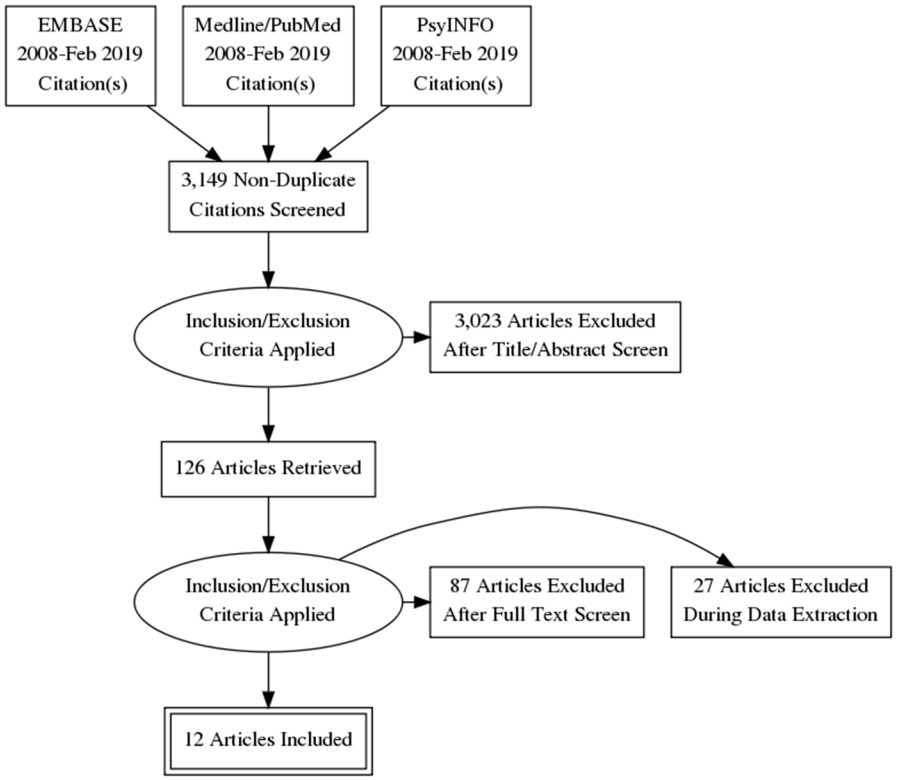
Chapter 3: Complementary and Integrative Health and other Non-Conventional Approaches for Treating Alcohol Use Disorder (AUD)

Results of the Literature Search for AUD

Extensive literature searches identified 3,149 citations (after duplicates removed) potentially addressing the CIH interventions and other non-conventional approaches 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, 7 addressed opioid use disorder and are discussed in the Chapter 2 and 19 were excluded for reasons listed in **Appendix A.**

Figure 1. Prisma Study Flow Diagram for Alcohol Use Disorder



Overall, 12 studies were included in the systematic review for AUD. **Table 1** presents a summary of the evidence (how many RCTs and/or SRs) for each CIH and other interventions.

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

Intervention	Number and Type of Studies for AUD
Accelerated Resolution Therapy (ART)	0
Acupuncture	1 SR (11 RCTs)
Art therapy	0
Cannabinoids	1 RCT
Chiropractic care	0
Equine therapy	0
Exercise therapy (outdoor therapy)	1 SR (4 RCTs); 2 RCTs
Healing Touch	0
Hyperbaric Oxygen Therapy	0
Massage therapy	0
Meditation	3 RCTs
Yoga	0
Music therapy	1 RCT
Tai chi	0
Relaxation therapy	2 RCTs
Training and caring for service dogs	0
Transcranial Magnetic Stimulation (TMS)	1 SR (6 RCTs)
Total Studies	**3 SRs (21 RCTs) and 9 RCTs**

RCT: Randomized controlled trial; SR: systematic review

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

Acupuncture

Evidence Base

Our searches of the literature identified 1 SR with an evidence base of 11 RCTs published between 1987 to 2015 that assessed the benefits and harms of acupuncture to treat alcohol withdrawal syndrome (AWS) (Liu et al. 2018). The trials in the review compared acupuncture to the following: acupuncture + medication vs. sham acupuncture + medications (5 RCTs), acupuncture + medication vs mediation alone (4 RCTs), acupuncture alone vs. sham acupuncture (2 RCTs), acupuncture vs medication (1 RCT). The medications used in the trials comparing acupuncture to medication included naltrexone, benzodiazepine, disulfiram, and fluoxetine. Overall, the trials enrolled a total of 875 patients between the age of 38 to 46 years. See **Table 2** for more information about the review and trials included in the review.

Study Quality

Using the AMSTAR instrument, we rated the quality of the systematic review moderate due primarily to that authors not providing a list of excluded studies with reasons for exclusion (see **Table 4** for ratings). The authors of the review used the Cochrane tool to assess the ROB of the included trials. The trials were rated moderate to high ROB due to lack of or not clearly reporting allocation concealment; blinding of patients, study staff, or outcome assessors; and selection bias.

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 + Medication vs Sham Acupuncture + Medication

- Evidence from 1 RCT suggests that acupuncture plus medication is more effective than sham acupuncture plus medication in improving overall psychological symptoms and anxiety. (SOE: Low)
- Evidence from 1 RCT suggests that there is no statistically significant difference between acupuncture plus medication and sham acupuncture plus medication in reducing cravings for alcohol. (SOE: Low)

Acupuncture + Medication vs Medication Alone

- Evidence from 1 RCT suggests that acupuncture plus medication is more effective than medication alone in improving overall psychological symptoms and anxiety. (SOE: Low)
- Evidence from 1 RCT suggests that there is no statistically significant difference acupuncture plus medication and medication alone in reducing alcohol consumption. (SOE: Low)

Acupuncture vs. Sham (placebo) Acupuncture

- Evidence from 1 RCT suggests that acupuncture is more effective than sham acupuncture in reducing cravings for alcohol. (SOE: Very low)

Acupuncture vs Medication

- Evidence from 1 RCT suggests that medication (disulfiram) is more effective than acupuncture in reducing immediate (<8 weeks) symptoms of alcohol withdrawal. (SOE: Low)
- Evidence from 1 RCT suggests that there is no difference between acupuncture and medication (disulfiram) in the number of patients who stopped drinking alcohol. (SOE: Very low)

Discussion

Overall, limited evidence suggests that acupuncture plus medication leads to improved overall psychological symptoms and symptoms of anxiety compared to sham acupuncture plus medication or to medication alone. However, the strength of the evidence for these outcomes was rated low due to an evidence base consisting of one small RCT with methodological limitations. Limited evidence (1 RCT) also suggests that there is no difference between acupuncture plus medication and sham acupuncture with or without medication in reducing cravings for alcohol or alcohol consumption after treatment. The findings of one study suggests that disulfiram is more effective than acupuncture alone in reducing immediate (< 8 weeks) symptoms of alcohol withdrawal symptoms. Three studies included in the systematic review reported on adverse events. Of those, one study found no difference in rate of adverse events, one study reported no adverse events, and one study reported that two patients in the acupuncture group fainted and eight patients in the disulfiram group experienced temporary nausea.

Table 1. Strength of Evidence for Acupuncture to Treat AUD

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 + Medication vs Sham Acupuncture + Medication									
Craving	1 RCT in 1 SR Liu et al. 2018	ACU+Med vs. Sham ACU+Med (72) 1 month	RR: 1.04, 95% CI 0.79 to 1.37, NS	Yes (-1)	No	No	Yes (-1); wide 95% CI	No	Low
Symptom Checklist	1 RCT in 1 SR Liu et al. 2018	ACU+Med vs. Sham ACU+Med (64)	MD: -3.05, 95% CI -3.63 to -2.47; favors real ACU+fluoxetine	Yes (-1)	No	No	Yes (-1); small sample size	No	Low
Anxiety (HAM-A)	1 RCT in 1 SR Liu et al. 2018	ACU+Med vs. Sham ACU+Med (64)	MD: 4.00, 95% CI 3.30 to 4.70; favors real ACU+fluoxetine	Yes (-1)	No	No	Yes (-1); small sample size	No	Low
Acupuncture + Medicine vs Medication Alone									
Alcohol consumption (after treatment)	1 RCT in 1 SR Liu et al. 2018	ACU+Med vs. Med (n=80)	MD: -0.08, 95% CI -2.32 to 2.16, NS	Yes (-1)	No	No	Yes (-1); wide 95% CI	No	Low
Symptom checklist-90	1 RCT in 1 SR Liu et al. 2018	ACU+Med vs. Med (n=60)	MD: 6.90, 95% CI 5.51 to 8.29; favors ACU+diazapam	Yes (-1)	No	No	Yes (-1); small sample size	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
Anxiety (HAM-A)	1 RCT in 1 SR Liu et al. 2018	ACU+Med vs. Med (n=60)	MD: 4.04, 95% CI 1.51 to 6.57); favors ACU+diazapam	Yes (-1)	No	No	Yes (-1); small sample size	No	Low
Acupuncture vs. sham (placebo) acupuncture									
Craving	1 RCT in 1 SR Liu et al. 2018	ACU vs. Sham ACU (n=20)	ACU more effective than sham, $p<0.01$	Yes (-1)	No	No	Yes (-2); very small sample size; no measure of dispersion reported	No	Very low
Acupuncture vs. Medication									
Withdrawal symptoms (as measured by the VAS scale)	1 RCT in 1 SR Liu et al. 2018	ACU alone vs. Med (n=68):	MD: -2.00, 95% CI -2.43 to -1.57, favors drug (disulfiram) *Difference was no longer observed after 8 weeks	Yes (-1)	No	No	Yes (-1); small sample size; no measure of dispersion reported	No	Low
Alcohol consumption	1 RCT in 1 SR Liu et al. 2018	ACU alone vs. Med (n=25) stopped drinking;	RR: 0.87, 95% CI 0.47 to 1.62; NS; 12 pts in the ACU group and	Yes (-1)	No	No	Yes (-2); very small sample size; no measure of dispersion reported	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
			13 in the disulfiram group						

ACU: acupuncture; AEs: adverse events; AWS: alcohol withdrawal syndrome; CCMD: Classification and Diagnostic Criteria of Mental Disorders; CI: confidence interval; CT: control group; DSM: Diagnostic Statistical Manual of Mental Disorder; ES: effective size; HAM-A: Hamilton Anxiety Scale; ICD-10: International Classification of Disease; I^2: % of heterogeneity between studies; MD: mean difference; mos.: months; NR: not reported; NS: not significant; RCT: randomized controlled trials; RR: relative risk; SE: standard error; 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 AUD

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
Reference: Liu et al. 2018 **Organization/Country:** China **Purpose:** To assess the effects and safety of acupuncture for AWS **AMSTAR Rating:** High **Overall RoB of Included Studies:** Moderate to high primarily due to lack of or not reporting allocation concealment, blinding of pts, study staff or outcome assessors, and selection bias	**Databases Searched:** Searched PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, PsycINFO, Cochrane library; Chinese Biomedicine Literature; China National Knowledge Infrastructure and Wan-Fang database. **Dates Searched:** Inception to September 2016; studies published between 1987 to 2015 **Inclusion/Exclusion Criteria:** RCTs reporting on the treatment effects of acupuncture for AWS. Trials must include description of randomization methods, explicit diagnosis of AWS, eligible outcomes, and appropriate statistical methods. Mechanistic studies, animal studies, narrative reviews or articles without full-text excluded. **Final Evidence Base:** 11 RCTs	**Diagnosis:** AUD and/or AWS using DSM (3 RCTs), ICD-10 (4 RCTs), CCMD (1 RCT), or self-diagnosis (3 RCTs) **Number of Patients:** 875 **Age (mean range):** 38 to 46 **Gender:** NR	**Intervention:** Acupuncture + drug (4 RCTs); electroacupuncture + drug (2 RCTs); acupuncture alone (5 RCTs) **Comparators:** Sham acupuncture+ drug (3 RCTs); Sham EA+ drug (2 RCTs); drug alone (4 RCTs); sham acupuncture alone (2 RCTs) Drugs used: naltrexone (1 RCT); benzodiazepine (2 RCTs); disulfiram (1 RCT); fluoxetine (1 RCT) **Follow-up:** NR **Outcomes:** Craving for alcohol, depression, alcohol consumption, and completion rate	**ACU+drug vs Sham ACU+drug** **Craving:** 1 RCT (n=72): RR: 1.04, 95% CI 0.79 to 1.37; NS at 1-month f/u **Completion rate:** 2 RCTs (n=168; 169): RR: 1.10, 95% CI 0.93 to 1.30, NS, I^2=25% **Symptom checklist 90:** 1 RCT (n=64): MD: -3.05, 95% CI -3.63 to -2.47; favors real ACU+fluoxetine **HAM-A:** 1 RCT (n=64): MD: 4.00, 95% CI 3.30 to 4.70; favors real ACU+fluoxetine **ACU+drug vs. drug alone** **Alcohol consumption (after treatment):** 1 RCT (n=80): MD: -0.08, 95% CI -2.32 to 2.16, NS **Symptom checklist-90:** 1 RCT (n=60): MD: 6.90, 95% CI 5.51 to 8.29; favors ACU+8iazepam **HAM-A:** 1 RCT (n=60): MD: 4.04, 95% CI 1.51 to 6.57); favors ACU+8iazepam **Acupuncture vs. sham (placebo) acupuncture** **Craving:** 1 RCT (n=20): ACU more effective than sham, p<0.01

