Annals of Internal Medicine ORIGINAL RESEARCH

Effect of Acupuncture for Methadone Reduction

A Randomized Clinical Trial

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Background: Methadone maintenance treatment (MMT) is effective for managing opioid use disorder, but adverse effects mean that optimal therapy occurs with the lowest dose that controls opioid craving.

Objective: To assess the efficacy of acupuncture versus sham acupuncture on methadone dose reduction.

Design: Multicenter, 2-group, randomized, sham-controlled trial. (Chinese Clinical Trial Registry: ChiCTR2200058123)

Setting: 6 MMT clinics in China.

Participants: Adults aged 65 years or younger with opioid use disorder who attended clinic daily and had been using MMT for at least 6 weeks.

Intervention: Acupuncture or sham acupuncture 3 times a week for 8 weeks.

Measurements: The 2 primary outcomes were the proportion of participants who achieved a reduction in methadone dose of 20% or more compared with baseline and opioid craving, which was measured by the change from baseline on a 100-mm visual analogue scale (VAS).

Results: Of 118 eligible participants, 60 were randomly assigned to acupuncture and 58 were randomly assigned to sham acupuncture (2 did not receive acupuncture). At week 8, more patients reduced their methadone dose 20% or more with acupuncture than with sham acupuncture (37 [62%] vs. 16 [29%]; risk difference, 32% [97.5% CI, 13% to 52%]; $P < 0.001$). In addition, acupuncture was more effective in decreasing opioid craving than sham acupuncture with a mean difference of −11.7 mm VAS (CI, −18.7 to −4.8 mm; $P < 0.001$). No serious adverse events occurred. There were no notable differences between study groups when participants were asked which type of acupuncture they received.

Limitation: Fixed acupuncture protocol limited personalization and only 12 weeks of follow-up after stopping acupuncture.

Conclusion: Eight weeks of acupuncture were superior to sham acupuncture in reducing methadone dose and decreasing opioid craving.

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Addiction to opioids remains a continuing problem globally. In 2020, an estimated 61.3 million persons had used opioids in the past year worldwide, which corresponds to 1.2% of the global population aged 15 to 64 years (1). Methadone maintenance treatment (MMT) has been widely used to decrease the use of opioids (2), suppress withdrawal symptoms induced by the abrupt withdrawal of opioids (3), and reduce criminal activities (4, 5). Patients with opioid use disorders (OUDs) must receive MMT for years or throughout their lives.

Although MMT has yielded some beneficial effects, its adverse effects have also been widely reported, such as constipation, dizziness, and debility (6, 7). Therefore, many MMT clients require or are experiencing methadone dose reduction (8). However, during the process of tapering methadone dosage, MMT clients often have persistent withdrawal symptoms, such as anxiety, depression, insomnia, and a heightened craving for opioids (9). These factors may reduce their adherence to MMT and increase the risk for opioid relapse (10).

Acupuncture has been recognized by the World Health Organization as an appropriate nonpharmacologic therapy for substance dependence (11). A systematic review supports the use of acupuncture to decrease methadone doses in MMT clients (12). Other studies have suggested the potential benefits of acupuncture in reducing cravings for opioids, accelerating the reduction of methadone doses, improving sleep quality, and improving symptoms of depression and anxiety (13–17). However, drawing reliable conclusions from these trials has been difficult because of the lack of methodological rigor, such as the absence of sham acupuncture as a

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placebo control. Therefore, we designed a randomized clinical trial among MMT clients using a nonpenetrating sham control and assessment of blinding to determine the efficacy and safety of acupuncture for methadone reduction in MMT clients.

METHODS

Trial Design

This multicenter, randomized, sham-controlled trial was done between April 2022 and April 2023 at 6 sites in China. The trial protocol was approved by the Ethics Committee of the Panyu Hospital of Traditional Chinese Medicine (2022029) and was overseen by an independent trial steering committee and data monitoring and ethics committee. Study participants were informed of all details of the study, and each participant provided written informed consent. Additional details are presented in the study protocol (available at Annals.org).

