folate (as well as vitamins B12 and B6) may lead to high homocysteine levels—which are associated with AD, among other conditions. Additionally, low folate levels can produce anemia. In pregnant women, a recent study¹⁰ of 388 pregnancies in 244 women confirmed “the prophylactic effect of folic acid supplementation on spontaneous abortion.” A few drugs are known to decrease folate levels. Among these are certain AEDs, including phenytoin, carbamazepine, and valproate.

All women of childbearing age should be getting 400mcg of folic acid each day, according to government guidelines, and should continue this amount while trying to get pregnant and during the first three months of pregnancy. If a woman is already pregnant, upping the dose to 600mcg is appropriate until breastfeeding, when the amount should be reduced to 500mcg. The AAN practice parameter recommendation is 0.4mg/day of folic acid in women of childbearing potential taking AEDs.

There is also some rationale behind the use of folic acid in depression as well as in stroke, but the support may be limited. According to a Mayo Clinic scale rating CAMs, the use of folic acid in depression receives a letter grade of “C” as it does separately for stroke—meaning there is unclear scientific evidence. On depression, the patient-friendly website (mayoclinic.com/health/drug-information/drugherbindex) summarizes: “Folic acid deficiency has been found among people with depression and has been linked to poor response to antidepressant treatment. Folate supplements have been used for enhancing treatment response to antidepressants. Limited clinical research suggests that folic acid is

not effective as a replacement for conventional antidepressant therapy.”¹¹

St. John’s Wort

Extract from the plant *Hypericum perforatum*, or St. John’s Wort, is best known for its work in patients with depression. It’s also had a wide scope of indications, including nerve pain, anxiety disorders, and, according to at least one website, bed wetting by children. Use of the plant dates back thousands of years. Ancient Greeks sniffed the plant to ward off evil spirits—a use alluded to in its botanical name.

For the previous two decades, St. John’s Wort has been extensively studied in Europe, and America has picked up ground in recent years. Some short-term studies suggest that the herb is more effective than placebo and just as effective as tricyclic antidepressants in the treatment of mild-to-moderate depression. Head-to-head studies of selective serotonin reuptake inhibitors and St. John’s Wort are more limited, but there is some encouraging data, and the agent scores a grade “A” on the Mayo Clinic rating scale—showing strong scientific evidence.

Hypericum has a more significant potential side effect profile than does Ginkgo biloba. As a complex herb, it activates liver enzymes and can undermine prescription and OTC medications. Be sure to tell feHypericum has a more significant potential side effect profile than does Ginkgo biloba. male patients it can interfere with oral contraceptive pills.

Acupuncture

Acupuncture uses very fine needles to pierce the skin to relieve pain, induce anesthesia, and achieve therapeutic ends.¹² Researchers believe that stimulation with the needles allows pain-killing endorphins to be

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released into the patient's system, thereby relieving pain.¹² Chronic head, neck, and back pain may respond to the treatment, but evidence in other areas is weak.

Some studies from the East have indicated therapeutic benefits in Parkinson's disease. However, one study¹³ published in August reviewed randomized controlled trials of acupuncture in PD and concluded, "the evidence for the effectiveness of acupuncture for treating PD is not convincing. The number and quality of trials as well as their total sample size are too low to draw any firm conclusion."

For headache, seven small trials of acupuncture have yielded mixed results.¹² One study that compared acupuncture with control treatment (no treatment or wait-list) showed significant improvement post-treatment with acupuncture (53 percent reduction in the frequency of disabling headache), but not with the control treatment (14 percent reduction); however, the importance of between-group differences was not tested.¹² Two trials comparing acupuncture with sham acupuncture found that the genuine intervention was significantly better at reducing headache intensity.¹² One of the two trials, though, had "serious" methodological problems.

If patients are set on visiting an acupuncturist, physicians should stress the importance of training, or possibly even direct them to properly trained and licensed practitioners to ensure safety.

The Right Approach

Whether a CAM is clearly indicated and provides much-needed benefit to a patient or a patient is set on trying an alternative therapy regardless of the clinical data, it's important to know the role you can play and how you can help.

Investigate the Ingredients. There's ample laboratory research to support various vitamins and components of supplements but ingredients are just the beginning. "You can know everything about ingredients," says Leslie Baumann, MD, a dermatologist and researcher who studies and writes about product ingredients and formulation.¹⁵ "But there's a lot more to the story...Just because something worked in the laboratory setting does not mean it will work in real life." Additional considerations include proper concentration and dosage, reliable bioavailability, and proper route of administration, among others.