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
				Completion rate: 2 RCTs (n=94): RR: 2.03, 95% CI: 0.24 to 16.96, I^2=60%, NS **ACU vs. drug** **Withdrawal symptoms (as measured by the VAS scale):** 1 RCT (n=68): MD: -2.00, 95% CI -2.43 to -1.57, favors drug (disulfiram) *Difference was no longer observed after 8 weeks **Completion rates:** 1 RCT (n=118): RR: 0.18, 95% CI 0.06 to 0.56, NS **Alcohol consumption**: 1 RCT (n=68): 12 pts in the ACU group and 13 in the disulfiram group stopped drinking; RR: 0.87, 95% CI 0.47 to 1.62; NS **Aes (reported in 3 RCTs):** 1 RCT found no difference in rate of Aes; 1 study reported no Aes, and 1 study reported that 2 pts in the ACU group fainted and 8 pts in the disulfiram group experienced temporary nausea

ACU: acupuncture; Aes: adverse events; AWS: alcohol withdrawal syndrome; CCMD: Classification and Diagnostic Criteria of Mental Disorders; CI: confidence interval; CT: control group; DSM: Diagnostic Statistical Manual of Mental Disorder; ES: effective size; HAM-A: Hamilton Anxiety Scale; ICD-10: International Classification of Disease; I^2: % of heterogeneity between studies; MD: mean difference; mos.: months; NR: not reported; NS: not significant; RCT: randomized controlled trials; RR: relative risk; SE: standard error; SMD: standardized mean difference

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

Question	Liu 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? RCTs?	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	**Moderate**

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

References

Liu, X., Qin, Z., Zhu, X., Yao, Q., & Liu, Z. (2018). Systematic review of acupuncture for the treatment of alcohol withdrawal syndrome. *Acupuncture in Medicine, 36*(5), 275-283.

Cannabinoids

Evidence Base

Our searches of the literature identified 1 RCT that assessed the benefits and harms of the cannabinoid receptor 1 blocker Rimonabant to treat alcohol dependence (Soyka et al., 2008). Soyka et al. (2008) randomized 258 adults with alcohol dependence to receive either 20 mg/day of Rimonabant (131 patients) or placebo (127 patients) for 12 weeks. Most of the enrolled patients were male (80%) with a mean age of 45 years. The primary outcomes of interest assessed in this study were days abstinent, relapse rate, anxiety, and depression and adverse events. See **Table 3** for more information about the study and patient characteristics.

Study Quality

Using the Cochrane RoB tool, we rated the methodological quality of the study as having some concerns (see **Table 4** for ratings). The concerns focused on lack of information about the randomization process and allocation concealment and moderate attrition. While we did not downgrade for funding or conflict of interest, it should be noted that the study was funded by the drug manufacturer and the lead author reported receiving travel and speaking grants from the funder.

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 there is no significant difference between Rimonabant and placebo in days abstinent, relapse to any or heavy drinking or in improving symptoms of anxiety or depression among alcohol dependent adults. (SOE: Low)

Discussion

The findings suggest that there was no statistically significant difference between Rimonabant and placebo in relapse rate. Overall, 41.5% of patients receiving Rimonabant relapsed to drinking and 47.0% of patients receiving placebo relapsed. Similarly, there were no significant differences between groups in the rate of relapse to heavy drinking (≥ 4 drinks) or in improvement of symptoms of anxiety and depression. The overall strength of the evidence for all outcome was rated low due to concerns about the methodological quality of the study and lack of precision surrounding the findings. According to the authors of the study, safety and tolerance of the study medication were good with similar rates of adverse events. See **Table 3** for specific adverse event rates.

Table 1. Strength of Evidence for Cannabinoids to Treat AUD

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
Abstinence	1 RCT Soyka et al. 2008	Rimonabant (131); PLA (127) 12 wks	**Cumulative (mean days, SD):** 71.2 (27.8); 68.6 (28.0), p=0.47, NS	Yes (-1)	No	No	Yes (-1); lack of precision around findings	No	Low
Relapse	1 RCT Soyka et al. 2008	Rimonabant (131); PLA (127) 12 wks	**Relapse rate (any drinking):** 41.1%; 46.0%, p=0.375 **Relapse rate (heavy drinking):** 26.0%; 32.5%, p=0.125, NS	Yes (-1)	No	No	Yes (-1); lack of precision around findings	No	Low
Anxiety/ Depression			**Anxiety** (mean btw groups difference from BL):1.1 (5.8); 0.4 (4.0), NS **Depression** (mean btw group difference from BL): 0.8 (4.4); -0.2 (3.5), p=0.05, NS	Yes (-1)	No	No	Yes (-1); lack of precision around findings	No	Low

AEs: adverse events; BL: baseline; CI: confidence interval; f/u: follow-up; HAM-A: Hamilton Anxiety Score; HAM-D: Hamilton Depression Score; NR: not reported; NS: not significant; PLA: placebo; RCT: randomized controlled trials; RoB: risk of bias; SAE: serious adverse event; SD: standard deviation

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 Cannabinoids to Treat AUD

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Soyka et al. 2008 **Purpose:** To assess the possible efficacy of the cannabinoid receptor 1 blocker, rimonabant 20 mg in the prevention of relapse to alcohol in recently detoxified alcohol dependent patients. **Setting:** Outpatient, fixed in place residence in Germany **Funding source:** Sanofi-Aventis	**Number of patients:** 258; n=131 Rimonabant; n=127 PLA **Inclusion criteria:** Male and female adults between 18 and 65 years with a diagnosis of alcohol dependence according to the DSM who were detoxified from alcohol for at least 7 days to a max of 28 days prior to randomization and be free of withdrawal symptoms. **Exclusion criteria:** Pts who showed symptoms of alcohol withdrawal or had at least 1 drink during the 3-day run-in period; pts with a lifetime history of post-withdrawal seizures or delirium, alcohol induced psychosis, Wernicke-Korsakoff syndrome, liver cirrhosis or liver impairment, lack of information about alcohol history, impending legal charges, low IQ (<80), or other severe or chronic. neurological, psychological or medical condition. **Pt. baseline characteristics (Rimonabant; PLA):** **Age (mean yrs., SD):** 45.6 (9.2); 44.0 (8.3) **Gender (% male):** 82.4%; 78.7%	**Intervention:** Rimonabant, 20 mg/d (two, 10-mg capsules once daily) **Control:** Placebo **Outcomes of Interest:** Days abstinent, relapse rate, average drinks per day, average drinking days, anxiety (HAM-A) and depression (HAM-D), and AEs **Follow-up:** 12 weeks	**12 weeks (Rimonabant; PLA)** **Completion:** 94 (72%); 79 (62%) **Cumulative abstinence (mean days, SD):** 71.2 (27.8); 68.6 (28.0), p=0.47, NS **Non-Relapse:** 46.5%; 40.3% **Relapse (drinking):** 41.1%; 46.0%, p=0.375, NS **Relapse (heavy drinking):** 26.0%; 32.5%, p=0.125, NS **Ave drinks/day when relapse:** 3.2 (6.5); 3.6 (5.7), p=0.652, NS **% of drinking days:** 5.7 (13.0); 6.0 (11.9), p=0.084, NS **Anxiety** (mean difference from BL):1.1 (5.8); 0.4 (4.0), NS **Depression** (mean difference from	**Conclusion:** The findings suggest that there was no statistically significant difference between Rimonabant and placebo in relapse rate. Overall, 41.5% of patients receiving Rimonabant relapsed to drinking and 47.0% of patients receiving placebo relapsed. Similarly, there were no significant differences between groups in the rate of relapse to heavy drinking (≥ 4 drinks) or in improvement of symptoms of anxiety and depression. According to the authors of the study, safety and tolerance of the study medication were good with similar rates of adverse events. **Limitations:** Pts in the placebo group had a similar response rate (8% decrease in relapse) as Rimonabant. **Study RoB:** Some concern due to lack of information about randomization process and allocation concealment and moderate attrition. **Author conflict:** Yes, main author received consultation and travel grants from study funder.

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
			BL): 0.8 (4.4); -0.2 (3.5), p=0.05, NS **AEs** (% Rimonabant; PLA: **Patients with any TEAE:** 53.3%; 48.8% **Patients with any SAE:** 9.2%; 11.8% **Deaths:** 0;0 **Most common TEAE:** Headache: 9.2%; 11.0% Alcoholism: 3.8%; 7.9% Diarrhea: 6.9%; 2.4% Fatigue: 4.6%; 2.4% Nausea: 4.6%; 1.8%	

AEs: adverse events; BL: baseline; CI: confidence interval; f/u: follow-up; HAM-A: Hamilton Anxiety Score; HAM-D: Hamilton Depression Score; NR: not reported; NS: not significant; PLA: placebo; RCT: randomized controlled trials; RoB: risk of bias; SAE: serious adverse event; SD: standard deviation; TEAEs: treatment emergent AEs; wks.: weeks

Table 4. Cochrane Risk of Bias 2.0 Tool for RCTs Cannabinoids for AUD

Reference	Soyka et al. 2008
➢ Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	Yes
➢ Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization, concealed envelopes)?	NI
➢ Did baseline difference between study groups suggest a problem with randomization?	Yes
Overall RoB for Randomization Process	**Some concern**
Deviation from Intended Intervention (Effect of Assignment)	
➢ Were participants aware of their assigned intervention during the trial?	No
➢ Were providers and people delivering treatment aware of assigned intervention during trial?	No
➢ Were there deviations from the intended intervention that arose because of the experimental context?	No
➢ Were these deviations from intended intervention balanced between groups?	NA
➢ Were these deviations likely to have affected the outcome?	NA
➢ Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
Overall RoB of Effect of Assignment	**Low**
Missing Outcome Data	
➢ Were data for this outcome available for all, or nearly all, participants randomized?	No
➢ Is there evidence that result was not biased by missing outcome data?	PN
➢ Could missingness in the outcome depend on its true value?	NI
➢ Do the proportions of missing outcome data differ between intervention groups?	No
➢ Is it likely that missingness in the outcome depended on its true value?	NI
Overall RoB of Missing Data	**Some concerns**
Measurement of the Outcome	
➢ Was the method of measuring the outcome inappropriate?	Yes
➢ Could measurement or ascertainment of the outcome have differed between intervention groups?	No
➢ Were outcome assessors aware of the intervention received by study participants?	Yes
➢ Could assessment of the outcome have been influenced by knowledge of intervention received?	No
➢ Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No
Overall RoB of Measurement of Outcome	**Low**
Selection of Reported Results	

Reference	Soyka et al. 2008
➢ Was the trial analyzed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?	NI
Overall RoB of Reported Results	**Some concern**
Overall Study RoB	**Some concern**

*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

Soyka, M., Koller, G., Schmidt, P., Lesch, O-M., Leweke, M., Fehr, C.,…Mann, K. (2008). Cannabinoid receptor 1 blocker rimonabant (SR 141716) for treatment of alcohol dependence: Results from a placebo-controlled, double-blind trial. *Journal of Clinical Psychopharmacology, 28*(3), 317-324.

