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<<st2>>ORIGINAL ARTICLE
<<rrh>>Knee OA Self-Acupressure Trial
<<lrh>>Li et al
<<title>>Self-Acupressure for Older Adults With Symptomatic Knee Osteoarthritis: A Randomized Controlled Trial

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Objective. This double-blind randomized controlled trial aimed to test the efficacy of self-administered acupressure for pain and physical function improvement for older adults with knee osteoarthritis (OA).

Methods. Participants were community-dwelling adults with symptomatic knee OA (n = 150, mean age 73 years), randomized to 1 of 3 groups: verum acupressure, sham acupressure, or usual care. Participants in the verum and sham groups, but not those in the usual care group, were taught to self-apply acupressure once daily, 5 days/week for 8 weeks. Assessments were collected during center visits at baseline, and at 4 and 8 weeks. Pain level was assessed using a numeric rating scale (NRS) during weekly phone calls to check on the participants. Outcomes included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (primary) and the NRS and physical function measures (secondary). Linear mixed regression analysis was conducted to test between-group differences in mean changes from baseline for the outcomes at 8 weeks.

Results. Compared with usual care, both verum and sham acupressure participants experienced significant improvements in WOMAC pain (mean difference −1.27 units [95% confidence interval (95% CI) −1.95, −0.58] and −1.24 units [95% CI −1.92, −0.55], respectively), NRS pain (−0.74 units [95% CI −1.24, −0.24] and −0.51 units [95% CI −1.01, −0.01], respectively), and WOMAC function (−4.83 units [95% CI −6.99, −2.67] and −4.21 units [95% CI −6.37, −2.04], respectively) at 8 weeks. There were no significant differences between the verum and sham acupressure groups on any of the outcomes.

Conclusion. Self-administered acupressure is superior to usual care in pain and physical function improvement for older adults with knee OA. The reason for the benefits is unclear, and the placebo effect may play a role.
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<<hd1>>**INTRODUCTION**

Knee osteoarthritis (OA) is one of the most prevalent conditions causing pain and disability among older adults (1). When patients with knee OA report pain, they typically are prescribed

nonsteroidal antiinflammatory drugs (NSAIDs) or acetaminophen. These drugs, however, have limited effects (2,3). For older adults, pharmacologic treatment options are limited due to adverse effects associated with long-term NSAID use, comorbid conditions, and polypharmacy. Nonpharmacologic treatments, therefore, are appealing.

<<significance&innovations>>

Significance & Innovations

- This is the first study to examine the efficacy of self-administered acupressure in older adults with symptomatic knee osteoarthritis (OA).
- The findings suggest that self-administered acupressure is superior to usual care in managing pain and improving physical function, although the placebo effect as an explanation cannot be ruled out.
- This study was rigorously conducted compared to prior acupressure trials, and suggests that more research is needed before adopting acupressure as a legitimate treatment approach for knee OA.

Acupressure is traditional Chinese medicine based on a philosophy similar to that of acupuncture. In contrast to acupuncture, which uses fine needles, acupressure involves using fingers or other devices to apply pressure on different acupuncture points (acupoints) to stimulate meridians and increase the flow of "qi" (life energy). An advantage of acupressure over acupuncture is that, once a person learns how to administer acupressure, he or she requires little or no assistance in completing his/her treatment. Thus, acupressure has the potential to be a low-cost and safe alternative to pain management.

Systematic reviews and meta-analyses have generally concluded that acupuncture, when compared to waitlist controls or usual care, resulted in statistically significant and clinically relevant improvements in OA and other chronic pain conditions (4,5). However, when compared to sham controls, the effect size for acupuncture was much smaller and the results were less conclusive. Relative to acupuncture, acupressure research is less developed. Systematic reviews of acupressure trials to date generally support the effectiveness of acupressure in managing various symptoms (e.g., fatigue, insomnia, or nausea), including various painful conditions (e.g., dysmenorrhea, labor pain, and lower back pain) (6–8). On the issue of sham controls, a recent review of 64 studies that involved comparing true and sham acupressure found that a majority (64%) reported true acupressure to be superior, and 13% reported positive effects but no statistically significant differences between true and sham acupressure (9). While the systematic reviews suggest that acupressure is promising, they all note that more rigorously designed trials are needed, as most past studies were of low to moderate quality (6–9).

