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Original article

Evidence for the efficacy of complementary and alternative medicines in the management of fibromyalgia: a systematic review

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Abstract

Objective. To critically evaluate the evidence regarding complementary and alternative medicines (CAMs) taken orally or applied topically for the treatment of FM.

Methods. Randomized controlled trials of FM using CAMs, in comparison with other treatments or placebo, published in English up to March 2009, were eligible for inclusion. They were identified using systematic searches of bibliographic databases and manual searching of reference lists. Information was extracted on outcomes, and statistical significance, in comparison with alternative treatment or placebo, and side effects were reported. The methodological quality of the primary studies was determined.

Results. Single studies on four CAMs, and three on different approaches to homeopathic care were identified. Their methodological quality was moderate. The homeopathy studies were small, but each reported an improvement in pain. The effects of anthocyanidins, capsaicin and *S*-adenosylmethionine each showed at least one statistically significant improved outcome compared with placebo. However, the studies of anthocyanidins and capsaicin only demonstrated an improvement in a single outcome, sleep disturbance and tenderness, respectively, of several outcomes considered. No evidence of efficacy was found regarding Soy in a single study. Most of these CAMs were free of major adverse effects and usually associated with only minor adverse effects such as dizziness, nausea and stomach upsets.

Conclusion. There is insufficient evidence on any CAM, taken orally or applied topically, for FM. The small number of positive studies lack replication. Further high-quality trials are necessary to determine whether these initial findings can be supported by a larger evidence base.

Key words: Fibromyalgia, Complementary and alternative medicine, Anthocyanidins, Capsaicin, Soy, *S*-adenosylmethionine, Homeopathy.

Introduction

FM is a chronic, generalized pain syndrome that affects the musculoskeletal system. It is characterized by widespread pain, the presence of multiple tender points, fatigue and sleep disturbances without any structural or inflammatory cause [1]. It is a common problem among the attendees to rheumatology clinics and usually amounts to 10–20% of new visits [2]. In 1990, the ACR proposed classification criteria for FM: these required chronic widespread pain, i.e. pain on both sides, upper and lower parts of the body and in the axial skeleton for at least 3 months, and presence of tenderness at 11 or more

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of 18 specific sites [3]. Prevalence in the general population has been reported as 2% in the USA and 3.3% in Canada and 0.7% in Denmark and Sweden [2, 4–6]. Studies consistently demonstrate a female predominance of the disease [2, 4–6] and show that FM is more frequent in older age and with lower levels of education [5].

A large number of different therapies for FM have been described. The European League Against Rheumatism (EULAR) has reviewed the available evidence and published guidelines for the treatment of FM in 2008 [6]. This guideline consists of nine specific recommendations [7].

Due to the chronic nature of the disease, its effects on quality of life, and the fact that most treatments will result only in modest improvement in symptoms and function, patients commonly try alternative methods of treatment [8]. These treatment methods are commonly categorized as complementary and alternative medicines (CAMs). The World Health Organization has defined CAM as 'A broad set of health care practices that are not part of the country's own tradition and are not integrated into the dominant healthcare system' [9]. Usage of CAM seems to be increasing in industrialized countries [10]. In the UK, for example, 46% of people use CAM during their lifetime and about 10% of the population will visit a complementary medical practitioner each year [11].

CAM is most popular among patients who are suffering from diseases for which conventional therapies have failed to offer a cure or satisfactory control [12]. Rheumatological problems are among the commonest disease conditions encountered by CAM practitioners with around four in five of their consultations related to rheumatological conditions [13]. For FM patients, CAM usage can be close to 100% [14, 15].

Given this popularity, it is important that patients and practitioners have accessible and clear evaluation of the efficacy and safety of these treatments. The purpose of the review is to summarize and critically evaluate the evidence from randomized controlled trials (RCTs) regarding CAMs taken orally or applied topically for the treatment of FM. We have ensured that, where possible, we report the conduct and results of the review according to the recently published guidelines on Transparent Reporting of Systematic Reviews and Meta-Analyses (PRISMA; http://www.prisma-statement.org/).

