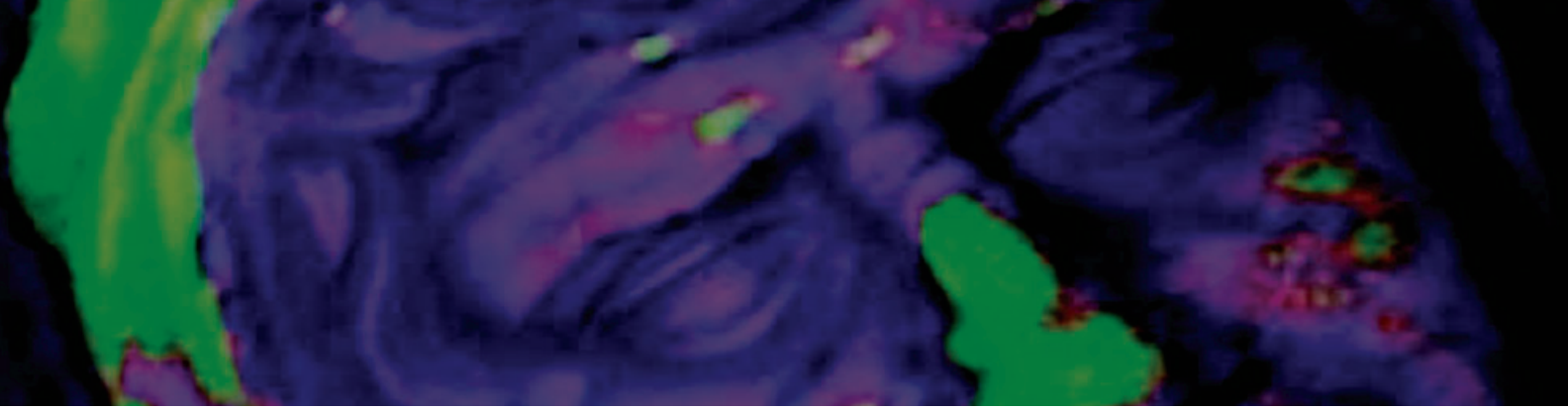

Headache Currents

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Headache Currents

Alternative Headache Treatments: Nutraceuticals, Behavioral and Physical Treatments

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There is a growing body of evidence supporting the efficacy of various complementary and alternative medicine approaches in the management of headache disorders. These treatment modalities include nutraceutical, physical and behavioral therapies. Nutraceutical options comprise vitamins and supplements (magnesium, riboflavin, coenzyme Q_{10}, and alpha lipoic acid) and herbal preparations (feverfew, and butterbur). Although controversial, there are some reports demonstrating the benefit of recreational drugs such as marijuana, lysergic acid diethylamide and psilocybin in headache treatment. Behavioral treatments generally refer to cognitive behavioral therapy and biobehavioral training (biofeedback, relaxation training). Physical treatments in headache management are not as well defined but usually include acupuncture, oxygen therapy, transcutaneous electrical nerve stimulation, occlusal adjustment, cervical manipulation, physical therapy, massage, chiropractic therapy, and osteopathic manipulation. In this review, the available evidence for all these treatments will be discussed.

Key words: complementary, alternative headache treatment, nutraceuticals, behavioral, physical treatment, biofeedback, acupuncture

INTRODUCTION

The use of complementary and alternative medicine (CAM) has been on the rise, as demonstrated by epidemiological studies in the USA and Europe over the past few decades.[1,2] More recently, the utilization of CAM has increased in patients with neurological disorders, and now appears to be in widespread use among patients even in tertiary headache care. In a recent questionnaire-based survey conducted in Germany and Austria, the majority (81.7%) of patients attending tertiary outpatient headache clinics reported use of CAM.[3] CAM usage is often motivated by dissatisfaction with conventional therapies and medication side effects, or a desire to be proactive against a disabling disorder.

Although there is no formal definition for CAM, the National Center for Complementary and Alternative Medicine considers it to be "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine."[4] For many patients, the appeal of CAM is in the holistic, empowering, and educational nature of the various treatment strategies. CAM modalities can generally be divided into nutraceutical, physical, and behavioral therapies. In the context of headache treatment, nutraceutical options include vitamins, supplements and herbal preparations, while non-pharmacological therapies include behavioral treatments, physical therapies, and acupuncture. Behavioral treatments usually comprise cognitive behavioral therapy (CBT) and biobehavioral training (biofeedback [BFB], relaxation training).

There is increasing evidence for the efficacy and tolerability of some CAM approaches in the management of headache disorders. Although these strategies may be used instead of traditional medications, using them in conjunction with conventional pharmacological therapies as part of a multidisciplinary treatment plan is more likely to result in optimum responses.[5-7] In this review, the evidence for various CAM therapies in headache treatment will be discussed.

METHODS

The National Library of Medicine (PubMed), The Cochrane Library, and the American Academy of Neurology's Evidence-Based Guidelines were searched through August 2010 to identify studies, reviews, case series, reports or other information that assessed the alternative treatment of headache or migraine. The key words used in the search were: alternative, complementary, magnesium, riboflavin, coenzyme Q_{10} (CoQ_{10}), alpha lipoic acid, butterbur, feverfew, marijuana, lysergic acid, psilocybin, nutraceutical, behavioral treatment, BFB, relaxation, cognitive behavioral training, physical treatment, acupuncture, and oxygen therapy, combined with the key words of headache or migraine.

NUTRACEUTICALS

Patients often seek nutraceuticals for headache treatment after finding conventional therapies ineffective or limited by side effects, believing that "natural" substances such as vitamins, minerals, and herbal remedies are less toxic than prescription medications. While the evidence for some of these nutraceuticals is promising, especially for magnesium, many of the existing studies are small and underpowered, sometimes showing inconsistent results. The available evidence for these treatments is discussed below, but larger, better-designed trials are necessary in order to establish strong evidence of efficacy for any of them.

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Accepted for publication September 7, 2010.

