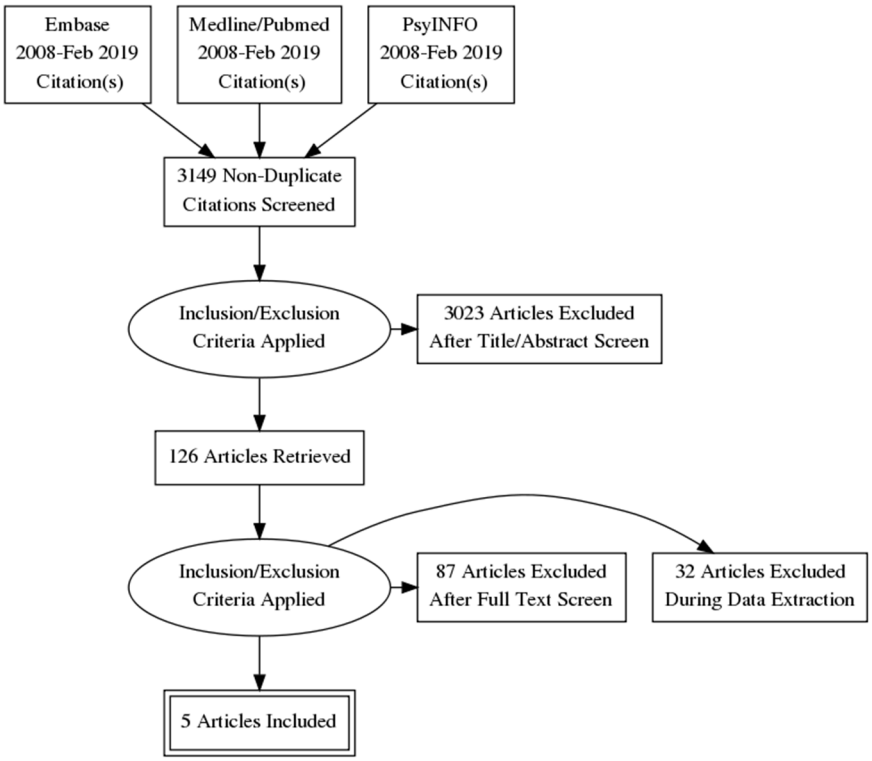
Chapter 2: Complementary and Integrative Health and other Non-Conventional Approaches for Treating Opioid Use Disorder (OUD)

Results of the Literature Search for OUD

Extensive literature searches identified 3,149 citations (after duplicates removed) potentially addressing the CIH and other non-conventional interventions of interest for the treatment of alcohol use or opioid use disorder. Of those, 3,023 were excluded upon title and abstract review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date, or not a full-length article). A total of 126 full-length articles were retrieved for review (See Error! Reference source not found. for the PRISMA diagram). Of those, 87 were excluded due to having the wrong intervention (36 studies), the wrong study design (32 studies), the wrong patient population (12 studies), less than 20 patients (10 studies), duplicates (1 studies), and wrong setting (1 studies). Thirty-nine full-length articles were further reviewed for inclusion. Of those, 32 potentially addressed alcohol use disorder and are discussed in **Chapter 3** and 2 were excluded for reasons listed in **Appendix A.**

Figure 1. Prisma Study Flow Diagram for Opioid Use Disorder



A total of 5 publications were included in the systematic review for OUD. **Table 1** presents a summary of the evidence (how many RCTs and/or SRs) for each CIH intervention.

Table 1. Overview of Evidence for CIH Interventions to Treat Opioid Use Disorder

Intervention	Number and Type of Studies for OUD
Accelerated Resolution Therapy (ART)	0
Acupuncture	1 SR (9 RCTs), 2 RCTs (published in 3 publications)
Art therapy	0
Cannabinoids	0
Chiropractic care	0
Equine therapy	0
Exercise therapy (outdoor therapy)	2 RCTs
Healing Touch	0
Hyperbaric Oxygen Therapy	0
Massage therapy	0
Meditation	0
Yoga	0
Music therapy	0
Tai chi	0
Therapeutic touch (Relaxation therapy)	0
Training and caring for service dogs	0
Transcranial Magnetic Stimulation (TMS)	0
Total Studies	**5 publications; 1 SR (9 RCTs) and 4 RCTs**

RCT: Randomized controlled trial; SR: systematic review

The full-text studies included in this report along with further details of the search terms and concepts used to guide the searches for OUD are provided in a supplemental file on Max.gov and can be accessed here: https://community.max.gov/display/VAExternal/OUD+Report+Supplementary+Materials

Acupuncture

Evidence Base

Our searches of the literature identified 1 SR and 2 additional RCTs published in 3 separate publications that assessed the use of acupuncture to treat adults with opioid use disorder (OUD). Chen conducted an SR that included 9 RCTs that examined acupuncture compared to no treatment (9 RCTs), sham acupuncture (7 RCTs), or medication (3 RCTs) (Chen et al. 2018). The authors of the review did not specify what medications were used in the studies, they just reported that the studies used either western medication or Chinese herbal supplements. The studies in the review included a total of 1,063 adults with OUD. The studies considered the efficacy of manual acupuncture (1 RCT), electroacupuncture (4 RCTs), auricular acupuncture (2 RCTs), and transcutaneous acupoint electrical stimulation (TEAS, 2 RCTs). Treatment sessions varied from 10 to 30 sessions lasting from 20 to 25 mins. The primary outcomes measured included opioid craving, anxiety, depression, pain and sleep quality. See **Table 2** for more information about the studies included in the SR.

Two additional RCTs published in 3 separate publications assessed the use acupuncture in adults with heroin addiction receiving methadone maintenance therapy (MMT). Chan et al. randomized 60 adults to receive real acupuncture plus MMT (n=30) or sham acupuncture plus MMT (n=30) (Chan et al. 2014). Lua et al. randomized 97 adults with heroin addiction to receive acupuncture plus MMT (n=55) or MMT only (n=42) (Lua et al. 2013; Lua et al 2013b). The primary outcomes in these RCTs was reduction in methadone consumption, withdrawal symptoms, and heroin craving. See **Table 6** for more information about the patients and interventions included in these studies.

Study Quality

Using the AMSTAR instrument, we rated the quality of the Chen review as High (See **Table 4** for ratings). The authors of the Chen review used the Cochrane tool to rate the RoB of the studies included in their review. The ROB ranged from moderate to high due to lack of reporting about allocation concealment (8 RCTs), lack of blinding of patients and outcomes assessors (9 RCTs) and lack of clearly reporting dropout rate (3 RCTs) or having >20% attrition (1 RCT). Using the Cochrane tool, we rated the ROB of the Chan RCT as having some concerns and the Lua RCT as high (See **Table 7** for ratings). The Lua RCT was rated high due to >20% attrition in the acupuncture group and not blinding the outcome assessors.

Key Findings

Below, we describe the key findings for the outcomes of interest with the GRADE strength of the evidence (SOE) rating. See **Table 1** for factors that influenced the SOE ratings.

