

Alternative Therapies for Traditional Disease States: Osteoarthritis

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Americans spend more on natural remedies for osteoarthritis than for any other medical condition. In treating osteoarthritis, glucosamine and chondroitin sulfate, two of the molecular building blocks found in articular cartilage, are the most commonly used alternative supplements. In randomized trials of variable quality, these compounds show efficacy in reducing symptoms, but neither has been shown to arrest progression of the disease or regenerate damaged cartilage. Although few clinical trials on S-adenosylmethionine exist, preliminary evidence indicates that it relieves pain to a degree similar to that of nonsteroidal anti-inflammatory drugs but with fewer side effects. Clinical trials of dimethyl sulfoxide offer conflicting results. Neither ginger nor cetyl myristoleate has proven clinical usefulness. (Am Fam Physician 2003;67:339-44. Copyright© 2003 American Academy of Family Physicians).

Osteoarthritis is the leading medical condition for which persons use alternative therapies.¹ Patients often seek alternative therapies after having side effects or gaining incomplete relief of symptoms with conventional medications. Alternative therapies used for the treatment of osteoarthritis include herbs, supplements, and nondrug modalities such as exercise, physical therapy, acupuncture, and electromagnets. Unlike manufacturers of conventional medications, the herbal and supplement industry is not regulated by the U.S. Food and Drug Administration (FDA); therefore, supplement composition (i.e., proportion of active ingredient in a preparation) usually varies. Physicians should be familiar with evidence regarding the safety and efficacy of alternative modalities used to treat osteoarthritis, so they can provide their patients with accurate and up-to-date information.

Glucosamine

Glucosamine sulfate, which is derived from oyster and crab shells, is a popular treatment for osteoarthritis symptoms. In vitro studies² have shown that glucosamine stimulates cartilage cells to synthesize increased amounts of glycosaminoglycans and proteoglycan ground substance. High dosages of glucosamine have

been shown to have mild anti-inflammatory effects in animal models.³ No published studies document arthroscopic improvement in arthritic cartilage with glucosamine use in humans.

Most human clinical trials⁴⁻⁷ have been relatively short term and have had varied results. A recent meta-analysis, funded by a grant from the National Institutes of Health (NIH), concluded that glucosamine may show some efficacy over placebo in relieving painful symptoms.⁸ [Evidence level A, meta-analysis]

A recent Cochrane Review concluded that current evidence from clinical trials (1) does not analyze the long-term effectiveness and toxicity of glucosamine; (2) does not differentiate which joints and which levels of severity of osteoarthritis warrant this therapy; (3) does not differentiate which dosage and route of administration are best; and (4) does not demonstrate whether glucosamine modifies the long-term progression of osteoarthritis.⁹ [Evidence level B, systematic review of lower-quality randomized controlled trials (RCTs)] In addition, 75 percent of the trials analyzed in the Cochrane Review⁹ used one brand exclusively, thus failing to shed light on the numerous other preparations available.

There have been no published studies documenting arthroscopic regeneration of articular cartilage following glucosamine adminis-

See page 237 for definitions of strength-of-evidence levels.

Glucosamine has been shown to be well tolerated, with few significant side effects compared with nonsteroidal anti-inflammatory drugs.

tration. Glucosamine is supplied in tablets and capsules. The usual dosing schedule for glucosamine is 1,500 mg per day in three divided doses⁹ (Table 1). Research suggests that the supplement must be taken for at least one month before improvement in symptoms can be expected to occur.⁸ Glucosamine has been shown to be well tolerated, with few significant side effects (mainly gastrointestinal discomfort) compared with nonsteroidal anti-inflammatory drugs (NSAIDs).

Chondroitin

Chondroitin sulfate also has demonstrated efficacy in improving the symptoms of osteoarthritis by acting as a building block of proteoglycan molecules.^{8,10,11} Commercially available chondroitin is derived mostly from shark and cow cartilage and is supplied in tablet and capsule form.

Like glucosamine, chondroitin's mechanism of action in osteoarthritis may involve both anti-inflammatory properties and substrate provision for proteoglycan synthesis. However, as with glucosamine, the role of substrate provision is theoretic and has not been proved to affect cartilage regeneration or repair.

