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Comments from the Acupuncture Now Foundation to the AHRQ draft report: Noninvasive, Nonpharmacological Treatment for Chronic Pain: A Systematic Review

By

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The Acupuncture Now Foundation is a U.S. based, international non-profit volunteer organization dedicated to providing accurate information about acupuncture's potential as a health care resource.

We applaud the recent efforts to investigate the potential for non-pharmacologic therapies to play a larger role in pain management. We offer the following feedback regarding acupuncture's potential to be considered for the AHRQ's final report. It is unfortunate that it has taken a catastrophic public health crisis caused by the misuse of a pain management drug with an extremely poor benefit to harm ratio to encourage health officials to finally look more seriously at safer non-pharmacologic alternatives. It should be noted, however, that our ongoing overdependence on drug-based therapies is causing harms in other areas of healthcare where non-pharmacologic therapies including acupuncture could also be playing a larger role. Health officials should not let the increased interest in non-pharmacologic therapies be limited to pain management. We should not wait for the next benefit to harm crisis to unfold before we look for safer alternatives in all areas of healthcare.

Based on the studies included for this review, we agree with the conclusion in the draft report's structured abstract that found acupuncture to be among the handful of non-pharmacologic therapies that may "slightly to moderately improve function and pain across multiple chronic pain conditions." This conclusion builds on several other reviews that have found acupuncture providing clinically effective and cost-effective results in a range of different chronic pain conditions. Unfortunately, the limited coverage for acupuncture services by third-party payment systems is hindering healthcare providers' ability to follow the growing number of guidelines that recommend acupuncture as a first-line treatment for managing pain. Many mainstream medical organizations have been calling for an

expansion of insurance coverage for these non-pharmacologic therapies including acupuncture (1) and we urge decision-makers in third-party payment systems to heed this call.

However, while it is a positive development that evidence-based reviews such as this latest by the AHRQ conclude that acupuncture is effective in pain management, there is also evidence that factors involved with acupuncture research are causing an underestimation of that therapy's true clinical effectiveness. We believe such an underestimation has happened with this draft report and want to detail some of those factors here to help your reviewers, as well as clinicians and policymakers, put acupuncture research into a more accurate perspective. While our area of expertise is in acupuncture's clinical effects, some of these flaws in research protocols may apply to other non-pharmacologic therapies while yet others seem unique to acupuncture therapy. We make three recommendations below.

Before we detail the specific factors that can lead to an underestimation of acupuncture's effectiveness within controlled trials and the review of those trials, it is important to acknowledge that there is a large body of evidence showing acupuncture having higher effectiveness rates than found in the trials utilized in this AHRQ review. Trials conducted in countries such as China, Korea, Japan, and Taiwan consistently show acupuncture having high effectiveness rates in the 75%-90+% range. In fact, these effectiveness rates are so consistently high some critics have questioned their validity (2). However, many acupuncturists claim similar effectiveness rates within their practices but such claims were difficult to support until recently. In 2016, the results of a 2 year AHRQ CG-CAHPS patient experience survey taken of 89,000 U.S. acupuncture patients found similar high rates of effectiveness in the treatment of their primary complaint (3).

Considering the above, when we state that there is good reason to believe there is an underestimation of acupuncture's effectiveness rates found in many research trials, we are not asking for a leap of faith. We are trying to reconcile the clinical experience of tens of thousands of acupuncturists around the world together with hundreds of trials done in the Far East with those trials done in the West.

There are three major problems with how acupuncture research is typically conducted and then reviewed that can cause an underestimation of acupuncture's true clinical effectiveness –

1. The clinical training/expertise of those who design the clinical aspects of acupuncture trials and those who perform the acupuncture in those trials.
2. The number and frequency of the acupuncture treatments.
3. A multitude of problems related to the placebo/sham control arms of acupuncture trials.

Problems with Sham Controlled Acupuncture Trials and Reviews of those Trials

When reviews of RCTs are undertaken to compare the effectiveness of non-pharmacologic therapies, it will often be found that the trials included for review will have a higher percentage of “sham controlled” trials for acupuncture than for most other therapies. That is the case with this current draft of the AHRQ’s review. In the case of the review for fibromyalgia, all of the trials included for evaluating acupuncture’s effects only compared verum/real acupuncture to sham acupuncture while none of the other therapies/interventions were compared to sham alone.

