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Complementary and Alternative Medicine for Pain: An Evidence-based Review

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Abstract Pain is one of the most prevalent conditions for which patients seek medical attention. Additionally, the number of patients who utilize complementary and alternative medicine as a treatment of pain either in lieu of, or concurrent with, standard conventional treatments continues to grow. While research into the mechanisms, side effect profiles, and efficacies of these alternative therapies has increased in recent years, much more remains unknown and untested. Herein, we review the literature on complementary and alternative medicine for pain, with particular emphasis on evidence-based assessments pertinent to the most common alternative therapies, including acupuncture, herbal therapy, massage therapy, hypnosis, tai chi, and biofeedback.

Keywords Complementary medicine · Alternative medicine · Holistic · Mind–Body · Pain · Pain treatment · Acupuncture · Herbal therapy · Hypnosis · Tai chi · Massage therapy · Biofeedback · Evidence

Introduction

The number of patients who utilize complementary and alternative medicine as a treatment of pain either in lieu of, or concurrent with, standard conventional treatments continues to grow. Over the last 20 years, Americans have sought a more "natural" or "holistic" approach to treatment of medical problems in general and pain in particular [1]. According to a 2007 National Institute of Health (NIH) survey, acupuncture, one of the more popular forms of alternative medicine, was utilized by 3.1 million Americans, nearly 1% of the population, within the prior year [2]. Among patients with unrelieved pain, there is an undertone of dissatisfaction with conventional treatment and a clear thirst for alternative strategies to combat their painful condition. While research into the mechanisms, side effect profiles, and efficacies of these alternative therapies has increased in recent years, much more remains unknown and untested. Herein, we review the literature on complementary and alternative medicine for pain, with particular emphasis on evidence-based assessments pertinent to the most common alternative therapies including acupuncture, herbal therapy, massage therapy, hypnosis, tai chi, and biofeedback.

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Acupuncture

Acupuncture is considered an ancient practice of traditional Chinese medicine (TCM) that began thousands of years ago. The basic principle of TCM relates to the concept of "qi" (or energy flow), whereby sickness results from the disruption of the flow of qi or imbalance between the yin and yang (opposing and inseparable life forces). Acupuncture describes a technique involving the stimulation of specific anatomical points on the human body. Furthermore, these acupuncture points, of which there are anywhere from 600 to 2000, are organized by specific energy pathways called meridians, which range in number from 14 to 20 [2]. According to the theory behind acupuncture, an internal imbalance between yin and yang can block the flow of qi, whereby acupuncture can restore balance and harmony within the body.

While acupuncture has been practiced worldwide for centuries, its widespread use in the United States began in the 1970 s. In 1976, California became the first state to institute a formal license for the practice of acupuncture, and now over 40 other states have adopted similar regulatory practice. In 1997, the NIH Consensus Development Conference on Acupuncture reviewed available data on acupuncture and concluded, "There are reasonable studies (although sometimes only single studies) showing relief of pain with acupuncture..." [3]. Subsequently, the NIH has developed an Office of Alternative Medicine, which is now known as the National Center for Complementary and Alternative Medicine (NCCAM). Today, NCCAM funds clinical trials to evaluate the efficacy of acupuncture.

As the number of practitioners providing acupuncture and the evidence base supporting the practice grow, so do the number of Americans who seek alternatives to conventional medicine. In a 2007 survey from the NIH, an estimated 3.1 million Americans had acupuncture treatment within the prior year; back pain ranked as the most common condition for which treatment was sought, followed by joint pain, neck pain, and headaches [2].

The validity of acupuncture for the treatment of pain is based on a body of evidence showcasing the neurophysiologic basis of its efficacy. In 1987, Pomeranz [4] theorized and then proved that acupuncture's effect begins with stimulation of Aδ and C-afferent fibers in muscle. Afferent signals then are transmitted to the spinal cord, midbrain, and hypothalamus. These signals also trigger the release of multiple mediators along its pathway, including endogenous opioids, such as dynorphin and enkephalins, and adrenocorticotropic hormone in the hypothalamus. Furthermore, the release of neurotransmitters such as serotonin, dopamine, and norepinephrine has been shown to cause both pre- and postsynaptic inhibition of central pain pathways [5••]. Another study by Han [6] demonstrated that the analgesic effects of acupuncture could be conferred from one animal to another via transfer of cerebrospinal fluid. Other studies have shown that acupuncture analgesia can be reversed by the opioid antagonist naloxone, demonstrating acupuncture's release of endogenous opioids [7]. Studies on electroacupuncture (EA) have shown that low-frequency EA releases enkephalin and β-endorphin, while high-frequency EA releases dynorphin [8].