Participants

Participants were MMT clients aged 18 to 65 years who met the diagnostic criteria for OUD as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (18) and had received MMT for more than 6 weeks. Key exclusion criteria included having a history of mental illness other than drug dependence and having received other treatment that may affect the efficacy evaluation of the present intervention. A complete list of the inclusion and exclusion criteria is provided in Supplement Figure 1 (available at Annals.org).

Randomization and Blinding

Eligible participants were randomly assigned in a 1:1 ratio to acupuncture or sham acupuncture group using a central web-based randomization system (South China Research Center for Acupuncture and Moxibustion). The randomization sequence was generated in a block size of 4. The participants were allocated by an independent researcher who was not involved in the outcome assessment. Acupuncturists were not blinded to group allocation. However, the outcome assessors, study site physicians and nurses, data collectors, and statisticians were all blinded to group allocations. An independent researcher supervised the conversation between participants and physicians to avoid them communicating issues related to the allocation.

Interventions

Six licensed acupuncturists with more than 3 years of clinic experience performed the interventions. According to the traditional acupuncture theory and our previous studies (13, 15), acupuncture interventions were developed by a consensus of acupuncture experts. The acupoints selected were "Dingshen-zhen," "Sishen-zhen," and "Shouzhi-zhen," which are commonly used to treat psychiatric disorders, such as opiate withdrawal (19). The acupoints used in the sham acupuncture group were the same as those in the acupuncture group. Descriptions of the acupoints, including their location and the depth of needle insertion, are shown in Supplement Table 1 and Supplement Figure 2 (available at Annals.org). Before the study initiation, the acupuncturists had special training to obtain a full understanding of the acupuncture intervention and received a brochure with detailed information on acupuncture manipulations, which is provided in Supplement Figure 3 (available at Annals.org). Participants assigned to each group received manual acupuncture or sham manual acupuncture for 30 minutes per session. Twenty-four sessions were delivered over 8 weeks (3 per week), followed by 12 weeks of follow-up.

To blind patients to the type of acupuncture, we used a special device that we have used previously (20). The device consisted of a plastic pedestal and a guide tube, and the same device was used for both types of acupuncture. The acupuncturist placed the device over an acupoint, inserted either a sharp or blunt needle into the guide tube, quickly tapped the top of the tube to make the needle go downward, and then removed the guide tube, leaving the device and needle in place. The device is depicted in Supplement Figure 4 (available at Annals.org).

We used sterile, stainless steel, sharp or blunt, disposable acupuncture needles (Huatuo; lengths and diameters: 25 × 0.3 mm). Sharp needles were inserted through the device into the deep tissue layers of acupoints (Supplement Figure 2), and the acupuncturist endeavored to elicit a *deqi* sensation by manually manipulating the needles. *Deqi* is a unique sensation felt by the recipient that is described as heaviness, soreness, or numbness. When blunt needles were used, patients felt a pricking sensation that simulated actual acupuncture, although blunt needles did not penetrate the skin. Acupuncturists followed the same procedure for each study group using standardized step-by-step instructions developed for the study (Supplement Figure 3). Acupuncture sessions lasted 30 minutes, and each acupoint was manipulated for 10 seconds with 3 repetitions at 10-minute intervals.

Outcomes

This trial had 2 primary outcomes. One primary outcome was defined as the proportion of participants who achieved a reduction in methadone dose of 20% or more compared with baseline after 8 weeks of intervention. All participants were expected to visit the clinic every day and ingest a methadone dose daily, which was administered by clinic physicians. Independent observers obtained daily consumption of methadone from physicians to document the methadone dose. On the basis of the standards and clinical guidelines of MMT in the United States and Canada, a biweekly reduction of 5% in methadone dose is considered an effective

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reduction. Previous studies also found that achieving a reduction in methadone dose of 20% or more at the end of acupuncture intervention was associated with clinically significant benefits and proven to be efficacious in preventing relapse (13, 15, 21, 22). Therefore, a 20% reduction in methadone dose was used as the threshold to define substantial improvement in tapering effectiveness.

