The American Journal on Addictions, 25: 592–602, 2016

ISSN: 1055-0496 print / 1521-0391 online
DOI: 10.1111/ajad.12453

The Use of Auricular Acupuncture in Opioid Use Disorder: A Systematic Literature Review

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Background and Objectives: Opioid use disorder (OUD) is a chronic disease with significant personal, societal, and public health consequences. Even for the minority who receive the most effective evidence-based treatments, morbidity, and mortality remain significant. These facts, along with the recovery movement calling for individualized, holistic, culturally sensitive care, have led to the exploration of adjunctive interventions including acupuncture. Despite hundreds of international trials, however, there is a lack of consensus regarding its efficacy in OUD due in large part to methodological issues of trials to date. In response to these issues, the National Acupuncture Detoxification Association (NADA) developed an operationalized manual auricular acupuncture protocol that has since become the most widely used in the US. This systematic review is the first to focus explicitly on randomized trials utilizing the NADA protocol as a complementary intervention to address OUD.
Methods: The methods utilized to identify studies for inclusion are based on a 2009 protocol developed by the Cochrane Collaboration.
Results: Four trials met inclusion criteria. Despite methodological issues, results indicate that while the NADA protocol may not be effective in reducing acute opiate craving or withdrawal, it may be effectively utilized as an adjunctive treatment to increase treatment retention and decrease methadone detoxification and maintenance dosages in OUD.
Conclusion and Scientific Significance: Incorporation of the NADA protocol into existing evidence-based treatment approaches may facilitate recovery and, through its impact on treatment retention and completion, indirectly impact morbidity, and mortality in individuals with OUD. Given the limitations of the current review, conclusions are tentative and directions for future research are discussed. (Am J Addict 2016;25:592–602)

INTRODUCTION

Like other substance use disorders (SUDs), opioid use disorder (OUD) is a chronic bio-psycho-social disease with complicated neurobiological foundations involving alterations of neural circuits and neurotransmitters involved in reward, motivation, and memory. Of specific significance to the dependence, tolerance, and relapse associated with OUD are the endogenous opiate system, mesolimbic reward system, and the limbic system.[1] OUD affects thousands of communities and millions of individuals worldwide, and has significant financial, personal, societal, and public health consequences.[2] Direct and indirect costs associated with OUD range from .2% to 2% of a country's gross domestic product.[3] Unsafe injection practices contribute significantly to the global epidemic of human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS), and account for nearly 90% of newly diagnosed Hepatitis C cases per year.[4,5] Of all illicit substances, heroin causes the second most harm to individuals and the community, an estimate that is based on mortality, damage, impairment of functioning, loss of relationships, injury, crime, economic cost, and community disruption.[6]

Heroin and opioid analgesics are the primary drugs implicated in overdose deaths, contributing to 75% of such fatalities worldwide.[2] Relative to the global picture, there is currently an OUD epidemic in the U.S. While the global prevalence of opioid and opiate abuse has remained stable at .7% and .4% of the world's adult population, respectively,[2] the U.S. Substance Abuse and Mental Health Services Administration (SAMHSA) reports that between 2007 and 2012 past-year users of heroin in the U.S. increased nearly twofold from 373,000 to 669,000,[7] and by 2014 had reached 914,000.[8] In 2014, 4.3 million Americans or 1.6% of the country's adult population reported abusing opioid analgesics, a figure that is relatively lower than that reported for the years 2002–2012, but roughly equal to that reported in 2013.[8] However, the 914,000 Americans or .3% of the country's adult population that reported abuse of heroin in 2014 is relatively higher than estimates reported for the years 2002–2013.[8] In 2014, 1.9 million Americans met diagnostic criteria for a substance use disorder involving opioid analgesics and 586,000 for a substance use disorder involving heroin.[8]

In 2013, the drug-related mortality rate in the U.S., disproportionately affected like the global rate by heroin and opioid analgesics, was nearly 5 times the global average.[2] In

Received March 20, 2016; revised September 8, 2016; accepted September 11, 2016.
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the U.S., while the total number of drug-related deaths involving opioid analgesics exceeded the number involving heroin from 2000 to 2013, trends in relative annual death rates related to each substance recently changed. Deaths involving opioid analgesics increased at a quicker pace than those involving heroin from 2000 to 2010, and stabilized somewhat from 2010 to 2013 at 5.1–5.4 per 100,000. Conversely, deaths involving heroin increased at a relatively slow pace from 2000 to 2010, followed by a dramatic increase of 37% per year from 2010 to 2013, or from 1.0 to 2.7 per 100,000.[9] Thus, the U.S. disproportionately contributes to the global drug-related fatality rate, due in part to disproportionate rates of opiate and opioid abuse, and current trends reflect that heroin abuse and related overdose deaths are particularly on the rise.