Several studies over the past few years have used the advanced technology of functional magnetic resonance imaging (fMRI) to visually identify the effects of acupuncture on the central nervous system. Wu et al. [9] used fMRI to demonstrate that acupuncture activates the hypothalamus and nucleus accumbens. Further, Zhang et al. [10] demonstrated that EA stimulated changes in the somatosensory and the medial prefrontal cortices, areas traditionally associated with both the sensory and emotional aspects of pain. Finally, Napadow et al. [11] compared traditional acupuncture with EA (tactile stimulation was used as a control), and discovered that low-frequency EA caused more fMRI changes compared to traditional acupuncture, and additionally demonstrated that both types of acupuncture produced greater fMRI changes when compared to tactile stimulation. Similar to previous studies indicating central nervous system activation from acupuncture, imaging revealed deactivation of the limbic and paralimbic areas of the brain, including the amygdala, hippocampus, and frontal and temporal lobes [5••], [11].

Evidence for Acupuncture in Specific Pain Conditions

Neck Pain

A Cochrane review in 2006 examined 10 randomized controlled trials that looked at acupuncture treatment of chronic neck pain (>90 days). A total of 661 patients were included in the meta-analysis. The authors concluded that there was moderate evidence that acupuncture was more effective than sham acupuncture, both immediately post-treatment and at 3-month follow-up [12]. In another study, Vas et al. [13] compared acupuncture with transcutaneous nerve stimulation for the treatment of chronic neck pain. In total, 123 patients were randomly assigned to one of the two groups, with the primary end point being pain intensity of the neck with motion after five treatment sessions. The authors were able to demonstrate a significant reduction in pain intensity using the visual analogue scale in the acupuncture group.

Shoulder Pain

A Cochrane review conducted in 2005 analyzed nine randomized controlled trials of patients with shoulder pain (>3 weeks duration). Based on the studies included in the meta-analysis, most of the patients had been diagnosed with either adhesive capsulitis or rotator cuff injury. However, when acupuncture was compared to placebo or other interventions (steroid injection or physiotherapy), the studies were neither statistically significant nor clinically significant [14]. This led the authors to conclude that there was little evidence to support or refute the use of acupuncture for shoulder pain. However, a randomized controlled trial from 2009 looked at the efficacy of acupuncture as treatment of chronic shoulder pain in patients with a diagnosis of osteoarthritis or rotator cuff tendonitis (>8 weeks). When compared to sham non-penetrating acupuncture, the mean total Shoulder Pain and Disability Index score improved in all three groups;

however, the change was clinically significant only in the two acupuncture groups [15].

Elbow Pain

Trinh et al. [16] conducted a systematic review of six randomized controlled trials looking at the efficacy of acupuncture for lateral epicondyle pain (ie, tennis elbow). All six studies demonstrated positive results, leading the authors to conclude that there is evidence that acupuncture is effective in the short-term relief of lateral epicondyle pain. However, there were some significant limitations of the studies analyzed, including small sample sizes and variability in the definition of short-term pain relief

Headache

In a Cochrane review in 2009, Linde et al. [17] examined acupuncture for tension-type headaches. The authors analyzed 11 randomized controlled trials totaling 2317 participants. Two of the large trials compared acupuncture and basic care to basic care alone (standard pain medications) and found that 47% of patients in the acupuncture group had at least a 50% decrease in the number of headache days versus 16% in the control groups. Acupuncture was compared with "sham" acupuncture (needles were inserted at incorrect points or did not penetrate the skin) in six trials, and 51% of patients in the acupuncture group were found to have at least a 50% decrease in the number of headache days compared to 41% in the sham group. Based on their meta-analysis, the authors concluded that the evidence suggests that acupuncture could be a valuable option for patients suffering from frequent tension-type headache.

