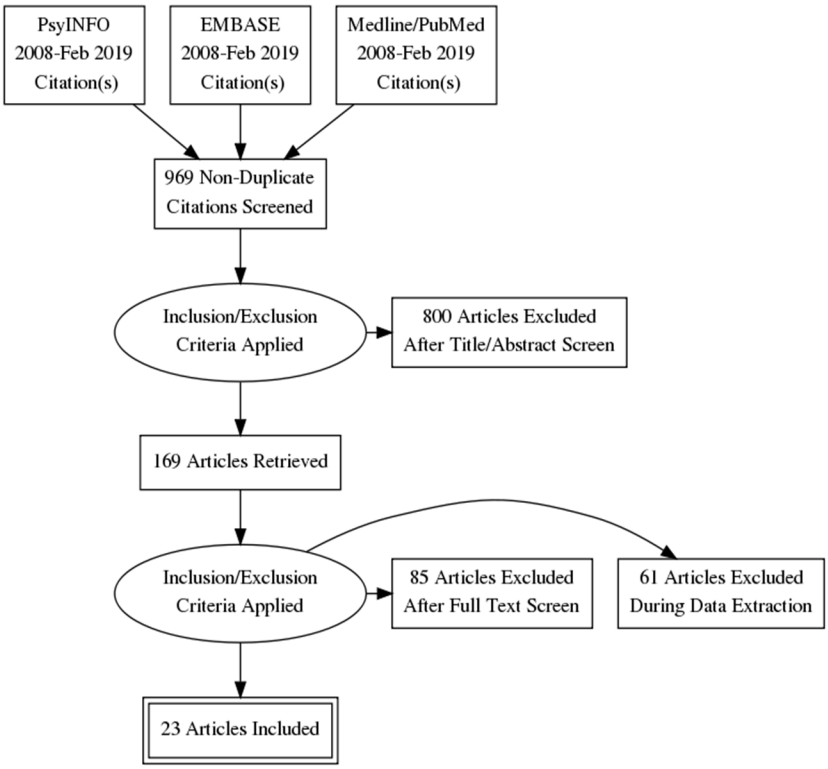
Chapter 7: Complementary and Integrative Health and other Non-Conventional Approaches for Treating Chronic Insomnia Disorder (CID)

Results of the Literature Search for CID

Extensive literature searches identified 969 citations (after duplicates removed) potentially addressing the CIH interventions and other non-conventional approaches of interest for the treatment of Chronic Insomnia Disorder (CID). Of those, 800 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 169 full-length articles were retrieved for review (See Error! Reference source not found. for the PRISMA diagram). Of those, 85 were excluded due to having the wrong patient population (49 studies), the wrong study design (24 studies), wrong comparator (4 studies), less than 20 patients (2 studies), more recent/comprehensive systematic reviews available (2 studies), wrong outcomes (2 studies); or were not in the English language (2 studies). An additional 61 studies were excluded during data abstraction. Reasons for these exclusions are listed in **Appendix B**.

Figure 1. Prisma Study Flow Diagram for Chronic Insomnia Disorder



Overall, 23 studies were included in the systematic review for CID. **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 and Other Non-Conventional Interventions to Treat Chronic Insomnia Disorder

Intervention	Number and Type of Studies
Accelerated Resolution Therapy (ART)	0
Acupuncture	2 SRs (41 RCTs); 5 RCTs (from 6 publications)
Art therapy	0
Cannabinoids	1 SR (2 RCTs)
Chiropractic care	0
Equine therapy	0
Exercise therapy (outdoor therapy)[1]	1 SR (9 RCTs); 2 RCTs
Healing Touch	0
Hyperbaric Oxygen Therapy	0
Massage therapy	1 RCT
Meditation	4 RCTs
Yoga	1 RCT
Music therapy	1 SR (17 RCTs; 3 non-randomized); 1 RCT
Tai chi	2 RCTs
Relaxation therapy	1 RCT
Training and caring for service dogs	0
Transcranial Magnetic Stimulation (TMS)	1 RCT
Total Studies	**23 studies (5 SRs with 69 RCTs and 3 non-randomized, and 18 additional 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 CID are provided in a supplemental file on Max.gov and can be accessed here: https://community.max.gov/display/VAExternal/Insomnia+Report+Supplemental+Materials

[1] It is important to note that types of exercise vary across studies and conditions. Outdoor therapy was identified in the CARA legislation, while exercise was identified by the COVER Commission as an intervention of interest. These have been combined due to the overlap in the studies.

Acupuncture

Evidence Base

Our searches of the literature identified two recently published systematic reviews (SRs) and another 5 individual RCTs (in 6 publications) that were not included in the SRs and met inclusion criteria and addressed one or more of the key questions.

The review published by Shergis et al., (2016) had as its purpose to perform a systematic review of and, if possible, to conduct a meta-analysis to examine the effects of acupuncture for the treatment of insomnia. In total, 30 RCTs were included, 26 of which had enough data to perform meta-analyses. The Pittsburgh Sleep Quality Index, or PSQI, was the primary outcome. Most of the included studies evaluated acupuncture against a pharmacological treatment group while a few assessed acupuncture against a more passive control such as placebo or sham acupuncture. A second systematic review by Lan et al., (2015) assessed the impact of a specific type of acupuncture, auricular (ear) acupuncture (AA) with seed or pellet attachments in the treatment of primary insomnia (acute, subacute and chronic). This SR identified 15 studies that assessed AA against comparators that included sham acupuncture, pharmacotherapy as well as other comparators such as other types of acupuncture.

In addition to the 2 SRs, 6 papers from 5 RCTs were identified, 4 of which were published after the end search dates of the SRs. The earlier RCT by Wang, et al., (2008) was the only study identified that specifically assessed the impact of abdominal acupuncture on insomnia in women only. The two papers by Bergdahl were reporting on a single RCT of adults with insomnia who had been treating their insomnia with benzodiazepines with limited success. The trial assessed the effectiveness of acupuncture vs. CBT-I (Cognitive behavioral therapy-insomnia) as methods to replace the use of benzodiazepines. CBT-I is considered to be an effective, evidence-based approach for treating chronic insomnia disorder. Two other recent RCTs (Yin, et al, (2017); Fu et al., (2017) tested acupuncture against carefully designed sham acupuncture interventions in an attempt to achieve true blinding of patients and outcome assessment. Fu et al., was testing acupuncture in a population of perimenopausal women. The RCT by Bo et al., (2016) was testing a specific form of acupuncture, called Mongolian medical warm acupuncture against medication for adults with primary insomnia.

Study Quality

Using the AMSTAR instrument, we rated the two SRs by Shergis et al., and Lan et al., as being of moderate to high quality with shortcomings due to the lack of detail about excluded studies and the lack of explicit statements regarding the review methods and funding sources of included studies. In all other regards, these were rigorously conducted SRs. Included studies in the SRs, however, were of lesser quality, from moderate to very low levels of evidence, primarily due unblinded participants and, often, the lack of blinding intervention providers and outcome assessors. Some studies also documented poor or vague attrition rates and the lack of intent-to-treat analysis. Similarly, the 5 RCTs (in addition to those within the SRs) ranged from moderate to very low quality for the same reasons.

Across the volume of evidence, there was considerable between-study heterogeneity, particularly regarding the wide range of acupuncture interventions tested; no two studies seemed to use identical or nearly identical acupoints as part of the testing acupuncture intervention. Despite study heterogeneity, in

both the population and interventions studied, and less-than-ideal evidence, some themes emerged from this review.

Key Findings

Below, we describe the key findings for the outcomes of interest with the GRADE strength of the evidence (SOE) rating regarding the effectiveness of acupuncture interventions compared to different control interventions for the treatment of primary chronic insomnia disorder (CID). See Table 1 for factors that influenced the SOE ratings.

Acupuncture (fine needle, auricular, abdominal)

- Combined evidence from 8 RCTS suggests that acupuncture statistically significantly reduces symptoms of Chronic Insomnia Disorder compared to placebo or sham acupuncture immediately following treatment. (SOE: Moderate to Low)
- 1 systematic review with 15 RCTS (Lan et al) suggests than auricular acupuncture with seeds or pellets is effective for primary insomnia, including CID. (SOE: Moderate).
- Combined evidence from 32 RCTS suggests that acupuncture is similar to or slightly better than pharmacological interventions for the treatment of chronic insomnia disorder with fewer adverse effects. (SOE: Low to Very Low)
- Evidence from 1 RCT suggests that acupuncture is less effective than Cognitive Behavioral Therapy (CBT-I) for the treatment of chronic insomnia disorder but its benefits are sustained or improved over 6 months' time. (SOE: Low)
- Combined evidence from 4 RCTs and 2 SRs suggests that acupuncture interventions improve subjective assessments of insomnia but may not have a discernible impact on objective parameters of sleep such as sleep efficiency, total sleep time, sleep onset latency, etc. (SOE: Moderate to Low)
- Combined evidence from 2 RCTs and 2 SRs suggests that acupuncture interventions result in few or very mild adverse effects such as redness and slight pain at acupoint sites (SOE: Moderate to Low)

Discussion

Overall, the findings of the 7 studies (5 RCTs and 2 SRs) suggest acupuncture reduces symptoms and severity of insomnia compared to passive controls such as placebo and sham acupuncture and may be as or more effective compared to medication with fewer adverse effects. The study quality and heterogeneity limit the ability to draw more specific or generalizable conclusions. The range of acupuncture interventions in the research included ear (auricular) acupuncture with varying attachments, electroacupuncture, warm acupuncture/needling, and fine needle full body acupuncture with varying number and location of acupoints. The Shergis et al. review reported, for example, 58 distinct points across 30 studies, with an average of 9.3 acupoints per study (range 3-24 points). When reported, needles were left in for 20 to 60 minutes per treatment and treatments lasted from 10 days to 6 weeks. While the Lan et al. review was limited to studies of auricular acupuncture with seeds or pellets, it is important to note that other studies included in this systematic review also examined various forms of ear

acupressure/acupuncture. Approaches to sham also varied considerably and pharmacological controls were most often either estazolam or zolpidem. Only the single study used CBT-I as a comparator and found CBT-I to be superior to acupuncture. No serious adverse events were reported. Sample sizes of studies were small with typically less than a hundred total participants and the largest studies identified in the Shergis et al., of 120 and 180 participants in total (both intervention and control arms). Most studies included more women than men and several were limited to women because of a focus on treatment of peri-menopausal or post-menopausal insomnia. Overall, the evidence supports the need for more research for both needle acupuncture as well as auricular acupuncture.

Table 1. Strength of Evidence for Acupuncture Interventions to Treat CID

Primary Outcomes	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
Pittsburgh Sleep Quality Index (PSQI)	26 RCTs from 1 SR (Shergis et al., 2016), 1 RCT (Fu et al, 2017)	Acu vs. sham/ placebo (4 studies): f/u 2-10 weeks	MD in SR= -0.79 (95% CI=-1.38, -0.19), p=0.009,	Yes (-1)	No	No	No	No	Moderate
		Acu vs. pharmacotherapy (23 studies)	MD= -2.79 (95% CI=-3.67, -1.85), p<0.00001,	Yes (-2)	No	No	No	No	Low
Effective/ Efficacy rate (proportion with meaningful/ obvious/ definite improvement)	15 RCTs from 1 SR (Lan et al, 2015[2]), 1 RCT (Bo et al., 2016)	Acu vs. sham/ placebo (7 studies):	Meta-analyses showed Acu effective > sham/placebo	Yes (-2)	No	No	No	No	Low
		Acu vs. pharmacotherapy (9 studies)	Meta-analyses showed some improved effective rate from acu but not always clinically significant	Yes (-2)	No	No	Yes (-1)	No	Very low[3]
Insomnia Severity Index	3 RCTs (Yin et al, 2017; Fu et al., 2017; Bergdahl et al, 2016)	Acu vs. sham (1 study, Yin et al)	Improvement in acu group of 17.1(4.1) to 9.6(4.2) in tx group vs. 17.0 to 14.4	Yes (-1)	No	No	No	No	Moderate

[2] Lan et al., 2015 is limited to studies of auricular acupuncture only.
[3] It is important to note that the SOE rating for Lan for the outcome of efficacy rate is slightly lower due to the methodological limitations of Bo et al., 2016.

Primary Outcomes	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
			in control/sham group						
		Acu vs. CBT-I (1 study, Bergdahl et al, 2016)	Favoring CBT-I group with -8.16 (SE 1.18) vs. acu group -2.07 (0.78) and at 6-month f/u (CBT-I group with -6.09 (SE 1.33) vs. acu group -3.27 (0.84).	Yes (-2)	No	No	No	No	Low
Leeds Sleep Evaluation Questionnaire (LSEQ)	1 RCT (Wang et al, 2008)	Acu vs sham acu, 7 days post treatment (11 days of treatment).	Improvement in LSEQ of of 18.78 (95% CI of -29.8- -7.76) compared to sham group	Yes (-1)	No	No	No	No	Moderate

AA: abdominal/ auricular acupuncture; ACU: acupuncture; CBT-I: cognitive behavioral therapy for insomnia; CI: confidence interval; CID: chronic insomnia disorder; CG: control group; ES: effect size; F/u: Follow-up; ISI: Insomnia Severity Index; mos.: months; MD: mean difference; NR: not reported; NS: not significant; PCT: QoL: Quality of Life; PSQI: Pittsburgh Sleep Quality Index; RoB: Risk of Bias; RCT: randomized controlled trials; SE: standard error; SHE: sleep hygiene education; SOL: Sleep onset latency; SMD: standardized mean difference; SM: self-monitoring; SR: systematic review; ss; statistically significant; Tx: treatment; TAU: treatment as usual; TWT: total wake time; TST: total sleep time; WASO: Wake after sleep onset; WL: waitlist

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 to Treat Chronic Insomnia Disorder

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
Reference: Shergis et al, 2016 **Organization/Country:** Academic medical centers in Vic, Australia and Guangzhou, China **Purpose:** to perform a systematic review and meta-analysis to examine the effects of acupuncture for insomnia **AMSTAR Rating:** *High* **Overall RoB of Included Studies:** Cochrane tool; moderate risk of bias due to lack of blinding and unclear bias of selective outcome reporting. 29 of 30 studies had low risk of bias for incomplete outcome data.	**Databases Searched:** 9 major English and Chinese databases including: PubMed, AMED, CINAHL, CENTRAL; and CBM, CNKI, CQVIP, and reference list of included studies **Dates Searched:** Inception to January 2016 **Inclusion/Exclusion Criteria:** Published RCTs with parallel design, Patients diagnosed with insomnia using standard criteria such as DSM-IV, ICSD, ICD or Chinese Classification of Mental Disorders (CCMD). Patients with comorbid conditions or with secondary insomnia were excluded. Interventions included needle acupuncture at one or more of the 3 insomnia points: HT7, GV20, and SP6. Needle acupuncture with other acupuncture studies were allowed, but non-penetrating (e.g., laser) acupuncture excluded. Comparators included medication, CBT, sham acupuncture or placebo. Included studies of full acupuncture, auricular acupuncture, and other specific body sites. **Final Evidence Base:** 30 RCTs in qualitative synthesis, 26 in quantitative synthesis.	**Diagnosis:** Insomnia (21 studies used CCM criteria, 6 ICD, 3 DSM). **Number of Patients:** 2,363 in 30 studies total **Age:** Range 17 to 75 years; **Gender:** 1225 female, 955 male, 183 gender not stated	**Interventions:** Acupuncture alone in 22 studies, 3 with ear acupressure and 3 with electroacupuncture, 1 with ear acupuncture and warm needling and 1 with ear acupuncture plus moxa **Comparators:** sham (2 studies), placebo (1 study), pharmacotherapy (26 studies), CBT not used in any studies. **Follow-up:** treatment lasted 10 days to 6 weeks, mode 4 weeks, 6 studies had f/u period between 1 and 3 months. **Outcomes:** Primary outcome was PSQI (all studies but 4 with insufficient data to pool), any ss difference between tx groups at the end of treatment. Secondary outcomes included: insomnia scales such as ISI, Athens Insomnia Scale (AIS—also able to be pooled), sleep parameters by diary, actigraphy, or polysomnography.	**PSQI: (ACU vs. sham/ placebo) 3 studies:** MD= -0.79 (95% CI=-1.38, -0.19), p=0.009, treatment duration was 2, 3, and 6 weeks (9-21 treatments). **PSQI: (ACU vs. pharmacotherapy) 23 studies:** MD= -2.79 (95% CI=-3.67, -1.85), p<0.00001, PSQI without sleep medication domain: MD= -1.04 (95% CI=-1.89, -0.19), p=0.02 **Subgroup analysis of 12 studies with adequate randomization:** MD= -2.71 (95% CI=-4.08, -1.35), p<0.00001 **Subgroup analysis of 3 studies acu+ ear acupressure:** MD= -4.89 (95% CI=-5.93, -3.85), p<0.00001 **Similar results when grouping interventions by duration of insomnia/ treatment.** f/u of 4 weeks in one study of acu vs. sham/ placebo: no difference between groups, f/u 1-3 months in 2 studies of acu vs. pharmacotherapy showed no difference between groups.