Treatment

Recovery is an individualized, holistic, process that encompasses more than merely illness and health; it also involves attention to the psychosocial and cultural aspects of an individual's life.[10] Considering the holistic nature of recovery as well as the chronic, multi-faceted nature of OUD, recovery-oriented treatment must be comprehensive in nature. As with other chronic diseases, with appropriate treatment individuals with OUD may go into remission; however, they remain vulnerable to relapse throughout their lifetime. This vulnerability is highlighted by the significant rate of relapse following detoxification or brief treatment. In 2010, Smyth et al. for example, found that of individuals with OUD that were admitted to a 6 week inpatient abstinence-based treatment program, 66% had used opiates or opioids and 59% had returned to daily use within 1 week of discharge. Of those that ultimately returned to daily use, 80% did so in the first month after discharge. Early relapse was predicted by failure to complete detoxification, the entire treatment program, and a failure to enter aftercare. As the authors point out, these findings are consistent with those of numerous others who have also noted a significant risk of early relapse in individuals with OUD.[11] Not only do the data show that individuals are particularly vulnerable to relapse in the immediate period following completion of detoxification or brief treatment, it also shows individuals are more susceptible to overdose and death during this time.[2,11]

Decades of research have revealed that medication-assisted-therapy (MAT), that is, buprenorphine, methadone, or naltrexone, in combination with psychosocial intervention is the most effective treatment for OUD in terms of time to relapse, treatment retention, decreased use of illicit opioids, HIV-risk behaviors and transmission, and overdose and all-cause mortality.[3,12,13] However, as many as 80% of individuals with OUD do not receive these or other needed services.[7,14] Even for those that do receive the most effective evidence-based treatments available, outcomes typically reveal less than 50% treatment retention with only 10–40% of individuals maintaining abstinence at follow-up.[3,12,13] The significant and pervasive consequences of OUD, lack of optimal outcomes predisposing to significant morbidity and mortality despite use of best conventional practices, and recovery movement in mental health and SUD treatment that prioritizes individualized, holistic, and culturally sensitive care have led to the exploration of complementary interventions to address OUD and other SUDs.

A History of Acupuncture Use in the Treatment of Addictions

Various complementary interventions have been explored through the years including homeopathy, naturopathy, and various treatments arising out of Ayurvedic medicine, traditional Chinese medicine, traditional African medicine, and Native American healing practices.[15,16] In 2009, Behere et al. reviewed the evidence for these interventions in addressing SUD and reported that while the data were inconclusive, acupuncture appeared to be 1 of few complementary interventions that showed promise in this area.[15] Indeed, acupuncture as an adjunctive, complementary intervention to address addiction in general, and OUD specifically has received much attention while also being the subject of much debate.

The practice saw its first applications to OUD in 1972 when a neurosurgeon in Hong Kong incidentally observed that while using acupuncture as an anesthetic, it also reduced the severity of opium withdrawal in a patient.[17] Since this time, hundreds of international trials have explored the utility of various acupuncture therapies in addressing SUD. While a comprehensive review of this literature is beyond the scope of this manuscript, we refer readers to existing reviews addressing this topic.[17–19] Results of individual trials have been historically confounded by the use of different acupuncture techniques including staplepuncutre, electroacupuncture, body acupuncture, and acupressure; different acupoints; lack of randomization or blinding; small sample sizes; different outcome measures; and, different control interventions. Such methodological issues render results equivocal, impeding a valid assessment of efficacy as well as comparison across trials.[20,21] This was 1 of many issues considered by the National Institutes of Health (NIH) when they hosted a 1997 conference in an attempt to evaluate the available data regarding the use of acupuncture in various conditions including SUD. During this conference, a panel of 12 considered relevant literature and testimony presented by 25 subject matter experts, with scientific evidence given precedence. The conference culminated in a 1997 Consensus Statement acknowledging that while methodological issues of available studies prevented a firm consensus regarding the efficacy of acupuncture use in treating addiction, there were some relevant positive trials rendering it a potentially useful adjunctive treatment approach.[21] SAMHSA, referencing various individual controlled trials, noted in a 2006 Treatment Improvement Protocol that acupuncture had shown specific utility as an adjunct to opioid agonist therapy, had been shown to improve treatment and retention and enhance engagement, and therefore showed promise as a complementary addition to MAT in a holistic treatment plan aimed at addressing SUD.[22]

In the U.S., studies of acupuncture in SUDs including OUD were spearheaded by a group of clinicians and researchers at New York's Lincoln Hospital.[23] Over a 10-year period beginning in 1974 and involving more than 800,000 treatments, this group of individuals developed and operationalized a 5 point manual auricular acupuncture (AA) procedure that reportedly significantly enhanced treatment retention, decreased opiate withdrawal symptoms, and decreased long-term morbidity in the form of secondary illicit drug use and adverse methadone reactions.[23,24] The 5 auricular points utilized in what came to be known as "The Lincoln Model" are referred to as the sympathetic, shen men, lung, kidney, and liver. In 1985, the National Acupuncture Detoxification Association (NADA) was developed in an effort to promote the Lincoln model and operationalize acupuncture for OUD partially in attempt to address methodological flaws of existing trials.[24] NADA has since trained over 7,000 clinicians, and is the most commonly used acupuncture therapy for SUD in the U.S., U.K., and Denmark.[23,25]

Although existing reviews have evaluated the evidence for acupuncture in OUD, none have focused solely on manual AA at the NADA-specified points despite the fact that it is the most commonly utilized acupuncture therapy to address SUD in various countries including the U.S. They have instead included trials of body acupuncture, acupressure, and electroacupuncture,[26–28] or have reported on the utility of acupuncture in addressing SUD in general as opposed to OUD specifically.[17,26] A 2013 exploratory review by White analyzed the efficacy of acupuncture in addressing SUD as a function of specific acupuncture therapy and illicit substances studied and found these variables to influence the results of individual trials and reviews.[29] To maximize validity, minimize the presence of confounding variables, and address methodological issues in previous trials and reviews, the current review focuses explicitly on randomized clinical trials (RCTs) utilizing manual AA, as specified by the NADA protocol, as an intervention to address OUD.