Exercise

Evidence Base

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

In brief, Hallgren et al. (2017) conducted an SR that evaluated the effects of mostly aerobic or strength training exercise for adults with AUD on multiple health outcomes that include alcohol use, physical fitness, depression, anxiety and self-efficacy (Hallgren et al. 2017). The evidence base for the SR included a total of 13 RCTs enrolling 1,202 patients (range per study 20 to 484). Two RCTs not included in the Hallgren review also examined the effects of exercise or physical activity for adults with AUD. Rossler et al. (2017) evaluated the effects of supervised group or individual exercise added to outpatient alcohol treatment compared to outpatient treatment alone among 175 adults with AUD (Rossler et al. 2017). Shin et al. (2012) examined the effects of forest therapy camp compared to inpatient alcohol treatment among 92 adults with chronic AUD and major depression (Shin et al. 2012).

Study Quality

Using the AMSTAR instrument, we rated the quality of the Hallgren review as moderate due primarily to the review authors not explicitly stating if the review methods were established prior to conducting the review or providing a list of excluded studies and reasons for exclusion (See **Table 4** for the review ratings). The authors of this review assessed the RoB of the RCTs using the Cochrane tool. The overall RoB of the trials included in the Hallgren review was either high or unclear primarily due to high attrition, unblinded participants, and no intent-to-treat analysis. 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 3 RCTs suggest that there is no significant difference between exercise and treatment as usual in reducing the number of drinks per day or week among adults with AUD. (SOE: Low)
- Evidence from 1 RCT suggests that there is no significant difference between exercise added to treatment as usual and treatment as usual alone in reducing excessive drinking or increasing the rate abstinence among adults with AUD. (SOE: Very low)
- Evidence from 4 RCTs suggest that exercise significantly reduces depression compared to treatment as usual among adults with AUD. (SOE: Low)
- Evidence from 3 RCTs suggest that there is no significant difference between exercise and treatment as usual in reducing anxiety among adults with AUD. (SOE: Low)

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

- Evidence from 1 RCT suggests that forest healing camp significantly reduces depression compared to inpatient alcohol treatment among adults with chronic AUD. (SOE: Very low)

Discussion

The findings of the evidence for exercise added to the treatment of individuals with alcohol use disorder suggest that exercise does not reduce substance use outcomes compared to outpatient or inpatient AUD treatment alone. However, exercise may help to alleviate co-occurring symptoms of depression. The overall strength of the evidence for exercise was rated low to 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.

Table 1. Strength of Evidence for Exercise to Treat AUD

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
Alcohol consumption	1 SR with 3 RCTs (Hallgren, 2017);	Exercise vs. TAU alone (therapy and medication) n=58 to 92 2 to 52 wks	# drinks/day (2 RCTs; n=84); SMD: -0.886, 95% CI -2.38 to 0.61, p=0.24, I^2=84%	Yes (-1)	No	No	Yes (-1); wide 95% CI	No	Low
			# drinks/wk (3 RCTs; n=92): SMD: -0.656; 95% CI -1.21 to -0.21, p=0.04, I^2=48%						
			AUDIT scores (2 RCTs; n=58); SMD: -0.378; 95% CI -0.94 to 0.18, p=0.18, I^2=0%						
	1 RCT (Roessler, 2017)	Group or individual exercise (n=76) vs TAU (n=37) 6 months	Excessive drinking: OR: 0.99, 95% CI 0.46 to 2.14, p=0.976; OR: 1.02, 95% CI 0.47 to 2.18, p=0.968	Yes (-2)	No	No	Yes (-1); wide 95% CI	No	Very low
	1 RCT (Roessler, 2017)	Group or individual exercise (n=76) vs TAU (n=37) 6 months	Abstinence rate: OR: 1.06, 95% CI 0.50 to 2.28; p=0.860; 094, 95% CI 0.43 to 2.02, p=0.86	Yes (-2)	No	No	Yes (-1); wide 95% CI	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
Depression	4 RCTs in 1 SR (Hallgren, 2017)	Exercise vs TAU alone (therapy and medication) Total n=133 2 to 52 wks	SMD: -0.867, 95% CI -1.49 to -0.24; p=0.006, I^2=63%	Yes (-1)	Yes (-1)	No	No	No	Low
Anxiety	3 RCTs in 1 SR (Hallgren, 2017)	Exercise vs. TAU alone (therapy and medication) Total n=74 2 to 52 wks	SMD: -0.353; 95% CI -0.82 to 0.11, p=0.11, I^2=0%	Yes (-1)	No	No	Yes (-1); wide 95% CI	No	Low
Depression	1 RCT (Shin, 2012)	Forest therapy (n=47) vs Inpatient alcohol treatment (n=45) 9 days	**BDI scores** Forest group: 5.52 (indicates no depression); CG: 15.36 (indicates moderate depression); 9.83, p<0.001 *Lower scores on BDI mean less depression	Yes (-2)	No	No	Yes (-1) Small sample size	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 Systematic Reviews on Exercise to Treat Alcohol Use Disorder

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
Reference: Hallgren et al. 2017 **Organization/Country:** Dept of Public Health Services, Stockholm, Sweden **Purpose:** To investigate the effects of exercise for people with AUDs across multiple health outcomes. **AMSTAR Rating:** Moderate **Overall RoB of Included Studies:** High or unclear (some concerns) due to high drop-out (mean rate across studies 40.3%), allocation concealment, and lack of blinding of pts, treating staff and outcome assessors. *A significantly larger proportion of males dropped out compared to females, p<0.001	**Databases Searched:** Medline, Embase, and PsycARTICLES **Dates Searched:** Inception to April 2016 **Inclusion/Exclusion Criteria:** RCTs or non-randomized CT that assessed acute (single session) or long-term exercise (≥2 wks) as an intervention for people with AUD; studies must have used established criteria for diagnosis of AUD and involved exercise (defined as planned repetitive movement) as the primary intervention. Excluded cross-sectional or prospective observational studies. **Evidence Base:** 21 studies: 13 RCTs and 8 CTs; only RCTs were used in the meta-analysis and reported on in this report. Not all of the RCTs were included in the meta-analysis.	**Diagnosis:** AUD with duration ranging from 4.4 to 18 yrs **Number of Patients:** 1,202, range per study 20 to 468 **Age (mean yrs):** 37.8 **Gender:** 13 studies reported gender; 5 were male only; 8 were mixed gender	**Intervention:** 17 examined long-term exercise ranging in duration from 2 to 52 wks and 4 studies used acute exercise. Average duration of exercise session was 43 mins. 13 studies involved aerobic exercise, 5 combination of aerobic and strength training, and 3 yoga and stretching. In most studies (k=17) the exercise was supervised by a physical therapist or trainer. **Comparators:** 17 studies involved an active control, which consisted of CBT, group counseling and/or pharmacotherapy; 1 study compared exercise to no treatment and 3 did not provide details about the control condition. **Follow-up:** 2 to 52 wks **Outcomes:** alcohol consumption (number drinks per day, number of drinks per week, and AUDIT), depression and anxiety	**# drinks/day** (2 RCTs; n=84); SMD: -0.886, 95% CI -2.38 to 0.61, p=0.24, I^2=84% **# drinks/wk** (3 RCTs; n=92): SMD: -0.656; 95% CI -1.21 to -0.21, p=0.04, I^2=48% **AUDIT scores (**2 RCTs; n=58); SMD: -0.378; 95% CI -0.94 to 0.18, p=0.18, I^2=0% **Depression:** (4 RCTs; n=133); SMD: -0.867, 95% CI -1.49 to -0.24; p=0.006, I^2=63% **Anxiety** (3 RCTs; n=74); SMD: -0.353; 95% CI -0.82 to 0.11, p=0.11, I^2=0% No reported AEs; no evidence of publication bias

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 4. Systematic Review Risk of Bias AMSTAR Checklist Table on Exercise for AUD

Question	Hallgren et al. 2017
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?	No
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? RCTs?	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	**Moderate**

RoB: risk of bias

Table 5. Evidence Table for RCTs on Exercise to Treat Alcohol Use Disorder

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Roessler et al. 2017 **Purpose:** To examine if physical activity as an adjunct to outpatient alcohol treatment effects alcohol consumption. Part of Healthy Lifestyle Study **Setting:** 2 alcohol outpatient treatment centers in Denmark **Funding source: NR**	**Number of patients:** 175; n=62 Grp exercise + TAU; n=60 individual exercise + TAU; n=53 TAU alone **Inclusion criteria:** Adults ≥18 years meeting ICD-10 criteria for harmful use of or dependence on alcohol, Danish speaking, no severe psychosis or cognitive impairment, no severe physical disabilities or medical problems and acceptance of participation in study. **Exclusion criteria:** NR **Pt. baseline characteristics (Grp EX, Ind EX, TAU):** **Age (mean, SD):** 44.8 (11.2); 43.8 (11.1); 46.9 (11.6) **% male:** 59; 77.6; 73.6 **Alcohol units consumed 30 day prior to tx (median):** 145.0; 281.0; 210.9 **% Excessive drinking:** 86.9; 94.8; 84.9 **% drinking days:** 50; 71.6% 73.3 **Drinks/day (mean):** 11.4; 15.1; 11.4 **ASI score:** 0.67; 0.71; 0.70 *ASI score of 0=no problem; 1=severe problem	**Intervention:** Group supervised brisk walking or running program lasting 24 wks with grp meeting 2x/wk. Independent, individual running program in which participants were given running instructions/plan and encouraged to run 2x/wk over the course of 24 wks. Both grp and individual running interventions also received TAU at outpatient treatment facility **Control:** TAU at outpatient alcohol treatment facility **Outcomes:** Addiction severity Index, alcohol consumption (Timeline Follow-back Questionnaire), and physical activity (International Physical Activity Questionnaire) **F/u:** 12 months	**6 mos f/u (**Grp Ex vs TAU; Ind EX vs TAU) **Excessive drinking:** OR: 0.99, 95% CI 0.46 to 2.14, p=0.976; OR: 1.02, 95% CI 0.47 to 2.18, p=0.968 **Abstinence rate:** OR: 1.06, 95% CI 0.50 to 2.28; p=0.860; 094, 95% CI 0.43 to 2.02, p=0.86 **NDD:** -2.68, 95% CI -8.48 to 3.13, p=0.37; -3.00, 95% CI -10.04 to 2.84, p=0.279 **DDD:** RR: 0.78, 95% CI 0.33 to 1.80, p=0.557; 0.39, 95% CI 0.15 to 1.01, p=0.059 **12-mos f/u:** **Dose response:** moderate (≥5 days of exercise) vs light exercise (<5 days) **Excessive drinking:** OR	Results suggest that at 6 mos follow-up all 3 study groups showed a significant reduction in excessive drinking with no between group difference found in the proportion of pts who drank excessively. Similarly, there was no significant between group difference in units of alcohol consumed per month or number of days abstinent. The number of days abstinent had increased while the number of drinks per day decreased across groups. However, a dose effect was found for exercise. The amount of alcohol consumption in the exercise groups decreased by 4% (p=0.015) for each increased exercising day. **Limitations:** Attrition, alcohol consumption outcomes measured using self-report, exercise activity was not measured in the control group, and adherence to exercise was not measured in the intervention groups. **Study RoB:** High due to lack of blinding of patients, treating staff and outcome assessors and attrition (37%) **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
			0.12, 95% CI 0.05 to 0.31, p<0.001 **Abstinence rate:** OR 5.23, 95% CI 2.19 to 12.50, p<0.001 No adverse events observed	
Reference: Shin et al. 2012 **Purpose:** To evaluate the effect of forest therapy camp on depression in individuals with AUD. **Setting:** Inpatient alcohol treatment center in S. Korea **Funding source:** Not reported	**Number of patients:** 92; n=47 in forest grp; n=45 in GG **Inclusion criteria:** Adults with chronic alcoholism that required inpatient treatment; pts had to be detoxified and oriented; but had not started psychological treatment **Exclusion criteria:** Pts who met criteria for any other psychoactive drug other than alcohol and/or who had a severe medical illness. **Pt. baseline characteristics (Forest; TAU):** **Age (mean, SD):** 44.6 (3.90); 45.8 (3.85) **Alcohol dependence level (based on mean score of ADS):** 37.3 (7.22); 37.17 (6.71) **BL BDI score:** 15.35; 15.33	**Intervention:** Pts participated in a 9-day forest healing camp that provided daily outdoor exercises that involved interacting with nature, mountain climbing, tracking, orienteering, meditation, and some counseling. **Control:** Received standard inpatient alcohol treatment that involved education and individual and group counseling. **Outcomes:** Depression (measured by the BDI) **F/u:** 9 days	**Post-treatment BDI*** (mean score for group, mean difference between groups, p-value): Forest group: 5.52 (indicates no depression); CG: 15.36 (indicates moderate depression); 9.83, p<0.001 *Lower scores on BDI mean less depression	Results suggest that the forest healing camp statistically significantly reduced severity of depression among pts with chronic alcoholism requiring inpatient treatment compared to inpatient treatment alone. **Limitations:** Methodological issues, small sample size, very limited follow-up **Study RoB:** High **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 6. Cochrane Risk of Bias 2.0 for RCTs on Exercise to Treat AUD

