Comparing and Contrasting Standard Pharmaco-therapeutic Treatments versus Alternative and Complementary Treatments for Migraine Headaches

Submitted by

Kristi Haverkamp

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We hereby recommend that the research project prepared under our supervision by Kristi Haverkamp entitled Comparing and Contrasting Standard Pharmaco-therapeutic Treatments versus Alternative and Complementary Treatments for Migraine Headaches be accepted as partial fulfillment for the degree of Master of Physician Assistant.

Approved:

Richard D. Muma, PhD, MPH, PA-C, Chair and Associate Professor
Department of Physician Assistant

Timothy Quigley, MPH, PA-C, Associate Professor, Research Advisor
Department of Physician Assistant

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Date

Abstract

Introduction: Migraine headaches affect an estimated 28 million Americans, cost the nation an estimated $14 billion annually, and are very difficult to treat effectively. The exact etiology of migraine headaches is still unknown, although many theories exist; this makes finding an effective treatment even more challenging. Methodology: This literature review sought to compare and contrast the effectiveness of standard pharmaco-therapeutic treatments versus alternative, complementary treatments for the treatment of migraine headache. Searches were performed in peer-reviewed journals dating from 1980. Search terms included migraine, drug therapy, diet therapy, prevention and control, and diagnosis. Results: The pharmacological studies were more recent controlled trials and had more standardized methods, which lead to production of stronger evidence. Nine randomized, controlled studies for pharmacological treatments were included for this review, and showed that triptans such as sumatriptan and zolmitriptan, as well as dihydroergotamine, were consistently effective in relieving migraine headache pain. The over the counter combination of acetaminophen, aspirin, and caffeine also showed to be beneficial. This review also included nine randomized, controlled studies of alternative treatments, but many were older and revealed more inconsistent conclusions. Results of acupuncture studies were contradicting. Biofeedback and relaxation techniques did show improvement of headache pain, however, a clear difference between the two groups did not emerge. Conclusion: Additional research that directly compares pharmacological treatments to alternative therapies needs to be done to adequately compare the two different treatment modalities. The strongest evidence to date appears to support use of pharmacological treatments.

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Introduction

Migraine headaches afflict an estimated 28 million Americans annually[1] and cost the nation over $14 billion annually in reduced productivity[2]. Common symptoms of a migraine headache include a unilateral, pulsating pain, nausea, vomiting, and sensitivity to light and sound. These headaches are often intense and debilitating, complicating the activities of daily living. Migraines can last from a few hours to a few days and greatly impact a person's ability to function both at work and at home. Migraines occur most frequently in the most productive years of life, between the ages of 25 and 55 years [3]. A greater prevalence of females typically suffers from migraines, 18.2%, compared to 6.5% in males [3]. According to the World Health Organization, migraine headaches rate #19 in the top twenty list of diseases responsible for years of life lived with disability.[4]

The International Headache Society (IHS), based on several criteria (Appendix A), has classified migraine headaches into two categories-with aura or without aura. An aura is a "subjective symptoms at the onset of a migraine headache."[5] This may include visual changes, parasthesias, paresis, and dysphasia. Migraines without aura strike the person without any such warning symptoms. Headaches must last at least four hours, according to the IHS criteria, may even last up to 72 hours, and are generally unilateral. Associated symptoms such as nausea, vomiting, phonophobia or photophobia are common [6].

An accurate diagnosis of migraine headaches must be based on the criteria set forth by the International Headache Society [6]. A very careful and detailed history of headache features and occurrences must be obtained. Alternative causes of the headache, such as an aneurysm, temporal arteritis, brain tumor, hypertension, allergies, infection, or

trauma, must be ruled out by performing a thorough, comprehensive physical exam. Migraine headaches must also be differentiated from cluster or tension headaches. It is often helpful to have patients keep a headache diary to distinguish between the different types of headaches; the diary often also helps patients to identify specific triggers than initiates their migraine, such as lack of sleep, poor diet or eating habits, hormonal changes, increased stress, odors, or environmental factors [3].

Despite the significant prevalence of migraines in the general population, many migraine sufferers are unable to find adequate relief for their headaches. Migraine specific-medications such as the triptans have been found to be ineffective at relieving symptoms for up to one-third of patients [2]. Many theories to explain the pathopysiology are under currently being researched. Because the specific cause or trigger of migraine headaches has yet to be identified, it has been difficult for general practioners to effectively treat their patients. The same treatment effective for alleviating the symptoms of one patient may have no effect on another patient. Treatment must be tailored individually to each patient, and often several trials of different therapies may be necessary.

Patients will also differ greatly on their preferred methods of types of therapies to trial. Many patients would rather not take any type of medication and would rather seek more natural, non-pharmacological means of relieving their headache pain. For those that prefer a more natural approach to therapy, many effective options exist.

Purpose of the Study

With the significant prevalence of migraine headaches in the general population and the wide variety of treatment options available, it is essential that practioners are

aware of the available options. Many studies have been performed that assess the effectiveness of many pharmacological therapies, and a growing number of studies are available to evaluate non-pharmacological means of treatment. This paper focuses on a comprehensive, evidence-based literature review that compares and contrasts standard pharmaco-therapeutic treatments versus alternative and complementary treatments for migraine headaches. This literature review focused on assessing the effectiveness of both pharmacological means of therapy as well as alternative or behavioral approaches.

Methodology

The data for this paper was collected by performing an evidence based literature review. Studies eligible for inclusion were required to be peer-reviewed. The Medline First Search database and the National Guideline Clearinghouse site were used, and MeSH terms used were migraine, migraine drug therapy, migraine diet therapy, migraine prevention and control, migraine therapy, and migraine diagnosis. The data collection was performed to include comprehensive studies focusing on both standard pharmacological treatments as well as alternative treatments. The search was limited to articles written in English. Publication dates were originally limited to those published after 1998, however after extensive research it was discovered that the dates would have to be expanded to address more options for the complementary or alternative approaches. Publications no later than 1980 were chosen to be included for this review. Assessment of effectiveness of each type of therapy differed slightly with each study, but was primarily based on percentage or proportion of patients that received relief of symptoms, complete or partial, after certain time intervals. Some studies also asked patients to rate their functional disability on a numbered scale before and after treatment to evaluate any

differences between the two scores. Headache intensity and frequency were also monitored as primary endpoints in several studies. With any type of treatment there often comes some degree of a side effect profile; most studies reviewed side effects reported by participants.

Studies that included different types of headaches or did not differentiate between the different types of headaches when analyzing data were excluded. This study also did not focus on means of prophylactically treating migraine headaches so these types of studies were also not evaluated for this review. This review was meant to focus on means of treating the acute migraine headache pain itself; therefore, studies investigating effectiveness of treatments on migraine headache associated symptoms, such as nausea, vomiting, phonophobia, and photophobia, were not reviewed.

Literature Review

Pharmacological Studies

Nine studies pertaining to pharmacological treatments met inclusion criteria for this review (Appendix B). These studies were all rated as Evidence Level I (Table 1), and were all randomized, controlled trials.

Results from the nine alternative treatment studies (Appendix C) were also randomized, controlled trials, however these studies were less well designed and met criteria for Evidence Level II.

Table 1-Levels of Evidence

I: Evidence obtained from at least one properly randomized controlled trial.
II-1: Evidence obtained from well-designed controlled trials without randomization.
II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

Eight studies initially evaluated were excluded for this review (Appendix D). One study by Diener, et al. assessed the effectiveness of the study drug on migraine headache associated symptoms, however, this review assessed the treatment for the acute migraine headache pain[7]. Loh, et al. was excluded based on the fact that their study considered a prophylactic means of treatment [8]. All other studies excluded included patients with types of headaches other than migraine headaches [9-14].

One class of drugs that has been used extensively in the treatment of migraine headaches is known as the "triptans." This class of drugs is specific for migraine treatment, and the FDA has approved the triptans for as treatment for acute migraine attacks. Triptans are serotonin agonists, or 5-HT_1 receptor agonists. Their mechanism of action in to vasoconstrict the vessels in the brain to reduce swelling and inflammation. The largest number of studies available pertained to this class of drugs. Another drug, dihydroergotamine, DHE, is also very commonly used for the acute treatment of migraine headaches. DHE is similar to the serotonin agonists triptans but also has agonistic properties for dopamine and other catecholamine receptors. [15]

All of the studies reviewed pertaining to pharmacological means of treatment had specific inclusion and exclusion criteria that had to be met for participants to be included in the study. In general, participants between the ages of 18 and 65 were allowed, and patients must have had at least a one-year history of migraine headaches with or without aura, as defined by IHS criteria. For at least two months before screening occurred, it was required that patients had experienced at least one but no more than six migraines per month that were considered moderate to severe in intensity. It was then necessary for all participants to sign an informed consent document. Several screening tests were then

performed, including a detailed medical history and physical exam, vital signs, a 12-lead EKG, and standard chemical and hematological laboratory tests, including a urinalysis.