Acupuncture vs. No Treatment

- Evidence from 1 RCT suggests that acupuncture led to greater reduction in opioid craving compared to no treatment among adults with OUD. (SOE: Low)
- Evidence from 2 RCTs suggest that there is no statistically significant difference in reducing symptoms of anxiety between acupuncture and no treatment among adults with OUD. (SOE: Very low)

- Evidence from 2 RCTs suggest that acupuncture led to greater reduction in symptoms of depression compared to no treatment among adults with OUD. (SOE: Moderate)

Acupuncture vs. Sham Acupuncture

- Evidence suggests that there is no statistically significant difference between real acupuncture and sham acupuncture for reducing opioid cravings (4 RCTs), pain (2 RCTs) or improving sleep quality (1 RCT) or symptoms of anxiety in adults with OUD (3 RCTs). (SOE: Very low)
- Evidence from 2 RCTs suggest that real acupuncture is more effective than sham in reducing symptoms of depression in adults with OUD. (SOE: Low)

Acupuncture + Methadone Maintenance Therapy (MMT) vs Sham Acupuncture + MMT

- Evidence from 1 RCT suggests that real acupuncture plus MMT significantly reduces daily consumption of methadone compared to sham acupuncture plus MMT among adults with OUD. (SOE: Low)
- Evidence from 1 RCT suggests that there is no statistically significant difference between real acupuncture plus MMT and sham acupuncture plus MMT in reducing heroin cravings or improving quality of life or sleep quality. (SOE: Low)

Acupuncture vs. Medication

- Evidence from 1 RCT suggests that there is no statistically significant difference between acupuncture and western medicine or Chinese herbal medicines in reducing cravings or symptoms of depression in adults with OUD. (SOE: Low)

Acupuncture + Methadone Maintenance Therapy vs MMT alone

- Evidence from 1 RCT suggests that there is no statistically significant difference between acupuncture + MMT and MMT alone in reducing daily methadone consumption, overall withdrawal symptoms or heroin cravings. (SOE: Very low)

Discussion

The evidence for acupuncture in the treatment of opioid use disorder was mixed and varied depending on the control condition. Acupuncture led to greater reduction in opioid cravings when compared to no treatment. However, no difference in cravings was observed between acupuncture (with or without MMT) versus sham acupuncture or medication alone. Similarly, evidence suggests that acupuncture led to a greater reduction in symptoms of depression when compared to no treatment or sham acupuncture. However, no difference in depression or in other psychophysiological outcomes, including sleep, anxiety or pain, was observed between acupuncture versus medication alone (including MMT). Acupuncture plus MMT significantly reduced daily consumption of methadone compared to sham acupuncture plus MMT. However, no reduction in methadone consumption was observed between acupuncture plus MMT versus MMT alone. In general, the strength of the evidence for all outcomes was rated low to very low due primarily to limitations in the methodological quality of the studies, small number of studies, small sample sizes, and lack of precision surrounding the estimated effect sizes. Finally, few studies reported on

adverse events. Among the studies that did, most AEs were mild and related to acupoint discomfort (e.g., slight bleeding, tingling).

Table 1. Strength of Evidence for Acupuncture to Opioid Use Disorder

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Acupuncture vs. No Treatment									
Opioid Craving	1 RCT in 1 SR Chen et al. 2018	ACU vs. No treatment (n=90)	MD: -2.18, 95% CI -3.10 to -1.26) P<0.00001 ; favors ACU	Yes (-1)	No	No	Yes (-1); small sample size	No	Low
Anxiety	2 RCTs in 1 SR Chen et al. 2018	ACU vs. No treatment (n=180)	SMD: -0.79, 95% CI -2.47 to 0.88), I^2=96%; p=0.35; NS	Yes (-1)	Yes	No	Yes (-1); wide 95% CIs	No	Very low
Depression	2 RCTs in 1 SR Chen et al. 2018	ACU vs. No treatment (n=180)	SMD: -1.50 (-1.85 to -1.15), I^2=42%; p<0.0001; favors ACU	Yes (-1)	No	No	No	No	Moderate
Acupuncture vs. Sham Acupuncture									
Opioid Craving	4 RCTs in 1 SR Chen et al. 2018	ACU vs. Sham (n=401)	SMD: -0.66, 95% CI: -1.97 to 0.64), I^2=70.6%; p=0.32; NS	Yes (-1)	Yes (-1)	No	Yes (-1); wide 95% CIs	No	Very low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Pain	2 RCTs in 1 SR Chen et al. 2018	ACU vs. Sham (n=229)	SMD: -0.89; 95% CI -2.54 to 0.76, I^2=96%; p=0.29; NS	Yes (-1)	Yes (-1)	No	Yes (-1); wide 95% CIs	No	Very low
Sleep Quality	1 RCT in 1 SR (n=48) Chen et al. 2018	ACU vs. Sham (n=48)	MD: -1.14, 95% CI: -3.58 to 1.30; p=0.36; NS	Yes (-1)	No	No	Yes (-2); wide 95% Cis and small sample size	No	Very low
Anxiety	3 RCTs in 1 SR Chen et al. 2018	ACU vs Sham (n=361)	SMD: -0.56, 95% CI -1.37 to 0.25), I^2=90.1%; p-0.17; NS	Yes (-1)	Yes (-1)	No	Yes (-1); wide 95% CIs	No	Very low
Depression	2 RCTs in 1 SR Chen et al. 2018	ACU vs Sham (n=180)	SMD: -1.07, 95% CI -1.88 to -0.25), I^2=10.1%; p=0.01; favors ACU	Yes (-1)	No	No	Yes (-1); wide 95% CIs	No	Low
Acupuncture vs. Medication (defined as Chinese herbs or Western medicine)									
Opioid Craving	1 RCT in 1 SR Chen et al. 2018	ACU vs. Medication (n=111)	MD: -0.01, 95% CI: -0.20 to 0.18;	Yes (-1)	No	No	Yes (-1); wide 95% CIs	No	Low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			p=0.92; NS						
Anxiety	1 RCT in 1 SR Chen et al. 2018	ACU vs. Medication (n=111)	MD: -0.06, 95% CI -0.24 to 0.12); p=0.51; NS	Yes (-1)	No	No	Yes (-1); wide 95% CIs	No	Low
Acupuncture + Methadone maintenance Therapy (MMT) vs. Sham ACU+MMT									
Decrease dosage of methadone	1 RCT Chan et al. 2014	ACU+MMT (n=30) vs Sham ACU+MMT alone (n=30) 4 weeks	**Mean reduction(SD):** -8.10 mg/day (13.37); 0.57 mg/day (7.86), p=0.004; favors ACU	Yes (-1)	No	No	Yes (-1); small sample size	No	Low
Quality of life	1 RCT Chan et al. 2014	ACU+MMT (n=30) vs Sham ACU+MMT alone (n=30) 4 weeks	**SF-36 Physical (mean score):** 76.0 (27.7); 75.2 (27.18); p=0.907; NS	Yes (-1)	No	No	Yes (-1); wide 95% CI	No	Low
			SF-36 Mental health	Yes (-1)	No	No	Yes (-1); NS	No	Low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			(mean score): 55.6 (23.9); 53.87 (19.02); p=0.757; NS						
Sleep Quality	1 RCT Chan et al. 2014	ACU+MMT (n=30) vs Sham ACU+MMT alone (n=30) 4 weeks	**PSQI (mean score):** 9.0 (4.8); 9.8 (4.17); p=0.46; NS	Yes (-1)	No	No	Yes (-1); NS	No	Low
Heroin Craving	1 RCT Chan et al. 2014	ACU+MMT (n=30) vs Sham ACU+MMT alone (n=30) 4 weeks	**Heroin craving (mean score):** 14.14 (22.1); 24.8 (26.5), p=0.101; NS	Yes (-1)	No	No	Yes (-1); NS	No	Low
Acupuncture + Methadone maintenance Therapy (MMT) vs. MMT alone									
Daily methadone dose (mg)	1 RCT Lua et al. 2013[1]; Lua et al. 2013[2]	ACU+MMT (55) vs MMT alone (42) 2 mos	Mean dose: 50.0 (23.8); 60.0 (20.0); p=0.05; favors ACU	Yes (-2)	No	No	Yes (-1); NS	No	Very low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Overall withdrawal symptoms	1 RCT Lua et al. 2013[1]; Lua et al. 2013[2]	ACU+MMT (55) vs MMT alone (42) 2 mos	Mean score: 1.90 (0.85); 2.0 (0.90); p=0.807; NS	Yes (-2)	No	No	Yes (-1); NS	No	Very low
Quality of life	1 RCT Lua et al. 2013[1]; Lua et al. 2013[2]	ACU+MMT (55) vs MMT alone (42) 2 mos	Mean score: 14.28 (2.68); 14.15 (2.99), p=0.947; NS	Yes (-2)	No	No	Yes (-1); NS	No	Very low

