

Complimentary and Alternative Treatment of Migraines:  
A Look at the Evidence

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Migraine headache is one of the most common ailments presented to primary care physicians. It occurs in 17.6% of females and 5.6% of males in their lifetimes making it three times more common in women than men. It also appears to be genetically linked with 80% prevalence of first-degree relatives with symptoms<sup>3</sup>. The different types of migraines include: classic (with aura), and common (without aura) but they both have subtypes such as: Transformed migraine, Basalar migraine, and Ophthalmoplegic migraine, just to name a few.

Given the sheer number of patients that experience migraine pain and the extreme disability they produce, the need for effective treatment is greater than ever. Allopathic medications such as the triptans, ergotomines, beta blockers, and NSAIDs have proven effective in many cases; however, the lack of wide efficacy leaves large gaps in treatment. Therefore, the exploration of CAM treatments of migraines is indicated to not only learn broader approaches and theories of etiology but to relieve much unneeded suffering of literally thousands of people.

Pathophysiology

The exact pathophysiology of the migraine headache is a subject of much research and little knowledge. In the past there have been several theories that have shown good evidence for truth at the time, but later found to be only partially correct. The most popular of these is the vascular theory. This deals with the idea that classic migraine (with aura) starts with a constriction of cerebral blood vessels (including those in the occipital cortex) causing the aura that then progresses to rebound dilation in the meninges which causes pain

This concept still holds much popularity (and truth) but only now is research uncovering more about the vascular theory than was once thought. The current understanding is more complicated involving a neuronal depolarization wave cascading throughout the brain beginning in the brainstem. This centrally mediated wave produces

vascular changes through release of vasoactive compounds such as substance P, calcitonin, and others. The wave is thought to be mediated by diffuse projection fibers of the locus ceruleus which causes excitement of a trigeminalvascular reflex to aid in its propagation<sup>1</sup>. This has been confirmed by Positron Emission Tomography studies in which blood flow to several areas of the brain was increased during acute attacks<sup>1</sup>.

Serotonin also plays a somewhat obscure role in the mechanism of migraine. Although, serotonin levels seem to decrease during acute migraine attacks, the exact mechanism is still unknown. Given the existence of many projections from the brainstem serotonergic nuclei, as well as the abortive and prophylactic effects of several serotonergic medications, the role of this neurotransmitter is undeniable but still needs more research<sup>2</sup>.

### Naturopathy

There are several medicinal herbs that have purported positive effects on migraine. Some of the most widely used include Feverfew, butterbur, belladonna, 5-HTP, and Ginger, just to name a few. The use of many of these natural substances is currently being researched and, no doubt, a need exists for more. However, in the small cohort of users and documented studies, effects have varied between very efficacious to not significantly different from placebo. The evidence for the most commonly prescribed and best documented is discussed below.

#### *Feverfew(Tanacetum parthenium)*

Feverfew is an herb that is dried or freeze-dried and usually encapsulated then taken in a strength of 50-400 mg with a standardized concentration of parthenolide (the purported active ingredient) of 0.2-0.75%. The active ingredient has been isolated but studies of effect from administration of pure parthenolide extract have not shown the positive results that the whole herb has suggesting other active ingredients are at work<sup>4,5</sup>. Its effects have been well researched with varied results but with strong suggestion of prophylactic prevention and not abortive effects on migraines.

The mechanism of Feverfew is still largely unknown but speculated to involve platelet aggregation inhibition and serotonin release blockade in both platelets and neutrophils. Feverfew also has some effect on prostaglandin synthesis and might therefore reduce vascular inflammation in the brain<sup>9</sup>. Its use in rheumatoid arthritis is also

recommended and thought to mainly exert anti-inflammatory effects through this mechanism.

Several well-designed studies using double-blind placebo controlled, cross over trials have shown efficacy. In one such study of 76 migrainers, a statistically significant reduction (24%) in frequency of migraine attacks was seen, although severity did not seem effected<sup>7</sup>. Another more recent study showed the symptomatology was reduced after taking a prophylactic dose of as little as 50 mg Feverfew per day<sup>8</sup>. These suggest that the effects of Feverfew are positive but as to the specific benefits on either symptoms or frequency, this may be individual or multiple.