The other primary outcome was the change from baseline in the opioid craving visual analogue scale (VAS) at week 8, which was assessed using a 100-mm VAS. The opioid craving VAS score was determined by measuring millimeters from the left-hand end of the line to the point marked by the participant (score range, 0 [no craving] to 100 [strongest craving]).

Secondary outcome measures were also measured at 8 weeks. They included the severity of opioid withdrawal symptoms (Clinical Opioid Withdrawal Scale; score range, 0 to 48, with 48 representing the severest withdrawal symptoms) (23); sleep quality (Pittsburgh Sleep Quality Index; score range, 0 to 21, with 21 indicating worst sleep quality) (24); anxiety (Beck Anxiety Inventory scale; score range, 0 to 63, with 63 indicating severest anxiety) (25); and depression (the Beck Depression Inventory II scale; score range, 0 to 63, with 63 indicating worst depression) (26). Independent research assistants helped participants to complete the opioid craving VAS and all secondary outcome measures in pen and paper format and evaluated their outcomes. In addition, all participants were requested to submit a urine sample at baseline and randomly during the study each month, which was used to test for opioid relapse.

Upon the culmination of 8 weeks of intervention, we assessed the efficacy of blinding on participants by inquiring whether they perceived the insertion of the needle tip into their skin. Any adverse events after each intervention were carefully documented, including subcutaneous hemorrhage, other bleeding, notable pain, fainting, and local infections.

Statistical Analyses

The calculation of the sample size was done using PASS 14 software (NCSS Statistical Software). Estimates of clinically meaningful differences between the acupuncture group and the sham acupuncture group were based on data from Nosyk and colleagues and our previous study (13, 15, 27). We assumed an

Figure 1. Flow chart for enrollments, allocation, follow-up, and analysis.

