

EXECUTIVE SUMMARY

BACKGROUND

Migraine is a common and disabling health problem among adult Americans. Surveys from the U.S. and elsewhere suggest that 6% of men and 15%-17% of women experience migraine headaches. These headaches result in significant disability and work loss; estimated aggregate indirect costs to employers in the U.S. for reduced productivity due to migraine range from 6.5 to 17 billion dollars annually. Even these measurements fall short of demonstrating the full impact of migraine on the individual and society because they fail to account for the substantial effect of migraine on other aspects of life.

There is now a broad array of drug therapies for the acute and preventive treatment of migraine, and almost all migraine sufferers have used drugs at one time or another to treat their headaches. But pharmacological treatments are not suitable for all patients, nor are they universally effective. Partly for these reasons, there is growing interest among patients and health care providers in alternative treatments for migraine, including behavioral and physical treatments.

Several behavioral treatments have been widely used over the past two decades in the management of recurrent migraine. The most frequently employed interventions fall into three broad categories: relaxation training, biofeedback training (often administered in conjunction with relaxation training), and cognitive-behavioral (or stress-management) therapy. Over the same period of time, there has also been an increase in the use of physical treatments for migraine, principally acupuncture, cervical manipulation, and mobilization therapies. Though there are exceptions, these behavioral and physical interventions are primarily aimed at the prevention of migraine episodes rather than the alleviation of symptoms once an attack has begun.

If effective and available, these non-pharmacological treatments may be the first choice for most patients and may also be well suited for the significant minority of migraine patients who: (a) have poor tolerance of pharmacological treatments; (b) have medical contraindications for pharmacological treatments; (c) experience insufficient relief from, or are unresponsive to, pharmacological treatment; (d) wish to become pregnant (or are nursing); (e) have a history of long-term, frequent, or excessive use of analgesic or abortive medications that can aggravate headache problems; and (f) simply prefer to avoid medication use.

SCOPE OF EVIDENCE REPORT

The objective of this evidence report is to provide a comprehensive review and analysis of published reports of randomized controlled trials (RCTs) and other prospective, comparative clinical trials of behavioral and physical treatments for migraine. The report is limited to therapies that have been studied specifically among populations of patients with migraine. As a result, some treatments used by health care providers to treat migraine may not be represented.

METHODOLOGY

The literature review addressed the question *What are the effects on headache pain and/or headache frequency when behavioral (physical) treatments are compared to no intervention (wait-list control), placebo or sham interventions, alternative behavioral or physical treatments, and drug therapies among patients with migraine headache? (A wait-list control is a group of patients who receive no treatment during the trial but who will be treated once the trial ends. This group therefore serves as a control with which to compare results from groups that do receive active treatment.)*

To be considered for this review, studies were required to be prospective, controlled trials of behavioral or physical treatments aimed at the prevention of attacks of migraine headache or the relief of symptoms of individual episodes of headache in patients with migraine. Behavioral treatments considered included the broad categories of relaxation, biofeedback, cognitive-behavioral (or stress-management) therapy, and hypnosis. Physical interventions considered included acupuncture, cold and heat therapies, ultrasound, transcutaneous electrical nerve stimulation (TENS), trigger point intervention, occlusal adjustment, cervical manipulation, mobilization therapy, exercise, diet, and hyperbaric oxygen therapy.

Although the use of a specific set of diagnostic criteria (e.g., those developed by the Ad Hoc Committee on the Classification of Headache and the Headache Classification Committee of the International Headache Society [IHS]) was not required, diagnoses were required to be based on at least some of the distinctive features of migraine, e.g., nausea/vomiting, severe head pain, throbbing character, unilateral location, phono/photophobia, or aura. As the IHS criteria allow, we considered patients described as having mixed migraine and tension-type headache or combination headache to have migraine.

Studies were included only if allocation to treatment groups was randomized or quasi-randomized (based on some non-random process unrelated to the treatment selection or expected response); concurrent cohort comparisons and other non-experimental designs were excluded. Control groups could comprise no intervention, placebo or sham interventions, usual care, or a specified alternative drug or non-drug treatment.

Relevant controlled trials were identified by searching MEDLINE (January 1966 through December 1996) using the MeSH term "headache" (exploded) and a published strategy for identifying randomized controlled trials. Additional search strategies included computerized bibliographical searching of PsycINFO and CINAHL databases; retrospective and prospective hand-searching of the journals *Headache*, *Cephalalgia*, and *Headache Quarterly* from the inception of each (1981, 1961, and 1990, respectively); searching the reference lists of review articles and included studies; searching books related to headache; and consulting experts in the field. We also searched a database of randomized trials in pain relief which is now part of the Cochrane Controlled Trials Register.

Studies identified by the literature search were screened for further review based on criteria focusing on patient population, intervention, study design, and type of outcome data reported.

