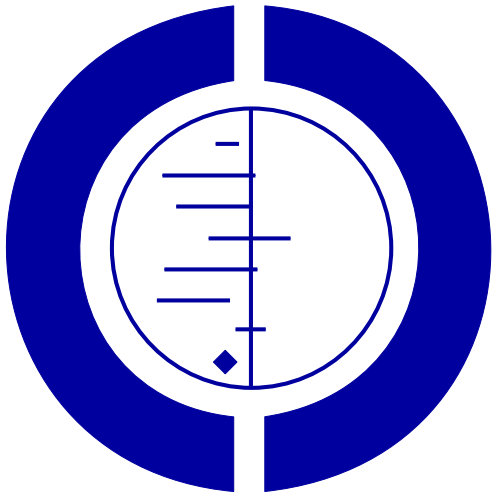
Feverfew for preventing migraine (Review)

Pittler MH, Ernst E



This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2006, Issue 3

http://www.thecochranelibrary.com

TABLE OF CONTENTS

Feverfew for preventing migraine (Review)

Pittler MH, Ernst E

This record should be cited as:
Pittler MH, Ernst E. Feverfew for preventing migraine. *Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD002286. DOI: 10.1002/14651858.CD002286.pub2.

This version first published online: 26 January 2004 in Issue 1, 2004.
Date of most recent substantive amendment: 18 November 2003

ABSTRACT

Background
Feverfew *(Tanacetum parthenium L.)* extract is a herbal remedy used for preventing attacks of migraine.

Objectives
To systematically review the evidence from double-blind randomised controlled trials (RCTs) assessing the clinical efficacy and safety of feverfew versus placebo for preventing migraine.

Search strategy
Publications describing (or which might describe) double-blind RCTs of feverfew extract for migraine were sought through the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 2, 2003); PREMEDLINE/MEDLINE (1966 to July 2003); EMBASE (1974 to July 2003); the trials register of the Cochrane Pain, Palliative and Supportive care group (July 2003); and AMED (1985 to July 2003). Manufacturers of feverfew were contacted and the bibliographies of identified articles checked for further trials.

Selection criteria
Randomised, placebo-controlled, double-blind trials assessing the efficacy of feverfew for preventing migraine were included. Trials using clinical outcome measures were included. Trials focusing exclusively on physiological parameters were excluded. There were no restrictions regarding the language of publication.

Data collection and analysis
Data on patients, interventions, methods, outcome measures, results and adverse events were extracted systematically. Methodological quality was evaluated using the scoring system developed by Jadad and colleagues. Two reviewers independently selected studies, assessed methodological quality and extracted data. Disagreements concerning evaluation of individual trials were resolved through discussion.

Main results
Five trials (343 patients) met the inclusion criteria. Results from these trials were mixed and did not convincingly establish that feverfew is efficacious for preventing migraine. Only mild and transient adverse events were reported in the included trials.

Authors' conclusions
There is insufficient evidence from randomised, double-blind trials to suggest an effect of feverfew over and above placebo for preventing migraine. It appears from the data reviewed that feverfew presents no major safety problems.

PLAIN LANGUAGE SUMMARY

There is insufficient evidence to conclude that feverfew is better than placebo for preventing attacks of migraine.

Feverfew *(Tanacetum parthenium L.)* extract is a herbal remedy used for preventing attacks of migraine. Five trials were identified that assessed the efficacy of feverfew (taken as an oral preparation) compared with placebo. Results from these trials were mixed and did not

convincingly establish that feverfew is more effective than placebo for preventing migraine. No major side effects were associated with feverfew in the included studies. Further large and rigorously conducted trials are needed.

BACKGROUND

The use of herbal medicinal products (HMPs) by the general US population increased by a staggering 480% between 1990 and 1997: according to a national survey (Eisenberg 1998), 1-year population prevalence estimates of HMP use rose from 2.5% in 1990 to 12.1% in 1997. The same survey found that HMPs were most commonly employed for allergies, insomnia, respiratory problems and digestive problems. Estimated 1997 out-of-pocket expenditures for HMPs in the US totaled US$5.1 billion (Eisenberg 1998). Faced with this remarkable interest in HMPs, mainstream healthcare professionals need to familiarise themselves with this subject. The most pressing questions are whether HMPs are effective and safe.