METHODS

The methods utilized to locate studies for inclusion in this systematic literature review are based on a 2009 Cochrane Collaboration protocol designed by Lui et al. designed to guide a systematic review in determining the effectiveness of AA for OUD.[30] In addition to being the first review to focus explicitly on AA as part of a comprehensive treatment approach to address OUD, this review is the first to utilize this protocol.

Inclusion and Exclusion Criteria

In line with the 2009 Cochrane protocol, this review included only controlled trials utilizing traditional or quasi-random methods of allocation, that is, RCTs. Trials of participants using multiple substances were included so long as opiates were the primary drugs of abuse, participants met diagnostic criteria for OUD, and results for opioid related outcomes were analyzed and presented independently. Trials involving variations of the NADA protocol were included, whereas those involving any other acupuncture technique were excluded. Studies that utilized control conditions including mock or sham acupuncture (that is, simulated acupuncture or acupuncture at "non-active" acupoints), treatment as usual, or traditional pharmacological interventions were included. Moreover, studies reporting on the following primary or secondary outcome measures, as suggested by Lui et al., were included in this review: reduction of opiate dependence, craving, or frequency of use (primary), treatment retention (primary), AA side effects, opiate withdrawal symptoms, and other psychological or emotional symptoms of OUD (secondary).

Search Strategy

Utilizing the above-specified criteria, the OVID database including OVID Journals Database for Abstracts & Tables of Contents, Full Text Journals, MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE 1946-present, MEDLINE without Revisions 1996-present, and MEDLINE Daily Update was searched in May 2015. The specific search terms and "and/or" combinations utilized are explicitly detailed in Appendix I of the 2009 Cochrane protocol. Additional limits included English language and human trials. An important deviation from the 2009 protocol is the exclusion of Chinese databases and trials published in Chinese. This was necessary due to a lack of staff fluent in the Chinese language and financial limitations prohibiting the funding of translation services. An identical search was run through CINAHL, PubMed, EMBASE, and the Cochrane Library. The reference lists of all relevant papers were also searched to identify trials meeting inclusion criteria for this systematic review.

Data Extraction and Quality Assessment

One author (TB) performed initial searches and read trial titles, abstracts, and full manuscript contents to assess trials for suitability for inclusion. The second author (GC) verified search methods, results, and appropriateness of including selected trials. Uncertainties were resolved through discussion until both authors agreed on the final list of included studies. Data were extracted and entered manually into table form by 1 author (TB) and verified for accuracy by the second author (GC). The following information was extracted from each trial: authors; publication year; setting; country; trial design; sample size; exclusion criteria; important participant baseline characteristics; characteristics of experimental and control interventions; and outcome measures. Results were reported with probability values utilized in the respective trials (p and Cohen's d). Due to variations in outcome measures and statistical analyses utilized in the selected trials in addition to incomplete information and lack of raw data provided in some, additional meta-analytic analyses were not able to be performed.

Included trials were rated as to their quality based on the Oxford Centre for Evidence-Based Medicine's 2011 Levels of Evidence, ranging from levels 1 to 5, where 1 indicates the highest quality level.[31] While previous reviews[27,28] have rated

trials based on the Jadad Scale, this scale places heavy emphasis on whether trials are double-blinded and description of blinding procedures with 2 of 5 possible points allocated for these criteria.[32] Hammerschlag has, among others however, noted the implausibility of blinding acupuncturists to certain treatment conditions, such as, sham or mock versus specific acupuncture.[33] This is particularly applicable to NADA-trained acupuncturists who are specifically trained in locating the 5 auricular NADA acupoints. Some studies additionally employ the use of a point detecting instrument in selecting active and inactive acupoints which by nature prohibits blinding.[34] Thus, the use of the Jadad Scale appears to place AA trials in OUD at an immediate disadvantage, and for this reason was not chosen to evaluate trial quality in this review.

RESULTS

Employing the specified search strategy, 1,103 results were returned from Ovid and MEDLINE, and after reading titles, abstracts, or full papers, only 3 were retained. Studies were primarily excluded because they were completely unrelated to the study question, employed acupuncture therapies other than AA, investigated the effects of acupuncture in non-opiate SUDs, investigated the effects of acupuncture on medical and psychiatric conditions other than OUD, and/or were non-RCTs. Searches of CINAHL, PubMed, EMBASE, the Cochrane Collaboration, and reference lists of relevant papers resulted in 1 additional unique RCT meeting eligibility criteria. Thus a total of 4 trials met inclusion criteria for and were included in the current systematic review. This selection process is presented visually in Fig. 1.

