

# COMMENTARY ON THE COCHRANE REVIEW OF CHINESE HERBAL MEDICINE FOR DYSMENORRHEA

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(*Explore* 2008; 4:389-391. © 2008 Published by Elsevier Inc.)

**P** primary dysmenorrhea, painful pelvic cramps associated with menstruation in the absence of identifiable pathology, is a common problem for women in their childbearing years. Due to its high prevalence and economic impact on women's working lives, primary dysmenorrhea has been identified as a major public health issue.<sup>1</sup>

Although useful pharmaceutical drugs such as the oral contraceptive pill and non-steroidal anti-inflammatory medicines are readily available to ease acute primary dysmenorrhea, women often seek complementary approaches, including traditional Chinese herbs. This article will evaluate a recent Cochrane review of Chinese herbs for primary dysmenorrhea.<sup>2</sup>

## ABSTRACT OF THE COCHRANE REVIEW

**Background:** Conventional treatment for primary dysmenorrhoea has a failure rate of 20% to 25% and may be contraindicated or not tolerated by some women. Chinese herbal medicine may be a suitable alternative.

**Objectives:** To determine the efficacy and safety of Chinese herbal medicine for primary dysmenorrhoea when compared to placebo, no treatment, and other treatment.

**Search Strategy:** The Cochrane Menstrual Disorders and Subfertility Group Trials Register (to 2006), MEDLINE (1950

to January 2007), EMBASE (1980 to January 2007), CINAHL (1982 to January 2007), AMED (1985 to January 2007), CENTRAL (The Cochrane Library, issue 4, 2006), Chinese National Knowledge Infrastructure (CNKI, 1990 to January 2007), Traditional Chinese Medicine Database System (TCMDS 1990 to December 2006), and the Chinese BioMedicine Database (CBM, 1990 to December 2006) were searched. Citation lists of included trials were also reviewed.

**Selection Criteria:** Any randomized controlled trials involving Chinese herbal medicines versus placebo, no treatment, conventional therapy, heat compression, another type of Chinese herbal medicine, acupuncture, or massage. Exclusion criteria were identifiable pelvic pathology and dysmenorrhoea resulting from the use of an intrauterine contraceptive device.

**Data Collection and Analysis:** Quality assessment, data extraction, and data translation were performed independently by two review authors. Attempts were made to contact study authors for additional information and data. Data were combined for meta-analysis by using either Peto odds ratios or relative risk (RR) for dichotomous data or weighted mean difference for continuous data. A fixed-effects statistical model was used, where suitable. If data were not suitable for meta-analysis, any available data from the trial were extracted and presented as descriptive data.

**Main Results:** Thirty-nine randomized controlled trials involving a total of 3475 women were included in the review. A number of the trials were of small sample size and poor methodological quality. Results for Chinese herbal medicine compared to placebo were unclear as data could not be combined (3 RCTs). Chinese herbal medicine resulted in significant improvements in pain relief (14 RCTs; RR 1.99, 95% CI 1.52 to 2.60), overall symptoms (6 RCTs; RR 2.17, 95% CI 1.73 to 2.73) and use of additional medication (2 RCTs; RR 1.58, 95% CI 1.30 to 1.93) when compared to use of pharmaceutical drugs. Self-designed Chinese herbal formulae resulted in significant improvements in pain relief (18 RCTs; RR 2.06, 95% CI 1.80 to 2.36), overall symptoms (14 RCTs; RR 1.99, 95% CI 1.65 to 2.40) and use of additional medication (5 RCTs; RR 1.58, 95% CI 1.34 to 1.87) after up to three months of follow-up when compared to commonly used Chinese herbal health products. Chinese herbal medicine also resulted in better pain relief than acupuncture (2 RCTs; RR 1.75, 95% CI 1.09 to 2.82) and heat compression (1 RCT; RR 2.08, 95% CI 2.06 to 499.18).

**Conclusions:** The review found promising evidence supporting the use of Chinese herbal medicine for primary dysmenorrhoea; however, results are limited by the poor methodological quality of the included trials.

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## COMMENTARY AND CRITIQUE OF THE REVIEW

This review explores research on the use of Chinese herbal medicines for primary dysmenorrhea. The authors developed a rigorous approach to their review, and importantly, were able to include Chinese language papers, which constituted 36 of the 39 papers evaluated. The review was pragmatic and included trials comparing Chinese herbs with a range of other treatments. The conclusion, that promising evidence was found to support the use of Chinese herbs for primary dysmenorrhea, is severely undermined by the poor quality of all the included trials.