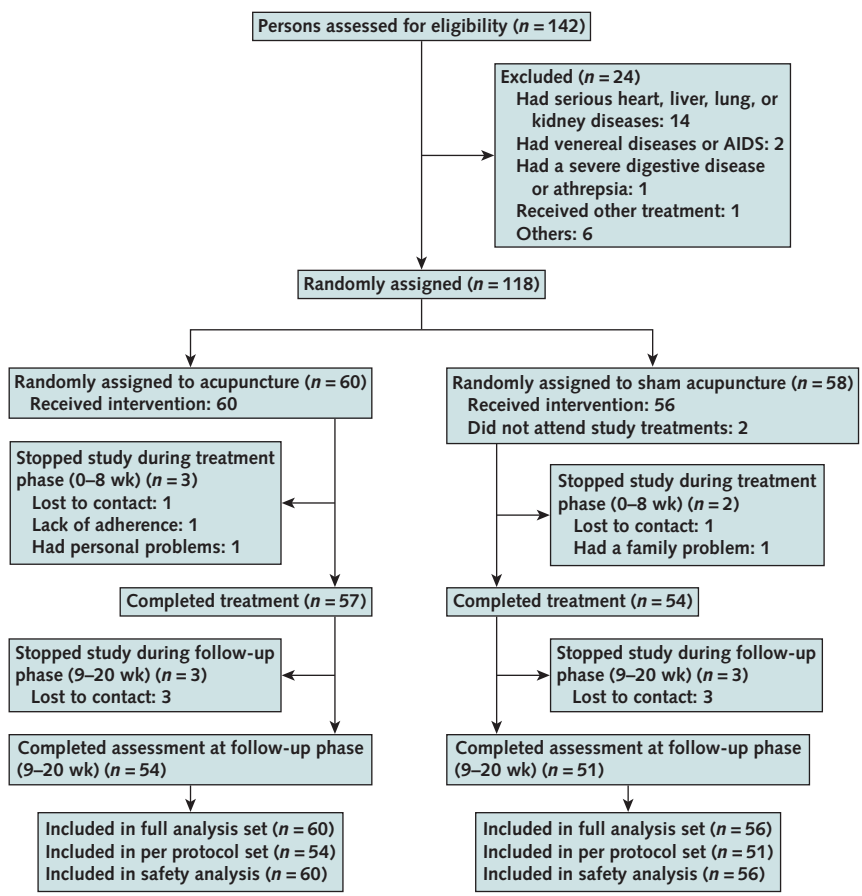

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Table 1. Characteristics of the Participants at Baseline (Full Analysis Set)

Characteristic	Acupuncture Group ($n = 60$)	Sham Acupuncture Group ($n = 56$)
Mean age (95% CI), *y*	47.2 (45.1–49.3)	49.0 (47.1–50.9)
Men, *n* (%)	52 (86.7)	51 (91.0)
Mean body mass index (95% CI), kg/m^2	23.2 (22.2–24.1)	23.5 (22.7–24.4)
Marital status, *n* (%)		
Married	45 (75.0)	40 (71.4)
Single	7 (11.7)	10 (17.8)
Divorce	8 (13.3)	6 (10.7)
Occupation, *n* (%)		
Employed	45 (75.0)	39 (69.6)
Unemployed	15 (25.0)	17 (30.4)
Education, *n* (%)		
Primary or middle school	46 (76.7)	45 (80.4)
High school or university	14 (23.3)	11 (19.6)
Mean years of opioid use (95% CI), *y*	13.7 (11.9–15.5)	15.2 (13.2–17.2)
Primary route of previous opioid use, *n* (%)		
Injection	41 (68.3)	45 (80.4)
Nasal or oral	19 (31.7)	11 (19.6)
Mean methadone dosage (95% CI), *mg*	43.0 (35.3–50.7)	40.9 (33.0–48.7)
Mean opioid craving VAS score (95% CI)*	84.0 (77.8–90.2)	80.6 (73.2–88.0)
Mean COWS score (95% CI)*	3.2 (2.31–3.99)	3.5 (2.6–4.3)
Mean PSQI score (95% CI)*	9.2 (8.2–10.2)	9.7 (8.8–10.7)
Mean BAI score (95% CI)*	7.6 (6.0–9.1)	7.8 (6.0–9.7)
Mean BDI-II score (95% CI)*	7.8 (6.3–9.3)	8.8 (6.7–10.8)
Opioid urine screen, *n* (%)		
Positive	0 (0.0)	0 (0.0)
Negative	60 (100.0)	56 (100.0)

BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-II; COWS = Clinical Opioid Withdrawal Scale; PSQI = Pittsburgh Sleep Quality Index; VAS = visual analogue scale.
* Higher scores indicate worse symptoms.

efficacy rate of 70% for the acupuncture group and 36% for the sham acupuncture group; 42 participants per group were needed at 5% significance with 90% power. This provided at least 99% power to detect a mean difference of 10 (SD, 8) in opioid craving VAS scores between the 2 groups at a 5% significance level for a 2-sided test. Thus, anticipating approximately 15% attrition, at least 50 participants per group ($n = 100$ total) were required. Due to the global COVID-19 pandemic occurring at the onset of our study, we anticipated an increase in dropout rates from the originally estimated 15% to 30%. Consequently, we increased our recruitment target to 120 participants in actual subject enrollment.

The primary analyses differed from the methods in the protocol at the request of the reviewers. The outcomes were analyzed using the full analysis set, comprising all randomized patients who received at least 1 session of acupuncture intervention and at least 1 efficacy measure. Missing data were filled by using multiple imputations (**Supplement Table 2**, available at Annals.org). For each time point, measurements of primary and secondary outcomes were imputed using groups and outcomes measurements before the time point as covariates in regression models. The estimated values were set as integers, and 20 different data sets were generated. Subsequently, each imputed set was analyzed, and the Rubin combining rule was applied. Continuous variables were reported as mean with SD or median and interquartile range and compared with *t* test or Wilcoxon rank-sum test as appropriate. Categorical variables were described as numbers and percentages. We applied a generalized linear model to analyze the binary outcome of proportion of participants with at least 20% reduction from baseline in the amount of methadone dose to analyze group effects. The model used a binomial probability distribution and a logit link function.

