Dynamic Chiropractic

HERBS/ TEAS & HOMEOPATHY

# Feverfew and Migraine: Background and Clinical Evidence

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An Old Therapy Is Rediscovered

In 1973, at the suggestion of a friend and apparently based on the advice of a traditional Welsh healer, a Welsh woman, Mrs. Anne Jenkins, tried taking three fresh leaves of feverfew each day in an attempt to rid herself of severe and recurrent migraines. After 10 months, Mrs. Jenkins' headaches had vanished and did not return so long as she kept taking feverfew. Her enthusiasm rapidly led to widespread use of feverfew in the U.K. Dr. Stewart Johnson a London migraine specialist, became interested and initiated a survey that was then followed up by a clinical trial.

The survey revealed some interesting findings:[1]

About 72 percent of those surveyed (253 suffering from true migraine) found that feverfew was helpful for the prevention of their headaches; 78 percent of the 23 people suffering from tension headaches also found that feverfew reduced headache frequency and severity. Of 242 patients who recorded the frequency of their headaches, 33 percent no longer had attacks and 76 percent had fewer migraines each month compared to before taking feverfew.

Associated nausea and vomiting decreased or disappeared. A proportion of patients experienced the migraine aura without the attack.

When attacks did occur, they responded better to conventional painkillers (e.g., aspirin). Feverfew users experienced no adverse interactions with their orthodox medication.

Many patients also suffering from arthritis found their symptoms somewhat relieved by feverfew.

The onset of the effect was slow and gradual, often taking several months, and the average dose used was very low – about two-and-a-half fresh leaves (1.5 inches long by 1.25 inches wide) per day. The average duration of treatment was 2.3 and 2.6 years for men and women, respectively. When individuals stopped taking feverfew, their migraines tended to return soon after.

The survey also revealed some side effects in a small percentage of users. Adverse effects included mouth ulcers inflammation. In contrast, a percentage of users experienced improved digestion, a sense of well-being and improved sleep.

Clinical Trials Evaluating Feverfew for Migraine

The initial survey above was followed up by a double-blind, placebo-controlled pilot clinical trial involving 17 patients who had been self-medicating with raw feverfew every day for three months. Eight of these patients received two capsules per day containing freeze-dried feverfew leaf powder (25 mg each) and nine received placebo for 24 weeks. Prior to the trial, the reduction in the frequency of migraines during self-treatment with feverfew was significant for both groups.

Compared to migraine frequency while self-medicating, there was no change in the frequency or severity of symptoms in the feverfew group during the trial. The placebo group, however, experienced a significant increase ($p<0.05$) in the frequency and severity of headaches when the results of the previous three months were considered. The placebo group also experienced a higher incidence and severity of nausea and vomiting than the feverfew group ($p<0.05$). The authors claimed a prophylactic benefit for feverfew in preventing migraine attacks.

Curiously, fewer adverse events were reported by those taking feverfew (four patients reported none), compared to placebo (all patients taking placebo reported at least one event).[2-3] Apparently, because of ethical reasons (feverfew was considered to have unknown safety by the scientists), the trial had this unusual design. The patients were already using feverfew, so the trial therefore observed the results of patients unknowingly stopping their herbal treatment. Such an abrupt discontinuance led to the recurrence of severe migraines in some patients. Perhaps more importantly, the study showed that long-term feverfew users were normal in terms of a large number of biochemical and hematological parameters.

A few years later, 59 patients with classical or common migraine completed a randomized, double-blind, placebo-controlled crossover study. Only 17 of these patients had previously tried feverfew. After a one-month single-blind placebo run-in, patients were randomly allocated to receive either one capsule of freeze-dried powdered feverfew (averaging 82 mg and containing 2.2 mmol parthenolide, approximately two medium-sized leaves) or placebo for four months and then crossed over to the other treatment for another four months.

Feverfew was associated with a 24 percent reduction in the mean number of attacks and a significant reduction in the degree of vomiting ($p<0.02$) in each two-month assessment period. There was also a trend toward a reduction in severity of attacks, although the duration of individual attacks was unaltered. Significant improvement in the feverfew group was also observed for visual analogue scores ($p<0.0001$). Treatment with feverfew did not produce any adverse effects.