Headache

Conflict of Interest: None

Magnesium

Magnesium, an essential cation that plays a vital role in multiple physiological processes, may have several roles in migraine pathogenesis. Deficiency in magnesium has been associated with cortical spreading depression,[8] neurotransmitter release,[9] platelet aggregation,[10] and vasoconstriction,[11,12] all of which are important aspects of our current understanding of migraine pathophysiology. In addition, magnesium concentration influences serotonin receptors, nitric oxide synthesis and release, inflammatory mediators, and various other migraine-related receptors and neurotransmitters.[13] Magnesium also plays a role in the control of vascular tone and reactivity to endogenous hormones and neurotransmitters, through its relationship with the NMDA receptor.[14,15] Deficiency in magnesium results in the generation and release of substance P,[16] which subsequently acts on sensory fibers, resulting in headache pain.[17]

Magnesium Deficiency

Although a relationship between migraine and magnesium deficiency had long been postulated, it was initially difficult to assess, owing to the absence of simple and reliable ways of measuring magnesium levels in soft tissues. While routine laboratory testing generally measures total magnesium levels, it is the ionized magnesium level that truly reflects perturbed magnesium metabolism.[18] The subsequent development of an ion-selective electrode for magnesium has allowed for the accurate and rapid measurement of serum ionized levels.[18,19]

A pilot study of 40 patients with an acute migraine attack found that 50% of the patients had low levels of ionized magnesium.[20] When these patients were given 1 g of intravenous magnesium, basal serum IMg^{2+} levels correlated with the efficacy of treatment.[20,21] Of the patients in whom pain relief was sustained over 24 hours, 86% had a low serum IMg^{2+} level; only 16% of patients who had no relief had a low IMg^{2+} level. Total magnesium levels in all subjects were within normal range. Systemic magnesium deficiency in migraineurs has also been suggested by magnesium retention after oral loading.[22]

Magnesium deficiency may be especially common in women with menstrually related migraine. A prospective study[23] with 270 women, 61 of whom had menstrually related migraine, showed that the incidence of IMg^{2+} deficiency was 45% during menstrual attacks, 15% during non-menstrual attacks, 14% during menstruation without a migraine, and 15% between menstruations and between migraine attacks.

Low levels of magnesium in the brain[24] and cerebrospinal fluid[25] have also been reported, but interictal studies on serum,[26-30] plasma,[31,32] and intracellular[28,29,32-34] magnesium levels in migraineurs and patients with tension-type headache (TTH) have produced conflicting results. However, interictal levels of red blood cell (RBC) magnesium have been shown to be decreased in migraineurs with[33] and without aura,[28,31] as well as in juvenile migraine patients with and without aura.[35] These results were supported by a study[36] that showed low total magnesium in erythrocytes and low ionized magnesium in lymphocytes in migraine patients, both of which increased significantly after a 2-week trial of drinking mineral water containing 110 mg/L magnesium. Given its commercial availability, the RBC magnesium assay may therefore be a good way of assessing for deficiency. Future trials should focus on patients with deficiencies in ionized or RBC magnesium, as improvements in clinical symptoms correlating with corrected levels would clearly demonstrate the benefits of magnesium supplementation.

Treatment With Oral Magnesium

Several randomized controlled trials (RCTs) have shown that Mg^{2+} supplementation is effective in migraine treatment. In the first, 24 women with menstrual migraine[31] received either 360 mg of magnesium pyrrolidone carboxylic acid or placebo in 3 divided doses. Women received 2 cycles of study medication, taken daily from ovulation to the first day of flow. Magnesium treatment resulted in a significant reduction of the number of days with headache ($P < .1$), total pain index ($P > .03$), as well as an improvement of the Menstrual Distress Questionnaire score in the treatment group compared to placebo.

A larger study comprising 81 migraineurs also showed a significant improvement in patients who received magnesium.[37] Attack frequency was reduced by 41.6% in the magnesium group and by 15.8% in the placebo group. The active treatment group received 600 mg of trimagnesium dicitrate in a water-soluble granular powder taken every morning. More recently, Koseoglu et al[38] studied the prophylactic effects of 600 mg/day of oral magnesium citrate supplementation in patients with migraine without aura and found that active treatment resulted in a significant decrease in migraine attack frequency and severity. A 4th RCT showed no effect of oral magnesium on migraine.[39] This negative result was likely because of the use of a poorly absorbed magnesium salt, as diarrhea occurred in almost half of patients in the treatment group.

The most common adverse effect associated with oral magnesium supplementation is diarrhea. While diarrhea itself usually prevents the development of magnesium-related toxicity, patients should be cautioned about this side effect. Magnesium toxicity is marked by the loss of deep tendon reflexes followed by muscle weakness. Severe toxicity can lead to cardiac muscle weakness, respiratory paralysis, and death. Patients with kidney disease are at higher risk of developing toxicity as magnesium is excreted through the kidneys.[40]

Treatment With Intravenous Magnesium

Several studies have evaluated the use of intravenous magnesium in acute migraine treatment, with conflicting results. In the pilot study[20] described under "Magnesium Deficiency" a strong correlation between the clinical response and the levels of serum IMg^{2+}

was found ($P < .01$). Although the study was not double-blinded or placebo-controlled, both the researchers and subjects were blinded to the IMg^{2+} levels. A subsequent study[21] showed that 1 g of magnesium sulfate resulted in rapid headache relief in patients with low serum IMg^{2+} levels.

In a single-blind RCT involving 30 patients with moderate to severe migraine attacks[41] treatment with 1 g intravenous magnesium sulfate was superior to placebo in terms of both response rate (100% for magnesium sulfate vs 7% for placebo) and pain-free rate (87% for magnesium sulfate and 0% for placebo). Mild side effects including flushing and a burning sensation in the face and neck were common during the infusion, but subjects were able to continue treatment. Of note, none of the subjects reported headache recurrence during the 24 hours after treatment. Bigal et al[42] in a double-blind RCT, showed that 1 g of magnesium sulfate resulted in a statistically significant improvement in pain and associated symptoms in subjects with migraine with aura, as compared to controls. Although migraine without aura patients did not show a significant difference in pain relief compared to those receiving placebo, they did have a significantly lower intensity of photophobia and phonophobia.

Two RCTs have been conducted in emergency room settings, neither of which showed that magnesium was more effective than placebo in aborting attacks.[43,44]

Supplements and Mitochondrial Dysfunction

Mitochondrial dysfunction, which leads to impaired oxygen metabolism, has been speculated to play a role in migraine pathophysiology[45,46] as migraineurs have been shown to have reduced mitochondrial phosphorylation potential in between headaches.[47,48] An impairment of mitochondrial oxidative metabolism might influence neuronal information processing, therefore reducing the threshold for migraine attacks.[49] This is the rationale for the use of supplements that enhance mitochondrial function in the treatment of migraine, such as riboflavin, CoQ_{10}, and alpha lipoic acid.

