INTEGRATIVE THERAPIES FOR CHRONIC PAIN AND INFLAMMATION MANAGEMENT

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INTRODUCTION

Physicians historically have been considered by the public to be experts in the diagnosis and treatment of acute and chronically painful conditions that afflict the human body. Many patients now see complementary and alternative medicine (CAM) practitioners for alternatives to these treatments. As with most conditions, the best solution for patients is the integration of CAM with conventional therapies. This article addresses natural therapies for the treatment of chronic pain and offers an evidence base for safe and effective use of these therapies.

CONVENTIONAL CHRONIC PAIN MANAGEMENT

Some chronic pain cases are iatrogenically induced as a result of less-than-desirable surgical outcomes. Other cases may result from the inability to adequately repair a traumatic injury, from the chronic pain of degenerative joint disease, or from malunions of fractures or surgical osteotomies.

Acute musculoskeletal pain can become chronic in some patients. Resolution of acute pain to no pain is the ideal scenario; however, some patients become chronic pain-management cases.

Chronic pain patients have available to them various levels of interventional therapy which allow them to perform daily-life activities.

Pain management specialists are usually anesthiologists that have advanced training in pain management. These specialists are proficient in assessing the patient's needs for various levels of intervention. Narcotic analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs) may be tried, along with physical medicine modalities (eg, whirlpools, ultrasound). Interventional pain pumps with various compounded analgesics may be used for ongoing pain management. Surgically implanted stimulation units are becoming popular with many pain specialists for the treatment of chronic pain.

Chronic pain patients who are not surgical candidates for electrical-stimulation implants or pain pumps need the expertise of CAM practitioners in the medical treatment of their chronic conditions. Oral and injectable opioid derivatives are excellent medications for short-term pain management; however, the risk of habituation is prevalent with long-term use.

Oral and injectable steroids are excellent anti-inflammatory agents for conditions where there is acute inflammation, but long-term use has demonstrated many adverse clinical reactions, such as weight gain and connective-tissue atrophy.

With the advent of NSAIDs, the treatment options for chronic pain management increased. However, NSAIDs were not without their own set of problems, as noted by recent US Food and Drug Administration (FDA) actions involving the cyclooxygenase-2 (COX-2) line of drugs, such as Vioxx, Celebrex, Bextra, and Mobic. The addition of "black box" warnings on the use of these COX-2 drugs regarding cardiovascular adverse reactions added to the existing list of adverse reactions of the NSAIDs involving both COX-1 and COX-2 drugs.

A comprehensive list comparing the toxicities of NSAIDs appeared in *Drug Consults*.[1] The list of adverse reactions caused by the use of NSAIDs included bone marrow depression, gastrointestinal irritation and bleeding, peptic ulcers, tinnitus, hepatitis, and renal dysfunction, and now with the COX-2 inhibitors, severe cardiovascular risks are being reported.

A rarely publicized side effect of chronic NSAID use is the reduction in thickness of the hyaline cartilage of joints. NSAIDs are prostaglandin inhibitors. It is also known that they are proteoglycan synthesis inhibitors. Proteoglycans are essential building blocks for cartilage growth and repair. NSAID-induced arthropathy and necrosis should be avoided in long-term joint pain management.[2,3]

The prudent physician who has made a diagnosis of a painful arthritic condition or neuromuscular pain syndrome should look for an integrative approach to help restore health and function and relieve pain in light of the recent FDA recalls of several COX-2 NSAIDs. An economic reaction that has resulted from these withdrawals has been the dramatic increase in the cost of the remaining available COX-l and COX-2 inhibitors.

THE NEED FOR ALTERNATIVES

In light of the NSAIDs' adverse reaction profiles and increased patient costs, the physician needs to explore the use of integrated therapies that have proven clinical results with minimal to no adverse reactions.

Many of my allopathically trained colleagues have voiced concerns regarding the use of integrative therapies in their practices. Some have said, "These things are unproven," "there is no FDA scrutiny over these products," "they don't work all the time," "junk science," "there is no scientific, double-blind, placebo-controlled studies on their safety or effectiveness," and "the FDA has pulled Ephedra off the market due to deaths caused by this substance."