Feverfew *(Tanacetum parthenium L.)* has traditionally been used for fever, women's ailments, inflammatory conditions, psoriasis, toothache, insect bites, rheumatism, asthma and stomach-ache. During the last decades, it has also been used for migraine prophylaxis. The sesquiterpene lactone parthenolide has been suggested as the main active component of feverfew. The role of parthenolide in migraine prophylaxis was supported by in vitro studies suggesting inhibition of serotonin release from blood platelets (e.g., Heptinstall 1985). This has, however, been contradicted by other evidence (de Weerdt 1996). At present, the identity of the principle active constituent(s) of feverfew remains unclear.

A systematic review first published in The Cochrane Library, Issue 3, 2000 (Pittler 2000), identified four randomised controlled trials (RCTs) comparing feverfew with placebo for the prevention of migraine, but the data were insufficient to establish the efficacy of feverfew beyond reasonable doubt. The present update sought to identify trials undertaken since the last systematic literature search in 1999 and to address, once again, the questions: (1) does feverfew prevent attacks of migraine, and (2) is it safe to use?

OBJECTIVES

To systematically review the evidence from double-blind randomised controlled trials (RCTs) assessing the clinical efficacy and safety of feverfew versus placebo for preventing migraine.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We included placebo-controlled trials that were both randomised (i.e., trials with a randomised generation of allocation sequences) and double-blind (i.e. trials where neither patients nor care/treatment providers knew whether the patient had received feverfew or placebo). No restrictions were imposed regarding the language of publication (Egger 1997).

Types of participants

Studies were included if participants were patients suffering from migraine. Information on the diagnostic criteria used in each study is provided in the 'Results' section, below, and in the 'Characteristics of included studies' table.

Types of intervention

We included trials conducted using oral preparations containing feverfew extract as the only component (mono-preparations). No restrictions were imposed regarding dosage. Trials assessing feverfew extract as one of several active components in a combination preparation or as a part of a combination treatment were excluded.

Both treatment studies and withdrawal studies (in which patients already on feverfew medication were randomised to continue on either placebo or feverfew) were considered for inclusion.

Types of outcome measures

Trials using clinical outcome measures were included. Trials focusing exclusively on physiological parameters were excluded.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Pain, Palliative and Supportive Care Group methods used in reviews.

ELECTRONIC DATABASES
Publications describing (or which might describe) randomised, double-blind trials of feverfew extract for migraine were sought through searches of:

- The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 2, 2003)
- PREMEDLINE/MEDLINE (1966 to July 2003)
- EMBASE (1974 to July 2003)
- The trials register of the Cochrane Pain, Palliative and Supportive Care group (PaPaS) (July 2003)
- Allied and Complementary Medicine Database (AMED) (1985 to July 2003)

The search terms listed below (free text and controlled vocabulary) were applied to the databases (numbers in square brackets at the end of each line indicate the number of trial reports retrieved). All electronic searches were based on the subject only; no filters for randomised controlled trials or controlled clinical trials were applied.

1. CENTRAL

#1 FEVERFEW single term (MeSH) [1]
#2 feverfew [17]
#3 (tanacetum next parthenium) [10]
#4 (chrysanthemum next parthenium) [2]
#5 mutterkraut [2]
#6 (#1 or #2 or #3 or #4 or #5) [18]
#7 MIGRAINE explode all trees (MeSH) [897]
#8 HEADACHE DISORDERS explode all trees (MeSH) [1005]
#9 (migrain* or headache* or cephalgi*) [7329]
#10 (#7 or #8 or #9) [7329]
#11 (#6 and #10) [11]

2. PREMEDLINE/MEDLINE

1 FEVERFEW.mp. [mp=title, abstract, rw, subject headings] [112]
2 (tanacetum adj parthenium).mp [45]
3 (chrysanthemum adj parthenium).mp [7]
4 mutterkraut.mp [0]
5 or/1-4 [122]
6 migraine.mp [13793]
7 headache disorders.mp [424]
8 (migrain$ or headache$ or cephalgi$).mp [40184]
9 or/6 -8 [40184]
10 5 and 9 [33]

3. EMBASE

1 FEVERFEW.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] [125]
2 (tanacetum adj parthenium).mp [61]
3 (chrysanthemum adj parthenium).mp [11]
4 mutterkraut.mp [2)
5 or/1-4 [143]
6 migraine.mp [13170]
7 headache disorders.mp [181]
8 (migrain$ or headache$ or cephalgi$).mp [57094]
9 or/6-8 [57094]
10 5 and 9 [54]