Riboflavin

Riboflavin, also known as vitamin B2, is a component of 2 coenzymes (flavin adenine dinucleotide and flavin mononucleotide) that are cofactors in the electron transport chain of the Krebs cycle. It plays a vital role in membrane stability and the maintenance of energy-related cellular functions. One well-designed RCT found that it is beneficial in migraine prophylaxis, showing that daily use of 400 mg riboflavin for 3 months resulted in a 50% reduction in attacks in 59% of patients, compared to 15% for placebo. Two minor adverse reactions, diarrhea and polyuria, were reported in the treatment group.[50] In a small study[51] investigating the effects of different treatments on auditory evoked cortical potentials in migrainers, riboflavin and beta-blockers were shown to act on 2 distinct aspects of migraine pathophysiology. The authors thus suggested that combining these treatments might increase their efficacy without concurrently increasing central nervous system side effects.

A recent pharmacogenetic study[52] demonstrated that riboflavin may be more effective in the treatment of migraine patients with non-H mitochondrial DNA haplotypes. As riboflavin is effective in deficiencies of the electron transport chain complex I but not in mitochondriopathies related to an isolated complex IV deficiency,[53,54] the authors suggested that mitochondrial haplogroups differentially influence the activity of the various complexes. These results may have ethnic implications, in that haplogroup H is predominantly found in the European population.

Coenzyme Q_{10}

Coenzyme Q_{10} is an endogenous enzyme cofactor involved in the mitochondrial electron transport chain, generating energy through its role in aerobic cellular respiration. Because of its activity in mitochondrial function and as an antioxidant, it has been hypothesized to be useful in migraine prevention. Two small studies thus far have shown some benefit of CoQ_{10} in migraine treatment. In the first, an open-label study[55] of 31 migraineurs who used 150 mg daily of CoQ_{10} for 3 months, 61% had at least a 50% reduction in migraine days. Notably, supplementation was effective within the first month of treatment. No significant adverse effects were noted. The second study,[56] a small (n = 42) RCT assessing the efficacy of 100 mg of CoQ_{10} 3 times daily, found that CoQ_{10} significantly decreased attack frequency, headache days, and days with nausea. Gastrointestinal disturbances and "cutaneous allergy" were reported at a low rate.

Coenzyme Q_{10} supplementation may be especially effective in the prophylaxis of pediatric migraine. CoQ_{10} levels were measured in a study[57] of 1550 pediatric patients (mean age 13.3 ± 3.5 years) with frequent headaches. Nearly one-third of subjects were below the reference range. Patients with low CoQ_{10} received supplementation with 1 to 3 mg/kg per day of CoQ_{10} in liquid gel capsule formulation, resulting in an improvement in total CoQ_{10} levels, headache frequency and degree of headache disability.

Alpha Lipoic Acid

Alpha lipoic acid, also known as thioctic acid, is a naturally occurring fatty acid that can be found in many foods such as yeast, spinach, broccoli, potatoes, and organ meats such as liver or kidney. Like riboflavin and CoQ_{10}, it augments mitochondrial oxygen metabolism and adenosine triphosphate production.[58] In 1 small RCT,[59] 54 subjects received either 600 mg alpha lipoic acid or placebo daily for 3 months. Although there was no significant difference between treatment and placebo for the primary endpoint (50% reduction of monthly attack frequency), there was a trend toward reduction of migraine frequency after treatment with alpha lipoic acid. Within-group analyses also showed a significant reduction in attack frequency, headache

days, and headache severity in the treatment group. While these results suggest that alpha lipoic aid may be effective in migraine prevention, larger trials are necessary.

Herbal Preparations

Butterbur (Petasites hybridus)

In recent years, *Petasites hybridus* root extract, also known as butterbur, has been touted as a promising new treatment for migraine prevention. The butterbur plant is a perennial shrub found throughout Europe and parts of Asia. It was used for many centuries as a remedy for pain, fever, spasms, and wound healing. Although its mechanism of action is not fully understood, *Petasites* likely acts through calcium channel regulation and inhibition of peptide leukotriene biosynthesis, thus influencing the inflammatory cascade associated with migraine.[60-62] The pharmacologically active compounds in butterbur are sesquiterpenes such as petasin and isopetasin. While the butterbur plant itself also contains pyrrolizidine alkaloids, which are hepatotoxic and carcinogenic, these substances are removed in the commercially available preparations, such as those manufactured by Weber & Weber (Inning am Ammersee, Germany; Petadolex® and others). Nonetheless, patients should be advised to use only butterbur products that are certified and labeled "PA-free."

The efficacy of *Petasites hybridus* in migraine prevention has been evaluated in several studies. In the first RCT,[63] 50 mg of Petadolex® twice daily showed a significantly reduced number of migraine attacks and migraine days per month compared to placebo. An independent re-analysis of efficacy criteria was subsequently performed[64] because of flawed statistical analyses in the original study, and confirmed the superiority of the butterbur extract over placebo for all primary variables of efficacy. Later, a 3-arm, parallel-group RCT of 245 patients comparing Petasites extract 75 mg twice daily, Petasites extract 50 mg twice daily, and placebo twice daily[65] showed that Petasites extract 75 mg twice daily was more effective than placebo in decreasing the number of monthly migraine attacks. Maximum response was achieved after 3 months, resulting in an attack reduction of 58% with the higher dose of Petadolex®, compared to the placebo response of 28%. Petadolex® was well tolerated in these studies, and no serious adverse events occurred. The most frequently reported adverse reactions were mild gastrointestinal events, especially eructation (burping). Petasites, like most other herbal preparations, should not be taken by pregnant women.

Given its safety and tolerability, Petadolex® may be a good option in the treatment of pediatric migraine. In a multicenter prospective open-label study[66] of Petadolex® in 109 children and adolescents with migraine, 77% of all patients reported a reduction in migraine frequency of at least 50%. Ninety-one percent of participants felt substantially or at least slightly improved after 4 months of treatment. More recently, a prospective, partly double-blind, RCT assessing the efficacy of Petadolex® and music therapy in primary school children with migraine[67] showed that at 6-month follow-up, both music therapy and butterbur root extract were superior to placebo ($P = .018$ and $P = .044$, respectively) in reducing headache frequency, but only among those that completed the study. In the analysis including all treated patients, treatment groups did not differ significantly during follow-up.