Two recently published meta-analyses indicated that chondroitin may be superior to placebo in reducing the pain of osteoarthritis.^{8,12} [Reference 12—Evidence level A, meta-analysis] One of these analyses⁸ cautioned that study results may have been exaggerated by publication bias related to the manufacturer's sponsorship. The second meta-analysis¹² found chondroitin to be superior to placebo in reducing the painful symptoms of osteoarthritis, but researchers cautioned that trials with larger cohorts of patients and over longer periods must be conducted to substantiate these claims. However, these studies suggest that chondroitin improves the symptoms of osteoarthritis.

Comparison of chondroitin with NSAIDs has shown that patients with osteoarthritis have fewer gastrointestinal side effects with

TABLE 1
Alternative Therapies for Osteoarthritis

<i>Agent</i>	<i>Usual dosage</i>	<i>Side effects of drug interactions</i>
Glucosamine ⁹	1,500 mg per day in three divided doses	Gastrointestinal discomfort*
Chondroitin ⁸	1,200 mg per day in three divided doses	Gastrointestinal discomfort
SAMe ¹⁷	400 to 1,200 mg per day	Gastrointestinal discomfort, mainly diarrhea
DMSO ³¹	Daily application of 25% topical gel	Skin rash, pruritus
Avocado/soybean unsaponifiables ³⁴	300 mg per day	None
Exercise	30 to 60 minutes of low-impact exercise	—

SAMe = S-adenosylmethionine; DMSO = dimethyl sulfoxide.

**—Some basic-science, nonhuman studies suggest the possibility that glucosamine raises blood glucose levels. Information from references 8, 9, 17, 31, and 34.*

chondroitin. Chondroitin is well tolerated; it appears to have a slower onset of action but to work longer than NSAIDs.¹³ Overall, chondroitin may offer a safe alternative in the treatment of the symptoms of osteoarthritis. The usual dosing schedule for chondroitin is 1,200 mg per day in three divided doses (*Table 1*). As with glucosamine, research indicates that the supplement must be taken for at least one month before any symptom relief occurs.⁸

Glucosamine/Chondroitin Combinations

The use of glucosamine and chondroitin together for the treatment of osteoarthritis has become extremely popular; however, there is little evidence that this combination is any more effective than either supplement alone.¹⁴ A randomized, double-blind, placebo-controlled trial¹⁵ studied the effect of a combination of glucosamine, chondroitin, and manganese ascorbate on osteoarthritis of the knee and lower back. The combination was given for 16 weeks to 34 men in the United States Navy. A significant improvement was found in subjects who had knee symptoms but not in those with low back symptoms. No significant side effects were reported.

Currently, the National Center for Complementary and Alternative Medicine (NCCAM), which is part of the NIH, is conducting the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), which will compare the efficacy of glucosamine, chondroitin, a glucosamine/chondroitin combination, a cyclooxygenase-2 (COX-2) inhibitor (celecoxib), and placebo in the treatment of knee pain associated with osteoarthritis.

S-Adenosylmethionine

S-adenosylmethionine (SAMe) is a naturally occurring compound found in all living cells that is commercially produced in yeast-cell cultures. A methyl donor, it is important in methylation reactions that aid in the production of cartilage proteoglycans.¹⁶ SAMe has been available by prescription in Europe since 1975, where it is used to treat arthritis

Chondroitin may offer a safe alternative in the treatment of the symptoms of osteoarthritis.

and depression.¹⁷ A number of studies have found SAMe to be more effective than placebo in improving pain and stiffness related to osteoarthritis.¹⁸⁻²² However, many of these studies were nonrandomized, uncontrolled, and unblinded, and some were flawed statistically. No studies documenting disease arrest or reversal are found in the literature.¹⁷ There is, however, some evidence that SAMe is often as effective as NSAIDs, with a lower incidence of side effects.^{18,21-27}

Persons interested in using this agent may find SAMe to have a prohibitively high cost. Reported dosage ranges vary from 400 to 1,200 mg per day.^{18,21-27} Side effects include occasional gastrointestinal disturbances, mainly diarrhea.¹⁷

Cetyl Myristoleate

A new agent promoted for osteoarthritis treatment is cetyl myristoleate, a material synthesized from cetyl alcohol and myristoleic acid. The rationale for its use in osteoarthritis stems from the hypothesis that cetyl myristoleate may inhibit the cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism and, therefore, decrease production of pro-inflammatory prostaglandins and leukotrienes. Physicians should hesitate to advocate the use of this product until higher-quality clinical evidence has been published.