We conducted a randomized controlled trial (RCT) to examine the efficacy of self-administered acupressure in older adults with symptomatic knee OA. To date, no acupressure studies have targeted older people with knee OA, a population that could potentially benefit greatly from this noninvasive intervention. Our primary outcome was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (10). Secondary outcomes were the numeric rating scale (NRS) for pain (11), and subjective and objective measures of physical function. Participants were randomly assigned to 1 of 3 arms: verum acupressure (verum), sham acupressure (sham), and usual care (UC). We hypothesized that verum participants would have greater improvement in pain and physical function than those in the UC and sham groups after 8 weeks of treatment.

MATERIALS AND METHODS

This RCT was approved by the investigators' university human subjects review board (HUM00071096). All participants provided written informed consent. A feasibility assessment of the study, which did not include any of the outcome analyses presented here, has been previously published (12).

Sample.
Community-dwelling older adults (≥65 years) with symptomatic knee OA were eligible to participate in this study. Subject inclusion and exclusion criteria are shown in Table 1.<<T1>> A comprehensive review of acupuncture versus sham therapy reported absolute improvement of 4 points for acupuncture and 3 points for sham on the WOMAC pain subscale (range 0–20) in 8 weeks (4). Based on these data, we targeted an effect size of 0.52 for the difference between verum and sham and a similar effect for the sham versus UC contrast. We determined that a sample size of 60 in each of the 3 arms would provide 81% power to test our hypotheses at a 0.05 significance level (2-sided). The power analysis did not include the midpoint at 4 weeks, thus presenting what was thought to be a conservative estimate, absorbing potential attrition loss. The minimum clinically important difference (MCID) for the WOMAC pain subscale was >12% improvement from baseline (13).

Participants were recruited via multiple methods, including advertisements in local newspapers and magazines, flyers in public places, a mailing to previous research participants, and referrals from physicians, between June 2013 and November 2014. We used a 2-level screening system. Initial screening was done by phone. Those deemed to meet preliminary eligibility requirements (i.e., age 65 or older, community-dwelling, adequate cognitive status, moderate to severe chronic pain, and no ineligible medical conditions and treatments) were invited to our center for additional screening by our research assistants, who used the American College of Rheumatology (ACR) clinical criteria for knee OA to determine the presence of symptomatic knee OA (14).

Randomization and masking.
Blocked randomization was used to assign participants to verum, sham, or UC (called treatments A, B and C, respectively). Block sizes were chosen randomly between 3 and 6. The randomization list was computer-generated by the study biostatistician (AT); no other investigators or staff knew the details of the randomization algorithm. Individual randomized treatment assignments were sealed in opaque envelopes, which were kept in the order of randomization. Once a participant passed the second-level screening and gave consent to our research assistant, the next envelope in the order was opened, and the treatment code (A, B, or C) was assigned. All investigators, staff, and participants, except the acupuncturist-investigator who developed the acupressure protocol (REH), were kept blinded to the assignment of verum and sham. REH had no interaction with any of the study participants and did not reveal the group assignment to anyone until all analyses had been completed. Participants were informed that they would be randomized into 1 of 3 groups: a group that involved learning pain-relief acupressure, a group that involved learning another form of acupressure that usually did not typically relieve pain, or a group that did not receive any intervention. All participants were asked to continue care as usual.

Interventions.
The intervention lasted 8 weeks. All participants attended 3 center visits, at baseline and at week 4 and week 8, and received weekly phone calls from a research assistant. The phone calls addressed issues related to study participation, adverse events, treatment adherence, and medication changes (13).

Participants of both acupressure groups were taught their respective acupressure protocol during their first visit by a research assistant. The instruction was complete when the participant demonstrated more than 90% accuracy in locating each acupoint, applying pressure, and understanding the self-practice requirement. A set of materials was given to acupressure participants at the end of their first visit, including a wooden handheld device designed for acupressure (Acu-Ki, Bodytools); a demonstration DVD; a diagram of the assigned acupoints with written instructions; and a timer for counting the minutes when applying pressure to each acupoint.