Although there was no washout period between feverfew and placebo treatments, patients receiving placebo after feverfew did not experience a decreased deterioration compared to placebo levels from the first phase of the trial.[4] No *ex vivo* reduction in serotonin secretion from platelets after ingestion of feverfew at four months could be demonstrated.[5]

A team of Dutch scientists who had been active in the field of feverfew research next tested the efficacy of a standardized extract for the prevention of migraine headaches. In a randomized, placebo-controlled, double-blind, crossover design, 50 patients who had never taken feverfew before and experienced at least one migraine attack per month were followed for four months of active treatment and four months of placebo. Active treatment consisted of 143 mg per day of a granulated ethanolic extract of feverfew containing 0.5 mg of parthenolide, corresponding to about 170 mg of original dried herb.

The feverfew preparation used in this study did not exert any significant preventative effect on the frequency of migraine attacks, although patients seemed to have a tendency to use fewer analgesic drugs while they were using feverfew.6 This result was not in accordance with the results from the above studies; the authors suggested this might be because the previous studies were conducted in patients who had already found feverfew to be beneficial (which is not actually the case – see above).

Other reasons provided by the authors were that a dried plant preparation was used or that an extract was prescribed, rather than the crude leaf. (The original popularity of feverfew was based on the consumption of the fresh leaves, although the two earlier clinical trials used freeze-dried leaves.) Initial users of raw feverfew found that it took six months of use or longer to establish a reduction in migraine frequency, so perhaps the duration of the trial was insufficient. It is also possible that only a subset of migraine sufferers are feverfew responders, and a benefit in this subset might have been missed in a randomized clinical trial.

In a subsequent double-blind, placebo-controlled trial, 57 chronic migraine sufferers (43 percent of whom suffered more than 10 attacks per month) were selected at random and divided into two groups. Both groups received powdered feverfew capsules (total of 100 mg per day of dried leaves containing 0.2 mg parthenolide) in the preliminary phase, which lasted two months. In the second and third phases, which continued for an additional two months, a double-blind, placebo-controlled crossover study was conducted.

The difference in pain intensity of migraines before and after treatment with feverfew (measured in phase I) was highly significant ($p<0.001$). In phase II, patients receiving feverfew continued to experience a decrease in pain intensity, while it increased in those on placebo. The difference between the two groups was significant ($p<0.01$). Moreover, a profound reduction was observed in typical migraine symptoms such as vomiting, nausea, and sensitivity to noise and light ($p<0.001$).

Transferring the feverfew-treated group to placebo in phase III resulted in an increase in pain intensity and other symptoms. In contrast, shifting the placebo group to feverfew therapy resulted in an improvement in pain and other symptoms. However, no information was provided concerning the frequency of migraine attacks.[7] In this trial, rather than acting to reduce the frequency of migraines, it appeared that feverfew reduced their severity. A longer treatment time or higher doses may have also seen an impact on migraine frequency.

A German research team next studied the efficacy of a supercritical CO2 extract of feverfew in two randomized, double-blind, placebo-controlled trials. In the first trial, the efficacy and tolerability of three different doses per day of the extract (6.24 mg, 18.75 mg and 56.25 mg, corresponding to 0.5

mg, 1.5 mg and 4.5 mg of parthenolide) were compared to a placebo.[8]

The patients (147 total) suffered from migraine with and without aura according to International Headache Society (IHS) criteria and were treated with one of the study medications for 12 weeks after a four-week baseline period. The primary efficacy parameter was the number of migraine attacks during each 28 days of the treatment period compared with baseline. Secondary endpoints were total and average duration and intensity of migraine attacks, mean duration of a single attack, number of days with accompanying migraine symptoms, number of days with inability to work due to migraine, as well as type and amount of additionally taken medications for the treatment of migraine attacks.

With respect to the primary and secondary efficacy parameters, a statistically significant difference was not found. The frequency of migraine attacks for a predefined confirmatory subgroup of patients (49) with at least four migraine attacks during the baseline period decreased in a dose-dependent manner (p=0.001). The highest absolute change of migraine attacks was observed under treatment with 6.25 mg three times daily (-1.8±1.5 per 28 days) compared with placebo (-0.3±1.9; p=0.02). Overall, 52 of 147 patients (35 percent) reported at least one adverse event. The incidence of these in the active treatment groups was similar to that in the placebo group, and no dose-related effect was observed for any safety parameter.