ACU: acupuncture; CI: confidence interval; CT: control group; ES: effective size; MMT: methadone maintenance; mos.: months; NR: not reported; NS: not significant; PSQI: Pittsburgh Sleep Quality Questionnaire; RCT: randomized controlled trials; SE: standard error; SF-36: Short Form-26; SMD: standardized mean difference

Table 2. GRADE Factors Used to Assess the Quality of a Body of Evidence

Evidence Category	Definition
Study Quality (Internal Validity or Risk of Bias)	Study quality considers the overall risk of bias rating of all the studies included in the evidence base. In this review, the overall risk of bias would be the average or median USPSTF rating for studies comprising an evidence base for a key outcome.
Consistency of Evidence	Consistency of evidence refers to the degree of similarity in the direction of effects or the degree of similarity in the effect sizes (magnitude of effect) across individual studies within an evidence base.
Directness of Evidence	Direct evidence directly compares interventions of interest in populations of interest and measures patient-oriented outcomes. Evidence can be indirect if the tested intervention differs from the intervention of interest, the study population differs from the population of interest, the outcomes differ from those of primary interest, or treatment comparisons have not been tested in head-to-head comparisons.
Precision of Evidence	Precision is the degree of certainty surrounding an estimate of effect with respect to an outcome. Precision is primarily assessed by examining the 95% confidence intervals around the summary effect size.

Link to GRADE Handbook: **http://gdt.guidelinedevelopment.org/app/handbook**

Table 3. Evidence Table for Systematic Reviews on Acupuncture for OUD

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
Reference: Chen et al. 2018 **Organization/Country:** China **Purpose:** To assess the efficacy of acupuncture in treating OUD. **AMSTAR Rating:** High **Overall RoB of Included Studies:** Moderate to High using Cochrane ROB tool due to lack of reporting about allocation concealment (8 RCTs), lack of blinding of patients and outcomes assessors (9 RCTs) and lack of clearly reporting dropout rate (3 RCTs) or having >20% attrition (1 RCT)	**Databases Searched:** Searched PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, PsycINFO, CINAHL, Web of Science, ProQuest Dissertation, AMED and Clinicaltrials.gov. **Dates Searched:** Inception to December 2017 **Inclusion/Exclusion Criteria:** RCTs and quasi-RCTs except crossover trials and cluster RCTs; non-pregnant adult patients diagnosed with OUD using recognized clinical criteria (e.g., DSM or ICD); acupuncture compared to no treatment, sham acupuncture, or other therapies such as psychotherapy or pharmacotherapy, or conventional interventions. **Final Evidence Base:** 9 RCTs; 5 in English and 4 in Chinese	**Diagnosis:** OUD **Number of Patients:** 1,063; ranging from 20 to 121 per arm **Age (mean):** 31.5 yrs **Gender:** 49% male	**Intervention:** Manual acupuncture (MA, 1 RCT)), electroacupuncture (4 RCTs), auricular acupuncture (AA, 2 RCTs), and transcutaneous acupoint electrical stimulation (TEAS, 2 RCTs). Treatment sessions varied from 10 to 30 sessions lasting from 20 to 25 mins. **Comparators:** No treatment (9 RCTs), sham acupuncture (7 RCTs), medication (3 RCTs) **Follow-up:** (duration of treatment) 4 days to 10 weeks; median 15 days **Outcomes:** Primary outcomes: intensity of withdrawal syndrome; duration of treatment; number of positive urine screens for opioids	**ACU vs. no Tx** **Craving:** 1 RCT (n=90), MD: -2.18, 95% CI -3.10 to -1.26) **Anxiety:** 2 RCTs (n=180), SMD: 0.79, 95% CI -2.47 to 0.88), I^2=96% **Depression:** 2 RCTs (n=180), SMD: -1.50 (-1.85 to -1.15), I^2=42% **ACU vs Sham** **Positive Urine Samples:** 1 RCT (n=13), RR: 2.22, 95% CI 0.37 to 13.4 **Craving:** 4 RCTs (n=401), SMD: -0.66, 95% CI: -1.97 to 0.64), I^2=70.6% **Pain:** 2 RCTs (n=229), SMD: -0.89; 95% CI -2.54 to 0.76, I^2=96% **Sleep Quality:** 1 RCT (n=48), MD: -1.14, 95% CI: -3.58 to 1.30 **Anxiety:** 3 RCTs (n=361), SMD: -0.56, 95% CI -1.37 to 0.25), I^2=90.1% **Depression:** 2 RCTs (n=180), SMD: -1.07, 95% CI -1.88 to -0.25), I^2=10.1% **ACU vs Med** **Craving:** 1 RCT (n=111), MD: -0.01, 95% CI: -0.20 to 0.18

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
				Anxiety: 1 RCT (n=111), MD: -0.06, 95% CI -0.24 to 0.12)

ACU: acupuncture; AEs: adverse events; CI: confidence interval; CT: control group; ES: effective size; I^2: % of heterogeneity between studies; mos.: months; NR: not reported; NS: not significant; RCT: randomized controlled trials; SE: standard error; SMD: standardized mean difference; TAU: treatment as usual; WL: waitlist

Table 4. Systematic Review Risk of Bias AMSTAR Checklist Table on Acupuncture for OUD

Question	Chen et al. 2018
Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
Did the review authors use a comprehensive literature search strategy?	Yes
Did the review authors perform study selection in duplicate?	Yes
Did the review authors perform data extraction in duplicate?	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	No
Did the review authors describe the included studies in adequate detail?	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
Did the review authors report on the sources of funding for the studies included in the review?	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes
Overall Quality	**High**

RoB: risk of bias

Table 5. AMSTAR Rating of Overall Confidence in Results of the Review

Category	Definition
High	*No or one non-critical weakness*: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.
Moderate	*More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.
Low or Very Low	*One or more critical flaw(s) with or without non-critical weaknesses*: the systematic review has one or more critical flaws and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.