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
				Other outcomes: AIS pooled for 2 studies showed ns difference between acu and pharmacotherapy. Adverse events: 7 studies reported 103 events, 39 in acu group and 64 in control groups. All events were mild in acu and control groups. **Limitations:** PSQI medication use domain may have skewed results towards Acu, many low quality RCTs included, and studies had high heterogeneity,
Reference: Lan et al, 2015 **Organization/Country:** Teaching hospital, Chengdu University of Traditional Chinese Medicine, Sichuan, China. **Purpose:** To evaluate any potential advantages of auricular acupuncture with seed or pellet attachments in the treatment of primary insomnia. **AMSTAR Rating:** High **Overall RoB of Included Studies:** Evidence quality assessed using GRADE; risk of bias/ study quality/ level of evidence ranged from moderate to very low, due to poor study design and reporting as well as imprecision (small sample size) and lack of detail in reports.	**Databases Searched:** 13 major English and Chinese databases including: PubMed, AMED, CINAHL, CENTRAL, CMR, ACP Journal Club, DARE, PQDT, ICTRP; and CBM, CNKI, CQVIP, Wangfang and reference list of included studies. **Dates Searched:** Inception to November 2013 **Inclusion Criteria:** RCTs with adults ages 18-80 and sleep dissatisfaction for 1 month or longer. Interventions: plant seeds, metal pellets, or magnets attached on the auricles. Comparison groups: sham AA, placebo, no treatment, or drug therapy. Limited to English and Chinese language only.	**15 studies total from 1993-2013,** 11 from China, 1 from Hong Kong, 2 from Taiwan, 1 from US. **Number of Patients:** 1,429 patients, 510 were male, ages 18-78, insomnia from 1 month to >10 years. 737 received AA vs 664 received control. Sample sizes ranged from 21 to 300. **Diagnosis:** Insomnia (8	**Interventions:** Seven studies used Semen Vaccariae for auricular attachment, six chose magnetic pearls, one study used seeds in one group and magnetic pearls in the other group, and 1 study did not specify. **Comparators:** Forms of sham (7 studies), pharmacotherapy with estazolam (4 studies) and diazepam (4 studies), standard points protocol (8 studies), individual prescriptions according to syndrome differentiation (7 studies). **Follow-up:** Only reported in 2 RCTs (12 days and 6 mos. to 1 yr.) **Outcomes: Primary outcome:** Effective rate = proportion of participants who had improved obviously (subjective assessment based on self-report). **Secondary outcomes:** Sleep parameters measured by either subjective or objective assessments,	Auricular acupuncture (AA) statistically significantly improved clinical effective rate, total sleep time, sleep efficiency, PSQI score, SOL, and number of awakenings compared to sham/placebo. When compared to medications, AA improved effective rate, sleep efficiency, PSQI score, and adverse effects. Adverse events: 4 studies reported adverse events in the comparisons between AA and medications with a greater number of AEs in medication groups compared to AA. In AA group, 2 cases of auricle pain, 2 cases of redness at attachment points and withdrew after treatment, RR

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
	Exclusion Criteria: comparisons of different auricular or stimulations were excluded	studies used CCM criteria, 1 ICD, 3 DSM, 6 PSQI).	including PSG, EEG, sleep diary, sleep efficiency, PSQI, ISI, Athens Insomnia Scale (AIS), adverse effects.	= 0.11 (95% CO=0.04-0.26) for AEs. **Limitations:** unclear auricular maps in 11/15 studies, too few sham/placebo controlled RCTs, limited to Chinese and English studies, combined interventions which may not be appropriate but limited by few studies.

AA: auricular/ abdominal acupuncture; ACU: acupuncture; AEs: adverse effects; CBT-I: cognitive behavioral therapy for insomnia; CI: confidence interval; CID: chronic insomnia disorder; CG: control group; ES: effect size; F/u: Follow-up; ISI: Insomnia Severity Index; mos.: months; MD: mean difference; NR: not reported; NS: not significant; PCT: QoL: Quality of Life; PSQI: Pittsburgh Sleep Quality Index; RoB: Risk of Bias; RCT: randomized controlled trials; SE: standard error; SHE: sleep hygiene education; SOL: Sleep onset latency; SMD: standardized mean difference; SM: self-monitoring; SR: systematic review; ss; statistically significant; Tx: treatment; TAU: treatment as usual; TWT: total wake time; TST: total sleep time; WASO: Wake after sleep onset; WL: waitlist

Table 4. Systematic Review Risk of Bias AMSTAR Checklist Table on Acupuncture to Treat CID

Question	Shergis et al., (2016)	Lan et al, (2015)
Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	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	Yes
Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes
Did the review authors use a comprehensive literature search strategy?	Yes	Yes
Did the review authors perform study selection in duplicate?	Yes	Yes
Did the review authors perform data extraction in duplicate?	Yes	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	No	No
Did the review authors describe the included studies in adequate detail?	Yes	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	Yes
Did the review authors report on the sources of funding for the studies included in the review?	Yes	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? RCTs?	Yes Yes	Yes 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	Yes
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	Yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	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	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes
Overall Quality	**High/Moderate**	**High/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

Table 6. Evidence Table for RCTs on Acupuncture to Treat Chronic Insomnia Disorder (CID)

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Yin et al. 2017 **Purpose:** To evaluate the efficacy and safety of acupuncture for primary insomnia. **Setting:** Shanghai Municipal Hospital, Shanghai, China **Funding source:** Government grants including from Science and Technology committee in Shanghai, China	**Number of patients:** 72 (n=36 acu; n=36 sham acu) **Inclusion criteria:** 18 to 65 yrs of age, met DSM-IV criteria for primary insomnia, insomnia history 1 month to 2 years, ISI 8-21 at baseline, SE <85%. **Exclusion criteria:** serious cardiovascular, liver, kidney or hematopoetic disease, insomnia secondary to CNS disease (e.g., stroke, Parkinson's) or mental illness, history of sleep apnea, pregnant or breastfeeding, recent use of psychotropic medications. **Pt. baseline characteristics (all pts):** Age (mean yrs.): 37.3-39.7yrs. Gender (male/female): 32/40, 43/72 married Education (years): 14.8-16.4 Significant differences between acu and sham in anxiety (p=0.011) and TST (p=0.003), with acu group having greater TST and lower anxiety at baseline	**Intervention:** 30-minute treatments, 3X/week for 4 weeks= 12 treatments by experienced acupuncturist, and controlled environment. Acu points: GV20, 24, 29, EX-HN22, and bilateral HT7, and SP6—needles inserted through tubes followed by rotation or deep thrusting manipulation for deqi sensation. **Sham/ Control:** same as intervention group except tubes used to simulate needles without needle insertion. **Both groups allowed to take estazolam as rescue medication for extreme difficulty sleeping** **F/u:** Post-tx 2 and 4 weeks, and then f/u 2 and 4 weeks after the end of treatment. **Outcomes: Primary:** ISI; **Secondary:** Total Sleep time (TST), Sleep awakenings (SA), sleep efficiency (SE), Self-rating anxiety scale (SAS), Self-rating depression scale (SDS).	**Primary outcome-- ISI:** change in ISI from baseline to 4 weeks f/u (8 weeks later) was (mean(SD)): 17.1(4.1) to 9.6(4.2) in tx group vs. 17.0 to 14.4 in control group, ss with p<=0.001 at all timepoints (2, 4, 6 and 8 weeks post tx). **Secondary outcomes:** ss between-group differences in TST, SDS, SE but not in SAS and SA initially, at 2-4 weeks f/u, between group differences observed in all secondary outcomes. **Dropout:** Acu n=4 (11%); sham: n=6 (16%); significance not reported, 3 dropped out as a result of unsatisfactory treatment, sensitivity analysis not reported.	**Conclusions:** Authors conclude acupuncture is more effective than sham for treatment of primary insomnia. **Limitations:** Small sample size, some baseline differences, short treatment duration and f/u. **Study RoB:** Some Concerns/Low, due to concerns about no provider blinding and small baseline differences between tx groups, differing dropout rates. But strength is careful blinding and intervention implementation, sleep parameters determined by actigraphy rather than sleep diary/self-report. **Author conflict:** Reported no conflicts.
Reference: Fu et al. 2017 **Purpose:** To evaluate the short-term efficacy of acupuncture for perimenopausal insomnia (PMI).	**Number of patients:** 76 (n=38 acu; n=38 sham acu) **Inclusion criteria:** peri-menopausal women with ICSD-3 diagnosis of insomnia, and no acu experience.	**Intervention:** Acu by experienced acupuncturist, at points BL23, BL18, LR14, GB25 for 20 minutes, 3X/week for 10 weeks. **Sham/ Control:** same as intervention group except tubes	**Primary outcome-- PSQI:** change from baseline to post treatment (10 weeks) was 8.03 in acu vs. 1.29 in placebo group. **Secondary outcomes:** ISI changed 11.35 in acu group vs. 2.87 in placebo group.	**Conclusions:** Authors conclude acupuncture is more effective than sham for treatment of primary insomnia. **Limitations:** Small sample size, some baseline

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Setting: Yueyang hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China **Funding source:** Government grants including from National Natural Science Foundation.	**Exclusion criteria:** menopause secondary to surgery, taking medications for insomnia, receiving hormonal therapy, psychiatric disorders, sleep apnea or other sleep disorder, serious physical illness, participation in another clinical trial. **Pt. baseline characteristics (all pts):** Age (mean yrs.): 52.0-52.5yrs. Married/cohabitating: 94-97% Normal weight: 78-86.5% No significant differences between acu and sham groups at baseline.	used to simulate needles without needle insertion. **Outcomes: Primary:** PSQI **Secondary:** ISI and polysomnography (SOL, TST, WASO, SE, Arl, percent of sleep stages)	For PSG data, acupuncture improved sleep efficiency, total sleep time, less wake after sleep onset and lower percent sleep stage 1. No significant change from baseline in the placebo group. **Dropout:** 1 drop out from each group, significance not reported, **Adverse effects:** no AEs related to acupuncture, 4/37 in sham group complained of worsening insomnia as AE. No other AEs reported.	differences, short treatment duration and f/u. **Study RoB:** Some Concerns, due to concerns about sample size, no ITT analysis but only one drop out from each group, no provider blinding. But strength is careful blinding of patients and outcome assessments. **Author conflict:** Reported no conflicts.
Reference: Bo et al., 2016 **Purpose:** To evaluate the role of Mongolian medical warm acupuncture in treating insomnia. **Setting:** Inner Mongolia Medical University, Hohhot, China **Funding source:** Public grants including from National Natural Science Foundation, China.	**Number of patients: 80** **Inclusion criteria:** aged 20-75 years, insomnia diagnosed by International Classification of Sleep disorders (ICSD-2), insomnia from 1 month to 2 years, ASOL: >30 min and awakening >= 2 times/ night. **Exclusion criteria:** pregnant or lactating, major depression, serious or terminal illness, patients with pain symptoms, night shift workers **Pt. baseline characteristics (all pts):** Age (mean yrs.): 43-47 yrs. Gender (male/female): 46/34, Years of disease: ~3-4. 8/80 with mild disease, 41 with moderate, 31 severe. No significant differences	**Intervention (n=40):** Warm Acu by experienced acupuncturist, at points Dinghui, Haoyi, and Xin—30 minutes 4/each day, 9 days was a course of treatment, six courses of treatment were needed and performed at interval of 3 days. **Control (n=40):** estazolam 1 mg 15-30 minutes before sleep, for 56 days total. ame as intervention group except tubes used to simulate needles without needle insertion. **Outcomes:** Mongolian Medicine Indicators, PSQI Efficacy according to the PSQI: percent of scores before treatment – scores after treatment/ 100%. >30%=efficacious, >70% =	**Primary outcome—** Mongolian Medicine scores (scores (95% CI)) improved in both acu (from 11.56 (3.64) to 3.64 (1.08)) and medication groups (from 12.27 (4.25) to (4.25 (1.69)) and ns difference between groups. **Clinical efficacy (>30%):** 85% in acu group vs. 70% in medication group, ns difference between tx. groups. PSG: sleep quality and times improved in both groups, slightly better in medication group, however awakenings were better in acu group compared to medication	**Conclusions:** Authors conclude warm acupuncture is efficient and safe for treating insomnia and point to its efficacy in PSG "compared to hypnotics" but this is not shown in the data. **Limitations:** Authors overstate the few positive findings and not the ns or negative results, stratified randomization used resulting in very small sample size per strata, non-standard outcome measurements and results not objectively reported, errors in inclusion criteria compared to results reported. **Study RoB:** High risk of bias

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	between intervention groups at baseline	significant efficacy, 90% = recovery, PSG: Total Sleep time (TST), Sleep awakenings (SA), REM and Non-REM time **f/u:** outcome assessment 7 days post treatment	group (related to medication withdrawal). **Dropout:** NR	**Author conflict:** Reported no conflicts.
Reference: Wang et al., 2008 **Purpose:** To evaluate the efficacy and safety of abdominal acupuncture for treating insomnia. **Setting:** University hospital, Ghaungzhou University of Chinese Medicine, Ghaungzhou, China **Funding source:** not reported	**Number of patients: 44** **Inclusion criteria:** women, aged 30-55 years, insomnia diagnosed by Chinese Classification of Mental Disorders (CCMD-3), insomnia primary symptom, insomnia >3x/week, insomnia for one from month or longer **Exclusion criteria:** pregnant or lactating, receiving psychotropic medications, severe physical or mental disorder, cancer **Pt. baseline characteristics (all pts):** Age (mean yrs.): 41.2-41.4 yrs. Months of disease (mean): 23.7-41.9; 32/44 married, Education: 22/44 8-11 years, 15/44 with >11 years, 43/44 with no caffeine intake, all baseline differences ns between tx groups except baseline Leeds Sleep evaluation questionnaire (LSEQ—also primary outcome measure) which was lower in acu group 62.4 vs. medication group 78.0, p=0.01. acu group with	**Intervention (n=21):** Acu at points CV10, CV4, CV 6, KI 17, ST 24. Needles encased in plastic sheaths, in place for 20 minutes, daily for 3 days and then every 3 days for rest of 11 day trial—also received medication placebo daily for 11 days. **Control/ medication (n=23):** Same acupoints as above with no needle insertion (plastic sheaths only), also received estazolam 1 mg daily for 11 days. **Outcomes:** Leeds Sleep evaluation questionnaire (LSEQ) results and multivariate analysis, Adverse effects. **f/u:** outcome assessment 7 days post treatment	**Primary outcome— LSEQ** Receiving acu associated with a decrease in LSEQ of 26.32 (95% CI=-37.4- -15.3) but after controlling for lower baseline LSEQ (and other ns variables), still with a reduction of 18.78 (-29.8- -7.76), ss compared to sham/medication group **Adverse effects**: none in acu group, 6 mild AE in sham/ medication group (1 dizziness, 2 vomiting, 3 "next day residual effects." **Dropout:** NR but appears to be zero.	**Conclusions:** Short term abdominal acupuncture was effective for treating insomnia in women and more effective than estazolam. **Limitations:** small sample size, patients can be aware they are not receiving acu despite sham, short duration of intervention. **Study RoB:** Some concerns due to unblinded providers delivering intervention and some baseline differences between intervention groups that may not be accounted for by multivariable analysis. **Author conflict:** Not reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	shorter duration of insomnia also but ns.			
Reference: Bergdahl et al., 2016 and Bergdahl et al, 2017. **Purpose:** (1). To compare treatments effects of auricular acupuncture with CBT-I and evaluate symptoms of insomnia severity, anxiety, depression and (2); to objectively examine how sleep patterns were affected using actigraphy **Setting:** Uppsala University hospital, Uppsala, Sweden **Funding source:** Ekhagastiftelsen	**Number of patients: 59 (67 randomized)** **Inclusion criteria:** men and women, aged 18-75 years, with insomnia diagnosed by DSM-V, had been using benzodiazepine medication 3x/week for 6 months or more and wanted to stop medication, comprehension of Swedish required. **Exclusion criteria:** substance dependence, severe psychiatric disease or somatic disease, antipsychotic or narcotic drug use, antidepressant or anxiolytic drug use within past 3 months, pregnant **Pt. baseline characteristics (all pts):** Age (mean yrs.): 60.5 yrs, 50 women and 9 men, 26/59 retired, 29 working, one studying. 3 on long term sick leave and/or disability pension, 1 unemployed. No differences between groups at baseline	**Acupuncture Intervention (n=27):** Acu according to NADA protocol, 5-point setting: sympathetic, Shen men, Kidney, Liver and Lung, needles inserted for 45 minutes. Treatments were twice a week for 4 weeks by trained acupuncturists. **CBT-I (n=32):** manual-based group treatment focused on cognitive restructuring, once a week for 6 weeks. Sessions contained information regarding sleep physiology, coping mechanisms, sleep restriction, stimulus control, relaxation techniques. Sessions lasted 90 minutes, given by trained therapists at hospital facility. **Primary outcomes:** Insomnia Severity Index (ISI). **Secondary outcomes:** Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS-16), Epworth Sleepiness Scale (ESS), the Hospital Anxiety and Depression Scale (HAD). **Actigraphy outcomes:** sleep efficiency, SOL, TST, TAT, **Health-related Quality of Life:** SF-12	**Primary outcome— ISI**: Significant between group improvements favoring CBT-I were found post-treatment CBT-I group with -8.16 (SE 1.18) vs. acu group -2.07 (0.78) and at 6-month f/u (CBT-I group with -6.09 (SE 1.33) vs. acu group -3.27 (0.84). **Secondary outcomes:** CBT-I had improvements in DBAS-16 post-treatment but no difference between groups at 6 months. Both groups improved in HAD and ESS but not between group differences in HAD or ESS. Actigraphy; both groups improved their sleep parameters compared to baseline, but comparisons were mixed: AA group slept more, and CBT-I group slept less after treatments but both groups reverted to original patterns at 6 months, little consistent correlation with subjective insomnia. **SF-12:** CBT-I group improved from baseline but no between group effects. **Adverse effects**: not reported **Dropout:** 8 dropouts, 5 from AA group and 3 from CBT-I	**Conclusions:** Compared to CBT-I, auricular acupuncture cannot be considered an effective stand-alone treatment for persons with insomnia disorder. Also, objective sleep time does not necessarily affect subjective perception of insomnia. **Limitations:** small sample sizes, low number of males, no measurements of expectations which may have explained dropouts, differences in treatment time between groups, no ITT analysis. **Study RoB: High** due to lack of documented blinding, lack of ITT analysis, differential dropout rates. **Author conflict:** Reported no conflicts

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
		f/u: outcome assessment after intervention and at 6 months follow up	group. No differences between dropouts and completers.	

