

The Role of Dietary Supplements in the Management of Pain

BY TIERAONA LOW DOG, MD

If there was ever a place that integrative medicine could play an important role in patient care, it is in the area of pain, especially chronic pain. You don't have to go very far back to recognize that plants have formed the foundation of our modern pharmacopeia. Hippocrates wrote more than 2,000 years ago about the use of the bark and the leaf of willow to manage fever and pain. In the 1830s, a German chemist was able to isolate salicin, which eventually led to the creation of acetylsalicylic acid, or aspirin. When you look at the history of herbal medicine, you cannot separate it from the history of western medicine because it was our pharmacopeia, our pharmacy. There is still much more we can learn about using plants to ease inflammation and pain.

The use of dietary supplements should be part of an integrative approach to pain management that includes appropriate conventional treatments, mind-body medicine, manual medicine, manipulative therapies, movement therapies, acupuncture, and nutrition. Supplements can be used to augment these other approaches, or may be preferable in some cases to conventional medications.

SAMe

S-adenosylmethionine (SAMe) is one of the most fascinating supplements for pain, depression, and mood. It donates the methyl group required in the final steps of neurotransmitter production (i.e., dopamine, norepinephrine, and serotonin). People with depression have been shown to have lower amounts of SAMe in their spinal fluid. A review of 10 studies by the Agency for Health Care Research and Quality (AHRQ), comparing SAMe to either placebo or to nonsteroidal anti-inflammatories (NSAIDs) for the relief of osteoarthritis (OA) pain, found it was similar in efficacy to NSAIDs, and superior to placebo (1). A later study compared celecoxib to SAMe (2). In the first month, celecoxib worked more rapidly than SAMe, but after two months of administration, there was no difference between the two treatments.

The AHRQ meta-analysis also looked at 28 clinical trials comparing SAMe to prescription antidepressants or placebo for depression (1). Overall, SAMe was found to be as effective as antidepressants and superior to placebo. It also has a relatively rapid onset of action for depression; antidepressant effects are usually noted within about one week.

SAMe is contraindicated in patients with bipolar disorder, but it doesn't appear to interact with most medications. Furthermore, there are very few adverse effects (AEs). It must be used as an enteric-coated product. Start low, go slow. The effective dose is 1,200 to 1,400 mg/day for depression and pain. Most of the time, you should start with 200 mg twice a day, and increase the dose every 3 to 5 days. Since it increases norepinephrine and serotonin, limited studies suggest SAMe might also be beneficial for fibromyalgia.

Rhodiola

Rhodiola rosea, which grows throughout Scandinavia and northern Europe, is a fascinating herb. Linnaeus, who gave us Latin binomials, wrote of the use of rhodiola to enhance mental clarity and fight fatigue. Currently, research is primarily being conducted in three therapeutic areas: depression, anxiety, and chronic fatigue syndrome. A phase 3 trial in 88 patients with depression found that 340 to 680 mg/day standardized extract improved depression and insomnia more than placebo (3). Another study found that 340 mg/day standardized extract significantly improved general anxiety disorder over 10 weeks (4). The most recent research suggests that rhodiola inhibits neurotransmitter degradation. Rhodiola can be adulterated in the marketplace, so I recommend that you purchase it from a company that standardizes the extract to the rosavin content.

MSM

Methylsulfonylmethane (MSM) is found in many glucosamine products. There is only one small 12-week pilot study on the use of MSM for knee OA (5). Is there any risk of harm? We don't think so. When our United

States Pharmacopeia (USP) committee looked at MSM safety, we didn't find any safety concerns but then again, there wasn't much to look at regarding evidence overall. If your patients are buying glucosamine and chondroitin, I recommend that they do not buy it with MSM.

Omega-3 and Omega-6 fatty acids

A 2004 AHRQ review found that omega-3 fatty acids, whether from fish or from supplements, reduces all-cause mortality (6). Current research shows that most people do not get enough omega-3 in their diet; many Americans consume only 300 to 600 mg/day. The Institute of Medicine recommends about 1.2 g/day, but admits that this figure may be conservative. Omega-3 fatty acids are important for reducing inflammation. A meta-analysis in *Pain* supports the hypothesis that omega-3 fatty acids improve pain outcomes after three months with respect to pain, duration of morning stiffness, number of painful joints, and NSAID use in patients with rheumatoid arthritis (RA) secondary to inflammatory bowel disease or dysmenorrhea (7). The review found that a dose of 2.7 g of EPA and DHA appears to be necessary for pain relief, which is higher than that recommended for other conditions.

Evening primrose oil, borage oil, and black currant seed oil all contain gamma-linolenic acid (GLA), an omega-6 fatty acid. GLA preferentially breaks down into dihomogamma-linolenic acid (DGLA), which competes with arachidonic acid, leading to a decreased production of inflammatory prostaglandins. There have been some studies on GLA for the treatment of RA, with very mixed results (8,9). A high dose—2.8 g/day GLA—appears necessary to achieve anti-inflammatory effects. Given the mixed research regarding GLA, and the high dose needed for pain relief, omega-3s are probably a better bet.

Bromelain

Bromelain is an enzyme found primarily in the stem of pineapple. It is available as a dietary supplement in the form of enteric-coated tablets and used widely, especially in plastic surgery, to minimize facial swelling and bruising. It is approved in European countries for acute swelling and inflammation. Bromelain is probably not very effective for chronic inflammation. It can affect fibrinogen and clotting if you use high doses, so it shouldn't be used before surgery, and exercise caution with warfarin as it inhibits CYP2D9. There have not been good safety studies on bromelain but the research shows that doses of 500 to 600 mg/day are not associated with significant AEs (10,11).