Exclusion criteria most commonly included patients with any evidence or history of ischemic heart disease, Raynaud's syndrome, Prinzmetal's angina, cerebrovascular pathology, diastolic blood pressure greater than 95, or systolic blood pressure greater than 160. Women who were pregnant, breast-feeding, or were of childbearing potential and not using adequate contraception were also excluded. Patients were required to be able to distinguish between a migraine headache and other types of headaches, such as tension or cluster headaches, and patients with a history of chronic tension or cluster headaches were excluded. Some studies also specified that those with a history of, or are currently, abusing drugs or alcohol or have an active psychological or neurological disorder other than migraine headaches not be included in the studies. Patients with any hypersensitivity to any of the medications used in the specific study were not allowed as subjects.

Several studies compared sumatriptan to a placebo. A double-blind, randomized, parallel-group study by Sargent, Kirchner, and Kirkhart sought to evaluate the efficacy and tolerability of different doses of oral sumatriptan. Doses of 25, 50, and 100 mg oral tablets were compared to placebo in a double-blind, randomized, parallel-group study. Patients used a four point scale to rate the intensity of their migraine: 0=no headache, 1=mild, 2=moderate, 3=severe pain.

One hundred eighty seven participants were randomized to receive one of the three doses of drug being tested or placebo to treat one migraine headache requiring a rating of a 2 or 3. Patients rated headache severity every 30 minutes up to 4 hours after

medication administration, and these ratings were compared with the baseline rating taken before drug administration.

The primary endpoint measurement for this study was the percentage of patients who received headache relief, a score of 2 or 3 reduced to a score of 0 or 1, at 4 hours.

At four hours post dose, 65% of patients in the 25 mg sumatriptan group, 70% of the 50 mg group, and 78% of the 100 mg group rated no pain or mild pain, compared to only 19% of the placebo group. When asked to assess meaningful relief, as defined by the patient, 69% of the 25 mg group, 73% of the 50 mg group, and 83% of the 100 mg group received meaningful relief, compared to 26% of placebo treated patients.

Percentage of patients reporting adverse events were similar in all treatment groups: 31% of the 25 mg group, 37% of the 50 mg group, 33% of the 100 mg group, and 30% of the placebo group. Side effects reported were not judged to be serious events and caused no patients to withdraw from the study [16].

Rederich, et al. evaluated the efficacy of 100 mg oral sumatriptan compared to placebo. This randomized, double-blind, placebo-controlled, crossover study assessed three different variables as primary outcome measurements. Patients rated headache intensity on four point scale, 0=no pain through 3=severe pain. Clinical disability was rated using a scale of 0=able to function normally, 1=working ability impaired to some degree, 2=severely impaired working ability, and 3=requires bed rest.

One hundred one patients participated in this study that was conducted over a one year time period. The migraine headaches were divided into three blocks of four attacks each. Patients were then randomized to receive placebo for one of the attacks in each block and sumatriptan 100 mg for the other three attacks in each block. Sumatriptan (S)

was administered to placebo (P) in a 3:1 ratio: PSSS, SPSS, SSPS, and SSSP. Migraine severity and clinical disability were to be rated hourly for the initial 12 hours post dose and then every 6 hours for the next 36 hours post dose.

Headache relief, determined as a reduction of a score of 2 or 3 to a score of 0 or 1, was obtained by 18 % of placebo treated patients and 49% of sumatriptan treated patients at 2 hours post dose over all attacks. At four hours post dose, 18% of placebo treated patients have received relief, compared to 61% of sumatriptan treated patients. Over all attacks, patients reporting no clinical disability, a score of 0, were 13% of placebo treated patients vs. 29 % of drug treated patients at 2 hours post dose and 13% placebo and 44% drug treated patients at 4 hours post dose. Adverse events were reported in 56% of the sumatriptan treated groups compared to 50% of placebo treated groups. Some of these adverse events reported were serious and caused 7 patients to withdraw from the study; however, the investigator present at the study site determined these events to be unrelated to the study drug [17].

For the migraine headache sufferer who experiences nausea and vomiting in addition to the headache pain, oral medications will be relatively ineffective if the patient is unable to keep the medication in their system long enough to be absorbed and become active. For these patients, a nasal spray would be a much more effective and tolerable option.

In a study conducted by Ryan, et al. comparing sumatriptan nasal spray to placebo, two double blind, randomized, parallel-group clinical trials were performed at two separate sites to determine the effectiveness of the sumatriptan nasal spray. This study sought to compare the efficacy of sumatriptan nasal spray 20 mg, 10 mg, and

placebo. Between both trials 845 patients participated in this study. Patients were instructed on how to rate their migraine headache pre-dose using the number scale indicating 0=no pain through 3=severe pain. Patients were then randomized to receive sumatriptan nasal spray 20 mg, 10 mg, or placebo in a 2:1:1 ratio to treat a migraine attack that rated a 2 or 3. Headache relief was defined as a reduction in pre-dose score of 2 or 3 to a score of 0 or 1 post-dose.

The primary measurement this study sought was headache relief obtained at two hours post-dose. Results from these two trials showed that at two hours post-dose 62% and 63% of patients in the 20 mg group and 43% and 54% of patients in the 10 mg group reported headache relief, compared with 29% and 35% of those in the placebo group.

No serious adverse events were reported in either trial. The most common side effects in all groups were taste disturbance, nausea and vomiting, disturbance of nasal cavity or sinuses, phonophobia, and throat symptoms. When incidence of the two most commonly reported side effects, taste disturbance and nausea and vomiting, were averaged between the two trials, 31% of the 20 mg group, 22% of the 10 mg group, and only 1% of the placebo group experienced tasted disturbance, and 17.5% of the 20 mg group, 17% of the 10 mg group, and 15% of the placebo group experienced nausea and/or vomiting[18].

Touchon, et al. compared the efficacy and tolerability of subcutaneous sumatriptan and DHE nasal spray. This study was a multicenter, randomized, double blind, double dummy, crossover design. 266 patients were to treat two migraine headaches, and were all randomized to receive either subcutaneous sumatriptan 6 mg plus a placebo form of the DHE nasal spray or DHE nasal spray 0.5 mg plus placebo form of

subcutaneous sumatriptan. After treating one migraine headache attack with one type of treatment, participants then treated a second attack with the cross over form of treatment. Headache severity was rated on a four point scale with 0=no pain and 3=severe pain.

The primary measurement for this study was the percentage of patients that obtained headache relief, a score of 2 or 3 reduced to a 0 or1, within two hours of administering the medication. The results indicated that sumatriptan was more effective than the DHE for the treatment of acute migraine attacks. At 2 hours post-dose, 80% of patients received relief when treated with sumatriptan as compared to 50% of patients when treated with the DHE. 65% of sumatriptan treated patients were completely headache free at two hours post-dose compared to only 30% of the DHE group.

When receiving subcutaneous sumatriptan, 43% of patients had at least one adverse side effect, and those most commonly were fatigue, flushing, nausea, tingling, and injection site reactions. These were mild side effects and quickly resolved. It was also reported that 3 patients in this group withdrew from the study due to pressure in the chest and some nonspecific neurologic symptoms; one other patient also withdrew from the study when treated with the DHE nasal spray due to myalgia and joint pain. Only 22% of the patients reported at least one adverse effect from the DHE nasal spray, and these most commonly were nausea and disorders of the nasal cavity.

The majority of patients in this study reported that the subcutaneous sumatriptan was preferred over the DHE nasal spray even though side effects were more commonly associated with the sumatriptan treatment [19].

A second study by Winner, et al. compared sumatriptan to DHE for the acute treatment of a migraine headache; this study, however, compared both of the

subcutaneous forms of each treatment. This was a double-blind randomized trial with parallel arms. Primary endpoint measurements were the percentage of patients receiving relief of pain at one, two, and four hours post-dose and recurrence of headache at 24 hours; pain relief was again indicated by a baseline score of 2 or 3 reduced to a 0 or 1 post-dose. 295 patients were randomized to receive either 1 mg subcutaneous DHE or 6 mg subcutaneous sumatriptan for the treatment of one acute migraine.

Patients reporting relief at one hour constituted 57% of the DHE group and 78% of the sumatriptan group. At two hours post-dose, 73% of the DHE group and 85% of the sumatriptan group had relief, and at four hours post-dose, 86% of patients in the DHE group and 83% in the sumatriptan group experienced relief. 90% of patients reported headache relief in the DHE group at 24 hours post-dose while 77% of patients in the sumatriptan group got relief of pain. When reassessed at 24 hours post-dose, 18% of patients reported no or mild pain, compared to 45% of the sumatriptan group.

