

# The combined effect of acupuncture and *Tanacetum parthenium* on quality of life in women with headache: randomised study

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Accepted 31 July 2012

## Abstract

**Background** The aim of the present study was to investigate the efficacy and tolerability of acupuncture (AC), *Tanacetum* (TAN) or combined treatment on quality of life in women with chronic migraine (CM).

**Methods** A total of 69 women volunteers were randomly divided into 3 groups: AC, acupuncture administered in 20 sessions over 10 weeks (n=22); TAN, at 150 mg/day (n=23); and AC+TAN (n=23). The primary outcome was Short-Form 36 (SF-36) quality of life assessment score. Secondary outcomes included the Migraine Disability Assessment (MIDAS) and visual analogue scale (VAS) score experienced after randomisation.

**Results** AC+TAN was statistically significantly more effective than AC or TAN alone in overall health-related quality of life (SF-36; p<0.05), on MIDAS score (−35.1 (10.6) AC vs −24.8 (11.7) TAN vs −42.5 (9.8) AC+TAN; p<0.05) and in reducing the mean score of pain on VAS (−5.6 (2.4) AC vs −3.7 (2.1) TAN vs −6.4 (3.1) AC+TAN; p<0.05).

**Conclusions** The present work shows an improvement of the quality of life and better analgesic effect of acupuncture combined with TAN treatment on migraine pain in women when compared with acupuncture or TAN alone.

## INTRODUCTION

In Western societies, headache is one of the most common symptoms. In a nationwide survey, 21% of men and 36% of women reported headache in the previous week.<sup>1</sup> Guidelines recommend treatment with several drugs for patients with chronic headache.<sup>2–3</sup> To avoid the risk of a drug-elicited headache, patients often request therapies without drugs. One of the most frequent non-pharmacological treatments used in patients with headache is acupuncture, and previous studies have compared the effectiveness of acupuncture and drug treatment.<sup>4</sup> According to the second edition of the International Classification of Headache Disorders (ICHD-II) criteria, chronic migraine

(CM) is characterised by headache on at least 15 days per month, of which at least 8 headache days per month meet the criteria for migraine without aura or response to migraine-specific treatment.<sup>5–6</sup> It is believed that medication overuse contributes to its development and blocks attempts at prevention.<sup>7</sup> Approximately 1.4% to 2.2% of the general population suffers from CM.<sup>8–12</sup> Patients with CM present a clinical treatment challenge. This population is associated with significant disability, psychological distress, reduced health-related quality of life and considerable healthcare costs.<sup>13–15</sup>

Acupuncture has a long tradition of use for the prevention and treatment of many pain conditions, including migraine.<sup>16</sup> According to international criteria, acupuncture seems to be a cost-effective treatment.<sup>17</sup> Moreover, there are fewer adverse effects associated with this treatment than with many standard drug treatments used for CM management.

Despite the great diversity among the various therapeutic approaches used in the different studies, in 2001 a first systematic Cochrane review on idiopathic headache judged acupuncture to be effective, although the proof of its efficacy was limited by methodological or reporting shortcomings in the studies.<sup>18</sup> Commonly, patients use many different herbs in combination with acupuncture. Although they are not conclusive, many studies show success when herbs are used in combination with acupuncture.<sup>19–22</sup>

The clinical management of patients with migraine remains unsatisfactory because benefit from even the most potent analgesic agents is limited.<sup>23</sup> Thus, greater emphasis has recently been placed on the prevention of attacks rather than on ingesting analgesic drugs during the attacks. Herbal treatments using various plant species are currently employed to prevent and treat headache and migraine, since several plant extracts have inhibitory effects on different parameters associated with the aetiology of migraine (eg, inhibition of platelet aggregation, eicosanoid

biosynthesis, phospholipase A2 and 5-hydroxytryptamine (5-HT) release).<sup>24</sup> *Tanacetum parthenium*, popularly called feverfew, is a herbal medication whose potential medical properties and notable headache relief were recognised even as far back as medieval times,<sup>25</sup> and it has been studied for migraine prophylaxis as well as for reduction of fever and inflammation.<sup>26</sup> Parthenolide, the sesquiterpene lactonic derivative that is the major component in the plant, may be one of its active ingredients.<sup>27 28</sup> Parthenolide is active against the mediators of inflammation, including cytokines.<sup>29 30</sup>