AA: auricular/ abdominal acupuncture; ACU: acupuncture; AEs: adverse effects; CBT-I: cognitive behavioral therapy for insomnia; CI: confidence interval; CID: chronic insomnia disorder; CG: control group; ES: effect size; F/u: Follow-up; ISI: Insomnia Severity Index; mos.: months; MD: mean difference; NR: not reported; NS: not significant; PCT: QoL: Quality of Life; PSQI: Pittsburgh Sleep Quality Index; RoB: Risk of Bias; RCT: randomized controlled trials; SE: standard error; SHE: sleep hygiene education; SOL: Sleep onset latency; SMD: standardized mean difference; SM: self-monitoring; SR: systematic review; ss; statistically significant; Tx: treatment; TAU: treatment as usual; TWT: total wake time; TST: total sleep time; WASO: Wake after sleep onset; WL: waitlist

Table 7. Cochrane Risk of Bias 2.0 for RCTs on Acupuncture to Treat CID

Reference	Yin et al., (2017)	Fu et al., (2017)	Bo et al., (2016)	Wang et al., (2008)	Bergdahl et al., (2016, 2017)
Randomization Process					
➢ Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	Yes	Yes	PY	Yes	NI
➢ Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization, concealed envelopes)?	Yes	Yes	NI	Yes	NI
➢ Did baseline difference between study groups suggest a problem with randomization?	No	No	No	PN	No
Overall RoB for Randomization Process	**Low**	**Low**	**Low**	**Low**	**Some concerns**
Deviation from Intended Intervention (Effect of Assignment)					
➢ Were participants aware of their assigned intervention during the trial?	No	No	Yes	No	Yes
➢ Were providers and people delivering treatment aware of assigned intervention during trial?	Yes	Yes	Yes	Yes	Yes
➢ Were there deviations from the intended intervention that arose because of the experimental context?	No	No	NI	No	PY
➢ Were these deviations from intended intervention balanced between groups?	NA	NA	NI	NA	PY
➢ Were these deviations likely to have affected the outcome?	NA	NA	NI	NA	No
➢ Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	PY	Yes	Yes	No
Overall RoB of Effect of Assignment	**Some Concerns**	**Some Concerns**	**Some Concerns**	**Some concerns**	**High**
Missing Outcome Data					
➢ Were data for this outcome available for all, or nearly all, participants randomized?	Yes	Yes	Yes	Yes	No
➢ Is there evidence that result was not biased by missing outcome data?	Yes	Yes	No	NI	No
➢ Could missingness in the outcome depend on its true value?	Yes	PN	PN	PN	Yes
➢ Do the proportions of missing outcome data differ between intervention groups?	PN	No	No	NI	PY

Reference	Yin et al., (2017)	Fu et al., (2017)	Bo et al., (2016)	Wang et al., (2008)	Bergdahl et al., (2016, 2017)
➢ Is it likely that missingness in the outcome depended on its true value?	No	No	NI	No	NI
Overall RoB of Missing Data	**Some concerns**	**Low**	**Low**	**Some concerns**	**Some concerns**
Measurement of the Outcome					
➢ Was the method of measuring the outcome inappropriate?	No	No	PN	No	No
➢ Could measurement or ascertainment of the outcome have differed between intervention groups?	No	No	NI	No	Yes
➢ Were outcome assessors aware of the intervention received by study participants?	No	No	NI	No	NI
➢ Could assessment of the outcome have been influenced by knowledge of intervention received?	No	No	Yes	No	Yes
➢ Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No	No	No	No	NI
Overall RoB of Measurement of Outcome	**Low**	**Low**	**Some concerns**	**Low**	**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?	Yes	NI	NI	Yes	NI
Overall RoB of Reported Results	**Low**	**Some concerns**	**Some concerns**	**Some concerns**	**Some concerns**
Overall Study RoB	**Some concerns**	**Some concerns**	**High**	**Some concerns**	**High**

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

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

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

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Cannabinoids

Evidence Base

Our searches of the literature identified 1 recently published review of systematic reviews (RSR) that met inclusion criteria and addressed one or more of the key questions. The review published by Contreras et al. (2018) assessed the clinical efficacy and safety of cannabinoids by examination of systematic reviews within the Epistemonikos database, stated as the "largest database of systematic reviews in health." Epistemonikos is maintained by screening multiple databases including MEDLINE, EMBASE, and the Cochrane database. This RSR extracted data from systematic reviews (SRs) and reanalyzed data from primary studies whenever available and possible. With this system, a structured summary results, entitled FRISBEE, or Friendly (i.e. accessible) Summary of Body of Evidence using Epistemonikos. This summary contains key messages, a summary of the evidence presented as an evidence matrix in Epistemonikos, meta-analysis results when possible, summary of findings using the GRADE approach and a table or notes or other considerations.

The evidence base for this review included 8 SRs which included 3 studies overall, of which 2 were RCTs with a total of 47 patients. Consistent with our approach, information from the third, observational study was not included as authors Contreras, et al (authors of the RSR) determined that the non-randomized study did not add to the certainty of the evidence nor provide additional relevant information—they did however include observational study findings regarding adverse effects. Only 1 of the 2 RCTs, however, the one by Carlini, et al. involved patients with a primary diagnosis of insomnia in the absence of other chronic diagnoses as aligned with our inclusion criteria (the second RCT, by Ware et al. was limited to patients with fibromyalgia and included 32 patients). Further, the RCT by Carlini et al, published in 1979 (well before our search date inclusion criteria), did not specify which insomnia diagnostic criteria were used for the 15 patients in the study. Thus, the small sample size as well as the lack of a clear insomnia diagnosis would both exclude the RCT by our criteria, but its conduct and results are described herein for completeness in the absence of other relevant results.

The Carlini trial compared cannabidiol at doses of 40, 80, and 160 mg versus nitrazepam 5 mg and versus placebo. All drugs were administered once a day at bedtime. The study measured the duration of sleep and the induction of sleep. The patients were followed for 6 weeks.

The control conditions included the following (the RCT had more than 2 arms):

- Key Question 1: Cannabinoids vs. Placebo
- Key Question 2: Cannabinoids vs. Nitrazepam

See **Table 3** for more information about the patients and interventions assessed in the SR addressing cannabinoids for chronic insomnia disorder.

Study Quality

Using the AMSTAR instrument, we rated the quality of the Contreras review (2018) as moderate (See **Table 4** for more information on the review ratings). The authors of this review assessed the RoB and other aspects of the certainty or quality of the evidence using the GRADE tool. Overall, the certainty of the evidence was very low or low for benefits of cannabinoids and moderate for adverse effects. The overall RoB of the trials was high due to small sample size and resulting imprecision, inconsistency of

results and discrepancies between study authors' conclusions. In addition, the lack of clear diagnostic criteria creates potential for additional heterogeneity; risk of bias is also increased due to the un-blinded outcomes (self-report) and unclear follow-up.

Key Findings

Below, we describe the key messages for the outcomes of interest as reported in the Contreras review of systematic reviews (RSR) that included 1 relevant study for the population of interest; patients with primary insomnia without other primary, co-occurring diagnoses. We also include reported adverse effects based on a single RCT in patients with fibromyalgia and a single observational study identified in the RSR.

- It is unclear whether cannabinoids have an effect on insomnia severity or sleep quality because the certainty/quality of the evidence is very low (SOE: Very low).
- Cannabinoids may have no benefits on sleep induction or duration and are probably associated with frequent adverse effects (SOE: Very low)

Discussion

Overall, there is an almost complete lack of research addressing the effectiveness or safety of cannabinoids for the treatment of primary chronic insomnia disorder. Notably, there are more studies that assess cannabinoids' efficacy for insomnia in the presence of other chronic conditions, including HIV infection and cancer. Also, there are a number of observational studies that describe insomnia-related outcomes among recreational users of cannabinoids. As these two categories of studies did not meet our inclusion criteria, their quality and results were not assessed and of limited relevance to our questions of interest. Thus, in conclusion, there is no evidence suggesting a role for cannabinoids in the treatment of patients with a primary diagnosis of chronic insomnia.

Table 1. Strength of Evidence for Cannabinoids to Treat CID

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision/ Uncertainty	Publication Bias	GRADE of Evidence for Outcome
Sleep induction	1 RCT in patients with primary insomnia without co-occurring disorders	Cannabidiol 40, 80 and 160 mg once a day at bedtime vs nitrazepam 5 mg and vs. placebo	No effect on sleep induction	Yes (-1)	Yes (-1) Substantial heterogeneity	Yes (-1), if study in patients with fibromyalgia included (was included in SR)	Yes (-1), small sample size	Unknown	Very Low
Sleep duration/ sleep quality	1 RCT (Carlini et al.)	Cannabidiol 40, 80 and 160 mg once a day at bedtime vs nitrazepam 5 mg and vs. placebo	significant increase in sleep duration in cannabidiol vs. nitrazepam	Yes (-1)	Yes (-1) Substantial heterogeneity	Yes, (-1), if study in patients with fibromyalgia included (was included in SR)	Yes (-1); small sample size	Unknown	Very low
Adverse effects	1 RCT in patients with fibromyalgia and 1 observational study	Cannabinoids vs. nitrazepam and placebo	More frequent adverse effects including dry mouth, nausea and somnolence	Yes (-1)	Yes (-1); substantial heterogeneity	Yes (-1), if study in patients with fibromyalgia included (was included in SR) and observational study	Yes (-1), small sample size	Unknown	Very low

AEs: adverse events; BL: baseline; CI: confidence interval; f/u: follow-up; NR: not reported; NS: not significant; PLA: placebo; RCT: randomized controlled trials; RoB: risk of bias; 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 Systematic Reviews on Cannabinoids to Treat CID

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
Reference: Contreras et al. 2018 **Organization/Country:** Pontificia Universidad Catolica de Chile, & Proyecto Epistemonikos, Santiago, Chile **Purpose:** To determine the clinical efficacy and safety of therapeutic use of cannabinoids for insomnia **AMSTAR Rating:** Moderate **Overall RoB of Included Studies:** High	**Databases Searched:** Epistemonikos which includes PubMed, Cochrane Database of Systematic Reviews, EMBASE, Clinicaltrials.gov and other databases, last updated August 2019 **Dates Searched:** unspecified, published January 2018 **Inclusion/Exclusion Criteria:** Not specified but implies that studies had to be RCTs—observational studies also assessed for useful information. Diagnosis of Insomnia but not required to have clear diagnostic criteria. Patients with other co-occurring disorders included but effect noted as indirect. Cannabinoids were intervention of interest. **Final Evidence Base:** 2 RCTs for SR, 1 RCT reported here in 15 patients without fibromyalgia	**Diagnosis:** Insomnia **Number of Patients:** 42 **Age:** Average age 49.5 years, 16% were men **Gender:** 16% were men	**Intervention:** The Carlini trial compared cannabidiol at doses of 40, 80, and 160 mg, administered once a day at bedtime. **Comparators:** 1 RCT, 2 arms: nitrazepam 5 mg and placebo, once a day at bedtime **Follow-up:** 6 weeks **Outcomes:** The study measured the duration of sleep and the induction of sleep as well as the occurrence of adverse effects.	No effect on **sleep reconciliation** on the use of cannabinoids vs. nitrazepam or placebo **Duration of sleep** was significantly increased in cannabinoids compared nitrazepam. Consistent results in patients with fibromyalgia **Adverse effects:** reported from patients with myalgia and observational study: dizziness, nausea, dry mouth, somnolence **Limitations:** Limited to small number of RCTs with very small sample size

AEs: adverse events; BL: baseline; CI: confidence interval; f/u: follow-up; NR: not reported; NS: not significant; PLA: placebo; RCT: randomized controlled trials; RoB: risk of bias; SD: standard deviation; wks.: weeks

Table 4. Systematic Review Risk of Bias AMSTAR Checklist Table on Cannabinoids for CID

Question	Contreras 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?	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?	No
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?	No
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?	N/a
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?	N/a
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No
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?	N/a
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No
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

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Massage Therapy

Evidence Base

Our searches of the literature identified 1 RCT that assessed the effectiveness of massage for patients with insomnia. (See **Table 3** for details on study characteristics). The strength of the evidence supporting the findings for massage in reducing insomnia was rated as very low due mainly to the identification of only one small study that demonstrated some inconsistency in results across outcomes and which did not conduct an intention-to-treat analysis.

The trial by Oliveira et al. (2012) randomized 44 post-menopausal women with insomnia to one of three intervention groups: therapeutic massage (n=15), passive movement (n=14), or control (n=15). Inclusion criteria for this study were: non-obese women between 50-65 years of age, no menstruation for the previous year, insomnia diagnosed by DSM-IV criteria and the absence of co-occurring conditions including cancer, diabetes, uncontrolled hypertension, psychiatric disorders. Current users of psychological treatment or massage and those with sleep disorders other than insomnia were also excluded.

After baseline polysomnography, women were randomized, treated and followed for 4 months. The massage and passive movement groups were seen twice a week for 1-hour sessions. Women randomized to massage received massage by one of the study authors that included therapeutic massage to the head, neck, trunk, and upper and lower limbs according to a sequence characteristic of Chinese traditional medicine. Conversation was neither restricted nor recommended. The passive movement group had their joints manipulated and the muscles flexed and extended by a trained professional but without massage or a therapeutic intent. Outcomes were assessed midway through the study and at the end of the study (4 months) using questionnaires including the ISI as well as by polysomnography.

Study Quality

We rated the RoB of the individual RCT as having a high risk of bias primarily because the authors reported that 8 of 52 patients dropped out of the study post-randomization. Although all 8 were in the two control arms of the intervention (passive movement and control groups), this suggests that the therapeutic massage group may have differed in significant ways from the other two treatment groups. Accordingly, the ISI scores were lower at baseline in the TM group as well. The rest of the results of the ISI and polysomnography outcomes are reported and analyzed for those that remained in the study. Furthermore, the authors did not state nor discuss this important limitation to their study results (see **Table 4** for the RoB ratings). Lastly, this study was limited to a small group of women of a certain age, therefore the results may not be generalizable to men or women at different age groups with insomnia.

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 therapeutic massage may improve insomnia as assessed by the Insomnia severity index compared to controls and passive movement exercises (SOE: Low)

- Evidence from this same single RCTs suggest that therapeutic massage has no effect on polysomnography sleep parameters including sleep latency, total sleep time and sleep efficiency. (SOE: Very Low)

Discussion

Overall, these very limited findings add little to the evidence base supporting the effectiveness of massage for insomnia. The high risk of bias in the single small study evaluating this question among an otherwise healthy population with insomnia limits its internal validity and its small sample size and focus on a specific age group and gender limits its external validity. As a result, the benefit of massage for reducing insomnia remains questionable and requires further study with well-designed RCTs.