The most commonly reported adverse event was injection site reaction or discomfort and was reported by 38% of the DHE group versus 18% of the sumatriptan treated group. Other reported side effects included nausea, vomiting, and chest pain; it was reported that two patients in the DHE group withdrew from the study due to chest tightness and severe nausea and vomiting.

This study showed that subcutaneous sumatriptan was faster acting than the dihydroergotamine but efficacy was clinically equal by four hours after medication administration. A significantly larger proportion of patients that took sumatriptan experienced refractory headaches than did those in the DHE group [20].

Solomon, et al. investigated the effects of 2.5 mg of zolmitriptan versus placebo for the acute treatment of migraine headaches in their randomized, double-blind, placebo-controlled trial and found zolmitriptan to be more effective than placebo at alleviating pain and preventing recurrence of headache than placebo. IHS criteria were used for accurate diagnosis of migraines in all 270 patients.

Sixty two percent of the patients in the zolmitriptan group reported pain relief versus 36% of the placebo group at two hours post-treatment. Headaches response was defined as improvement of intensity of headaches from moderate or severe to none or mild; 47% of the zolmitriptan group reported headache response versus only 24% of the placebo group. Of those patients that did respond, mean time of recurrence was 10.8 hours for the zolmitriptan group versus 4.8 hours for the placebo group; recurrence rate was 22% for the drug group and 30% for the placebo group. 46% of patients in the drug group and 39% of patients in the placebo group reported at least one adverse side effect[21].

Visser, et al. compared different doses of zolmitriptan to placebo and found the drug to be superior in pain relief compared to placebo. In this randomized, double blind, placebo-controlled trial, 84 patients participated and received 1 mg, 5 mg, or 25 mg of zolmitriptan or placebo for the acute treatment of one migraine headache, as diagnosed according to IHS criterion. Patients rated headache intensity on a 4 point scale in which 0=no pain and 3=severe pain; headache response was defined as a reduction of a score of 3 or 2 to a score of 0 or 1 and was used at the primary endpoint for this study.

At two hours post-treatment, headache response was achieved in 15% of the placebo group, 27% of the 1 mg zolmitriptan group, 62% of the 5 mg zolmitriptan group, and 81% of the 25 mg zolmitriptan group. Those patients that were pain free at two

hours post-treatment comprised 5% of the placebo group, 9% of the 1 mg drug group, 14% of the 5 mg group, and 38% of the 25 mg group. Adverse events did tend to rise with increasing dosages of the drug, however no patient withdrew from the study due to adverse side effects[22].

In Gallagher's study comparing 2 mg or 3 mg dihydroergotamine nasal spray with placebo, it was found that the 2 mg dose of DHE nasal spray was superior to the 3 mg dose and placebo for pain relief. 263 patients diagnosed with migraine headaches according to the IHS criterion participated in this randomized, double blind, placebo controlled trial. Patients were randomized to receive either 2 mg or 3 mg DHE nasal spray or placebo for the treatment of one acute migraine headache.

Patients with no pain or mild pain at four hours post-treatment were 60% of the 3 mg DHE group, 70% of the 2 mg DHE group, and 28% of the placebo group. A larger percentage of patients in the 2 mg DHE group also rated their functional ability as normal at four hours post-treatment compared to the 3 mg DHE group or placebo.

While the incidence of adverse effects reported in this study did increase with increasing dosage of medication, the most commonly reported side effects were rhinitis, taste perversion, nausea, application site reaction and dizziness. A total of 14 patients withdrew from the study due to adverse events [23].

Three large-scale studies were performed by Lipton, et al. to investigate the effectiveness of the combination of aspirin, acetaminophen, and caffeine for migraine headache treatment. In this double blind, randomized, placebo-controlled, parallel group, single dose study, a total of 1,247 patients participated and the results from all three trials were pooled together for analysis. Patients were randomized to receive either placebo or

two tablets of Excedrin Migraine, aspirin 250 mg, acetaminophen 250 mg, and caffeine 65 mg for the treatment of one migraine headache.

At two hours post-treatment, 59% of the patients treated with the drug reported mild or no pain, compared with 39% of the placebo group. This study reports that no serious adverse events were reported and a similar number of severe adverse events were reported for each group; most commonly reported adverse events included nausea, nervousness, dizziness, dyspepsia, abdominal pain, and vomiting [24].

Migraine Headache Nonpharmacological, Alternative/Behavioral Therapy Studies

There may be several options for treating a migraine headache with medication; however, some patients are still left with little or no relief. Medications have a higher incidence of side effects; consequently, the patient may experience some relief of the headache pain but the side effects of the medication are intolerable. For these patients or for those who simply prefer to not take medications, alternative behavioral therapies for migraine headache treatment do exist.

Linde, et al. sought to investigate the effectiveness of true acupuncture versus sham acupuncture for the treatment of migraine headaches, and found no difference in the effectiveness between the two types of treatments. This randomized, multi-center, double blind trial used data from patients at 18 different outpatient centers in Germany that were diagnosed with migraine headaches according to the IHS criterion. 132 patients completed this trial and were randomized in a 2:1: ratio to receive either true acupuncture sessions utilizing traditional and basic points, sham acupuncture using nonacupuncture points and superficial needling, or a waiting list group. Acupuncture groups each received 12 sessions over an 8-week period and were assessed at four weeks before

randomization (baseline) and were then followed up for 16 weeks after the treatment period.

The primary endpoint measurement for this study was the difference in the number of days with a migraine headache of moderate to severe intensity at baseline compared to weeks 9-12 after treatment; both the true and sham acupuncture groups had a reduction of 2.2 headache days compared to 0.8 days in the wait list group. Responders were classified as experiencing a reduction of migraine headache days with moderate to severe pain of at least 50%; responders in the true and sham acupuncture groups were 51% and 53%, respectively and 15% in the wait list group.

Adverse events were reported by 25% of the true acupuncture group and only 16% of the sham acupuncture group reported side effects [25].

Vincent preformed another study investigating the effects of acupuncture in a randomized, controlled, single blind study. Patients were randomized to receive either acupuncture using traditional Chinese principles or acupuncture using non-classical needle points and using only light needling. 30 patients completed this trial of 6 weekly sessions and were assessed at four weeks prior to treatment (baseline) and at 6 weeks post-treatment.

Results were calculated weekly using pain scores that patients reported in their headache diaries. The true acupuncture group showed a 43% reduction in weekly pain score from baseline to follow-up, compared to 14% of patients in the sham acupuncture group. Both groups had similar improvements in pain free days from baseline to follow-up [26].

The effects of relaxation training and stress-coping for migraine treatments were compared in randomized, controlled trial conducted by Sorbi and Tellegen. Patients that were taught relaxation training used an audiotape to teach relaxation techniques using suggestions of "heaviness, warmth, calmness, and regular breathing, while successively concentrating on parts of their body from the feet to the head." Patients were instructed to use a cue word to induce these relaxation techniques, to apply these practices to everyday life, and to practice at home at least twice daily.

Those in the stress-coping group were taught how identify current stressors in their lives and their bodily reactions to those stressors. Treatment sessions were then individualized to teach each patient how to effectively deal with these life stressors.

Randomization into one of these two groups occurred and patients recorded data on headache frequency, intensity, and duration during 8 weeks before training (baseline), 8 weeks of training, and for 8 weeks post-training.

Total headache frequency from baseline to post-training was reduced by 40% in the relaxation group and 31% for the stress-coping group. Headache intensity difference for the relaxation group was only 3% compared to 22% for the stress-coping group, and headache duration difference was 18% in the relaxation group and 19% in the stress-coping group [27].

In a study by Kewman and Roberts investigating the effects of raising digital skin temperature versus lowering digital skin temperature for the treatment of migraine headaches, it was found that both groups did show improvement in ratings of impairment with a migraine; however, there did not appear to be any change in frequency or duration of migraine headaches.

Thirty-four patients completed this study and were randomly assigned to a group taught to raise digital skin temperature, lower digital skin temperature, or a control group that received no treatment. Training occurred in 10 weekly sessions each lasting one hour, and patients were trained to respond to a tone or meter in response to a change in their skin temperature. Subjects were unaware of whether the tone indicated an increase or decrease in skin temperature. Patients were instructed to practice these techniques at home and at the onset of migraine symptoms.

The conclusions of this study seemed to suggest that while some improvements were seen in both treatment groups, this effect was not necessarily due to the specific physiological effects of changes in skin temperature, but rather due to the attention of therapists and keeping headache diaries [28].

A study by Daly, et al. investigated the efficacy of progressive relaxation, fingertip temperature training, and electromyograph (EMG) training of the frontalis muscles in the treatment of migraine headaches. This study did show an improvement in symptomatology in all three groups but no significant difference was shown between the groups.