Despite its apparent effectiveness, Feverfew does have adverse reactions. The emergence of a “post Feverfew syndrome” seems to manifest when patients stop taking the herb too quickly. This syndrome has been researched and mainly consists of increased headache frequency and greater intensity, which may be due to a rebound mechanism<sup>10</sup>. This is likely because of a group of active ingredients showing effect and tissue adaptation although these specific compounds are still unidentified.

Overall, Feverfew is likely the most popular and widely used herb directly prescribed for migraine headaches. Past studies have supported its efficacy but the lack of standardization of formula and the inability to elucidate a single active ingredient continue to trouble reliable research.

#### *Butterbur(Petasites (P.) hybridus (Petadolex))*

Butterbur is a less researched herb whose active ingredient is unknown but whose preparation is normally standardized to 25 milligrams of carbon dioxide extracted P. Hybridus. Administration twice daily is often prescribed as prophylactic treatment of migraines.

The effects of butterbur have been researched in one particularly good study involving a double blind, placebo controlled trial of 60 subjects that found reduction of both frequency and symptoms of migraines. The subjects in the treatment group reported a 74% reduction in frequency and severity compared with 26% in the placebo group<sup>11</sup>.

Butterbur’s mechanism of action has been researched and is likely related to its ability to inhibit leukotriene synthesis<sup>12</sup>. It has also been used for other ailments including allergic rhinitis, bronchial asthma, and gastric ulcer. The mechanism of its anti-

spasmodic, anti-inflammatory, and gastroprotective effects all relate to inhibition of leukotiene synthesis through blockage of several enzymes in differing chemical synthetic pathways. The biochemical basis of this blockade can be proven but its in-vitro efficacy still needs research. Butterbur's clinical relevance has, unfortunately, not been researched enough to make it a reliable treatment in migraines.

### *Ginger*

One case report in 1990 suggested the efficacious use of Ginger root in treatment of migraines. A 42 yr old woman with a 16 year history of migraines was successfully treated with 1.5-2 grams ginger root per day. The woman reported reduction in both frequency and severity of migraine attacks<sup>13</sup>. This can be hypothesized due to ginger's antithrombotic effects of inhibition of thromboxane A2 and platelet aggregation although this herb also has antiulcer, cardotonic, thermogenic, and immune system effects. Ginger is thought to exert several effects, one of which being the increased production of certain leukotrienes which would seem to contradict the mechanism of benefit of butterbur. Since there is a paucity of research as well as multiple mechanisms and reported uses/benefits of ginger, more research still needs to be done.

### Dietary Supplements

There has been some suggestion of supplementation of certain vitamins and minerals helping migraine headaches. This theory is rooted in the thought that people often have occult vitamin and mineral deficiencies. Although other causes may be elucidated, dietary deficiencies of these can be the main culprit and therefore conscious increase in daily ingestion of foods rich in the vitamin/mineral in question is always best. The most commonly and best supported deficiencies are discussed below.

### *Magnisium*

Magnesium is a mineral that acts as a major co-factor in many important enzymic reactions in the human body. Because of its positive divalent status, the ion stabilizes many negatively charged molecules and enzymes that in-turn have varied effects on immunity, metabolism, growth, and adaptation. The level of magnesium in the human body, therefore, varies a great deal from the site checked. Research conducted to compare magnesium levels of serum have correlated with response to magnesium restoration of migraine headaches<sup>14</sup>. Researchers in this study used a serum level of 0.54 mmoles/liter

as a comparison and found that 86% of patients with serum ionized Mg below this level and only 16% of those with levels above responded to intravenous Mg sulfate. Since using serum magnesium in research is not universal, comparing studies can be difficult.

As far as oral magnesium replacement for prophylactic treatment of migraines, two large multicenter placebo controlled trials show conflicting results. One with an n=81 and one with n=69 both done in 1996 compared oral magnesium administration and although the first showed that after 9 weeks of administration a significant reduction in overall migraine frequency, days per month migraine free, and intensity of migraines had improved, the second study refuted all these factors<sup>15,16</sup>. Both these studies were essentially equal and both used a 12 week evaluation period, however, the second (that refuted benefit) did admit subjects were allowed to use triptans for migraine abortion which might have confounded results. An earlier study of oral administration in 1991 did show benefit of tid dosing and differed in that the evaluation period was 5 months long and positive results were seen in the 2<sup>nd</sup> and 4<sup>th</sup> months<sup>18</sup>.