Table 1. Strength of Evidence for Massage Therapy to Treat CID

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
Insomnia Severity Index	1 RCT (Oliveira, et al, 2012)	Therapeutic massage (TM) (n=15), passive movement (PM) (n=14), or control (n=15)/ f/u 4 months	TM: change from 14.2 to ~7.1; PM 16.9 to ~11.0; CTL 15.2 to `14.0; Both TM and PM ss improved compared to baseline and compared to CTL; TM group effect size ss greater than PM	Yes (-2)	No	No	No	NA	Low
Polysomnography Sleep Parameters: sleep onset latency, total sleep time, sleep efficiency	1 RCT (Oliveira, et al, 2012)	Therapeutic massage (TM) (n=15), passive movement (PM) (n=14), or control (n=15)/ f/u 4 months	TM: ~8 min decrease in sleep onset latency after treatment compared to PM 24 min; CTL ~1 min; total sleep time ~11 min increase after treatment compared to PM 20 min; CTL ~2 min; sleep efficiency 0.5 % improvement after treatment in TM group, compared to PM 5% min; CTL 4%; all results ns thus effect size=0	Yes (-2)	Yes (-1)	No	No	NA	Very Low

AEs: adverse events; BL: baseline; CI: confidence interval; CTL: control; F/u: follow-up; NA: not applicable; NR: not reported; NS: not significant; PM: passive movement; RCT: randomized controlled trials; RoB: risk of bias; SD: standard deviation; TM: therapeutic massage; 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 Massage Therapy to Treat CID

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Oliveira, 2012 **Purpose:** To evaluate the effect of therapeutic massage on insomnia and climacteric symptoms in postmenopausal (PM) women. **Setting:** Division of Gynecology, Universidade Federal de Sao Paulo, Brazil **Funding source:** AFIP (Associação Fundo de Incentivo à Psicofarmacologia), FAPESP/CEPID (Fundação de Amparo à Pesquisa do Estado de São Paulo/Centro de Pesquisa. Inova- ção e Difusão) and CNPq (Conselho Nacional de Desenvol- vimento Científico e Tecnológico).	**Number of patients:** 44 (TM 15, PM=14, CTL+15) **Inclusion criteria:** non-obese women between 50-65 years of age, no menstruation for the previous year, insomnia diagnosed by DSM-IV criteria and the absence of co-occurring conditions including cancer, diabetes, uncontrolled hypertension, psychiatric disorders. **Exclusion criteria:** Current users of psychological treatment or massage and those with sleep disorders other than insomnia were also excluded.	**Intervention:** Provided 1 hr., 2x per week, TM received therapeutic massage to the head, neck, trunk, and upper and lower limbs according to a sequence characteristic of Chinese traditional medicine. PM group had joints manipulated and the muscles flexed and extended by a trained professional but without massage or a therapeutic intent. **Outcomes:** Assessed midway through the study and at the end of the study (4 months) using questionnaires including the ISI as well as by polysomnography. **F/u:** Post-tx at 4 months	**ISI:** TM: change from 14.2 to ~7.1; PM 16.9 to ~11.0; CTL 15.2 to ~14.0; Both TM and PM ss improved compared to baseline and compared to CTL; TM group effect size ss greater than PM and CTL **Polysomnography:** no statistically significant results from baseline to post treatment, no ss differences between groups. Drop-out: 8 dropped out of CTL and PM groups, no ITT analysis	Results suggest that TM statistically significantly improved ISI compared to baseline and PM and control groups, but no ss effects on sleep parameters. Authors conclude that "massage could be considered an option for treatment in postmenopause, with clearn gains …in sleep quality." **Limitations:** Small sample size, inconsistent results among outcomes assessed, no ITT analysis with differential drop-out rates between treatment groups **Study RoB:** High **Author conflict:** Authors report no conflicts of interest

AEs: adverse events; BL: baseline; CI: confidence interval; CTL: control group; F/u: follow-up; ISI: insomnia severity index; ITT: intention to treat; MD: mean difference; MT: massage therapy; NR: not reported; NS: not significant; PM: postmenopausal; RCT: randomized controlled trials; RoB: risk of bias; SD: standard deviation; TM: therapeutic massage; tx: treatment

Table 4. Cochrane Risk of Bias 2.0 Tool for RCTs on Massage Therapy to Treat CID

Reference	Oliveira et al., (2012)
➢ 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)?	NI
➢ Did baseline difference between study groups suggest a problem with randomization?	No
Overall RoB for Randomization Process	**Some concerns**
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?	PY
➢ 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?	No
Overall RoB of Effect of Assignment	**High**
Missing Outcome Data	
➢ Were data for this outcome available for all, or nearly all, participants randomized?	NI
➢ Is there evidence that result was not biased by missing outcome data?	Ni
➢ Could missingness in the outcome depend on its true value?	NI
➢ Do the proportions of missing outcome data differ between intervention groups?	NI
➢ 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?	No
➢ Could measurement or ascertainment of the outcome have differed between intervention groups?	No
➢ Were outcome assessors aware of the intervention received by study participants?	NI
➢ Could assessment of the outcome have been influenced by knowledge of intervention received?	PN
➢ 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	Oliveira et al., (2012)
➢ 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 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

Oliveira, D. S., Hachul, H., Goto, V., Tufik, S., & Bittencourt, L. R. (2012). Effect of therapeutic massage on insomnia and climacteric symptoms in postmenopausal women. *Climacteric: The Journal of the International Menopause Society*, *15*(1), 21–29. https://doi.org/10.3109/13697137.2011.587557

Relaxation Therapy (or techniques)

Evidence Base

Our searches of the literature identified 1 RCT that met inclusion criteria and assessed the efficacy of relaxation therapy or training (RT) for postmenopausal women with insomnia. This study, by Duman et al. (2018) compared a program of sleep hygiene education and progressive relaxation exercises to routine nursing care for health problems that did not address insomnia or the need to relax.

This RCT took place in the community of family health centers in the providence of Diyarbakir, Turkey. **Inclusion criteria for the study were:** women defined as postmenopausal, diagnosed with insomnia according to the Women's Health Initiative Insomnia Scale (WHIIRS), able to communicate in Turkish, mentally and physically healthy as well as being willing to participate in the RCT. Women excluded were those who were unable to read and understand Turkish, were substance abusers or alcohol users, current smokers, users of hormonal therapy, had another other sleep disorder, psychiatric disease or dementia, or had a serious medical illness such as cancer. The intention was to address insomnia among a large group of postmenopausal women who were otherwise healthy. Baseline characteristics of the study population described participants of a mean age of 53-54 years, the vast majority of whom were unemployed, more than half with middle incomes but with about half never having finished primary school. Mean BMI indicated they were overweight but not obese. Baseline characteristics did not differ between intervention groups.

The RT intervention was delivered through 2 home visits that were primarily instructive and use of written materials with an audio CD that was intended to be listened to 3 times a day for 8 weeks, for a total of 15 minutes initially that increased to 40 minutes per day at the end of 8 weeks. Instructors made additional home visits for those who could not attend initially. The CD was 70 minutes long—10 minutes instructions, 30 minutes of relaxation instructions with sound of a river, and 30 minutes of relaxing music with no instructions. The women were asked to do the relaxation exercises every day for 8 weeks 3 times a day for progressively longer times. The primary outcome was the Women's Health Initiative Insomnia Scale (WHIIRS). Adverse events were also monitored. 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 as moderate (some concerns) due to concerns about the lack of blinding of patients and treating clinicians. The RoB of the RCT by Duman was rated as High due to lack of information about the randomization process and lack of blinding of the patients, clinicians and outcome assessors. See **Table 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 RCT suggests that relaxation training was associated with improved symptoms of insomnia among postmenopausal women with insomnia. Authors also affirm that improvements in insomnia were also observed 3 months after program completion but do not provide details at this follow-up time. (SOE: Low)

- Evidence from 1 RCT suggests the absence of adverse effects but no details were given for either the intervention or control group (SOE: Very Low)

Discussion

The strength of the evidence was rated as low due to the limited evidence base (1 RCT with 161 patients), an unblended intervention as well as the questionable generalizability of this RCT that took place in Turkey among post-menopausal women with a relatively low educational level. However, results were both statistically and clinically meaningful and sustained, as stated by authors but without details at 3 months. Similarly, authors assert the absence of adverse effects which is likely considering the nature of the intervention. A strength of this study is its relatively large sample size as well design of an intervention that can be implemented at home at relatively low cost and intensity.

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

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
Insomnia according to the Women's Health Initiative Insomnia Scale (WHIIRS)	1 RCT--Duman et al, 2018	RT (81) vs control group (CG) (80)—8 weeks, 3 months	WHIIRS for treatment group, 14.03 ± 3.40 decreased to 7.09 (3.40) vs. control group: 14.35 ± 3.20 to 13.66 (4.30), p< 0.001for between group differences	Yes (-1)	No	Yes (-1), unclear how generalizable this group of women for US patients with insomnia	No; single study but relatively large with ss difference between groups	No	Low
Adverse effects	1 RCT—Duman et al, 2018	RT (81) vs control group (CG) (80)—8 weeks, 3 months	No adverse physical or psychological effects	Yes (-1)	No	Yes (-1), unclear how generalizable this group of women for US patients with insomnia	Yes (-1); single study but relatively large with ss difference between groups	No	Very Low

AEs: adverse events; BL: baseline; CG: control group; CI: confidence interval; NR: not reported; NS: not significant; RCT: randomized controlled trials; RoB: risk of bias; RT: relaxation training; SD: standard deviation; SMD: standardized mean difference; TAU: treatment as usual; WHIIRS: Women's Health Initiative Insomnia Scale; 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 CID

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Duman et al, 2018 **Purpose:** To determine the effect of progressive relaxation exercises and sleep hygiene training for postmenopausal women with insomnia. **Setting:** family health centers in the providence of Diyarbakir, Turkey. **Funding source:** The authors received no financial support for the article. The article is part of the first author's doctoral thesis.	**Number of patients:** 161 patients **Inclusion criteria:** women defined as postmenopausal, diagnosed with insomnia according to the Women's Health Initiative Insomnia Scale (WHIIRS), able to communicate, mentally and physically healthy, willing to participate. **Exclusion criteria:** unable to read and understand Turkish, substance abuser or alcohol user, current smoker, use of hormonal therapy, other sleep disorder, psychiatric disease or dementia, serious medical illness such as cancer. **Pt. baseline characteristics:** Age: mean of 53-54 years, 89-92.5% unemployed, education level: about half did not finish primary school, 64-65% middle income Years since menopause: ~4, Mean BMI: 27.88-28.1 No ss difference between intervention groups.	**Intervention:** **Sleep hygiene education and relaxation training (n=81):** Intervention group received sleep hygiene presentation lasting 30 minutes and booklet and CD in a home visit, followed by 45 min training on progressive relaxation exercises. The CD was 70 minutes long—10 minutes instructions, 30 minutes of relaxation instructions with sound of a river, and 30 minutes of relaxing music with no instructions. The women were asked to do the relaxation exercises every day for 8 weeks; instructors made additional home visits for those who could not attend initially. **Control group (n=80):** received regular nursing care in the clinic during the study including examination, treatment, referral, etc. as needed for routine health problems without sleep or relaxation-related interventions. **Outcomes:** Women's Health Initiative Insomnia Scale (WHIIRS); adverse effects. **F/u:** 8 weeks (post-treatment)	**Post-treatment:** **Women's Health Initiative Insomnia Scale (WHIIRS):** in treatment group, 14.03 ± 3.40 decreased to 7.09 (3.40) vs. control group: 14.35 ± 3.20 to 13.66 (4.30), p< 0.001for between group differences **Adverse effects:** No adverse physical or psychological effects.	**Conclusions:** Sleep hygiene education and PMR can reduce insomnia symptoms in otherwise healthy postmenopausal women. All improvements were present in experimental group 3 months after programme completion (results not shown). High sample size is a strength of this study. **Limitations:** Menopausal determination was not made by clinical judgment. **Study ROB:** Some concerns **Author conflict:** Authors report no conflicts.

AEs: adverse events; BL: baseline; BMI: body mass index; CI: confidence interval; F/u: follow-up; NR: not reported; NS: not significant; PMR: progressive muscle relaxation; RCT: randomized controlled trials; RoB: risk of bias; SD: standard deviation; SMD: standardized mean difference; TAU: treatment as usual; WHIIRS: Women's Health Initiative Insomnia Scale; wks.: weeks

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

Reference	Duman et al., 2018
➢ 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)?	Yes
➢ Did baseline difference between study groups suggest a problem with randomization?	No
Overall RoB for Randomization Process	**Low**
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?	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	**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?	NI
➢ Could missingness in the outcome depend on its true value?	Yes
➢ 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?	No
Overall RoB of Missing Data	**Some concerns**
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?	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?	Yes
➢ Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No
Overall RoB of Measurement of Outcome	**Some Concerns**
Selection of Reported Results	

Reference	Duman et al., 2018
➢ Was the trial analyzed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?	Yes
Overall RoB of Reported Results	**Low**
Overall Study RoB	**Some concerns**

*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

Duman, M., & Taşhan, S. T. (2018). The effect of sleep hygiene education and relaxation exercises on insomnia among postmenopausal women: a randomized clinical trial. *International Journal of Nursing Practice*, *24*(4), 1–8. https://doi.org/10.1111/ijn.12650

Transcranial Magnetic Stimulation (TMS)

Evidence Base

Our searches of the literature identified 1 RCT that assessed the efficacy of repetitive (r) TMS used for treating adults with Chronic Insomnia Disorder (CID). The strength of the evidence supporting the findings for rTMS for symptoms of Chronic Insomnia Disorder was rated as low to very low due to the identification of only 1 RCT assessing the effectiveness of rTMS and the methodological limitations of the included study.

The clinical trial published by Jiang et al. (2013) randomized 120 patients to one of 3 groups (40 in each group): rTMS, medication or psychotherapy. Study participants were required to meet criteria for chronic primary insomnia according to the Diagnosis and Statistical Manual (DSM-IV) of Mental Disorders. In addition, included patients had sleepiness scale scores >6 points, night polysomnography results documenting sleep induction times of >30 minutes, total sleep time of <6 hours and sleep efficiency of <80%. In addition, patients were required to be right-handed. Exclusion criteria were positive individual or family history of seizures, use of psychotropic drugs within a month of the study, and diseases that affect cortisol secretion.

The study groups were comparable in terms of age (average age 47-48 years), gender (~42-44% male), duration of insomnia (~10-12 months) and insomnia severity (Pittsburgh sleepiness score ~13-15). Patients in the rTMS group received stimulation at the right dorsolateral prefrontal cortex (DLPFC) with a 1 Hz frequency, intensity of 80% of motion threshold, stimulation number of 30 pulses per string, 2 sec string interval, total of 60 strings, total stimulation pulses of 1800 with a total stimulation time of 30 minutes, once a day for 2 weeks. Patients in the medication group received 2 mg estazolam every night for 2 weeks. The psychotherapy group received 2 weeks of cognitive behavioral therapy that included sleep health education, relaxation training, stimulus control therapy, sleep restriction therapy, and cognitive therapy.

The primary outcomes (blinded) assessed in this trial were: the Pittsburgh Sleep Quality Index (PSQI), sleep monitoring (sleep parameters and sleep structure) using polysomnography, as well as laboratory measurements (adrenal and thyroid hormone levels) of the activation of the hypothalamic-pituitary-thyroid (HPT) axis and the hypothalamic-pituitary-adrenal (HPA) axes indicating excessive arousal associated with poor sleep. Relapse and recurrence rates at 3 months after treatment were determined by telephone calls (presumably unblinded).

Study Quality

Using the Cochrane Risk of Bias 2.0 Tool, we rated the quality of the RCT as having a high risk of bias (poor quality) due, primarily, to the possibility of missing outcome data (see Table 3 for the quality ratings). In this RCT, all results (including baseline characteristics) and outcomes were reported as mean (average) values (mean ± SD) without an indication of the sample size included in each outcome. Indeed, the baseline table describing study sample gender suggests that 45, rather than 40, patients were included in each treatment group whereas the rest of the study text and tables reports 40 patients in each treatment group, and 120 patients overall. As a result, it is difficult to trust the results reported overall without an understanding of the correct number of patients randomized. In addition, for the sleep parameters of sleep efficiency, latency and total sleep time, the medication (2 mg of estazolam every night for 2 weeks) group

performed better than the rTMS group and the psychotherapy group demonstrating some inconsistency across outcomes and results. The published rTMS study by Jiang et al. has some inconsistent and imprecise results. Larger well-designed RCTs are needed.

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.

Pittsburgh Sleep Quality Index (PSQI): **rTMS vs. medication vs. psychotherapy**

- Evidence from 1 RCT suggests rTMS statistically significantly reduces insomnia symptoms compared to medication and psychotherapy. (SOE: Low)

Relapse rate (PSQI): **rTMS vs. medication vs. psychotherapy**

- Evidence from 1 RCT suggests rTMS statistically significantly reduces insomnia relapse compared to medication and CBT. (SOE: Low)

Recurrence Rate within 3 months: **rTMS vs. medication vs. psychotherapy**

- Evidence from 1 RCT suggests rTMS statistically significantly reduces insomnia recurrence compared to medication and CBT. (SOE: Low)

Sleep parameters (sleep efficiency, latency, total sleep time): **rTMS vs. medication vs. psychotherapy**

- Evidence from 1 RCT suggests rTMS statistically significantly improves sleep efficiency compared to CBT but less well than medication. (SOE: Very Low)
- Evidence from 1 RCT suggests rTMS statistically significantly reduces sleep latency compared to CBT but less well than medication. (SOE: Very Low)
- Evidence from 1 RCT suggests rTMS statistically significantly improves total sleep time compared to CBT but less well than medication. (SOE: Very Low)

Discussion

Given that the SR found only a single RCT and the methodological limitations of that single RCT, the true effect of rTMS for patients with insomnia remains unknown. No studies were found comparing rTMS to sham for treatment of CID. Notably, there is also a complete absence of information regarding the safety or presence of adverse effects associated with rTMS.