Feverfew

Feverfew is an herbal preparation that was used for centuries in the treatment of fevers, headache, infertility, toothaches, inflammation and arthritis. Although the feverfew plant was originally native to the Balkan mountains in Eastern Europe, it now grows throughout Europe, North America, and South America. It is commercially available as the dried leaves of the weed plant *Tanacetum parthenium*, and its anti-migraine action is probably related to the parthenolides within these leaves. Feverfew may act in migraine prophylaxis by inhibiting platelet aggregation as well as the release of serotonin from platelets and white blood cells. It may also act as an anti-inflammatory agent through the inhibition of prostaglandin synthesis and phospholipase A.[68-71]

The efficacy of feverfew in migraine prophylaxis has been controversial, as many RCTs[72-77] conducted in the past 3 decades have yielded contradictory results. In addition, a 2004 Cochrane review[78] of double-blind RCTs assessing the clinical efficacy and safety of feverfew in migraine prevention concluded that there was insufficient evidence to suggest that feverfew is more effective than placebo in migraine prophylaxis. No major safety or tolerability issues were identified, although side effects reported in the RCTs included gastrointestinal disturbances, mouth ulcers, and a "post-feverfew syndrome" of joint aches.

Inconsistent results from the above studies were attributed to wide variations in the strength of the parthenolides[79] and differences in the stability of feverfew preparations[80] and subsequently, a new, more stable feverfew extract (MIG-99) was created. In an initial RCT involving 147 patients,[81] none of the MIG-99 doses were significant for the primary endpoint, although a subset of high-frequency migraineurs appeared to benefit from treatment. In a follow-up multicenter RCT with 170 subjects[82] randomized to 6.25 mg t.i.d. of MIG-99 or placebo, a statistically significant and clinically relevant reduction in migraine frequency in the MIG-99 group compared to placebo was reported.

Feverfew should not be used by pregnant women, as it may cause uterine contractions resulting in miscarriage or preterm labor. It can also cause allergic reactions; patients with allergies to other members of the daisy family, including ragweed and chrysanthemums, are more likely to be allergic to feverfew.

Recreational Drugs

Although controversial, the evidence for the use of recreational drugs such as marijuana, lysergic acid diethylamide (LSD) and psilocybin is worth mentioning for the insight it provides regarding the pathophysiology of migraine and cluster headache.

Further research on the effects of these substances may result in a greater understanding of the mechanisms of these headache disorders.

Marijuana

The recreational and medicinal use of marijuana, or *cannabis*, has been documented for thousands of years.[83] In the second half of the 19th century, *cannabis* was a well-regarded acute and preventative treatment for headache in USA and UK, and was even included in the mainstream pharmacopeias for this use.[83]

Synthetic cannabinoids such as dronabinal and nabilone (used in the UK) have been established as useful in the treatment of nausea and vomiting associated with cancer chemotherapy. However, the role of cannabinoids in pain management is less clear. Preclinical evidence has shown that endogenous cannabinoids such as anandamide and cannabinoid agonists are antinociceptive and antihyperalgesic, reducing the allodynia associated with formalin, capsaicin, carrageenan, nerve injury, and visceral persistent pain.[84] After entering the bloodstream, cannabinoids are differentially distributed in the brain and reach high concentrations in the neocortex (especially the frontal cortex), limbic areas, sensory areas, motor areas, and the pons.[85] Therefore, cannabinoid receptors and endogenous cannabinoids may modulate pain, psychomotor control, memory function, appetite, and emesis. Cannabinoid receptors and endogenous cannabinoids are located throughout the pain pathways in peripheral sensory nerve endings, spinal, and supraspinal centers.[86] In migraine, cannabinoids may be effective via an inhibitory effect on serotonin type 3 (5-HT3) receptors[87] or antinociceptive effects in the periaqueductal gray matter.[88]

Clinical data on therapeutic uses of marijuana have been conflicting. A meta-analysis of clinical trials of cannabinoid derivatives in the treatment of pain[89] showed that cannabinoids are no more effective than codeine in pain management, and that central nervous system depressant side effects limit their use in clinical practice. The authors thus concluded that more research is necessary before these treatments could be recommended for neuropathic pain or spasticity. Later, a small RCT[90] showed that the synthetic cannabinoid 1′,1′dimethylheptyl-Delta8-tetrahydrocannabinol-11-oic acid (CT-3) was effective in reducing chronic neuropathic pain when compared with placebo. With regard to headache, evidence thus far has been limited to case reports describing the effective use of cannabis or cannabinoids in "chronic headaches,"[91] migraine,[92] pseudotumor cerebri[93] and cluster headache.[94]

Lysergic Acid Diethylamide and Psilocybin

A 2006 report[95] on 53 cluster headache patients who used either the ergot alkaloid derivative LSD or the related indolalkylamine psilocybin for their headaches described intriguing results. Twenty-two of 26 psilocybin users reported that psilocybin aborted attacks while 25 of 48 psilocybin users and 7 of 8 LSD users reported cluster period termination. In addition, 18 of 19 psilocybin users and 4 of 5 LSD users reported remission period extension, meaning that the next expected cluster period was delayed or prevented. These results are interesting not only because they describe the effective use of illicit drugs in cluster headache, but also because no other medication has been reported to terminate a cluster period. Furthermore, the drugs were effective at subhallucinogenic doses and effective treatment required very few doses of either drug. LSD reportedly terminated cluster periods after only 1 dose, and psilocybin rarely required more than 3 doses. The study was unblinded, uncontrolled and limited by recall and selection bias. However, further research on the effects of LSD and psilocybin on cluster headaches may be warranted, given the efficacy described in this report.

BEHAVIORAL AND PHYSICAL THERAPIES

Behavioral treatments are divided into the categories of CBT and biobehavioral training (BFB, relaxation training). Physical treatments are not as well defined but generally include acupuncture, cervical manipulation, transcutaneous electrical nerve stimulation (TENS), occlusal adjustment, physical therapy, massage, chiropractic therapy, and osteopathic manipulation. Oxygen therapy is included in this section as well. Patient education is a crucial part of any of these modalities.

