

**EDITORIAL**

# Acupuncture and Knee Osteoarthritis: Does Dose Matter?

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Osteoarthritis (OA) is an extraordinarily prevalent and disabling disease (1). Current management options for pain and functional limitation are constrained by modest efficacy or a range of unwanted side effects. Our society is being impacted through underemployment and the opioid epidemic, and our health care systems are overstretched, as a consequence of the trajectory of increasing joint replacement requirements (2). In this context, development of new treatments or identification of the efficacy of existing therapies to address the huge unmet need of pain management are strongly desired.

Acupuncture is a component of traditional East Asian medicine and has been used as a healing practice for many centuries (3). Acupuncture is generally thought to have arisen in China with documented clinical practice in the Huangdi Neijing “Yellow Emperor’s Inner Classic” more than 2,000 years ago. However, ancient Chinese burial sites have uncovered acupuncture tools (Bian stones) that predate this period. Following its development in ancient China, acupuncture spread throughout Southeast Asia and Europe, and is becoming increasingly popular in North and South America.

Acupuncture typically involves the insertion of thin (32–36-gauge) solid needles into specific points in the body (acupoints). Once needles are inserted, they may be stimulated mechanically, electrically, or thermally. Needles are then retained in the body for 20–30 minutes during a single session. When provided as a course of treatment, acupuncture is performed during multiple sessions spread over a number of weeks.

The efficacy of acupuncture in the context of pain, and knee OA more specifically, is a subject of controversy. The initial literature struggled to consistently demonstrate efficacy of acupuncture over and above sham treatment. However, the Acupuncture Trialist Collaborative showed, in an individual participant meta-analysis ( $n = 20,827$  patients; 39 trials), that acupuncture was superior to sham acupuncture for multiple pain conditions: OA had an effect

size of 0.20–0.30 (4). While this is statistically significant ( $P < 0.001$ ), the clinical relevance is questionable, with most guidelines conditionally recommending the use of acupuncture for OA (5,6).

In this issue of *Arthritis & Rheumatology*, Tu et al report findings of a multicenter, randomized, sham-controlled trial that included 480 patients with knee OA who were randomly assigned to receive electroacupuncture (EA), manual acupuncture (MA), or sham acupuncture (SA) 3 times weekly for 8 weeks (7). Participants, outcome assessors, and statisticians were blinded with regard to treatment group assignment. Compared with SA, intensive EA resulted in less pain and better knee function at week 8, and these effects persisted through week 26. Intensive MA had no benefit for knee OA at week 8, although it showed benefits at week 26.

A key issue in the field of acupuncture research is the notion of “dose.” It is unknown what the optimal dose of acupuncture is and, even more importantly, how to classify dose. Does dose reflect the number of treatments, the number of needles, the depth of penetration, the amount or type of stimulation, or the duration of needle retention? In this study, Tu and colleagues used 3 treatments a week, which is more frequent than typical studies conducted in the West and may not be feasible in some health care settings. A recent systematic review suggests that treatment frequency matters, and a dose of 3 sessions per week may be superior to less frequent treatment (8).

Another key issue in acupuncture research is when to assess efficacy. Some prior studies have assessed treatment efficacy shortly after the last acupuncture treatment. However, findings from the Acupuncture Trialist Collaborative have demonstrated that treatment effects can persist up to 3 to 12 months following treatment. The clinical usefulness of this means that a patient may not need to seek acupuncture for months after the initial round of treatments has been completed. Indeed, in this present study, Tu et al found that acupuncture effects persisted up to 26 weeks

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posttreatment, and for MA versus SA, surprisingly, the effects become significant at 26 weeks, when they were not at 8 weeks.

In the present study, response rates at week 8 were 60.3% for EA, 58.6% for MA, and 47.3% for SA. The between-group differences were modest and favored EA. A remarkably consistent finding in the acupuncture clinical literature on pain is the marked improvement of patients with SA. This has been attributed to a high placebo response with this intervention. Indeed, the field of placebo effects has benefited somewhat from studies on acupuncture. When acupuncture is compared with more noninvasive controls or a wait list, the effect size of acupuncture for OA increases to 0.50–0.60, which is of clinical importance (4). Interestingly, SA is more effective for pain than a placebo pill (9). This suggests that not all placebos are equal (for example placebo pills may have less analgesic action than placebo surgery), resulting in potentially more invasive placebo maneuvers producing more clinical action. Approximately 40% of participants in this trial by Tu and colleagues had previously received acupuncture; however, this did not appear to influence response rate.

Another aspect of acupuncture therapy to consider is safety. Acupuncture is generally considered to be safe, with few adverse events recorded in the literature. This is important to consider, as some existing treatments for knee OA are accompanied by significant side effects, e.g., opioids and nonsteroidal antiinflammatory drugs (gastrointestinal bleeding). As a consequence, the number needed to treat relative to the number needed to harm for this intervention is quite favorable. Another factor to consider with acupuncture is cost, particularly considering the number of visits required and the fact that many health systems do not reimburse for this treatment, leading to substantial out-of-pocket expense. When examined in Europe, acupuncture in general has been shown to be cost-effective (10–12).

This trial has some notable limitations. The significant size of the placebo effect seen in the SA group means that some of the action of this intervention is simply needle insertion, irrespective of location. Other contextual effects and non-needling components have been demonstrated to be important for this intervention (13). Also, it is difficult to double-blind an acupuncture study, as the acupuncturist typically knows if they are performing real or sham acupuncture. There is a double-blind needle that has been developed, wherein the acupuncturist does not know if they are inserting a needle into the skin or not, but those sham needles were not used in this study. In future studies, it will be important to clarify the contribution of efficacy expectations as communicated by those administering the treatment, as prior work has demonstrated this to be substantial (14). For clinicians, recognizing the potent effects of placebo and the optimization of contextual effects through enhanced care is worthy of further consideration (15).

So, is acupuncture ready for prime time and further dissemination? Acupuncture is already widely practiced and readily available in many countries and health care systems. In some systems, reimbursement is limited, which may be a barrier to

further implementation, with heterogeneity of protocols an additional concern. Will authors of guidelines ultimately consider this evidence and change conditional recommendations to be more positive? Time will tell. In the interim, there continues to be further need for research, specifically on dose-response relationships, effects of acupuncturist blinding, feasibility of thrice weekly regimens, and clarifying the mechanism of effect, particularly given the persistence of benefit. There is some suggestion that the benefit is partly mediated by changes in major inflammatory factors (tumor necrosis factor, interleukin-1 $\beta$ , and interleukin-13), which may in part explain the persistence of effect (16).

## AUTHOR CONTRIBUTIONS

Drs. Hunter and Harris drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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