Methods

Eligibility criteria

The following criteria were used to select the articles: (i) the study was an RCT involving a CAM; (ii) the route of administration was oral or topical; (iii) comparison was made with placebo or other treatment; (iv) a complementary medicine substance was available in the UK; (v) involved human subjects with FM; (vi) the study used recognized criteria for FM; and (vii) the study was published in English. Publications up until the end of March 2009 were included in the review.

Information sources

Publications included in the present review were retrieved using computerized searches of the following databases: EMBASE (1980 to March 2009), Ovid MEDLINE (1950 to March 2009), Allied and Complementary Medicine (1985 to March 2009), EBM Reviews—ACP Journal Club (1991 to March 2009), EBM Reviews—Cochrane Central Register of Controlled Trials (First Quarter 2009), EBM Reviews—Cochrane Database of Systematic Reviews (First Quarter 2009) and EBM Reviews—Database of Abstracts of Reviews of Effects (First Quarter 2009).

Search

Two hundred and eighteen names of complementary medicinal substances that are commonly used in rheumatic diseases and the key words: alternative medicine, complementary medicine, fibromyalgia, (randomized controlled) trials, (systematic) reviews and meta-analysis were used in the search.

Study selection

Two reviewers independently screened the titles of the selected articles and excluded duplicates and those obviously irrelevant. Abstracts of the selected articles were examined independently by two reviewers who applied the selection criteria. If the information in the abstracts was insufficient to make a decision, full papers were retrieved and used for this purpose. The references of all selected relevant articles including systematic reviews and meta-analysis were manually searched to obtain additional relevant publications. During consensus meetings, disagreements of selections were resolved.

Data extraction and items

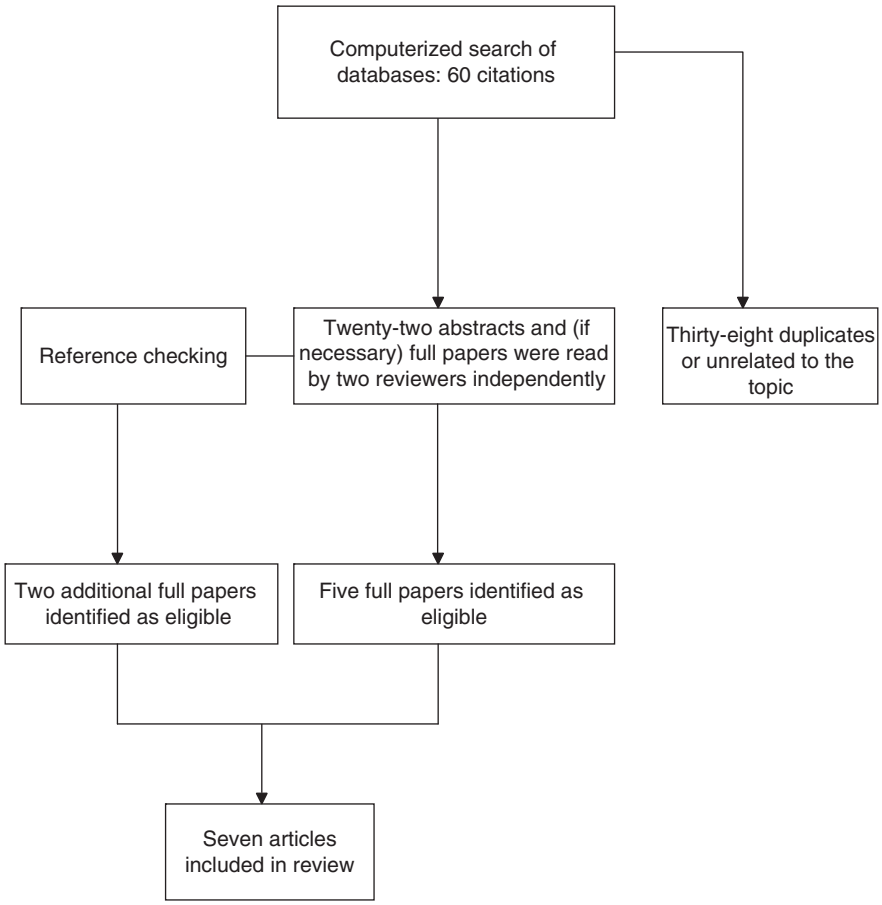
Data were extracted by a single reviewer and checked by a second reviewer. Data extracted were: CAMs under investigation, number of persons recruited to the trial, length of follow-up, outcome measurements studied, data on statistical significance of change of CAM treatment in relation to the comparator and side effects reported. The 5-point Jadad scoring system was used to assess the methodological quality of the selected trials with increasing score indicating a higher quality of study [16].