In 2000, the US Headache Consortium issued evidence-based guidelines for the treatment and management of migraine headache, based on a review of the medical literature and expert consensus.[96] According to these guidelines, behavioral and physical treatments may be particularly beneficial in patients with one or more of the following characteristics:

- patient preference for non-pharmacological interventions;
- poor tolerance for specific pharmacological treatments;
- medical contraindications for specific pharmacological treatments;
- insufficient or no response to pharmacological treatment;
- pregnancy, planned pregnancy, or nursing;
- history of long-term, frequent, or excessive use of analgesic or acute medications that can aggravate headache problems (or lead to decreased responsiveness to other pharmacotherapies);
- significant stress or deficient stress-coping skills.

Behavioral Treatments

Behavioral medicine involves the integration of behavioral, psychosocial, and biomedical disciplines in the diagnosis, treatment, rehabilitation, and prevention of illness. The interactions of behavior with biology and the environment are studied and taken into consideration in the treatment and understanding of diseases and disorders. Migraine and other primary headache disorders are particularly well suited to the practice of behavioral medicine, in that complex relationships between biology, environment, behavior, cognition, and emotion are known to

affect the course of the disorder. Once behavioral treatments and techniques are learned, patients can utilize their skills in recognizing and mediating the effects of stress at any time and in any context.

Behavioral treatments have become standard components of multidisciplinary treatment plans at headache centers and pain management programs as guidelines, such as those published by the US Headache Consortium,[96] established that they may be considered as treatment options for migraine prevention. In its evidence-based guidelines for behavioral and physical treatments in migraine, the US Headache Consortium[96] recommended that relaxation training, thermal BFB combined with relaxation training, electromyography (EMG) BFB, and cognitive behavioral therapy be considered as treatment options for prevention of migraine, based on Grade A evidence. For TTH, the 2010 European Federation of Neurological Societies guidelines on the treatment of TTH[97] states that non-pharmacological modalities should always be considered, although the scientific evidence is limited. The available evidence shows that EMG BFB is effective, and cognitive behavioral therapy and relaxation training most likely are effective as well for TTH treatment.

Behavioral treatment may be administered in clinic-based, limited-contact, and home-based formats, and patients may be seen individually or as part of a group. Limited-contact treatment usually involves 3 or 4 monthly treatment sessions during which skills are introduced. Audiotapes and manuals are subsequently used at home for practicing and refining skills, with clinicians assisting occasionally via telephone. Limited-contact, home-based, and clinic-based treatment formats have demonstrated similar results when compared directly[98-100] or by meta-analysis.[101] Furthermore, the cost-effectiveness of home-based treatments has been found to be more than 5 times that of clinic-based therapies.[101]

Biofeedback

Biofeedback is a common intervention utilized in the treatment of pain disorders. It involves the monitoring and voluntary control of physiologic processes, allowing patients to take an active role in managing their pain. This in turn results in improved coping with the psychological and psychosocial consequences of their condition. BFB is often combined with relaxation and cognitive behavioral strategies such as stress management.

Different types of BFB are used depending on the patient's diagnosis. All forms of BFB involve the conversion of biologic or physiologic information into a signal that is then "fed back" in auditory form (such as clicks varying in rate) or visual form (such as bars varying in length). In migraine, peripheral skin temperature feedback (TEMP-FB), blood-volume-pulse feedback (BVP-FB) and electromyographic feedback (EMG-FB) are most commonly used. For TTH, EMG-FB, which is directed at reducing pericranial muscle activity, is the most frequently applied behavioral treatment modality.[102] Relaxation skills such as diaphragmatic breathing or visualization are usually taught in conjunction with BFB to produce a relaxation response. BFB training usually involves 8-12 office visits spaced 1 to several weeks apart, although evidence suggests that treatment can be effective in a reduced-contact or home-based approach.[101] Once the patient has developed the skills necessary to control targeted physiologic processes, the BFB device can be eliminated.

BIOFEEDBACK FOR MIGRAINE TREATMENT

A 2007 meta-analysis,[103] which included 55 studies, provided strong evidence for the efficacy of BFB in the preventative treatment of migraine. BFB demonstrated superior clinical results when compared to waiting list control and was shown to be at least equally effective in comparison to psychological placebo controls, relaxation, and pharmacotherapy. Also noted were reductions in the associated symptoms of depression and anxiety, and an increase in patients' sense of self-efficacy. Additional home training enhanced the direct and the follow-up treatment effect sizes, and was an important predictor of long-term outcome. None of the reviewed studies reported any adverse effects of BFB. The different forms of BFB—BVP-FB, EMG-FB and TEMP-FB—all appeared to be equally efficacious alone or in combination in the treatment of migraine. However, BVP-FB showed the numerically highest effect size of all examined feedback modalities.

Not only did BFB result in symptom reduction of over half a standard deviation, the treatment effects remained stable over a follow-up period of more than 1 year, on average. Furthermore, these effects appeared to be amplified over the long term. This may be explained by several factors, such as improved self-efficacy[104] and the continued practice and application of BFB at home.[105] Self-efficacy itself yielded higher effect sizes than the actual pain-related outcome measures of BFB, suggesting that the treatment effects of BFB may be influenced by changes in coping strategies,[106] illness perceptions, and subsequent improvements in treatment compliance.[107]

The authors concluded that "BFB can be recommended to therapists, physicians and health care providers as an efficacious non-medical treatment alternative for highly chronified migraine patients; suitable also for the long-term prevention of migraine attacks."

BIOFEEDBACK IN TENSION-TYPE HEADACHE

A recent meta-analysis of BFB in TTH[108] evaluated 53 outcome studies, which included a total of more than 400 patients, and found a significant medium-to-large effect size that was stable over an average follow-up period of 15 months. Superior effect sizes for BFB were noted when compared to psychological placebo and relaxation therapies. This effect was clinically meaningful in that they demonstrated symptoms improvements of nearly one standard deviation. While the largest improvements were shown in headache frequency, significant effects were also

seen for muscle tension, self-efficacy, symptoms of anxiety and depression, and analgesic medication consumption. Using BFB in conjunction with relaxation training increased treatment efficacy, and effects appeared to be particularly notable in children and adolescents. Furthermore, courses of BFB treatment were short and cost-effective, taking place over an average of 11 sessions. The authors concluded that the efficacy of BFB in TTH is supported by scientifically sound evidence.