Before incorporating integrative therapies into my practice more than 12 years ago, I entertained many of those same questions regarding integrative medicine and nutriceuticals. My training in podiatry school was allopathically-based, so it was difficult for me to assimilate a new medical model and an integrative approach to disease treatment. However, during my training at the National College of Naturopathic Medicine, I discovered the scientific basis for the use of many nutriceuticals. Indeed, there were numerous double-blind, placebo-controlled studies involving many nutriceuticals. I also learned that all nutriceutical manufacturers are not alike, because most are not FDA-approved as pharmaceutical manufacturers. However, there are several nutriceutical companies in the United States that are now approved by the FDA and have voluntarily submitted to credentialing as a good manufacturing practice (GMP) facility, with rigorous standard operating procedures. Many of these ethical companies import nutriceuticals from countries like Germany, Japan, Sweden, and Italy, which produce them in licensed pharmaceutical manufacturing plants. Some of these products are available by prescription only in those countries.

I would like to offer to my colleagues some nutriceutical options to consider for chronic pain management for patients who suffer from chronic joint and neuromuscular pain. Some of these options are available from GMP-certified manufacturers.

Patients like to have a doctor's recommendation and dosing instructions for nutriceuticals, rather than taking a chance on an inferior product through a retailer or the Internet. Not knowing a nutriceutical's appropriate dosing, warnings, adverse reactions, and drug-to-nutriceutical interactions can be dangerous. In addition, patients who self-treat may have the wrong diagnosis and may be treating with an inappropriate nutriceutical regimen.

Botanical-based extracts that I use for chronic joint pain in combinations are: turmeric, boswellia serrata, ginger extract, and white willow bark extract. I also use capsaicin topically for certain types of pain syndromes, such as diabetic neuropathy, post-herpetic neuralgia, and arthritis pain.

The following brief synopsis of each of these botanical extracts outlines the mechanisms of action in the relief of pain, and cites peer-reviewed clinical studies supporting their use.

Natural Therapies for Pain Control

Turmeric

Turmeric (from the dried root of *Curcuma longa*), whose major pigment compound is curcumin, has been shown to have potent anti-inflammatory activities with specific lipoxygenase- and COX-2- inhibiting properties, including cytokines (TNF alpha and IL-1 beta).[4]

Curcminoids have been shown to suppress super oxide anions and inhibit lipid peroxidation. In a study by Mukhopadhyay et al, curcumin was shown to demonstrate only one-half the effectiveness of cortisone or phenylbutazone for chronic inflammation in rats.[5]

Interactions: Curcumin should be used with caution in patients who are taking metformin due to potential constriction of the afferent renal arteriols with resultant hypertension.

Dosage: 200 to 500 mg 4 times daily.[4,6]

Boswellia

An *in vitro* study of Boswellia (also known as frankincense) demonstrated a marked inhibitory effect on both the classical and alternate complement systems. Immatkar et al, in a randomized, double-blind study, found Boswellia to be effective in the treatment of osteoarthritis (OA) of the knee.[7]

An *in vitro* study of the effects of Boswellia specifically, and in a dose-dependent manner, showed that Boswellia blocks the synthesis of pro-inflammatory products of 5-lipoxygenase, including leukotriene B4 (LTB4).[8]

A negative placebo-controlled study on rheumatoid arthritis (RA) found no significant differences in pain relief between the 2 groups in any measured parameters. However, NSAID dosage decreased 5.8% in the treatment group, compared to 3.1% in the placebo group.[9]

Interactions: None reported.

Dosage: 300 mg 3 times daily.[7,8]

White Willow Bark Extract

White Willow bark extract (*Salix alba*), an extract of the willow tree bark, is effective for the treatment of pain, especially low back pain. In a study comparing the efficacy of white willow bark extract to refecoxib in 228 randomly-assigned individuals with low back pain, subjects were treated for a period of 4 weeks. In all measures of pain relief, White Willow bark extract was found to be as effective as refecoxib.