Fibromyalgia

In 2005, Assefi et al. [18] studied acupuncture versus sham acupuncture for the treatment of fibromyalgia pain. In a randomized controlled trial, 100 participants were either given 24 treatments of acupuncture or sham acupuncture and the visual analogue scale served as the primary outcome measure. The authors reported no difference between the pain ratings among the two groups and concluded that acupuncture was no better than sham acupuncture for treating pain related to fibromyalgia. However, in 2006, Martin et al. [19] conducted a randomized controlled trial with 50 patients and compared acupuncture to sham acupuncture. The authors found that patients in the acupuncture group reported an improvement in their fibromyalgia symptoms, especially after 1 month, when using the Fibromyalgia Impact Questionnaire (FIQ) to assess outcome. In 2009, Martin-Sanchez et al. [20] reviewed six randomized controlled trials comparing acupuncture and EA to a sham technique in patients with fibromyalgia. The authors found no statistically significant differences between the two acupuncture groups in terms of pain scores on the visual analogue scale.

Low Back Pain

Brinkhaus et al. [21] conducted a randomized controlled trial looking at the effectiveness of acupuncture for chronic low back pain (>6 months). The authors studied 298 patients comparing acupuncture with minimal acupuncture (superficial needling at nonacupuncture points) to a control. Pain intensity on the visual analogue scale decreased by 28.7 in the acupuncture group (SD±30.3) versus 23.6 (SD ± 31) in the sham group and 6.9 (SD±22) in the control group 8 weeks after treatment. The authors concluded that acupuncture was more effective than no acupuncture for the treatment of chronic low back pain, but found no significant difference between acupuncture and sham procedure. Similarly, in 2009, Cherkin et al. [22] found that while acupuncture was superior to conventional treatment (medicine and physical therapy) for chronic low back pain, there was no statistical significance between real and sham acupuncture. In 2007, one of the largest clinical acupuncture studies, called the German Acupuncture Trials (GERAC), compared traditional Chinese acupuncture to sham acupuncture (needles were inserted in nonacupuncture points) as well as to conventional therapy (medications, physical therapy, and exercise). In GERAC, 1162 patients with a history of chronic low back pain (mean: 8 years) were randomized to the three different treatment arms. The group found that 6 months post-treatment, the effectiveness of acupuncture was almost twice that of conventional therapy, with response rates of 47.6% to true acupuncture, 44.2% to sham acupuncture, and 27.4% to standard treatment [23].

Knee Pain

In 2007, Manheimer et al. [24] performed a meta-analysis looking at acupuncture for treatment of pain related to knee osteoarthritis. Nine randomized controlled trials were examined, and the authors found clinically significant improvement in pain when comparing acupuncture to control groups. However, when comparing sham to true acupuncture, there was no clinical benefit between the two groups. In contrast, the GERAC knee trial, another large study on the effectiveness of acupuncture for knee osteoarthritis, found that acupuncture was twice as effective as standard therapy [25]. This study did not find any statistical significance between true and sham acupuncture. More recently, a randomized trial of acupuncture (manual and EA) for osteoarthritis pain in the knee found a

significant improvement in pain compared to nonpenetrating sham acupuncture [26].

There are numerous clinical studies demonstrating the efficacy of acupuncture for pain; however, a number of limitations on the validity of this growing body of evidence remain. Many of the problems associated with research on acupuncture are not specific to this area of alternative medicine, and include small sample sizes, poor follow-up, and variability in outcomes studied. However, there also are problems that are specific to the research related to acupuncture. For example, acupuncture tends to be an individualized treatment, which can be very difficult to standardize among a group of patients. Furthermore, there are many different styles and techniques involved in the practice of acupuncture. There also is an inherent difficulty in finding an ideal control for acupuncture; consequently, most studies incorporate sham acupuncture, where a needle penetrates the skin but not at a true acupuncture point. For the aforementioned reasons, it is difficult to definitively assess the totality of the evidence for or against the use acupuncture for pain. Many studies appear to indicate benefit while others fail to show clinical improvement. Note that there are few contraindications to the use of acupuncture, and the risks of the procedure are fairly low. Therefore, acupuncture may offer a reasonable treatment option for patients with painful conditions, given the understanding that definitive evidence is nonetheless lacking.