BIOFEEDBACK EFFICACY RECOMMENDATIONS

A 2008 comprehensive efficacy review,[102] which drew upon the 2 meta-analyses discussed above[103,108] and incorporated one additional study,[109] provided efficacy recommendations for BFB in the treatment of migraine and TTH. These recommendations were in accordance with criteria established by the Association for Applied Psychophysiology and Biofeedback (AAPB) and the International Society for Neurofeedback and Research (ISNR).[110]

For migraine, the evidence indicated that BFB can be supported as an efficacious treatment option (Level 4 evidence according to the AAPB/ISNR criteria[110]). Multiple studies using clearly defined diagnostic criteria and outcome measures as well as appropriate data analysis demonstrated the efficacy of BFB over no-treatment control groups.

For TTH, the evidence indicated that BFB can be supported as an efficacious and specific treatment option. The efficacy recommendation given was Level 5, the highest level of evidence according to the AAPB/ISNR criteria, granted in cases where Level 4 evidence has been established and additional superior treatment results in comparison to credible sham therapy or alternative bona fide treatments have been shown.

Relaxation Training

Relaxation training can be considered a core component of behavioral treatment, as it can be used either alone or in conjunction with other behavioral modalities.[111] Relaxation techniques are used to decrease sympathetic arousal and physiologic responses to stress by enhancing the awareness of tense and relaxed muscles. Several techniques and procedures have been employed in relaxation training. Progressive relaxation training is the classic form and is still widely used. It promotes the recognition of tension and relaxation in the course of daily life. Patients are taught to sequentially tense and relax various muscle groups while taking note of the opposing sensations. Initially 16 muscle groups are involved, and as treatment proceeds, muscle groups are progressively combined, resulting in 4 groups at the end of therapy. Once this initial stage is learned, skills such as relaxation by recall, cue-controlled relaxation, and differential relaxation (in which relaxation of muscles not required for current activities is maintained) are taught. Patients can typically learn progressive relaxation training in less than 10 sessions. While techniques are usually learned in a dark, quiet setting, they can be subsequently applied to everyday situations.[112]

Autogenic training is another popular form of relaxation training. Autosuggestion, the process by which one induces self-acceptance of an opinion, belief, or plan of action, plays a central role in the process. In autogenic training, mental and somatic functions are concurrently regulated by passive concentration on formulas such as "my forehead is cool."[113] Various other traditional relaxation techniques include visual or guided imagery, cue-controlled relaxation, diaphragmatic breathing, and hypnosis.[114] With regular practice, patients often find that relaxation techniques become automatic and are carried out without conscious effort.[111]

Cognitive Behavioral Therapy

Cognitive behavioral therapy is a form of psychotherapeutic treatment that addresses the relationships between stress, coping, and headache using cognitive and behavioral strategies. While cognitive strategies focus on identifying and challenging dysfunctional thoughts and the beliefs that give rise to these thoughts, behavioral strategies aim to help identify behaviors that may trigger, increase or perpetuate headaches. CBT is usually most beneficial in patients with concurrent significant psychological or environment problems that exacerbate headaches or prevent the implementation of self-regulation skills, such as chronic work stress, mood disorders, or adjustment problems. As such, it is also used to address and manage headache co-morbidities such as depression, anxiety, panic attacks, eating disorders, and sleep disorders.[114,115]

Research has shown that low levels of self-efficacy and an external locus of control (ie, a belief that only the physician or medication can alter a cycle of pain) predict poorer outcome,[116,117] and that "catastrophizing" thinking patterns that promote a sense of hopelessness predict poor outcomes and reduced quality of life.[118] Therefore, in headache-related CBT, goals include the development of self-efficacy and an internal locus of control (the belief in oneself as an agent of change) as well as a change in "catastrophizing" thinking. Pain management strategies such as imagery training and attention-diversion training are frequently taught in conjunction with CBT. Patient education in the form of dietary interventions, lifestyle modification, and contingency management are usually provided as well.[112,119]

The US Headache Consortium found that CBT in the preventative treatment of migraine was supported by Grade A evidence.[96] While CBT can decrease TTH activity by 40-50% or more,[120] combining it with relaxation training and BFB may increase treatment efficacy, especially in patients with psychiatric co-morbidities, high levels of stress, or poor coping.[121] Furthermore, combining CBT with pharmacological treatment such as amitriptyline may result in more improvement than either treatment alone, as demonstrated in a large RCT for chronic TTH.[122]

Physical Treatments

Physical treatments in headache management include acupuncture, TENS, occlusal adjustment, physical therapy, massage, chi-

ropractic therapy, and osteopathic manipulation. Many of these therapies are prescribed in the treatment of migraine and TTH in an effort to relieve the neck pain that frequently accompanies these headache disorders.[123] High levels of muscle tenderness, as well as postural and mechanical abnormalities, have also been reported in tension-type and migraine headache.[124-126]

Analyses and reviews on physical treatments in headache are fraught with difficulty owing to many factors, including inconsistencies in the definitions of treatments such as physical therapy, chiropractic, or osteopathic manipulations, and a heterogeneity in the interventions and patient populations that have been studied. Furthermore, many of the published case series and controlled studies are of low quality. The US Headache Consortium[96] found that evidenced-based treatment recommendations were not yet possible regarding the use of acupuncture, TENS, cervical manipulation, or occlusal adjustment as preventive or acute therapy for migraine. The use of acupuncture has since received considerable support and is discussed in a separate section.

More recently, a structured review[123] on physical treatments for headache was undertaken, and found only modest support for the use of physical treatments in selected circumstances. Positive recommendations could be made in only a few clinical scenarios.[123] For migraine, recommendations were made for physical therapy combined with aerobic exercise, as well as physical therapy combined with relaxation therapy and thermal BFB. For TTH, there was a trend toward benefit from chiropractic manipulation in TTH, although the evidence was weak. Physical therapy was recommended, especially in high-frequency TTH cases. Cervical spinal manipulative therapy was found to be as effective as amitriptyline in short-term use for chronic tension-type headache (CTTH), and more effective than massage for cervicogenic headache. Other recent studies[127,128] have reported that physical therapy can be effective in reducing headache frequency, intensity and duration in CTTH patients. Overall, these physical treatments are most beneficial when integrated into a multimodal treatment plan including exercise, stretching, and ergonomics training for both the home and the workplace. Patients who express an interest in physical treatments are more likely to benefit from active strategies such as exercise than passive ones such as massage and heat or cold application.[129]

Some have suggested that the insufficient evidence supporting or refuting the effect of physical treatments on headache disorders might be related to problems in identifying subgroups of patients who might benefit from the intervention.[130] Fernández-de-las-Peñas et al[131] thus devised a preliminary clinical prediction rule to identify CTTH patients who experience short-term success with muscle trigger point therapy, using variables such as headache frequency, duration, bodily pain, and vitality scores. The implementation of clinical decision rules identifying these patients prior to carrying out randomized clinical trials was therefore suggested as a way of attaining stronger effect sizes.[131]

Although cervical spinal manipulative therapy may provide benefit in some clinical cases as described above, it has been associated with a 6-fold[132] increase in the risk of vertebral artery dissection and stroke or transient ischemic attack. As such, one should be cautious when considering a recommendation for this treatment, and patients who express interest in chiropractic maneuvers should be warned of this potential complication.[123] Otherwise, the use of physical treatments in headache is unlikely to be harmful in patients who express interest in these modalities.