#### *Riboflavin (Vitamin B<sub>2</sub>)*

Riboflavin is a coenzyme in the electron transport chain and is thought to enhance cerebrovascular tone during and between migraine attacks<sup>9</sup>. Two well designed randomized placebo controlled trials have shown the statistically significant effects of Riboflavin on migrainers. The benefits include reduction in overall duration of migraines, frequency of attacks, and an increase in days per month spent migraine free. Both studies used doses of 400 mg/day and are easily comparable. The differences seen were that one study with 53 subjects showed benefit at both 1 and 3 months treatment while the other didn't show this double peak benefit<sup>4,18</sup>.

#### Relaxation training

Relaxation training, to include thermal biofeedback, electromyographic biofeedback, and cognitive-behavioral therapy has been researched and reviewed by an authoritative group called the US Headache Consortium (a collaboration of 7 medical societies). After review of these techniques their recommendation was in their Category A classification (the highest available) which meant a consistent pattern of findings in multiple randomized trials was available and showed efficacy<sup>18</sup>. Each of these techniques is different but all revolve around the shared mechanism of self awareness and self

actualization of one's therapy of their disease. Indeed, many techniques could be included here from self hypnosis to yoga. In fact, a study of 30 schoolchildren with migraines at Minneapolis Children's Medical Center found self hypnosis was effective in treating their migraines in reduction of both frequency and severity<sup>19</sup>. However, since the subjects were children, consistent, reliable, techniques were considered a confounding factor. Thus, this is a broad category that does include many mind-body techniques.

The problem that tends to supplant this category is the lack of universal technique within each system. Self actualization techniques are often taught and practiced differently with every individual subject. Therefore, what is self hypnosis to some may just be relaxation to others. For this reason, conclusive, broad range data on effectiveness of these differing techniques is hard to find and compare. It is, never the less, obvious in the research that does exist that these self awareness and manipulation techniques do have good outcomes and, given their lack of side effects, remain a viable alternative for treatment.

### Acupuncture

Acupuncture is an ancient Chinese medical procedure that uses specific points on the body, named after specific organs, which work with the body's energy flow pathways to produce beneficial effects. The theory is that manipulating these unseen energy flow pathways with either needles (acupuncture) or pressure (acupressure) can be helpful to correct irregularities and produce healing. Interestingly, for migraines, one helpful point is large intestine 4 (in the webspace between 1<sup>st</sup> and 2<sup>nd</sup> digits)<sup>9</sup>.

Acupuncture for migraine has been researched and reviewed by major scientific bodies although results suggest only mild efficacy. Recent articles lend evidence to the low side effect profile but only slight improvement of symptoms after multiple exposures to acupuncture. In a recent study in 2003, 173 patients were enrolled in a partially blind, placebo controlled comparison to find a difference between Sumatriptan, acupuncture, and placebo for migraines. The results did show some efficacy between acupuncture and placebo and Sumatriptan and placebo but demonstrated Sumatriptan was superior to either overall<sup>20</sup>. A review article in 2000 did, however, show that in 27 studies, although the majority were uncontrolled, that at least some evidence supported the conclusion of benefit from acupuncture<sup>26</sup>. It has been hypothesized in several reviews that the differing

results to effect are due to some crucial methodological flaws in current studies of acupuncture and the significant differences in technique used by practitioners. A large amount of the research is also done in foreign languages with only summaries available in English. So overall, although the current evidence does show a small but statistically significant benefit to multiple acupuncture treatments, further evidence is still needed before confident conclusions can be drawn<sup>21,22</sup>.

### Chiropractic

Chiropractic treatment of migraine uses several techniques and focuses on adjusting the cervical spine. It is particularly important that the chiropractor diagnostically separates migraines from other types of headaches to determine genuine benefit to migraines and not commonly comorbid headaches that have a greater musculoskeletal etiology.

Research into efficacy of chiropractic benefits on migraines, while present, is less in amount than other modalities. A systemic review in 1999 of six studies showed that chiropractic manipulation was equivalent to other treatments such as ice-packs and massage but since 5 of the 6 studies reviewed were not controlled, little can be inferred as to overall benefit<sup>24</sup>. A separate study from Australia of 85 patients, however, did find benefit in reduction of overall severity although no difference in frequency, duration, or disability as compared to manipulation by a medical practitioner or physiotherapist<sup>23</sup>. Accompanying these results are reports of significant side effects of manipulation (even stroke or arterial dissection), which have tempered some practitioners hopes of using chiropractic in treatment<sup>25</sup>.