Characteristics of Included Studies

Complete trial details are summarized in Table 1. The 4 trials reviewed included a total of 350 participants. Most trials were given a quality rating of 2 with the exception of the 2013 Lua and Talib study. Despite reported randomization, there were numerous significant baseline differences between groups: compared to the control group, the intervention group included more participants that were single, divorced, unemployed, living alone, of lower socioeconomic status, had longer addiction histories, more mixed positive and less negative toxicology screens, reported higher withdrawal scores and overall symptom frequency, and reported worse physical, psychological, and overall health-related quality of life (HRQoL).[35] No trials were double-blinded, 3 were of a single-blind design,[34,36,37] and 1 was unblinded.[35] All but 1 trial[36] were conducted in an outpatient setting. AA sessions were delivered for approximately the same amount of time and in the same types of group settings in all trials. In the inpatient Bearn et al. trial,[36] AA was given 5 days per week, and in the outpatient trials it was offered 3–7 days per week.[34,35,37] Two trials involved participants in the acute detoxification phase of treatment,[36,37] 1 involved participants in the maintenance phase,[35] and 1 involved a mix of participants in both phases.[34] Follow-up periods ranged from 2 weeks to 6 months. All trials except 1[37] included AA as an adjunctive treatment to methadone detoxification and/or maintenance. Wells et al. also included a historical comparison group and further divided their experimental group into a "minimally treated" group consisting of participants who received <8 AA treatments.[34] For control conditions, 1 trial used mock AA,[36] 1 used methadone maintenance treatment (MMT) alone,[35] and 2 used sham acupuncture.[34,37] Only 1 trial reported on all primary outcome measures.[34] Two reported on outcomes regarding opiate dependence in the form of MMT doses[34,35] and 2 on outcomes regarding craving.[34,36] While all 4 trials reportedly collected information related to frequency of use in the form of toxicology screens and severity of withdrawal, only 3 reported on the former[34,35,37] and on the latter.[34–36] None reported information related to side effects of AA, while 2 reported on treatment retention,[34,37] and 1 additionally explored cigarette consumption, HRQoL, and AA acceptability.[35]

Efficacy of Auricular Acupuncture on Outcome Measures

Complete trial results are summarized in Table 1. Regarding the primary outcome of opiate dependence, Lua and Talib found that the experimental group receiving MMT + AA required significantly lower methadone doses per week compared to the MMT alone control group at the end of the trial, differences that were not present at baseline.[35] Wells et al. reported that at 6 months, methadone doses were significantly higher in the sham AA group with a mean of 64.23 mg than in the historical comparison group with a mean of 54.64 mg, but not the specific AA group with a mean of 53 mg.[34] Considering these numbers, the difference in post-intervention methadone dose between the specific and sham AA groups appears to have at least trended toward significance with the specific AA group having lower 6 month doses; however, the authors do not offer a p value for interpretation. Neither of the 2 trials that reported on the primary outcome of craving found the addition of AA to methadone beneficial.[34,36] Furthermore, Wells et al. found that in comparison to the sham AA group, the specific AA group had significantly higher median craving scores and cravings per day for weeks 12–26 and 16–26, respectively. These differences remained significant during weeks 16–19 only with removal of data pertaining to "minimally treated" participants. Authors also reported a relatively longer duration of craving in the specific AA group during weeks 16–19, although this became insignificant with removal of "minimally treated" participant data.[34]

The 3 trials that reported on frequency of use based on urine toxicology did not find any differences in the number of post-intervention positive or negative screens between groups,[34,35,37] although urine screening was voluntary and results were not based on samples from all participants. Regarding the last primary outcome measure, treatment retention, Washburn et al. found that compared to the sham AA group, more participants in the specific AA group attended treatment each day, attended significantly more days overall, remained in