Verum participants were taught to apply pressure using the handheld device to 9 acupoints on their body. These points were: Yintang, Anmian, heart 7, spleen 6, and liver 3 (Figure 1).<<F1>> Anmian, heart 7, spleen 6, and liver 3 were stimulated bilaterally (marked with an asterisk in Figure 1). These acupressure points were chosen because previously they had been shown to decrease pain (potentially through increasing somatic function) in a sample of breast cancer survivors (15). In addition, this set of points also reduced fatigue and sleep disturbance, common comorbidities in patients with OA and pain. These findings were largely replicated in another trial (16). Participants were instructed to apply 3 minutes of continuous pressure in clockwise or counterclockwise circles to each point. They were told that the pressure should be sufficient enough to evoke a "de qi" sensation (i.e., dull ache, tingling, or soreness). Participants were instructed to apply acupressure once daily, 5 days per week for 8 weeks.

Sham participants were given the same instructions as those for verum participants. The only difference was that they were taught to apply pressure to 9 points that were not on acupuncture meridians (Figure 1). UC participants did not perform acupressure, but had the opportunity to learn both verum and sham protocols at the end of study participation. Both types of acupressure were offered in order to keep the research assistants, as well as the participants, blind to acupressure group assignment. All participants were asked to refrain from seeking information about acupuncture or acupressure during their participation in the study.

<<hd3>>**Outcome measures.** <<hd4>>Primary outcome. The WOMAC pain subscale consists of 5 items, each rated on a 5-point scale (10). The scale score is the sum of the 5 items (range 0–20). The WOMAC pain subscale has been widely used as an outcome measure in intervention studies of knee and hip OA. In our sample, internal reliability was adequate ($\alpha = 0.80$).

<<hd4>>Secondary outcomes. The NRS for pain was used to assess the average pain level in participants over the previous week (11). The scale ranges 0–10, with a score of 0 representing no pain and 10 the worst possible pain. Subjective physical function was assessed using the WOMAC function subscale, which is based on self-reported restriction in physical function (10). It consists of 17 items, each rated on a 5-point scale. We summed all items to obtain scale scores (range 0–68). The internal reliability of this scale was high ($\alpha = 0.93$). Objective physical function was measured by the timed up-and-go (TUG) test and the comfortable gait speed (CGS) assessment. The TUG was designed to assess functional mobility and has shown good psychometric properties (17). It measures the time to get up from a chair, walk 9 feet, and then return to the chair. CGS measures the time to complete a 20-foot course at normal walking pace and was measured in meters/second. Gait speed has been shown to predict adverse health outcomes in community-dwelling older adults (18). Both the TUG and CGS were done 3 times, and the average of the 3 trials was used.

The NRS for pain was administered during weekly phone calls. All other outcomes were assessed at center visits (at baseline and at 4 and 8 weeks). To secure effective blinding when

assessing the outcomes, the research assistants were blinded to study hypotheses and they left the room while participants filled out questionnaires collecting data on self-reported outcomes during center visits. Higher scores indicated worse status for all outcomes except CGS, for which they indicated better status.

<<hd3>>**Statistical analysis.** An intent-to-treat principle was used in the analysis, where the group as randomized rather than actual treatment was used as a covariate. Differences in mean changes from the baseline assessment for each outcome at eight weeks were compared between groups using linear mixed regression models. This method allowed for inclusion of all available time points in the analysis, and correctly accounted for correlated data resulting from repeated measurements on the same subjects. A subject-specific Gaussian intercept term was used to model correlation induced by measurements taken on the same subject. The models included interaction terms for time and treatment groups. In the models for outcomes assessed during center visits, time was coded categorically (visit 1, 2, and 3). In the model for NRS pain, time was used as a continuous variable (number of weeks since baseline). A quadratic term of time was not included because it was not statistically significant. All models adjusted for baseline outcome scores, age (in years), race (white versus nonwhite), sex (male versus female) and body mass index. The analysis was conducted using Stata, version 13 (StataCorp). All hypotheses were tested using 2-sided likelihood ratio tests at a significance level of 5%. Independent t-tests and chi-square analyses were used to compare treatment groups on baseline characteristics, attrition rates, and MCID for the WOMAC pain subscale, as well as to compare withdrawn and continued participants.