4. PaPaS trials register

The following terms were used to search the trials register of the Cochrane Pain, Palliative and Supportive Care group: ((feverfew OR "tanacetum parthenium" OR "chrysanthemum parthenium" OR mutterkraut) AND (migrain* OR headache* OR cephalgi*))

5. AMED

1 exp feverfew/ [8]
2 feverfew.mp. [mp=abstract, heading words, title] [38]
3 "tanacetum parthenium".mp [32]
4 "chrysanthemum parthenium".mp [4]
5 mutterkraut.mp [0]
6 or/1-5 [47]
7 migraine/ [328]
8 exp Vascular headache/ [343]
9 exp Headache/ [861]
10 headache$ [924]
11 (migrain$ or cephalgi$).mp [408]
12 or/7-11 [1023]
13 6 and 12 [21]

HAND SEARCHING
A manual search was performed using the bibliographies of articles located through the computer search, and through scanning our own files.

PERSONAL CONTACT
In addition, manufacturers of feverfew preparations were asked to contribute relevant published and unpublished material.

METHODS OF THE REVIEW

SELECTION OF STUDIES
The studies retrieved through searching were independently screened for inclusion in the review by two reviewers (MHP, EE).

DATA EXTRACTION
Two reviewers (MHP, EE) also systematically and independently extracted data from each trial report. Data extracted included patient characteristics, interventions, methods, outcome measures, results and adverse events.

METHODOLOGICAL QUALITY
The methodological quality of the included studies was evaluated using the scoring system developed by Jadad et al (Jadad 1996). This scale quantifies the likelihood of bias inherent in a trial based on the description of randomisation, blinding and withdrawals provided in the trial report. The assessment was performed independently by two reviewers (MHP, EE).

Disagreements in all aspects of the evaluation of trials were resolved through discussion, and consensus was reached in all cases.

DATA ANALYSIS
Meta-analyses of data on the frequency and severity of migraine attacks, the incidence and severity of nausea/vomiting, and the global assessment of efficacy were considered, but were abandoned when the scarcity of both trials and common outcome measures became apparent. Quantitative data reported for the above outcomes are summarized in the 'Results' section, below.

DESCRIPTION OF STUDIES

The literature search identified six double-blind RCTs. One was excluded because it did not report on clinical outcomes (Kuritzky 1994). The other five trials met the inclusion criteria and were reviewed. No relevant unpublished trials were identified.

In total, 343 patients participated in the included studies. Three trials (Murphy 1988; de Weerdt 1996; Palevitch 1997) were crossover trials, while two (Johnson 1985; Pfaffenrath 2002) used a parallel-group design. Two studies were withdrawal studies (Johnson 1985; Palevitch 1997), and three were treatment studies (Murphy 1988; de Weerdt 1996; Pfaffenrath 2002). Three trials administered dried powdered feverfew extract (Johnson 1985; Murphy 1988; Palevitch 1997), one used an alcoholic feverfew extract (de Weerdt 1996), and another used a CO_2 extract (Pfaffenrath 2002).

METHODOLOGICAL QUALITY

All of the included trials scored at least 3 of 5 points on the scale used to assess methodological quality (Jadad 1996). The three studies that reported results in favour of feverfew scored 3 to 4 points (Johnson 1985; Murphy 1988; Palevitch 1997), while the trials that reported no differences between feverfew and placebo for their primary outcome measures scored the maximum of 5 points (de Weerdt 1996; Pfaffenrath 2002). The quality scores for each trial are reported in the 'Characteristics of included studies' table.

RESULTS

As stated in the 'Methods of the review' section, above, planned meta-analyses of data on the frequency and severity of migraine attacks, the incidence and severity of nausea/vomiting and the global assessment of efficacy were not conducted due to the scarcity of trials and the lack of common outcome measures. The methods and results of each of the five included studies are summarised below to provide an indication of the benefits and harms of feverfew for the prevention of migraine.