In this double-blinded study, both patients suffering from migraine headaches and those with tension headaches were included; this study was not excluded because results for the migraine groups specifically were provided. 31 patients diagnosed with migraine headaches by a member of the research team were assigned by the team physician into one of three groups. Patients in the EMG group were attached to an electrode and instructed that the goal was a reading of less than five microvolts. Temperature training subjects had a goal of raising the temperature of their fingertips at least 2.5 degrees

within 30 seconds of the onset of the first migraine symptoms and maintain that increase for ten minutes. The last group used an audiotape to teach relaxation sequences. All groups were exposed to the same autogenic phrases, which were intended to aid in relaxation.

Patients received nine half-hour sessions over a five-week period. Patients were required to keep a headache diary for the five weeks of training and for the three month follow-up period and were to rate migraine headache intensity on a 5 point scale where 1=mild headache only noticed if attention is devoted to it and 5=intense and incapacitating headache.

The primary outcomes for this study were gross improvement in symptomatology and complete absence of or control over symptoms from start of training to three months after training. In the EMG, relaxation, and temperature training groups, 70%, 55% and 80%, respectively of each group experienced a gross improvement in symptoms. Complete absence of symptoms occurred in 50% of the EMG group, 36% of the relaxation group, and 50% of the temperature-training group [29].

Gauthier, et al. assessed the relative effectiveness of finger warming and temporal blood volume pulse (BVP) reduction biofeedback in the treatment of migraine headaches in a randomized, controlled trial. Twenty-two females completed this study and were randomized into one of two treatment groups or put in a wait list control group. Patients were to respond to an auditory feedback signal to either increase digital skin temperature or constrict their temporal artery. Instructions on how to accomplish these targets were not provided; patients had to find what thoughts or feelings worked best for them. Patients were encouraged to practice daily at home and when migraine symptoms began.

Training consisted of 12 sessions over a 6-week period. A headache diary was kept to record frequency, intensity and duration of headache as well as number of headache days; diaries filled out for five weeks before treatment and then five weeks after treatment.

Primary outcome was defined as a 50% or greater improvement from pre-treatment to post-treatment for each variable. In the temperature group, 62.5% of patients were successful compared to 57% of the BVP group at reducing the frequency of headaches by at least 50%. Successful reduction in intensity was achieved by 75% of the temperature group and 71% of the BVP group; duration decrease was in 62.5% of the temperature group and 71% of the BVP group. The number of headache days was reduced by at least half in 62.5% of the temperature group and 57% of the BVP group.

Although both groups did show an appreciable improvement in the variables considered, there was not a significant difference between the two groups [30].

A single-blind, controlled study designed by Lacroix, et al. to assess the relative effectiveness of thermal biofeedback, frontalis EMG biofeedback, and relaxation training in the treatment of migraine headaches reported a reduction in headache frequency for all three groups; however, more of an improvement was seen in the thermal biofeedback and relaxation groups than in the EMG group.

Participants in this study consisted of 23 in-patients and 4 staff members in a rehabilitation hospital; the patients were in the hospital because of industrial accidents and were then diagnosed by the staff physician as also suffering from migraine headaches. Patients were assigned into one of three groups based on order of referral into the study; the relaxation group used audiotapes to aid in relaxation and the two biofeedback groups used visual cues to aid in warming hand skin temperature or relaxing

their frontalis muscle. Eighteen training sessions and six test sessions were followed up on at eight weeks and six months post-training.

Patients were not required to keep a headache diary for this study but were instead asked to give a global rating of improvement on a five point scale with 1=no change and 5=symptom free. Patients in the thermal biofeedback group improved most of all initially and the relaxation group had continued improvement through the six-month follow-up while the EMG group remained stable [31].

Bild and Adams sought to compare the effectiveness of cephalic blood volume pulse (BVP) training to frontalis EMG in the treatment of migraine headache in a randomized, controlled. Although both treatment groups did experience a reduction in headache frequency, intensity, duration, and number of headache days per week, this study did not demonstrate any difference between the two groups.

Nineteen participants were randomly assigned to a BVP, EMG, or a wait list group. Training sessions consisted of an auditory tone that patients were to learn to control by either constricting the temporal artery or relaxing the frontalis muscle; patients were exposed to this training for ten one-hour sessions, two to three times per week. Headache characteristics, including frequency, intensity, and duration, were recorded in headache diaries for six weeks before and six weeks after training.

From pre-treatment period to the six-week follow-up period, the BVP groups experienced an average reduction of 1.7 headaches per week, the EMG group a reduction of 0.8, and the wait list group 0.4 headaches. The BVP group reduced headache duration by an average of 21.9 hours per week, the EMG group 14 hours per week, and the wait list group actually reported an increase of 1 hour per week [32].

In a randomized, controlled study by Sargent, et al., the effects of autogenic phrases for relaxation, EMG biofeedback, and thermal biofeedback were compared for the treatment of migraine headaches. One hundred thirty-six patients were randomly assigned to one of four groups and kept daily headache diaries of symptoms, including frequency, location, duration, severity, and disability for 36 weeks. The first group received no training and only kept daily records. The second group was exposed to autogenic phrases, which promoted relaxation. The third group were exposed to the same autogenic phrases and encouraged to relax the frontalis muscle while receiving EMG feedback. The training for the last group was intended to train the patients to increase blood flow to the hands while receiving temperature feedback and listening to the same set of autogenic phrases. Each patient participated in 22 sessions.

This study reported that all four groups showed a decrease in headache frequency and intensity, with the no treatment group showing the least reduction. However, there was no statistically significant difference between the three treatment groups [33].

Discussion

Evidence in the Literature

After analyzing the literature for both types of migraine headache treatment, it has become clear that the strongest evidence supports the use of pharmacological treatments as first-line therapy. Each of the nine studies for the medication treatments reviewed were randomized, controlled trials that were all published within the past eleven years.

Each study was well designed and methodology and results were clearly described. Most studies clearly specified both inclusion and exclusion criteria, and this criteria tended to be very similar in all the drug trials. One very important inclusion

criteria for these studies was that diagnosis of migraine headache was made according to the criterion issued by the International Headache Society; which specifically lists both symptoms, duration of the headache and associated symptoms, and number of headaches per month necessary for accurate diagnosis of migraine headache.

More study participants was another advantage of these studies; this increased number of patients in each trial lends credibility and validity to the results and makes the conclusions of the study more applicable to the general migraine headache population.

These variables were all taken into consideration when assigning ratings of levels of evidence for these trials. All nine of the pharmacological studies included for this review were rated as Evidence Level I; each study was controlled, randomized, and double-blinded, producing consistent and more reliable results.

Analysis of studies of alternative treatments yielded less reliable and consistent results and were rated Evidence Level II. Description of study participants and methodology were often unclear or nonspecific. Lacroix, et al. and Daly, et al did not specify inclusion and exclusion criteria in the studies. In the studies by Sorbi, et al., Kewman, et al. and Bild et al., some criteria used was listed but is still very nonspecific as compared to the criteria set forth by the pharmacological studies.

With the exception of one study, articles of alternative treatments were all published in the 1980's. The criterion set forth by the International Headache Society for diagnosis of migraine headaches was not published until 1988; therefore, only Linde, et al. used these diagnostic criteria for their study. The patient's personal physician or the team physician or neurologist made the diagnosis of migraine based merely on characteristic symptoms of migraine headaches in the remainder of the studies. This lack

of very specific diagnostic criterion in almost all of the alternative studies leads to production of weaker results. Characteristic symptoms of migraine headaches were recognized in these studies but inclusion criteria were much less specific than the criteria of the IHS.

Seven of the nine alternative studies reviewed reported less than 35 study participants. This modest number of participants in each study makes it difficult to generalize the results to the migraine population and assess statistical significance.

When considering treatment options for migraine headache, both the practioner and the patient must take into consideration the side effect profile of any given treatment. It would be expected that the studies involving medications would produce a greater incidence of side effects. Six of the nine drug studies reported at least one study dropout due to adverse events. No adverse events due to the study drug were reported to be serious. As with most medications, the benefits of migraine medications must be weighed against the burden of the possibility of side effects.

Because participants in the alternative treatment studies were consuming no chemical of any sort, very few side effects would be expected. It was, however, difficult to analyze this because only one of the alternative studies reported what side effects their participants experienced. It seems hard to believe that none of the patients in these remaining eight studies experienced any side effects whatsoever. The trials would seem incomplete if side effects were not assessed along with improvement of symptoms; or perhaps the publication of the trials were incomplete when no mention of the presence or absence of side effects is made. In either case, the side effect profile is a very important

factor in choosing treatments and practioners need to have all of the facts to make their decisions.

Review of the methodology and results of trials in each category also showed that these two forms of treatment, pharmacological and alternative could be used to complement each other. Eight of the nine pharmacological studies used their specific treatment to treat only one or two migraine headaches, while studies of the alternative therapies were conducted over several weeks and usually reassessed treatment efficacies several weeks after treatment sessions had concluded. This would lead to a conclusion that the alternative therapies present a better prophylactic form of migraine treatment than an acute form of treatment. It would seem that most efficacy a patient could gain would be to use medication for the acute treatment of the migraine headache and to supplement treatment with daily behavioral therapies to try to prevent the migraines from occurring at all.