<<hd1>>**RESULTS**

<<hd3>>**Flow and demographics of study participants.** More than half (n = 211) of the 412 people who underwent initial screening failed to meet the inclusion criteria (Figure 2).<<F2>> Thirty-two of those deemed eligible were lost to followup. Consequently, 169 were invited for additional screening. Of these, 19 were excluded for various reasons (Figure 2). In total, 150 older adults were enrolled, with 50 randomly assigned to each group.

Participants ranged from 65 to 96 years old (mean age 73) (Table 2).<<T2>> Most were women (62%), white (87.8%), and college or post-college graduates (82%). There were no significant between-group differences in baseline demographic characteristics, except that the verum group had more nonwhites (n = 10) than the UC group (n = 2).

<<hd3>>**Attrition, adherence, and adverse events.** The attrition rate was 14% at visit 2 and 17% at visit 3 (Figure 2). The 3 groups did not differ in attrition rates. A higher percentage of nonwhites (33%, n = 6) than whites (15%, n = 20) withdrew, and withdrawn participants performed significantly better on the TUG (t = 2.6, P = 0.01) and CGS (t = 2.7, P = 0.007) at baseline than those who completed the study.

At visit 2, the vast majority of verum and sham participants scored 100% correct on a competency checklist; only 5 of 85 (5.9%) missed the location of 1 or 2 acupoints. Treatment adherence was high: 81–90% reported practicing the acupressure protocol as instructed most of the time across all weekly telephone contacts (12).

A total of 30 adverse events were recorded, only 3 of which were judged to be related to the study and 1 possibly related to the study (12). The related events were broken skin and soreness in acupoint areas, which were likely caused by incorrect use of the handheld device for acupressure.

Effects of treatment on outcomes.

<<hd3>>**Effects of treatment on outcomes.** Descriptive statistics for the primary and secondary outcomes that were assessed during center visits are shown in Table 3.<<T3>> There were no significant between group differences in these outcomes at baseline. The NRS for pain was measured during weekly phone contacts; on average the participants were assessed 5.2 times. There were no significant between-group differences in the NRS at the first assessment (mean ratings were 5.3, 5.2, and 5.5 for the verum, sham, and UC groups, respectively). Approximately 46%, 63%, and 36% of verum, sham and UC participants, respectively, met the MCID criterion for pain improvement at 4 weeks (Table 3). The corresponding figures at 8 weeks were 56%, 71%, and 50%. Group differences in the percentage of participants achieving MCID improvement at both visits were mostly not statistically significant; only the sham group had a significantly higher percentage than the UC group at visit 2 ($\chi^2 = 6.2$, P = 0.013). The results of the linear mixed regression models to test our hypotheses are shown in Table 4.<<T4>>

Compared with the UC group, both the verum group (mean difference −1.27 units [95% confidence interval (95% CI) −1.95, −0.58]) and the sham group (mean difference −1.24 units [95% CI −1.92,−0.55]) had a greater reduction in WOMAC pain at 8 weeks, and the differences were statistically significant. But there were no significant differences between the verum and sham groups in WOMAC pain at 8 weeks (mean difference −0.03 units [95% CI −0.72, 0.67]). The same pattern was observed for NRS pain and WOMAC function. There were no significant between-group differences in TUG test scores at 8 weeks. On the CGS, the verum group had significantly more improvement than the UC group at 8 weeks, while the differences between the sham and UC groups and between the verum and sham groups were not statistically significant.

<<hd1>>**DISCUSSION**

In this double-blind RCT, we found that participants performing verum acupressure experienced significantly more improvement in pain and physical function than UC participants after 8 weeks of treatment. However, a similar pattern of differences was also found between the sham and UC groups, and the verum and sham groups did not differ significantly in any primary or secondary outcomes at 8 weeks. Our findings are very similar to some acupuncture studies, especially those with adequate blinding, which show no significant differences between true and sham acupuncture on pain, and that both were superior to usual care or waitlist controls (19–21).