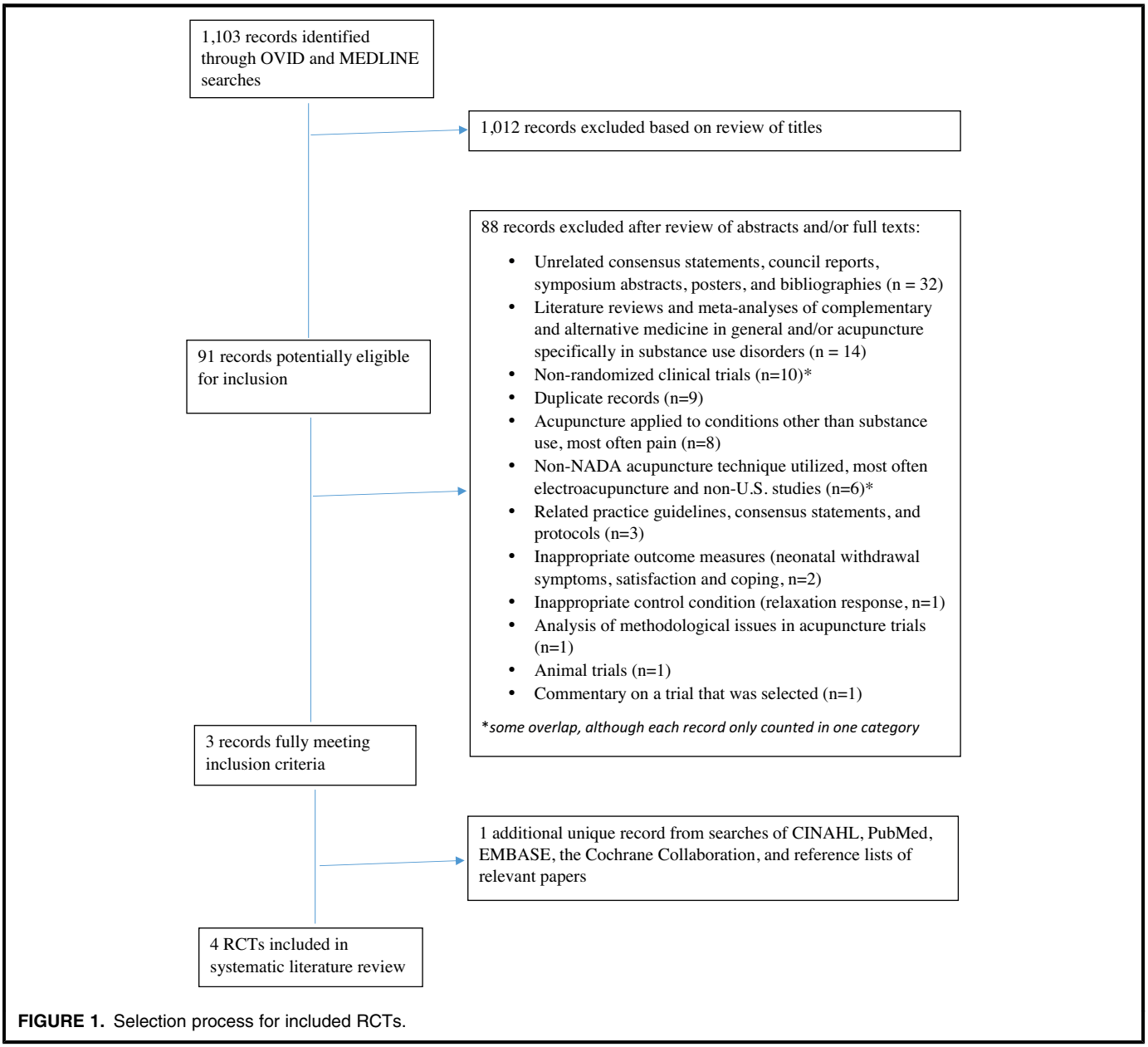

FIGURE 1. Selection process for included RCTs.

treatment for longer, and were more likely to continue treatment beyond the 21 day protocol.[37] Wells et al. did not find the addition of AA to significantly increase retention, although reported that 11.3% more participants in the specific than sham AA group completed the 6 month treatment.[34]

Regarding the secondary outcome measure of withdrawal, Bearn et al. did not find the addition of AA to significantly influence this variable.[36] Wells et al. found no significant between group differences in symptoms pre- and post-intervention, and reported that while the specific AA group had relatively fewer days of nausea and vomiting during weeks 4–7, they had more days of muscle aches and poor sleep during weeks 20–26 compared to the sham AA group. No separate analyses were reported regarding the "minimally treated" subgroup of specific AA participants.[34] Lua and Talib reported a positive effect of AA on both withdrawal symptoms and other emotional symptoms related to OUD. At this trial's baseline, the experimental MMT + AA group reported a significantly higher frequency of 5 out of 10 withdrawal symptoms, higher symptom frequency, and worse HRQoL as compared to the MMT alone group. There were no significant between group differences in these variables post-intervention, which was reportedly due to the MMT + AA, but not the MMT control group, experiencing significant reductions over time in withdrawal symptoms, and improvement over time in physical, psychological, environmental, and overall HRQoL.[35]

TABLE 1. Summary of studies included in this review

Author, setting	Level of evidence, study design, participants	Intervention and control groups	Outcome measures	Results
Bearn et al.[36]	Level = 2, RCT (single-blind, sham controlled)	Both groups received symptom controlled methadone detoxification days 1–3 with decreasing doses days 10–14. Some also received diazepam for comorbid BNZ dependence[a].	Withdrawal severity (SOWS) and craving (MCS) —measured at 10am for the first 14 days of detoxification	Eleven participants dropped out[b]. Baseline analyses including these 11 revealed no differences between groups via logistic regression analysis in terms of age, gender, drugs used, or injecting status ($p = .963$).
Voluntary inpatient detox unit in London	$N = 93$	*Intervention*—daily AA treatment on weekdays for 14 days with 32-gauge needles at 5 NADA points for 30–40 min	Urine screening 3×/week	Other results based on final 82, analyzed with and without imputed mean scores for missing data:
	Exclusion criteria—major medical or psychiatric diagnosis, antidepressant or antipsychotic medication, pregnancy, ear infection, eczema	*Control*—mock AA (applied oil and 5 metal clips to ear at unspecified points) at same time/room as experimental group, described to participants as active AA		– **Withdrawal severity**—NS differences in mean SOWS scores between 2 groups on any of 14 days ($p = .381$, $d = .21$) – **Craving**—NS differences in mean MCS scores between 2 groups on any of 14 days ($p = .283$, $d = -.28$) – No information on results of urine screens given
Lua and Talib[35]	Level = 2/3, RCT (longitudinal, open-label)	Both groups received MMT over 2 months beginning with 15–20 mg and increasing based on symptoms, mean of latest dose = 57 mg	Withdrawal symptoms (10 symptoms rated for frequency on 4-point scale), AA acceptability, daily methadone dose, and # of weekly cigarettes smoked, questionnaires in Malay and developed by research team	Twenty-six MMT + AA participants dropped out (refused urines, had <8 AA sessions) versus 2 MMT so authors employed intention-to-treat principle in analyses
Three voluntary outpatient MMT centers in Malaysia	$N = 97$ (100% male, mean age = 37.7 yrs, 97.9% Malay)	*Intervention* ($n = 55$)—MMT + AA in groups of 6 –10 at 5 NADA points bilaterally to depth of 1–3 mm, 3×/week for 30 min	WHOQOL-BREF (Malay)—physical, psychological, social, environmental, and overall HRQoL, and general health Urine screening biweekly	– **Methadone, smoking**—MMT + AA group had lower methadone doses and # of cigarettes smoked/week versus MMT alone ($p = .044$, .003);
	Exclusion criteria—violence, suicidality, psychosis, HIV, HBV, metal allergies, involvement in criminal activities	*Control* ($n = 42$)—MMT alone **At baseline MMT+AA group significantly differed from control*[c]: more were single, divorced, unemployed, living alone, had lower education and income, and more mixed positive and less negative urines (for all, $p < .001$) than control group; 5/10 withdrawal sxymptomsand overall sxymptom frequency higher than in control group ($p = .004$ to .041); rated all but social and general health indices on WHOQOL-BREF as worse than control group ($p = .003$ to .015); no differences in methadone doses or cigarette smoking		– **Withdrawal symptoms**—NS between group differences; NS within group differences on any measures for MMT group; within group differences for MMT + AA group = decrease over time in cramps, craving, lethargy, chills, pains, and overall withdrawal symptom frequency ($p = .011$ to .053) – **WHOQOL-BREF**—NS between groups differences in any HRQoL domain; MMT + AA group had increase in overall, physical, psychological, environmental, and total HRQoL over time ($p = <.001$ to .034, $d = .41$ to .72); – **Urine screens**—NS differences in ± urines; – **Acceptability**—93% of MMT + AA participants thought AA improved symptoms and 95% would recommend AA