Salicin from White Willow bark extract is converted in the liver to acetyl salicylic acid (ASA). This liver conversion of salicin to ASA helps to prevent some of the gastrointestinal complications associated with the chronic use of oral aspirin.[10]

Interactions: Should not be used in patients taking warfarin or heparin.

Dosage: 25 mg 4 times daily.

Capsaicin

Topical preparations of capsaicin, ranging in strength from 0.025% to 0.075%, have been available over the counter for several years. This substance is derived from cayenne pepper, the fruit of *Capsicum frutescens*. Studies have shown that capsaicin has been effective in the treatment of OA, RA, and peripheral neuropathic pain secondary to diabetes and phantom pain post-amputation.[11]

When applied topically, the active ingredient of capsaicin first stimulates, then blocks small-diameter pain fibers by depleting them of their neurotransmitter substance "P." Substance P is thought to be the principal chemo-mediator of pain impulses from the periphery via the "C" fibers.[12]

Interactions: When treatment first begins, this topical has a burning sensation when applied to the skin. If applied 3 to 4 times a day, the burning sensation subsides. Care must be taken to not apply this to mucus membranes, open wounds, or the eyes.

Dosage: Topical application.

Ginger

Topically applied combinations of ginger rhizome extract (*Zingiber officinalis*) have been shown in studies to inhibit prostaglandin (PGE2) and leukotriene synthesis. Ginger also inhibits platelet aggregation and contains proteases similar to Bromelain, an enzyme derived from pineapples, which will be discussed in the next section.[13,14]

Interactions: While some theoretical issues have been raised, no interactions have been documented regarding ginger.

Dosage: 250 mg 3 times daily.

Bromelain

Bromelain is derived from the stem of the pineapple plant *Ananas comosus*. It is a mixture of sulfur-containing proteolytic enzymes or proteases and has been used to speed healing time and reduce pain post-operatively and in athletic injuries.

Several anti-inflammatory mechanisms have been reported in the literature, such as Bromelain's activation of plasmin production from plasinogen, reduction of kinin via inhibition of conversion of kinogen to kinin, and proteolytic degradation of circulating immune complexes.

Bromelain's activity is measured in milk-clotting units (MCUs), and the standard dose for a product at the potency of 1,800-2,000 MCUs is 125-450 mg. This dosage can be taken 3 times a day on an empty stomach. Bromelain has been shown to help reduce the amount of steroids needed for clinical pain relief in RA patients.[15,16]

Two studies demonstrated that Bromelain, when given in high doses, has the potential risk of increasing the incidence of tachycardia in patients with pre-existing hypertension.[17] Bromelain also has been shown to cause an IgE-mediated respiratory allergic reaction in some patients.[18]

Interactions: Increases absorption of tetracycline.

Dosage: 125-450 mg.

Glucosamine Sulfate

Glucosamine sulfate (GS) is one of several naturally occurring amino sugars that are essential for the rebuilding and healthy maintenance of connective tissue by stimulating proteoglycan synthesis and inhibiting degradation of protoglycans. As the body ages, there is an increase in glycation of hyaline cartilage, which reduces the production of proteoglycans involved in joint cartilage maintenance, joint movement, and lubrication. Medical science has recognized that this loss of joint lubrication will result in decreased interarticular hydration and joint pain. This glycation of cartilage in the joint can be reversed in some cases. Synvisc Hylan G-F20 is an injectable glycosaminoglycan hylan polymer produced from chicken combs.[19] This viscous material is injected into knee joints to relieve symptoms associated with OA. Relief of symptoms is usually temporary, and the injections may need to be repeated.

Glucosamine sulfate is an essential component of proteoglycans and is required to re-establish proteoglycan levels and promote incorporation of essential sulfur into cartilage. A meta-analysis of 13 double-blind, placebo-controlled clinical trials revealed that stabilized oral glucosamine sulfate was statistically superior to placebo in all 13 studies, as measured by global pain scores in the treatment of OA.[20]

In other clinical trials in which stabilized glucosamine sulfate was compared to NSAIDs, long-term reductions in pain were greater in patients receiving glycosaminology (GAG) care for the treatment of OA.[21] One study found that patients with polyarthritis and arthritis of the hip had only a 43% and 49% positive response rate to GS therapy.[17]

The most common side effects reported with GS use include epigastric discomfort, heartburn, diarrhea, nausea, dyspepsia, vomiting, and constipation. Complaints are generally mild and can be reduced or eliminated by taking GS with food. All gastrointestinal (GI) complaints are reversed when treatment is discontinued.