Avocado-Soy Unsaponifiables

Avocado-soy unsaponifiables (ASUs) are powerful anti-inflammatory agents that have a very beneficial effect on the articular chondrocytes. Four high-quality studies demonstrate that ASUs improve the pain and stiffness of knee and hip OA and reduce the need for NSAIDs (12). The dose is usually 300 mg twice a day, over an extended period of time. They have an excellent safety profile, and there are no known AEs.

Devil's claw

Devil's claw (*Harpagophytum procumbens*), a plant from the southern areas of the African continent, has been approved by the German health authorities as a treatment for rheumatic complaints. There have been three randomized controlled trials for acute back pain and eight trials for OA (13). Most of the studies found that devil's claw was equivalent to NSAIDs and COX-2 inhibitors for pain relief (14). Devil's claw is very well tolerated; the only adverse effect is gastrointestinal discomfort. I often combine it with bromelain for acute back pain.

Willow

There are many salicin-containing plants, including willow, meadowsweet, cottonwood, aspen, poplar, and wintergreen. Some people may not get the pain relieving effect of willow (*Salix spp*), since the conversion of salicin to the more active salicylic acid seems to be genetically predetermined and influenced by gut flora. Studies on willow bark are few, methodologically poor, and provide mixed results for acute back pain and OA (15,16). One issue with willow bark products is that the level of salicin can vary dramatically across various willow species, from 2% to 11% depending upon the species and the time of year it was harvested. It is probably advisable, if using willow bark, to use a standardized extract that provides a daily dose of 240 mg salicin. A full dose of willow extract, 240 mg/day, has less of an inhibitory effect on platelet aggregation than 100 mg/day of aspirin, so it may offer a safer alternative for some patients (17).

Ginger and Turmeric

Many researchers are exploring the use of ginger (*Zingiber officinale*), boswellia (*Boswellia serrata*), and turmeric (*Curcuma longa*) for pain relief. They all inhibit COX-2, as well as other inflammatory mediators. Ginger is effective but requires a high dose to achieve pain relief. In clinical trials, blinding was often ineffective since one of the major side effects noted was burping up

ginger and heartburn (18). Ginger is a prokinetic agent, and is effective for gastroparesis and constipation-dominant irritable bowel syndrome (IBS). A study in 24 healthy individuals showed that 1,200 mg of dried ginger (1/4-1/3 teaspoon of ginger powder) accelerated gastric emptying and stimulated antral contractions more than placebo (19).

Currently, there are 21 phase 2 or phase 3 studies on turmeric being conducted at the NIH for a variety of conditions. Turmeric is one of my favorite botanicals for a variety of reasons. It's undoubtedly a very powerful anti-inflammatory for the GI tract, and was shown to be effective in reducing polyp formation in patients with familial adenomatous polyposis (FAP) (20). However, the question for patients using turmeric for arthritis or chronic back pain is how to get the active curcuminoids out of the gastrointestinal tract and into the systemic circulation. To enhance bioavailability and absorption, patients should take turmeric with food, use a lipid based extract, and/or purchase a product that contains piperine, an alkaloid from black pepper that can dramatically increase bioavailability.

Peppermint oil

Peppermint oil (*Mentha piperita*) is excellent for diarrhea-dominant IBS. It significantly prolongs orocecal transit time and directly inhibits smooth muscle contractions by interacting with calcium channels. Since it is fat soluble, a product that is enteric-coated is needed (21). A 2005 review of 12 controlled trials concluded that it was superior to placebo. All three studies that compared it smooth muscle relaxants showed that it was equally effective (22). This is especially good news given the poor pharmaceutical alternatives.

Topicals

Various topical analgesics are effective for pain. Capsaicin is highly effective in relieving neuropathic pain. One can pretreat the associated burning sensation with baby aspirin. After about 10 days of using it three times a day, the pain diminishes dramatically in many patients. Topical gels of arnica are effective for OA pain (23). Products in the United States sold as homeopathica arnica can be an excellent choice since they contain 10% herbal arnica extract. Topical arnica also works well for bruises, sprains, and strains. Comfrey root, which used to be known as knit bone, is very popular in Europe for the relief of minor aches and pains. A recent study found that 4 g/day

comfrey root extract ointment was superior to placebo for relief of acute back pain. It is fast acting; effects are achieved in less than an hour (24). Make sure not to use arnica or comfrey root ointments on open wounds.

Nature has provided us with many remedies that can help reduce pain. One of the beauties of herbal medicine that researchers are beginning to appreciate is that they don't work on one single pathway. They affect multiple enzyme systems, multiple biochemical pathways, meaning that although the overall effect may be subtler than conventional therapies, their side effect profile is often also much less.

There are a lot of things to think about when considering dietary supplements. Think carefully about the potential benefits and risks. Also, one must pay attention to quality. The FDA released new good manufacturing practices (GMPs) in 2007, which should do a lot to help tighten up quality in the industry. Unfortunately, some small companies may not survive the transition, but the overall quality of supplements should increase, which is good news for our patients.

There are many resources available for information related to dietary supplement quality, including consumerlabs.com, which lists companies that consistently pass independent third-party testing. You can also look for the USP or NSF quality seals, and lastly, look for products that have been used in clinical trials. ■



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