One explanation of our findings is the placebo effect, that is, the verum intervention may not have a specific therapeutic effect, and a strong placebo effect may have contributed to better outcomes for verum than UC. Two considerations should be kept in mind with this interpretation. First, theoretically, sham interventions should not be distinguishable from the active ones and should be inert (9). However evidence suggests that sham acupuncture (and likely acupressure) is a procedure that is not inert and is a more effective analgesic than a placebo pill (22). For example, one study of acupuncture in patients with irritable bowel syndrome shows that the sham intervention had a dose-dependent response, i.e.., greater improvement in pain for patients receiving a greater dose of sham acupuncture (23). Second, evidence from neuroimaging studies has shown that different patterns of brain activation are associated with true and sham acupuncture, although the clinical symptom improvement is identical (24,25). It is possible that verum acupressure acts on neuropathways that are different from those acted on by sham acupressure, while both produce significant analgesic effects.

However, to date, there are no published neuroimaging studies investigating the effects of acupressure on the brain.

Another explanation of the findings is that our verum acupressure protocol, including selection of acupoints, frequency, and duration, may not be an effective prescription for people with symptomatic knee OA. There is no standard protocol of acupressure treatment. Our verum protocol was developed based on a pilot study of breast cancer survivors. In previous acupressure trials, different acupoints were selected even when the same disease was treated (6,8). It is fair to say that in clinical practice, acupoint selection and dosage are individualized. In that respect, using a standardized protocol may not be a fair test of the efficacy of acupressure. But from a research perspective, consistency in the administration of acupressure protocol is needed to establish evidence. Innovative studies such as the one reported here are needed to build a knowledge base on acupressure and identify effective prescriptions for specific conditions.

Another side of the protocol argument is that our sham intervention may be too good. It should be noted that leaders within the acupuncture field have failed to agree upon what constitutes an appropriate sham control (9,22), which is applicable for acupressure studies. We used non-acupoint stimulation, which was the most commonly used sham control in acupressure trials (9). The routine of self-practice of the protocol may have increased the positive expectation and sense of control that contribute to symptom relief (9). But our findings suggest that practicing verum acupressure did not have an additional effect.

Compared to prior acupressure studies, this study was rigorously conducted. It also is one of the few acupressure studies that specifically targeted older adults. We have improved upon prior acupressure studies by conducting a true double-blind RCT, although obviously the assignment to usual care cannot be masked. Most acupressure and acupuncture studies to date have been single-blind, wherein the individual performing the intervention knew whether or not they were performing verum or sham treatment. We also utilized adequate randomization and both subjective and objective outcome measures. Importantly, the use of a 3-arm design enabled us to examine differences between verum and sham acupressure in treatment outcomes.

Our study has some limitations. First, sample recruitment was a challenge, and we recruited fewer participants (50 per arm) than intended (60 per arm) (12). A post hoc reassessment of our data shows a small effect size of 0.01 between the verum and sham groups and a low power of 5% with either intended or actual recruitment. So the results would likely not have changed even if we had obtained the intended sample size. However, compared to other acupressure studies, our trial involved a relatively large sample. Some have suggested that for acupuncture, fairly large sample sizes (i.e., numbering in the hundreds) are needed to achieve significant differences between verum and sham treatments (26). Second, although we have made an effort to blind both research personnel and study participants to the verum and sham group assignments, it may not have been completely successful. An assessment of the success of blindness would have been useful information. Third, some participants may have engaged in other treatments or behaviors, a new exercise program, for example, that could have affected their pain, and these new treatments were not tracked in our study. Fourth, our sample was mostly white and had relatively high levels of education. The extent to which the findings are applicable to other older populations, such as ethnic minorities and those with low levels of education, is unclear. Finally, we have tested one particular protocol of acupressure and we do not know the efficacy of any others.

In conclusion, the findings show that self-administered acupressure is superior to usual care in managing pain and improving physical function for older adults with symptomatic knee

OA. The reason for the positive benefits is unclear, and the placebo effect may have played a role. Previous acupressure trials have predominantly reported positive findings, which fuels the idea of integrating acupressure into current clinical care (7). Our findings suggest that such enthusiasm be tempered with caution. At least for knee OA, more research is needed before adopting acupressure as a legitimate treatment approach. However, for some older adults with symptomatic knee OA, especially those with a high pill burden, acupressure may be considered as an adjunct to usual care. Further research to understand the neurophysiological and neurochemical responses, if present, associated with verum and sham acupressure would help to illuminate the physiological effects associated with acupressure. Future studies would benefit from having a larger sample size and longer followup, as well as assessing and controlling for treatment expectation in their trial design.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Li had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Li, Harris, Struble, Murphy.
Acquisition of data. Li, Harris, Murphy.
Analysis and interpretation of data. Li, Harris, Tsodikov, Murphy.