Measuring the effects of an active therapy versus a sham control will invariably yield a lower result than comparing an active therapy versus no care, waitlist controls or even, in many cases, to usual care. With acupuncture research, the differential in the effectiveness rates are often unreasonably large. A prime example of this is the case of two major trials on the effects of acupuncture in treating chronic low back pain. One large trial conducted in Germany found acupuncture to be twice as effective as usual care(4) and was followed-up by a second trial in the U.S. that found acupuncture to be one and a half times to twice as effective as usual care (including opioids)(5).

Chronic low back pain is one of the most common, expensive and difficult to manage conditions we face. It is also a leading reason opioids are prescribed. Normally, having multiple studies finding a seldom used and safer therapy to be twice as effective in managing this condition would be considered an important breakthrough. However, because both these studies also found that the “real” acupuncture did not outperform the “sham” acupuncture, they have been repeatedly reviewed as a negative finding.

This was the case in a recent review completed by the Institute of Clinical and Economic Review (ICER): “Cognitive and Mind-Body Therapies for Chronic Low Back and Neck Pain: Effectiveness and Value”. In that review the ICER reviewers found acupuncture to cause “Significant reductions in disability and pain” for both chronic low back and neck pain; a level greater than any other therapy reviewed. Yet, in their report, they downgraded the rating for acupuncture’s effects to being “small” – the same rating as the other therapies. They justified doing this in part because of those two studies that found “real” acupuncture to not outperform the “sham” stating this was evidence that acupuncture’s effects were mostly likely due to the placebo effect.

It is our opinion that sham controls in acupuncture trials are so flawed they should not be considered as a valid test of how much of acupuncture's positive clinical effects may be due to the placebo effect. Besides placebo, there are three more likely reasons discussed in peer reviewed literature why real acupuncture might not outperform sham:

1. Some or all of the five different types of sham acupuncture procedures used in acupuncture RCTs may not be inert but rather cause the body to produce pain reducing and anti-inflammatory chemistry as has been shown for real acupuncture. This problem has been highlighted by a number of researchers (6-11). Interestingly, while similarities in physiological effects have been identified between sham and verum acupuncture protocols, distinct differences have also been identified, including differences in activation and deactivation of brain and brain stem centers on fMRI, brain connectivity networks and mu opioid receptor binding potential (10-13). It is now clear that the assumption that the effects of sham acupuncture protocols being most likely due to placebo effects is not supported by the evidence (16, 17).
2. Many studies are underpowered using too few subjects to reliably show real acupuncture's effectiveness over sham. The most rigorous studies investigating if real acupuncture outperformed sham as the central question found there is a statistically significant difference between acupuncture and sham, however the size of the difference (effect size) was in the region of 0.2 (18,19). This means you would need a much larger sample size than is typically utilized in most sham-controlled acupuncture trials to allow this difference to show itself.
3. There are no clinical quality guidelines to help researchers ensure the real acupuncture achieves its maximum benefit. There have been important questions raised about the level of clinical quality controls related to how the real/verum acupuncture arms of acupuncture RCTs have been designed and conducted (20,21). There is even question of if the trials being used to draw conclusions about how much of acupuncture's effects may be due to placebo effects were even designed to address this issue(22).

It would be helpful, at very least, if this review would separate the findings of effectiveness ratings of these therapies compared to sham controls from those compared to other controls as was done in the AHRQ's Comparative Effectiveness Review #169, "Noninvasive Treatments for Low Back Pain". In that review, acupuncture vs. no acupuncture was found to have a rating of a moderate magnitude of effect for both pain and function while acupuncture vs. sham had a moderate magnitude of effect for pain but no effect on function. Detailing the effects as compared to those in each type of control in this manner allows for more accurate (apples to apples) comparisons of the different therapies.

Recommendation #1. Separate effectiveness rates for the types of controls employed especially to segregate sham controls from other types of controls.

The number and frequency of the acupuncture treatments

Any acupuncturist with any level of experience will agree that the number and frequency of acupuncture treatments have an impact on that therapy's clinical effectiveness. If not, why ever do more than just one treatment? Unfortunately, addressing the clinical rationale behind the number and frequency of acupuncture treatments are seldom accounted for in the design of acupuncture RCTs or the analysis of reviews of those trials. This AHRQ review also failed to take the number and treatment frequency into account of its analysis of acupuncture trials.

