REVIEW ARTICLE

Assessing Complementary Pain Management Options for Chronic Pain Management

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KEYWORDS:

Natural Pain Relief

Herbal Pain Relief Treatment

Opioid Alternatives

OTC Pain Therapies

Addiction Medicine

In light of the current opioid epidemic, this article reviews natural chronic pain management agents along with evidence-based documentation of their effectiveness, recommended dosing and administration, mechanism of action and potential side effects.

INTRODUCTION

Approximately 100 million Americans suffer from chronic pain.[1] Chronic pain is defined by the United Surgeon General as:

> Chronic pain continues beyond the normal time expected for healing and is associated with the onset of pathophysiologic changes in the central nervous system that may adversely affect an individual's emotional and physical well-being, cognition, level of function and quality of life. Chronic pain serves no apparent useful purpose for the individual and may be diagnostically and therapeutically approached as a chronic disease process. It cuts across the boundaries of mind, brain, and body, resulting in a common symptomatic and functional spectrum of physical, cognitive, psychological and behavioral effects. Chronic pain can be described as ongoing or recurrent pain, lasting beyond the usual course of acute illness or injury or more than 3 to 6 months, and which adversely affects the individual's well-being. A simpler definition of chronic or persistent pain is pain that continues when it should not.[2]

A large number of chronic pain sufferers create the need for family physician's to provide effective pain management programs.[3] Conventional approaches to chronic pain management include prescription medicine or invasive procedures. A 2011 population-based survey documents that as part of their treatment plan over 50% of chronic pain patients take over the counter or prescription medication.[4]

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 Print ISSN: 1877-573X

Complementary integrative medicine (CIM) acknowledges the person as a whole and empowers patients to self-manage, which is a cornerstone philosophy of osteopathic medicine. Current research supports that acceptance is growing for CIM usage in chronic pain management.[5] Many clinicians incorporate natural chronic pain management agents such as herbal therapies, spices, liniments, topicals, ointments, gels, and rubs into pain treatment plan options.

The following reviews natural chronic pain management agents along with evidence-based documentation of their effectiveness, recommended dosing and administration, mechanism of action and potential side effects.

CAPSAICIN (CHILI PEPPER)

Capsaicin is the active component of Capsicum, a small spreading shrub from the chili plant that the native people of the American tropics used for hundreds of years topically for osteoarthritis, rheumatoid arthritis, post-herpetic neuralgia, HIV-associated neuropathy, fibromyalgia, trigeminal neuralgia, and diabetic neuropathy. It is also used for back pain, myofascial pain, and post-surgical neuralgias. The FDA has approved, the active capsicum constituent capsaicin in topical format to relieve chronic pain.[6]

Capsicum contains capsaicinoids, the most common of which is capsaicin.[7] It is the capsaicin and other capsaicinoids that makes capsicum taste hot. Naturally-occurring capsaicin exists only in the trans-stereoisomer form. However, the cis-isomer, known as civamide, also has pharmacological activity. Some evidence suggests that civamide is more potent and causes less irritation than naturally occurring capsaicin.[8]

THE CAPSAICIN PAIN TREATMENT NATURAL MEDICINES COMPREHENSIVE DATABASE EFFECTIVENESS RATINGS ARE:[9]

Likely effective in the treatment of diabetic peripheral neuropathy, pain and postherpetic neuralgia.

Possibly effective in the treatment of back pain, cluster headache, postoperative pain.

Insufficient reliable evidence in the treatment of fibromyalgia, HIV-associated peripheral neuropathy, joint pain, migraine headache and myofascial pain.

See Table 1 *(page 25)* for the parameters of the Natural Medicines Comprehensive Database's Effectiveness Ratings.

THE RECOMMENDED CAPSAICIN DOSING & ADMINISTRATION FOR CHRONIC PAIN CONDITIONS ARE:[10]

Back Pain: Topical

Capsicum-containing plasters providing 11 mg of capsaicin per plaster or 22 mcg of capsaicin per square centimeter of plaster applied have been used. The plaster is applied once daily in the morning and left in place for 4-8 hours.[11]

Cluster Headache: Intranasal

Capsaicin suspension 0.1 mL of a 10 mm, providing 300 mcg/day of capsaicin, applied to the ipsilateral nostril, has been used. Applications of the suspension continued once daily until a burning sensation was no longer experienced. [12]A capsaicin 0.025% cream (Zostrix, Rodlen Laboratories) applied daily for 7 days has been used to treat acute cluster headache attacks.[13] Due to severe pain associated with intranasal capsaicin administration, pretreatment with intranasal local anesthetic is usually used.