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Figure 1. Point locations for verum and sham acupressure. * = bilateral. Ht = heart; Sp = spleen; Liv = liver.

Figure 2. Flow of participants through the study.

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Table 1. Subject inclusion and exclusion criteria*

Inclusion criteria
  Age 65 years or older
  Community dwelling (i.e., own home, senior residence, apartment)
  Meets the ACR clinical criteria for knee osteoarthritis (14)†
  Have moderate to severe knee pain (≥3 on a 0–10 NRS) lasting 3 months or longer†
  Body mass index ≤45
  Ability to speak and write in English
  Adequate cognitive status (score >5 on the 6-item screener) (27)
  Adequate functional ability to administer the acupressure protocol (e.g., able to use fingers or device
    to apply pressure to acupoints and able to easily reach feet to access acupoints)
  Ability to understand the treatment protocol through demonstration after being instructed
  Ambulatory with or without an assistive device
  Adequate hearing and vision to follow study protocol
  Have a telephone and television
Exclusion criteria
  Have cancer or received cancer treatment within last 6 months (exception: skin cancer where the
    location is not around acupoints)
  Have any bleeding diathesis conditions or taking anticoagulant/antiplatelet medications
  Have health conditions that could confound the effect of acupressure (e.g., rheumatoid arthritis,
    lupus, multiple sclerosis, diabetic neuropathy, peripheral neuropathy, Parkinson's disease, arm
    or leg paralysis)
  Have ever had knee replacement surgery
  Have received in the last 2 months: occupational or physical therapy, acupuncture or acupressure
    therapy, opioid therapy, cognitive–behavioral therapy, arthritis self-management programs,
    arthroscopic procedure, or knee injection
  Planned or scheduled new treatment for knee pain in the next 3 months
  Regular current use of narcotics or centrally acting agents (Pristig, Duragestic, Fentora, Actiq,
    hydrocodone, Lorcet/Lortab, Norco, Cadeline, hydromorphone, Dilaudid, Demerol, Exalgo,
    methadone, tramadol, Ultram, Meperidline, Dolophine, Methadose, Percocet, morphine, MS
    Contin, Oxycodone, Oxycontin, and fentanyl)

* ACR = American College of Rheumatology; NRS = numeric rating scale.
† If bilateral symptoms were present, the most symptomatic knee was evaluated.

Table 2. Baseline characteristics of all participants and by treatment group*				
	Total **(n = 150)**	**Verum acupressure** **(n = 50)**	**Sham acupressure** **(n = 50)**	**Usual care** **(n = 50)**
Age, mean ± SD years	72.7 ± 6.5	71.7 ± 5.7	73.2 ± 7.4	73.3 ± 6.2
Women, %	62	66	54	66
Race, %				
White	87.8	80	87.5	95.9
Nonwhite	12.2	20	12.5	4.1
Education, %				
< college degree	17.6	16	16.3	20.4
College degree	33.1	28	40.8	30.6
Graduate degree	49.3	56	42.9	49.0
Annual income, %				
<$30,000	13.7	4.3	19.5	18.6
$30,000–49,999	19.1	21.3	7.3	27.9
$50,000–69,999	22.9	25.5	24.4	18.6
$70,000–89,999	16.0	23.4	19.5	14.0
≥$90,000	28.3	25.5	29.3	20.9
Marital status, %				
Married	54.8	58	59.2	46.8
Divorced/separated	23.3	20	18.4	31.9
Widowed	11.7	10	10.2	14.9
Never married	7.5	8	10.2	4.3
Other	2.7	4	2	2.1
Body mass index, mean ± SD kg/m^2	29.1 ± 5.6	29.7 ± 6.1	29.0 ± 5.3	28.7 ± 5.5