Our limited time/resources did not allow us to carefully review every trial used in the AHRQs review, however, we did note some problems with reporting clinical quality issues, and especially treatment numbers, in the review of osteoarthritis of the knee.

One of the studies included in this review of acupuncture trials for osteoarthritis of the knee was the 1999 Berman trial. In Table 29, you summarized that trial as consisting of "20 minute treatments, 2/week for 8 weeks "when actually the trail utilized "26 weeks of gradually tapering treatment according to the following schedule: 8 weeks of 2 treatments per week followed by 2 weeks of 1 treatment per week, 4 weeks of 1 treatment every other week, and 12 weeks of 1 treatment per month."

This study had the highest effectiveness rates than any other study included in your review on acupuncture for knee osteoarthritis. Accurately reporting the details of the number and frequency of treatments over this longer period of time is important because this study was the only one in your review that utilized enough treatments over a long enough period of time to allow the real acupuncture to achieve its fuller potential. It found that while the true/real acupuncture group showed higher effectiveness rates for the WOMAC function scores than the sham acupuncture group at 8 weeks (mean difference, 2.9 [95% CI, 5.0 to 0.8]; P 0.01) it did not show better effectiveness rates in WOMAC pain score (mean difference, 0.5 [CI, 1.2 to 0.2]; P 0.18) or the patient global assessment (mean difference, 0.16 [CI, 0.02 to 0.34]; P> 0.2). In other words, at eight weeks, the true/verum acupuncture did not clearly outperform the sham. However, when measured at 26 weeks, the true acupuncture group

experienced significantly greater improvement than the sham group in the WOMAC function score (mean difference, 2.5 [CI, 4.7 to 0.4]; P 0.01), WOMAC pain score (mean difference, 0.87 [CI, 1.58 to 0.16]; P 0.003), and patient global assessment (mean difference, 0.26 [CI, 0.07 to 0.45]; P 0.02).

The important findings of this study regarding true acupuncture gaining in effectiveness over longer periods of time while sham acupuncture's effectiveness rate fell over those times were seen in another study of osteoarthritis of the knee published in 2007: "Delayed Effect of Acupuncture Treatment in OA of the Knee: A Blinded, Randomized, Controlled Trial", Ehud Miller et al. This study utilized 2 treatments a week for 8 weeks in both the real/true and sham acupuncture arms and then measured the results at the end of the treatment series (8weeks) and then again 4 weeks later (12 weeks). The authors concluded that "the maximal effect of acupuncture was seen after 12 weeks. Importantly, our results demonstrated that the effect of acupuncture was preserved during the period of 4 weeks following termination of treatment, while KSS knee, function and pain scores improved in the intervention group, they dropped in the sham group." It also appears this study would meet your inclusion criteria.

Both of these studies utilized a higher total number of treatments over a longer period of time than is frequently the case in acupuncture trials done in the West but a lower number than is typically utilized in trials on acupuncture done in the Far East. Trials done in the Far East also typically find higher effectiveness rates for acupuncture.

Another helpful study that looked at treatment number/frequency was in a recent Cochrane systematic review on acupuncture for migraine prophylaxis. In that study, Linde et al performed a subgroup analysis on the number of treatment sessions given (11). The review excluded studies which were of less than 8 weeks duration. The effect size of the response at follow-up (Outcome 18), expressed as a Z number, for the studies which used 12 treatments or less was Z=2.32, while for studies using 16 or more treatments, Z=4.06. The effect size for headache frequency reduction after treatment (Outcome 19), for 12 treatments or less was Z=1.64 while for 16 or more treatments, Z=3.52. The effect size for headache frequency reduction at follow-up (Outcome 20), for the 12 treatments or less was Z=1.61 while for 16 or more treatments, Z=3.62. The effect size for response after treatment (Outcome 21), for 12 treatments or less was Z=2.09 while for 16 or more treatments, Z=3.74. In other words, on all measures used in the sub-group analysis, the studies which used 16 treatments or more achieved superior outcomes to those that used 12 treatments or less.