A number of clinical trials have demonstrated a good risk–benefit ratio for feverfew in the prophylactic treatment of migraine.<sup>31</sup> About 70% of patients claimed their migraine attacks were less frequent or less painful after consuming fresh leaves of feverfew for 2.5 years.<sup>32</sup> The patients taking feverfew also suffered a far lower incidence of nausea and vomiting.<sup>33</sup> Concerning the safety and tolerability of feverfew, there is no evidence of serious adverse effects in clinical trials or in self-reporting long-term users. Nonetheless, up to now the clinical efficacy of feverfew in the prevention of migraine has not been established beyond reasonable doubt.<sup>34</sup>

Given the controversy surrounding the use of acupuncture and feverfew for the treatment of pain syndromes related to migraine, the aim of this study was to test the effect of acupuncture treatment on symptoms and quality of life in women with migraine without aura, comparing it to a feverfew protocol and a combined acupuncture/feverfew treatment.

## METHODS

### Patients

The study was carried out at the general outpatient service of the Instituto Paulista de Estudos Sistêmicos, Brazil, in accordance with the Declaration of Helsinki, and enrolled 94 patients, diagnosed as migraine without aura following the International Classification of Headache Disorders.

The inclusion criteria were as follows: women patients between 18 and 56 years of age with a diagnosis of migraine without aura according to International Headache Society criteria;<sup>1</sup> migraine attacks for at least 1 year and age at onset <50 years; an average of two to six migraine attacks per month within the last 3 months prior to study entry; two to six migraine attacks within the 4-week baseline period; a total of at least 36 h with migraine during the baseline period; stable drug treatment regimen for migraine attacks; patients' ability to distinguish between migraine and other headaches; no prophylactic migraine treatment within 4 weeks prior to screening.

The exclusion criteria were: hypersensitivity to study medication; pregnancy; intake of analgesics, ergot preparations or other established drugs for the acute migraine attack on >10 days per month, the use of antidepressants, neuroleptics, tranquillizers, medications for headache prophylaxis, medications with headache as side

effect, magnesium-containing drugs as well as additional non-drug therapies for migraine; >10 days with headaches other than migraine per month; experience with more than three different migraine prophylactic drugs in the past; drug misuse or dependency; expected lack of compliance; psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV); confirmed diagnosis of gastrointestinal or cardiovascular complaints; other severe diseases including hepatic, renal, gastrointestinal, pulmonary, cardiac, metabolic or endocrine disorders; participation in other clinical trials within the last 3 months or simultaneous participation in another clinical investigation.

After the inclusion/exclusion criteria were applied, 69 patients were eligible (figure 1). According to a predetermined computer-generated randomisation list, the eligible patients were randomly and blindly assigned to the following three groups: acupuncture group (AC; n=16) (average age 33.93 years, range 18–50), *Tanacetum* group (TAN; n=16) (average age 35.2 years, range 19–56) and TAN/AC group (n=16) (average age 34.2 years, range 19–52).

Before enrolment, each patient was asked to give an informed consent to participation in the study. The intake of migraine preparations for treatment of acute attacks was permitted, but had to be stable during the trial.