Acupuncture

Acupuncture is a fundamental component of traditional Chinese medicine, and is one of the most commonly utilized complementary therapies in many countries.[133] In recent years, interest in acupuncture in the Western world has grown, with 2.13 million people in the USA currently undergoing treatment.[134] Population-based studies in the USA have shown that 4.1% of respondents report lifetime use of acupuncture,[134] and in Germany, 8.7% of adults surveyed reported that they had undergone acupuncture during the previous year.[135] Acupuncture is used in the treatment of a variety of conditions including addiction, stroke rehabilitation, headache, menstrual cramps, fibromyalgia, myofascial pain, osteoarthritis, low back pain, carpal tunnel syndrome, and asthma, and may be particularly effective in post-operative and chemotherapy-induced nausea and vomiting, and post-operative dental pain.[136] Headache treatment accounts for approximately 10% of visits to acupuncturists.[134]

The goal of acupuncture is to restore a state of equilibrium that has been disrupted by illness. The concept of *qi* refers to the life energy that normally flows through 12 organs and 12 meridians, arriving at the surface at 359 classical acupuncture points. Various illnesses and disorders are thus described in terms of too little *qi* or too much *qi* in particular organs or areas of the body, resulting from blockages in the flow of blood and *qi*. The activation of classic acupuncture points, which are distributed along the meridians, serves to clear the blockages, re-establishing the flow of *qi*. However, as recent studies have offered a more scientific explanation of the mechanism of acupuncture, some acupuncture practitioners now conceptualize the treatment in terms of conventional neurophysiology rather than in restoring the flow of *qi*.[137]

MECHANISM OF ACTION

While the mechanism by which acupuncture provides an analgesic effect in migraine treatment is not fully understood, several theories have been hypothesized. Acupuncture has been shown to activate nervous system structures in the control of pain perception, which include the prefrontal cortex, the rostral anterior cingulated cortex and the brainstem, as demonstrated by studies where acupuncture-induced analgesia was inhibited by the experimental blockade of the pituitary gland,[138,139] the arcuate nucleus of the hypothalamus,[140,141] and the periaqueductal

gray.[142] Other theories postulate that serotonergic projections from the raphe nucleus to higher areas of the brain as well as descending projections to the spinal cord may contribute to the effectiveness of acupuncture,[143-145] and an anti-inflammatory effect of acupuncture may also be significant.[146,147]

However, other factors, including the psychological effects of acupuncture and the physiological effects of sham acupuncture related to superficial skin penetration, are likely to play an important role in treatment efficacy.

Positive patient expectations about acupuncture, negative experiences with traditional pharmacologic therapy, the intensity of care provided by the acupuncturist, and many other psychological variables may influence treatment outcome more so than the treatment itself. Furthermore, given that sham acupuncture provides a therapeutic effect in some patients, unknown factors independent of acupuncture methodology must exist that provide a reduction in migraine symptoms.[148]

EVIDENCE SUPPORTING THE USE OF ACUPUNCTURE IN HEADACHE TREATMENT

In a 2001 Cochrane review[149] of 16 randomized studies on acupuncture in the treatment of idiopathic headache, the authors concluded that evidence in support of acupuncture for migraine prophylaxis was considered promising but insufficient. A meta-analysis of the studies could not be performed because of the heterogenous nature of the available data, differences in the choice of acupuncture points used, small sample sizes, methodological problems, and insufficient reporting of study details. In the intervening years between 2001 and an updated Cochrane review in 2009, several large trials were published. The largest of these studies,[150] which enrolled 15,056 patients with primary headache, compared the effectiveness of acupuncture in addition to routine care with routine care alone. The effect of acupuncture in randomized compared to nonrandomized patients was also studied. After 6 months, patients randomized to the acupuncture group showed a decrease in the number of headache days ($P < .001$) as well as improvements in pain intensity and quality of life ($P < .001$). Non-randomized subjects showed outcome changes that were similar to those in the randomized group. There were, however, some methodological limitations of this study. It was randomized but not blinded, and real acupuncture was not compared with a sham acupuncture procedure. Also, the study groups included patients with migraine, TTH, and a combination of both, and did not differentiate between the headache types when reporting the results.

The updated Cochrane review published in 2009 was split into separate reviews on migraine[137] and TTH[151] because of the increased number of studies and clinical differences observed amongst study subjects. The migraine review[137] included randomized trials comparing the clinical effects of acupuncture with a control (no prophylactic treatment or routine care only), a sham acupuncture intervention, or another intervention in migraineurs. Results from the 22 trials, comprising 4419 participants, showed consistent evidence that acupuncture provides more benefit than routine care or acute treatment alone. The available studies also indicated that acupuncture is at least as effective as, or possibly more effective than, traditional prophylactic therapy such as metoprolol, with fewer side effects. Furthermore, there is no evidence that "true" acupuncture is more effective than sham interventions. As such, specific aspects of acupuncture methodology such as point selection, needling stimulation, and needling depth may not be as important as a regular needling schedule of approximately 10 sessions carried out on a twice-weekly basis. The authors thus concluded that acupuncture should be considered a treatment option for patients willing to undergo the treatment. The review on acupuncture in the treatment of TTH[151] included 11 trials with 2317 participants. Of these trials, 2 enrolled only patients with episodic TTH, 2 comprised only patients with CTTH, and 7 included both forms. Results of 2 large-scale studies showed that adding acupuncture to routine care or to acute treatment only reduces the short-term (3 months) frequency and intensity of headaches. Longer-term effects were not investigated. Six trials compared acupuncture with various sham interventions and collectively showed a small but significant reduction of headache frequency for true acupuncture as compared to sham procedures, over a 6-month period of time. The remaining trials compared acupuncture with physiotherapy, massage, or exercise, but none revealed any superiority of acupuncture. For some outcomes better results were suggested in the control groups but these findings were difficult to interpret because of methodological or reporting issues. The authors concluded that acupuncture "could be a valuable non-pharmacological tool in patients with frequent episodic or chronic tension-type headaches."