Weaknesses/gaps in the literature

After an extensive search of the available literature addressing migraine headache treatment options, it has become clear that there is still much research to be done. Until a specific cause or etiology for migraine headaches is determined, finding a reliable and effective treatment will continue to elude practioners.

Almost all of the studies of alternative treatments are older studies. Better evidence could be obtained from these types of studies with more standardized approaches and specific methodology. It seems reasonable that these types of alternative behavioral therapies can be beneficial but strong, consistent evidence from recent, well-designed trials just does not exist yet.

It is also difficult to adequately compare the effectiveness of pharmacological versus alternative treatments without well-designed trials directly comparing the two treatment approaches. It is not difficult to see that at least both forms of treatment can attain some form of relief but until head-to-head trials are performed with migraine-only participants, a superior treatment option will still continue to be unclear.

Conclusion

After careful review of the literature, the strongest evidence appears to support the use of pharmacological treatment for an acute migraine headache. High quality evidence supports the use of oral zolmitriptan as well as the subcutaneous and nasal spray forms of dihydroergotamine and all three forms of sumatriptan. Evidence Level I studies also supports the use of the combination of acetaminophen, aspirin, and caffeine. This over-the-counter treatment would seem to be a good choice for first-line treatment due to effectiveness, ease of attaining product, and decreased cost. A Grade A recommendation (Table 2) for all four of these medicinal treatments is made based on consistent Evidence Level I studies (Table 3).

Table 2-Strength of Recommendation

Strength of Recommendation	Definition	Implication for Practice
A	Recommendation based on consistent and good quality patient-oriented evidence.	You should do this unless there is a compelling reason not to.
B	Recommendation based on inconsistent or limited quality patient-oriented evidence.	You should strongly consider doing this.
C	Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, and case series for studies of diagnosis, treatment, prevention, or screening.	The evidence that this improve patient outcomes is weaker for this recommendation.

Studies of alternative treatments yielded weaker, more inconsistent results. According to the evidence presented, these forms of treatment should be considered only after pharmacological treatment attempts have failed or proven inadequate for pain relief.

A Grade B recommendation is made for relaxation training and biofeedback training such as fingertip warming, reducing cephalic blood volume pulse, and decreasing frontalis muscle EMG. These therapies did show some degree of improvement of symptomatology and seem to offer considerably fewer side effects than medications. Inconsistent evidence for use of acupuncture led to a Grade C recommendation.

Table 3 Clinical Recommendations

Key Clinical Recommendation	**Strength of Recommendation**	**Reference(s)**	*Comment*
OTC combination of acetaminophen, aspirin, and caffeine best 1st-line choice.	A	24	Level I evidence based on large, well-designed, randomized, controlled trial.
Oral, SQ, nasal spray forms of sumatriptan, SQ and nasal spray forms of DHE, and oral form of zolmitriptan all effective.	A	16-23	Consistent level I evidence in well designed randomized, controlled trials.
Relaxation training and/or biofeedback training may be attempted when pharmacological treatment fails.	B	27-33	Treatment does not appear to offer any harm to patients, but currently available evidence is weaker.
Acupuncture may be effective.	C	25, 26	Conflicting evidence found.

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Appendix A

INTERNATIONAL HEADACHE SOCIETY DIAGNOSIS CRITERIA FOR MIGRAINE HEADACHE

Without aura:

At least 5 attacks that meet the following criteria:

A. Headache attack lasts 4-72 hours (untreated or unsuccessfully treated)
B. Headache has at least 2 of the following:
    1. Unilateral location
    2. Pulsating quality
    3. Moderate to severe intensity (interferes with daily activity)
    4. Aggravation by routine physical activity such as walking down stairs
C. During headache, at least one of the following symptoms:
    1. Nausea and/or vomiting
    2. Photophobia and phonophobia

At least one of the following:

1. Examination and/or assessment including history, physical, and neurologic do not suggest another disorder.
2. Examination and/or assessment including history, physical, and neurologic suggest another disorder that is subsequently ruled out by further investigation.
3. Secondary disorder that may represent an alternative cause is present; but there is no temporal relationship between the first onset of headache and the onset of the disorder.

With Aura:

At least 2 attacks that meet three of the four criteria:

1. One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem dysfunction.
2. At least one aura symptoms develops gradually over more than 4 minutes, or two or more symptoms occur in succession.
3. No aura symptom lasts more than 60 minutes; if more than one aura symptom is present, accepted duration is proportionally increased.
4. Headache follows aura with a free interval of less than 60 minutes (it may also begin before or simultaneously with the aura).

At least one of the following 3 characteristics is present:

1. History and physical and neurological examinations do not suggest another disorder
2. History and physical and neurological examinations do suggest another disorder, but it is ruled out by appropriate investigations.
3. Another disorder is present but migraine attacks do not occur for the first time in close temporal relation to the disorder.

Appendix B
Pharmacological Studies

Level of evidence	Study	Issue	Participants	Interventions	Outcomes	Results	Adverse events, Dropouts
1 Double-blind, random-ized, parallel-group IHS criteria utilized.	Oral suma-triptan is effective and well tolerated for the acute treatment of migraine. J. Sargent, J.R. Kirchner, R. Davis, B. Kirkhart *Neurology* 1995	Evaluate the efficacy and tolerability of 25 mg, 50 mg, 100 mg oral sumatriptan vs. placebo and to identify optimal dose for the treatment of migraine	n=187 Referred by family practitioners or by HA specialists at 1 of 15 participating sites 4-pt. scale used to rate severity of HA: 0=no pain, 1=mild pain, 2=moderate pain 3=severe pain	Pts. randomized to receive either 25 mg, 50 mg, or 100 mg oral sumatriptan or placebo for treatment of one severe migraine	Primary: percentage of pts. who received HA relief at 4 hours HA relief defined as change in score from 3 or 2 at baseline to 0 or 1 post-dose Secondary: pt. defined meaningful relief	Oral sumatriptan was effective in treating an acute migraine vs. placebo HA relief @ 4 hrs. post-dose: 25 mg: 65% 50 mg: 70% 100 mg: 78% placebo: 19% Pt. defined meaningful relief: 25 mg: 69% 50 mg: 73% 100 mg: 83% placebo: 26%	No significant difference b/w drug groups and placebo No dropouts reported.

Level of evidence	Study	Issue	Participants	Interventions	Outcomes Measured	Results	Adverse events, Dropouts
1 Randomized, double-blind, placebo-controlled, crossover study IHS criteria utilized.	Oral sumatriptan for the long-term treatment of migraine: Clinical findings. G Rederich, A Rapoport, N. Cutler, R. Hazelrigg, B. Jamerson Neurology 1995	Study the efficacy and tolerability of sumatriptan 100 mg administered for up to nine attacks over the course of 1 year compared to placebo administered for three attacks.	101 participants Pts. referred by fam. pract. drs. or HA specialists from participating sites. HA severity 0=no pain, 3=severe pain Clinical disability: 0=able to work/fxn. 3=requires bed rest	Migraine attacks divided into 3 blocks of 4 attacks each. Pts. randomized to receive placebo for one HA and sumatriptan 100 mg for other three attacks in each block (PSSS, SPSS, SSPS, SSSP) Study measured over 1 yr.	Primary: Relief rates (score of 2 or 3 to 0 or 1) @ 2 and 4 hrs. post-dose (avg. of all attacks) Clinical disability (no disability) @ 2 and 4 hrs. post dose (avg. of all attacks)	Sumatriptan consistently more effective than placebo. HA relief @ 2 hours: drug: 49% placebo: 18% HA relief @ 4 hours post dose: drug: 61% placebo: 18% No disability @ 2 hrs. post dose: drug: 32-39% placebo: 11-14% No disability at 2 hrs. post dose: drug: 44-48% placebo: 13-18%	56% of administrations of sumatriptan 50% of administrations of placebo Most common: N/V, discomfort of sinuses, HA, dizziness, neck pain 10 pts. withdrew from study: 7 due to adverse events, 3 due to pregnancy.