GS administration should be monitored in patients with type 2 diabetes because there was evidence in one study that in some patients, GS may cause an activation of the hexosamine pathway and may induce insulin resistance in multiple insulin-sensitive tissues.[22]

Interactions: No drug interactions have been reported.

Dosage: The recommended dose of GS is 1,500 mg daily, preferably taken away from food, unless GI upset is noted. Patients should be advised that clinical results may not be noted for at least 6 weeks.

Chondroitin Sulfate

Chondroitin sulfate (CS) is a glycosaminoglycan that is a major component of cartilage, which is rich in sulfur and related to GS. The sources of CS are shark cartilage, bovine cartilage extracts, and sea cucumber.

CS contains a mixture of intact or partially-hydrolyzed GAGs, with molecular weights ranging from 14,000 to more than 30,000. Although CS is popular with the public, it is less effective than GS in relieving joint pain. Better clinical results are seen with GS, primarily due to better intestinal absorption. Absorption rates for stabilized GS are 90%-98%, while absorption rates for CS are estimated at anywhere from 0%-13%. CS molecules are 50 to 300 times larger than GS.[23] If you prescribe CS, use a marine-sourced low molecular weight (less than 16,000 Daltons) for better absorption, mixed with stabilized GS.

Interactions: No drug interactions have been reported.

Dosage: 1,200 mg/daily, taken on an empty stomach.

S-Adenosylmethionine

S-Adenosylmethionine (SAMe) is formed in the body from the essential amino acid methionine with adenosyl-triphospate (ATP). The most researched form of supplemental SAMe comes from Italy. SAMe was discovered by Cantoni in 1952. However, not until the mid-1970s was it possible to stabilize a salt of this physiological molecule, which made it possible for clinical investigation.[24] During clinical trials evaluating the mood-modulating activity of SAMe, it was discovered that some depressed patients with OA reported a marked improvement in their degenerative joint disease (DJD) after taking SAMe.[25]

Further studies on the treatment of OA confirmed that SAMe was as affective as ibuprofen and ketoprofen in controlling the symptoms of OA, without the negative effects of NSAIDs.[26,27]

Harmand et al showed that SAMe appears to enhance native proteoglycan synthesis and secretion in human chondrocyte cultures arising in the cartilage of patients with OA.[28]

SAMe does not appear to share with NSAIDs a common effect on the eicosanoid system, so the pharmacological mechanisms are still unclear. However, we do know that SAMe increases hexuronic acid (marker of the sugar chains of proteoglycans).

SAMe is well tolerated by the GI, as well as by other organs. Data from a study by Stramentinoli did not find any interference of SAMe with the eicosanoid system.[29]

A SAM deficiency in joint tissue leads to a loss of the gel-like nature of shock-absorbing qualities of hyaline cartilage.

In published clinical double-blind trials utilizing 400 mg of oral SAMe given 3 times daily, 21,524 patients with painful OA were treated with SAMe. The trial results demonstrated reductions in global pain scores and clinical symptoms similar to those from NSAIDs such as ibuprofen, indomethacin, naproxen, and piroxicam.[30]

SAMe is one of the most effective natural anti-depressants when given in an oral dose of 400 mg 4 times daily on an empty stomach, which is as effective as intravenous (IV) dosing. SAMe is better tolerated and has a quicker onset of action than tricyclic anti-depressants.[31,32]

SAMe is thermo-labile and will degrade quickly if stored in a warm place. Refrigerating SAMe helps retain its potency. Because of the methionine content in SAMe, co-factors, such as a B-vitamin complex, should be given to help reduce the formation of excessive homocysteine which, in elevated amounts, is a cardiac risk factor.

Interactions: No drug interactions have been reported.

Dosage: 400 mg 3 times daily.