Herbal Therapy for Pain

The use of herbal therapy has increased sharply over the past 20 years as Americans look for a more "natural" approach to medicinal therapies. A 2005 survey showed that more than 38 million Americans use herbal therapy [1] to self-treat a variety of ailments including allergies, insomnia, respiratory problems, gastrointestinal problems, and chronic pain.

Two common complaints reported by patients with chronic pain include chronic migraine, which has a 17% prevalence in women and 6% prevalence in men [27], and low back pain, which has an estimated 14% prevalence nationwide [28]. Tanacetum parthenium (feverfew) is perhaps the most common herbal remedy used to treat migraines, and harpagophytum procumbens (devil's claw) and salix alba (white willow bark) are commonly used to treat chronic low back pain.

Feverfew traditionally has been used to treat many ailments including inflammatory, rheumatologic, gastrointestinal, and respiratory conditions. It has seen an increase in use as a preventative therapy for migraine headache over the past 20 years. Parthenolide, a sesquiterpene lactone that may inhibit serotonin release, is hypothesized as the active ingredient for migraine prophylaxis [29].

A Cochrane review from 2004 [30] identified five randomized controlled studies examining the efficacy of feverfew as a preventative therapy for migraine. Although 3 of the 5 studies reported positive results for feverfew as a migraine prophylactic, each lacked components necessary for valid experimental design. For instance, the studies included deficiencies in diagnostic criteria, an absence of intent-to-treat analysis, and inadequate placebo groups. The two studies showing no benefit in the review both had valid experimental design and scored 5 out of 5 on a methodological quality scale [30].

In summary, the five randomized controlled trials that examined clinical outcomes in patients taking feverfew for prevention of migraine reported mixed results and used varying degrees of valid study design. Considering the lack of evidence for feverfew, its routine use for migraine prophylaxis is not recommended based on current literature.

Low back pain is one of the most common causes of disability in Americans younger than 45 years old. The rising cost of health care coupled with debilitating mental and physical distress that accompanies lower back pain has driven Americans to search for alternative herbal therapies. Devil's claw, a flowering plant native to southern Africa, and white willow bark are the two most-studied herbs to treat chronic back pain. White willow bark and devil's claw both offer analgesic benefit, though white willow bark produces an antiplatelet effect and devil's claw has anti-inflammatory properties [31].

A Cochrane review in 2006 [32] and a more recent review from 2010 [33•] examined randomized controlled studies of herbal medicine for low back pain. Three studies in the review examined devil's claw. Two studies by Chrusbasik [34, 35] compared devil's claw to placebo and reported significant benefits for devil's claw in controlling acute exacerbations of chronic low back pain. In contrast, Chrubasik's third study [36] showed no benefit of devil's claw compared to 12.5 mg of oral rofecoxib. None of these studies met the 11 criteria necessary for valid experimental design in the Cochrane database [32].

The most common problems included a lack of reporting of allocation concealment, compliance rates, controls for cointerventions, and acceptability of withdrawal or drop-out rates during the follow-up period [32]. Importantly, these limitations weaken the conclusions of each study. Although devil's claw may offer limited benefit in easing low back pain, some evidence suggests that anti-inflammatory drugs may be more effective.

Three randomized controlled trials [37–39] have examined white willow bark as a treatment of acute exacerbation of chronic low back pain according to a 2006 Cochrane review [32]. Two of the studies [37, 38] showed positive

outcomes for the use of white willow bark compared to placebo, and the third study [39] stated that fewer patients in the treatment group required less rescue pain medicine (tramadol). However, these trials were limited methodologically by not reporting allocation concealment, compliance rates, controls for cointerventions, or the acceptability of withdrawal or drop-out rates during the follow-up period [32]. Similar to devil's claw, a few studies have demonstrated a positive effect from white willow bark, but the small number of studies, substandard design quality, and dearth of studies analyzing longitudinal safety make it problematic to recommend it based on evidence alone. A greater number of well-designed studies showing statistically significant effects of white willow bark for low back pain are needed.