Reference	Roessler et al. 2017	Shin et al. 2012
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)?	NI	NI
➢ Did baseline differences between study groups suggest a problem with randomization?	No	No
Overall RoB for Randomization Process	**Some concerns**	**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?	No	Yes
➢ Is there evidence that result was not biased by missing outcome data?	NI	NA
➢ Could missingness in the outcome depend on its true value?	NI	NA
➢ Do the proportions of missing outcome data differ between intervention groups?	No	NA
➢ Is it likely that missingness in the outcome depended on its true value?	NI	NA
Overall RoB of Missing Data	**High**	**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	NI

Reference	Roessler et al. 2017	Shin et al. 2012
➢ Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NI	NI
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 7. 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

Hallgren, M., Vancampfort, D., Giesen, E., Lundin, A., & Stubb, B. (2017). Exercise as treatment for alcohol use disorders: Systematic review and meta-analysis. *British Journal of Sports Medicine, 51*, 1058-1064.

Roessler, K., Bilberg, R., Nielsen, A., Jensen, K., Ekstrom, T., & Sari, S. (2017). Exercise as adjunctive treatment for alcohol use disorder: A randomized controlled trial. *PLoS ONE, 12*(10), 1-14.

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Meditation

Evidence Base

Our searches of the literature identified 3 RCTs that assessed the use of meditation in the treatment of adults with AUD. Wongtongkam et al (2018) randomized 55 adults with a diagnosis of alcohol dependence receiving treatment in a residential alcohol treatment center to receive Vipassana mindfulness mediation 2 hours per day for 5 days (n=23) or to continue with routine physical activity (n=22) (Wongtonkam et al. 2018). Each meditation session alternated between 30-minutes of sitting meditation and 30-minutes of walking meditation. The primary outcome of interest measured in this study was depression.

The other RCTs randomized adults with AUD to mindfulness-based relapse prevention in which meditation was a central component or to a group-based addiction support therapy. In Garland et al. (2010), patients were randomized to MORE (n=26, Mindfulness-oriented recovery enhancement) or to a social worker led support group that focused on issue related to addiction (n=26) (Garland et al. 2010). The primary outcomes of interest measured in this study were cravings for alcohol, perceived stress, and global psychiatric symptoms. Bowen et al. randomized adults who had completed intensive inpatient or outpatient treatment for substance abuse (primarily alcohol abuse) to receive group mindfulness-based relapse prevention (n=93) that included guided meditation or to continue to receive standard outpatient group therapy that was designed to help maintain abstinence through 12-step oriented process (n=70)(Bowen et al. 2009). The primary outcomes measured in this study were alcohol or drug use and cravings. See **Table 3** for more information about the patients and interventions in these studies.

Study Quality

Using the Cochrane tool, the ROB of all 3 RCTs was rated High. All RCTs lacked information about the randomization process (specifically if there was allocation concealment), did not mask patients, providers, or outcome assessors, and reported high attrition (>20%). See **Table 4** for individual study ratings.

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.

Vipassana Mindfulness Meditation

- Evidence from 1 RCT suggests that there is no difference between Vipassana mindfulness meditation and routine physical activity in reducing symptoms of depression among adults with AUD receiving care at a residential alcohol treatment center. (SOE: Very low)

Mindfulness-based Relapse Prevention

- Evidence from 1 RCT suggests that meditation within the context of mindfulness-based relapse prevention reduces cravings for alcohol compared to group-based addiction support therapy. (SOE: Very low)
- Evidence from 1 RCT suggests that meditation within the context of mindfulness-based relapse prevention reduces alcohol or drug use at 2 months follow-up compared to group-based addiction support therapy. (SOE: Very low)

- Evidence from 1 RCT suggests that meditation within the context of mindfulness-based relapse prevention reduces perceived stress compared to group-based addiction support therapy. (SOE: Very low)
- Evidence from 1 RCT suggest that there is no difference between mindfulness-based relapse prevention and group-based addiction support therapy in reducing global psychological symptoms. (SOE: Very low)

Discussion

Limited evidence suggests that meditation used in the context of mindfulness-based relapse prevention reduces cravings, post-intervention alcohol or drug consumption, and perceived stress. However, the overall strength of the evidence for these outcomes was rated as very low due to the evidence base for each outcome consisting of small studies with methodological limitations that include lack of clarity about the randomization process; not blinding patients, providers or outcome assessors; and attrition. The evidence is also limited due to inconsistencies in the findings across studies and time points. Two RCTs assessed the effects of meditation on cravings. However, the findings were inconsistent with one study suggesting that meditation was more effective than the control in reducing cravings (Bowen 2009), and the other finding no difference between meditation and control (Garland 2010). Similarly, the findings of Garland et al. suggest that meditation reduces alcohol and drug consumption at 2 months post-intervention compared to control, but not at 4 months. No difference was observed between Vipassana mindfulness meditation and routine physical activity in reducing symptoms of depression among adults with AUD receiving care at a residential alcohol treatment center.

Table 1. Strength of Evidence for Mind-Body Interventions to Treat AUD

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
Vipassana Mindfulness Meditation									
Depression	1 RCT Wongtongkam, 2018	Vipassana mindfulness meditation (23) vs routine physical activity (inpatient treatment facility, 22) 1 month	**BDI (mean total, SD):** 13.7 (9.18); 16.7 (8.54); p=0.29, NS	Yes (-2)	No	No	Yes (-1)	No	Very low
Mindfulness-based Relapse Interventions									
Cravings	2 RCTs Garland, 2010; Bowen, 2009	Mindfulness-based relapse (119) vs Control (group-based therapy focusing addiction (96) 10 to 16 wks	**Mean PACS** Garland: 4.6 (5.3), 3.2 (3.6), p=0.31, NS Bowen: **2 mos:** 1.0 (1.0); 1.4 (1.5), p=0.02 **4 mos:** 1.1 (1.3); 1.3 (1.5), p=0.03	Yes (-2)	Yes (-1); findings from Garland study do not suggest a difference btw groups on reduction in cravings	No	No	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
Alcohol/drug use	1 RCT Bowen, 2009	Mindfulness-based relapse (93) vs Control (group-based therapy focusing addiction (70) 2 and 4 mos	**2 mos:** 2.1 (7.2), 5.4 (14.7), p=0.01, favors meditation **4 mos**: 5.1 (14.7); 5.1 (15.3), NS	Yes (-2)	Yes (-1); findings favor meditation at 2 mos f/u, but no difference at 4 mos	No	No	No	Very low
Perceived stress	1 RCT Garland, 2010	Mindfulness-based relapse (26) vs Control (group-based therapy focusing addiction (26) 10 wks	**Perceived stress (mean PSS, SD):** 10.8 (5.3), 14.5 (5.8), p=0.03, favors meditation	Yes (-2)	No	No	Yes (-1); small sample size	No	Very low
Global psychiatric symptoms	1 RCT Garland, 2010	Mindfulness-based relapse (26) vs Control (group-based therapy focusing addiction (26) 10 wks	**Global psychiatric symptoms (mean BSI, SD):** 19.6 (12.5), 31.8 (21.4), p=0.48, NS	Yes (-2)	No	No	Yes (-1); wide dispersion measures	No	Very low

AAQ: Acceptance and Action Questionnaire; AUD: alcohol use disorder; BDI: Beck Depression Inventory; BSI: Brief Symptom Inventory; CI: confidence intervals; mos: months; IRISA: Impaired Alcohol Response Inhibition Scale; IRI: Interpersonal Reactivity Inventory; MAAS: Mindfulness Attention Awareness Scale; MBRP: mindfulness-

base relapse program; MORE: mindfulness-oriented recovery enhancement; NS: not significantly different; PACS: Penn Alcohol Craving Scale; PSS: Preceived Stress Scale; RoB: risk of bias; SD: standard deviation; SIP: Short Inventory of Problems; SMD: standarized 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 RCTs on Meditation to Treat AUD