Diabetic Peripheral Neuropathy: Topical

Cream that contains 0.075% capsaicin, the active constituent of capsicum, has been used topically four times daily for 8 weeks.[14] A single application of a patch containing 8% capsaicin (Qutenza, NeurogesX Inc., San Mateo, CA, USA) has been used for 60-90 minutes.[15]

Fibromyalgia: Topical

Cream containing 0.025% to 0.075% capsaicin, the active constituent of capsicum, has been applied 3-4 times daily for 4-6 weeks.[16]

HIV-Associated Peripheral Neuropathy: Topical

A single patch (Qutenza, NeurogesX Inc.) containing 8% capsaicin, the active capsicum constituent, has been applied for 30-90 minutes.[17]

Migraine Headache: Intranasal

Capsaicin 0.075% applied to the nasal mucosa has been used.[18]

Pain: Topical

Creams contain the active capsicum constituent capsaicin and are typically applied 3-4 times daily. It can take up to 14 days for the full analgesic effect. Most creams contain 0.025% to 0.075% capsaicin concentrations.[19]

Postoperative Pain: Topical

A capsicum-containing plaster has been applied to acupoints on the hands or near the knees of adults 30 minutes before anesthesia and left in place for 6-8 hours daily for up to 3 days after surgery.[20] The capsicum-containing plaster used in these studies (Sinsin PAS, Sinsin Pharm Co.) is standardized to contain capsicum 345.8 mg and capsicum tincture 34.58 mg per sheet.[21] Capsaicin 15 mg has been instilled during surgery immediately before wound closure.[22]

Postherpetic Neuralgia: Topical

A single patch containing 8% capsaicin (Qutenza, NeurogesX Inc.), the active capsicum constituent, has been used for 60-90 minutes.[23]

Joint Pain: Oral

A specific combination product (Instaflex Joint Support, Direct Digital, Charlotte, NC) containing glucosamine sulfate 1500 mg/day, methylsulfonylmethane 500 mg, white willow bark extract 250 mg, ginger root concentrate 50 mg, Boswellia extract 125 mg, turmeric root extract 50 mg, cayenne 40 m H.U. 50 mg, and hyaluronic acid 4 mg per day in three divided doses has been used daily for 8 weeks.[24]

CAPSAICIN INTERACTIONS WITH DISEASES TO BE AWARE:

Bleeding Disorders

Theoretically, capsicum might increase the risk of bleeding.[25] However, conflicting results show that capsaicin, a constituent of capsicum, does not decrease platelet aggregation.[26] Until more is known, use cautiously in patients with bleeding disorders.

Damaged Skin

Capsicum is contraindicated in situations involving the injured skin. Do not apply capsicum if the skin is open.

Diabetes

Theoretically, capsicum might affect blood glucose levels in people with diabetes.[27] Monitor blood glucose levels closely. Doses of conventional antidiabetes medications may need to be adjusted.

Hypertension

In animals, intravenous administration of a high dose of capsaicin, the active constituent of capsicum, increases blood pressure.[28] Also, cases of an arterial hypertensive crisis have been reported for individuals who consumed an abundant amount of chili peppers.[29] Theoretically, ingesting a significant amount of chili peppers might worsen high blood pressure in humans.

Surgery

Capsicum has antiplatelet effects. Capsicum might cause excessive bleeding if used perioperatively. Tell patients to discontinue capsicum at least 2 weeks before elective surgical procedures.[30]

DEVIL'S CLAW

Devil's Claw is a perennial South African plant found in the Kalahari Desert and Namibian steppes region. Taken orally, devil's claw is purported to ease muscular tension and/or pain in the major joints, i.e., back, shoulders and neck and is a popular treatment for osteoarthritic pain. Devil's claw is prepared from the secondary tuberous roots and the applicable part of devil's claw is a tuber. Devil's claw contains iridoid glycoside constituents primarily harpagoside, but also including harpagide, harpagide derivatives, and procumbide.[31] It also contains the phenylethanol derivative acteoside (verbascoside) and isoaceteoside, and the oligosaccharide stachyose.[32] The phenol glycoside constituent 6-acetylacteoside allows distinction between the two species of devil's claw.[33]

DEVIL'S CLAW NATURAL MEDICINES COMPREHENSIVE DATABASE EFFECTIVENESS RATINGS[34] ARE:

Likely effective for back pain and osteoarthritis.