(*Continued*)

TABLE 1. Continued

Author, setting	Level of evidence, study design, participants	Intervention and control groups	Outcome measures	Results
Washburn et al.[37]	Level = 2, RCT (longitudinal, single-blind, sham controlled)	Twenty-one day study period to provide results comparable to 21-day methadone detoxification programs. No methadone or other medications given, only AA and support services (counseling, discharge planning, HIV education)	Withdrawal symptoms based on a "weekly checklist"	No baseline differences in sociodemographics or withdrawal symptoms. Significant attrition in both groups reported but no raw data given.
Outpatient non-profit human services agency in San Francisco, CA	$N = 100$ (100% IV heroin users)	*Intervention* ($n = 55$)—AA at 4 NADA points (did not include liver) for 20–45 min in room with up to 40 participants	Urines 1×/week	– **Withdrawal symptoms**—no data given
	Exclusion criteria—pregnancy, parole, probation	*Control* ($n = 45$)—sham AA at 4 points not specific to addiction at same time/room as experimental group	Retention (total # of days receiving treatment, last day of 21 day period receiving treatment, # staying in tx beyond 21 days)	– **Urines**—NS between group differences, 4.4% and 6.7% of sham and 10.9% and 7.3% of experimental urines negative at weeks 2 and 3 – **Retention**—both groups had sharp initial decrease in attendance, sham group moreso (on day 2 <20% of sham participants and <40% of experimental remained); more participants in experimental than sham attended each day, attended more total days than controls (mean of 2.1 days in treatment for sham group versus 4.2 in experimental), remained in treatment longer (mean last day of treatment 6.6 versus 3.8 for sham) and were more likely to continue past 21 days with almost 1/3 continuing AA tx (all $p < .05$) – **Frequency of use**—light users (<1×/day) in both groups had more days in treatment over a longer time period than medium (2–3×/day) orheavy (>3×/day) users ($p < .05$)
Wells et al.[34]	Level = 2, RCT (longitudinal, single-blind, sham controlled, 3-armed with historical comparison)	Both groups received regular methadone detoxification/MMT servicesd. All participants encouraged to attend AA at same time in group room 5 days/week 1st 2 weeks then daily for 6 months, sessions offered for 20–45 min w/ participants controlling length	Opiate withdrawal symptoms averaged over weeks 4–7, 8–11, 12–15, 16–19, 20–26 ("weekly questionnaire" including 30 symptoms)	No baseline differences in sociodemographics, cravings, or opiate use severity between study groups.
Outpatient methadone detoxification and MMT programs in a private, nonprofit treatment program or VAMC in Seattle, WA	$N = 60$, 19 of whom entered 6 month methadone detox versus MMT[d]	*Intervention* ($n = 31$)—AA at 5 specific NADA points identified by point detector	Attendance and retention (median # of AA sessions, weeks attended)	– **Withdrawal symptoms**—NS differences in symptom changes pre- and post-AA; specific group had fewer days of nausea/vomiting weeks 4–7 and more days of muscle aches and poor sleep weeks 20–26 versus sham ($p < .05$) ○ No analyses on "minimally treated"
	Exclusion criteria—pregnancy, enrolled in separate methadone study	– Authors further divided this group into a "minimally treated" group for some analyses that included individuals who received <8 treatments for weeks 2–5 ($n = 22$)	Methadone dosage requirements at 4, 12, 26 weeks	– **Attendance**—NS differences on median # of AA sessions, weeks attended (10 for both groups), or weeks in project; 25.8% versus 34.5% of real and sham participants dropped out or were discharged before 6 months (NS) ○ No analyses on "minimally treated"

(*Continued*)

TABLE 1. Continued

Author, setting	Level of evidence, study design, participants	Intervention and control groups	Outcome measures	Results
		Control ($n = 29$)—sham AA at 5 nonspecific points 1–3 mm away from specific identified by point detector, same frequency as intervention group	Cravings ("weekly questionnaire")	– **Methadone dosage**—median dose NS different between study groups or historical comparison at 3 months; at 6 months, control group had higher doses than historical comparison ($p < .05$) but not specific group (no p value given) ○ No analyses on "minimally treated" – **Cravings**—specific AA group had higher median craving scores and # of cravings/day weeks 12–26 and 16–26, respectively, with removal of "minimally treated" only significant weeks 16–19 ($p < .05$); longer duration of craving weeks 16–19 in specific AA group versus sham ($p < .05$), although NS with removal of "minimally treated"; – **Urine screens**—NS differences in positive screens in study groups; historical comparison had more positive screens than 2 study groups combined for weeks 6, 12, and 13.
		Historical comparison group in lieu of "no acupuncture" control ($n = 57$ MMT clients from another study, not equivalent)	Urine screens weekly (voluntary) Historical comparison had methadone dosing data over time and weekly urines (mandatory)	