Level of evidence	Study	Issue	Participants	Interventions	Outcomes Measured	Results	Adverse events, Dropouts
1 Random-ized, double-blind, parallel group, single attack study. IHS criteria utilized.	Sumatriptan nasal spray for the acute treatment of migraine: results of two clinical studies. R Ryan, A Elkind, CC Baker, W Mullican, S DeBussey, M Asgharnejad *Neurology* 1997	Evaluate the efficacy and tolerability of sumatriptan nasal sprays 20 mg or 10 mg compared to placebo in the acute treatment of migraine.	845 participants. No reference made to how pts. referred to study Pain scale: 0=no pain, 3=severe pain Clinical disability: 0= work/fxn. Normally 3=requires bed rest	Pts. randomized to treatment (2:1:1) for 20 mg, 10 mg, placebo Pts. to use study medication to treat a single moderate or severe (2 or 3) migraine attack at home.	Primary: HA relief at 2 hrs. post dose HA relief defined as: reduction in pain severity from 3 or 2 to a 0 or 1 Others: % pts. pain free @ 2 hrs. Pt. defined meaningful relief @ 2 hrs. Clinical disability at 2 hrs. post dose	Sumatriptan nasal spray effective over placebo. HA relief 2 hrs. post dose: 20 mg: 63% 10 mg: 43% placebo: 29% Pt. defined meaningful relief 2 hrs. post dose: 20 mg: 59% 10 mg: 45% placebo: 26% Clinical disability: 20 mg: 73% 10 mg: 62% placebo: 53%	Most common: taste disturbance: 20 mg: 31% 10 mg: 22% placebo: 1% Frequency of all other adverse events reported similar in drug groups and placebo. One dropout reported: no mention of cause of dropout.

Level of evidence	Study	Issue	Participants	Interventions	Outcomes	Results	Adverse events, Dropouts
1 Multi-center, random-ized, double-blind, double-dummy, Crossover study. All pts. diagnosed according to IHS criteria.	A comparison of subcutaneous sumatriptan and dihydro-ergotamine nasal spray in the acute treatment of migraine. J Touchon, L Bertin, AJ Pilgrim, E Ashford, A Bes *Neurology* 1996	Compare the efficacy and tolerability of subcutaneous sumatriptan and DHE nasal spray	266 pts. How pts. referred for this study not stated. Rate HA severity: 3=severe pain, 0=no HA pain Clinical disability: 0=fxn. normally 3=bed rest required Pt. defined meaningful relief.	Pts. to treat 2 migraine HA's that rate a 2 or 3 at baseline. Randomized to receive either SQ sumatriptan 6 mg (plus placebo DHE nasal spray) OR DHE nasal spray 1 mg (plus placebo SQ sumatriptan). Pts. to treat first migraine with one form of treatment, then cross-over and treat second migraine with other treatment.	Primary: % of pts. with HA relief 2 hrs. post dose Secondary: improvement of clinical disability 1 hr. post dose (rating of 0) Meaningful relief as defined by pt.	Sumatriptan more effective but with more side effects. HA relief: sumatriptan: 80% DHE: 50% Clinical disability: sumatriptan: 38% DHE:16% Meaningful relief: sumatriptan: 76% DHE: 46%	% of pts. reporting at least one adverse event: sumatriptan: 43% DHE: 22% Events considered mild. 4 pts. dropped out of study due to adverse events.

Level of evidence	Study	Issue	Participants	Interventions	Outcomes	Results	Adverse events, Dropouts
1 Random-ized, double-blind trial with parallel arms. Pts. diagnosed according to IHS criteria.	A double-blind study of subcutaneous dihydroergot-amine vs. subcutaneous sumatriptan in the treatment of acute migraine. Paul Winner, Bruce Le Force, Joel Saper, Betty Margul *Archives of* *Neurology* 1996	Assess the efficacy and tolerability of subcutaneous sumatriptan vs. subcutaneous dihydroergot-amine for the acute treatment of migraine headache.	295 pts. No reference to recruitment of participants. HA pain: 0=no pain, 3=severe pain Recurrence: increase in HA pain at least 2 hrs. after discharge from clinic of those that received initial relief.	Pts. with HA score of 2 or 3 randomized to receive either 1 mg SQ DHE or 6 mg SQ sumatriptan.	Relief of HA pain and recurrence of migraine HA.	SQ sumatriptan worked faster than SQ DHE but efficacy equal by 3 hrs. post dose. Less recurrence with DHE. Relief rates: 1 hr.: Sum.: 78% DHE: 57% 4 hrs: Sum: 83% DHE: 86% Recurrence: Sum: 45% DHE: 18%	2 pts. in DHE dropped out: chest/neck tightness, severe N/V Injection site discomfort: Sum: 18% DHE: 38% Nausea: Sum: 6% DHE: 16% Vomiting: Sum: 4% DHE: 7% Chest pain: Sum: 6% DHE: 1%

Level of evidence	Study	Issue	Participants	Interventions	Outcomes	Results	Adverse events, Dropouts
1 Random-ized, double-blind, placebo-controlled study. All pts. diagnosed according to IHS criteria.	Clinical efficacy and tolerability of 2.5 mg zolmitriptan for the acute treatment of migraine. G.D. Solomon, R.K. Cady, J.A. Klapper, N.L. Earl J.R. Saper, N.M. Ramadan *Neurology* 1997	Evaluate the efficacy of a single 2.5 mg dose of zolmitriptan in treatment of migraine HA.	270 pts. Pts. recruited from 22 neurology or primary care clinics. HA pain: 0=no pain -- 3=severe pain Complete HA response: score of 0 or 1 @ 2 hrs. post dose and no recurrence in 24 hr. F/U. HA recurrence: initial response, then recurrence of pain in 24 hr. F/U.	Pts. randomized to treat one migraine HA rated a 2 or 3 with either 2.5 mg zolmitriptan or placebo.	Primary: HA response @ 2 hrs. post dose (score of 3 or 2 initially, reduced to score of 0 or 1 post dose.) Complete HA response HA recurrence	Zolmitriptan more effective than placebo at relieving HA pain and preventing recurrence of migraine HA. HA response @ 2 hrs.: Zolm: 62% placebo: 36% Complete HA response: Zolm: 47% placebo: 24% Recurrence: Zolm: 22% placebo: 30%	Reported at least 1 adverse effect: Zolm: 46% placebo: 39% Occurring in at least 5% of pts. in either group: **Nausea**: drug: 11% placebo: 6% **Dizziness**: drug: 9% placebo:3% **Parasthesias**: drug: 6% placebo: 4% **Chest tightness:** drug: 5% placebo: 1% **Somnolence**: drug: 5% placebo: 2% **Vomiting**: drug: 2% placebo: 5%

Level of evidence	Study	Issue	Participants	Interventions	Outcomes	Results	Adverse events, Dropouts
1 Random-ized, double-blind, placebo controlled, parallel group trial. All pts. diagnosed according to IHS criteria	311C90, A new central and peripherally acting 5-HT_{1D} receptor agonist in the acute oral treatment of migraine. W.H. Visser, K.B. Klein, R.C. Cox, D. Jones, M.D. Ferrari *Neurology* 1996	Determine the efficacy and safety of various doses of oral 311C90 in the acute treatment of migraine.	84 patients Recruitment: pts. from neurology clinic of Leiden Univ. Hospital and by referral from other neurologists and general practitioners. HA severity: 0=no pain – 3=severe pain	Pts. randomized to receive 1mg, 5mg, or 25mg of 311C90 or placebo for treatment of one migraine HA rating a 2 or 3.	Primary: HA response at 2 hrs. post dose (score of 2 or 3 at baseline reduced to 0 or 1 post dose). HA recurrence: initial HA response at 2 hrs. post treatment, then recurrence of pain in the 24 hr. F/U Pain free at 2 hours post dose.	Relief rates increase with increasing dose of drug; all doses more effective than placebo. HA response: placebo: 15% 1 mg: 27% 5 mg: 62% 25 mg: 81% HA recurrence: placebo: 33% 1 mg: 33% 5 mg: 36% 25 mg: 7% Pain free: placebo: 5% 1 mg: 9% 5mg: 14% 25mg: 38%	No dropouts due to adverse events. Placebo group: 2 adverse events reported: dyspepsia & abd. pain. Drug grp. most commonly reported: asthenia, somnolence, dry mouth, and pressure. Incidence of adverse events rose with increased dosages.

Level of evidence	Study	Issue	Participants	Interventions	Outcomes	Results	Adverse events, Dropouts
1 Random-ized, double-blind, placebo-controlled, parallel-group trial. All pts. diagnosed according to IHS criteria.	Acute treatment of migraine with dihydroergot-amine nasal spray. R. Michael Gallagher for the Dihydroergot-amin Working Group Archives of Neurology 1996	Assess the efficacy and safety of an intranasal spray formulation of dihydro-ergotamine mesylate in the treatment of migraines.	263 pts. Pts. recruited from 25 participating treatment centers. HA pain: 0=no pain – 3=severe pain Functional ability: 0=normal 1=mildly impaired 2=severely impaired 3=bed rest required	Pts. randomized to receive either 2 mg or 3 mg DHE nasal spray or placebo for the treatment of two migraine headaches.	Pts. to evaluate HA pain, relief of pain, and functional ability at 4 hrs. post treatment. HA relief: reduction of a score of 2 or 3 to score of 0 or 1 at 4 hrs. post treatment	2 mg dose of DHE nasal spray more effective than 3 mg dose or placebo. HA relief: 3 mg: 60% 2 mg: 70% placebo: 28% Normal functioning ability at 4 hrs. post treatment: 3 mg: 45% 2 mg: 56% placebo: 17%	14 dropouts due to adverse events. Most side effects reported in 2 mg group including: rhinitis, taste perversion, nausea, application site rxn., and dizziness.