Ginger

Ginger (*Zingiber officinale*), obtained from the root of the ginger flower, has been used in Ayurvedic medicine (a traditional Hindu system of medicinal practices using combinations of herbs, purgatives, rubbing oils, etc.) for the treatment of inflammation and rheumatism. It is believed that ginger inhibits

Many of the studies supporting the use of S-adenosyl-methionine for improving osteoarthritis-related pain were nonrandomized, uncontrolled, and unblinded, and some were flawed statistically.

prostaglandin and leukotriene synthesis.²² A recent randomized trial²⁸ comparing ginger and ibuprofen showed greater efficacy of ibuprofen and no significant difference between ginger and placebo. No side effects or drug interactions have been reported.

Dimethyl Sulfoxide (DMSO)

Dimethyl sulfoxide (DMSO), a sulfur-containing substance produced from wood pulp,²⁹ has been used topically for relief of osteoarthritis symptoms. It is a scavenger of reactive oxygen species, and it functions as an anti-inflammatory agent.³⁰

One study³¹ conducted in Germany examined the effect of percutaneous treatment with DMSO in patients with osteoarthritis. In this double-blind, placebo-controlled study, daily use of a 25-percent gel preparation of DMSO for three weeks resulted in improvement in

pain symptoms during activity and at rest. These results have not been replicated in any trials in the United States. Side effects include skin rash and pruritus; drug interactions are unknown.²⁹ DMSO is available as a gel, liquid, or roll-on.

Boron

The element boron plays a key role in the chemical make-up of bones and joints through its effects on calcium metabolism. In areas of the world where dietary boron intake is usually 1 mg or less per day, the estimated incidence of osteoarthritis ranges from 20 to 70 percent, while in areas of the world where boron intake is 3 to 10 mg per day, the incidence of osteoarthritis is only zero to 10 percent.³² Evidence from one small, double-blind, randomized, placebo-controlled trial³³ suggests that boron supplementation may benefit patients with osteoarthritis.

Other Herbs/Supplements

A recent Cochrane review³⁴ focusing on osteoarthritis attempted to identify evidence for several herbal products, including *tipi*, capsaicin, *reumalex*, and avocado/soybean unsaponifiables. For the most part, this review found only sparse and insufficient studies of these products. However, avocado/soybean unsaponifiables in a 300-mg daily dosage did reduce NSAID use and provide long-term symptomatic relief in two well-done clinical trials of three and six months. Patients with osteoarthritis of the hip appeared to attain a greater degree of benefit.³⁴

Nondrug Modalities

Several systematic reviews of RCTs suggest that exercise and physical therapy result in a reduction of disability and pain in patients with osteoarthritis. However, blinding of such trials is problematic, and the participants in these trials may not have been representative of the general population.³⁵

A 1997 NIH Consensus Statement³⁶ on acupuncture listed osteoarthritis as one of the

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disorders “for which the research evidence is less convincing but for which there are some positive clinical trials.” Proponents of acupuncture have argued that proper acupuncture modalities were not used in these trials. Although acupuncture has been promoted as a safe therapy, significant infections have occurred, including human immunodeficiency virus and hepatitis, as a result of the use of unsterilized needles.³⁷

As shown in *in vitro* studies, electromagnetic fields stimulate chondrocyte proliferation and increase synthesis of proteoglycan.^{38,39} Two recent RCTs^{40,41} of pulsed electromagnetic field therapy for knee osteoarthritis showed this treatment to be superior to placebo in reducing symptoms. More research in this area is needed.

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