We performed sensitivity analyses by replicating the analyses in the per protocol set, which included all randomized patients who completed all of the intervention and 20-week follow-up assessments. Safety analysis was done in the safety data set, which included all randomized patients who received at least 1 session of acupuncture.

Statistical analyses were done by an independent statistician using SAS, version 9.4 (SAS Institute). Primary outcomes used 2-sided tests at the 2.5% significance level (28).

Role of the Funding Source

The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

RESULTS

Participants

From April 2022 to April 2023, a total of 142 patients were screened, and 118 patients were enrolled and randomly assigned to either the acupuncture group ($n = 60$) or the sham acupuncture group ($n = 58$). Before the initiation of any intervention, 2 patients withdrew from the study. Thus, 116 patients were included in the full analysis set. The main reason for exclusion was having serious heart, liver, lung, or kidney disease at baseline (**Supplement Table 3**, available at Annals.org). Among all patients, 105 completed all 8 weeks of intervention plus an additional 12 weeks of follow-up (**Figure 1**). Baseline characteristics of patients are shown in **Table 1**.

Primary Outcomes

At week 8, more patients reduced their methadone dose 20% or more with acupuncture than with sham acupuncture (37 [62% {97.5% CI, 48% to 76%}] vs. 16 [29%, {CI, 15% to 43%}]; risk difference, 32% [CI, 13% to 52%]; $P < 0.001$) (**Table 2**; **Figure 2**; and **Supplement Table 4**, available at Annals.org). The mean VAS score for opioid craving with acupuncture was 84.0 (CI, 76.9 to 91.1) at baseline and 67.8 (CI, 60.9 to 74.7) at 8 weeks for a difference of −16.2 (CI, −20.8 to −11.6).

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Table 2. Primary Outcome Measurements in Full Analysis Set Population at Week 8*

Outcomes	Acupuncture ($n = 60$)	Sham Acupuncture ($n = 56$)	Acupuncture Versus Sham, MD or RD (97.5% CI)	*P* Value
Proportion of participants with ≥20% reduction in methadone dose compared with baseline, *n* (binominal proportion [97.5% CI])	37 (0.62 [0.48 to 0.76])	16 (0.29 [0.15 to 0.43])	0.32 (0.13 to 0.52)	<0.001
Opioid craving VAS, MD (97.5% CI)†	−16.2 (−20.8 to −11.6)	−4.5 (−9.7 to 0.7)	−11.7 (−18.7 to −4.8)	<0.001

MD = mean difference; RD = risk difference; VAS = visual analogue scale.
* Outcomes measured at other time points are shown in Supplement Tables 4 and 5 (available at Annals.org). Negative estimates indicate improvement.
† The estimates were mean changes of the outcomes relative to baseline scores.

The mean VAS score for opioid craving with sham acupuncture was 80.6 (CI, 72.1 to 89.2) at baseline and 76.2 (CI, 67.4 to 84.9) at 8 weeks for a difference of −4.5 (CI, −9.7 to 0.7). Participants who received acupuncture had a greater reduction in their mean opioid craving VAS score than those in the sham acupuncture group (mean difference, −11.7 [CI, −18.7 to −4.8]; $P < 0.001$) (Table 2; Figure 3; Supplement Figure 5 and Supplement Tables 4 and 5, available at Annals.org).

For the sensitivity analyses, we found that the intergroup comparison results for the 2 primary outcomes of the full analysis set were consistent with the results of the per protocol data set. The per protocol analysis results measured over time are shown in Supplement Tables 6 and 7 (available at Annals.org).