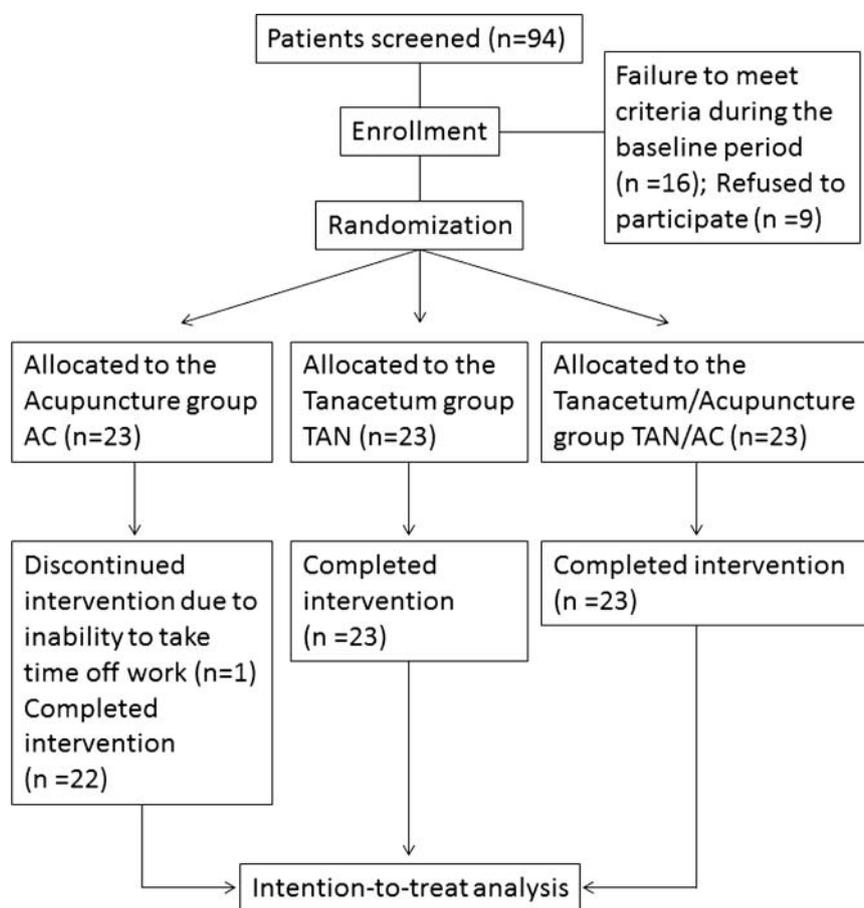
### Clinical assessments

All participants began the study by completing a set of outcome measures: the Migraine Disability Assessment (MIDAS), Short-Form 36 (SF-36) and visual analogue scale (VAS) rated from 0 (pain free) to 10 (unbearable pain). All three questionnaires were administered on day 1 of the baseline period and repeated at the end of the treatment phase. To ensure consistency, the evaluating doctor was the same person on each occasion for each patient, and was blinded to the type of treatment.

### Treatments

The acupuncture protocol consisted of 20 sessions of 30 min, administered over 10 weeks (two sessions per week).<sup>35</sup> Each patient had fixed and classic acupuncture points, bilateral *Shuai Gu* (GB8), *Yang Bai* (GB14), *Bai Hui* (GV20), *Shen Men* (HT7), *Xing Jian* (LR2) and *He Gu* (LI4) in their 10 sessions without modification for the specific symptoms of the patient. We placed patients in the sitting position and acupuncture needles were tapped into place through sterile plastic guide tubes. At each point, the needle was manipulated by twirling with lifting–thrusting slowly until the participant felt *de qi* (an awareness of warmth, numbness, soreness, swelling, heaviness or radiation deemed to indicate proper needle position and effective needling).

Eleven sterile disposable steel needles (gauge and size: 0.25 mm×40 mm) were used without electrical stimulation or moxibustion. Participants were free to discontinue the treatment any time, for any reason. All treatments



**Figure 1** Flow chart of study.

were performed by one acupuncturist at the same facility, and the acupuncturist was asked to have the least possible communication with the patients to minimise bias in conformance to the standards for reporting interventions in controlled trials of acupuncture (STRICTA, table 1).<sup>36</sup>

The *T parthenium* leaves were harvested at the onset of flowering. After harvesting, the leaves were washed in water and soaked in a solution of 0.5% (v/v) sodium hypochloride for 10 min in order to reduce bacterial contamination. After rinsing in water, the leaves were dried in a stove heated to 45°C and then stored at 4°C until the onset of the clinical experiment. A total of 150 mg of fine-powdered leaves was packed in small gelatine capsules. Patients assigned to the TAN groups also underwent treatment for 10 consecutive weeks. During this period, participants took *T parthenium* 150 mg/day at bedtime.<sup>26</sup> All participants were required to follow the same schedule. Patients assigned to the TAN plus acupuncture group received both treatments for 10 consecutive weeks.