Notes: Level of evidence based on the Oxford Centre for Evidence-Based Medicine's Levels of Evidence (2011): http://www.cebm.net/ocebm-levels-of-evidence/. d = Cohen's d—measure of effect size whereby <.20 is considered small, .50 medium, and .80 large. AA, auricular acupuncture; BNZ, benzodiazepine; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HRQoL, health-related Quality of Life; MCS, Maudsley craving scale; MMT, methadone maintenance treatment; NADA, National Acupuncture Detoxification Association; NS, non-significant; RCT, randomized controlled trial; SOWS, short opiate withdrawal scale; VAMC, Veterans Afairs Medical Center; WHOQOL-BREF, World Health Organization's Quality of Life-BREF.

[a]The authors do not provide any information as to how many participants received BNZ, which groups they were in, or doses received; [b]the authors do not provide additional information regarding which assignment these 11 individuals belonged to; [c]the authors do not provide any information regarding attempts to control for baseline differences other than use of non-parametric analyses; [d]the authors do not offer a breakdown of how many participants in each phase of treatment, that is, methadone detoxification versus maintenance, are in their control and experimental groups and do not utilize phase of recovery as a variable in data analysis.

DISCUSSION

Despite an attempt to minimize confounds noted in previous reviews by the application of rigorous inclusion standards to the current review, there were methodological issues between and within all trials that limit comparisons across them as well as interpretation of individual results. Trials included participants in various stages of treatment, and 1 included those in both acute detoxification and maintenance without providing information regarding how many participants in each phase were in their control and experimental groups and without utilizing phase of recovery as a covariate.[34] This seriously confounds results for methadone dose, cravings, and withdrawal symptoms. Trials had varying control conditions including 1 with an idiosyncratic mock acupuncture method[36] and 2 utilizing sham AA at supposedly inactive acupoints[34,37]; however, many researchers claim there are no truly inactive acupoints.[24,33,38] Many authors did not provide important information such as raw data,[37] effect sizes, or specific p values for all results. One omitted information regarding how many participants received diazepam for comorbid benzodiazepine dependence, which groups they were in, doses received, as well as information regarding which assignment the 11 participants that dropped out belonged to.[36] As discussed, the randomization scheme in 1 trial appeared unsuccessful, and at baseline the experimental group fared worse on many variables that could have influenced results.[35] This group also did not include a mock or sham acupuncture group which prevented blinding and introduced the possibility that findings were related to non-treatment related aspects of the intervention.

Despite these limitations, relevant findings did emerge in this systematic review regarding the efficacy of the NADA protocol in adressing OUD. The 2 RCTs that reported on craving did not find the addition of AA to MAT beneficial,[34,36] nor did the 3 reporting on frequency of opiate use based on urine toxicologies.[34,35,37] Two of 3 trials did not find any additional benefit of AA in reducing withdrawal symptoms,[34,36] while 1 did.[35] Of the 2 trials that explored effects on MMT dose, 1 reported that adjunctive AA allowed for a significant dose reduction,[35] while the other reported data appearing to trend in that direction.[34] Of the 2 trials that reported on treatment retention, 1 reported a statistically significant positive effect of AA;[37] while the other did not, it reported that 11.3% more participants receiving NADA-specified AA completed the treatment program relative to the control group,[34] a potentially clinically significant finding given the implications of treatment completion. No trials reported on side effects. The 1 trial exploring psychosocial and HRQoL outcomes important to recovery reported a significantly positive impact of AA.[35] Although baseline differences existed between study groups, they did not favor the AA group, would by and large have been expected to predict worse outcomes in this group, and it is therefore doubtful they significantly influenced positive findings.

There is a paucity of relevant literature to which to compare our findings given this is the first review to explicitly focus on RCTs utilizing NADA-specified manual AA as part of a treatment approach to address OUD. Our findings are consistent with those of a meta-analysis conducted in 2009 comparing RCTs ($n = 11$) employing MAT alone versus those employing complementary electroacupuncture, body needle puncture, or AA in acute opioid detoxification. This analysis reported that the addition of acupuncture to MAT allowed for significantly decreased MAT dosage and resulted in a decrease in MAT-related side effects.[28] However, while 2 out of 3 of our RCTs that reported on such did not show a positive impact of AA on withdrawal symptoms, Liu et al. report on a pooled analysis of 7 RCTs that revealed the addition of acupuncture to result in significantly lower withdrawal severity on days 1, 7, 9, and 10 of a 10 day detoxification treatment.[28] They did not report on treatment retention or other outcomes considered in this review. Another 2011 review of RCTs ($n = 10$) of electroacupuncture, body needle puncture, or AA with or without MAT found acupuncture to be associated with significantly reduced withdrawal scores and significantly decreased craving in 6 of 7 and 2 of 4 trials reporting on such, respectively, which is in contrast to our findings. The authors also reported a positive effect of acupuncture on other psychological symptoms of OUD in 3 of 4 RCTs reporting on such,[27] similar to our limited findings regarding psychosocial outcomes. These reviews considered RCTs from both English and Chinese databases, addressing 1 of the limitations of the current review. The 2009 meta-analysis, however, ultimately included only RCTs conducted outside the U.S., limiting its generalizability.[28] The 2011 review included Western and Chinese trials, and noted that type of acupuncture and needling method tended to differ between trials from China and Western countries; those from China more often used electroacupuncture whereas those from other countries more often used manual AA, and the Western trials more often used the 5 NADA acupoints in AA than did trials from China.[27] In general, the authors reported the articles from China to have more favorable outcomes. Comparisons of the current review to these others are limited by different acupuncture techniques and outcome measures which could in part account for the inconsistent findings noted.