Secondary Outcomes

The Pittsburgh Sleep Quality Index showed a greater reduction in score for the acupuncture group than the sham acupuncture group at week 8 (mean difference, −2.3 [95% CI, −3.4 to −1.2]) (Table 2 and Figure 4). All participants tested negative for opioid use over the course of the study.

Treatment Blinding

At the end of the intervention, we assessed the credibility of blinding participants. The results indicated that there were no meaningful differences between the acupuncture and the sham acupuncture groups regarding patients' ability to accurately discern their assigned intervention status (Table 3).

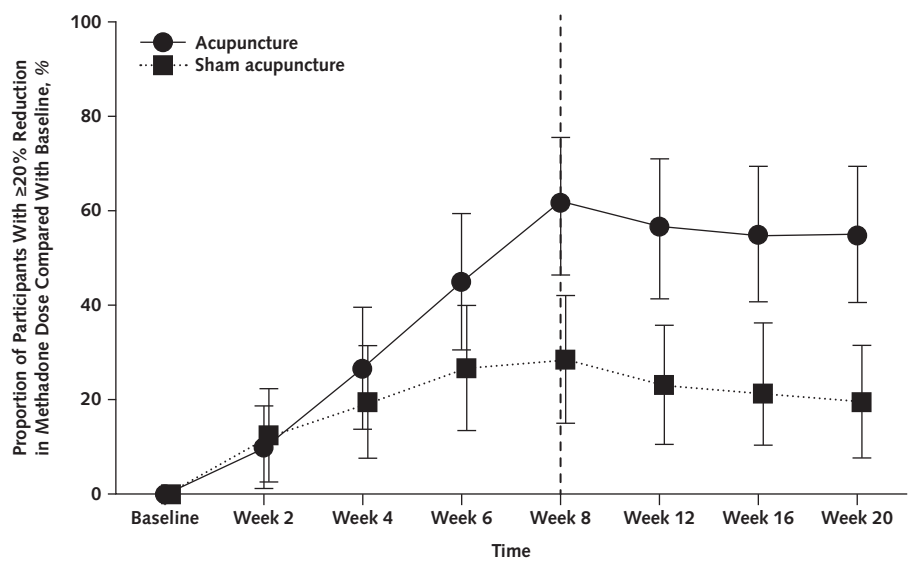
Adverse Events

Four patients (6.7%) reported subcutaneous hemorrhage in the acupuncture group compared with no patients in the sham acupuncture group. No patients had severe adverse events (Supplement Table 8, available at Annals.org).

Discussion

This multicenter, randomized, sham-controlled trial showed that for MMT clients with OUD, acupuncture

Figure 2. Efficacy rate of methadone dose reduction.



Efficacy rate of methadone dose reduction was defined as the proportion of participants who achieved a reduction in methadone dose of ≥20% compared with baseline. In the line plot, the area to the right of the vertical dashed line represents the follow-up period, when participants were not receiving manual or sham acupuncture. Error bars represent 97.5% CIs.