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Wongtongkam et al. 2018 **Purpose:** To assess the effectiveness of Vipassana mindfulness on alcohol intake, depression and emphatic responses at a rehabilitation center. **Setting:** Drug and Alcohol Inpatient Rehabilitation Center in Thailand **Funding source:** NR	**Number of patients:** 55, n=23 mindfulness meditation; n=22 TAU **Inclusion criteria:** Adults age ≥18 yrs with a diagnosis of alcohol dependence and proficient in Thai language **Exclusion criteria:** Patients who showed severe psychotic symptoms, disruption to others, or who were unable to control their behaviors while meditating. **Pt. baseline characteristics (Meditation; routine physical activity):** **Age (mean yrs, SD):** 40.7 (8.24); 39.7 (9.23) **Duration of substance use (mean yrs, SD):** 16.7 (8.04); 17.0 (8.3) **Drinking frequency (% everyday):** 85.7%; 87.5% **Amount of alcohol (% on weekends):** ➢ 1-5 glasses: 14.4%; 0 ➢ 1 bottle: 14.4; 31.2 ➢ 2 bottles: 28.6%; 37.5% ➢ > 2 bottles: 42.8%; 31.2% **Amount of alcohol (% occasionally):** ➢ 1-5 glasses: 7.1%; 0 ➢ 1 bottle: 21.4%; 18.7% ➢ 2 bottles: 21.4%; 37.5%	**Intervention:** Guided Vipassana mindfulness meditation; provided for 2-hours/day for 5 days broken into 30-minute sessions of alternating sitting and walking meditation **Control:** Routine physical activity provided at residential alcohol rehabilitation center; specific activities not reported **Outcomes:** Depression (measured using the BDI); mindfulness (measured using the MAAS); empathy (measured using the IRI) **F/u:** 1-month	**1-month posttreatment (meditation vs. routine physical activity)** **Mindfulness (mean, SD):** 55.3 (12.8); 59.4 (8.24), p=0.24, NS **Empathy (mean total, SD):** 53.3 (7.75); 51.7 (9.68); p=0.58, NS **BDI (mean total, SD):** 13.7 (9.18); 16.7 (8.54); p=0.29, NS	Results suggest that adding mediation to treatment as usual in a residential alcohol rehabilitation program does not significantly improve mindfulness or empathy or reduce symptoms of depression **Limitations:** Methodological limitations, small sample size, male only participants, limited follow-up **Study ROB:** High; due to lack of information on randomization process and allocation concealment and blinding of patients, providers and outcome assessors **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	➢ > 2 bottles: 50%; 43.7% **Mindfulness (mean, SD):** 58.6 (8.5); 59.8 (7.9) **Empathy (total mean score, SD):** 54.2 (7.2); 50.5 (10.2) **BDI (total mean score, SD):** 16.0 (6.5); 17.3 (7.8)			
Reference: Garland et al. 2010 **Purpose:** To compare the therapeutic effects of a mindfulness-oriented recovery enhancement (MORE) to an evidence-based alcohol dependence support group. **Setting:** Residential alcohol treatment center, North Carolina, USA **Funding source:** Grant funded	**Number of patients:** 53; n=26 MORE; n=26 support group **Inclusion criteria:** Adults ≥18 yrs with a lifetime diagnosis of alcohol dependence according to DSM-IV residing in residential treatment facility for ≥18 months **Exclusion criteria:** Scored <16 on the AUDIT, or if they endorsed screening questions indicating active psychosis or suicidality **Pt. baseline characteristics (MORE; support group):** **Age (mean yrs, SD):** 39.9 (8.7); 40.7 (10.2) **Gender (% male):** 81.5%; 76.9% **Length of stay in residential program (mean day, SD):** 22.4 (2.6); 22.2 (4.6) **Drinks/day prior to entering treatment (mean, SD):** 21.4 (11.9); 16.6 (9.5) **Perceived stress (mean total score, SD):** 15.6 (4.7); 16.0 (7.6) **Craving (mean, SD):** 4.7 (5.5); 4.9 (4.4)	**Intervention:** MORE; manualized intervention adapted for alcohol dependence from Mindfulness based Cognitive Therapy. In this study MORE involved 10-sessions of mindful breathing and walking meditation along with experiential exercises relating mindfulness principles to addiction-specific issues. Sessions were led by a social worker trained in meditation practices. **Control:** Social worker led social support group that focused on issues related to addiction. **Outcomes:** Psychosocial factors related to alcohol dependence (measured using BSI), cravings (measured using PAC and IRISA), and perceived stress (measured using the PSS) **F/u:** 10 weeks	**<u>10 weeks F/u</u>** 69% (n=37) of pts remained in study at f/u; n=18 MORE, n=19 support group MORE led to significant reduction in stress and global psychiatric symptoms from baseline to follow-up **<u>BtW group Difference</u>** **Perceived stress (mean PSS, SD):** 10.8 (5.3), 14.5 (5.8), p=0.03, favors MORE **Global psychiatric symptoms (mean BSI, SD):** 19.6 (12.5), 31.8, p=0.48, NS **Thought suppression (mean IRISA, SD):** 50.1 (7.9); 53.5 (9.4),	Results suggest that mindfulness training significantly reduced stress compared to supportive therapy among adults with AUD in residential treatment. No significant differences were observed between treatment groups for reducing global psychiatric symptoms or cravings for alcohol. **Limitations:** Small sample size, study methodological limitations, limited follow-up and patients at lower risk of relapse due to having 18 months sobriety. **Study ROB:** High; due to lack of information on randomization process and allocation concealment, lack of blinding of patients, providers and outcome assessors, and high (>20%) attrition. **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	Global psychiatric symptoms (mean, SD): 42.7 (36.4); 46.7 (33.0)		p=0.04, favors MORE **Craving (mean PACS, SD):** 4.6 (5.3), 3.2 (3.6), p=0.31, NS	
Reference: Bowen et al. 2009 **Purpose:** To compare MBRP to TAU on substance use outcomes among adults with AUD. **Setting:** Alcohol and drug treatment center in Washington, USA **Funding source:** Grant funded	**Number of patients:** 168; n=93 MBRP; n=70 TAU **Inclusion criteria:** Adults ages 18 to 70 years fluent in English who had completed intensive inpatient or outpatient treatment for substance abuse (primarily alcohol abuse; 45.2%) in the previous 2 weeks and were medically cleared for participation. **Exclusion criteria:** Patients with psychosis, dementia, imminent suicide risk, significant withdrawal risk, or need for more intensive treatment. **Pt. baseline characteristics (All pts):** **Age (mean yrs, SD):** 40.5 (10.3) **Gender (% male):** 63.7 **MBRP; TAU** **Alcohol or drug use (AOD, mean days prior to treatment, SD):** 27.0 (24.0); 28.9 (24.8) **SIP:** 11.1 (5.4); 11.7 (4.7) **PACS:** 1.6 (1.1); 1.7 (1.4)	**Intervention:** 8-weekly, 2-hour sessions with 6 to 10 pts facilitated by 2 therapists. Each session followed the MBRP manual and included meditation practices and discussions related to relapse prevention. **Control (TAU):** Pts remained in standard outpatient aftercare which was designed to maintain abstinence through a 12-step process-oriented format. Pts meet as a group 1 to 2 times/week for 1.5 hours per session. **Outcomes:** Substance use, alcohol or drug craving (measured using PACS), alcohol and drug use consequence (measured using SIP) **F/u:** 4 months	**2 and 4 mos F/u:** **Completion rate:** 57% (2 mos), 73% (4 mos) **MBRP; TAU** (reporting only f/u data for which btw grp difference reported) **Alcohol or drug use (AOD, mean days, SD):** **2 mos:** 2.1 (7.2), 5.4 (14.7), p=0.01 4 mos: 5.1 (14.7); 5.1 (15.3), NS **Cravings (PACS)** **2 mos:** 1.0 (1.0); 1.4 (1.5), p=0.02 **4 mos:** 1.1 (1.3); 1.3 (1.5), p=0.03	Results suggest that MBRP lead to significantly greater in alcohol use at 2 months post-intervention compared to TAU. However, this finding was not sustained at 4 months. MBRP also significantly reduced cravings compared to TAU at 2 and 4 months follow-up. **Limitations:** Small sample size, study methodological limitations, limited follow-up, and drop out **Study ROB:** High; due to lack of allocation concealment, lack of blinding of patients, providers and outcome assessors, and high (>20%) attrition. **Author conflict:** None reported

AAQ: Acceptance and Action Questionnaire; AUD: alcohol use disorder; BDI: Beck Depression Inventory; BSI: Brief Symptom Inventory; CI: confidence intervals; mos: months; IRISA: Impaired Alcohol Response Inhibition Scale; IRI: Interpersonal Reactivity Inventory; MAAS: Mindfulness Attention Awareness Scale; MBRP: mindfulness-base relapse program; MORE: mindfulness-oriented recovery enhancement; NS: not significantly different; PACS: Penn Alcohol Craving Scale; PSS: Preceived Stress Scale; RoB: risk of bias; SD: standard deviation; SIP: Short Inventory of Problems; SMD: standarized mean difference

Table 4. Cochrane Risk of Bias 2.0 Tool for RCTs on Mind-Body Interventions to Treat AUD

Reference	Wongtonkam 2018	Garland 2010	Bowen 2009
Randomization Process			
➢ Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	NI	NI	Yes
➢ Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization, concealed envelopes)?	NI	NI	No
➢ Did baseline difference between study groups suggest a problem with randomization?	No	No	No
Overall RoB for Randomization Process	**Some Concerns**	**Some Concerns**	**Some Concerns**
Deviation from Intended Intervention (Effect of Assignment)			
➢ Were participants aware of their assigned intervention during the trial?	Yes	Yes	Yes
➢ Were providers and people delivering treatment aware of assigned intervention during trial?	Yes	Yes	Yes
➢ Were there deviations from the intended intervention that arose because of the experimental context?	No	No	No
➢ Were these deviations from intended intervention balanced between groups?	NA	NA	NA
➢ Were these deviations likely to have affected the outcome?	NA	NA	NA
➢ Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	NI	Yes
Overall RoB of Effect of Assignment	**Some Concerns**	**Some Concerns**	**Some Concerns**
Missing Outcome Data			
➢ Were data for this outcome available for all, or nearly all, participants randomized?	Yes	No	No
➢ Is there evidence that result was not biased by missing outcome data?	NA	No	Yes (notes that prediction models were not significantly associated with missing data for dependent variables)
➢ Could missingness in the outcome depend on its true value?	NA	No	No
➢ Do the proportions of missing outcome data differ between intervention groups?	NA	No	No

Reference	Wongtonkam 2018	Garland 2010	Bowen 2009
➢ Is it likely that missingness in the outcome depended on its true value?	NA	No	No
Overall RoB of Missing Data	**Low**	**High**	**High**
Measurement of the Outcome			
➢ Was the method of measuring the outcome inappropriate?	No	No	No
➢ Could measurement or ascertainment of the outcome have differed between intervention groups?	No	No	No
➢ Were outcome assessors aware of the intervention received by study participants?	Yes	Yes	Yes
➢ Could assessment of the outcome have been influenced by knowledge of intervention received?	NI	NI	NI
➢ Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	PN	NI
Overall RoB of Measurement of Outcome	**High**	**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?	NI	NI	NI
Overall RoB of Reported Results	**Some Concerns**	**Some Concerns**	**Some Concerns**
Overall Study RoB	**High**	**High**	**High**

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

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Garland, E., Gaylord, S., Boettiger, C., & Howard, M. (2010). Mindfulness training modifies cognitive, affective, and physiological mechanisms implicated in alcohol dependence: Results of a randomized controlled pilot trial. *Journal of Psychoactive Drugs, 42*(2), 177-192.

Wongtongkam, N., Lampoo, S., Choocherd, P., & Chiangkuntod, S. (2018). Partial efficacy of vipassana mindfulness approach in alcohol-dependent persons. *Alcoholism Treatment Quarterly, 36*(1), 3-14.

Music Therapy

Evidence Base

Our searches of the literature identified 1 RCT that met inclusion criteria and assessed the effects of music therapy (MT) on symptoms of withdrawal and cravings in adults with substance use disorder (mainly AUD) (Silverman M. 2015). Silverman randomized 144 patients in a hospital-based detoxification unit to receive a single session of music therapy (60 patients) or to a non-active control condition (84 patients). Patients randomized to MT participated in a single session of group MT that utilized lyric analysis of a popular song to distract patients from withdrawal symptoms while facilitating discussion on how to manage cravings and prevent relapse. Patients in the control group participated in a recreational music activity.

Study Quality

Using the Cochrane tool, we rated the ROB of the Silverman RCT as High due to no information provided about the randomization process, no allocation concealment, and no blinding of patients, providers or 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.

- Evidence from 1 RCT suggests that there is no significant difference between music therapy and a non-active control intervention in reducing symptoms of withdrawal or cravings among adults (majority with AUD, 42%) in a hospital-based detoxification unit. (SOE: Very low)

Discussion

The findings of the Silverman RCT suggest that there was no statistically significant difference between music therapy delivered as a single group session in a hospitalized detoxification unit and a non-active control intervention in reducing withdrawal symptoms or cravings among adults with mostly AUD (42%). The overall quality of the evidence for music therapy was rated as very low due to limitations in methodological quality of the study and lack of precision surrounding the treatment effect. The evidence was also limited as the findings were based on a single, small study in which the intervention was delivered as a single session with no follow-up. Plus, the self-reported outcomes of withdrawal and cravings were measured only at post-intervention without any pre-intervention assessment of patient's symptoms.

Table 1. Strength of Evidence for Music Therapy to Treat AUD

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
Withdrawal	1 RCT Silverman, 2015	MT (60); CG (84)	MD (ARSW): -9.74; p=0.055, NS	Yes, (-2)	No	No	Yes (-1)	No	Very low
Cravings	1 RCT Silverman, 2015	MT (60); CG (84)	MD (BSCS) -0.093, p=0.085, NS	Yes, (-2)	No	No	Yes (-1)	No	Very low

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 Music Therapy to Treat AUD

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Silverman, 2015 **Purpose:** To determine if music therapy can affect withdrawal and craving in patients on a detoxification unit for substance abuse. **Setting:** Hospital detoxification unit in the Midwest **Funding source:** Grant funded	**Number of patients:** 144; n=60 MT; n=84 CG **Inclusion criteria:** All consenting adult patients on the detoxification unit who could read and write in English. **Exclusion criteria:** NR **Pt. baseline characteristics (MT; CG):** **Age (mean yrs., SD):** 36.6 (13.3); 36.9 (14.9) **Substance of Choice (n):** ➢ Alcohol: 30; 33 ➢ Cocaine: 2 ➢ Heroin: 21; 39 ➢ Prescription drug: 7; 7 ➢ Other: 1; 0 **Gender (n male):** 33; 46 **Times admitted to substance abuse facility (mean, SD):** 4 (4); 5 (5.5) **Days on unit (mean, SD):** 3.4 (2.0); 4.0 (3.3)	**Intervention:** MT consisted on lyric analysis with and without accompanying music of a popular song with the intent of distracting patients from cravings and withdrawal symptoms while facilitating active discussion about relapse prevention. MT took place within the hospital unit in a single, 45-minute group session. MT was provided by a trained music therapist. Each group consisted of 6 or 7 participants. The study period lasted for 6 months providing a total of 12 sessions of MT. **Control:** 1, 45-minute recreational music intervention that included 6 to 7 patients over a 6-month period for a total of 12 sessions. **Outcomes of Interest:** Withdrawal (as measured by the ARSW; high scores more symptoms), cravings (as measured by the BSCS; high scores more cravings) **Follow-up:** Post-treatment	Post-treatment **Withdrawal (mean, SD ARSW MT; CG):** 38.7, 28.7; 48.5, 30.3; MD btw group: -9.74, p=0.055, NS Cravings (mean BSCS, SD MT; CG): 4.38, 2.61; 5.31. 3.4; MD -0.093, p=0.085, NS	**Conclusion:** The findings of this RCT did not provide evidence that music therapy delivered as a single group session in a hospitalized detoxification unit statistically significantly reduces withdrawal symptoms of cravings compared to a non-active control intervention among adults with substance abuse (mainly alcohol abuse). **Limitations:** Single session intervention, no follow-up, small sample, no pretest measures for outcomes; and methodological limitations of study **Study RoB:** High, Due to no information about randomization process, no allocation concealment, and no blinding of patients, providers or outcome assessors. **Author conflict:** None reported