Testing complementary approaches of healing by rigorous scientific evaluation can present difficulties. Randomized controlled trials (RCTs) were introduced to medicine by pharmaceutical researchers and aim to eliminate as much bias as possible to accurately test whether a therapy causes a health outcome. In pharmaceutical research, of course, drugs and placebo medicines can be precisely manufactured and measured to be identical in appearance and taste. Therefore, all researchers and participants can be blinded to the therapy used, while all other aspects of the experiment are kept constant. Although RCT methods fit well with the reductionist principles underpinning conventional medicine, care may be needed in testing with RCTs complementary approaches of healing, which are by their nature holistic.<sup>3</sup> Traditional Chinese Medicine (TCM) is based on an entirely different health/illness paradigm to conventional medicine, with different diagnoses and approaches to making a diagnosis and treatment. One hallmark of TCM is that practitioners individualize treatments and modify them during the patient's health journey. Therefore, the problems that might have arisen in this review include inability to find an equivalent TCM diagnosis for the conventional one of primary dysmenorrhea, lack of precisely defined and constant interventions and comparators, and lack of agreed outcome measures. However, the major problem was not due to paradigm differences between TCM and conventional medicine, but rather due to the methodological problems of the included trials, as discussed below.

Firstly, the lack of precisely defined and constant therapies or interventions is worth discussing further. Rather than being precisely defined, as expected in a drug trial, the interventions were a heterogeneous bunch, treated by the reviewers pragmatically as "black boxes"; some treatments were tailored, some changed over time, and both single herbs and combinations of different herbs were included. Loosely or undefined interventions may be also necessary in RCTs of conventional therapies, such as in trials of counseling practice or where a comparison group receives "usual care by general practitioner." Although this approach has its merits, it does also limit somewhat the applicability of the results of the review to both TCM and conventional practice. Only 23 studies used some modification of herbs to fit TCM diagnostic patterns. The review concluded that it could not answer whether tailored treatment was more beneficial than standard formulae. Although future studies should aim to allow more fully for usual TCM practices to be evaluated, the results of RCTs of standard formulae applied to conventional diagnoses of primary dysmenorrhea would be more readily applicable to Western medical practice.

However, the major problem in this review was that not one of the studies included in the review was methodologically sound, using the authors' appropriate criteria. Therefore, the review's conclusions may be affected by all kinds of biases. In a review into a more developed research area, such as drugs for hypertension, it is unlikely that any of these studies would have been included. However, one has to start somewhere and the review does important work in providing an overview of the current state of play and clarifying where future research efforts need to be directed. Some of the other methodological problems are discussed below.

The most serious flaws in the studies included in the review relate to randomization and allocation concealment. Randomization is a process of allocating participants to study groups, whereby each participant has an equal chance of being placed into any study group. Allocation concealment refers to a process whereby an unbiased allocation sequence is used to place participants into study groups, whereby no person can know beforehand into which group a participant will be po-

sitioned.<sup>4</sup> This process prevents those responsible for assigning participants to treatment groups from knowingly or unknowingly influencing which group individuals will enter. In our case, good processes of randomization and allocation concealment would prevent researchers from somehow putting all the women with extremely bad dysmenorrhea into the placebo group, for example. Allocation concealment seems to be the most important indicator of trial quality, with one review finding that trials that inadequately managed allocation concealment had odds ratios of effect sizes 41% higher than trials that adequately managed it.<sup>4</sup> Only three of the studies in the review clearly stated their methods for randomization, and adequate allocation concealment was reported in only two studies of 39.

Ideally, all involved in RCTs will be blind to which treatment each participant is receiving. Blinding minimizes treatment bias when researchers care for the treatment group differently,<sup>4</sup> and observer bias, where those measuring the trial outcomes give more favorable ratings to participants in the treatment group.<sup>5,6</sup> Lack of blinding may inflate the effect size by 17%.<sup>6</sup> In our review, blinding was poorly done. There were four single-blinded and three double-blinded studies, and only two trials reported that there was no difference in appearance, taste, etc between the herbal formulations being tested and the comparison treatment.

Finally, all participants randomized in a trial must be accounted for in the final analysis of results, even if they did not complete all parts of the RCT or even withdrew altogether. This principle is known as "intention-to-treat" analysis and aims to prevent bias due to different rates of loss of participants in the two groups being compared, which may cause loss of baseline equivalence in, for example, method of contraception in our review. This close attention to accounting for all participants once randomized in a trial may also identify practical problems in adherence to a trial protocol, affecting external validity, or how the treatment would be used in the "real world." For example, trial results may find a treatment to be effective, but if most participants did not complete the protocol due to unacceptable side effects, the context in which these results were interpreted would be af-

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fect. None of the studies included in the review utilized intention-to-treat analysis. Withdrawals were reported in only two trials. Only eight trials reported on adverse events. Given some concerns over the quality of some Chinese herbs, this data would have been useful.<sup>7</sup>

Traditional Chinese Medicine has stood the test of time and deserves to be evaluated thoroughly to broaden its use where supported by evidence of safety and effectiveness. This thorough review of the use of Chinese herbal medicines to treat primary dysmenorrhea has been an important addition to our knowledge, despite the poor quality of the trials included. The use of RCTs to evaluate Chinese herbs and other complementary therapies is a relatively recent development. Using thoughtful and innovative methods, it is usually possible to test both a therapy and its paradigm, such as certain Chinese herbs for dysmenorrhea and TCM meth-

ods of diagnosis and care. Now that the paucity of evidence has been recognized, the identified problems in existing trial quality are not onerous to remedy, and we can anticipate reliable results from well-conducted RCTs in the future. The results of these trials will be useful to women and clinicians to guide treatment decisions and improve patient care.

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