EFFICACY

Johnson et al (Johnson 1985) conducted a study including 17 patients who had taken raw feverfew leaves every day for the previous 3 to 4 years. Patients with a history of common or classical migraine (diagnostic criteria not specified) for a duration of at least 2 years, with eight or fewer attacks per month, were randomised to receive either two capsules of powdered freeze-dried feverfew leaves (50 mg total) daily or identical placebo for 24 weeks. Diary cards were used to assess the frequency of migraine and the incidence of nausea and vomiting. The results showed a significant ($p < 0.02$) increase in the number of attacks per month in the placebo group (mean, 3.1; standard error [SE], 0.8) compared with baseline, while attack frequency remained constant in patients receiving feverfew (mean, 1.7; SE, 0.6). Forty-two per cent and 79% of attacks were associated with nausea and vomiting in the feverfew and placebo groups, respectively ($p < 0.05$). The incidence of bouts of nausea/vomiting was significantly ($p < 0.05$) lower in the feverfew group than in the placebo group (39 and 116, respectively). The global assessment of efficacy by patients indicated a significant ($p < 0.01$) difference in favour of feverfew: 6/8 patients in the feverfew group rated the overall treatment effect as moderately good to excellent, while this result was reported by only 3/9 patients in the placebo group.

Murphy et al (Murphy 1988) randomised 72 patients with common or classical migraine (as defined by Blau 1984) to receive either one capsule of dried feverfew leaves (mean weight, 82 mg) or placebo for 4 months after a 1-month placebo run-in period. Patients were then transferred into the other group for the second 4-month period. There was no wash-out period between the treatment periods. Outcomes were assessed using a diary of migraine symptoms provided every 2 months. The results suggested a significant ($p < 0.005$) difference in the number of attacks per 2-month period during feverfew treatment (mean, 3.6; SE, 0.2) compared with placebo (mean, 4.7; SE, 0.3). Among patients with classical migraine ($n = 17$), the number of attacks per 2-month period was significantly ($p < 0.05$) lower with feverfew (mean, 2.9; SE, 0.4) than with placebo (mean, 4.3; SE, 0.5); among patients with common migraine ($n = 42$), headache frequency was similar during the feverfew (mean, 3.9; SE, 0.3) and placebo (mean, 4.9; SE, 0.4) periods ($p = 0.06$). In the study population as a whole, the total number of attacks rated as severe or very severe was 178/424 (42%) with feverfew and 258/559 (46%) with placebo. Nausea and vomiting accompanied the attacks in 207/424 (49%) and 313/559 (56%) cases treated with feverfew and placebo, respectively ($p < 0.02$). The global assessment of efficacy, measured on a 100-mm visual analogue scale with 'worst ever' and 'best ever' as the two extremes, indicated a significant ($p < 0.0001$) difference in favour of feverfew compared with placebo (mean, 74; SE, 2 versus mean, 60; SE, 3, respectively). Among patients with classical migraine, global assessment scores were significantly ($p < 0.01$) higher during treatment with feverfew (mean, 78; SE, 4) than during treatment with placebo (mean, 57; SE, 5); among patients with common migraine, scores for the two treatment periods were similar (mean, 72; SE, 2 for feverfew and mean, 61; SE, 3 for placebo).

De Weerdt et al (de Weerdt 1996) assessed 50 patients diagnosed according to the criteria of the International Headache Society (IHS 1988). Patients suffering from migraine with or without aura received either one capsule of an alcoholic feverfew extract (143 mg) or placebo daily in a randomised crossover trial. A 1-month placebo run-in phase was followed by two 2-month treatment periods. There was no wash-out period between the treatment

periods. The investigators reported that no significant effects on the number or severity of headaches were observed.

The crossover trial conducted by Palevitch et al (Palevitch 1997) included 57 patients with migraine diagnosed by medical examination (diagnostic criteria not specified). During the preliminary, open phase of the trial, each patient received 100 mg feverfew daily for 2 months. Thereafter, in the double-blind crossover phase, one group received placebo for 30 days, while the other continued taking feverfew. Patients in the active treatment group were then transferred to the placebo arm and vice versa. There was no wash-out period between the treatment periods. The severity of migraine attacks was measured by patients on a numerical scale of 0 ('no pain') to 10 ('most severe pain'), and the severity of nausea and vomiting was assessed using a numerical analogue scale and by questionnaire. The results of the preliminary, open phase showed a significant decrease in migraine severity after treatment with feverfew compared with baseline ($p < 0.001$). In the first crossover phase there was a further reduction of migraine severity in the feverfew group (mean, 1.5; SE, 0.7), and an increase in severity in the placebo group (mean, 1.6; SE, 0.9) ($p < 0.01$). In the second phase of the crossover, these trends continued: migraine severity decreased among patients taking feverfew (mean, 4.0; SE, 1.1) and increased among patients taking placebo (mean, 1.4; SE, 1.1). In addition, there was a significant ($p < 0.001$) difference in the severity of nausea and vomiting in favour of feverfew.