AMSTAR checklist, go to https://amstar.ca/Amstar_Checklist.php

Table 6. Evidence Table for RCTs on Acupunture in the Treatment of OUD

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Chan et al. 2014 **Purpose:** To examine the effectiveness of AUC for people with heroin addiction on MMT **Setting:** China Medical University, China **F/u:** 4 weeks post treatment **Funding source:** Grant funded	**Number of patients:** 60; n=30 ACU+MMT; n=30 Sham ACU+MMT **Inclusion criteria:** Adults ≥20 yrs with a diagnosis of opioid dependence using DSM criteria who have been receiving MMT for >1 month. **Exclusion criteria:** Received any antidepressant or neuroleptic medication; received acupuncture in the past 30 days; had an adverse event related to previous acupuncture; had a serious medical illness, at risk of suicide; had an infection close to selected acupoints; pregnant or planning to get pregnant; had a bleeding disorder that required an anticoagulant drug; or HIV positive **Pt. baseline characteristics (ACU; Sham):** **Age (mean yrs., SD):** 37 (7.25); 35.3 (6.6) **Gender (male/female):** 26/4; 23/7 **Heroin use (mean yrs., SD):** 6.53 (4.4); 7.57 (5.0) **SF-36 physical function (mean, SD):** 76.6 (22.18); 78.0 (19.28) **SF-36 mental health:** 50.4 (18.9); 53.87 (15.6) **PSQI total (mean total score, SD):** 12.03 (3.94); 10.2 (4.22) **Heroin craving score:** 50.6 (33.3); 44.7 (34.6)	**Intervention:** Auricular acupuncture and body electroacupuncture + cont. MMT; ACU delivered by trained acupuncturist 2x/wk for 4 weeks; each session lasted 20 mins. MMT dosage was adjusted by an independent psychiatrist. **Control:** Sham ACU applied superficially at the same acupoints as real ACU + MMT. **Outcomes of Interest:** Daily methadone use, quality of life (measured with the SF-36), sleep quality, heroin craving, and AEs	**4 weeks post-treatment (ACU vs Sham; mean, SD, btw grp p-value)** **Decrease dosage of methadone:** -8.10 mg/day; 0.57 mg/day, p=0.004 **SF-36 Physical:** 76.0 (27.7); 75.2 (27.18); p=0.907 **SF-36 Mental health:** 55.6 (23.9); 53.87 (19.02); p=0.757 **PSQI:** 9.0 (4.8); 9.8 (4.17); p=0.46 **Heroin craving:** 14.14 (22.1); 24.8 (26.5), p=0.101 **AE's:** ACU: bleeding (n=2), hand numbness (n=1); Sham: bleeding (n=1)	**Conclusion:** The findings suggest that real ACU+MMT led to a significant reduction in daily dose of methadone compared to Sham ACU+MMT alone. However, no differences were found between the two groups for quality of life, sleep quality, or heroin craving. **Limitations:** Treatment providers not blinded, small sample size, short duration of treatment and limited follow-up. **Study RoB:** Some concerns due to no blinding of providers and self-reported outcome measures. **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Lua et al. 2013[1]; Lua et al. 2013[2] Publications reported on different outcomes of the same pt. population **Purpose:** To compare clinical outcomes of MMT + auricular acupuncture vs MMT alone in adults with drug dependence **Setting:** 3 MMT centers in Malaysia **F/u:** 2 mos; postintervention **Funding source:** Grant funded	**Number of patients:** 97; n=55 ACU+MMT; n=42 MMT alone **Inclusion criteria:** Established opioid dependence through clinical criteria and urine test; participant in an MMT program; ≥18 yrs; and able to understand Malay. **Exclusion criteria:** Individuals displaying violent, suicidal or psychotic behavior; infected with HIV or Hepatitis B; or involved in criminal activities. **Pt. baseline characteristics (ACU+MMT; MMT):** **Age (mean yrs., SD):** 37.7 yrs; range 23 to 59 **Gender (% male):** 100% **Daily dose methadone (mean mg):** 55.0 (26.25); 60.0 (24.4); **Overall withdrawal symptoms:** 2.20 (0.80); 1.95 (0.97); significant difference p=0.006 *1=never to 4=frequent **Total HRQoL (mean, SD):** 13.02 (2.59); 14.5 (2.85); significant difference p=0.004 Higher scores better	**Intervention:** Auricular acupuncture delivered 3 times/week for 2 mos with each session lasting 30 mins; MMT initiated at 15 to 20 mg, and then increased to meet patient's needs **Control:** MMT initiated at 15 to 20 mg, and then increased to meet patient's needs **Outcomes of Interest:** Daily methadone dose, withdrawal symptoms, acceptance of treatment, HRQoL (using the WHOQoL-BREF), patient satisfaction (measured with the PSPCQ), relapse, and cigarettes smoked	**<u>Post-intervention</u>** ACU+MMT (n=29); MMT (n=40): mean, SD, btw grp p-value) **Daily methadone dose (mg):** 50.0 (23.8); 60.0 (20.0); p=0.05 *Note: no significant **Overall withdrawal symptoms:** 1.90 (0.85); 2.0 (0.90); p=0.807 **HRQoL:** 14.28 (2.68); 14.15 (2.99), p=0.947 **Relapse** (as measured through urine screen): **Negative (8 wks):** 25 (86.4); 34 (91.9), p=0.690 **Positive (8 wks):** 3 (8.1); 4 (13.8) **Satisfaction:** No significant difference (p>0.05) on any item.	**Conclusion:** The findings suggest that there was no significant difference at 2 months post-intervention in daily dose of methadone, withdrawal symptoms, quality of life, relapse or patient satisfaction with treatment between patient who received acupuncture and MMT and who received MMT alone. Patients who received ACU + MMT showed a significant reduction in overall withdrawal symptoms from pre-treatment to post-treatment, but pre-treatment scores on craving indices were higher at baseline for the acupuncture group than for the control group. Attrition was high in the ACU group with 50% or more of the patients in this group experiencing mild to moderate AE's mostly due to needle application. **Limitations:** High attrition in the ACU + MMT group (47%); no sham ACU in the control group, small sample, and limited follow-up **Study RoB:** High; due to high (>20%) in the acupuncture group and not blinding the outcome assessors **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
			AEs (ACU+MMT grp only): **Dizziness:** 65.5% **Tingling sensation:** 65.5% **Nausea:** 65.5% **Slight fever:** 65.5% **Light headache:** 58.6% **Pain:** 58.6% **Dry mouth:** 51.7% **Slight bleeding:** 48.3% **Drowsiness:** 37.9% All AE's mild and resolved without intervention	

AA: auricular acupuncture; ACU: acupuncture; AE: adverse event; HRQoL: health related quality of life; MMT: methadone maintanence therapy; OUD: opioid use disorder; SPSQI: Pittsburgh Sleep Quality Index; SD: standard deviation**;** PSPCQ: Patient Satisfaction with Pharmaceutical Care Questionnaire; SF-36: short-form 36; WHOQoL: World Health Organization Quality of Life Scale