Methylsulfonylmethane

Methylsulfonylmethane (MSM) is a naturally occurring compound and nutritional component of many foods. MSM is found in the normal diets of humans and almost all other vertebrates.

In its pure manufactured form, MSM is an oxidized metabolite of dimethylsulfoxide (DMSO). The proper chemical name for MSM is dimethylsulfone, or DMSO 2. MSM is a rich source of organic sulfur, which is essential for skin, hair, cartilage, and connective tissue health. MSM supports bodily functions that are dependent upon sulfur and methyl groups. MSM taken orally and DMSO applied topically share several pharmacological properties, such as anti-inflammatory actions and softening of collagen.

MSM is non-toxic. There are, however, related toxic chemicals, such as dimethylsulfate, dimethyl sulfite, and dimethyl sulfide, which should be avoided.[33]

Interactions: No drug interactions have been reported.

Dosage: 500 to 1,000 mg 3 times daily.

Cetyl Myristoleate

Cetyl Myristoleate (CM) is a naturally occurring ester of a myristolic acid that is commercially obtained from palmitic acid. This natural anti-arthritic substance was discovered during an investigation into why mice do not get arthritis. These studies led to the discovery of CM as the protective agent responsible for preventing mice from getting arthritis.

Diehl et al, in a study done at the Medical College of Virginia and reported in the *Journal of Pharmaceutical Sciences*, found that CM has several mechanisms of action. CM serves as a lubricant for joints, functions as an immune modulator, and mediates the inflammatory response, promoting a balanced T-Helper I to T-Helper II cellular response.[34,35]

Interactions: No drug interactions have been reported.

Dosage: Apply topically 3 times daily, and rub in well.

Oral Type II Collagen

Orally administered, cartilage-derived type II collagen (CII) has been shown to ameliorate arthritis in patients with joint inflammation in a multi-site, randomized, placebo-controlled study of RA patients, using a dose of 20, 200, 500 or 2,500 µg per day.[36]

There is a growing body of evidence indicating that type II collagen is a major structural protein responsible for tensile strength and toughness in the cartilage, and is also a potential antigen in people who have RA. If the activity of T cells that release joint-destroying factors could be reduced, outcomes for patients suffering from RA could be improved. A method of achieving the down-regulation of T-cell activity is termed "oral tolerance," a concept that is proving useful in the treatment of autoimmune diseases. "Oral tolerance" describes a state of immune hypo-responsiveness following oral ingestion of a protein.

One study showed that denatured type II collagen had no impact on the severity of the disease or the associated pain.[37] In several studies, a dosage of 10 mg or less taken on an empty stomach, appeared to suppress T-cell-mediated inflammation, which is characterized by cytokines, interleukin-4, and interleukin-10, which is seen in the synoviums of both OA and RA patients.[38]

Interactions: No drug interactions have reported.

Dosage: 10 mg or less taken on an empty stomach.

Acetyl-L-Carnitine

Antioxidant therapy has been shown to prevent nerve dysfunction in diabetes mellitus patients in several randomized, controlled studies. Sima and his research team are currently working with the FDA toward getting approval for acetyl-L-carnitine (ALC) to treat pain associated with diabetic neuropathy. Recent studies have shown that ALC promotes nerve regeneration and improves symptoms of distal symmetrical polyneuropathy (DSP), which occurs as a side effect in 11%-66% of patients receiving certain nucleoside analog reverse transcriptase inhibitors for the treatment of human immunodeficiency virus (HIV).

ALC is the acetylated form of L-carnitine, and the 2 compounds share similar energy- and metabolism-promoting properties. ALC naturally occurs in the body and supports the availability of acetyl-CoA, an important energy-generating metabolite. Carnitine is primarily synthesized by the body in the liver and kidneys. ALC supports proper mitochondrial function and cell-membrane stability. The acetyl group from ALC is an important factor in the production of the neurotransmitter acetylcholine.

In long-term, double-blind, randomized, placebo-controlled studies, ALC has been shown to slow negative cognitive changes and support memory and attention. And when taken in doses of 1,000 mg 3 times daily, ALC has been efficacious in alleviating pain in patients with chronic diabetic neuropathy. The clinical data has shown significant improvement in nerve regeneration and vibratory perceptions.[39-41]

Interactions: No drug interactions have been reported.