Pfaffenrath et al (Pfaffenrath 2002) conducted a double-blind, placebo-controlled, multicentre RCT. Three dosage regimens (2.08 mg versus 6.25 mg versus 18.75 mg, each administered three times daily for 12 weeks) of a novel CO_2 feverfew extract were compared with placebo. One hundred and forty-seven patients with migraine with or without aura according to IHS criteria (IHS 1988) were enrolled. The primary endpoint was pre-defined as the total number of migraine attacks during the last 28 days of treatment compared to the 4-week baseline period. Secondary endpoints included total and average duration and intensity of migraine attacks and number of days with accompanying migraine symptoms. There were no statistically significant effects for either primary or secondary outcomes measures. Accordingly, a dose-response relationship could not be observed. Subgroup analysis including patients with at least four migraine attacks during baseline evaluations ($n = 49$) showed a significant effect when the 6.25-mg dose was compared with placebo ($p = 0.02$).

ADVERSE EVENTS/SAFETY

Feverfew was well tolerated in the included trials, and adverse events were generally mild and reversible. Two studies (Johnson 1985; Murphy 1988) reported a higher incidence of adverse events during treatment with placebo than with feverfew. In total, 12 withdrawals were necessitated by adverse events associated with feverfew, compared with 7 withdrawals due to adverse events associated with placebo. In the study by Pfaffenrath et al (Pfaffenrath 2002) the incidence of adverse events was similar for all treatment groups. A 'post-feverfew syndrome' -- including a rebound of migraine symptoms, anxiety, insomnia and muscle and joint stiffness -- has been described among patients switched from treatment with feverfew to placebo (Johnson 1985). Feverfew did not appear to affect blood pressure, heart rate, body weight or haematological and biochemical safety parameters.

DISCUSSION

The results of the studies included in this systematic review were mixed, and most studies were not fully satisfactory in terms of methodological quality. Collectively, the data reviewed do not convince that feverfew is efficacious beyond placebo for preventing migraine.

While the two studies with the highest methodological quality (de Weerdt 1996; Pfaffenrath 2002) showed no beneficial events, three others (Johnson 1985; Murphy 1988; Palevitch 1997) were in favour of feverfew. Amongst the four trials with an acceptable sample size (Tfelt-Hansen 1987), two studies (Murphy 1988; Palevitch 1997) reported feverfew to be superior to placebo, while two (de Weerdt 1996; Pfaffenrath 2002) did not. In these studies, the frequency of migraine was reduced by feverfew in two trials (Johnson 1985; Murphy 1988), while two (de Weerdt 1996; Pfaffenrath 2002) reported no such effect. Feverfew reduced the severity of migraine in one trial (Palevitch 1997), while three studies (Murphy 1988; de Weerdt 1996; Pfaffenrath 2002) reported no such effect. The incidence of nausea and vomiting was positively affected in two trials (Johnson 1985; Murphy 1988).

Concerning the safety of feverfew, toxicity studies have shown that chronic prophylactic use of feverfew does not affect the frequency of chromosomal aberration in lymphocytes or urine mutagenicity (Anderson 1988). Anecdotal reports describe contact dermatitis (e.g., Burry 1980; Hausen 1983). In the reviewed trials the adverse events reported were generally mild and reversible. Mouth ulceration and gastrointestinal symptoms were reported most frequently and were also experienced by long-time feverfew users. Obviously such problems can be avoided through the use of more carefully prepared formulations of feverfew. A post-feverfew syndrome was reported by long-time feverfew consumers after discontinuation of feverfew intake (Johnson 1985). Collectively these data imply that oral feverfew medication is relatively safe. However, more information is needed, particularly on long-term clinical use.