AEs: adverse events; ARSW: Adjective Rating Scale for Withdrawal; BL: baseline; BSCS: Brief Substance Craving Scale; CI: confidence interval; CT: control group; f/u: follow-up; MD: mean difference; MT: music therapy; NR: not reported; NS: not significant; RCT: randomized controlled trials; RoB: risk of bias; SD: standard deviation

Table 4. Cochrane Risk of Bias 2.0 Tool for RCTs on Music Therapy to Treat AUD

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

Reference	Silverman, 2015
Overall RoB of Reported Results	**Some concerns**
Overall Study RoB	**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

Silverman, M. (2016). Effects of a single lyric analysis intervention on withdrawal and craving with inpatients on a detoxification unit: A cluster-randomized effectiveness study. *Substance Use & Misuse, 51*(2), 241-249.

Relaxation Therapy (or techniques)

Evidence Base

Our searches of the literature identified 2 RCTs that met inclusion criteria and compared the efficacy of cognitive behavioral therapy (CBT) adapted to treat patients with comorbid anxiety or depressive disorder with progressive muscle relaxation training (PMRT). Kushner et al. randomized 344 adults with co-occurring alcohol dependence and anxiety disorder to receive six, 1-hour group sessions of CBT (171 patients) or to the same number and duration of sessions of PMRT (173 patients) (Kushner et al. 2013). In this study CBT was manualized and the sessions were split into three primary content domains: psychoeducation, cognitive restructuring, and exposure habituation. Each session alternated between focusing on the anxiety disorder and the alcohol disorder. PMRT also followed a manual and the trainings were scripted. During each session, patients were taught a muscle-group tension-release routine that varied by muscle group and number of muscles involved. Patients were instructed to practice the routines on their own when possible. All participants also received treatment as usual in a community-based 21-day residential AUD program that followed a primary goal of lifetime abstinence using a 12-step model.

Brown and colleagues randomized 166 adults with alcohol dependence to receive eight, 45-minute individual sessions of CBT (83 patients) or eight, 45-minute individual sessions of PMRT (83 patients) (Brown et al., 2010). Therapy in both groups was delivered over the course of 6-weeks. The *Coping with Depression* course severed as the basis for the CBT treatment, but was modified for use with alcohol dependent patients. Each session incorporated training in depression-relevant skills, including constructive thinking, pleasant activities, daily mood monitoring, social skills, and assertiveness. Each session of PMRT included muscle group tension-release training along with practice in deep-breathing, meditation and guided imagery. All patients received treatment as usual at a private partial hospital treatment program, which was an abstinent-oriented program grounded in cognitive social learning model and 12-step participation. See **Table 3** for more information about the characteristics of the patients and interventions assessed in these RCTs.

Study Quality

Using the Cochrane tool, we rated the RoB of the RCT by Kushner as High due lack of reporting about patient, provider or outcome assessor blinding and high overall and differential attrition between groups. Significantly more patients in this study dropped out of the CBT group than the PMRT. The authors of the study suggest that this may be due to the additional demands of treatment in the CBT group (e.g., homework, etc).The RoB of the RCT by Brown was rated as some concerns due to lack of information about the randomization process and lack of information about blinding of the patients, clinicians and outcome assessors. See Error! Reference source not found.**4** for study quality ratings.

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 RCTs suggests that CBT adapted for adults with co-occurring alcohol dependence and anxiety disorder reduces rates of relapse to any drinking and to heavy drinking compared to PMRT. (SOE: Low)

- Evidence from 1 RCT suggests that CBT adapted for adults with co-occurring alcohol dependence and anxiety disorder may reduce general symptoms of anxiety compared to PMRT. (SOE: Low).
- Evidence from 1 RCT suggests that there is no difference in CBT adapted for adults with co-occurring alcohol dependence and depressive disorder and PMRT in relapse or symptoms of depression at 12 months posttreatment. (SOE: Very low)

Discussion

Overall, the evidence from 1 RCT suggests that CBT modified to treat adults with co-occurring alcohol dependence and anxiety may reduce the rate of relapse and general symptoms of anxiety compared to PMRT among adults undergoing residential treatment for AUD. However, the strength of the evidence for these outcomes was rated low largely due to the differential rate of attrition of patients in the CBT group compared to patients in the PMRT group. The authors of the study suggest that more patients in the CBT group dropped out due to additional demands of treatment in the CBT group, such as regular homework assignments. The findings of another RCT, however, showed no difference between CBT modified to treat adults with co-occurring alcohol dependence and depression compared to PMRT in improving alcohol or depression outcomes. Both patient groups in this study showed similar rates of abstinence and improvement in symptoms of depression at 12-months posttreatment. No adverse events were reported in either of the RCTs included as evidence for relaxation therapy.

Table 1. Strength of Evidence for Relaxation Therapy to Treat AUD

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
CBT vs PMRT for Patients with Co-occurring Alcohol Dependence and Anxiety Disorder									
Relapse	1 RCT Kushner et al. 2013	344; n=171 CBT; n=173 PMRT 4 months	**Relapse (any drinking):** CBT: 41%; PMRT: 54%; OR=1.68, 95% CI, 1.01 to 2.78, p=0.04, favors CBT **Relapse (3 consecutive days):** CBT: 19.8%; PMRT: 30.3%; OR: 1.78, 95% CI 1.99 to 3.20, p<0.05	Yes (-2)	No	No	No	No	Low
Trait Anxiety	1 RCT Kushner et al. 2013	344; n=171 CBT; n=173 PMRT Post-treatment; 4 months	**Post-treatment:** 42.8 (10.8); 42.8 (10.4), p=0.27 % Below cutoff for clinical anxiety: 51.8 %; 45.5%, p=0.34	Yes (-2)	No	No	No	Yes (-1)	Very low
			4 mos f/u: 41.4 (12.3); 44.07 (12.4), p=0.03	Yes (-2)	No	No	No	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
			% Below cutoff for clinical anxiety: 53.5%; 39.3%, p=0.04, favors CBT						
State Anxiety	1 RCT Kushner et al. 2013	344; n=171 CBT; n=173 PMRT Post-treatment; 4 months	**Posttreatment:** 40.3 (12.4); 30.0 (11.9), p=0.40 **4 mos f/u:** 37.5 (12.9); 39.1 (13.3), p=0.11	Yes (-2)	No	No	No	Yes (-1)	Very low
CBT vs PMRT for Patients with Co-occurring Alcohol Dependence and Depressive Disorder									
Abstinent (%)	Brown, et al. 2010	166; n=83 CBT; n=83 PMRT	% abstinent: 70%; 79%, p=0.92, NS	Yes (-1)	No	No	No	Yes (-1)	Low
Drinks/day	Brown, et al. 2010	166; n=83 CBT; n=83 PMRT	Drinks/day: 5; 3.5, p=0.83, NS	Yes (-1)	No	No	No	Yes (-1)	Low
Depression	Brown, et al. 2010	166; n=83 CBT; n=83 PMRT	BDI total score: 9.0; 7.0, p=0.31, NS MHRSD total score: 10.0; 9.0; p=0.27, NS	Yes (-1)	No	No	No	Yes (-1)	Low

AEs: adverse events; BDI: Beck Depression Inventory; BL: baseline; CBT: Cognitive behavioral therapy; CI: confidence interval; GAD: Generalized anxiety disorder; HADS: Hamilton Anxiety or Depression Scale; MHRSD: Modified Hamilton Rating Scale for Depression; NR: not reported; NS: not significant; PD: Panic disorder; PMRT: Progressive muscle relaxation training; QoL: Quality of life; RCT: randomized controlled trials; RoB: risk of bias; RTC: relaxation training control; SAD: Social anxiety disorder; SD: standard deviation; SMD: standardized mean difference; STAI: State-or Trait Anxiety Index; TAU: treatment as usual; TLFB: Time Line Followed Back Interview; 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 Relaxation Therapy to Treat AUD