Table 3. Mean ± SD scores at baseline, 4 weeks, and 8 weeks by treatment group*

	Verum acupressure			Sham acupressure			Usual care		
	Baseline (n = 50)	4 weeks (n = 44)	8 weeks (n = 41)	Baseline (n = 50)	4 weeks (n = 41)	8 weeks (n = 41)	Baseline (n = 50)	4 weeks (n = 44)	8 weeks (n = 42)
Primary outcome									
WOMAC pain†	6.5 ± 2.6	5.4 ± 2.7	4.8 ± 2.9	6.8 ± 3.2	6.0 ± 2.9	5.5 ± 2.8	6.9 ± 2.9	6.5 ± 3.2	6.3 ± 3.3
% MCID‡		45.5	56.1		63.4	70.7		36.4	50
Secondary outcomes									
WOMAC function†	20.5 ± 8.3	16.4 ± 9.0	14.4 ± 7.8	23.9 ± 10.5	20.7 ± 10.5	18.3 ± 10.5	22.2 ± 9.5	20.6 ± 9.6	19.9 ± 10.9
TUG, seconds	10.55 ± 2.66	9.98 ± 2.32	9.38 ± 1.86	11.20 ± 3.16	10.76 ± 2.89	10.45 ± 2.83	10.37 ± 2.23	10.09 ± 2.21	9.83 ± 2.03
CGS, meters/second	1.09 ± 0.23	1.13 ± 0.21	1.18 ± 0.17	1.05 ± 0.25	1.08 ± 0.23	1.11 ± 0.23	1.11 ± 0.21	1.11 ± 0.22	1.12 ± 0.19

* Higher scores on WOMAC subscales and TUG, and lower scores on CGS, indicate worse status. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; MCID = minimum clinically important difference; TUG = timed up-and-go; CGS = comfortable gait speed.

† WOMAC pain range 0–20 and WOMAC function range 0–64.
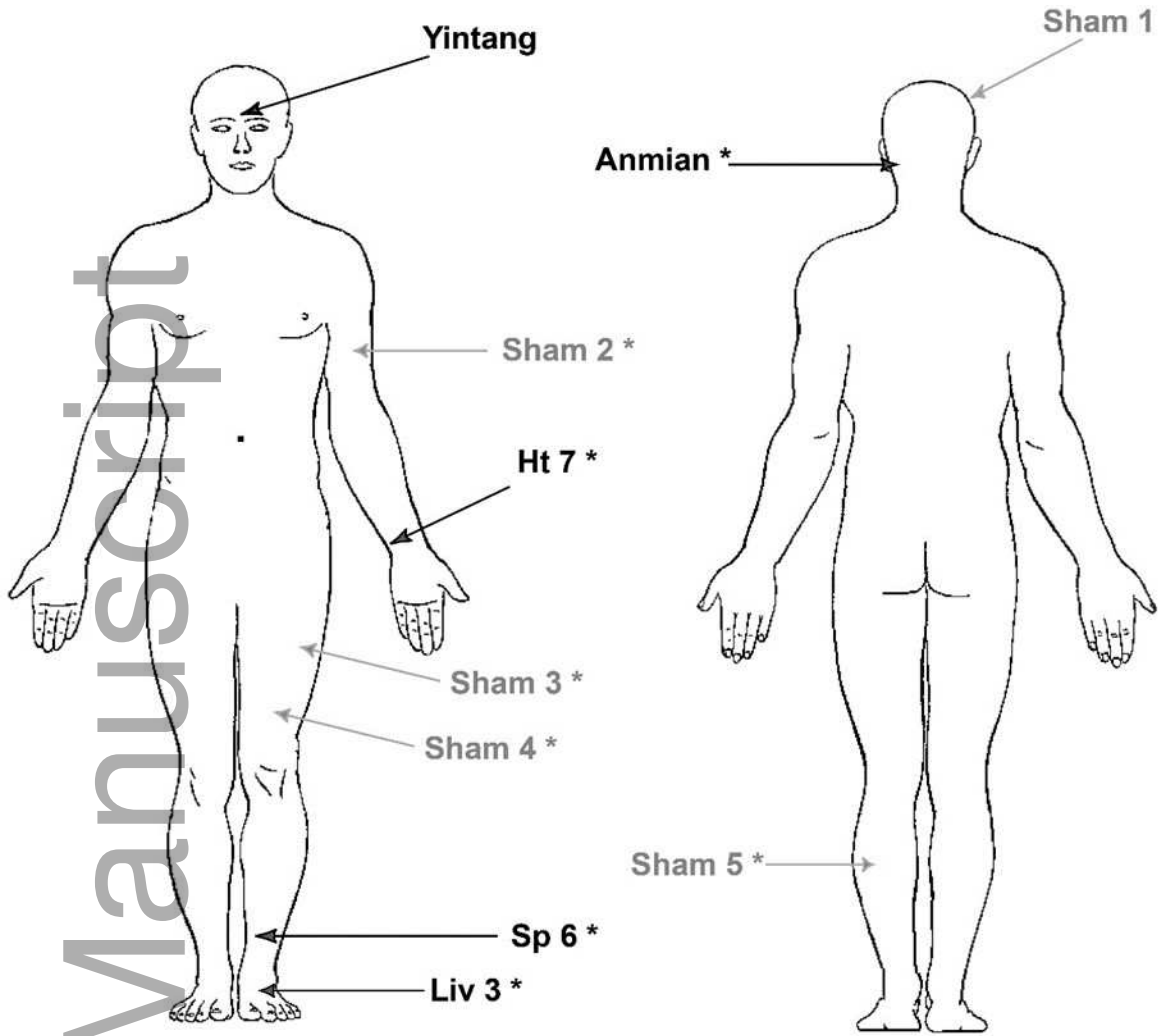
‡ MCID defined as >12% of baseline WOMAC pain.