We required that the acute headache medication be the same throughout the baseline period and for the duration of treatment period, and this was documented daily throughout the course of the study. After enrolment, participants in the TAN group were required to return for a doctor visit once a week during the period, and then

return to monitor any adverse effects (AEs) of the drug at the end of treatment period. Participants in the acupuncture group were seen twice a week for acupuncture treatment and to monitor AEs in each session for the whole 10 weeks (20 visits in total). We recorded AEs such

**Table 1** Standards for reporting interventions in controlled trials of acupuncture (STRICTA)

Acupuncture rationale and needling details	
Fixed and classic acupuncture points	GB8, GB14, GV20, HT7, LR2 and LI4 in the 10 sessions
Depth of insertion	Standard to each point according to classic acupuncture point
Responses elicited	<i>De qi</i> sensation
Manual	Twirling with lifting-thrusting method
Time	Needles retained 30 min
Needle type	Stainless steel; 32 (Chinese) gauge, 25–40 mm (body points); gauge and size: 0.25×40 mm
Treatment regimen	Twice per week for 10 weeks
Cointerventions	None: no herbs, moxibustion, cupping, rehabilitation, advice regarding dietary or lifestyle modifications
Practitioner background	License certified by SOBRAFISA (Brazilian Society of Acupuncture and Physiotherapy)

**Table 2** Baseline demographics and characteristics of the three groups

	AC	TAN	AC+TAN
N	22	23	23
Age, years	38.2 (7.4)	37.3 (8.6)	40.6 (9.1)
Duration of CM, years	12.2 (3.8)	11.6 (5.6)	12.4 (3.2)
Mean headache days per month	20.6 (1.6)	24.2 (2.3)	23.5 (2.1)
Mean moderate/severe headache days per month	19.8 (2.1)	21.7 (2.3)	20.4 (1.6)
Mean VAS	8.3 (1.3)	8.5 (0.9)	8.9 (1.1)
Mean MIDAS score	60.1 (5.6)	60.3 (6.2)	60.4 (5.1)
Mean domain of SF-36			
Physical function (PF)	63.3 (9.2)	61.6 (8.1)	63.8 (9.4)
Role physical (RP)	50.2 (8.6)	49.6 (8.9)	49.8 (6.8)
Bodily pain (BP)	52.8 (3.7)	51.4 (7.3)	51.1 (5.2)
General health (GH)	49.8 (8.9)	47.6 (6.7)	49.7 (8.9)
Vitality (VT)	38.7 (7.0)	37.2 (6.9)	38.1 (5.1)
Social functioning (SF)	60.7 (6.4)	62.2 (7.7)	61.9 (7.2)
Role emotion (RE)	49.9 (12.3)	48.4 (11.6)	51.4 (11.6)
Mental health (MH)	56.5 (8.3)	56.7 (8.0)	55.6 (7.9)

Values are n, mean (SD).

AC, acupuncture; CM, chronic migraine; MIDAS, Migraine Disability Assessment; SF-36, Short-Form 36; TAN, Tanacetum; VAS, visual analogue scale.

as nausea, dizziness, paraesthesia, fatigue, dyspepsia, somnolence and rash for all enrolled patients.<sup>37</sup>

The statistical analysis was conducted by means of factorial analysis of variance (ANOVA) with groups and time (three levels and two points) and multiple test with Bonferroni adjustment, for a significance level of  $p=0.05$ . All statistical analyses were performed using SPSS V.15.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

## RESULTS

A total of 69 patients who were eligible and agreed to participate in our study were randomly allocated to either the acupuncture or TAN treatment groups. Of the 69 patients, one patient in the acupuncture group dropped out owing to an inability to take time off work.