Table 7. Cochrane Risk of Bias 2.0 Tool for RCTs on Acupuncture for OUD

Reference	Chan et al. 2014	Lua et al. [1,2]
➢ Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	Yes	Yes
➢ Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization, concealed envelopes)?	Yes	Yes
➢ Did baseline difference between study groups suggest a problem with randomization?	No	No
Overall RoB for Randomization Process	**Low**	**Low**
Deviation from Intended Intervention (Effect of Assignment)		
➢ Were participants aware of their assigned intervention during the trial?	No	No
➢ Were providers and people delivering treatment aware of assigned intervention during trial?	Yes	Yes
➢ Were there deviations from the intended intervention that arose because of the experimental context?	No	No
➢ Were these deviations from intended intervention balanced between groups?	NA	NA
➢ Were these deviations likely to have affected the outcome?	NA	NA
➢ Was an appropriate analysis used to estimate the effect of assignment to intervention?	NA	NA
Overall RoB of Effect of Assignment	**Some concerns**	**Some concerns**
Missing Outcome Data		
➢ Were data for this outcome available for all, or nearly all, participants randomized?	Yes	No
➢ Is there evidence that result was not biased by missing outcome data?	NA	No
➢ Could missingness in the outcome depend on its true value?	NA	No
➢ Do the proportions of missing outcome data differ between intervention groups?	NA	Yes
➢ Is it likely that missingness in the outcome depended on its true value?	NA	No
Overall RoB of Missing Data	**Low**	**High**
Measurement of the Outcome		
➢ Was the method of measuring the outcome inappropriate?	Yes	Yes
➢ Could measurement or ascertainment of the outcome have differed between intervention groups?	No	No
➢ Were outcome assessors aware of the intervention received by study participants?	No	Yes
➢ Could assessment of the outcome have been influenced by knowledge of intervention received?	No	No
➢ Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No	No
Overall RoB of Measurement of Outcome	**Low**	**High**

Reference	Chan et al. 2014	Lua et al. [1,2]
Selection of Reported Results		
➢ Was the trial analyzed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?	Yes	Yes
Overall RoB of Reported Results	**Low**	**Low**
Overall Study ROB	**Some concerns**	**High**

*Responses: Y=Yes, PY=Probably Yes, N=No, PN=Probably No, NI=No Information; ROB: risk of bias

Table 8. Cochrane Risk of Bias 2.0 Overall Risk of Bias Judgement

Category	Definition
Low risk of bias	The study is judged to be at **low risk of bias for all domains** for this result.
Some concerns	The study is judged to be at **some concerns** in at least one domain for this result.
High risk of bias	The study is judged to be at **high risk of bias** in at least one domain for this result. OR The study is judged to have **some concerns** for **multiple domains** in a way that substantially lowers confidence in the result.

References

Chan, Y-Y., Lo, W-Y., Li, T-C., Shen, L-J., Yang, S-N., Chen, Y-H., & Lin, J-G. (2014). Clinical efficacy of acupuncture as an adjunct to methadone treatment services for heroin addicts: A randomized controlled trial. *The American Journal of Chinese Medicine, 42*(3), 569-586. doi: 10.1142/S0192415x14500372

Chen, Z., Wang, Y., Wang, R., Xie, J., & Ren, Y. (2018). Efficacy of acupuncture for treating opioid use disorder in adults: A systematic review and meta-analysis. *Hindawi, 2018*(3724708), 1-15. doi: 10.1155/2018/3724708

Lua, P. & Talib, N. (2013). Auricular acupuncture for drug dependence: An open-label randomized investigation on clinical outcomes, health-related quality of life, and patient acceptability. *Alternative Therapies, 19*(4), 28-42.

Lua, P., Talib, N., & Ismail, Z. (2013b). Methadone maintenance treatment versus methadone maintenance treatment plus auricular acupuncture: Impacts on patient satisfaction and coping mechanism. *Journal of Pharmacy Practice, 26*(6), 541-550.

Exercise

Evidence Base

Our search of the literature identified 2 RCTs that assessed exercise[1] as an adjunct in the treatment of opioid use disorders (OUD). See **Table 3** and **Table 5** for details about the patients, interventions, outcomes and findings of the identified studies.

Two RCTs evaluated the use of exercise as an adjunct to treatment among patients with OUD. Colledge et al. (2017) evaluated the feasibility of providing exercise therapy (mostly running) to 50 adults receiving heroin-assisted treatment (HAT) (Colledge et al. 2017). HAT is provided to opioid addicted patients who have not had success with methadone substitution or abstinence-oriented treatment. In HAT, patients receive a dose of clinical-standard heroin, which they inject or ingest once or twice a day. Cutter et al. (2014) examined the impact of providing exercise in the form of Active Game Play using Wii Fit Plus to 29 adults receiving methadone maintenance therapy (MMT) (Cutter et al. 2014).

Study Quality

Using the revised Cochrane tool, we rated the ROB of the individual RCTs as high primarily due to lack of allocation concealment and lack of blinding of patients, study staff and outcome assessors (See **Table 6**).

Key Findings

Below, we describe the key findings for the outcomes of interest with the GRADE strength of the evidence (SOE) rating. See **Table 1** for factors that influenced the SOE ratings.

- Evidence from 1 RCT suggests that exercise plus heroin-assisted therapy significantly improves physical function compared to heroin-assisted therapy plus a non-exercise activity for adults with OUD. (SOE: Very low)
- Evidence from 1 RCT suggests that there is no significant difference between exercise plus heroin-assisted therapy and heroin-assisted therapy plus a non-exercise activity in improving substance use (use of illicit heroin or other substances) or psychological measures (depression, stress, sleep quality and self-control). (SOE: Very low)
- Evidence from 1 RCT suggests that there is no significant difference between exercise plus methadone maintenance therapy and methadone maintenance plus a non-active activity in reducing use of opioids or other substances or in improving perceived stress or optimism. (SOE: Very low)

Discussion

The findings of the evidence for exercise added to the treatment of individuals with opioid use disorder suggest that exercise does not reduce substance use compared to medication maintenance for OUD. However, exercise may help to improve physical function. The overall strength of the evidence for exercise was rated very low due to limitations in study methodology (e.g., lack of blinding, attrition), lack of precision around the effect size estimates, small sample sizes, and limited follow-up.

[1] It is important to note that types of exercise vary across studies and conditions.

Table 1. Strength of Evidence for Exercise to Treat OUD

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Substance Use	2 RCTs (Colledge, 2017; Cutter, 2015)	EX (n=28) vs. CG (n=26) 8 to 12 wks	No significant difference over time or between groups EX and CG for days of secondary drug use or use of illicit heroin.	Yes (-2)	No	No	Yes (-1); wide 95% CI	No	Very low
Quality of life	1 RCT (Colledge, 2017)	EX (n=13) vs CG (n=12) 12 wks	The EX group scored significantly higher than the CG on the physical function component of the SF-36 (F statistic: 6.95, p=0.0016)	Yes (-2)	No	No	Yes (-1); small sample size	No	Very low
Psychological measures (depression, stress, sleep quality or self-control)	2 RCTs (Colledge, 2017; Cutter, 2015)	EX (n=28) vs. CG (n=26) 8 to 12 wks	No significant difference b/w EX and CG	Yes (-2	No	No	Yes (-1); wide 95% CI	No	Very low

AUDIT: Alcohol Use Disorder Identification Test; BDI: Beck Depression Inventory; CG: control group; CI: confidence interval; ES: effect size; EX: exercise; f/u: follow-up; NR: not reported; NS: not significant; OR: odds ratio; RCT: randomized controlled trials; RoB: risk of bias; SD: standard deviation; SF-36: Short-Form 36; SMD: standardized mean difference; TAU: treatment as usual; wks: weeks

Table 2. GRADE Factors Used to Assess the Quality of a Body of Evidence

Evidence Category	Definition
Study Quality (Internal Validity or Risk of Bias)	Study quality considers the overall risk of bias rating of all the studies included in the evidence base. In this review, the overall risk of bias would be the average or median USPSTF rating for studies comprising an evidence base for a key outcome.
Consistency of Evidence	Consistency of evidence refers to the degree of similarity in the direction of effects or the degree of similarity in the effect sizes (magnitude of effect) across individual studies within an evidence base.
Directness of Evidence	Direct evidence directly compares interventions of interest in populations of interest and measures patient-oriented outcomes. Evidence can be indirect if the tested intervention differs from the intervention of interest, the study population differs from the population of interest, the outcomes differ from those of primary interest, or treatment comparisons have not been tested in head-to-head comparisons.
Precision of Evidence	Precision is the degree of certainty surrounding an estimate of effect with respect to an outcome. Precision is primarily assessed by examining the 95% confidence intervals around the summary effect size.