Table 1. Strength of Evidence for Transcranial Magnetic Stimulation (TMS) to Treat CID

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
rTMS vs medication vs. psychotherapy									
Pittsburgh Sleep Quality Index (PSQI): difference before to after treatment	1 RCT (Jiang, 2013)	rTMS (40)/ estazolam 2 mg (40)/ psychotherapy (40)/ 2 weeks	Change in PSQI: rTMS group went from 15.6 (±4.61) to 8.02 (±2.53), med group 14.2 (±6.73) to 0.37 (±3.09), psych group 13.6 (± 5.56) to 11.45 (±6.14), all 3 groups ss difference ($p<0.05$) after treatment, rTMS group ss improvement compared to other groups ($p<0.05$)	Yes (-1); Most of the judgement of high RoB related to unknown numbers of patients in outcome assessments	No	No	Yes (-1); wide confidence intervals within and across treatment groups before and after treatment	No	Low
Relapse Rate (%)	1 RCT (Jiang, 2013)	rTMS (40)/ estazolam 2 mg (40)/ psychotherapy (40)/ 3 months	rTMS: 23.75 ±7.48; med group 70.41±12.35; psych group: 40.39±16.89 —rTMS group ss improved	Yes (-1)	No	No	Yes (-1); wide confidence intervals within and across treatment groups	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
			compared to other groups (p<0.05)						
Recurrence rate within 3 months (%)	1 RCT (Jiang, 2013)	rTMS (40)/ estazolam 2 mg (40)/ psychotherapy (40)/ 3 months	rTMS: 36.28 ±11.57; med group 96.34±29.01; psych group: 56.27±15.57 —rTMS group ss improved compared to other groups (p<0.05)	Yes (-1)	No	No	Yes (-1); wide confidence intervals within and across treatment groups	No	Low
Polysomnography outcomes: Sleep efficiency (%)	1 RCT (Jiang, 2013)	rTMS (40)/ estazolam 2 mg (40)/ psychotherapy (40)/ 2 weeks	rTMS: rTMS group went from 66.34 (±8.56) to 83.23 (±26.23), med group 67.35 (±9.01) to 86.34 (±21.02), psych group 65.12 (± 11.23) to 72.15 (±30.76), all 3 groups ss difference (p<0.05) after treatment, med group ss	Yes (-1)	Yes (-1); medication group improved more than rTMS group	No	Yes (-1); wide confidence intervals within and across treatment groups	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
			improvement compared to other groups ($p<0.05$), rTMS more improved than psych group ($p<0.05$)						
Polysomnography outcomes: Sleep latency (min)	1 RCT (Jiang, 2013)	rTMS (40)/ estazolam 2 mg (40)/ psychotherapy (40)/ 2 weeks	rTMS group went from 44.03 (±9.25) to 26.15 (±10.28), med group 39.25 (±10.31) to 15.67(±5.05), psych group 43.15 (± 11.12) to 30.02 (±12.32), all 3 groups ss difference ($p<0.05$) after treatment, med group ss improvement compared to other groups ($p<0.05$), rTMS more improved than psych group ($p<0.05$)	Yes (-1)	Yes (-1); medication group improved more than rTMS group	No	Yes (-1), wide confidence intervals within and across treatment groups	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
Polysomnography outcomes: Total sleep time (min)	1 RCT (Jiang, 2013)	rTMS (40)/ estazolam 2 mg (40)/ psychotherapy (40)/ 2 weeks	rTMS group went from 330.24 (±81.01) to 408.05 (±68.12), med group 331.56 (±70.12) to 426.14 (±73.25), psych group 328.73 (± 90.56) to 387.56 (±87.47), all 3 groups ss difference ($p<0.05$) after treatment, med group ss improvement compared to other groups ($p<0.05$), rTMS more improved than psych group ($p<0.05$)	Yes (-1)	Yes (-1); medication group improved more than rTMS group	No	Yes (-1), wide confidence intervals within and across treatment groups	No	Very low

AE: adverse events; CI: confidence interval; DLPFC: dorsolateral prefrontal cortex; F/u: follow-up; I^2: % of heterogeneity between studies; med group: medication treatment group; mos.: months; NA: not applicable; NR: not reported; NS: not significant; PSQI: Pittsburgh Sleep Quality Index; psych group: psychotherapy treatment group; RCT: randomized controlled trials; RoB: risk of bias; rTMS: repetitive transcranial magnetic stimulation treatment group; SD: standard deviation; SMD: standardized mean difference; ss: statistically significant(ly)

Table 3. Evidence Table for RCTs on TMS to Treat CID

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Jiang et al, 2013 **Purpose:** To determine the effect of rTMS for adults with chronic primary insomnia. **Setting:** Outpatient and inpatient departments of Daping Hospital in China **Funding source:** NR	**Number of patients:** 120 patients total; rTMS (n=40); medication (n=40); psychotherapy (n=40) **Inclusion criteria:** Adults with chronic primary insomnia (according to DSM-IV); sleepiness scale score of >6 points; night polysomnography monitoring results to show sleep introduction time of >30 min.; total sleep time of <6 hrs.; sleep efficiency of <80%; patients were right-handed **Exclusion criteria:** Positive individual or family history of seizures; use of psychotropic drugs for 1 month prior to study; diseases affecting cortisol secretion **Pt. baseline characteristics (rTMS; medication; psychotherapy):** Age (mean yrs. [SD]): 48.31(8.45); 48.11(7.51); 47.02(6.33) Gender (m/f): 21/24; 19/26; 20/25 Insomnia severity (Pittsburgh sleepiness score): 15.06(4.61); 14.25(6.73); 13.61(5.56)	**Intervention:** **rTMS (n=40):** Intervention group received stimulations at the right dorsolateral prefrontal cortex (DLPFC) at a frequency of 1 Hz and intensity of 80% of motion threshold. Stimulation consisted of 30 pulses/string with string intervals were 2 seconds with a total of 60 strings (1,800 total pulses in 30 min.). Treatment was applied once per day for 2 wks. **Control groups:** **Medication (n=40):** Received 2mg estazolam every night for 2 wks. **Psychotherapy (n=40):** Received 2 wks. of CBT including sleep health education, relaxation training, stimulus control therapy, sleep restriction therapy, and CT. **Outcomes:** Quality of sleep, sleep induction time, sleep time, sleep disorder, sleep efficiency, sleep medication, and daytime function measured by PSQI and polysomnography; relapse; recurrence **F/u:** 3 months (post-treatment)	**Post-treatment (2 wks.):** Change in PSQI: rTMS group went from 15.6 (±4.61) to 8.02 (±2.53), med group 14.2 (±6.73) to 0.37 (±3.09), psych group 13.6 (± 5.56) to 11.45 (±6.14), all 3 groups ss difference ($p<0.05$) after treatment, rTMS group ss improvement compared to other groups ($p<0.05$) Sleep efficiency: rTMS: rTMS group went from 66.34 (±8.56) to 83.23 (±26.23), med group 67.35 (±9.01) to 86.34 (±21.02), psych group 65.12 (± 11.23) to 72.15 (±30.76), all 3 groups ss difference ($p<0.05$) after treatment, med group ss improvement compared to other groups ($p<0.05$), rTMS more improved than psych group ($p<0.05$) Sleep latency: rTMS group went from 44.03 (±9.25) to 26.15 (±10.28), med group 39.25 (±10.31) to 15.67(±5.05), psych group 43.15 (± 11.12) to 30.02 (±12.32), all 3 groups ss difference ($p<0.05$) after treatment, med group ss improvement compared to other groups ($p<0.05$), rTMS more	**Conclusions:** The findings suggest that rTMS statistically significantly reduces insomnia symptoms, relapse rates, and recurrence rates compared to medication and psychotherapy. In addition, rTMS statistically significantly improved sleep efficiency, sleep latency, and total sleep time compared to psychotherapy, but not as well as medication. **Limitations:** Possibility of missing outcome data **Study ROB:** High **Author conflict:** NR

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
			improved than psych group (p<0.05) Total sleep time: rTMS group went from 330.24 (±81.01) to 408.05 (±68.12), med group 331.56 (±70.12) to 426.14 (±73.25), psych group 328.73 (± 90.56) to 387.56 (±87.47), all 3 groups ss difference (p<0.05) after treatment, med group ss improvement compared to other groups (p<0.05), rTMS more improved than psych group (p<0.05) **3 months f/u:** Relapse rate: rTMS: 23.75 ±7.48; med group 70.41±12.35; psych group: 40.39±16.89—rTMS group ss improved compared to other groups (p<0.05) Recurrence rate: rTMS: 36.28 ±11.57; med group 96.34±29.01; psych group: 56.27±15.57—rTMS group ss improved compared to other groups (p<0.05) **Adverse effects:** NR	

AE: adverse events; CI: confidence interval; DLPFC: dorsolateral prefrontal cortex; F/u: follow-up; I^2: % of heterogeneity between studies; med group: medication treatment group; mos.: months; NA: not applicable; NR: not reported; NS: not significant; PSQI: Pittsburgh Sleep Quality Index; psych group: psychotherapy treatment group; RCT: randomized controlled trials; RoB: risk of bias; rTMS: repetitive transcranial magnetic stimulation treatment group; SD: standard deviation; SMD: standardized mean difference; ss: statistically significant(ly)

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 4. Cochrane Risk of Bias 2.0 Tool for RCT on TMS to Treat CID

Reference	Jiang et al., (2013)
➢ 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)?	NI
➢ Did baseline difference between study groups suggest a problem with randomization?	No
Overall RoB for Randomization Process	**Some Concerns**
➢ Were participants aware of their assigned intervention during the trial?	Yes
➢ 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?	NI
➢ Were these deviations from intended intervention balanced between groups?	N/a
➢ Were these deviations likely to have affected the outcome?	N/a
➢ Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY
Overall RoB of Effect of Assignment	**Some Concerns**
➢ Were data for this outcome available for all, or nearly all, participants randomized?	NI
➢ Is there evidence that result was not biased by missing outcome data?	No
➢ Could missingness in the outcome depend on its true value?	Yes
➢ Do the proportions of missing outcome data differ between intervention groups?	NI
➢ Is it likely that missingness in the outcome depended on its true value?	Yes
Overall RoB of Missing Data	**High**
➢ Was the method of measuring the outcome inappropriate?	No
➢ Could measurement or ascertainment of the outcome have differed between intervention groups?	No
➢ Were outcome assessors aware of the intervention received by study participants?	No
➢ 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**
➢ Was the trial analyzed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?	Yes
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

Jiang, C. G., Zhang, T., Yue, F. G., Yi, M. L., & Gao, D. (2013). Efficacy of repetitive transcranial magnetic stimulation in the treatment of patients with chronic primary insomnia. *Cell Biochemistry and Biophysics*, *67*(1), 169–173. https://doi.org/10.1007/s12013-013-9529-4

Tai Chi

Evidence Base

Our searches of the literature identified two SRs (Raman et al, 2013 and Wang et al, 2019), from which 2 RCTs (Irwin et al, 2014; and Hosseini et al, 2011) were identified that met inclusion criteria and addressed one or more of the key questions. Other RCTs included in the SRs either didn't focus on adults with an insomnia diagnosis or included adults with other primary disorders in addition to insomnia, or both. Indeed, even of the two RCTs that were identified, Hosseini focused on adults with moderate sleep complaints consistent with, and not excluding, an insomnia diagnosis but without a definitive diagnosis by established criteria. Both RCTs, by Hosseini et al and Irwin et al, focused exclusively on older adults as sleep problems are common in the elderly.

Study Quality

The strength of the evidence for the reported outcomes ranged from moderate to very low due to methodological limitations of the included studies, including lack of blinding, between-study heterogeneity of comparison groups as well as other differences.

Further, the well-designed Irwin study (moderate strength of evidence) showed consistently that CBT was more effective than Tai Chi and more effective than sleep education for sleep outcomes; for most outcomes, tai chi did not differ compared to the control arm which was sleep education. In contrast, the Hosseini study lacked detail leading to unclear risk of bias but concluded that tai chi was more effective than usual care without exercise for insomnia.

In the Hosseini study, 62 sedentary patients were randomized to tai chi vs. usual care without exercise. The study population consisted of elderly adults who lived in a nursing home in Iran, were older than 60 years, and had PSQI scores of >5, consistent with moderate sleep complaints or insomnia. The average age of the participants was 68-69 years, with about half female and male participants. About half of the study population were deemed "illiterate" without a clear description of how illiterate was defined or determined. The tai chi sessions took place three times a week for 12 weeks—the exercise was initiated for 5 minutes per session and gradually increased over the weeks of the intervention to about 20-25 minutes per session by the midpoint of the intervention. Change in PSQI was reported post intervention with the tai chi group demonstrating a reduction in PSQI from 10.3 to 8.96, a difference that was statistically significantly different than controls. A significant limitation of this study was the lack of ITT analysis resulting in an overall very low quality of evidence.

In the Irwin study, authors compared CBT to Tai Chi to a sleep education intervention. A total of 123 patients were randomized, 50 to CBT, 48 to tai chi and 25 to the sleep education intervention. This study also included elderly patients with a mean age 64-66, 18-39% female, almost all White and with a high education level (mean 15.3-15.8 years), all of whom had an insomnia diagnosis according to DSM-IV criteria. In this study the active interventions were delivered by a single trained therapist (for each intervention) in 2-hour group sessions weekly for 4 months. Outcomes post treatment and measured at 7 and 16 months were assessed. Outcomes included insomnia remission, sleep parameters, depressive symptoms as well as the PSQI. CBT was shown to be consistently superior to Tai Chi, with most outcomes showing no statistical difference between Tai Chi and the education control.

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 CBT is more effective than Tai chi for the remission and improvement of insomnia in older adults. (SOE: Moderate to Low)
- Inconsistent evidence from 2 RCTs suggests the Tai Chi may be better than (or equal to) sleep education or other passive control/usual care for insomnia complaints among elderly adults. (SOE: Low to Very Low)

Discussion

Despite a number of studies in the literature evaluating the impact of tai chi on sleep quality and quantity, very few studies focus on adults with primary insomnia in the absence of other conditions that also impact sleep. The two studies that were identified were small and of moderate to very low quality and focused specifically on the geriatric/elderly population. Tai Chi, at best, seems to have an impact less than CBT but perhaps greater than a passive control group. For example, adults with insomnia who received CBT had remission of their insomnia at 4 months (post-treatment) at a rate of 54.2% compared to 29.7% in the group who received tai chi vs. 20.8% in those who received sleep education. There was no statistically significant difference between tai chi and sleep education. Although there was a trend indicating tai chi is better than passive controls in both studies, the study quality was overall very low so conclusions cannot be made. Also, in the study where tai chi may have shown a benefit, the control group was a sedentary population so the benefit could be due to activity in general and not specific to tai chi. As expected by the low risk interventions studied, no adverse effects were reported. Although blinding of participants is difficult in assessing the impact of tai chi, other methodological limitations could be improved upon in future research. In addition, tai chi for younger adults or adults in general and its impact on insomnia remains unknown.

Table 1. Strength of Evidence for Tai Chi to Treat Chronic Insomnia 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
Insomnia remission	1 RCT: Irwin et al, 2014	123 (n=50 to CBT, 48 to tai chi, n=25 to sleep seminar education (SS)/ f/u 4 months (post-tx), 7 months, 16 months	54.2% in CBT group vs. 29.7 in TCC vs. 20.8% in SS at 4 months. ns difference between TCC and SS.	Yes (-1)	No	No	No	No	Moderate
PSQI/ Athens insomnia scale	2 RCTs: (Hosseini et al, 2011 and Irwin et al, 2014)	Tai Chi vs. usual care, N total=62 (n=31 to tai chi, 31= usual care without exercise	Tai Chi: PSQI decreased from 10.33+/- 2.236 to 8.963 +/- 2.695 (ss, p=0.001) while in control group, ns change from 10.413 +/- 2.43 to 10.069 +/- 2.3. Between group	Yes (-2)	Yes (-1)	No	No	No	Very Low

			difference = 0.031						
		123 (n=50 to CBT, 48 to tai chi, n=25 to sleep seminar education (SS)/ f/u 4 months (post-tx), 7 months, 16 months	Insomnia improved more in CBT group than TCC and SS, TCC improved more than SS at 4 and 7 months but not 16 months. No relationship between TCC practice time and symptoms.	Yes (-1)	No	No	No	No	Low
Sleep parameters, depression symptoms	1 RCT (Irwin et al, 2014)	123 (n=50 to CBT, 48 to tai chi, n=25 to sleep seminar education (SS)/ f/u 4 months (post-tx), 7 months, 16 months	Sleep parameters : CBT improved in SOL, SE and WASO but not TST compared to other groups. No other between group differences	Yes (-1)	No	No	No	No	Moderate

			Fatigue and depression: For fatigue and depressive symptoms, CBT improved more than TCC and SS and TCC improved more than SS.						