CONCLUSION AND SCIENTIFIC SIGNIFICANCE

Utilizing rigorous inclusion standards, this systematic review aimed to provide clarity as to the efficacy of adjunctive manual AA as defined by the NADA protocol, the most commonly utilized AA protocol in the U.S.,[23,25,27] in addressing OUD. As a function of the relatively low quality of trials of AA in addressing OUD as well as our rigorous inclusion standards, only 4 RCTs met inclusion criteria, which in addition to methodological issues renders conclusions tentative. This review nonetheless fills an important gap in the literature as previous reviews have included trials conducted

only outside of the U.S.[28] and focused among other things on various acupuncture techniques[18,26–28] which have been shown to significantly influence outcomes.[27,29] Based on the results presented herein, while AA may not be beneficial in decreasing craving or withdrawal symptoms associated with OUD, in conjunction with MAT it may allow for reduced methadone doses, aid in treatment retention and completion, and be a useful adjunct to address psychosocial aspects of recovery. The RCTs reviewed only had follow up periods of 2 weeks to 6 months. However, a significant percentage of individuals with OUD including those receiving the most effective evidence-based treatments available, relapse within weeks of detoxification or treatment,[3,11–13] are more prone to overdose during this critical period,[2] and predictors of early relapse include failure to complete detoxification or treatment.[11] While included trials did not directly explore relapse, contact with treatment is inversely associated with relapse,[12,39] and studies have shown that during off-treatment periods, individuals with OUD face a risk of dying some 2.5 times higher than that faced during on-treatment periods.[40] It is therefore plausible that through its ability to improve treatment retention and completion, complementary AA may indirectly improve morbidity and mortality in individuals with OUD. Future high-quality trials with longer follow up periods providing direct data on relapse, overdose, development of injection-related disease, and mortality are warranted to further investigate this tentative but clinically significant conclusion.

Given our understanding of OUD as a bio-psycho-social disease, and of recovery as a holistic, individualized process, the potential of adjunctive AA to decrease required methadone doses, as also noted by other reviews, has important implications. Some individuals may be poor candidates for MAT due to medical comorbidities or other factors. Also, as noted in the 2015 American Society of Addiction Medicine (ASAM) guidelines regarding pharmacotherapy of OUD, individuals appropriate for methadone as opposed to buprenorphine MAT differ in important variables.[41] Such variables may not only impact response to MAT but also to adjunctive interventions such as AA, which in addition to data supporting the notion that buprenorphine is at least as likely as methadone to result in completion of withdrawal,[42] could render trials of AA in buprenorphine detoxification or maintenance treatment informative. No such trials were returned in our extensive literature search. At our current stage of understanding the mechanism of AA in addressing OUD, it is not clear that trials of AA in conjunction with naltrexone would be warranted given that opiate antagonists could potentially block the therapeutic effects of AA insofar as they are mediated by the production of endogenous opiate compounds.[18]

A final recommendation for future studies involves the comorbidity between chronic pain and SUD in general and OUD specifically. Some studies estimate that up to 48% of individuals diagnosed with chronic pain have a comorbid SUD, frequently OUD.[43] Such individuals are more likely to be prescribed higher doses of opioid medications and experience worse health outcomes including higher rates of morbidity and mortality including that associated with overdose.[44] There is an abundance of data showing efficacy of acupuncture in treating various pain disorders, and a paucity of research exploring adjunctive acupuncture in individuals with comorbid pain and OUD. Insofar as AA may allow for decreased analgesic or MAT dosage in these individuals, who are known to be prescribed higher opioid doses which subjects them to higher morbidity and mortality, exploring the potential use of AA in this population may reveal clinically significant findings.

It is noteworthy that only 4 trials met inclusion criteria based on rigorous Western scientific research standards. The appropriateness of applying such standards to acupuncture trials has been challenged by some who feel it ignores important qualitative data on the human experience central to recovery.[33,38] Personal factors such as coping, managing negative emotions, having purpose in life, subjective experiences, and individualized treatment planning are known to influence relapse and recovery.[12] Therefore, the focus on objective, rigorously controlled outcomes in AA research is very likely missing important clinical variables associated with recovery. A suitable balance needs to be found between the objective, quantitative medical model and subjective, qualitative, recovery-oriented humanistic model in designing future protocols.

This material is the result of work supported with resources and the use of facilities at the Veterans Affairs Boston Healthcare System. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

The Boston VA Healthcare System Psychiatric-Mental Health Nurse Practitioner Residency Program (PMHNPRP) is supported by the Office of Academic Affiliations and the Department of Veterans Affairs. The authors acknowledge the mentorship of Dr. Sherley Belizaire DNP, PMHNP-BC, FNP-BC, Director of PMHNPRP, Boston VAMC.

Declaration of Interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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