Studies passing the initial screen were reviewed for methodological quality based on the following considerations: the use of random allocation; description of an adequate method of concealment of allocation; the use of double-blinding; description of an adequate method of blinding; and a description of drop-outs sufficient to determine the number of patients in each treatment group entering and completing the trial. Each trial could score one point for each criterion (for a total of from 0 to 5 points), with higher scores indicating higher quality in the conduct or reporting of the trial.

Efficacy data were abstracted from the original reports onto specially designed forms. We collected trial data on symptomatic outcomes related to head pain (frequency, severity/intensity, and duration) and other symptoms of migraine (nausea, vomiting, photophobia, phonophobia). Secondary outcomes recorded included medication use, functional status (disability), and quality of life. We did not consider physiological or other measures not directly relevant to the patients symptomatic experience.

We preferred that outcome data be based on daily recording of headache symptoms by patients, rather than on global or retrospective assessments performed by patients or investigators. Outcomes were recorded post-treatment and at follow-up, if available.

We preferred combined measures of headache symptoms such as headache indexes (variously defined combinations of frequency, intensity, and duration). In the absence of a headache index, we recorded headache frequency alone. If neither headache index values nor frequency data were reported, we analyzed data on headache intensity.

For dichotomous outcomes (e.g., success/failure), we required that the threshold for distinguishing between success and failure be clinically significant; for example, we interpreted a 50% or more decrease in headache frequency or headache index (two of the most common definitions) as meeting this criterion. Dichotomous outcomes meeting our definition of a clinically significant threshold were reported as proportions (or response rates for each treatment)

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which may be directly compared (difference in proportions). We also used these proportions to calculate odds ratios in the case of the physical treatment trials.

In the few instances in which outcome data were reported on an ordinal scale (e.g., for reduction in headache frequency: none, some, moderate, significant, very significant), we selected a threshold based on the definition of clinically significant improvement (discussed above) and converted these data into a dichotomous outcome.

Most of the behavioral treatment trials and a few physical treatment trials reported outcomes on a continuous scale (e.g., mean headache index or mean headache frequency). In these cases, whenever variance estimates were also available, we re-scaled and standardized the continuous outcome data for each treatment condition in each study using a published method. In the case of the behavioral trials, we then used the resulting standardized outcome measures to calculate summary effect sizes for each type of treatment, using a multi-variable, random-effects model, controlling for study. For the purposes of this meta-analysis, the behavioral interventions were grouped into categories based in part on statistical considerations and in part on clinical considerations.

Because some of the behavioral trials that reported continuous data did not permit effect size calculation, the sample of studies included in the meta-analysis may be subject to bias. To investigate this potential bias, we calculated another measure of effectiveness, the percentage of improvement (in headache index or frequency) from pre- to post-treatment. Because large differences between the percentage improvement scores from studies *included in the meta-analysis* and those from studies *excluded from the meta-analysis* would suggest bias, we compared the mean percentage improvement scores (weighted for sample size) of the two groups.

We also used the standardized outcome measures described above to calculate individual effect sizes for pair-wise comparisons of active behavioral treatments with control treatments for every trial with a control arm; and to calculate effect sizes for all pair-wise comparisons in the only trial of physical treatments for which effect sizes could be calculated.

Throughout the report, wherever we have used the word *significant* to describe results, we mean *statistically significant* at an alpha level of 0.05 for the two-sided alternative hypothesis. Wherever we have reported on results that are clinically, rather than statistically, significant, we have explicitly used the word *clinically*.

SUMMARY OF FINDINGS

Behavioral treatments

Thirty-nine trials of behavioral treatments were included in the report; eighteen of these reported continuous outcome data and variance data and were included in a meta-analysis. The principal findings of our analysis were:

Behavioral treatments for migraine have a consistent body of research indicating efficacy. The effect size data suggest that relaxation training, thermal biofeedback combined with relaxation training, EMG biofeedback, and cognitive-behavioral therapy are all modestly effective in treating migraine when compared to wait-list control. Trials using thermal biofeedback alone yielded an effect size point estimate similar to these treatments, but the estimate was not statistically significant, perhaps because only three studies contributed data. Trials of thermal biofeedback combined with cognitive-behavioral therapy also yielded an effect size that failed to reach statistical significance, though the point estimate was not higher than that for cognitive-behavioral therapy alone and fairly similar to those for other treatments involving thermal biofeedback.

A large number of studies could not be included in the meta-analysis because they did not report variance data, even though they met all other inclusion criteria. Comparison of percentage improvement scores from trials included in, and excluded from, the meta-analysis did not substantially change our interpretation of the effect-size data.

The results of the meta-analysis provided little guidance for choosing among the treatments considered.

Inconclusive results were reported on the following topics: whether there is an incremental benefit to adding one type of behavioral therapy to another; comparisons of behavioral therapies and drug treatments for migraine; and the relative efficacy of different methods of delivering behavioral therapies (home- vs. clinic-based treatment, standard vs. minimal therapist contact therapy, standard vs. standard + booster treatments).