ACUPUNCTURE FOR ACUTE MIGRAINE TREATMENT

Few studies have sought to evaluate the use of acupuncture in acute migraine treatment. In practicality, patients are unlikely to seek acupuncture as acute treatment in the early stages of migraine, and acupuncture treatment on an emergency basis may not be readily available.[148] Nonetheless, in the first study,[152] subjects received acupuncture, subcutaneous sumatriptan, or placebo (subcutaneous injection of NaCl solution); each group included approximately 60 patients. Although the acupuncture methodology was not well described, results showed that both acupuncture and sumatriptan prevented a full migraine attack in 35-36% of patients, as compared to only 18% in the placebo group. However, sumatriptan provided a faster response, and was also more effective when used as a second intervention in patients who developed a full attack.

A second RCT[153] was intended not only to investigate the use of acupuncture in acute migraine treatment, but also to examine

whether verum acupuncture is more effective than sham acupuncture in reducing migraine pain. In this multicenter trial, 175 subjects were randomized to a verum acupuncture treatment group or to 1 of 2 sham acupuncture groups. The 2 sham acupuncture groups were defined by different methods for locating the non-acupuncture points. Sham acupuncture group 1 was treated with acupuncture needles placed halfway between traditional acupuncture points, and sham acupuncture group 2 was treated with acupuncture needles placed outside the head region. The primary end point was headache intensity on a visual analogue scale ranging from 0 (no pain) to 10 (very severe pain) at 4 time points (0.5, 1, 2, and 4 hours).

Results demonstrated that verum acupuncture was more effective than sham acupuncture in reducing the pain of acute migraine 2 and 4 hours after treatment, although sham acupuncture was equally as effective at earlier time points (30 and 60 minutes post treatment). However, based on descriptions of the treated attacks, it is possible that up to 50% of patients did not actually have a migraine headache as defined by the International Headache Society. Furthermore, the clinical relevance of a 1-point reduction in headache intensity after several hours, as reported for the subjects who received true acupuncture, is debatable.[154]

Acupuncture is a viable treatment alternative for migraine patients, especially those with contraindications to traditional pharmacological therapy or those with headaches that remain refractory to multiple trials of medications. Although the evidence supporting its use in TTH is not as strong, acupuncture could be beneficial in those patients with frequent episodic or chronic forms of the disorder. Several studies have also demonstrated that it is cost-effective in the treatment of headache.[155-157] In order to continue improving our understanding of acupuncture in headache treatment, the importance of trial design cannot be overstated, as discussed in a 2008 editorial by Diener.[158] Future studies must be held to the same rigorous standards as those used in investigating the efficacy of pharmacological therapies.

Oxygen and Hyperbaric Oxygen Therapy

Oxygen therapy has been widely observed to be effective in the treatment of cluster headache, and is considered to be one of the standard acute treatments for the disorder.[159,160] Its use in cluster headache was described by Kudrow in 1981,[161] when 75% of 52 randomly selected cluster patients demonstrated significant pain relief after treatment with 100% oxygen inhaled through a facial mask at 7 L/minute for 15 minutes. Although the efficacy of high-dose, high-flow oxygen therapy has been commonly observed in clinical practice since then, only 2 controlled studies have undertaken to confirm its safety and efficacy in aborting cluster attacks.[162,163] The use of oxygen therapy is advantageous in that it can be combined with other acute therapies, and used several times daily. It is also cheap, safe, and easy to use. However, treatment may not be readily available, and although small portable cylinders can be used, some patients find them inconvenient and unwieldy.

While oxygen inhalation therapy usually refers to the administration of oxygen at 1 atmosphere (normobaric oxygen), the use of hyperbaric oxygen therapy (HBOT), which involves 100% oxygen at environmental pressures greater than 1 atmosphere, has also been suggested. The rationale for oxygen therapy in headache treatment is based in the ability of oxygen to constrict distal cerebral resistance vessels[164,165] while preserving tissue oxygenation, even at pressures above 1 atmosphere.[166] This observation led to the proposal that HBOT might be beneficial in the treatment of vascular-related headaches refractory to traditional pharmacological therapy. HBOT may be effective via its effect on several aspects of migraine pathogenesis, via activity as a serotonergic agonist and an immunomodulator of response to substance P.[167,168] In addition, the role of HBOT in moderating inflammatory pathways may be useful in targeting migraine, both as acute and preventative treatment.[169,170] Practical limitations of HBOT include the requirement of a compression chamber and potential adverse effects such as pressure-related damage to the ears, sinuses, and lungs, temporary worsening of myopia, claustrophobia and oxygen poisoning.[171]

A recent Cochrane Review[171] assessing the safety and effectiveness of HBOT and normobaric oxygen therapy (NBOT) in the treatment and prevention of migraine and cluster headaches found only 9 small randomized trials, with a total of 201 participants. Five trials compared HBOT with sham therapy for acute migraine treatment, 2 compared HBOT to sham therapy for cluster headache, and 2 assessed NBOT for cluster headache. Although there was some evidence suggesting that HBOT was effective in acute migraine treatment as compared to sham therapy, there was no evidence that it was useful in preventing migraine or reducing the incidence of nausea, vomiting, or the need for rescue medication. The use of NBOT in the termination of cluster headaches was supported only by weak evidence from 2 small randomized trials, but given the safety and ease of treatment, the use of NBOT will likely continue. There is insufficient evidence from randomized trials to establish whether HBOT is effective in the acute treatment of cluster headache. Lastly, there was no evidence to suggest that either NBOT or HBOT were effective in the prevention of either migraine or cluster headaches.

CONCLUSIONS

There is a growing role for CAM treatment in the multidisciplinary management of headache disorders. In addition to their potential in decreasing headache frequency and intensity, these modalities also serve to provide the patient with a greater sense of self-efficacy. However, despite the supporting evidence discussed in this review, there is still much to be learned about these therapeutic options and how they influence the course and

outcome of headache disorders. Future research should focus on extending the current evidence base using updated standards and more rigorous methodology, and identifying which patients would be responsive to such approaches.

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