Table 4. Estimated differences between treatment groups in mean change in outcomes at 8 weeks*

Outcome measures	Verum acupressure vs. usual care		Sham acupressure vs. usual care		Verum vs. sham acupressure	
	Estimates (95% CI)	P	Estimates (95% CI)	P	Estimates (95% CI)	P
Primary						
WOMAC pain†	−1.27 (−1.95, −0.58)	< 0.001	−1.24 (−1.92, −0.55)	< 0.001	−0.03 (−0.72, 0.67)	0.93
Secondary						
NRS pain†	−0.74 (−1.24, −0.24)	0.004	−0.51 (−1.01, −0.01)	0.05	−0.23 (−0.74, 0.28)	0.38
WOMAC function†	−4.83 (−6.99, −2.67)	< 0.001	−4.21 (−6.37, −2.04)	< 0.001	−0.62 (−2.83, 1.59)	0.58
TUG†	−0.22 (−0.64, 0.21)	0.32	0.09 (−0.33, 0.52)	0.67	−0.31 (−0.74, 0.12)	0.16
CGS‡	0.05 (0.02, 0.09)	0.003	0.03 (−0.01, 0.07)	0.09	0.02 (−0.01, 0.06)	0.22

* Linear mixed regression models were estimated. All models adjusted for baseline value of the outcome measure, age, sex, race, and body mass index. 95% CI = 95% confidence interval; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; NRS = numeric rating scale; TUG = timed up-and-go; CGS = comfortable gait speed.
† Negative values indicate better mean in the first-named group than the comparison group.
‡ Positive values indicate better mean in the first-named group than the comparison group.

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Initial Phone Screening (n=412)

Inclusion criteria not met (n=211)

Eligible (n=201)

Lost to follow up (n=32)

Screen failures (n=19)
-Ineligible medications (n=6)
-Ineligible interventions (n=5)
-Ineligible health conditions (n=6)
-Other (n=2)

Second-level screening (n=169)

Randomized (n=150)

Allocated to verum acupressure (n=50)
• Completed visit 1 (n=50)

Allocated to sham acupressure (n=50)
• Completed visit 1 (n=50)

Allocated to usual care (n=50)
• Completed visit 1 (n=50)

Completed visit 2 (n=44)

-6 withdrew
• interference of other health conditions (3)
• time constrain (2)
• sought other therapies (1)

Completed visit 2 (n=41)

-9 withdrew
• Interference of other health conditions (3)
• lost interest (3)
• time constraint (2)
• sought other therapies (1)

Completed visit 2 (n=44)

-6 withdrew
• Time constraint (2)
• Sought other therapies (4)

Completed visit 3 (n=41)

-3 withdrew
• Interference of other health conditions (2)
• Sought other therapies (1)

Completed visit 3 (n=41)

Completed visit 3 (n=42)

-2 withdrew
• Lost interest (2)

50 used for linear mixed regression analysis

50 used for linear mixed regression analysis

50 used for linear mixed regression analysis