**Table 3** Mean changes from baseline of the three groups

Category	AC	TAN	AC+TAN	F	p Value	Order
Mean VAS	-5.6 (2.4)	-3.7 (2.1)	-6.4 (3.1)	4.201	0.021	AC+TAN>AC>TAN
Mean MIDAS score	-35.1 (10.6)	-24.8 (11.7)	-42.5 (9.8)	4.022	0.025	AC+TAN>AC>TAN
Mean domain of SF-36						
Physical function (PF)	13.3 (5.3)	13.1 (6.1)	16.7 (5.7)	5.257	0.044	AC+TAN>AC>TAN
Role physical (RP)	27.2 (6.6)	18.3 (5.9)	31.3 (4.8)	5.281	0.017	AC+TAN>AC>TAN
Bodily pain (BP)	18.5 (9.7)	13.3 (8.3)	24.4 (8.7)	4.399	0.018	AC+TAN>AC>TAN
General health (GH)	12.3 (4.3)	7.9 (3.7)	14.7 (5.6)	2.967	0.031	AC+TAN>AC>TAN
Vitality (VT)	8.2 (3.1)	5.7 (2.9)	6.3 (2.2)	3.539	0.041	AC+TAN>AC>TAN
Social functioning (SF)	15.2 (2.3)	11.2 (3.4)	16.9 (2.2)	4.119	0.008	AC+TAN=AC>TAN
Role emotion (RE)	15.9 (12.3)	12.4 (8.6)	21.5 (9.7)	4.382	0.023	AC+TAN>AC>TAN
Mental health (MH)	16.3 (5.3)	13.7 (2.0)	16.6 (6.1)	3.621	0.033	AC+TAN=AC>TAN

Values are mean change (SD).

F and p values from analysis of variance (ANOVA) to compare the mean changes from baseline between groups

AC, acupuncture; MIDAS, Migraine Disability Assessment; SF-36, Short-Form 36; TAN, *Tanacetum*; VAS, visual analogue scale.

The randomised groups were comparable with regard to baseline characteristics (see table 2). The acupuncture (AC) treatment group showed a significantly greater improvement when compared to TAN treatment in overall health-related quality of life (SF-36) ( $p<0.05$ ), as measured by changes from baseline for all participants (table 3).

Statistically significant and clinically meaningful differences for acupuncture with TAN versus acupuncture or TAN were observed in the mean change from baseline to endpoint in MIDAS score for all participants ( $p<0.05$ ) (table 3).

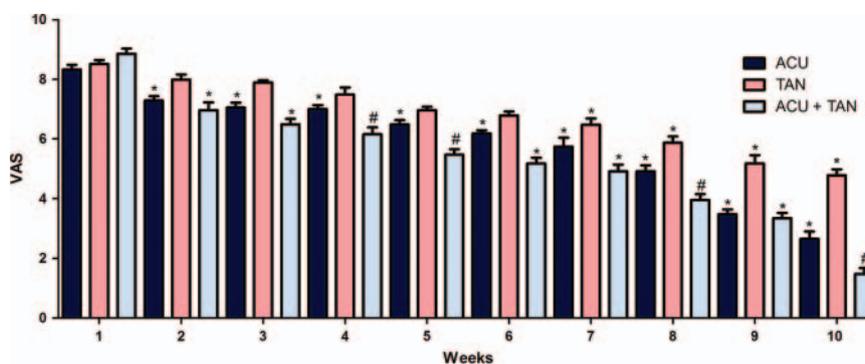
There was a substantial mean reduction from baseline in the VAS outcome measure in both treatment groups (table 3). However, AC+TAN was statistically significantly more effective than AC or TAN alone in reducing the mean of score of pain in VAS (-5.6 (2.4) AC+TAN vs -3.7 (2.1) AC vs -6.4 (3.1) TAN;  $p<0.05$ ) (table 3).

We found significant differences for all three groups compared with first week for the VAS during the 10-week period of treatment (figure 2). We also found that the AC+TAN group reported greater improvement of migraine compared with patients in the control acupuncture or TAN alone.