Link to GRADE Handbook: **http://gdt.guidelinedevelopment.org/app/handbook**

Table 3. Evidence Table for RCTs on Exercise to Treat Opioid Use Disorder

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Colledge et al. 2017 **Purpose:** Randomized trial to assess the feasibility, acceptance, and effects of an exercise intervention for individuals receiving outpatient heroin-assisted treatment. **Setting:** Outpatient heroin assisted treatment facility in Switzerland **Funding source:** Grant funding	**Number of patients:** 24 pts; n=13 exercise; n=11 CG **Inclusion criteria:** Adults 18 yrs or older with opioid addiction. Pts were not aiming for abstinence at the time of the study. **Exclusion criteria:** Pts with psychological or physical impairment precluding participation in light exercise. **Pt. baseline characteristics (Ex; CG):** **Age (mean yrs):** 42.7 (6.5); 45.8 (4.2) **% male:** 69%; 62.5% **Daily heroin dose (mean mg):** 377 (164); 400 (162) **% Psychiatric comorbidity:** 46.2%; 54.5%	**Intervention:** HAT+Ex; HAT is provided to opioid addicted pts who have not had success with methadone substitution or abstinence-oriented treatment. In HAT, pts received a dose of clinical-standard heroin, which they inject or ingest once or twice a day. Exercise consisted of 2 grps-one for non-disabled participants that involved a mix of different activities, including aerobics, strength training, boxing, or climbing; and one for less-abled pts that involved athletic activities tailored to their abilities. Exercise took place 2x/wk for 12 weeks. **Control:** HAT+ more sedentary activities, such as board games, occasional short walks, and painting **Outcomes:** Depression symptoms (using the ESDS); subjective sleep (using the ISI); self-control (using the BSCS); perceived stress (using the PSS), quality of life (using the SF-36); and substance use (using the TLFB) **F/u:** 12 wks	**12 weeks f/u:** **Compliant** (% Ex vs. % CG): 38.5% vs 45.5%, p=0.029 **Semi-compliant:** (% Ex vs. % CG): 53.8% vs 9.1% **Non-compliant:** (% Ex vs % CG): 7.7% vs 45.5% **Psychological measures:** The EX group scored significantly higher than the CG on the physical function component of the SF-36 (F statistic: 6.95, p=0.0016 No significant differences found over time (BL to f/u) or between groups at any timepoint for symptoms of depression, stress, sleep quality or self-control. **Substance use:** No significant difference over time or between groups for days of secondary drug use or use of illicit heroin.	Results suggest that exercise therapy is feasible among individuals with OUD who receive heroin-assisted treatment. Exercise participants scored significantly higher than the control group on the physical function component of the SF-36. However, no significant differences were observed over time or between groups for other psychological measures (depression, stress, sleep quality and self-control) or for days of use of substances (alcohol, street heroin, cigarettes or other illicit drugs) other than that provided through HAT. **Limitations:** Methodological limitations, use of self-reported measures for all outcomes, small sample size, and limited follow-up **Study RoB:** High due to lack of blinding of patients, treating staff and outcome assessors. **Author conflict:** None reported
Reference: Cutter et al. 2015	**Number of patients:** 29; n=15 in active game play;	**Intervention**: Daily, 20 to 25 minutes of physical activity 5 days/wk	**8 wks f/u:**	Results suggest active game play was acceptable to adults with opioid use

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Purpose: To examine the feasibility and compare the effectiveness of a video game exercise intervention using Wii Fit compared to sedentary video games. **Setting:** Outpatient methadone maintenance treatment (MMT) program in the USA **Funding source:** Yale University grant and National Institute of Drug Abuse	n=14 in sedentary game play **Inclusion criteria:** Ability to read and understand English and past-week use of illicit opioids or cocaine by self-report or toxicology. **Exclusion criteria:** Current suicide of homicide risk; unable to complete informed consent; known seizure disorder; or medical condition that would interfere with daily, low-to-moderate physical exercise. **Pt. baseline characteristics (Active game; sedentary game):** **Age (mean yrs):** 42.8; 44.0 **% male:** 47%; 36% **Yrs of opioid use (mean, SD):** 19.3 (11.9); 11.1 (7.4) **Days of opioid use in past 30 days (mean, SD):** 2.7 (7.1); 0.4 (0.9) **# times in drug abuse tx (mean, SD):** 10.1 (9.3); 5.9 (5.5)	delivered through WiiFit plus. Pts were required to include aerobic exercise, strength training, and yoga in the course of the week. **Control:** Daily, 20 to 25 minutes of sedentary video game playing 5 days/wk through WiiFit plus, including such games as Super Mario Brothers and Jeopardy. Both groups received MMT, which consisted of group counseling 1x/month and daily methadone. **Outcomes:** Pt. satisfaction (measured through a Likert scale), Physical activity, substance us (weekly log), and perceive stress (measured by PSS) F/u: post-intervention at 8 wks	**Acceptability:** 93% pts completed study and attended over 65% of sessions with no difference between groups. Overall acceptability was rated high in both groups. **Substance use:** There was a significant difference in opioid and cocaine use from BL to f/u (from 3 days/wk to 1.7 days, $p<0.001$) in both groups, but no between grp difference. **Psychological wellness:** There was a significant difference in perceived stress ($p=0.04$) and optimism ($p=0.04$) for both groups over time, but no significant between group difference.	disorder receiving MMT and led to higher levels of overall physical activity. Both active and sedentary game play significantly decreased opioid use and improved stress and optimism from baseline to follow-up. However, there was no significant differences observed between the active and inactive group for any of the outcomes. **Limitations:** Small sample size, use of self-report to measure drug use, and limited follow-up. **Study RoB:** High due lack allocation concealment and lack of blinding of pts, study staff, and outcome assessors **Author conflict:** None reported

ASI: Alcohol severity index; AEs: adverse events; AUD: alcohol use disorder; AUDIT: Alcohol Use Disorder Identification Test; BDI: Beck Depression Inventory; BL: baseline; BSCS: Brief Self-control Scale (higher scores more self-control); CG: control group; CI: confidence interval; ES: effect size; ESDS: Epidemiological Studies Depression Scale (lower scores less depression); EX: exercise; f/u: follow-up; HAT: heroin-assisted therapy; ISI: Insomnia Severity Scale (lower scores less insomnia); MMT: methadone maintenance treatment; NR: not reported; NS: not significant; OR: odds ratio; OUD: opioid use disorder; PSS: Perceived Stress Scale (lower scores less stress); RCT: randomized

controlled trials; RoB: risk of bias; SD: standard deviation; SF-36: Short-Form 36; SMD: standardized mean difference; TAU: treatment as usual; TLFB: Timeline Follow-back Questionnaire (measures substance use)