### Case Report

During the last 3.5 weeks of this rotation the opportunity to use a subject in the investigation of a CAM treatment method for migraine headaches became available. That subject was the author's wife who agreed with experimentation to a treatment. After evaluation in the Integrative medicine clinic at OHSU and exposure to several CAM options, it was determined the experimental modality would be oral administration of 370 mg Feverfew at 0.7% parthenolide concentration. Since the subject had started a migraine headache diary before the experimental period, this would suffice well for a pre-medication assessment of frequency of symptoms. The subject also kept this format of

documentation throughout the study period. Along with the migraine diary, the subject has been interviewed to determine her subjective evaluation of severity and frequency of migraines and migraine symptoms during the experimental period.

Results: Migraine diary kept on home calendar and reflects: Days migraine began, symptoms of either-Migraine with spots (aura), or migraine without spots (without aura), and severity on 0-10 scale. A headache spanning overnight and continuing in the morning is considered one migraine. Diary also reflects when qd dosing of Feverfew began as well as beginning and end of menstruation. Also recorded was other rescue medication used- Ibuprofen (how many tabs of 200 mg) and Midrin dosages.

Brand of Feverfew was Nature's Way<sup>27</sup>.

Before Feverfew → 7 migraines (with or without aura) in 4.5 weeks = 1.555 migraines per week.

Mean Severity →  $3.71/10$

After Feverfew → 4 migraines (with or without aura) in 2 weeks = 2 migraines per week.

Mean Severity →  $3.75/10$

Rescue medication usage was recorded but not used in evaluation since it was sporadic and did not follow an objective pattern.

Discussion: As seen above, Feverfew has had no beneficial effects on frequency or severity of migraines in this subject. Several significant confounding factors, however, do exist. First, the patient's menstrual cycle is subjectively strongly linked to symptoms of migraines and menstruation did take place 5 days after Feverfew was started. The headache diary does, in fact, show that 3 of the 4 migraines during Feverfew administration started concurrently with the beginning of menses. Second, Feverfew has been reported to only be effective 2-6 weeks after first dosage. This test period was only 2.0 weeks long since this paper had to be submitted on time, therefore, a longer test period is certainly indicated.

Overall the design of this case study was fairly good. The patient was given a standardized dosage and although not placebo controlled, the patient did, fortunately, keep good data before the testing period. The most effective conclusions can, therefore, only be drawn after a significant time period on Feverfew can be allowed (optimally 3-4 months). This would test both menstruation relation and allow sufficient time for Feverfew effect.

### Summary

The clinical application of CAM approaches discussed in this paper should be taken with side effect and benefit profiles in mind. A possible ranking of CAM clinical approaches can thus be elucidated. The top ranking most clinically relevant intervention is likely the use of relaxation techniques due to both efficacy and extremely low side effect profile. Next, supplements have shown good efficacy with very low side effects since adverse reaction from these is very rare. The use of naturopathic herbs would wisely be treated as a drug with a strong effect but accompanying set of side effects much like medications. Then come acupuncture and chiropractic therapies that both show mild to no effect on migraines but have some potential for adverse effects. Overall, all these techniques are very hard to compare to allopathic remedies based on the extreme volume of good research supporting medications. This, of course, largely due to money for allopathic drug research invested by large drug companies with a vested interest in the outcome. Given the results of this review however, the role in CAM interventions for migraine headaches is undeniable.

This paper has produced much evidence supporting the clinical usage of many CAM methods to treat migraine headache. Migraine is a condition that affects many thousands of people worldwide and consequently different philosophies have evolved to address it. The investigation of the techniques these approaches have fostered must be undertaken and, given the results of this review, will likely show great positive effect. I do believe that our western ways of investigation are the best approach to evaluate efficacy of treatments. Thus, the good investigation of these new and important techniques can open up the opportunity for relief of great suffering to thousands of people.