This was followed up by the second trial that assessed the efficacy of only the 18.75 mg/day dose against placebo.[9] Patients (n=170) suffering from migraine according to the IHS criteria were treated for 16 weeks after a four-week baseline period. The primary endpoint was the average number of migraine attacks per 28 days during treatment months two and three compared with baseline. Safety parameters assessed included adverse events, laboratory parameters, vital signs and physical examination.

Migraine frequency decreased by 1.9 attacks per month in the feverfew group and by 1.3 attacks in the placebo group (p=0.0456). Logistic regression of responder rates showed an odds ratio of 3.4 in favor of feverfew (p=0.0049). Adverse events possibly related to study medication were 9/107 (8.4 percent) with feverfew vs. 11/108 (10.2 percent) with placebo (p=0.654). The authors concluded that the feverfew extract was effective and shows a favorable risk-benefit ratio.

A later study has suggested that a higher dose of feverfew than used in the earliest studies (600 mg/day), together with a relatively small dose of willow bark (*Salix alba,* 600 mg/day) might bring on a quicker result in migraine prophylaxis. The herbal combination was standardized for parthenolide (0.2 percent) and salicin (1.5 percent).[10] A prospective, open-label study was performed in 12 patients diagnosed with migraine without aura. Twelve weeks of treatment with the herbal combination was administered to determine the effects of therapy on migraine attack frequency, intensity and duration, and quality of life, together with tolerability for patients.

With the herbal treatment, attack frequency was reduced by 57.2 percent at six weeks (p<0.029) and by 61.7 percent at 12 weeks (p<0.025) in nine of 10 patients, with 70 percent of patients having a reduction of at least 50 percent. Attack intensity was reduced by 38.7 percent at six weeks (p<0.005) and by 62.6 percent at 12 weeks (p<0.004) in all 10 patients, with 70 percent having a reduction of at least 50 percent.

Attack duration decreased by 67.2 percent at six weeks (p<0.001) and by 76.2 percent at 12 weeks (p<0.001) in all 10 patients. Two patients were excluded for reasons unrelated to treatment. Self-assessed general health, physical performance, memory and anxiety also improved by the end of the study. The herbal treatment was well-tolerated and no adverse events occurred.

Although this was an open-label trial and hence lacking a placebo group, the results are quite striking. They suggest that combining feverfew in higher doses with willow bark might result in significant clinical improvement in migraine frequency within six weeks. The obvious next step is to conduct a placebo-controlled trial for this combination.

Feverfew (100 mg/day containing 0.7 mg parthenolide) in combination with 300 mg/day magnesium (as the citrate and oxide) and 400 mg/day riboflavin was compared against a "placebo" containing 25 mg of riboflavin in a 30-month randomized, double-blind, placebo-controlled trial involving 49 patients with migraine.[11] The placebo contained what the authors considered to be an ineffective dose of riboflavin because of the yellow color it gives to urine, which might have alerted patients that they were receiving active treatment. Both interventions showed comparable clinical effects in reducing migraine frequency. Since the placebo response exceeded that reported for other migraine prophylaxis studies, the authors suggested that 2 mg riboflavin may be an active comparator. Nonetheless, there seemed to be little additional benefit from the feverfew.

Conclusions and Recommendations

Overall, there is good clinical evidence that feverfew can help prevent migraine. However, a few important practical considerations relating to dosage should apply. The adequate dose varies with the quality of the herb, and the severity and frequency of migraines. In addition, it is more likely that a higher starting dose establishes the prophylactic effect more rapidly. Probably because of the initial use and promotion of a low dose of the fresh leaves, there is a tendency to recommend quite low doses of feverfew for migraine prophylaxis. However, the use of such doses often means that it can take 6–9 months before any effective migraine prophylaxis occurs.

With this length of time, the patient might give up treatment before any benefit is established; hence, the early use of higher doses of feverfew in migraine prevention is recommended for a faster clinical effect. Also, it can be combined with other relevant herbs to maximise the magnitude and speed of the onset of such prophylaxis. Typically, doses of at least 3–5 mL per day of the 1:5 tincture in 60 percent ethanol (to extract the lactones) or its equal in tablets or capsules (600-1,000 mg/day of dried herb equivalent) are recommended initially. Once sufficient prophylaxis takes place, the dose can be reduced to a suitable level to maintain the clinical effect.

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