Insufficient reliable evidence for rheumatoid arthritis.

RECOMMENDED DEVIL'S CLAW DOSING & ADMINISTRATION FOR CHRONIC PAIN CONDITIONS[35] ARE:

Back Pain: Oral

A specific devil's claw extract product (Doloteffin, Ardeypharm) 2400 mg taken in three divided doses daily for up to 1 year has been used.[36] Another specific devil's claw extract (WS 1531, Dr. Willmar Schwabe GmbH & Co.) 200-400 mg three times daily for 4 weeks has been used.[37] An additional devil's claws extract product (LI 174; Rivoltan, Krewel Meuselbach GmbH) 480 mg twice daily for 4-8 weeks has also been used.[38]

Osteoarthritis: Oral

A specific devil's claw root extract product (Doloteffin, Ardeypharm) 2400 mg taken in three divided doses daily for 8-12 weeks has been used.[39] Another specific powdered devil's claw root product (Harpadol, Arkopharma) 2610 mg daily for 4 months has been used.[40] A specific combination product containing devil's claw 300 mg/capsule, turmeric 200 mg/capsule, and bromelain 150 mg/capsule (AINAT, Laboratoire de Rhumatologie Appliquee) two capsules three times daily for 2 weeks or two capsules twice daily for 2 months has been used.[41]

DEVIL'S CLAW INTERACTION WITH DISEASES

Cardiac Disorders, Hypertension, Hypotension

Since devil's claw can affect heart rate, contractility of the heart, and blood pressure,[42] it might adversely affect people with cardiovascular conditions; use cautiously.

Diabetes

Devil's claw might decrease blood glucose levels[43] (and have additive effects with medications used for diabetes. Monitor blood glucose levels closely. Dose adjustments may be necessary.

Gallstones

Devil's claw might increase bile production and adversely affect people with gallstones;[43] avoid using.

GAMMA-LINOLENIC ACID

Gamma linolenic acid (GLA) is found in various plant seed oils such as borage oil and evening primrose oil and is an omega-6 fatty acid. The body can convert GLA to substances that reduce inflammation and cell growth. GLA can be converted to compounds that have anti-inflammatory properties.[44] Some research suggests that dihomogammalinolenic acid, a metabolite of GLA and precursor of prostaglandin E1, might act directly on T-cells to modulate an immune response in diseases such as rheumatoid arthritis (RA).[45] There is also some evidence that GLA might reduce interleukin-1-beta (IL-1-beta) autoinduction, which is thought to be the cause of synovitis in patients with RA.[46] People take this orally as a chronic pain treatment option for back pain.

The Gamma-linolenic Acid Natural Medicines Comprehensive Database Effectiveness Rating is insufficient reliable evidence to rate for back pain.[47]

RECOMMENDED GAMMA-LINOLENIC ACID DOSING & ADMINISTRATION FOR CHRONIC PAIN CONDITIONS IS:

Back Pain: Oral

Alpha-lipoic acid 600 mg plus gamma-linolenic acid 360 mg daily for 6 weeks has been used.[48]

GAMMA-LINOLENIC ACID INTERACTIONS WITH DISEASES ARE:

Bleeding Disorders

Gamma-linolenic acid has platelet-inhibiting effects.[49] There is some concern that gamma linolenic acid might prolong bleeding time and increase the risk of bruising and bleeding.

Surgery

Gamma-linolenic acid has antiplatelet effects.[50] Gamma linolenic acid might cause excessive bleeding if used perioperatively. Tell patients to discontinue gamma linolenic acid at least 2 weeks before elective surgical procedures.