While we understand this AHRQ review did not include migraines as a condition to be reviewed, we shared the information above to underscore how significant clinical quality issues such as the number/frequency of acupuncture treatment can be and how useful it is for reviewers to look at those

treatment numbers in their review. Studies like these strongly suggest that in order for true acupuncture to reach its potential in addressing chronic pain, more frequent treatments (at least twice a week) carried out over longer periods of time (greater than eight weeks) are needed than are typically utilized in acupuncture studies done in the West. In this AHRQ review on osteoarthritis of the knee none of the included studies other than the Berman study utilized more than 12 treatments. One study, Yurtkuran, 2007, also utilized a highly questionable treatment protocol of laser acupuncture on just one acupuncture point that is located inches below the knee joint (Sp9) and was by far the most negative study of those included in this review.

Recommendation #2. Consider conducting a subgroup analysis for clinical quality issues such as treatment number/frequencies over time or at least explain your reviewers rationale for how clinical quality issues such as these were considered or not considered in developing the research inclusion criteria. Also consider adding the 2007 E. Miller “Delayed Effects” trial to your review.

The clinical training/expertise of those who design the clinical aspects of acupuncture trials and those who perform the acupuncture in those trials

Acupuncture is a hands-on therapy that has been continuously practiced for more than two thousand years. Over that time countless techniques have been developed covering every aspect of how points are selected for treatment, how they are located on the body, and needling considerations including the angle, depth, and types of stimulation that are employed, etc. It is reasonable to question the degree of clinical training/expertise those involved designing acupuncture research trials may have as well as that of the acupuncturists doing the needling. Trials investigating surgical procedures would, no doubt, take some care to assure only qualified surgeons were involved in the study design and implementation.

The World Health Organization published recommended standards for acupuncture training in 1999 (21). It was recommended that medical practitioners required a minimum of 200 hours specific acupuncture training to practice in a “limited” capacity and 1,500 hours of acupuncture training to practice in a (full capacity) (23). For those who were not already qualified medical practitioners the recommendation was 2,500 hours of training including acupuncture and biomedical subjects (23). This latter standard of 2,500 hours is met or exceeded in many countries where acupuncturists are registered/licensed including China, Japan, Korea, Australia and various states of the USA.

A number of large acupuncture trials have been conducted in Germany over the past decade or more which are referred to as the GERAC studies (24-29). In most of these trials the training standard of the treating practitioners has been described as medical practitioners with a minimum of 140 hours of specific acupuncture training, which falls below the WHO recommendation for even “limited” practice (8). In some trials the reported training level is a minimum of 140 hours with a mean of 500 hours (31-33). Unfortunately, this does not provide any indication of how many practitioners in such a trial had completed either 200 or 1,500 hours of acupuncture training. A 2017 study on acupuncture for Irritable Bowel Syndrome indicated the acupuncture was performed by “a trained acupuncturist” but that training turns out to have been just 36 hours. (“Sham acupuncture is as efficacious as true acupuncture for the treatment of IBS: A randomized placebo controlled trial” C. Lowe A. Aiken A. G. Day W. Depew S. J. Vanner

In the Cochran review on Migraine prophylaxis mentioned previously, 8 of the 22 studies included used 16 treatments or more and without exception, these were also the studies conducted by acupuncturists with the most extensive training and experience. Those studies most likely also had their clinical protocols including the treatment numbers designed by clinicians with more clinical experience. Two of these studies were conducted in China using 4 to 5 treatments per week, three in Spain and two in Italy using twice weekly treatments, and one in Australia commencing at twice weekly for four weeks and then tapering in three steps to once per month. Since, in this review, the studies with the greatest number of treatment sessions were also the studies conducted and likely designed by acupuncturists with the highest levels of training and experience, it is impossible to assess how much of this difference in outcomes was due to the number of treatment sessions alone and how much was due to the training and acupuncture expertise of the practitioners.

Recommendation #3 Where possible, this review should make note of the training level of the practitioners.

Conclusion

We have attempted to offer some specific suggestions regarding acupuncture for improving the accuracy of your important review on non-pharmacologic therapies for chronic pain that we hope will be of use to your reviewers. We also tried to offer a bigger picture perspective about problems with acupuncture research in general that many reviewers may not be aware of.

Being that the sham acupuncture included in this AHRQ review may not be a true sham, the real/verum acupuncture may not be designed to allow maximum effectiveness, and many trials in this review may be underpowered, acupuncture's actual effectiveness ratings are likely being underestimated.

We invite feedback and further communication regarding acupuncture's clinical strengths and weaknesses as well as that of acupuncture research. Please contact the Acupuncture Now Foundation for further information.

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