Results

Study selection

A total of 60 citations were identified through our searches. From these, 38 were excluded by examination of their titles. Excluded studies were mainly duplicates, studies on rheumatic diseases other than FM, study designs other than RCTs, studies on fractures, studies of other forms of complementary medicine such as acupuncture and massage, studies on animals and studies published in languages other than English. Abstracts of the remaining 22 articles and studies identified by the screening of references of relevant original and review articles were scrutinized by the two reviewers. From this

Fig. 1 Process of selecting articles for inclusion in the review.



process, a total of seven RCTs were included in the review. The process of identifying relevant studies is detailed in Fig. 1.

Study characteristics and results

There were single RCTs identified for four CAMs used in FM and three RCTs concerning different approaches to homeopathic care (Table 1).

Anthocyanidins. This is a food supplement that belongs to the flavonoid group of plant-derived chemicals. It has been commonly used for the treatment of chronic diseases. We found one RCT that tested the efficacy of anthocyanidins in the treatment of FM compared with a placebo group. The product used in this study is available in the UK under the trade name of Colladeen. Anthocyanidins in this product were derived from grape seeds, bilberries and cranberries. Only 12 patients participated in a cross-over study, where all patients received four different treatments in sequence. The order of assignment to treatment was randomly determined: anthocyanidins 120, 80 and 40 mg/day or an indistinguishable placebo capsule. The total trial period was 52 weeks with each treatment given for 12 weeks, preceded by a 4-week baseline period. There were no wash-out periods between treatments. Pain, fatigue and sleep disturbances were measured as the outcomes, and all were recorded using a 5-point scale: for pain and fatigue, from 'no symptoms' to 'very severe symptoms' and for sleep, from 'sleep well all night' to 'sleep very severely affected by FM'. Only sleep disturbance was significantly improved by active treatment. The largest improvement was observed with the dose of 80 mg/day ($P = 0.004$). No significant improvements were observed in pain or fatigue scores. Minor adverse effects such as indigestion, nausea and sinusitis were reported [17].

Capsaicin. This is a herbal medicinal extract from chili peppers. One RCT tested the efficacy of the local application of 0.025% capsaicin in the treatment of FM compared with a placebo cream. The product used in this study is available under the trade name of Zostrix. Forty-five patients were randomly assigned to one of the four groups: (i) right side, 0.025% capsaicin; left side, control; (ii) right, placebo; left, control; (iii) right, control; left, 0.025% capsaicin; and (iv) right, control; left, placebo. After 4 weeks of double-blind treatment, patients were reassessed for pain, tenderness and quality of sleep. Pain and quality of sleep were assessed using a visual analogue scale (VAS), whereas tenderness was measured