Table 4. Cochrane Risk of Bias 2.0 for RCTs on Exercise to Treat OUD

Reference	Colledge et al. 2017	Cutter et al. 2015
Randomization Process		
➢ Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	Yes	Yes
➢ Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization, concealed envelopes)?	Yes	NI
➢ Did baseline differences between study groups suggest a problem with randomization?	No	No
Overall RoB for Randomization Process	**Low**	**Some concerns**
Deviation from Intended Intervention (Effect of Assignment)		
➢ Were participants aware of their assigned intervention during the trial?	Yes	Yes
➢ Were providers and people delivering treatment aware of assigned intervention during trial?	Yes	Yes
➢ Were there deviations from the intended intervention that arose because of the experimental context?	No	No
➢ Were these deviations from intended intervention balanced between groups?	NA	NA
➢ Were these deviations likely to have affected the outcome?	NA	NA
➢ Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	Yes
Overall RoB of Effect of Assignment	**Some Concerns**	**Some Concerns**
Missing Outcome Data		
➢ Were data for this outcome available for all, or nearly all, participants randomized?	Yes	Yes
➢ Is there evidence that result was not biased by missing outcome data?	NA	NA
➢ Could missingness in the outcome depend on its true value?	NA	NA
➢ Do the proportions of missing outcome data differ between intervention groups?	NA	NA
➢ Is it likely that missingness in the outcome depended on its true value?	NA	NA
Overall RoB of Missing Data	**Low**	**Low**
Measurement of the Outcome		
➢ Was the method of measuring the outcome inappropriate?	No	No
➢ Could measurement or ascertainment of the outcome have differed between intervention groups?	No	No
➢ Were outcome assessors aware of the intervention received by study participants?	Yes	Yes
➢ Could assessment of the outcome have been influenced by knowledge of intervention received?	NI	NA

Reference	Colledge et al. 2017	Cutter et al. 2015
➢ Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NI	NA
Overall RoB of Measurement of Outcome	**High**	**High**
Selection of Reported Results		
➢ Was the trial analyzed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?	Yes	NI
Overall RoB of Reported Results	**Low**	**Some concerns**
Overall Study RoB	**High**	**High**

*Responses: Y=Yes; PY=Probably Yes; N=No; PN=Probably No; NA=Not Applicable; NI=No Information; RoB: risk of bias

Table 5. Cochrane Risk of Bias 2.0 Overall Risk of Bias Judgement

Category	Definition
Low risk of bias	The study is judged to be at **low risk of bias for all domains** for this result.
Some concerns	The study is judged to be at **some concerns** in at least one domain for this result.
High risk of bias	The study is judged to be at **high risk of bias** in at least one domain for this result. OR The study is judged to have **some concerns** for **multiple domains** in a way that substantially lowers confidence in the result.

References

Colledge, F., Vogel, M., Dursteler-Macfarland, K., Strom, J., Schoen, S., Puhse, U., Gerber, M. (2017). *Journal of Substance Abuse Treatment, 76*, 49-57.

Cutter, C., Schottenfeld, R., Moore, B., Ball, S., Beitel, M., Savant, J., …Barry, D. (2014). *Journal of Substance Abuse Treatment, 47*(4), 299-305. doi: 10.1016/j.jsat.2014.05.007.

Summary of Evidence of CIH and Other Interventions for Opioid Use Disorder

This systematic review assessed the efficacy of specific CIH, and other interventions used in the treatment of individuals with OUD. The overall evidence base included 5 publications (1 SRs with 9 RCTs plus 4 additional RCTs) that met inclusion criteria and addressed acupuncture (1 SR plus 2 RCTs) or exercise therapy (2 RCTs). The literature searches did not identify any publications meeting inclusion criteria for the following interventions: accelerated resolution therapy (ART), art therapy, cannabinoids, chiropractic care, equine therapy, healing touch, hyperbaric oxygen therapy, massage therapy, meditation, music therapy, Tai Chi, therapeutic touch, training and care of service dogs, or transcranial magnetic stimulation.

Overall, the evidence for acupuncture in the treatment of OUD was mixed and varied depending on the control condition. Acupuncture led to greater reduction in opioid cravings when compared to no treatment. However, no difference in cravings was observed between acupuncture (with or without methadone maintenance therapy [MMT]) versus sham acupuncture or medication alone. Similarly, evidence suggests that acupuncture led to a greater reduction in symptoms of depression when compared to no treatment or sham acupuncture. However, no difference in depression or in other psychophysiological outcomes, including sleep, anxiety or pain, was observed between acupuncture versus medication alone (including MMT). Acupuncture plus MMT significantly reduced daily consumption of methadone compared to sham acupuncture plus MMT. However, no reduction in methadone consumption was observed between acupuncture plus MMT versus MMT alone. Few studies reported on adverse events. Among the studies that did, most adverse events were mild and related to acupoint discomfort (e.g., slight bleeding, tingling).

The findings of the evidence for exercise added to the treatment of individuals with OUD suggest that exercise does not reduce substance use compared to medication maintenance for OUD. However, exercise may help to improve physical function among adults with OUD receiving mediation maintenance.

In general, the strength of the evidence for acupuncture and exercise was rated low to very low due primarily to limitations in the methodological quality of the studies (lack of blinding, attrition), small number of studies, small sample sizes, lack of precision surrounding the estimated effect sizes, and limited follow-up. **Table 1** below provides an overview of the evidence and findings for acupuncture and exercise used in the treatment of OUD.

Table 1. Summary of Finding of CIH for OUD

	Craving			Methadone Consumption			Depression			Anxiety		
Intervention	**EB**	**Findings**	**SOE**	**EB**	**Findings**	**SOE**	**EB**	**Findings**	**SOE**	**EB**	**Findings**	**SOE**
ACU vs No treatment	1 RCT	+	L	NR	NR	NR	2 RCTs	+	MOD	2 RCTs	NS	VL
ACU vs Sham ACU	4 RCTs	NS	VL	NR	NR	NR	NR	NR	NR	3 RCTs	NS	VL
ACU+MMT vs Sham ACU+MMT	1 RCT	NS	L	1 RCT	+	L	NR	NR	NR	NR	NR	NR
ACU vs Med*	1 RCT	NS	L	NR	NR	NR	1 RCT	NS	L	NR	NR	NR
ACU+MMT vs MMT	1 RCT	NS	VL	1 RCT	NS	VL	NR	NR	NR	NR	NR	NR
Exercise vs non-active control	NR	NR	NR	1 RCT	NS	VL	1 RCT	NS	VL	NR	NR	NR

*In this RCT, specific medication was not reported.