Feverfew, devil's claw, and white willow bark rank as the more popular herbal remedies; yet, other herbal remedies exist for pain, including qishe, huangqi, lujiao, and topical application of capsicum frutescens and extractum nucis vomicae. Due to the frequency of use of herbals in the United States, physicians should carefully elicit a history that includes herbal products. This will ensure a safer and more complete treatment plan for their patients.

Massage Therapy for Pain

Massage therapy dates back to ancient civilizations. It gained popularity in the United States in the 1800 s and since has gained widespread acceptance and expanded rapidly. It is the practice of skin, connective tissue, and muscle manipulation in an effort to promote relaxation, well being, and pain relief in certain cases. Science explains pain relief from massage to be secondary to large-diameter nerve fiber stimulation, which inhibits T cells at the spinal cord, thus decreasing pain sensation [40].

Massage as a treatment of low back pain, neck pain, headache, postexercise muscle pain, and cancer pain all have been studied. Our review will focus primarily on massage for low back pain given the ubiquity of this chronic pain condition.

There have been several studies that reviewed randomized controlled trials on the efficacy of massage for the relief of low back pain [41•, 42, 43]. These comprehensive reviews have focused attention on 13 randomized controlled studies that compared massage to inert therapy (ie, sham therapy), active therapy, or different types of massage. Two studies that compared massage to inert therapy showed positive results, although there was a significantly higher risk of bias in one study according to a Cochrane review [42].

Eight studies compared massage to active therapies. Two of these studies compared massage to early joint mobilization and exercise, respectively, and both reported positive results with low risk of bias according to Cochrane reviewers. Massage compared to relaxation therapy provided mixed results according to the aforementioned reviews [41–43].

Massage is generally a low-risk option for patients, though it should not be performed over regions of cancer, inflammation, bone fracture, burn, or deep venous thrombosis. The most common adverse effects include soreness the day after treatment and potential allergic reactions to oils used during therapy. Although many of the randomized controlled trials contain flaws in experimental design, there is a consensus that massage offers little downside [42]. Considering a low risk of harm, massage can be a useful adjunct for the treatment of low back pain.

Hypnosis

The scientific evidence for hypnosis as a potential treatment of pain remains scant. Furthermore, there is little published on the mechanism by which hypnosis relieves pain, given the inherent difficulty in studying this modality. However, several studies have been performed to date. In 2000, Faymonville et al. [44] used positron emission tomography to examine the effects of hypnosis on the brain in response to noxious stimuli. The authors found that noxious stimuli increased cerebral blood flow in specific areas of the brain implicated in pain processing, such as the thalamic nuclei, anterior cingulate, and insular cortices, while the hypnotic state induced activation of the anterior cingulate cortex.

In 2007, Grondahl and Rosvold [45] published a pilot study looking at the effect of standardized hypnosis treatment of chronic musculoskeletal pain (>3 years). In this study, 18 patients were randomized to receive either hypnosis in additional to conventional care or just standard treatment. After 10 consecutive weekly treatments of hypnosis, the treatment group decreased their pain scores while the control group increased theirs. The authors concluded that hypnosis may produce a positive effect on pain, but noted their limited sample size. A related study by Jones et al. [46] examined the role of hypnotherapy for noncardiac chest pain. The authors randomized 28 patients to either 12 sessions of hypnotherapy or supportive therapy with placebo medications and found a statistically and clinically significant improvement in pain for both groups. Specifically, 80% of the hypnotherapy patients compared to just 23% of the control group experienced improvement.

In sum, the current literature on hypnosis for the treatment of pain demonstrates that the quality and quantity of research are insufficient to form definitive conclusions, and indicates a significant need for further scientific inquiry into this area.

Tai Chi

Tai chi is a traditional Chinese martial art that combines slow and controlled movements combined with deep diaphragmatic breathing and meditation. Though the practice dates back to the 13th century, its benefit on health and physical well being only recently have begun to be explored scientifically. However, an inherent difficulty in studying tai chi in randomized control trials is lack of an appropriate control because there is no currently validated form of sham tai chi. Nevertheless, there are a number of studies that have shown that tai chi may be a useful treatment modality for pain.