CBT: Cognitive Behavioral Therapy; CI: confidence interval; CT: control group; ES: effective size; mos.: months; NR: not reported; NS: not significant; PSQI: Pittsburgh Sleep Quality Index; PSG: polysomnography; RCT: randomized controlled trials; SE: Sleep Efficiency; SMD: standardized mean difference; SoL: sleep onset latency; SS: sleep seminar; TAU: treatment as usual; TC: Tai Chi; TCC: Tai Chi Chih; TST: total sleep time; Tx: treatment; WASO: Wake After Sleep Onset; WL: waitlist

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 Tai Chi to Treat Chronic Insomnia Disorder

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Hosseini et al, 2011 **Purpose:** to evaluate the effects of Tai Chi Exercise on sleep quality of elderly residents in a elderly care home **Setting:** University of Isfahan, Iran. **Funding source:** NR, derived from a master's thesis	**Number of patients:** 62 (n=31 to tai chi, 31= usual care without exercise **Inclusion criteria:** Elderly in nursing home >60 years of age, not regular exercisers, with PSQI >5 **Exclusion criteria:** Lack of consent or medical approval to participate after blood test and EKG. **Pt. baseline characteristics (all pts):** Age (mean yrs.): 68.74-69.42 yrs. Gender (% male): 51.6-45.1% BMI: 24.37 to 22.96 Bach 2 Depression Questionnaire score: 16.35 to 18.09 Illiterate: 41.9% to 51.6%	**Intervention:** Tai chi 3X per week for 12 weeks, duration of exercise was 5 minutes at first session which gradually increased to 20-25 minutes by midpoint of intervention. **Control:** usual daily activities **Outcomes:** PSQI **F/u:** Post-tx at 8 weeks	**PSQI:** Tai Chi Intervention Group: PSQI decreased from 10.33+/-2.236 to 8.963 +/-2.695 (ss, p=0.001) while in control group, ns change from 10.413 +/-2.43 to 10.069 +/-2.3. Between group difference = 0.031 **Dropout** Tai Chi: n=3; CG: n=2; statistical significance not reported	Results suggest that tai chi can have significant benefit on sleep quality in older adults **Limitations:** No ITT analysis **Study RoB:** Some concerns **Authors conflict:** Reported no conflicts
Reference: Irwin et al, 2014 **Purpose:** To investigate the comparative efficacy of Cognitive Behavioral Therapy (CBT), Tai Chi Chih (TCC) and sleep seminar education control (SS) on insomnia diagnosis and secondary outcomes of sleep quality, fatigue, depressive symptoms, and inflammation in older adults with insomnia. **Setting:** University of California, Los Angeles, CA, US. **Funding source:** NIH (NIA)	**Number of patients:** 123 (n=50 to CBT, 48 to tai chi, n=25 to health education **Inclusion criteria:** community-dwelling adults >55 years who met criteria for primary insomnia according to DSM-IV-TR and general insomnia in International Classification of Sleep Disorders, 2nd edition, in self-reported good health, >= 59 years of age, **Exclusion criteria:** DSM-IV exclusion criteria for medical and psychiatric disorders as well as other sleep disorders, shift work or irregular sleep pattern, regular use of hypnotic medications or alcohol for sleep, current depression, cognitive	**Intervention: CBT** modified to incorporate mood management and behavioral management of insomnia. **Intervention: TCC:** emphasized control over physical function and arousal-related responsiveness through repetitious slow movements. **Control: Sleep seminar:** Education about aging and sleep problems. All interventions delivered by one experienced therapist, though not in sleep medicine, for 2-hour group sessions weekly for 4 months.	**Remission of insomnia: F/u: 7 and 16 months.** 54.2% in CBT group vs. 29.7 in TCC vs. 20.8% in SS at 4 months. CBT > TCC and SS and ns difference between TCC and SS. **PSQI:** Insomnia improved more in CBT group than TCC and SSS, TCC improved more than SS at 4 and 7 months but not 16 months. No relationship between	Results suggest CBT is better for treating and sustaining late-life insomnia. TCC has role for symptom management but but findings do not support its use for clinically significant insomnia. **Limitations:** Not blinded to intervention, therapists' skills may have differed between treatment groups, mood enhancement aspect of CBT disadvantaged TCC, generalizability may be limited due to lack of diversity in the sample, no effects on PSG seen but aligned with other studies.

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	impairment, abnormal screening labs, tobacco smoking, BMI>35, debilitating condition, unavailability during the study period. **Pt. baseline characteristics (all pts, range across treatment groups):** Age (mean yrs.): 64.4-66.4 yrs. Gender (% female): 18-39% Ethnicity—3% Hispanic Race: 4-7% Non-white BMI: 25.4 to 26.4 Depression history: 8-12% Education (years): 15.3-15.8	**F/u: 7 and 16 months.** **Outcomes:** Primary outcome was remission of insomnia diagnosis by DSM-IV-R, secondary outcomes were PSQI, Athens insomnia scale, sleep diary for sleep parameters, and polysomnography. Additional outcomes included daytime fatigue, and depressive symptoms.	TCC practice time and symptoms. Sleep parameters: CBT improved in SOL, SE and WASO but not TST compared to other groups. No other between group differences. Fatigue and depression: For fatigue and depressive symptoms, CBT improved more than TCC and SS and TCC improved more than SS. **Dropout:** 8% dropped out of initial treatment period and 11% dropped out by 16-month f/u. TCC had more dropouts at 4 months but not by 16 months.	**Study RoB:** Some concerns **Authors conflict:** Reported no conflicts

CBT: Cognitive Behavioral Therapy; CI: confidence interval; CT: control group; ES: effective size; ITT: intention to treat; mos.: months; NR: not reported; NS: not significant; PSQI: Pittsburgh Sleep Quality Index; PSG: polysomnography; RCT: randomized controlled trials; SE: Sleep Efficiency; SMD: standardized mean difference; SoL: sleep onset latency; SS: sleep seminar; TAU: treatment as usual; TC: Tai Chi; TCC: Tai Chi Chih; TST: total sleep time; Tx: treatment; WASO: Wake After Sleep Onset; WL: waitlist

Table 4. Cochrane Risk of Bias 2.0 for RCTs on Tai Chi to Treat CID

Reference	Hosseini et al., (2011)	Irwin et al., (2014)
Randomization Process		
➢ Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	NI	Yes
➢ Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization, concealed envelopes)?	NI	Yes
➢ Did baseline difference between study groups suggest a problem with randomization?	No	No
Overall RoB for Randomization Process	**Some concerns**	**Low**
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?	NI	No
➢ Were these deviations from intended intervention balanced between groups?	NA	Yes
➢ Were these deviations likely to have affected the outcome?	NA	NA
➢ Was an appropriate analysis used to estimate the effect of assignment to intervention?	No	Yes
Overall RoB of Effect of Assignment	**High**	**Low**
Missing Outcome Data		
➢ Were data for this outcome available for all, or nearly all, participants randomized?	NI	Yes
➢ Is there evidence that result was not biased by missing outcome data?	NI	No
➢ Could missingness in the outcome depend on its true value?	NI	Yes
➢ Do the proportions of missing outcome data differ between intervention groups?	No	Yes
➢ Is it likely that missingness in the outcome depended on its true value?	No	Probably no
Overall RoB of Missing Data	**Low**	**Some concerns**
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?	Yes	No
➢ Were outcome assessors aware of the intervention received by study participants?	NI	No
➢ Could assessment of the outcome have been influenced by knowledge of intervention received?	Yes	Yes
➢ Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No	No

Reference	Hosseini et al., (2011)	Irwin et al., (2014)
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?	No	Yes
Overall RoB of Reported Results	**Some concerns**	**Low**
Overall Study RoB	**High**	**Some concerns**

*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

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Yoga

Evidence Base

Our searches of the literature identified one recent SR (Wang et al, 2019), from which 1 RCTs (Afonso et al, 2012) was identified that met inclusion criteria and addressed one or more of the key questions. Other RCTs included in the recent and previous SRs either didn't focus on adults with a diagnosis of insomnia or included adults with other primary disorders contributing to and comorbid with insomnia.

Study Quality

The strength of the evidence for the reported outcomes ranged from low to very low due to the high risk of bias in the single RCT. The high risk of bias was related to the lack of participant blinding but also to the lack of an intention-to-treat analysis with high and differing dropout rates among treatment groups.

Furthermore, the study population in the RCT was limited to post-menopausal women with a diagnosis of insomnia according to DSM-IV. Part of the intention for this study was to determine if yoga might substitute for hormone therapy (HT) as a treatment for insomnia given hormone therapy's side effects. Thus, women receiving hormone therapy for menopausal symptoms were excluded from the study. Other exclusion criteria were the presence of significant medical or psychiatric illness, use of psychotropic medications (which could also impact sleep) and signs of sleep apnea. Baseline characteristics of the study population as a whole or by treatment group were not reported in the publication so there could be baseline differences between treatment groups that influenced the outcome.

The yoga intervention (n=24) itself consisted of 2 1-hour sessions per week for 4 months led by a yoga teacher with the opportunity to make up missed sessions. The yoga sequence followed a set program called yoga HT (developed by one of the authors) and consisted of stretching positions along with strong and fast breathing called bellows breathing, followed by directed relaxation. The two other arms of the study were passive stretching (n=14), also with 2 1-hour sessions per week for 4 months, performed by a physical therapist and the control group (n=15) who received no intervention but were invited to yoga at the end of the study.

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 yoga is more effective than passive stretching and wait-list controls for the severity of insomnia. (SOE: Very low)
- Evidence from 1 RCT suggests that yoga is equally effective compared to passive stretching and wait-list controls for reducing anxiety, depression, and sleep parameters based on polysomnography (SOE: Low)

Discussion

Overall, the findings of the study by Afonso et al demonstrate that yoga, 2 sessions a week for 4 months resulted in improved insomnia severity according to the Insomnia Severity Index (ISI). Most of the outcomes—including insomnia severity, anxiety, depression, and the Epworth sleepiness scale (ESS) improved over time for all three intervention groups. The single outcome that showed a statistically

significant difference (at $p<0.05$) between women randomized to yoga and women randomized to passive stretching or wait-list controls was in insomnia severity as measured by the ISI. For women in the yoga group, ISI decreased from 14.1 (SE=1.2) to 9.7 (1.2) compared to a decrease from 15.2 (1.2) to 13.7 (1.2) in the control group and 16.9 (1.2) to 11.4 (1.3) in passive stretching group. Yoga was more effective than other interventions for ISI, $p<0.05$. In contrast, polysomnography results showed no differences within or across treatment groups over time.

Although the authors conclude that yoga shows promise as an effective intervention for postmenopausal women with insomnia, the low quality of the study limits the ability to draw these conclusions. In particular, the lack of baseline data and the differing dropout rates among the intervention groups suggest that women in the treatment groups differed in important ways that likely impacted the results. Further, the study itself is small in size and limited to a specific age and gender population so generalizability is further limited.

Table 1. Strength of Evidence for Yoga to Treat Chronic Insomnia 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
Insomnia severity index (ISI)	1 RCT: Afonso et al, 2012	Yoga Intervention (n=15), Passive stretching (n=14), Control (n=15): f/u at 4 months post treatment	Yoga group with ss improvement in ISI compared to passive stretching and control groups, $p<0.05$	High (-2)	No	No	Yes (-1), small sample size and some overlap of confidence intervals	No	Very Low
Beck Anxiety Inventory (BAI)	1 RCT: Afonso et al, 2012	Yoga Intervention (n=15), Passive stretching (n=14), Control (n=15): f/u at 4 months post treatment	No ss difference between tx groups	High (-2)	No	No	No	No	Low
Beck Depression Inventory (BDI)	1 RCT: Afonso et al, 2012	Yoga Intervention (n=15), Passive stretching (n=14), Control (n=15):	No ss difference between tx groups	High (-2)	No	No	No	No	Low

		f/u at 4 months post treatment							
PSG	1 RCT: Afonso et al, 2012	Yoga Intervention (n=15), Passive stretching (n=14), Control (n=15): f/u at 4 months post treatment	No ss difference between tx groups or within groups (pre to post treatment)	Yes (-2)	No	No	No	No	Low

CI: confidence interval; CT: control group; ES: effect size; mos.: months; f/u: follow-up; ISI: Insomnia Severity Index; NR: not reported; NS: not significant; PSG: polysomnography; RCT: randomized controlled trials; SE: standard error; ss: statistically significant; tx: treatment; WL: waitlist

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 RCTs on Yoga to Treat Chronic Insomnia Disorder (CID)

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Afonso et al, 2012 **Purpose:** to evaluate the effect of yoga practice on the physical and mental health and climacteric symptoms of post-menopausal women with insomnia. **Setting:** University medical center, San Paulo, Brazil **Funding source:** public foundation: São Paulo Research Foundation, Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP)	**Number of patients:** 44 **Inclusion criteria:** Postmenopausal, literate women 50-65 years of age, not receiving hormone therapy with diagnosis of insomnia according to DSM-IV. Also, with BMI <30 and FSH >=30 mIU/ml. **Exclusion criteria:** uncontrolled illnesses including hypertension, diabetes and cancer; use of hormone therapy; use of psychotropic drugs, apnea-hypopnea index greater than 15, participation in psychological treatment of menopausal symptoms. **Pt. baseline characteristics:** none reported	**Intervention (n=15):** 2 1-hour sessions of yoga HT for menopause per week, includes stretching and breath work, taught by a yoga teacher and ends with directed relaxation. **Passive stretching (n=14):** 2 1-hour sessions of passive stretching per week for 4 months, performed by a physical therapist **Control (n=15):** no procedure (invited to yoga at the end of the study) **Outcomes:** Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), ISI, Menopause-Specific Quality of Life Questionnaire, Inventory of Stress Symptoms for Adults (ISSL); PSG one night before tx and one night 4 months later **F/u:** Post-tx at 4 months	**Pre to post treatment: mean (SE):** **Beck Anxiety Inventory (BAI)** decreased in all 3 groups, yoga group, 15.3 (2.5) to 8.8 (1.9); **Beck Depression Inventory (BDI)** (15.1 – 11.0), **ISI:** 14.1(1.2) to 9.7 (1.2) compared to 15.2 (1.2) to 13.7 (1.2) in control group and 16.9 (1.2) to 11.4 (1.3) in passive stretching group. Yoga ss more effective than other interventions for ISI, $p<0.05$. **PSG:** no intragroup or intergroup differences. **Dropout:** 1 in control group, 6 in passive stretching, and 9 from yoga group	Study showed that a specific sequence of yoga might be effective in reducing insomnia [and menopausal symptoms…] in postmenopausal women with insomnia **Limitations:** small sample size, differing dropout rates between treatment groups, no ITT analysis **Study RoB:** High **Authors conflict:** Reported no conflicts except one author (DR) developed yoga routine and teaches it in practice.

BMI: Body Mass Index; CI: confidence interval; CT: control group; DSM-IV: Diagnostic and Statistical Manual—4th edition; ES: effect size; mos.: months; FSH: Follicle Stimulating Hormone; f/u: follow-up; HT: Hormone therapy; ISI: Insomnia Severity Index; ITT: Intention-to-treat; NR: not reported; NS: not significant; PSG: polysomnography; pt: patient; RCT: randomized controlled trials; RoB: Risk of Bias; SE: standard error; ss: statistically significant; tx: treatment; WL: waitlist

Table 4. Cochrane Risk of Bias 2.0 for RCT on Yoga to Treat CID

Reference	Afonso et al, 2012
Randomization Process	
➢ 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)?	NI
➢ Did baseline difference between study groups suggest a problem with randomization?	No
Overall RoB for Randomization Process	**Some concerns**
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?	Probably no
Overall RoB of Effect of Assignment	**High**
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?	No
➢ Could missingness in the outcome depend on its true value?	Yes
➢ Do the proportions of missing outcome data differ between intervention groups?	Yes
➢ Is it likely that missingness in the outcome depended on its true value?	Yes
Overall RoB of Missing Data	**High**
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?	Yes*
➢ Were outcome assessors aware of the intervention received by study participants?	No
➢ 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	**Some concerns**

Reference	Afonso et al, 2012
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
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:
*Administers of the questionnaires were unaware of study but questionnaires based on self-report.