Until recently it was generally assumed that parthenolide represented the active component of feverfew extract. This hypothesis was supported by in vitro experiments that emphasised the biological activity of feverfew. These studies demonstrated that the plant has inhibitory effects on platelet aggregation and on the release of serotonin from blood platelets and leucocytes (Heptinstall 1985; Heptinstall 1987). Furthermore, feverfew seems to exert inhibiting effects on prostaglandin biosynthesis (Pugh 1988) by interfering with phospholipase A (Makheja 1982). However, a definitive

chemical link between the etiology of migraine and parthenolide or any other of the feverfew constituents has still not been established (Kuritzky 1994). One trial using an extract of feverfew with a standardised and constant concentration of parthenolide to treat migraine did not show any beneficial effect (de Weerdt 1996). This lack of efficacy may be due to the absence of essential therapeutic components of the granulated feverfew leaves, which were either not sufficiently extracted, or perhaps degraded during the preparation (de Weerdt 1996). One study (Goadsby 1997) suggests only a secondary role for serotonin in the etiology of migraine. Assuming whole-leaf preparations are effective, this would direct attention more towards other components of the feverfew leaf (Awang 1998). This is also suggested by the Dutch study (de Weerdt 1996), which indicates that the essential oil constituent of feverfew, chrysanthenyl acetate, may be important. This component inhibits prostaglandin synthetase in vitro and seems to possess analgesic properties (Pugh 1988). Other investigators agree that parthenolide is not the only pharmacologically active constituent in feverfew (Hendriks 1996; Brown 1997). A link between the relatively high concentration of melatonin in different feverfew varieties (Murch 1997) and a decrease in melatonin excretion during migraine attacks has been suggested (Brun 1995). An alternative explanation for negative trial results is offered by the fact that some commercial preparations are under-dosed, possibly due to the instability of the active constituents in these extracts (Willigmann 1999).

AUTHORS' CONCLUSIONS

Implications for practice

The above data indicate that there is not sufficient evidence from rigorous clinical trials to convincingly suggest an effect of feverfew over and above placebo for preventing migraine.

Implications for research

Future studies should be more rigorously executed and reported, as suggested by the CONSORT statement (Begg 1996), to facilitate the abstraction and analysis of data. Detailed description of randomisation and double-blinding procedures should be included in trial reports. More rigorous clinical trials assessing larger patient samples are required.

POTENTIAL CONFLICT OF INTEREST

None known.

ACKNOWLEDGEMENTS

We thank Sylvia Bickley, Trials Search Co-ordinator for the Cochrane Pain, Palliative and Supportive Care group, for her help in revising the search strategy for this review.

SOURCES OF SUPPORT

External sources of support

- International Headache Society (for administrative costs associated with editorial review and peer review) TRANSNATIONAL

Internal sources of support

- No sources of support supplied

REFERENCES

References to studies included in this review

de Weerdt 1996 *{published data only}*

de Weerdt CJ, Bootsma HPR, Hendriks H. Herbal medicines in migraine prevention: randomized double-blind placebo-controlled crossover trial of a feverfew preparation. *Phytomedicine* 1996;**3**:225–30.

Johnson 1985 *{published data only}*

Johnson ES, Kadam NP, Hylands DM, Hylands PJ. Efficacy of feverfew as prophylactic treatment of migraine. *BMJ* 1985;**291**:569–73.

Murphy 1988 *{published data only}*

Murphy JJ, Heptinstall S, Mitchell JRA. Randomized double-blind placebo-controlled trial of feverfew in migraine prevention. *Lancet* 1988;**2**:189–92.

Palevitch 1997 *{published data only}*

Palevitch D, Earon G, Carasso R. Feverfew (Tanacetum parthenium) as a prophylactic treatment for migraine: a double-blind placebo-controlled study. *Phytotherapy Research* 1997;**11**:508–11.

Pfaffenrath 2002 *{published data only}*

Pfaffenrath V, Diener HC, Fischer M, Friede M, Henneicke-von Zeppelin HH. The efficacy and safety of Tanacetum parthenium (feverfew) in migraine prophylaxis -- a double-blind, multicentre, randomized placebo-controlled dose-response study. *Cephalalgia* 2002;**22**:523–32.

References to studies excluded from this review

Kuritzky 1994

Kuritzky A, Elhacham Y, Yerushalmi Z, Hering R. Feverfew in the treatment of migraine: its effect on serotonin uptake and platelet activity. *Neurology* 1994;**44 Suppl 2**:A201.

Additional references

Anderson 1988

Anderson D, Jenkinson PC, Dewdney RS, Blowers SD, Johnson ES, Kadam NP. Chromosomal aberrations and sister chromatid exchanges in lymphocytes and urine mutagenicity of migraine patients: a comparison of chronic feverfew users and matched non-users. *Human Toxicology* 1988;**7**:145–52.