## References

1. Weiller, C, May, A, Limmroth, V, et al. Brain stem activation in spontaneous human migraine attacks. *Nat Med* 1995; 1:658.
2. Winner, P, Ricalde, O, Le Force, B, et al. A double blind study of sub-cutaneous dihydroergotamine vs subcutaneous sumatriptan in the treatment of acute migraine. *Arch Neurol* 1996; 53:180.
3. Griffith's 5 minute clinical consult. Dambro, M. LWW mobile. Skyscape. Ver:5.0.139u/2003.5.27
4. Uptodate Online. Pathophysiology, clinical manifestations, and diagnosis of migraine headache in adults. Bajwa ZH, Sabahat A, Ver 12.1. 2004.
5. Awang DVC: Parthenocide: the demise of a facile theory of feverfew activity. *J Herbs Spices Med Plants* 1998; 5(4):95-98.
6. De Weerd CJ, Boostma HPR & Hendriks H: Herbal medicines in migraine prevention. *Phytomedicine* 1996; 3(3):225-230
7. Murphy JJ, Heptinstall S & Mitchell JRA: Randomised double-blind placebo-controlled trial of feverfew in migraine prevention. *Lancet* 1988; 2(8604):189-192
8. Palevitch D, Earon G & Carasso R: Feverfew (*Tanacetum parthenium*) as a prophylactic treatment for migraine: a double-blind placebo-controlled study. *Phytother Res* 1997; 11:508-511.
9. Peters, K,. *Complementary and Alternative Medicine Secrets. Questions and Answers About Integrating CAM Therapies into Clinical Practice.* Edited Kohastu, W. Headache. Pp 345-351.
10. Johnson ES, Kadam NP, Hylands DM et al: Efficacy of feverfew as prophylactic treatment of migraine. *Br Med J (Clin Res Ed)* 1985; 291(6495):569-573.
11. Grossmann M & Schmidramsl H: An extract of *Petasites hybridus* is effective in the prophylaxis of migraine. *Int J Clin Pharmacol Ther* 2000; 38(10):430-435.
12. Thomet OAR, Wiesmann UN, Schapowal A et al: Role of petasin in the potential anti-inflammatory activity of a plant extract of *Petasites hybridus*. *Biochem Pharmacol* 2001; 61(8):1041-1047.
13. Mustafa T & Srivastava KC: Ginger (*Zingiber officinale*) in migraine headache. *J Ethnopharmacol* 1990; 29(3):267-273.

14. Mauskop A & Altura BM: Magnesium for migraine: rationale for use and therapeutic potential. *CNS Drugs* 1998; 9:185-190
15. Peikert A, Wilimzig C & Kohne-Volland R: Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study. *Cephalgia* 1996; 16:257-263.
16. Pfaffenrath V, Wessely P, Meyer C et al: Magnesium in the prophylaxis of migraine-- a double-blind, placebo-controlled study. *Cephalgia* 1996; 16:436-440.
17. Facchinetti F, Sances G, Borella P et al: Magnesium prophylaxis of menstrual migraine: effects on intracellular MAGNESIUM. *Headache* 1991b; 31:298-301.
18. Silberstein, SD, for the US Headache Consortium. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review). *Neurology* 2000; 55:754.
19. Olness K, Hypnosis: The Power of Attention. *Mind Body Medicine*. Ch 16. 1993. pp 277-290.
20. Melchart D, Thormaehlen J, Hager S, Liao J, Linde K, Weidenhammer W. Acupuncture versus placebo versus sumatriptan for early treatment of migraine attacks: a randomized controlled trial. *J Intern Med*. 2003;253:181-8.
21. Matchar DB. Et al. StatRef!. Search term: headache and acupuncture. ACP's PIER: The Physicians' Information and Education Resource. Treatment for Specific Diseases. Headache (complimentary and Alternative therapy) Module 4. Treatment with No Evidence. 2004.
22. Pizzorno: Textbook of Natural Medicine, 2nd ed., Copyright © 1999 Churchill Livingstone, Inc. Accessed via MDConsult. 2004.
23. Parker GB, Tupling H, Pryor DS. A controlled trial of cervical manipulation for. Migraine. *Aust NZ J Med* 1978; 8: 589–593
24. Vernon H, McDermaid CS, Hagino C. Systematic review of randomized clinical trials of complementary/alternative therapies in the treatment of tension-type and cervicogenic headache. *Compl Ther Med* 1999;7(3):142-55.
25. Mauskop A. Alternative therapies in headache: is there a role? *Med Clin North Am* 2001;85(4):1077-84.
26. Manias P, Tagaris G, Karageorgiou K. Acupuncture in headache: a critical review. *Clin J Pain* 2000;16(4):334-9

27. Feverfew. Nature's Way Premium Extract. Nature's Way Products Inc. Springville, Utah, 84663.