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

Afonso, R. F., Hachul, H., Kozasa, E. H., De Souza Oliveira, D., Goto, V., Rodrigues, D., … Leite, J. R. (2012). Yoga decreases insomnia in postmenopausal women: a randomized clinical trial. *Menopause*, *19*(2), 186–193. https://doi.org/10.1097/gme.0b013e318228225f

Meditation

Evidence Base

Our searches of the literature identified 2 SRs and 2 RCTs from which a total of 4 RCTs were identified that assessed the impact of meditation for insomnia in otherwise healthy populations. In this review, we did not include Mindfulness-Based Stress Reduction (MBSR) as a meditation intervention as this has already been established as a programmatic treatment for insomnia. MBSR was included as a comparative intervention in one of the 4 RCTs.

Study Quality

The overall strength of the evidence for mindfulness and/or meditation interventions for Chronic Insomnia Disorder ranged from moderate to low depending on the outcome. The nature of the interventions prevented blinding of patients and instructors or those who carried out the intervention. Blinding of outcome assessors was also inconsistent across studies. Although the strength of evidence (SOE) ratings emerge as moderate to low, it is worth noting that each outcome of interest was evaluated by only one study since the variation in control or comparison interventions across studies didn't allow for summative conclusions. Thus, the few studies with small sample sizes allow for a small quantity or body of evidence for each key question and outcomes. Some general trends were observed and are described below in key findings and the discussion. The findings in related SRs are also briefly discussed.

Studies and Interventions

The study by Ong et al (2014) compared mindfulness-based training for insomnia against two other treatment arms, mindfulness-based stress reduction (MBSR) and a more passive self-monitoring control group. Both meditation interventions were delivered in weekly 2.5-hour meetings for 8 weeks. Although both mindfulness-based therapy for insomnia (MBTI) and MBSR include meditation practice as part of the intervention, the didactic component of MBSR is replaced by specific behavioral strategies for insomnia during MBTI. For both MBSR and MBTI, participants were instructed to practice meditation at home for 30-45 minutes daily. In contrast, the self-monitoring group was only instructed to keep a sleep diary. The sleep diary was kept by participants in all 3 treatment groups and used for self-reported outcome measures including sleep onset latency (SOL), total sleep time, sleep efficiency, and total wake time. Fifty-four patients total were included in the study, with mean age of `43 years, about ¾ of whom were female, 2/3 were white and mean education was 15.8 years. In this study, both meditation groups experienced improved sleep parameters compared to the sleep monitoring group but without a significant difference between MBTI and MBSR. For example, 50% of participants who received MBTI had insomnia remission at 6 months compared to 42% in the MBSR group, a difference between the two groups that was statistically non-significant.

The study by Black et al (2014) focused on a mindfulness-based intervention for elderly adults with insomnia. This intervention was called MAPs or Mindfulness Awareness Practices and involved 6 weekly group meetings lasting 2 hours each, delivered by an experienced teacher. Sessions included sitting meditation, mindful eating, loving-kindness meditation, mindful waking and other movement. Again, participants were instructed to practice mindfulness activities at home for 5-20 minutes as guided by a book and CD. The control arm of this study received sleep hygiene education (SHE), similarly delivered in 2-hour weekly sessions for the 6 weeks of the program. The Pittsburgh Sleep Quality Index

(PSQI) was the primary outcome and showed a 1.8-point difference between MAPs and SHE groups post treatment. Secondary outcomes include the Beck Anxiety and Depression Inventories (BAI and BDI), the Athens Insomnia Scale (AIS). There were small improvements in the BDI and AIS in the treatment group as well.

The third meditation-related study was by Lipschitz et al (2016) which evaluated the impact of Mind Body Bridging Intervention to Zolpidem among active duty military personnel with insomnia. Seventy-one patients were included in this trial, ages 20-51 (mean age 30.0), 85% male, and 62% white and 20% black. MBB involves 3 weekly sessions, 2 hours each, delivered by a social worker. MBB uses awareness practices to transform disharmonious mind-body states into harmonious ones, calming and relaxing the body. The sleep focused MBB implemented here addressed thoughts and sensations while falling asleep, reduce daytime stress and how to identify and understand Requirements, expectations associated with their identities. The Zolpidem/ TAU group received 5 mg males/ 2.5 mg females of Zolpidem for 3 weeks, one tablet to be taken at bedtime, with tapering the 3rd week of treatment. The TAU group also met for 30 minutes as a group where they received Sleep hygiene education and instructions for Zolpidem and participated in a group discussion regarding sleep concerns. In this study, the Zolpidem group fared better than the MBB group regarding sleep quality and outcomes, but both groups improved considerably and over time the MBB experienced benefits that were comparable to medication (and presumably with fewer side effects). For example, total sleep time (TST) improved from 293 min to 387 min over the course of the intervention compared to going from 339.6 min to 368.8 min in the MBB group. There was no difference between the two groups for waking after sleep onset (WASO) and sleep onset latency (SOL).

Lastly, the study by Garcia focused on postmenopausal women with insomnia, including 35 women, mean ages 55-57 years. This mindfulness intervention was called Mindfulness & Relaxation Training for Insomnia (MRTI) and involved 8 weekly sessions in clinic, lasting 30 minutes each, with use of an Audio CD at home. Guidance for home-based instruction suggested increasing the length of time spent on relaxation training, mindfulness technique of body scan, and breath work from initially 8 minutes long 3x/day to 16 min, 3x/day for a total of ~40 min/day. In this study, the control group also met in clinic and was instructed to spend a similar amount of time at home but working on crossword puzzles rather than practicing meditation. In this study, active intervention participants experienced modest but statistically significant benefits on sleep indexes including the PSQI and ISI, but without statistically significant differences between treatment groups by polysomnography.

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 suggests that mindfulness and meditation-based interventions may be similar to other active (MBSR and Zolpidem as TAU) or inactive (Sleep monitoring, standard nursing care) interventions for improving sleep parameters including total sleep time, total wake time, waking after sleep onset and sleep efficiency (SOE: Moderate).

- Evidence from 4 RCTs suggests that mindfulness and meditation-based interventions may be similar to active interventions and more effective than inactive interventions for self-reported sleep indices including the PSQI and ISI. (SOE: Low- Moderate)

- Evidence from 2 RCTs suggests there is no statistically significant difference between mindfulness and meditation-based interventions and active controls (MBSR and Zolpidem) in rates of remission or relapse of chronic insomnia disorder at 2-6 months post treatment. (SOE: Low- Moderate)
- Evidence from 1 RCT suggests mindfulness and meditation-based interventions may be effective for reducing depression. (SOE: Moderate)
- Evidence from 1 RCT suggest there is no statistically significant difference between mindfulness and meditation-based interventions and controls for reducing anxiety. (SOE: Low)

Discussion

The paucity of studies and variation between studies in terms of study populations, details of the interventions delivered, duration of follow-up, type of control groups, and outcomes assessed, limit the ability to draw generalizable and definitive conclusions about the effectiveness of mindfulness and meditation interventions for the amelioration of primary chronic insomnia disorder. The larger systematic reviews (Wang, Rusch) that have assessed this body of evidence have also included more standard psychotherapies such as Mindfulness-Based Stress Reduction and have included more diverse clinical populations, ranging from patients with cancer, fibromyalgia, and chronic fatigue syndrome. Despite the variation within and across studies however, there is a trend suggesting mindfulness and meditation-based interventions may be similarly effective to other active treatments for insomnia, as measured by the Pittsburgh Sleep Quality Index and the Insomnia Severity Index. Of note, all the mindfulness-based interventions include a significant home-based practice, typically daily, which, over time, constitutes more time than the in-person, supervised instruction and may, in fact, be the important aspect of mindfulness-based interventions for insomnia. In the single study conducted among military populations, most directly relevant for our review, a mind-body bridging intervention (MBB) was slightly less effective than Zolpidem (the treatment-as-usual) initially but had similar outcomes post-treatment and 2 months later, without the considerable risk associated with chronic use of pharmacologic agents.

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

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
Sleep parameters including: Total sleep time/ total wake time, Sleep onset latency (SOL), wake after sleep onset (WASO),	3 RCTs (Ong et al, 2014; Lipschitz et al, 2016; Garcia et al, 2018).	Ong et al: MBTI (19) vs. MBSR (19), vs. SM (16); 6 mos f/u	TWT decreased by 49.63 min per day at 6 mos, ss compared to SM with p<0.001	Yes (-1)	No	No	No	No	Moderate
		Lipschitz et al: MBB (40) vs. TAU (Zolpidem) (31), f/u 2 months	TST improved more in TAU (from 293 to 387 min vs. 339.6 to 368.8 min but no ss difference for WASO and SOL.	Yes (-1)	Yes (-1)	No	No	No	Low
		Garcia et al: MRTI (21) vs. CG (14), f/u 8 weeks (post-tx)	No significant differences in sleep efficiency, WASO, SOL	Yes (-1)	Yes (-1)	No	No	No	Low
ISI	3 RCTs (Ong et al, 2014; Lipschitz et al, 2016; Garcia et al, 2018).	Ong et al: MBTI (19) vs. MBSR (19), vs. SM (16); 6 mos f/u	**ISI:** MBTI and MBSR had -5.03 vs. +0.06 in SM, ss with p<0.000, MBTI had	Yes (-1)	No	No	No	No	Moderate

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
			improved ISI at 3 mos vs. MBSR ($p<0.05$) but not ss at 6 months						
		Lipschitz et al: MBB (40) vs. TAU (Zolpidem) (31), f/u 2 months	TAU group improved from 20.52 to 11.22 at 2-month f/u, better than MBB group (18.92 to 13.44) but no ss difference at 1 week and 2 months post treatment.	Yes (-1)	No	No	No	No	Moderate
		Garcia et al: MRTI (21) vs. CG (14), f/u 8 weeks (post-tx)	MRTI group improved from 18.31 to 3.26 vs. CG: 18.81 to 17.18 $p<0.05$.	Yes (-1)	No	No	No	No	Moderate
PSQI	2 RCTs (Black et al, 2014; Garcia et al, 2018).	Black et al: MAPs (24) vs. SHE (25), f/u 10 weeks	MAPs with reduction of 2.8, ss improvement vs. SHE with 1.1 reduction	Yes (-1)	No	No	No	No	Moderate

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
		Garcia et al: MRTI (21) vs. CG (14), f/u 8 weeks (post-tx)	MRTI group improved from 12.57 (1.6) to 4.36 (1.8) vs. control group 12.63 (1.43) to 10.45 (2.25), $p<0.05$.	Yes (-1)	No	No	No	No	Moderate
Remission/ Relapse	2 RCTs (Ong et al, 2014; Lipschitz et al, 2016).	Ong et al: MBTI (19) vs. MBSR (19), vs. SM (16); 6 mos f/u	**Remission/ Relapse:** MBTI 50% at 6 months, no relapse in 78.6% at 6 months, MBSR 42% and stable, no ss difference between the 2 meditation groups.	Yes (-1)	No	No	No	No	Moderate
		Lipschitz et al: MBB (40) vs. TAU (Zolpidem) (31), f/u 2 months	both groups had similar percentages of patients who no longer required further treatment	Yes (-1)	Yes (-1)	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
			for insomnia at 2 months f/u (TAU: 58.3% and MBB: 57.1%).						
Beck Depression Inventory (BDI)	1 RCT (Black, 2014)	Black et al: MAPs (24) vs. SHE (25), f/u 10 weeks	MAPs group improved from 10.9 to 7.0 vs. 11.0 to 10.9 in SHE group, ss	Yes (-1)	No	No	No	No	Moderate
Beck Anxiety Inventory (BAI)	1 RCT (Black, 2014)	Black et al: MAPs (24) vs. SHE (25), f/u 10 weeks	MAPs group improved from 13.5 to 10.6 vs. 13.4 to 10.8 in SHE group, p=0.85 (ns)	Yes (-1)	No	No	Yes (-1)	No	Low
Other insomnia scales: Medical Outcomes Study – Sleep Scale (MOS-SS),	1 RCT (Lipschitz, 2016)	Lipschitz et al: MBB (40) vs. TAU (Zolpidem) (31), f/u 2 months	MOS-SS: TAU group improved more (ss) than MBB, from 67.53 to 40.46 at 2-month f/u vs. 63.37 to 45.21 at 2 month but no ss	Yes (-1)	Yes (-1)	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
			difference post treatment.						
Other insomnia scales: Athens Insomnia scale (AIS)	1 RCT (Black, 2014)	Black et al: MAPs (24) vs. SHE (25), f/u 10 weeks	MAPs group with r= -0.53, vs. r=-0.23 in the SHE group, p<0.05 between group differences.	Yes (-1)	No	No	No	No	Moderate

CI: confidence interval; CG: control group; ES: effective size; F/u: Follow-up; I^2: % of heterogeneity between studies; ISI: Insomnia Severity Index; MAPs: Mindfulness Awareness Practices; MBB: Mind-Body Bridging; MBSR: mindfulness-based stress reduction; MBTI; Mindfulness Based therapy for Insomnia; mos.: months; NS: not significant; PCT: Quality of Life: QoL;PSQI: Pittsburgh Sleep Quality Index; RoB: Risk of Bias; RCT: randomized controlled trials; SE: standard error; SHE: sleep hygiene education; SOL: Sleep onset latency; SMD: standardized mean difference; SM: self-monitoring; ss; statistically significant; Tx: treatment; TAU: treatment as usual; TWT: total wake time; TST: total sleep time; WASO: Wake after sleep onset; WL: waitlist

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 Interventions to Treat CID

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Ong et al, 2014 **Purpose:** To evaluate the efficacy of mindfulness meditation for the treatment of chronic insomnia. **Setting:** Rush Medical Center; Chicago, Illinois, USA **Funding source:** NIH, National Center for Complementary and Alternative Medicine	**Number of patients:** 54 patients **Inclusion criteria:** over 21, diagnosed with insomnia, sleep onset latency >30 min at least 3 nights per week, symptoms lasting ≥ 6 months, & at least one symptom of heightened arousal **Exclusion criteria:** uncontrolled medical or psychiatric condition, comorbid sleep disorders, use of hypnotic or sedating medications for insomnia, inadequate proficiency in English to complete protocol **Pt. baseline characteristics (MRP; PCT):** Age (mean, yrs.): 42.9 (SD=12.2); 49.5 (14.5) Gender (% female): 74% female Race/ethnicity: 67% White, 24% Black Education (mean): 15.8 years 37% partnered, BMI (mean): 24.1	**Intervention:** **MBTI (n=19)** involves 8 weekly group meetings, lasting 2.5 h each + 6 hour meditation retreat between week 6 and 8. Meetings included one quiet and one movement meditations, discussion led by MBTI instructor, the first author, & specific behavioral strategies for insomnia such as sleep restriction therapy, stimulus control, and sleep hygiene. In addition, participants received instruction on home meditation, kept a meditation and sleep diary and given a book and CD on guided meditation. **MBSR (n=19), or Mindfulness-Based Stress Reduction** is a standard meditation program not tailored for insomnia and involves 8 weekly group meetings, lasting 2.5 h each + 6 hour meditation retreat between week 6 and 8. Meetings included meditation, general discussion about at home practice and education about meditation, led by MBSR-experienced instructors. **Self-monitoring control group (SM) (m=16):** Self-	**6 mos. f/u: mean change, between group p-value):** **TWT:** reduction of 5.27 min per treatment week in meditation groups, 49.63 min reduction at 6 months f/u ($p<0.001$) **ISI:** meditation groups had reduction in ISI (-5.03) compared to SM (+ 0.06) ($p<0.0001$); MBTI improved ISI at 3 mos compared to MBSR ($p<0.05$) but not ss at 6 months **Remission:** MBTI 50% at 6 months, MBSR 42% at 6 months, no ss difference between the 2 meditation groups. **Relapse:** response stable over time in MBSR and continued to increase in MBTI to 78.6% at 6 months. no ss difference between the 2 meditation groups.	Findings indicate interventions featuring mindfulness meditation have positive patient-reported outcomes and could be viable treatment option for patients w insomnia. **Limitations:** Small sample size of mostly white females, with hyperarousal which may not be generalizable, limited set of providers and only one author delivered MBTI, other aspects of treatment also uncontrolled and could account for some of the differences, study not blinded. **Study ROB: Some concerns** **Author conflict:** Authors report no conflicts.