Awang 1998

Awang DVC. Prescribing therapeutic feverfew (Tanacetum parthenium (L.) Schultz-Bip., syn. Chrysanthemum parthenium (L.) Bernh.). *Integrative Medicine* 1998;**1**:11–3.

Begg 1996

Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996;**276**:637–9.

Blau 1984

Blau JN. Towards a definition of migraine headache. *Lancet* 1984;**1**: 444–5.

Brown 1997

Brown AMG, Edwards CM, Davey MR, Power B, Lowe KC. Pharmacological activity of feverfew (Tanacetum parthenium (L.) Schultz-Bip.): assessment by inhibition of human polymorphonuclear leucocyte chemiluminescence in-vitro. *Journal of Pharmacy and Pharmacology* 1997;**49**:558–61.

Brun 1995

Brun J, Claustrat B, Saddier P, Chazor G. Nocturnal melatonin excretion is decreased in patients with migraine without aura attacks associated with menses. *Cephalalgia* 1995;**15**:136–9.

Burry 1980

Burry JN. Compositae dermatitis in South Australia: contact dermatitis from Chrysanthemum parthenium. *Contact Dermatitis* 1980; **6**:445.

Egger 1997

Egger M, Zellweger-Zahner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. *Lancet* 1997;**350**:326–9.

Eisenberg 1998

Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA* 1998;**280**: 1569–75.

Goadsby 1997

Goadsby PJ. How do the currently used prophylactic agents work in migraine?. *Cephalalgia* 1997;**17**:85–92.

Hausen 1983

Hausen BM, Osmundsen PE. Contact allergy to parthenolide in Tanacetum parthenium (L.) Schulz-Bip. (feverfew, Asteraceae) and cross-reactions to related sesqiterpene lactone containing Compositae species. *Acta Dermato-Venereologica* 1983;**63**:308–14.

Hendriks 1996

Hendriks H, Bos R, Woerdenbag HJ. The essential oil of Tanacetum parthenium (L.) Schultz-Bip. *Flavour and Fragrance Journal* 1996; **11**:367–71.

Heptinstall 1985

Heptinstall S, White A, Williamson L, Mitchell JRA. Extracts of feverfew inhibit granule secretion in blood platelets and polymorphonuclear leucocytes. *Lancet* 1985;**1**(8437):1071–4.

Heptinstall 1987

Heptinstall S, Groenewegen WA, Spangenberg P, Loesche W. Extracts of feverfew may inhibit platelet behaviour via neutralization of sulphydryl groups. *Journal of Pharmacy and Pharmacology* 1987;**39**: 459–65.

IHS 1988

Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia* 1988;**8 Suppl 7**:1–96.

Jadad 1996

Jadad AR, Moore RA, Carrol D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**: 1–12.

Makheja 1982

Makheja AN, Bailey JM. A platelet phospholipase inhibitor from the medicinal herb feverfew (Tanacetum parthenium). *Prostaglandins Leukotrienes and Medicine* 1982;**8**:653–60.

Murch 1997

Murch SJ, Simmons CB, Saxena PK. Melatonin in feverfew and other medicinal plants. *Lancet* 1997;**350**:1598–9.

Pugh 1988

Pugh WJ, Sambo K. Prostaglandin synthetase inhibitors in feverfew. *Journal of Pharmacy and Pharmacology* 1988;**40**:743–5.

Tfelt-Hansen 1987

Tfelt-Hansen P, Nielsen SL. Patient numbers needed in prophylactic migraine trials. *Neuroepidemiology* 1987;**6**:214–9.

Willigmann 1999

Willigmann J, Freudenstein J. Production of a stable feverfew (Tanacetum parthenium) extract as an active substance for a pharmaceutical product. Internal document, Schaper Brummer GmbH and Co., 1999.

References to other published versions of this review

Ernst 2000

Ernst E, Pittler MH. The efficacy and safety of feverfew (Tanacetum parthenium L.): an update of a systematic review. *Public Health Nutrition* 2000;**3**:509–14.

Pittler 2000

Pittler MH, Vogler BK, Ernst E. Feverfew for preventing migraine (Cochrane Review). In: *The Cochrane Library*, 3, 2000. Chichester, UK: John Wiley & Sons, Ltd.

Vogler 1998

Vogler BK, Pittler MH, Ernst E. Feverfew as a preventive treatment for migraine: a systematic review. *Cephalalgia* 1998;**18**:704–8.