Physical treatments

Eleven controlled trials of physical treatments were reviewed. The main findings were as follows:

Six small trials of *acupuncture* yielded mixed results. A single study using a wait-list control (no intervention) failed to find a significant result. Two trials comparing

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acupuncture to sham acupuncture in a single-blind fashion found a statistically significant benefit to genuine acupuncture. A single trial comparing acupuncture with sham TENS found no significant difference between the two interventions. None of the trials comparing acupuncture to active pharmacological or behavioral treatments found acupuncture to be clinically or statistically significantly better than the comparator.

Two trials of *TENS* provided little support for the effectiveness of this treatment for migraine.

One trial compared *three manual interventions*: a control group (cervical mobilization), cervical manipulation performed by a medical practitioner or physiotherapist, and cervical manipulation performed by a chiropractor. The results provided little support for the use of manipulation or mobilization in patients with migraine.

A single trial of *occlusal adjustment* among patients with migraine and mixed migraine and tension-type headaches found no significant effect among migraine patients and a modest, but statistically significant, effect among mixed headache patients.

One small pilot study of *hyperbaric oxygen* for the treatment of acute migraine suggested a large effect. However, even if further research were to verify these results, the rare availability and high cost of the equipment involved would limit the clinical application of this treatment.

FUTURE RESEARCH NEEDS

Further research is required into the efficacy of currently available physical and behavioral treatments if their use for migraine is to be optimized. The following recommendations may be made:

Conduct and reporting of trials

- (1) The diagnosis of migraine -- even when made according to specific criteria such as the IHS criteria for migraine with aura and migraine without aura -- encompasses a wide range of symptomatology. Researchers should be as precise as possible in describing any operational inclusion or exclusion criteria they employ in addition to headache diagnosis, such as headache frequency, severity, and chronicity. Furthermore, researchers should state whether patients with co-existing tension-type headache were excluded. In addition to describing the inclusion and exclusion criteria applied, researchers should describe the relevant characteristics among the population actually enrolled.

- (2) Comparisons using recruitment from well-described clinical populations such as primary care practices or managed care organizations should be performed to expand the generalizability of the results reviewed in this report.
- (3) Future studies should include extended periods of follow-up for patients receiving behavioral or physical treatments and control subjects to evaluate the long-term effectiveness of such treatments.
- (4) There was tremendous variety in the way patients respond to the treatments reviewed in this report. Individual trials may not be able to identify patient characteristics that may predict a positive response to one treatment or another, but if trials were to report individual patient data, meta-analysis of such trials might have sufficient power to do this. Better data on predictors of good response to behavioral and physical treatments may help to select patients most likely to benefit from these treatments.
- (5) Adoption of certain standards recommended by the International Headache Society would strengthen the validity and comparability of trials of physical and behavioral treatments; these standards include:
 - Use of a prospective baseline period of at least one month;
 - Use of a treatment period of at least three months;
 - Use of a daily headache diary;
 - Use of frequency of attacks per 4 weeks as main efficacy parameter rather than headache index or other measures; and
 - Use of a 50% reduction in attack frequency compared with baseline as the criteria for individual response.

Future research directions: physical treatments

- (6) Research needs to be conducted to fill important gaps in the literature on physical treatments for migraine. None of the physical treatments has a sufficient body of evidence from which to draw firm conclusions about efficacy for migraine. Frequently-used physical treatments such as massage or mobilization therapy have not been tested at all against appropriate controls.
- (7) Sham acupuncture may result in opioid and other neuromediator changes in central nervous system and immune system cells, and may therefore be an inappropriate active control for studies of acupuncture. Although the Office of Alternative Medicine of the National Institutes of Health (NIH) does not recommend use of double-blinding in studies of acupuncture, research on the effect of various sham acupuncture techniques should be performed to develop an empirical basis for selecting an acceptable control treatment.

We note that NIH has recently targeted acupuncture as a priority for research funding. The NIH issued a program announcement in February 1998 to support pilot studies to establish the methodological feasibility of and to strengthen the scientific rationale for proceeding to full-scale, randomly controlled trials (RCTs) on the use of acupuncture to prevent, manage, or treat various symptoms/disorders. The emphasis of this program is on developing an appropriate study design rather than on attempting to complete insufficiently powered trials.

Future research directions: behavioral treatments

- (8) Further research needs to be conducted comparing behavioral and drug treatments for migraine and exploring possible combinations of these therapies. This type of research may have been hampered in the past by the fact that behavioral and drug therapies are usually provided, institutionally, by different professionals.
- (9) Research is also needed on acceptable control treatments for studies of behavioral treatments.
- (10) A number of behavioral treatments have provided evidence that they are effective. To help the largest number of patients possible, it would be beneficial to obtain more information about the optimal order or combination of those treatments.
- (11) More collaborative and multi-site studies of behavioral trials are needed. Much of the research on behavioral therapies has been performed at a relatively small number of centers by a few investigators and their trainees. The complex and subjective nature of much of the training leads to questions about whether the results observed with these interventions can be reproduced in other practice settings.