GLUCOSAMINE SULFATE

Glucosamine is an amino sugar[51] and is required for the synthesis of glycoproteins, glycolipids, and glycosaminoglycans (also known as mucopolysaccharides).[52] These carbohydrate-containing compounds are found in tendons, ligaments, cartilage, synovial fluid, mucous membranes, structures in the eye, blood vessels, and heart valves. Glucosamine is also a component of biologically active compounds such as heparin, but it does not react with heparin-induced thrombocytopenia (HIT) antibodies.[53] It is a substrate used in the biosynthesis of the macromolecules found in articular cartilage. As a dietary supplement, glucosamine is available as glucosamine hydrochloride, glucosamine sulfate, and N-acetyl glucosamine. Some products in the U.S. that are labeled glucosamine sulfate are glucosamine hydrochloride with added sulfate.[54]

In Europe, glucosamine is a registered drug approved for the treatment of osteoarthritis (OA) due to its symptomatic, slow acting effect in promoting cartilage and joint health. In the U.S. it has been designated as an over the counter dietary supplement by the U.S. Food and Drug Administration. People use this in their chronic pain management treatment plan for knee and back pain.

The Glucosamine Sulfate Natural Medicines Comprehensive Database Effectiveness Rating is:

Insufficient reliable evidence to rate for joint pain,[55] knee pain,[56] and temporomandibular disorder (TMD).[57]

Recommended Glucosamine Sulfate Dosing & Administration for Chronic Pain Conditions are:

Joint Pain: Oral

A specific combination product (Instaflex Joint Support, Direct Digital, Charlotte, NC) providing glucosamine sulfate 1500 mg/day, m methylsulfonylmethane 500 mg/day, white willow bark extract 250 mg/day, ginger root concentrate 50 mg/day, Indian frankincense extract 125 mg/day, turmeric root extract 50 mg/day, cayenne 40 m H.U. 50 mg/day, and hyaluronic acid 4 mg/day, taken in three divided doses daily for 8 weeks, has been used.[58]

Knee Pain: Oral

Glucosamine sulfate 500 mg three times daily for 28 days has been used. [59] A specific combination product (Instaflex Joint Support, Direct Digital, Charlotte, NC) providing glucosamine sulfate 1500 mg/day, methylsulfonylmethane 500 mg/day, white willow bark extract 250 mg/day, ginger root concentrate 50 mg/day, Indian frankincense extract 125 mg/day, turmeric root extract 50 mg/day, cayenne 40 m H.U. 50 mg/day, and hyaluronic acid 4 mg/day, taken in three divided doses daily for 8 weeks, has been used.[60]

GLUCOSAMINE SULFATE INTERACTIONS WITH DISEASES ARE:

Asthma

Glucosamine might exacerbate asthma by an unidentified allergic mechanism. Use cautiously in patients with asthma.[61]

Diabetes

Some preliminary research and case reports have raised concerns that glucosamine sulfate might increase insulin resistance or decrease insulin production, resulting in elevated blood glucose levels.[62] However, clinical studies show that various forms of glucosamine do not have adverse effects on blood glucose or hemoglobin A1C (HbA1C) in healthy, obese, patients with type 2 diabetes or impaired glucose tolerance.[63]

Glaucoma

There is some concern that taking glucosamine sulfate might increase intraocular pressure in patients with glaucoma.[64] Patients with severe glaucoma should avoid glucosamine sulfate. Patients with mild-to-moderate glaucoma should be monitored for changes in intraocular pressure within 3 months of starting glucosamine. If intraocular pressure increases, glucosamine may need to be discontinued.

Hyperlipidemia

There has been concern that glucosamine sulfate might cause metabolic disturbances that could result in increased cholesterol and triglyceride levels. Some preliminary research has suggested that glucosamine might increase insulin levels. Hyperinsulinemia is associated with elevated cholesterol and triglycerides.[65] Animal model research has also shown that glucosamine might exacerbate hyperlipidemia.[66] But research in humans has not shown this effect. Glucosamine does not seem to increase lipid levels in people over age 40 who take glucosamine sulfate for up to 3 years.[67]

Hypertension

There has been concern that glucosamine sulfate might cause metabolic disturbances resulting in increased blood pressure.[68] Some preliminary research has suggested that glucosamine might increase insulin levels. Hyperinsulinemia is associated with elevated blood pressure.[69] But research in humans has not shown this effect. Glucosamine does not seem to increase blood pressure in people over age 45 who take glucosamine sulfate for up to 3 years.[70]