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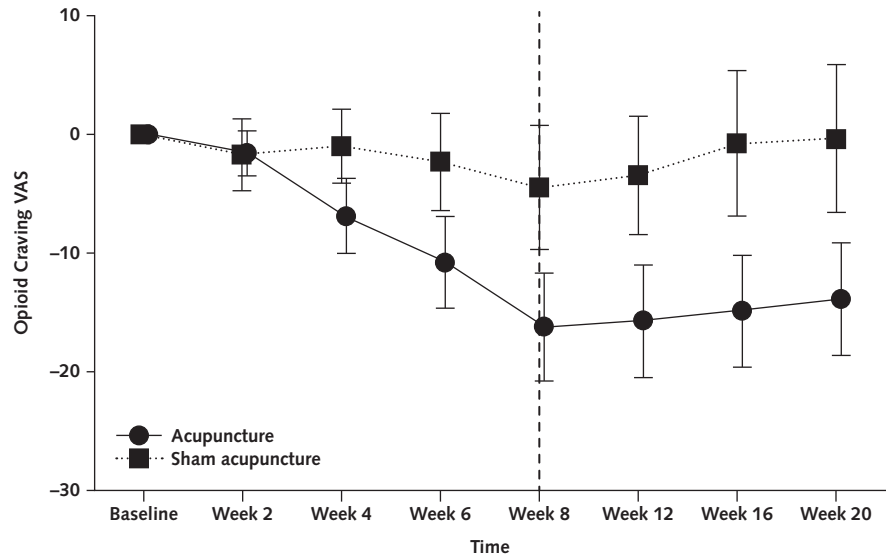
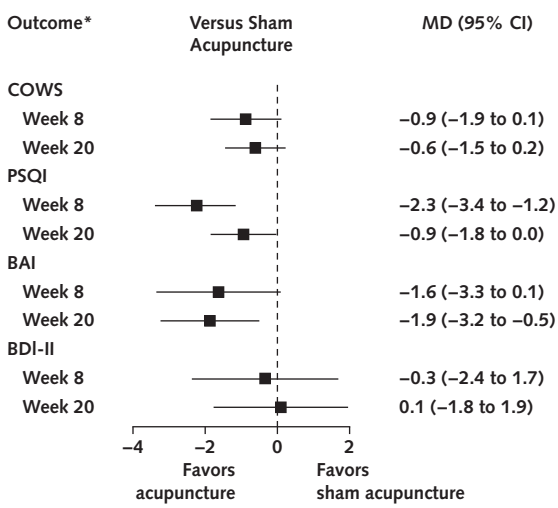
Figure 3. Changes in opioid craving VAS.



Opioid craving VAS is measured using a 100-mm VAS, with higher scores indicating higher craving for opioid. The area to the right of the vertical dashed line represents the follow-up period, when participants were not receiving manual or sham acupuncture. Error bars represent 97.5% CIs. VAS = visual analogue scale.

improved methadone dose reduction and reduced opioid craving VAS more than sham acupuncture. Patients in the acupuncture group also had improvements in sleep quality. The results of this trial are consistent with our previous similar studies (13, 15).

Figure 4. Secondary outcomes measured at week 8 and 20.



The estimates were mean changes of the secondary outcomes relative to baseline scores. Secondary outcomes measured at other time points are shown in **Supplement Tables 4** and **5** (available at Annals.org). BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-II; COWS = Clinical Opioid Withdrawal Scale; MD = mean difference; PSQI = Pittsburgh Sleep Quality Index.

* Higher scores on the COWS, PSQI, BAI, and BDI-II scales indicate more severe symptoms of opioid withdrawal, sleep disturbance, anxiety, and depression, respectively. Negative values favor acupuncture.

In the United States and the United Kingdom, auricular acupuncture stands as the most prevalent form of acupuncture for treating OUD (29, 30). Currently, more than 250 medical institutions in these 2 nations are engaged in auricular acupuncture treatments following the protocol developed by the National Acupuncture Detoxification Association (31). However, there is limited high-quality evidence supporting the efficacy of auricular acupuncture for OUD. A systematic review did not support ear acupuncture as an adjunct to MMT because it had no effect on the severity of withdrawal symptoms, opioid cravings, or attendance at MMT dispensing sites (32). A network meta-analysis suggested that manual acupuncture was the optimal intervention for reducing methadone doses in acupuncture therapy, demonstrating efficacy surpassing that of auricular acupuncture (12). In our study, methadone dosage was lower than the baseline in the acupuncture group after 8 weeks of intervention. This is similar to previous studies with positive results (33, 34).