## DISCUSSION

A clearly described procedure for acupuncture treatment following the STRICTA guidelines makes our study reproducible,<sup>36</sup> and our study demonstrated the efficacy in the prophylactic treatment of CM in both the treatment groups. We found a significant improvement in overall health-related quality of life (SF-36), reduction in pain and MIDAS score.

Current theories suggest that migraine is a neurovascular disorder involving cortical spreading depression, neurogenic inflammation and vasodilation.<sup>38</sup> Sensitisation and facilitation of pain transmission in central trigeminal sensory pathways may have a particularly important role in the development of CM.<sup>39</sup>



**Figure 2** Mean of visual analogue scale (VAS) score for migraine during the study period of 10 weeks. Baseline was collected during the first week period. \* $p < 0.05$  from baseline, # $p < 0.05$  difference of all groups. Groups: AC, acupuncture; AC+TAN, acupuncture and Tanacetum; TAN, Tanacetum.

Despite major recent advances in our understanding of migraine pathophysiology, migraine treatment is far from being satisfactory. Serotonin has been consistently implicated in migraine,<sup>40–43</sup> which is suggestive too of a role for its receptors. In particular, 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors are considered to be the main molecular targets of sumatriptan and congeners in acute treatment,<sup>44–45</sup> whereas 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors are targeted by 5-HT antagonists, such as methysergide, oxetorone, pizotifen and cyproheptadine, which are used in migraine prophylaxis.<sup>46–48</sup>

The mechanism of action of TAN is not well understood, but 5-HT receptor-blocking properties have been reported,<sup>49–52</sup> and inhibition of binding to 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors, and to a lesser extent 5-HT<sub>1B</sub> receptors,<sup>53</sup> has been suggested to play a role.

There are several limitations to our study that deserve consideration. The most relevant is the use of an active comparator without sham controls, which cannot rule out the possibility of a placebo effect. A high placebo response has been observed in migraine prophylaxis studies, which may also contribute to the between-group difference observed in our study.<sup>54</sup> Another limitation of our trial includes a short follow-up period and self-reported outcome measures, despite MIDAS outcome being demonstrated valid in short periods of evaluation.<sup>55–56–57</sup>

Regarding the safety of TAN, the users who were admitted to this study tolerated the daily intake of leaves well and complained only of the herb's disagreeable flavour, but with no side effects.

Moreover, the consistency of the analgesic effect of acupuncture and TAN on migraine pain in women, and eventually, for the prophylactic treatment of migraine without aura, needs to be tested and confirmed in larger controlled studies.

In summary, women patients with headache treated with acupuncture showed significant improvements in symptoms and quality of life. When TAN was combined to acupuncture the results were better when compared with patients who received acupuncture or TAN alone.

These findings indicate that the benefits of the acupuncture treatment were clinically meaningful to the patients with CM. It can thus be concluded that acupuncture treatment has a superior efficacy when associated with TAN treatment for women patients with CM.

### Summary points

- ▶ Both Tanacetum (feverfew) and acupuncture are effective for preventing migraine.
- ▶ This RCT shows their combination is more effective than either therapy alone.

**Contributors** ECF and APB were the major performers of the experiments and APB drafted the manuscript. MLS and JRJS were actively involved in the studies including treatment experiments, outcomes, data analysis, etc. IEFs provided essential technical support all through the experiments and gave helpful suggestions. JRJS was the principal designer of the studies and was responsible for all aspects of this work. MLS also critically revised the manuscript.

**Funding** This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** The authors declare that they have no competing interests.

**Patient consent** Obtained.

**Ethics approval** This study was conducted with the approval of Research Ethics Committee of the Clinics Hospital of the Faculty of Medicine of Ribeirão Preto, University of São Paulo.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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## The combined effect of acupuncture and *Tanacetum parthenium* on quality of life in women with headache: randomised study

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*Acupunct Med* published online September 8, 2012  
doi: 10.1136/acupmed-2012-010195

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