Level of evidence	Study	Issue	Participants	Interventions	Outcomes	Results	Adverse events, Dropouts
1 Three independent double-blind, randomized parallel group, placebo controlled, single dose studies. All pts. diagnosed according to IHS criteria.	Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain. Richard B. Lipton, Walter F. Stewart, Robert E. Ryan, Joel Saper, Stephen Silberstein, Fred Sheftell *Archives of* Neurology 1998	Assess the effectiveness of non-prescription combination of acetamino-phen, aspirin, and caffeine to treat migraine HA.	1,247pts. from three identical studies combined. Recruitment: random digit dialing, private practice pts. and referrals, and local advertising. HA pain: 0=no pain – 3=severe pain (pts. requiring bed rest for migraine excluded)	Pts. randomized to receive either Excedrin Extra Strength (250 mg acetaminophen, 250 mg ASA, 65 mg caffeine) or placebo to treat one migraine HA.	Pain intensity difference from baseline and percentage of pts. with pain reduced to mild or none (score of 0 or 1) at two hours post treatment.	Excedrin more effective than placebo. Data pooled from all 3 studies. No or mild pain at 2 hrs.: drug: 60% placebo: 33% No pain 2 hrs. post dose: drug: 21% placebo: 7%	One dropout due to vomiting and chills. Nausea: drug: 5% placebo: 2% Nervousness: drug: 4% placebo: 1% Dizziness: drug: 3% placebo: 1%

Level of Evidence, Methods	Study	Issue	Participants	Interventions	Outcomes	Results	Adverse Events, Dropouts
1 Randomized, multi-center, double-blind controlled trial from patients at 18 different outpatient centers in Germany. All pts. diagnosed according to IHS criteria.	Acupuncture for patients with migraine: a randomized controlled trial. Klaus Linde, Andrea Streng, Susanne Jurgens, et al. *JAMA* 2005	Investigate the efficacy of acupuncture compared with sham acupuncture and no acupuncture in the treatment of migraine.	132 patients Recruitment by local newspapers or pts. contacting the trial centers. All pts. required to keep HA diaries for 4 wks. before randomization (baseline), during the 12 wks. after randomization, and during weeks 21-24 after randomization.	Pts. randomized in 2:1:1 ratio of acupuncture, sham or wait-list control. Real and sham groups received 12 sessions of same duration over 8 wks. Acupuncture trtmt. was semistandarized. All pts. allowed to treat acute HA prn.	Primary: difference in # of days with a migraine of mod. to severe at baseline compared to 9-12 wks. after treatment. Responders: reduction of HA days w/ mod. to severe pain by at least 50%.	No difference b/w real and sham acupuncture groups, but both more effective than wait-list. Primary endpoint: Real: 2.2 days Sham: 2.2 days Control: 0.8 days Proportion of Responders: Real: 51% Sham: 53% Control: 15%	Reported adverse events: Real: 25% Sham: 16% Treatment triggered migraine: Real: 10 pts. Sham: 2 pts. Fatigue: Real: 6 pts. Sham: 1 pt. Hematoma: Real: 4 pts. Sham: 2 pts.

Level of Evidence, Methods	Study	Issue	Participants	Interventions	Outcomes	Results	Adverse Events, Dropouts
2 Randomized, single-blind, controlled trial. Pts. diagnosed by neurologist.	A Controlled trial of the treatment of migraine by acupuncture. C.A. Vincent The Clinical Journal of Pain 1989	To assess if acupuncture is and effective treatment for alleviating migraine headache pain.	30 pts. Recruitment: referral from neurologist or recruited from British Migraine Assoc. Pts. completed HA diary for 4 wk. baseline period, during treatment, and for 6 wk. follow-up period. HA intensity rated 4 times daily on a 6-pt. scale.	Pts. randomized to receive either acupuncture or sham (light needling @ nontraditional locations). Pts. all received 6 weekly treatments. HA diaries kept the 4 wks. before, 6 wks. of, and 6 wks. after treatment. No restriction on medication intake for acute HA.	Reduction in weekly pain score from baseline to follow-up. Mean pain free days from baseline to follow-up.	Acupuncture affected intensity of HA pain. Reduction of weekly pain scores: True: 43% Sham: 14% Mean pain free days: True: baseline: 3.0 d F/U: 4.3 d Sham: baseline: 3.3 d F/U: 4.2 d	Adverse events not reported. 2 drop outs recorded.

Level of Evidence, Methods	Study	Issue	Participants	Interventions	Outcomes	Results	Adverse Events, Dropouts
2 Randomized trial Pts. diagnosed according to a questionnaire developed at the St. Lucas Hospital in Amsterdam.	Differential effects of training in relaxation and stress-coping in patients with migraine. Marjolijn Sorbi, Bert Tellegen *Headache* 1986	To compare the effects of relaxation training and stress-coping training for the treatment of migraine.	29 pts. Referred by general practitioner or self-referred. HA diaries kept during 8 wks. before treatment (baseline), 8 wks of training, 8 wks post training. F/U performed after 8 months. HA intensity: 1=only aware of pain of attn. devoted to it 5=incapacitating HA	Pts. randomized to receive either relaxation or stress-coping training. Relaxation: 9 weekly sessions, 1 hr. each. Audiotape used to teach relaxation techniques; pt. to practice at home. Stress-coping: Unclear how many sessions. Sessions tailored to pts. personality to teach to cope with daily stressors.	Avg. HA frequency, intensity, and duration difference b/w baseline and post treatment.	HA frequency difference: RT: 40% 27% at F/U SCT: 31% 36% at F/U HA intensity difference: RT: 3% 16% at F/U SCT: 22% 32% at F/U HA duration difference: RT: 18% 16% at F/U SCT: 19% 38% at F/U	Adverse events not reported. 3 drop outs at beginning of training. 9 pts. in study lost to follow-up.

Level of Evidence, Methods	Study	Issue	Participants	Interventions	Outcomes	Results	Adverse Events, Dropouts
2 Randomized, double-blind study. Pts. diagnosed with migraines by their personal physician.	Skin temperature biofeedback and migraine headaches. Donald Kewman, Alan H. Roberts Biofeedback and Self-Regulation 1980	Investigate the effects of raising digital skin temperature vs. lowering skin temperature in the treatment of migraine headaches.	34 pts. All female. Recruitment by physician referrals and newspaper press releases. Pts. required to fill out diary forms for each migraine: symptoms checklist, time of HA, amt. of impairment. Pts. returned diaries weekly. Pts. in control grp.(kept records only) specifically assigned to that group (11 pts).	Pts. randomized to 1 of 2 groups: 11 pts. taught to raise finger temp. and 12 pts. taught to lower finger temp. 10 weekly sessions. Pts. unaware which they were being taught. Diaries kept for 6 wk. baseline, 9 wks treatment, and 6 wk F/U. Pts. trained to respond to tone or meter in response to change in body temp.	Improvement in ratings of impairment, number of symptoms experienced, frequency or minutes of HA.	All groups showed some improvement. No difference b/w groups. "No significant change in frequency or minutes of migraine episodes per week."	Adverse events not reported. No dropouts reported.

Level of Evidence, Methods	Study	Issue	Participants	Interventions	Outcomes	Results	Adverse Events, Dropouts
2 Double-blind study. Pts. diagnosed with migraine HA by medical member of research team through interviews and HA chart of pts.	Biofeedback applications to migraine and tension headaches: a double blinded outcome study. Edward J. Daly, Patsy A. Donn, Marjorie J. Galliher, Jay S. Zimmerman Biofeedback and Self Regulation 1983	Investigate the efficacy of progressive relaxation, fingertip temperature training, and EMG training of the frontalis muscles in the treatment of migraine headaches.	31 migraine pts. completed trial. Recruitment: Advertise-ments and local referrals. Pts. kept chart of HA intensity: 1=mild HA only noticed it attn. to it 5=intense, incapacitating HA Charted 4 x's daily for 5 wks. of training and 3 month F/U.	Pts. assigned by physician to 1 of 3 groups: **1)** Pts. attached to EMG electrodes and instructed that goal was reading <5 mV. (10 pts.) **2)** Temp. subj. had goal of temp. rise of at least 2.5^0 w/i 30 sec. of onset of 1^{st} symptoms and maintain for 10 min. (10 pts.) **3)** Relaxation grp. used audiotape to teach relaxation sequences. (11 pts.) All grps. exposed to same autogenic phrases, intended to aid in relaxation. Pts. received 9 half-hour sessions over 5 wk period.	Gross improvement in symptom-atology from start to 3 mon. post training. Complete absence of or control over symptoms 3 months after treatment.	Essentially an inconclusive study. Gross improvement: EMG: 70% Relax: 55% TT: 80% Symptoms: EMG: 50% Relax: 36% TT: 50%	Adverse events not reported. 6 drop-outs (schedule conflicts)