Dosage: 1,000 mg 3 times daily.

Alpha Lipoic Acid

Alpha lipoic acid (ALA), also known as thioctic acid, is a natural antioxidant that is both water- and fat-soluble. It is manufactured in the body, where it acts as a potent antioxidant that neutralizes harmful free radicals and enhances the activity of vitamins C and E. ALA produces energy in muscles and directs calories into energy production. ALA was shown in three studies to be an effective and safe treatment for diabetic polyneuropathy.[42-44]

I have used a combination of ALC and ALAfor treating diabetic neuropathies over a 10-year period, and have found repeated success in compliant patients who also keep their HbAlc levels between 5 and 6.

Interactions: No drug interactions have been reported. Allergic skin reactions have been reported as a side effect in humans.

Dose: 500 mg to 1,000 mg 4 times daily on an empty stomach.

Celadrin

Celadrin is a proprietary blend (from MediPlex) of esterified fatty-acid carbons which, when combined with un-denatured type II collagen in an oral form, demonstrates significant relief in joint pain.

In a double-blind, placebo-controlled study of patients with knee pain, researchers found that 100% of patients using Celadrin topically were able to move faster with less joint pain when climbing stairs or rising from a chair. This data, along with previous research data on the oral and topical use of Celadrin, has shown promise in the treatment of degenerative joint disease. Celadrin is an all-natural compound with no reported side effects.[45,46] Toxicity testing has shown Celadrin to be safe and non-toxic at high dose levels.

Interactions: No drug interactions have been reported.

Dosage: 350 mg 3 times daily.

Flavocoxid

Limbrel (flavocoxid) is a prescription-only medical food for the treatment of mild to moderate arthritic pain. This combination of extracts of *Scutellaria* and *Acacia* form the active ingredients. Flavocoxid exhibits anti-inflammatory and analgesic activity in animal and human models. The mechanism of action is believed to be the inhibition of cyclo-oxygenase and 5-lipoxygenase pathways.

Animal studies that were placebo-controlled with healthy subjects of similar ages and sexes did not demon-

strate any changes in renal, hepatic, gastric, or duodenal histology. Blood electrolytes were unchanged and liver enzyme levels were within normal limits.[47]

Limbrel has demonstrated significant improvements in the clinical dietary management of OA in a 90-day trial of 60 OA patients, compared to placebo, in a randomized, double-blind, placebo-controlled clinical trial. Limbrel is not recommended for patients under 18 years of age.[47]

Interactions: No drug interactions have been reported.

Dosage: 250 mg every 12 hours on an empty stomach.

Omega-3 Fatty Acids

Multiple clinical studies have demonstrated that the daily use of 1.8-9.1 of deep-water fish oil containing 645-830 mg of eicosapentaenoic acid (EPA) and 380-540 mg of docosahexaenoic acid (DHA), reduce the pain and stiffness in patients with RA. Eskimo-3 fish oil from Sweden is one of the most extensively researched and documented fish oil supplements on the market today. In a study in *The Lancet*, clinical findings demonstrated that after 12 weeks, the treated group had significantly less morning stiffness compared to the control group. Joints were less tender and Hgb was improved.[48-50]

Interactions: Due to anti-platelet aggregation activity, Omega-3 fish oil should be used with caution in patients taking coumadin.

Dosage: 270 mg EPA and 175 mg DHA 3 times daily.

Summary

As I've shown in these examples, there are several natural alternatives to opioids and NSAIDs for the treatment of chronic joint pain and neuromuscular pain. While some of these alternatives have been subjected to well-designed clinical efficacy studies demonstrating their safety and efficacy, others have received only limited human research. The negative clinical studies presented in this paper should be weighed against the well-documented adverse reactions of some NSAIDs. Alternatives are available for the treatment of peripheral neuropathies associated with diabetes mellitus that rival the efficacy of traditional medications, and with a better safety profile. With a growing body of evidence of safety and efficacy, physicians are now being able to confidently prescribe integrative therapies to help their patients who suffer from chronic musculoskeletal pain and neuropathies.

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