In 2009, Hall et al. [47] published a review and meta-analysis on the effectiveness of tai chi for chronic musculoskeletal pain. After looking at seven randomized controlled trials, most comparing tai chi to minimal care or control, the authors demonstrated an approximate reduction of 10 points on both the pain and disability scales with tai chi. Major deficiencies of the study, as noted by the authors, include the lack of placebo control and the questionable quality of performance measures used for assessment. The benefits of tai chi for rheumatoid arthritis were investigated in a 2010 study by Uhlig et al. [48•] where 15 patients were instructed in tai chi exercise for 12 weeks. The authors found that the exercises improved muscle function in the lower extremities, and patients reported less pain in daily life. Moreover, a randomized controlled trial by Wang et al. [49] looked at the effectiveness of tai chi on osteoarthritis. In this study, 40 patients with tibiofemoral osteoarthritis were randomly assigned to biweekly tai chi or wellness education/stretching classes for 12 weeks. The authors found that patients in the tai chi group reported better pain scores on the Western Ontario and McMaster Universities Osteoarthritis Index. Recently, Wang et al. [50] conducted another randomized trial looking at the effect of tai chi on fibromyalgia pain. Similar to the previous study, 66 patients were randomized to either tai chi or wellness education/stretching classes for 12 weeks. The primary outcome measure was the FIQ score. The authors concluded that when compared to the control group, patients who underwent tai chi had a change in their FIQ score of –18.4 points.

Biofeedback for Pain

Biofeedback refers to the use of electronic devices to help people learn to control body functions that are normally controlled unconsciously, such as heart rate or respiratory rate, to promote relaxation, health, and pain relief. Biofeedback has been used for many chronic pain conditions such as temporomandibular joint (TMJ) dysfunction [51], patella femoral pain [52], and fibromyalgia [53].

Crider's [51] 2005 review of biofeedback for TMJ dysfunction examined six randomized controlled studies. Although 5 of the 6 studies showed biofeedback to be an effective treatment of the treatment of TMJ dysfunction, all studies had some limitations in experimental design. Although well-designed randomized controlled trials have not proven biofeedback to be efficacious, there are few drawbacks to therapy aside from potential cost and accessibility.

Patella femoral pain has responded less conclusively to biofeedback than TMJ dysfunction. One randomized controlled study [52] of 30 patients receiving biofeedback in addition to an exercise program versus 30 matched patients on an exercise program alone indicated that biofeedback provided no additional benefit. Other studies have shown trends toward improved pain scores in the biofeedback groups, but these trends were not statistically significant.

Biofeedback has been used as an adjunctive therapy for patients with fibromyalgia. Randomized controlled studies [53] have shown statistically significant benefit of biofeedback for fibromyalgia pain, although experimental design was evident. Other studies examining biofeedback for fibromyalgia have failed to demonstrate a clinical benefit [54]. Given the treatment difficulty of this syndrome, biofeedback can be considered if cost and accessibility are within a reasonable range. Although biofeedback cannot be recommended based solely on evidence from well-designed studies, it may be a part of the multimodal treatment of fibromyalgia, providing needed relief to some.

Conclusions

Complementary and alternative medicine encompasses a wide diversity of therapeutic options that have become increasingly popular treatment modalities for patients with pain, particularly when conventional strategies fail or provide only partial relief. The quality and quantity of research surrounding each distinct therapy vary tremendously. Furthermore, many of the studies suffer from flaws in experimental design that make definitive conclusions about efficacy difficult and, in some cases, impossible. As suggested by prior reviews of randomized controlled studies [55], failure to satisfy even one criterion necessary for valid experimental design potentially may invalidate a study. However, despite this stringent research framework, the alternative medicine options discussed here are widely available and appear to offer a reasonable degree of safety. Moreover, these therapies are increasingly sought by patients. Thus, it is incumbent upon physicians and other

health care providers to acquire some knowledge of the current state of complementary and alternative therapies for pain.

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