TABLE 1 RCTs of CAMs in the treatment of FM

References	CAM compound studied	Comparison group	Sample size	Jadad score	Outcome measured	Duration of study	Outcome of the study in CAM treatment *vs* comparison group
Edwards *et al*. [17]	Anthocyanidins	Placebo	12	3	Pain, fatigue, sleep disturbance	52 weeks	Significant improvement in sleep disturbance
McCarty *et al*. [18]	Capsaicin topical application	Placebo	45	4	Pain, tenderness quality of sleep	4 weeks	Significant improvement in tenderness
Wahner-Roedler *et al*. [19]	Soy dietary supplement	Placebo	50	4	Scores of FIQ and CES-D	6 weeks	No significant difference in outcome measurements
Jacobsen *et al*. [20]	SAMe	Placebo	44	3	Tenderness, pain, fatigue, morning stiffness, mood, clinical disease activity, tender point score, muscle strength	6 weeks	Significant improvements in pain, fatigue, morning stiffness, mood and clinical disease activity
Fisher *et al*. [21]	Homeopathy (*R. toxicodendron*)	Placebo	30	3	Tenderness, pain, sleep disturbance	2 months	Significant improvement in tenderness, pain and sleep was observed
Fisher [22]	Homeopathy (*Arnica, Bryonia, R. toxicodendron*	Placebo	24	1	Pain, sleep	3 months	Significant improvement in pain and sleep
Bell *et al*. [23]	Homeopathy treatment	Placebo	62	5	Tenderness, tender point pain, tender point count, quality of life, global health, depression	4 months	Significant improvement in tender point pain, tender point count, quality of life and global health and depression

using a dolorimeter. Significant improvement of tenderness was associated with capsaicin. However, there was no improvement in pain or quality of sleep. Transient stinging or burning at the application sites were reported as adverse effects. Due to the burning effect of capsaicin on the skin, it is questionable whether this trial was double-blind [18].

Soy. The efficacy of this commonly used dietary supplement has been tested in one RCT. Fifty patients were randomly assigned to receive either Soy or placebo shakes (casein) once a day for a period of 6 weeks. Patients were assessed with the FM Impact Questionnaire (FIQ) and the Centre of Epidemiologic Studies Depression (CES-D) scale at baseline and after 6 weeks of treatment. There was no statistically significant benefit of Soy compared with placebo. No adverse effects were reported [19].

S-adenosylmethionine. The chemical compound of this nutritional supplement is derived from two acids: methionine, an amino acid, and adenosine triphosphate, a nucleic acid. One RCT compared the efficacy of *S*-adenosylmethionine (SAMe) with placebo. Forty-four patients with FM were randomly assigned to receive either SAMe 400 mg tablet or identical placebo tablets twice a day for a period of 6 weeks. Pain, fatigue, quality of sleep and clinical disease activity were measured using a VAS. After the treatment, significant improvements were observed in pain experienced during the last week ($P = 0.002$), clinical disease activity ($P = 0.04$), morning stiffness ($P = 0.03$), fatigue ($P = 0.02$) and mood evaluated by face scale ($P = 0.006$) among the SAMe-treated patients compared with the placebo group. However, there was no significant difference in tender point score, mood (evaluated by the Beck Depression Inventory) or isokinetic muscle strength. Mild adverse effects such as stomach upset and dizziness were reported [20].

Homeopathy. Three RCTs compared the efficacy, against placebo, of three different homeopathic approaches. In the first trial, 30 patients were randomly assigned to receive either *Rhus toxicodendron* (6c potency) put up on 125 mg lactose or identical placebo tablets three times per day [21]. This was a cross-over study with treatment phases of 1 month each in random sequence. Patients receiving the active treatment had significantly fewer tender points ($P < 0.005$), improved pain and sleep ($P < 0.005$), as assessed by VAS. Only patients in whom '*Rhus toxicodendron* was positively indicated after a homeopathic consultation' were included in this trial. In the second trial, 24 patients were allocated to receive one remedy from *Arnica montana*, *Bryonia alba* and *R. toxicodendron* (all of 6c potency) based on a homeopathic consultation or a matching placebo [22]. All the patients received the same treatment throughout a 3-month period. Homeopathic treatments significantly improved pain ($P < 0.05$) and sleep ($P < 0.05$) compared with placebo as assessed by VAS. This study received the lowest quality score. In the third trial, 62 patients were