Level of Evidence, Methods	Study	Issue	Participants	Interventions	Outcomes	Results	Adverse Events, Dropouts
2 Randomized, controlled trial. Diagnosis of migraine headaches made by team neurologist.	Biofeedback Control of Migraine Headaches: A Comparison of Two Approaches. Janel Gauthier, Renee Lacroix, Alain Cote, Julien Doyon, Michel Drolet Biofeedback and Self Regulation 1985	Assess the relative effectiveness of finger warming and temporal blood volume pulse reduction biofeedback in the treatment of migraine headaches.	22 pts. Completed study. Recruitment: Females only. Local advertisements. Pts. required to fill out HA diary for 5 weeks pre-treatment and 5 weeks post-treatment. Pts. to rate HA frequency (total # of HA's), intensity of HA (rated on 1-5 scale), and duration of HA.	Pts. randomly assigned into finger warming group, temporal blood volume pulse group or wait-list control group. Pts. participated in 12 sessions over 6 wks. Photoplethysmographic transducers used for measurement of temporal and digital blood volume pulse. Pts to respond to feedback (auditory signal) to achieve target. Pts. not given instructions on how to accomplish this—they were to find what worked best for them (involving thoughts or feelings). Pts. to practice technique daily and when sx. of migraine.	Frequency Intensity Duration of HA Number of HA days Success defined as 50% or greater improvement from pre- to post-treatment.	No significant diff. b/w two treatment groups. Frequency: Temp: 62.5% BVP: 57.1% Intensity: Temp: 75% BVP: 71.4% Duration: Temp: 62.5% BVP: 71.4% Days: Temp: 62.5% BVP: 57.1%	No adverse events reported. No dropouts reported.

Level of Evidence, Methods	Study	Issue	Participants	Interventions	Outcomes	Results	Adverse Events, Dropouts
2 Randomized, controlled trial. Pts. diagnosed with migraine headaches by staff physician.	Biofeedback and Relaxation in the Treatment of Migraine Headaches: Comparative effectiveness and Physiological Correlates Michael Lacroix, Melissa Clarke, J. Carson Bock, Neville Doxey, Anne Wood, Sandra Lavis Journal of Neurology, Neurosurgery, and Psychiatry 1983	Study the relative effectiveness of thermal biofeedback, frontalis EMG biofeedback, and relaxation training in the treatment of migraine headaches.	27 pts. completed study Recruitment: 23 in-pts. and 4 staff members at workers' comp. And rehab. Hospital. Pts. in hospital for another reason and were also diagnosed w/ migraines. Pts. rated selves on scale of improvement: 1=no change, 3=moderately improved, 5= symptom free	Groups trained to increase skin temp., decrease frontalis muscle EMG, or progressive relaxation. Assigned to grps. Based on order of referral to study. 18 training sessions and 6 test sessions. Pts. f/u at 8 wks. Post-treatment and 6 months post-treatment.	Primary: Therapeutic success based on 5-pt. scale Reduction of HA frequency.	HA frequency decreased in all groups. Greater decrease seen in thermal biofeedback and relaxation groups. Global rating of improvement: Thermal biofeedback improved most of all initially, relaxation group improvement continued throughout 6 mo. f/u period, EMG group essentially remained stable.	No adverse events reported. 3 dropouts reported.

Level of Evidence, Methods	Study	Issue	Participants	Interventions	Outcomes	Results	Adverse Events, Dropouts
2 Randomized, controlled trial. Pts. diagnosed with migraine using the Ad Hoc Committee on Classification of Headache (1962).	Results of a Controlled, Experimental, Outcome Study of Nondrug Treatments for the Control of Migraine Headaches. Joseph Sargent, Patricia Solbach, Lolafaye Coyne, Herbert Spohn, John Segerson Journal of Behavioral Medicine 1986	Determine whether increasing blood flow in the hands at will is specifically effective in the treatment of migraine headache.	136 pts. completed study. Recruitment: Referral by physician or self-referred. Pts. to keep daily records of HA frequency, location, duration, severity, disability, and associated symptoms. Not required to be drug-free during trial but not to change meds.	36-week trial. 22 sessions. Pts. randomly assigned into 1 of 4 groups: **1)** No treatment **2)** Autogenic Phrases: to encourage relaxation & blood flow into hands. **3)** EMG Biofeedback: used autogenic phrases & received EMG feedback from the frontalis area. **4)** Thermal Biofeedback: used autogenic phrases and received temp. feedback from rt. hand.	Only frequency and intensity scores valid for analysis.	All 4 groups showed decrease in HA frequency and intensity; No treatment group showed least reduction. No significant difference b/w 3 treatment groups.	No adverse events reported. 45 dropouts due to loss of interest, other priorities, or moved from area.

Level of Evidence, Methods	Study	Issue	Participants	Interventions	Outcomes	Results	Adverse Events, Dropouts
2 Randomized, controlled trial. Pts. diagnosed with migraine according to the Ad Hoc Committee on Classification of Headaches (1962).	Modification of Migraine Headaches by Cephalic Blood Volume Pulse and EMG Biofeedback. Raquel Bild, Henry Adams Journal of Consulting and Clinical Psychology 1980	Evaluate the effectiveness of cephalic blood volume pulse training in treatment of migraine headache, using frontalis EMG as a control.	19 pts. completed study. Recruitment: Local advertising and physician referral. Pts. required to complete HA diary daily rating: frequency, intensity, duration, and degree of disability.	Pts. randomly assigned to: BVP group, EMG group, or wait list (no treatment) group. HA activity measured 6 wks. before and 6 wks. after treatment. 10 one hour sessions. Pts. instructed to concentrate to constrict temporal artery or relax frontalis muscle to turn off the tone given.	Reduction in frequency and duration of migraines per week.	All 3 groups showed decrease in frequency and duration of headache from pre-treatment to post-treatment, with wait list group showing least improvement. However, differences did not reach significance.	No adverse events reported. 2 dropouts reported.

Appendix D
Excluded Studies

STUDY	REASON FOR EXCLUSION
Relaxation for the Treatment of Headache Behavior Modification. July 1984. Vol. 8 No. 3: 407-424	Patients with classic or common migraine, muscle-contraction headache, or mixed headache included.
A Controlled Evaluation of Thermal Biofeedback and Thermal Biofeedback Combined with Cognitive Therapy in the Treatment of Vascular Headache. Journal of Consulting and Clinical Psychology. 1990. Vol. 58 No. 2: 216-224	Patients included had vascular headaches—migraine or combined migraine and tension headaches.
Efficacy of 1,000 mg Effervescent Acetylsalicylic Acid and Sumatriptan in Treating Associated Migraine Symptoms European Neurology. 2004. Vol. 5, No. 2: 50-56	This review focused on the acute treatment of migraine headaches and not on the associated symptoms.
The Efficacy and Cost-effectiveness of Minimal-therapist-contact, Non-drug Treatments of Chronic Migraine and Tension Headache. Headache. 1985. Vol.25: 214-220	Participants were tension headache patients and vascular (both migraine and combined migraine and tension) headache patients.
Recurrent Vascular Headache: Home-Based Behavioral Treatment Versus Abortive Pharmacological Treatment. Journal of Consulting and Clinical Psychology. 1988. Vol. 56, No. 2: 218-223	Treatment was for both recurring migraine headaches and mixed migraine and tension headaches.
Multimodal Migraine Treatment: Does Thermal Feedback Add to the Outcome? Headache. 1984. Vol. 24: 249-255	Patients included suffered from migraine headaches or combined migraine-tension headaches.
Treatment of Headache by Transcutaneous Electrical Stimulation. Headache. 1985. Vol. 25: 12-15	Patients with migraine or muscle contraction headaches or both studied.
Acupuncture versus Medical Treatment for Migraine and Muscle Tension Headaches. Journal of Neurology, Neurosurgery, and Psychiatry. 1984. Vol. 47: 333-337	Study treatment intended for prophylactic treatment for headaches. Patients with migraine or muscle tension headaches included.

Vita

Name: Kristi Haverkamp

Date of Birth: 10-16-81

Place of Birth: Belleville, Kansas

Education:

2004-2006	Master – Physician Assistant (M.P.A.) Wichita State University, Wichita, Kansas
2000-2004	Bachelor of Science-Biology Kansas State University, Manhattan, Kansas

Professional Experience:

2002-2004	Reception Supervisor, Phlebotomist ZLB Plasma Services Manhattan, Kansas
2001	Nurse's Aide Anthony Hospital Anthony, Kansas