TABLES

Characteristics of included studies

Study	Johnson 1985
Methods	Randomised, placebo-controlled, double-blind trial. Two parallel groups. Withdrawal study.
Participants	17 patients (age range not reported). Data from all 17 patients evaluated. Common and classical migraine (diagnostic criteria not specified).
Interventions	Two capsules (25 mg each) of powdered feverfew leaves daily for 6 months.
Outcomes	Frequency of headache. Incidence of nausea and vomiting. Global assessment of efficacy.
Notes	All patients had taken raw feverfew leaves for the previous 3-4 years. Small sample size. Jadad score: 4.
Allocation concealment	B – Unclear

Study	Murphy 1988
Methods	Randomised, placebo-controlled, double-blind trial. Crossover. Treatment study.
Participants	72 patients aged 24-72 years. Data from 59 patients evaluated. Common and classical migraine (as defined by Blau 1984).
Interventions	One capsule (mean weight 82 mg) of powdered feverfew daily for 4 months.
Outcomes	Frequency and severity of headache. Incidence of nausea and vomiting. Global assessment of efficacy.
Notes	Heterogeneous patient sample. 1-month placebo run-in. No wash-out period. Sub-group analysis in classical/ common migraine patients. Jadad score: 4.
Allocation concealment	B – Unclear

Study	Palevitch 1997
Methods	Randomised, placebo-controlled, double-blind trial. Crossover. Withdrawal study.
Participants	57 patients aged 9-65 years. Data from all 57 patients evaluated. Migraine diagnosed by medical examination; probably migraine with and without aura, though this is unclear (diagnostic criteria not specified).
Interventions	Two capsules (50 mg) of powdered feverfew daily for 1 month.
Outcomes	Severity of headache. Severity of nausea and vomiting.
Notes	Both groups were treated with feverfew in the preliminary period for 60 days. No wash-out period. No mention of migraine history, inclusion criteria, or withdrawals. Jadad score: 3.
Allocation concealment	B – Unclear

Study	Pfaffenrath 2002
Methods	Randomised, placebo-controlled, double-blind trial. Four parallel groups. Treatment study.
Participants	147 patients aged (mean, sd) 43, 11) years. Data from all 147 patients evaluated. Migraine with and without aura (IHS diagnostic criteria).
Interventions	2.08, 6.25, 18.75 mg CO2 extract three times daily for 3 months.
Outcomes	Number of migraine attacks. Duration and intensity of migraine attacks.
Notes	According to the intention-to-treat analysis, a dose-response relationship could not be observed. Jadad score: 5.
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	de Weerdt 1996
Methods	Randomised, placebo-controlled, double-blind trial. Crossover. Treatment study.
Participants	50 patients aged 18-64 years. Data from 44 patients evaluated. Migraine with and without aura (IHS diagnostic criteria).
Interventions	One capsule (143 mg) of granulated feverfew daily for 4 months.
Outcomes	Frequency and severity of headache.
Notes	A different drug preparation was used. 1-month placebo run-in period. No wash-out period. Jadad score: 5.
Allocation concealment	A – Adequate

Abbreviation: IHS = International Headache Society

Characteristics of excluded studies

Kuritzky 1994 No clinical outcomes reported.

GRAPHS AND OTHER TABLES

This review has no analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

Migraine Disorders [*prevention & control]; *Phytotherapy; Plant Extracts [therapeutic use]; Randomized Controlled Trials; *Tanacetum parthenium

MeSH check words

Humans

COVER SHEET

Title	Feverfew for preventing migraine
Authors	Pittler MH, Ernst E
Contribution of author(s)	Information not supplied by author
Issue protocol first published	2000/3
Review first published	2000/3
Date of most recent amendment	05 January 2006
Date of most recent SUBSTANTIVE amendment	18 November 2003
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author

Date new studies found and included/excluded	18 November 2003
Date authors' conclusions section amended	18 November 2003
Contact address	Dr Max Pittler Research Fellow Department of Complementary Medicine Peninsula Medical School, Universities of Exeter and Plymouth 25 Victoria Park Road Exeter Devon EX2 4NT UK E-mail: max.pittler@pms.ac.uk Tel: +44 1392 424872 Fax: +44 1392 427562
DOI	10.1002/14651858.CD002286.pub2
Cochrane Library number	CD002286
Editorial group	Cochrane Pain, Palliative and Supportive Care Group
Editorial group code	HM-SYMPT