randomly assigned to receive either an individually selected homeopathic remedy or placebo [23]. In this study, pain was assessed using the McGill Pain Questionnaire [24], quality of life was assessed using the FM quality of life scale [25] and global health was assessed using a global self-rated health scale [26]. After 4 months of treatment, patients who received homeopathic remedies demonstrated significantly better improvements in tender point pain, tender point count, quality of life, global health and depression compared with patients who received placebo. This study received the highest quality score. Allergic reactions were reported as adverse effects.

Discussion

Summary of evidence

The present review was carried out to determine the efficacy of CAMs in treating FM using the available evidence in the form of published RCTs. The review was limited to CAMs that were used orally or topically. The major finding of the review is that there is little evidence available to permit firm conclusions about the efficacy of any CAM in the treatment of FM.

There was some evidence from three small studies regarding three different homeopathic approaches. Each demonstrated an improvement in pain in those receiving the standardized or individualized homeopathic remedy (compared with placebo) and two studies demonstrated improvement in sleep. While one of these trials received the lowest of all Jadad scores [22], another received the maximum score [23]. The third study [22] has been independently re-analysed and 'no firm support for the efficacy of homeopathic treatment' was found [27]. The effects of anthocyanidins, capsaicin and SAMe have only been reported in a single study, each of which showed some positive results. However, studies of anthocyanidins and capsaicin only demonstrated an improvement in a single outcome, sleep disturbance and tenderness, respectively, of several outcomes considered. No evidence of efficacy was found regarding Soy in a single study. Most of these CAM compounds were free of major adverse effects; minor effects reported included dizziness, nausea and stomach upsets. Capsaicin cream was associated with transient stinging or burning at the application sites.

Limitations

Interpretation and utilization of the above evidence, in practice, must be carried out with caution given some methodological concerns: there is insufficient evidence base for any compound; evidence regarding all CAMs except homeopathy are based on a single trial; and most of the trials were carried out using a small number of patients. According to the Jadad quality scoring system, the median score was 3, indicating that the trials were of moderate quality. Moreover, each of the homeopathy trials used different remedies. Thus all of these studies await independent replication. All of the RCTs included in this review had small sample sizes. Our review has several important limitations. Publication bias is a major concern in the interpretation since each of these compounds may have had other (unpublished) evaluations—given that the trials that show no effect are less likely to be published, it would only take a very small number of such unpublished null trials to outweigh the positive results shown for some compounds. We have selected only RCTs published in the English language for the present review. Therefore, we may have missed some evidence on CAM products published in other languages. In the search conducted as part of this review, however, only two studies were rejected because they were not available in English. Finally, although we have considered the therapies on an individual basis, this may not reflect the reality of how CAMs are commonly used or prescribed. Nevertheless, before consideration of the more complex question of the efficacy of combination of therapies, it is reasonable to consider whether there is any evidence that these approaches are efficacious individually.

Future research in this area should overcome the methodological flaws of the current data. In particular, sample sizes should be calculated based on the reliable pilot data, treatment periods should be long enough for a therapeutic effect to show, cross-over studies should include a wash-out period and trial reporting should follow the Consolidated Standards of Reporting Trials guidelines [28].

Conclusions

Although CAM is highly popular among FM patients, this review failed to find any RCT for many CAM compounds that are frequently used in its treatment. Even for those studied in RCTs, there is insufficient evidence for any single compound to make a conclusion on efficacy. Further methodologically robust trials are warranted to extend the evidence base.

Rheumatology key messages

- Most CAMs (taken orally or applied topically) for FM do not have any evidence available on their efficacy from RCTs.
- Of those tested in RCTs, there is insufficient evidence of efficacy for any single CAM.

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Appendix 1

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