For patients with OUD, the craving for opioids has a strong influence on methadone consumption. The results of the primary outcomes showed that acupuncture reduced the craving for opioids. Our results showed that the decrease in VAS score reached the minimal clinically important difference of 4.0 points (35–37) at week 8 and exceeded 4.0 points at week 20. Consistent with the present study, the research done by Southern and colleagues demonstrated a correlation between the use of acupuncture and a reduction in drug cravings and withdrawal symptoms among persons with alcohol addiction (38). Some researchers believe that the mechanism for acupuncture decreasing drug craving is an

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increase in the levels of endogenous opioids and hormones, such as endorphins, enkephalin, adrenalin, noradrenalin, serotonin, and dopamine, in the central nervous system and plasma (39).

Another important finding of this study was that sleep quality improved after 8 weeks of acupuncture intervention, which is similar to findings in a previous study (40). Others have suggested that acupuncture could be a potential treatment of sleep disturbance during morphine withdrawal by producing a considerable increase in rapid eye movement sleep, non–rapid eye movement sleep, and total sleep time (41), but additional research is needed to delineate the mechanisms of action further.

We observed relatively tolerable adverse effects of acupuncture in this study. Other studies have also indicated that the most reported adverse effects of acupuncture involved only mild nausea and pain and slight bleeding at the site of the needle insertion (42, 43). In addition, the 8-week course of acupuncture 3 times weekly used in this study was well tolerated and accepted by most participants who were attending clinic daily to receive their methadone doses. These features suggest that similar acupuncture protocols could be integrated relatively easily into existing MMT treatment programs.

The main advantage of this study was its successful blinding. To ensure the success of blinding study participants, our research team devised a sham acupuncture device with 3 channels that facilitated needle placement from various angles and thus closely resembled oblique needling, which has not been possible with most sham devices used in other studies. Furthermore, all study personnel other than the acupuncturists were blinded to the study group assignment, including the outcome assessors, the physicians prescribing methadone to patients, the nurses responsible for documenting the daily dosage of methadone, data collectors, and statisticians. After completing the study, we asked patients which type of acupuncture they thought they received, and there were no important differences in their answers when analyzed by actual receipt of acupuncture versus sham acupuncture.

Our study has limitations. First, our study used a fixed acupuncture protocol. Personalized acupuncture intervention planning based on the acupuncturists' experiences may have been more effective. In traditional Chinese medicine, acupuncture is often combined with individualized herbal mixtures, which were prohibited in the protocol to avoid confounding. Second, due to the effect of the COVID-19 pandemic, we encountered challenges in the timely enrollment of patients. Third, due to concerns regarding patient adherence and the feasibility of the study, the follow-up period of our research lasted only 12 weeks. For a comprehensive understanding of the sustained effects of acupuncture in MMT, it would be advantageous for future investigations to extend the follow-up period to at least 6 months or more.

Table 3. Assessment of Blinding of the Full Analysis Set Population

Blinding for Treatment	Acupuncture ($n = 60$), *n* (%)	Sham Acupuncture ($n = 56$), *n* (%)
Penetrating acupuncture	17 (28.3)	17 (30.4)
Nonpenetrating acupuncture	23 (38.3)	25 (44.6)
Don't know	20 (33.3)	14 (25.0)

In conclusion, among persons enrolled in MMT clinics, the administration of acupuncture resulted in meaningful improvements in the amount of methadone reduction and the decrease in opioid craving VAS score when compared with sham acupuncture. Although further research is needed to measure long-term clinical outcomes and to determine how acupuncture can best be incorporated into a comprehensive substance misuse treatment programs, we believe these findings support the consideration of acupuncture for methadone reduction for persons who are receiving MMT.

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Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M23-2721.

Data Sharing Statement: The authors have indicated they will not be sharing data. Additional context: The raw trial data after de-identification can be shared on individual request to Dr. Lu at lulimingleon@126.com.

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Correction: This article was amended on 30 September 2025 to correct an error in the Primary Outcomes subsection of the Results section. A correction has been published (doi:10.7326/ANNALS-25-04162).

Author contributions are available at Annals.org.

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