+ favors intervention; - favors control; NS: no significant difference between intervention and control; ACU: acupuncture; EB: evidence base; L: Low strength of evidence; Med: medication; MMT: methadone maintenance therapy; MOD: Moderate strength of evidence; NR: not reported; RCT: randomized controlled trial; SOE: strength of evidence; SR: systematic review; VL: very low strength of evidence

Appendix A

Inclusion Criteria:

- **Publications type:** Systematic reviews (SRs) and randomized controlled clinical trials (RCTs) published in English language in peer reviewed journals.
- **Search date:** 01/01/2008 to present
- **Population:** Adults 18 years or older meeting diagnostic criteria for OUD
- **Intervention (s):**
    - Complementary and integrative health (CIH) and other non-pharmacologic treatments: music therapy; equine therapy; training and caring for service dogs; yoga therapy; tai chi; acupuncture therapy; meditation therapy; outdoor sports therapy; hyperbaric oxygen therapy; accelerated resolution therapy; art therapy; magnetic stimulation therapy; massage; healing touch; therapeutic touch; cannabinoids; chiropractic care
    - Pharmacological treatments: buprenophine/naloxone, methadone, ketamine
    - Psychological treatments: cognitive behavioral therapy (CBT), motivational enhancement therapy, combined CBT/motivational enhancement therapy
- **Outcomes:** time to relapse, relapse, adherence with treatment or abstinence, retention/engagement in treatment program, number lost to treatment, duration of involvement in treatment, adverse events, morbidity, mortality, overdoses, quality of life, functional status, patient satisfaction, anxiety, insomnia, pain
- **Timing:** no minimum follow-up
- **Setting(s):** primary care; specialty care; general mental health care

Exclusion Criteria:

- **Wrong publication type**: narrative review article, case reports editorial, commentary, protocol of randomized trial without results, any article without original data, abstract alone.
- **Wrong study design:** Observational study (for example, cohort study, case control study, cross-sectional study); treatment study without randomization, randomized study with less than 20 patients (10 per study group).
- **Wrong population**: animal studies, children or adolescents less than 18 years of age (studies must have enrolled a patient population in which at least 80% of patients were diagnosed with OUD.
- **Wrong language:** Study in language other than English.
- **Wrong or no intervention:** CIH treatments other than those listed in inclusion criteria; medications other than those listed in inclusion criteria; psychological treatments other than those listed in inclusion criteria
- **Wrong comparator:** CIH treatments other than those listed in inclusion criteria; medications other than those listed in inclusion criteria; psychological treatments other than those listed in inclusion criteria
- **Wrong outcome(s):** Any study that does not have at least one of the included outcomes of interest. Any subjective outcome (e.g. symptoms; quality of life) not measured using a validated instrument.

Appendix B

Table 1. Studies Excluded at Data Abstraction Level

Authors	Reason for Exclusion
Acupuncture	
Pirnia, B. et al. 2018	Wrong design; Letter to Editor; does not contain all necessary information to assess study quality and cannot locate full-text article.
Meade C. et al. 2010	Included in Chen SR

SR: systematic review

References

Meade, C., Lukas, S., McDonald, L., Fitzmaurice, G., Eldridge, J., Merrill, N., & Weiss, R. (2010). A randomized trial of transcutaneous electric acupoint stimulation as adjunctive treatment for opioid detoxification. *Journal of Substance Abuse Treatment, 38*(1), 12-21.

Pirnia, B., Pirnia, K., Mohammadpour, S., Malekanmehr, P., Soleimani, A., Mahmoodi, Z.,…Zahiroddin, A. (2018). The effectiveness of acupuncture of HPA functional status in depressed patients under methadone maintenance treatment, a randomized double-blind sham-controlled trial. *Asian Journal of Psychiatry, 36*, 62-63.

Appendix C

See **Figures 2 and 3** below for bubble maps. Bubble maps provide a visual overview of the distribution of evidence for the complementary and integrative health and other interventions included in these systematic reviews. The bubble maps display information about the research meeting the inclusion and exclusion criteria (see Appendix A) for these reviews and include the following:

- **The strength of evidence** (y-axis)
  - The y-axis provides an overview of the quantity of research for an intervention. For this estimate, we used the number of individual RCTs and/or the number of RCTs included in previously published systematic reviews. The color of the bubbles indicates the strength of evidence (SOE). The lighter the color of a bubble, the higher the SOE and vice versa.
- **The direction of findings** (x-axis)
  - The x-axis provides an estimate of the clinical effectiveness of an intervention with the bubble maps differentiating the findings with three different categories, which are, "favors control"; "no difference"; and "favors intervention". Control groups are important to consider and have been noted in the maps as well, given that some studies have an active control and others do not.
- **The confidence in the reported effect** (bubble size)
  - The size of a bubble indicates the level of confidence in the reported effect. Next to each bubble we abbreviate the intervention, the control group, and note the number of studies conducted.

It is important to note that, due to the number of studies included and the scope of these systematic reviews, the bubble maps may only represent limited information.

Figure 2. Bubble Plot of Findings for OUD Cravings

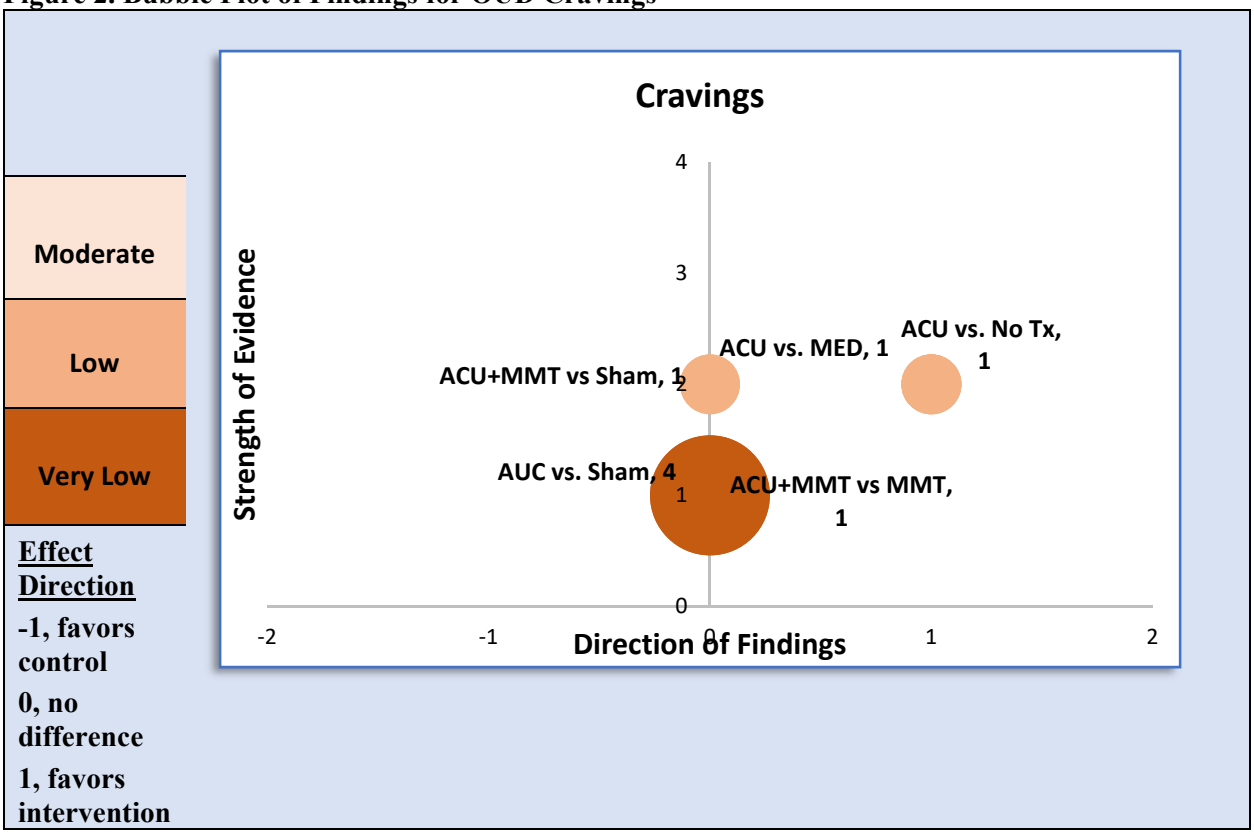


Figure 3. Bubble Plot of Findings for OUD Depression