Investigate Products and Manufacturers. Unfortunately, few published studies document the efficacy of specific supplement products in humans. Well-known and long-established brands may be expected to contain the ingredients claimed. As a further measure, look for products sold in Germany, where supplements are much more stringently regulated than in the US, Dr. Baumann suggests. "Products sold in Germany are probably better because

Current Complementary and Alternative Medicine Research Centers

The National Institutes of Health's National Center for Complementary and Alternative Medicine (NCCAM) has extended five-year research grants to a total of 11 Centers of Excellence for Research on Complementary and Alternative Medicine (CERCs). Of the four newest centers, announced last month, two may be relevant to neurology:

Wisconsin Center for the Neuroscience and Psychophysiology of Meditation at the University of Wisconsin, Madison:

Richard J. Davidson, PhD and his team "will examine the impact of two forms of meditation—loving-kindness/compassion meditation and mindfulness meditation—on the brain and body, focusing on the regulation of emotion and on emotional reactivity. Potential applications in health include biological and behavioral processes linked with emotions and/or stress, such as recurrent depression," according to an NCCAM announcement.

CAM as Countermeasures Against Infectious and Inflammatory Disease at Montana State University, Bozeman:

This center will "study biologically based CAM therapies and their effects on immune system function in infectious and inflammatory diseases. One project focuses on effects of botanical extracts—from apple polyphenols, which are concentrated in apple skins, and from yamoa, which comes from the bark of an African gum tree—on white blood cells, using models of infection and inflammation of the intestinal mucosa. A second project examines two compounds in licorice root—glycyrrhizin and 18-glycyrrhetic acid—for their potential antiviral effects in models of influenza and stomach virus. A third project will focus on bacterial products to see how they treat autoimmune diseases, like arthritis, which may also help build understanding of probiotic's action," according to NCCAM.

For information on the remaining nine CERCs and other currently funded research sites, visit <http://nccam.nih.gov/training/centers/descriptions.htm#4>.

Online Resources for Physicians and Patients

- The Mayo Clinic offers a comprehensive guide to both pharmacologic therapies and complementary medicine. The searchable database is user friendly, offering a grading system that weighs the evidence available for various CAM interventions:

mayoclinic.com/health/druginformation/drugherbindex

- The NIH's National Center for Complimentary and Alternative Medicine also provides a database on information about various alternative therapies, though reviews are not as in-depth as those offered by the Mayo Clinic. NCCAM does offer information about current trials and reports of broader issues related to CAM:

nccam.nih.gov/

- ConsumerLab.com offers some information about the research and purported benefits of various vitamins and supplements, but it's best known for its independent quality analyses. The group tests various products to ascertain whether they contain the active ingredients claimed in the stated concentrations and whether any potentially harmful ingredients may be included. There is a fee to access most reviews, though top-line results and warnings about potentially harmful products are available free of charge:

consumerlab.com

they're more regulated," she explains. Nonetheless, she says, don't automatically count out smaller brands without investigation.

Don't Judge by Cost. Well-known and established brands may be more reliable, but there is no relationship between cost and quality. High-cost formulations may be no more effective than cheaper ones. Dr. Baumann says she has seen the same formulations of Co-Q10 ranging in price from around \$30 up to \$100. She personally uses and recommends a low-cost formulation since she saw no discernable difference between it and the higher-priced one.

Don't Overlook Medical Uses for Supplements. Discussion of supplements and vitamins often focuses on restorative, rejuvenating, or cosmetic effects, like those in dermatology. However, supplements may benefit a wide range of neurology patients.

For example, because they do not eat meat, eggs, and dairy products, vegans do not receive omega-3 fatty acids through their diets. For possible heart health, Alzheimer's disease pre-

vention, improvement of depression, and other benefits, these individuals should be advised to take omega-3-rich Flaxseed oil supplements.

Good sources of omega-3 fatty acids include:

- Coldwater fish, like mackerel, tuna, salmon, and sardines
- Flaxseed and canola oils
- Soybeans and tofu
- Walnuts

The American Heart Association recommends people consume fish at least twice a week to increase their intake of omega-3 fatty acids. Patients concerned about this should also know that eating fewer foods with omega-6 fatty acids—like some meats, eggs, and oils—can also improve levels of omega-3 fatty acids in the body. People in the US have diets that have at least 10 times as many omega-6 as they do omega-3 fatty acids.¹⁴ One study has even found that mice that ate chow laced with omega-3 fatty acids had better brain defenses against Parkinson's disease.

Know the Risks. When there's evidence that a supplement can provide benefit, even if the physician cannot predict the degree of benefit, it is generally safe to recommend standard doses in otherwise healthy patients, Dr. Baumann says.

Some agents require caution. Because patients can overdose on vitamins A, D, E, and K, they should be advised to carefully follow dosage recommendations. **PN**

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