Shellfish Allergy

For those who are sensitive to shellfish, there is concern that glucosamine products might cause allergic reactions as Glucosamine is derived from the exoskeletons of shrimp, lobster, and crabs. But, allergic reactions in people with shellfish allergy are caused by IgE antibodies to antigens in the meat of shellfish, not to antigens in the shell. Albeit, some evidence suggests that patients with shellfish or shrimp allergy can safely take glucosamine products[71] although a possible allergic reaction was reported in a clinical trial.[72]

Surgery

Glucosamine sulfate might affect blood glucose levels. Theoretically, glucosamine sulfate might interfere with blood glucose control during and after surgical procedures. Tell patients to discontinue glucosamine sulfate at least 2 weeks before elective surgical procedures.

CONCLUSION

Natural medicine is difficult; however, we see more of our patients wanting to try the natural route first versus prescription drugs. Due to the lack of trials and studies, we, as doctors, have to spend more time educating ourselves on what are the latest evidence-based results for the natural management of chronic pain. With more and more of our patients demanding natural based chronic pain management as their first option to control their pain and the explosion of the opioid epidemic, family physicians are at the forefront of educating patients on their options before turning to prescription pain medicine. As family physicians, we need to constantly educate ourselves on the most recent evidence-based studies and trials as it relates to natural pain management options so we can provide the highest quality and most effective treatment plan for our patients.

TABLE 1:

Definitions of Evidence-based Safety Ratings by the Natural Medicines Comprehensive Database:[1]

	TO ACHIEVE THIS EFFECTIVENESS RATING A PRODUCT IS SUPPORTED BY ALL OF THE FOLLOWING:
EFFECTIVE	• Evidence consistent with or equivalent to passing a review by the Food and Drug Administration (FDA), Health Canada, or similarly rigorous approval process. • Evidence from multiple (2+) randomized clinical trials or meta-analysis including several hundred to several thousand patients (level of evidence = A). • Studies have a low risk of bias and high level of validity by meeting stringent assessment criteria (quality rating = A). • Evidence consistently shows POSITIVE outcomes for a given indication without valid evidence to the contrary.
LIKELY EFFECTIVE	• Evidence from multiple (2+) randomized clinical trials or meta-analysis including several hundred patients (level of evidence = A). • Studies have a low risk of bias and high level of validity by meeting stringent assessment criteria (quality rating = A). • Evidence consistently shows POSITIVE outcomes for a given indication without significant valid evidence to the contrary.
POSSIBLY EFFECTIVE	• One or more randomized clinical trials or meta-analysis (level of evidence = A or B) or two or more population based or epidemiological studies (level of evidence = B). • Studies have a low to moderate risk of bias and moderate to high level of validity by meeting or partially meeting assessment criteria (quality rating A or B). • Evidence shows POSITIVE outcomes for a given indication without substantial valid evidence to the contrary. Some contrary evidence may exist; however, valid positive evidence outweighs contrary evidence.
POSSIBLY INEFFECTIVE	• One or more randomized clinical trials or meta-analysis (level of evidence = A or B) or two or more population based or epidemiological studies (level of evidence = B). • Studies have a low to moderate risk of bias and moderate to high level of validity by meeting or partially meeting assessment criteria (quality rating A or B). • Evidence shows NEGATIVE outcomes for a given indication without substantial valid evidence to the contrary. Some contrary evidence may exist; however, valid positive evidence outweighs contrary evidence.
LIKELY INEFFECTIVE	• Evidence from multiple (2+) randomized clinical trials or meta-analysis including several hundred patients (level of evidence = A). • Studies have a low risk of bias and high level of validity by meeting stringent assessment criteria (quality rating = A). • Evidence consistently shows NEGATIVE outcomes for a given indication without significant valid evidence to the contrary.
INEFFECTIVE	• Evidence from multiple (2+) randomized clinical trials or meta-analysis including several hundred to several thousand patients (level of evidence = A). • Studies have a low risk of bias and high level of validity by meeting stringent assessment criteria (quality rating = A). • Evidence consistently shows NEGATIVE outcomes for a given indication without valid evidence to the contrary.
INSUFFICIENT EVIDENCE	There is not enough reliable scientific evidence to provide an Effectiveness Rating.

AUTHOR DISCLOSURES:
No relevant financial affiliations

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