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Kushner et al. 2013 **Purpose:** To compare the impact of CBT adapted to treat individuals with co-occurring AUD and anxiety disorder and PMRT in reducing anxiety and alcohol related outcomes. **Setting:** Community based residential treatment center for AUD in the Mid-west. **Funding source:** Grant funded	**Number of patients:** 344; n=171 CBT; n=173 PMRT **Inclusion criteria:** Adults ≥18 yrs with current (within past 30 days) alcohol dependence and at least one of the following anxiety disorders: panic disorder, social anxiety disorder or generalized anxiety disorder. **Exclusion criteria:** Pts with bipolar disorder, schizophrenia, cognitive impairment or serious ongoing suicidality, patients unable to read or understand English, and patients with substance abuse problems other than alcohol. **Pt. baseline characteristics (CBT; PMRT):** **Age (mean yrs., SD):** 39.19 (9.72); 39.5 (10.58) **Gender (% female):** 37%; 42% **% on anti-anxiety medication**: 63%; 65% Principle anxiety disorder (%): ➢ GAD: 39%; 38% ➢ PD: 17%; 17% ➢ SAD: 44%; 46%	**Intervention:** CBT was manualized and consisted of six 1-hour group sessions that were split into 3 primary content domains: psychoeducation, cognitive restructuring, and exposure habituation. Each session alternated between focusing on the anxiety disorder and the AUD. **Control:** The PMRT followed a manual and the trainings were scripted. The number and duration of sessions followed the CBT and consisted of six 1-hour group sessions. During each session, pts were taught and also practiced a muscle-group tension-release routine that varied in muscle group and number of muscles involved. Pts were instructed to practice the routines on their own when possible. *All participants received TAU in a community-based 21-day residential AUD program that follows a primary goal of lifetime abstinence using a 12-step model. **Outcomes of Interest:** Anxiety symptoms (measured using the STAI) and alcohol consumption (measured using the TLFB) **Follow-up:** Post-treatment and 4 months after treatment and post-discharge from treatment center.	**4-months f/u:** **Completion** **Posttreatment (CBT; PMRT):** 127, 74.3%; 148, 85.5%, p=0.01 **4 mos: (CBT; PMRT):** n=116 (72%); 131 (78.9%) **Relapse (any drinking):** CBT: 41%; PMRT: 54%; OR=1.68, 95% CI, 1.01 to 2.78, p=0.04, favors CBT **Relapse (3 consecutive days):** CBT: 19.8%; PMRT: 30.3%; OR: 1.78, 95% CI 1.99 to 3.20, p<0.05 Moderator analysis found that the findings for CBT were dependent on the STAI cutoff; with the difference in relapse between CBT and PMRT more likely occurring in patients with higher levels of anxiety (score above 44, which indicates clinically significant anxiety) **Anxiety (mean score, SD, btw group p-value)** **Trait Anxiety** **Baseline:** 58.03 (10.67); 56.02 (10.18), p=0.9 **Post-treatment:** 42.8 (10.8); 42.8 (10.4), p=0.27	**Conclusion:** The findings suggest that augmenting AUD treatment with CBT significantly improves the overall risk of relapse to any drinking compared to AUD treatment augmented with PMRT. Symptoms of anxiety appeared to improve in both treatment groups from baseline to posttreatment and follow-up with a significant number of patients in each group falling below the threshold for what is considered clinical anxiety. However, the only between group difference was observed in trait anxiety at 4 months, with patients in the CBT demonstrating a significant reduction in the overall score compared to patients in the PMRT group. No adverse events reported. **Limitations:** Overall and between group attrition at posttreatment and 4 months follow-up. Significantly more patients dropped out of the CBT group than the PMRT at posttreatment. The authors suggest that this may be due to the additional demands of treatment in the CBT group (e.g., homework, etc). **Study RoB:** High, due lack of reporting about outcome assessor blinding and attrition. **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
			% Below cutoff for clinical anxiety: 51.8 %; 45.5%, p=0.34 **4 mos f/u:** 41.4 (12.3); 44.07 (12.4), p=0.03 **% Below cutoff for clinical anxiety**: 53.5%; 39.3%, p=0.04, favors CBT **State Anxiety** **Baseline:** 52.9 (12.9); 50.3 (12.3), p=0.07 **Posttreatment:** 40.3 (12.4); 30.0 (11.9), p=0.40 **4 mos f/u:** 37.5 (12.9); 39.1 (13.3), p=0.11	
Reference: Brown, et al. 2010 **Purpose:** To assess if CBT for depression along with TAU in a partial hospital treatment center reduces levels of depression and alcohol use over a 12-month period compared to PMRT. **Setting:** Partial hospital treatment center for AUD in Rhode Island. **Funding source:** Grant	**Number of patients:** 166; n=83 CBT; n=83 PMRT **Inclusion criteria:** Adults 18 to 65 years who met diagnosis according to DSM-IV criteria for alcohol dependence as determined through a diagnostic interview and had a BDI score of 15 or greater. **Exclusion criteria:** Current suicidality or homicidality, history of psychotic disorder or current psychotic symptoms, diagnosis of opioid dependence, diagnosis of bipolar disorder, and/or marked organic impairment.	**Intervention:** *The Coping with Depression* course severed as the basis for the CBT treatment, but was modified for use with alcohol dependent patients. The treatment was delivered in 8, 45 min individual sessions over 6-wks. Each session incorporated training in depression-relevant skills, including constructive thinking, pleasant activities, daily mood monitoring, social skills, and assertiveness. **Control:** Patients in the PMRT received 8 individual sessions of PMRT that also included practice in deep breathing, meditation and guided imagery. Each session lasted 45-mins and was provided over the course of 6 wks. All patients received TAU at the partial hospital treatment program,	**Completion:** 90%; 90% in CBT; 90% in PMRT **Attendance:** CBT pts attended 6.7/8 sessions; PMRT pts attended 7.2/8 session, NS btw groups **12 mos f/u (CBT; PMRT)** Both groups demonstrated significant improvement in drinking and depression outcomes over time, but no significant between group differences were observed at any timepoint. **% abstinent**: 70%; 79%, p=0.92, NS **Drinks/day:** 5; 3.5, p=0.83, NS	**Conclusion:** The findings suggest that both CBT and PMRT improved alcohol related outcomes and symptoms of depression over the study period. However, there was significant difference between groups for any of the outcomes at any time point. **Limitations:** Methodological limitations related to lack of reporting of allocation concealment and blinding. **Study RoB:** Some concerns due to not reporting allocation concealment or blinding of patient, providers, or outcome assessors **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	Pt. baseline characteristics (All pts): **Age (mean yrs., SD):** 40.8 yrs **Gender (% female):** 33.0% BL Mean BDI score: 25.6 (8.0) BL MHRSD score: 17.2 (8.9) **6 months prior to treatment** Abstinent out of possible drinking days: 38.8% Drinks/day drinking: 13.3 (9.3)	which was an abstinent-oriented program grounded in cognitive social learning model and 12-step participation. **Outcomes of Interest:** Symptoms of depression (measured using BDI and MHRSD) and alcohol use (measured using the TLFB). **Follow-up:** Post-intervention at 6 weeks, 3 mos, 6 mos, and 12 mos..	**BDI total score:** 9.0; 7.0, p=0.31, NS **MHRSD total score:** 10.0; 9.0; p=0.27, NS No adverse events reported	

AEs: adverse events; BDI: Beck Depression Inventory; BL: baseline; CBT: Cognitive behavioral therapy; CI: confidence interval; GAD: Generalized anxiety disorder; HADS: Hamilton Anxiety or Depression Scale; MHRSD: Modified Hamilton Rating Scale for Depression; NR: not reported; NS: not significant; PD: Panic disorder; PMRT: Progressive muscle relaxation training; QoL: Quality of life; RCT: randomized controlled trials; RoB: risk of bias; RTC: relaxation training control; SAD: Social anxiety disorder; SD: standard deviation; SMD: standardized mean difference; STAI: State-or Trait Anxiety Index, State Index measures symptoms present during the time of assessment vs Trait Index that measures symptoms in general; TAU: treatment as usual; TLFB: Time Line Followed Back Interview; wks.: weeks

Table 4. Cochrane Risk of Bias 2.0 Tool for RCTs on Relaxation Therapy to Treat AUD

Reference	Kushner et al. 2013	Brown et al. 2010
➢ 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 difference between study groups suggest a problem with randomization?	Yes	Yes
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?	NI	NI
➢ Were providers and people delivering treatment aware of assigned intervention during trial?	NI	NI
➢ 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?	No	Yes
➢ Is there evidence that result was not biased by missing outcome data?	No	Yes
➢ Could missingness in the outcome depend on its true value?	NI	NA
➢ Do the proportions of missing outcome data differ between intervention groups?	Yes	NA
➢ Is it likely that missingness in the outcome depended on its true value?	NI	NA
Overall RoB of Missing Data	**High**	**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?	NI	NI
➢ 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

Reference	Kushner et al. 2013	Brown et al. 2010
Overall RoB of Measurement of Outcome	**Some Concerns**	**Some Concerns**
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?	NI	NI
Overall RoB of Reported Results	**Some Concerns**	**Some Concerns**
Overall Study RoB	**High**	**Some Concerns**

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

Brown, R., Ramsey, S., Kahler, C., Palm, K., Monti, P., Abrams, D.,…Miller, I. (2011). A randomized controlled trial of cognitive-behavioral treatment for depression versus relaxation training for alcohol-dependent individuals with elevated depressive symptoms.

Kushner, M., Maurer, E., Thuras, P., Donahue, C., Frye, B., Menary, K.,…Van Demark, J. (2013). Cognitive behavioral therapy versus relaxation training for co-occurring anxiety and alcohol disorder: A randomized clinical trial. Journal of Consulting and Clinical Psychology, 81(3), 429-442.

Transcranial Magnetic Stimulation (TMS)

Evidence Base

Our searches of the literature identified 1 SR by Maiti et al (2017) that assessed the efficacy of repetitive (r) TMS used as an adjunctive treatment for treating adults with AUD (Maiti et al. 2017). The evidence base in this review included 6 RCTs that randomized a total of 162 adults with AUD to receive either real rTMS (87 patients) or sham rTMS (75 patients). High frequency (10 to 20 Hz) rTMS was delivered to the left (1 study), right (3 studies), or bilateral (2 studies) dorsolateral prefrontal cortex (DLPFC). The rTMS protocol varied across studies in terms of number of sessions (range 1 to 20) and time of application (range: 12 to 42 seconds). In 5 of the RCTs, rTMS was compared to sham rTMS that was delivered in a similar manner as the real rTMS without active stimulation. Use of other interventions (medication or therapy) in the included RCTs were not reported by the authors of the Maiti review. One study was reported to compare rTMS as an "add-on" to standard drug therapy. The primary outcome of interest was reduction in alcohol craving. See **Table 3** for more information on the patient and study characteristics of the RCTs included in the Maiti review.

Study Quality

Using the AMSTAR instrument, we rated the quality of the review by Miati et al. as moderate due primarily to the review authors not reporting if study selection or data abstraction were performed in duplicate (see **Table 4** for the quality ratings). The ROB of the RCTs included in the Miati review was assessed using the Cochran tool. The overall ROB was rated moderate (or some concerns) due to unclear reporting about allocation concealment or outcome assessor blinding.

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.

High Frequency Bi-lateral or Uni-lateral TMS (≥1 Hz) vs Sham TMS

- Combined evidence from 6 RCTs suggests that there is no statistically significant difference in craving reduction between high frequency rTMS and sham rTMS for adults with AUD. (SOE: Low)

Discussion

The evidence base for TMS consisted of 1 SR with 6 RCTs that assessed the use of rTMS to reduce cravings among adults with AUD. The findings of this review suggest that there was no significant difference between real rTMS and sham rTMS in reducing cravings for alcohol. The overall strength of the evidence included in the review was rated low due to methodological limitations of the included trials (unclear reporting of allocation concealment and outcome assessor blinding) and imprecision surrounding the pooled effect size estimates. The evidence was further limited due to variations in the delivery of rTMS in terms of number of sessions and duration of stimulation across studies and unspecified follow-up times.

Table 1. Strength of Evidence for Transcranial Magnetic Stimulation (TMS) to Treat Alcohol 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
Bi-lateral or Unilateral rTMS (HIGH Frequency ≥1 Hz) vs Sham									
Cravings	6 RCTs in 1 SR (Maiti et al, 2017)	rTMS (87) vs. sham rTMS (75) **F/u:** NR; number of session ranged from 1 to 20	SMD: -0.06, 95% CI: -0.89 to 0.77, no significant between real rTMS and sham rTMS or for rTMS as an add-on to standard drug therapy (1 study; SMD: 1.40, 95% CI -0.94 to 3.74)	Yes (-1)	No	No	Yes (-1)	No	Low

ACQ-NOW: Alcohol Craving Questionnaire; AE: adverse events; AUD: alcohol use disorder; CI: confidence interval; DLPFC: dorsolateral prefrontal cortex; F/u: follow-up; I^2: % of heterogeneity between studies; mo.: months; NR: not reported; NS: not significant; OCDs: Obsessive Compulsive Drinking scale; RCT: randomized controlled trials; RoB: risk of bias; SMD: standardized mean difference; rTMS: repetitive TMS; TMS: transcranial magnetic stimulation; VAS: Visual Analog Scale

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 Transcranial Magnetic Stimulation (TMS) to Treat AUD

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
Reference: Maiti et al. 2017 **Organization/Country:** India **Purpose:** To conduct a meta-analysis of the effect of high frequency rTMS on craving in substance use disorder and to investigate the reasons behind the inconsistency across studies. **AMSTAR Rating:** Moderate due to not reporting if study selection or data abstraction were conducted in duplicate. **Overall RoB of Included Studies:** Some concerns (moderate ROB) due to unclear reporting of allocation concealment and outcome assessor blinding.	**Databases Searched:** MEDLINE and Cochrane database **Dates Searched:** Inception to 2015 **Inclusion/Exclusion Criteria:** Included controlled trials on TMS in patients with substance use disorder published in English in peer reviewed journals. All studies included in meta-analyses were RCTs that included a sham control and had craving reduction as primary outcome and assessed craving levels in alcohol, nicotine, cocaine, and methamphetamine-dependent patients. Excluded letters to editor, case series, and case reports. **Final Evidence Base:** 6 RCTs served as evidence for AUD	**Diagnosis:** AUD **Number of Patients:** 162: n=87 real rTMS; n=75 sham rTMS **Age:** Adults; age NR **Gender:** NR	**Intervention:** High-frequency (10 to 20 Hz) rTMS delivered to the left (1 study), right (3 studies), or bilateral (2 studies) DLPFC over the course of 1 to 20 sessions with duration of application ranging for 12 to 42 seconds. **Comparators:** Sham rTMS (4 studies); standard drug tx (1 study); Other therapies used in the included RCTs not reported by authors of the review **Follow-up:** NR **Outcomes:** Alcohol craving as measured using the ACQ-NOW (1 study); OCDs (4 studies) or VAS (1 study)	**Cravings:** SMD: -0.06, 95% CI: -0.89 to 0.77, no significant between real rTMS and sham rTMS or for rTMS as an add-on to standard drug therapy (1 study; SMD: 1.40, 95% CI -0.94 to 3.74) **AEs:** None reported **Limitations:** SR included limited number of studies with small sample sizes and limited follow-up to detect AEs. The rTMS protocol varied across studies in terms of number of sessions and time of application.

ACQ-NOW: Alcohol Craving Questionnaire; AE: adverse events; AUD: alcohol use disorder; CI: confidence interval; DLPFC: dorsolateral prefrontal cortex; I^2: % of heterogeneity between studies; mo.: months; NR: not reported; NS: not significant; OCDs: Obsessive Compulsive Drinking scale; RCT: randomized controlled trials; RoB: risk of bias; SMD: standardized mean difference; rTMS: repetitive TMS; TMS: transcranial magnetic stimulation; VAS: Visual Analog Scale

Table 4. Systematic Review Risk of Bias AMSTAR Checklist Table on TMS to Treat AUD

Question	Maiti et al., (2017)
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?	No
Did the review authors perform data extraction in duplicate?	No
Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
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? RCTs?	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	**Moderate**

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

Reference

Maiti, R., Mishra, B., Hota, D. (2017). Effect of high-frequency transcranial magnetic stimulation on craving in substance use disorder: A meta-analysis. *Journal of Neuropsychiatry and Clinical Neurosciences, 29*(2), 160-171.

Summary of Evidence of CIH and other Interventions for AUD

This systematic review assessed the efficacy of specific CIH, and other interventions used in the treatment of individuals with AUD. The overall evidence base included 12 publications (3 SRs with 21 RCTs and 9 additional RCTs) that met inclusion criteria and addressed the following interventions: acupuncture (1 SR with 11 RCTs), cannabinoids (1 RCT), exercise (1 SR with 4 RCTs and 2 additional RCTs), meditation (3 RCTs), music therapy (1 RCT), relaxation therapy (2 RCTs), and transcranial magnetic stimulation (TMS, 1 SR with 6 RCTs). The literature searches did not identify any publications meeting inclusion criteria for the following interventions: accelerated resolution therapy (ART), art therapy, chiropractic care, equine therapy, healing touch, hyperbaric oxygen therapy, massage therapy, Tai Chi, therapeutic touch, or training and care of service dogs.

Overall, limited evidence suggests that acupuncture plus medication leads to improved overall psychological symptoms and symptoms of anxiety compared to sham acupuncture plus medication or to medication alone. Limited evidence also suggests that exercise added to the treatment of individuals with AUD may improve symptoms of depression. Additionally, there is evidence to suggest that meditation used in the context of mindfulness-based relapse prevention reduces cravings, post-intervention alcohol or drug consumption, and perceived stress. **Table 1** presents the key findings for the interventions assessed in this section.

However, no differences were observed between acupuncture plus medication and sham acupuncture (with or without medication) in reducing cravings for alcohol or alcohol consumption after treatment. The findings of one study suggests that disulfiram is more effective than acupuncture alone in reducing immediate (< 8 weeks) symptoms of alcohol withdrawal symptoms. Limited evidence also found no statistically significant difference between Rimonabant (a cannabinoid receptor) and placebo in relapse to any drinking or to heavy drinking. Overall, 41.5% of patients receiving Rimonabant relapsed to drinking and 47.0% of patients receiving placebo relapsed. Similarly, adding exercise, music therapy, or TMS to the treatment of adults with AUD did not significantly improve alcohol related outcomes compared to controls. Finally, evidence from one RCT suggests that CBT modified to treat adults with co-occurring alcohol dependence and anxiety may reduce the rate of relapse and general symptoms of anxiety compared to relaxation therapy among adults undergoing residential treatment for AUD.

Few studies reported on the occurrence of adverse events. Three studies reported on adverse events associated with acupuncture. Of those, one study found no difference in rate of adverse events, one study reported no adverse events, and one study reported that two patients in the acupuncture group fainted and eight patients in the disulfiram group experienced temporary nausea. And, the authors of the single study reporting on the use of Rimonabant in the treatment of AUD indicated that the overall safety and tolerance of Rimonabant was good with rates of reported adverse event were like placebo.

The overall strength of the evidence for the CIH and other interventions assessed in this section for use in the treatment of adults with AUD was rated low to very low due to the evidence base for most outcomes consisting of a single study with methodological limitations that generally included lack of clarity about the randomization process; not blinding patients, providers or outcome assessors; and high attrition. The evidence was further limited due imprecision of the findings and to the relatively short duration of treatment with either no or limited follow-up times. For treatments, such as TMS or Rimonabant, this limitation prevented a more comprehensive assessment of adverse events.

imprecision surrounding the pooled effect size estimates. The evidence was further limited due to variations in the delivery of rTMS in terms of number of sessions and duration of stimulation across studies and unspecified follow-up times.

Table 1. Summary of Finding of CIH for AUD

	Cravings/withdrawal			Relapse			Alcohol Consumption			Anxiety			Depression		
Intervention	**EB**	**Findings**	**SOE**	**EB**	**Findings**	**SOE**	**EB**	**Findings**	**SOE**	**EB**	**Findings**	**SOE**	**EB**	**Findings**	**SOE**
ACU+Med vs Sham+Med	1 RCT	NS	L							1 RCT	+	L			
ACU+Med vs Med alone							1 RCT	NS	L	1 RCT	+	L			
ACU vs Sham ACU	1 RCT	+	VL												
ACU vs Med	1 RCT	_	L												
Cannabinoid vs PLA				1 RCT	NS	L				1 RCT	NS	L	1 RCT	NS	L
EX vs TAU							3 RCTs	NS	L	3 RCTs	NS	L	4 RCTs	+	L
Vipassana vs Cont.													1 RCT	NS	VL
MBRP vs. Support therapy	1 RCT	+	VL				1 RCT	+	VL	1 RCT	+	VL			
Music therapy	1 RCT	NS	VL												
RT vs CBT for anxiety				1 RCT	+	L				1 RCT	+	L			
RT vs CBT for Depression				1 RCT	NS	L							1 RCT	NS	L

	Cravings/withdrawal			Relapse	Alcohol Consumption	Anxiety	Depression
rTMS vs. Sham rTMS	6 RCTs	NS	L				

+ favors intervention; - favors control; NS: no significant difference between intervention and control

ACU: acupuncture; EB: evidence base; L: Low strength of evidence; MBRP: meditation-based relapse prevention; Med: medication; NR: not reported; PLA: placebo; RCT: randomized controlled trial; SOE: strength of evidence; SR: systematic review; TAU: treatment as usual; TMS: Transcranial Magnetic Therapy; 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 AUD
- **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: acamprosate, disulfiram, naltrexone, topiramate, ketamine
    - Psychological treatments: behavioral couples' therapy, cognitive behavioral therapy (CBT), community reinforcement approach, motivational enhancement therapy, 12-step facilitation
- **Outcomes:** return to heavy drinking, drinking/heavy days, drinks per day, time to relapse, relapse, adherence with treatment or abstinence, adverse events, morbidity, mortality, 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 AUD.
- **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 Full-text Level

Authors	Reason for Exclusion
Acupuncture	
Lee, J. et al. 2015	Included in Liu, 2018
Exercise	
Bichler, C. et al. 2017	Fewer than 20 patients enrolled in study
Brown, R. et al. 2016	Wrong study design; Post-hoc analysis of Brown, 2014 (in Hallgren)
Brown, R. A. et al. 2014	Included in Hallgren SR
Meditation	
Grow, et al. 2015	Wrong study design; Post-hoc analysis of Bowen looking at how many previous study participants practice at home.
Crescentini, et al. 2015	Wrong study design (not randomized) and wrong outcomes (measured character traits)
Witkiewitz & Bowen, 2010	Wrong design; post-hoc analysis of data in Bowen.
Relaxation Therapy	
Ciraulo, D. A. et al. 2013	Primary intervention Venlafaxine vs CBT
Tai Chi	
Oh, C. U. & Kim, N. C., 2016	Wrong study design (not an RCT and enrolled only patients who were assessed as being motivated to change based on a screening questionnaire)
Transcranial Magnetic Stimulation (TMS)	
den Uyl, et al. 2018	Wrong intervention (uses transcranial direct current stimulation which has not been approved by the FDA for clinical use in the United States)
Uyl, et al. 2017	Wrong intervention (uses transcranial direct current stimulation which has not been approved by the FDA for clinical use in the United States)
del Uyl, et al. 2016	Wrong pt. population (not diagnosed with AUD; volunteers who reported heavy drinking)
Del Felice, et al. 2016	Fewer than 20 pts enrolled in study
Rapinesi, C. et al. 2015	Fewer than 20 pts enrolled in study
Mishra, B. R. et al. 2015	Included in Maiti SR
Girardi, P. et al. 2015	Included in Maiti SR
Hoppner, J. et al. 2011	Included in Maiti SR
Mishra, B. R. et al. 2010	Included in Maiti SR

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Appendix C

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”.
- **The confidence in the reported effect** (bubble size)
  - The size of a bubble indicates the level of confidence in the reported effect.

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 AUD Cravings

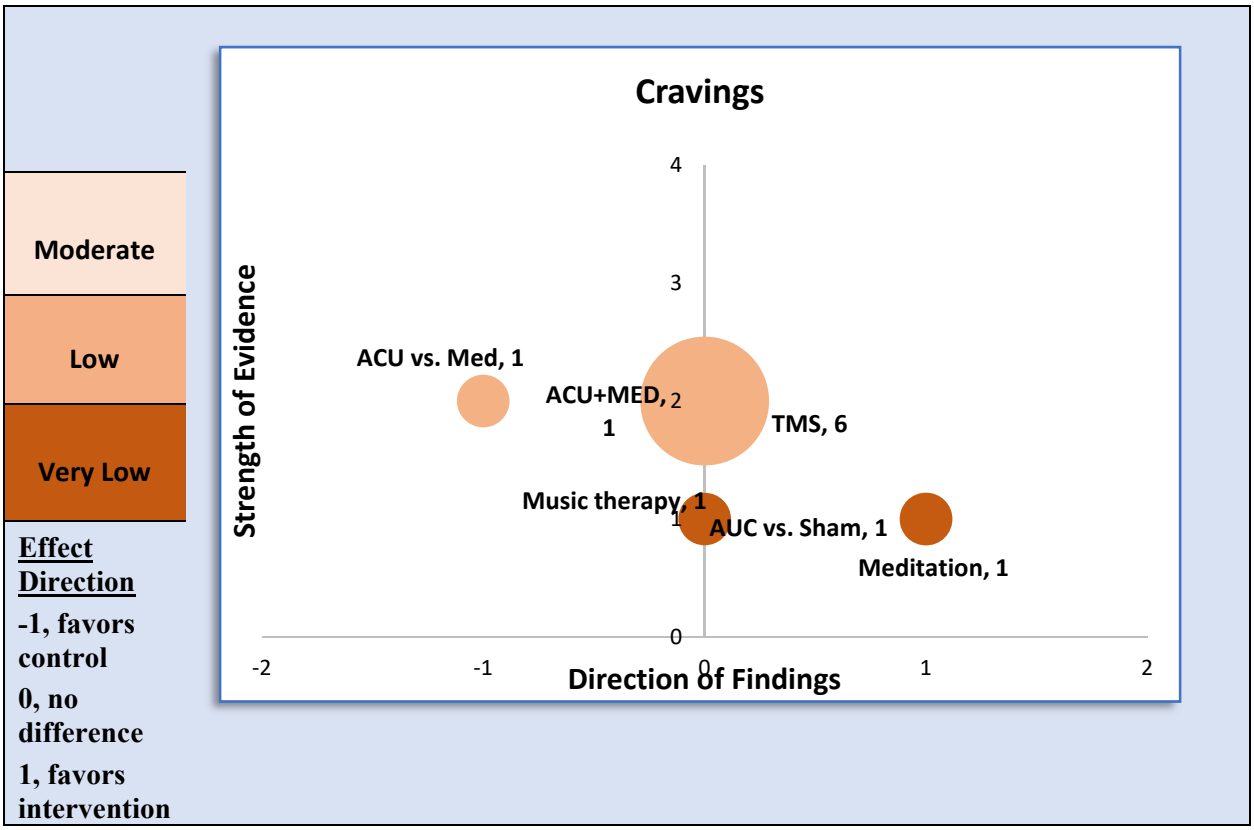

Figure 3. Bubble Plot of Findings for AUD Depression/Anxiety