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
		monitoring using daily sleep/wake diaries for 8 weeks. **Outcomes:** Sleep parameters including sleep onset latency, wake after sleep onset, number of awakenings, total sleep time, time in bed, sleep efficiency, Insomnia Severity Index (ISI); laboratory PSG and actigraphy were secondary outcomes. **F/u:** 6 months		
Reference: Black et al, 2014 **Purpose:** To determine the efficacy of mindfulness meditation intervention to promote sleep quality in older adults with moderate sleep disturbances. **Setting:** UCLA Medical research center and community centers, Los Angeles, California, USA **Funding source:** UCLA & NIH/NIMH grants; the Cousins Center for Psychoneuroimmunology, the Pettit Family Foundation and the Furlotti Family Foundation.	**Number of patients:** 49 patients **Inclusion criteria:** Age ≥ 55 years, and PSQI >5 at screening **Exclusion criteria:** current smoking, substance dependence, inability to speak English, depression, cognitive impairment, current meditation practice, obesity, current inflammatory disorder, sleep apnea, restless legs syndrome, chronic illness including diabetes and cancer, acute infection **Pt. baseline characteristics** Age (mean (SD), yrs.): 66.3 y (7.4); Gender (% female): 67% female	**Intervention:** **Mindful Awareness Practices (MAPs) for daily living-- (n=24)** involves 6 weekly group meetings, lasting 2 h each, delivered by experienced mindfulness instructor. Exercises included sitting meditation, mindful eating, appreciation meditation, loving-kindness meditation, mindful walking and other movement. 10-30 minutes of meditation exercises are included in each session along with didactic instruction and group discussion. A book, CD and 5-20 minutes of practice constitute the home-based practice. **Sleep Hygiene Education (SHE)-- (n=25)** also involves 6 weekly group meetings, lasting 2 h each, delivered by	**Post-treatment (~10 weeks after baseline assessments)** **PSQI:** MAPs group with mean improvement/ reduction of 2.8 (ss) on PSQI vs. SHE with 1.1 reduction (ns). Between group difference of 1.8 (ss), 95% CI 0.6-2.9 **Athens Insomnia Scale:** MAPs group with r= -0.53, vs. r=-0.23 in the SHE group, $p<0.05$ between group differences. **Beck Depression Inventory:** MAPs group improved from 10.9 to 7.0 vs. 11.0 to 10.9 in SHE group, $p<0.05$ between group differences. **Beck Anxiety Inventory:** MAPs group improved from 13.5 to 10.6 vs. 13.4	Findings suggest that mindfulness meditation may be a short-term solution for older adults with moderate sleep disturbances. Such interventions feasible and low cost in communities (compared to other intensive and costly therapies). **Limitations:** Small sample size of mostly white females, highly educated may limit generalizability, dropout rate was 12% but ITT analysis used, had moderate or worse sleep disturbances but did not require insomnia diagnosis so slightly less affected study population compared to other studies **Study ROB:** Some concerns, mostly related to

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	Race/ethnicity: 84% White, 4% Black, 10% Hispanic Education (mean): 16.6 (3.0) years Unemployed; 69% 51% married BMI (mean (SD)): 24.8 (3.9) Baseline PSQI (mean)= 10.2 (3.2); Beck Depression Inventory (mean)= 11.0 (9.1), Beck Anxiety Inventory (mean)=13.7 (9.3).	health educator. Active components included knowledge of sleep biology, stress and stress reduction, self-monitoring, relaxation methods and sleep hygiene strategies. Homework included practicing sleep hygiene and weekly reading. **Outcomes:** Sleep quality as measured by the PSQI was the primary outcomes. Secondary outcomes included: Athens Insomnia Scale, Beck Depression Inventory II, Beck Anxiety Inventory, P **F/u: post-treatment:** 10 weeks after pre-intervention assessments (6-week intervention)	to 10.8 in SHE group, p=0.85 (ns) between group differences, ss improvement over time in both groups.	differential follow-up/dropout rate between treatment groups which could bias the results **Author conflict:** Authors report no conflicts.
Reference: Lipschitz et al, 2016 **Purpose:** To evaluate the impact of Mind Body Bridging Intervention compared to sleep pharmacotherapy Army active duty military personnel with insomnia. **Setting:** Evans Army Community Hospital and associated medical clinics Fort Carson, Colorado, USA **Funding source:** Mind-Body Research Fund, Department of Anesthesiology, University of Utah	**Number of patients:** 71 patients **Inclusion criteria:** Active duty personnel, ages 18-55, judged to suffer from primary or secondary insomnia and thought to be a candidate for Zolpidem Rx. **Exclusion criteria:** insomnia from sleep apnea, COPD, restless legs, were currently using Zolpidem or medication for sleep, had a relatively severe or chronic mental disorder, uncontrolled hypertension	**Intervention:** **Mind Body Bridging Intervention (MBB) (n=40):** Involves 3 weekly MBB sessions, lasting 2 h each, over 3 consecutive weeks delivered by certified (in MBB) licensed clinical social worker. MBB uses awareness practices to transform disharmonious mind-body states into harmonious ones, calming and relaxing the body. The sleep focused MBB implemented here addressed thoughts and sensations while	**Post-treatment:** **MOS-SS:** TAU group (score improved from 67.53 to 40.46 at 2-month f/u) fared better than MBB group (score improved from 63.37 to 45.21 at 2-month f/u) during treatment but no ss difference between groups at 1 week and 2 months post treatment. **ISI:** Again, TAU group (score improved from 20.52 to 11.22 at 2-month f/u) fared better than MBB group (score improved	Conclusions: While TAU showed greater efficacy overall, both treatment groups demonstrated improvements in insomnia –the effects of Zolpidem were seen early compared to MBB but the benefits of MBB were comparable post treatment. **Limitations:** Lack of other insomnia assessments such as actigraphy, smaller sample size than originally

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	or diabetes, pregnant, previously had poor experience with Zolpidem, substance use disorder, enrolled in another study. **Pt. baseline characteristics:** Age (mean (SD), yrs.: 30.0 y (7.4), range 20-51; Gender: 84.5% male Race/ethnicity: 62% White, 19.7% Black, 15.5% Hispanic Baseline PSQI (mean)= 10.2 (3.2); Beck Depression Inventory (mean)= 11.0 (9.1), Beck Anxiety Inventory (mean)=13.7 (9.3).	falling asleep, reduce daytime stress and how to identify and understand Requirements, expectations associated with their identities. **Treatment as Usual w/ Zolpidem (TAU) (n=31):** prescribed 5 mg males/ 2.5 mg females of Zolpidem for 3 weeks, one tablet to be taken at bedtime, with tapering the 3rd week of treatment. The TAU group also met for 30 minutes as a group where they received Sleep hygiene education and instructions for Zolpidem and participated in a group discussion regarding sleep concerns. **Outcomes:** Primary outcome was the Medical Outcomes study-sleep scale (MOS-SS). Secondary outcomes were ISI, sleep diary for SOL, WASO, TST and clinical assessment **F/u: post-treatment:** 1 week and 2 months post treatment weeks after pre-intervention assessments (6-week intervention)	from 18.92 to 13.44 at 2-month f/u) during treatment but no ss difference between groups at 1 week and 2 months post treatment. **Sleep diary:** TAU group had ss greater improvement than MBB group for TST (TST improved from 293 min to 387 min vs. 339.6 min to 368.8) min but no difference between intervention groups for WASO and SOL. Clinical assessment: both groups had similar percentages of patients who no longer required further treatment for insomnia at 2 months f/u (TAU: 58.3% and MBB: 57.1%).	intended, lack of blinding, possible therapist effect on MBB group with a single therapist, imbalanced dropouts/ lack of follow up between groups. **Study ROB: Some concerns** **Author conflict:** Authors report no conflicts.
Reference: Garcia et al, 2018 **Purpose:** To evaluate the effects of mindfulness and relaxation training for insomnia and quality of life in postmenopausal women	**Number of patients:** 35 patients **Inclusion criteria:** women ages 50-65, amenorrhea for at least 1 year, insomnia	**Intervention:** **Mindfulness & Relaxation Training for Insomnia (MRTI)(n=21):** Involves 8 weekly MBB sessions in clinic, lasting 30 minutes each, with use of an Audio	**Post-treatment:** **PSQI (mean (SD)):** MRTI group improved from 12.57 (1.6) to 4.36 (1.8) vs. control group 12.63 (1.43) to 10.45 (2.25), $p<0.05$.	Conclusions: MRTI, conducted 3 times/ day for 8 weeks was shown to be valuable new format, using short frequent practice to reduce complaints of insomnia. Authors also

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Setting: Universidade Federal de Sao Paulo; San Paulo, Brazil **Funding source:** The present study was supported by the Associac¸a˜o Fundo de Incentivo a` Pesquisa (AFIP), Coordenac¸a˜o de Aperfeic¸oamento de Pessoal de Nı´vel Superior (CAPES), Fundacao de Amparo a Pesquisa (FAPESP), and CNPq. These are nonprofit organizations that sponsor research in Brazil.	diagnosis, non-obese, FSH levels ≥ 30 mIU/ml. **Exclusion criteria:** current use of psychotropic medications, current psychiatric or psychological treatment, history of serious neurological or psychiatric disease, depression diagnosis, those who drank more than 2 cups of coffee per day, other sleep disorders **Pt. baseline characteristics:** Age: mean of 55.1-56.7 years, education level: 11.25-12.6, Years since menopause: mean of 5.4-6.3 No ss difference between intervention groups.	CD at home with increasing length of time spent on relaxation training, mindfulness technique of body scan, and breath work. Initial home sessions are 8 minutes long, 3x/day and increase to 16 min, 3x/day for a total of 40 min/day. **Control group (n=14):** met in clinic for 30 min weekly for 8 weeks for general discussion with instructions to work on crossword puzzles at home for the same length of time as the mindfulness sessions in the treatment group. **Outcomes:** PSQI, ISI as well as Menopausal Symptoms including Menopause-specific quality of life scale that included a single question on general quality of life. **F/u:** 8 weeks (post-treatment)	**ISI: (mean (SD)):** MRTI group improved from 18.31 (2.76) to 3.26 (2.8) vs. control group 18.81 (2.89) to 17.18 (2.85), p<0.05. **Polysomnography parameters:** **Sleep efficiency (%):** MRTI group went from 78.82 (10.32) to 79.91(11.19) vs. control group 82.76 (10.13)) to 78.72 (5.97), p=ns **WASO (min (SD)):** MRTI group went from 74.96 (44.54) to 69.25(45.07) vs. control group 61.09 (42.60) to 66.9 (22.73), p=ns **Sleep latency (min):** MRTI went from 14.26 (14.04) to 12.31 (10.94) vs. control group 11.12 (9.93) to 22.99(17.91), p=ns No results reported for general QOL	conclude this improves overall quality of life as well as the condition of menopause. **Limitations:** Lack of blinding, subjective improvements did not correlate with polysomnography findings (similar to other studies), did not measure physical activity or treatment expectations and satisfaction. **Study ROB: Some concerns** **Author conflict:** Authors report no conflicts.

CI: confidence interval; CG: control group; ES: effect size; F/u: Follow-up; I^2: % of heterogeneity between studies; ISI: Insominia Severity Index; MAPs: Mindfulness Awareness Practices; MBB: Mind-Body Bridging; MBSR: mindfulness-based stress reduction; MBTI; Mindfulness Based therapy for Insomnia; mos.: months; NS: not significant; PCT: Quality of Life: QoL;PSQI: Pittsburgh Sleep Quality Index; RoB: risk of bias; RCT: randomized controlled trials; SE: standard error; SHE: sleep hygiene education; SMD: standardized mean difference; SM: self-monitoring; ss; statistically significant; Tx: treatment; TAU: treatment as usual; TWT: total wake time; TST: total sleep time; WL: waitlist

Table 4. Cochrane Risk of Bias 2.0 Tool for RCTs on Meditation Interventions to Treat CID

Reference	Ong et al. (2014)	Black et al, (2015)	Lipschitz et al, (2016)	Garcia et al, (2018)
Randomization Process				
➢ Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	Yes	Yes	Yes	Yes
➢ Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization, concealed envelopes)?	Yes	Yes	Yes	No
➢ Did baseline difference between study groups suggest a problem with randomization?	No	No	No	No
Overall RoB for Randomization Process	**Low**	**Low**	**Low**	**Low**
Deviation from Intended Intervention (Effect of Assignment)				
➢ Were participants aware of their assigned intervention during the trial?	Yes	Yes	Yes	Yes
➢ Were providers and people delivering treatment aware of assigned intervention during trial?	Yes	No	Yes	Yes
➢ Were there deviations from the intended intervention that arose because of the experimental context?	No	No	Yes	No
➢ Were these deviations from intended intervention balanced between groups?	NA	NA	No	No
➢ Were these deviations likely to have affected the outcome?	NA	NA	NI	No
➢ Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	Yes	Yes	Yes
Overall RoB of Effect of Assignment	**Some concerns**	**Some concerns**	**Some concerns**	**Some concerns**
Missing Outcome Data				
➢ Were data for this outcome available for all, or nearly all, participants randomized?	No	No	No	No
➢ Is there evidence that result was not biased by missing outcome data?	NI	NI	NI	Yes

Reference	Ong et al. (2014)	Black et al, (2015)	Lipschitz et al, (2016)	Garcia et al, (2018)
➢ Could missingness in the outcome depend on its true value?	NI	NI	Yes	NI
➢ Do the proportions of missing outcome data differ between intervention groups?	Yes	Yes	Yes	Yes
➢ Is it likely that missingness in the outcome depended on its true value?	No	No	No	No
Overall RoB of Missing Data	**Some concerns**	**Some concerns**	**Some concerns**	**Some concerns**
Measurement of the Outcome				
➢ Was the method of measuring the outcome inappropriate?	No	No	No	Yes
➢ Could measurement or ascertainment of the outcome have differed between intervention groups?	Yes	No	Yes	Yes
➢ Were outcome assessors aware of the intervention received by study participants?	Yes	No	No	No
➢ Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably No	No	Yes	Yes
➢ Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No	No	No	No
Overall RoB of Measurement of Outcome	**Some concerns**	**Low**	**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?	Yes	Yes	Yes	Yes
Overall RoB of Reported Results	**Low**	**Low**	**Low**	**Low**
Overall Study RoB	**Some concerns**	**Some concerns**	**Some concerns**	**Some concerns**

*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.

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Exercise

Evidence Base

Our searches of the literature identified 1 SR and 2 RCTs that assessed the impact of integrating exercise[4] interventions into care for the treatment of adults with Chronic Insomnia Disorder and insomnia symptoms (See **Tables 3 and 6** for details on study characteristics). The SR by Banno et al. (2018) was a meta-analysis of RCTs that examined the efficacy of physical exercise as a treatment of depression, both as an independent intervention and as an adjunctive treatment to pharmacotherapy. Physical exercise could be of any intensity, duration, or frequency. The primary outcomes of interest to this review included sleep efficiency and insomnia severity. Secondary outcomes included sleep onset latency, total sleep time, and adverse events. A total of 9 RCTs and 557 subjects were included in the Banno review, however only the 6 RCTs that included patients with a primary insomnia diagnosis (n=322), the condition of interest, are included in this review.

D'Aurea et al. (2019) conducted an RCT in which 20 patients began the intervention programs and 8 remained in the control group, Control (n=8) Stretching (n=10) Resistance (n=10). The available patients were randomly allocated into resistance exercise or stretching. There was a high risk of bias because of concerns in couple of domains, patients unavailable for the intervention program were assigned (non-randomly) to the non-intervention control treatment, and there were other methodological flaws or information not reported. The participants were 40-46 years old and had insomnia duration of 5-9 years. The primary outcomes of interest in the RCT were insomnia (insomnia severity index), total sleep time (or sleep duration), wake after sleep onset, sleep latency, Quality of life, Functional status, Anxiety, Pain, and Depression. The active interventions were resistance exercise training and stretching vs. a control group. The resistance exercise sessions were scheduled three times a week for four months (48 total sessions), focusing on the upper and lower limbs, abdominals, and paravertebral areas. Each session included four exercises for the upper limbs: biceps, triceps, back, and pectorals; four exercises for the lower limbs: flexors, extensors, abductors, and adductors; one trunk flexion exercise for the abdominal area; and one trunk extension exercise for the paravertebral area (spinal stabilizers). Initially, an intensity corresponding to 50% one-repetition maximum (1RM) was used, which was then increased to 60% 1RM after the 2nd month. Each exercise was performed in three series of 12 repetitions with 30-s intervals between series and 1-min intervals between the different types of exercise. Each full training session lasted approximately 50 min. Before and after the exercise sessions, the participants stretched for 5 min and warmed up/cooled down on an ergometric bicycle (Life Cycle 9100) for 5 min. All exercise sessions were performed at the same time of the day, 5 to 6 p.m. Stretching consisted of 48 stretching sessions, including 60 min of low intensity stretching, three times a week, from 5 to 6 p.m., for 4 months. The session began with a 5-min walk around the room, followed by 45 min of stretching exercises involving the upper and lower limbs, with 8-10 types for each body region. All insomnia patients successfully completed the 48 exercise sessions. When a session was missed, it was rescheduled on any other weekday in the same week.

Yeung et al. (2018) In this pilot randomized controlled trial, 37 physically inactive adults with the mean age: 49.9 years; SD: 13.6 and 91.9% female fulfilling the diagnostic criteria of insomnia disorder recruited from the community were randomly assigned to ZTEx training or sleep hygiene education

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

(SHE) groups. Subjects in the ZTEx group (n=18) attended two 2-hour training lessons to learn ZTEx which they then practiced daily for eight weeks. Subjects in the SHE group (n=19) attended two lessons of the same schedule and duration. The primary outcome measure was the Insomnia Severity Index (ISI). Intervention: Subjects in the ZTEx group (n=18) attended two 2-hour training lessons in small groups of 5-7. to learn ZTEx which they then practiced daily for eight weeks. Subjects in the SHE group (n =19) attended two lessons of the same schedule and duration. The first 2-hour session aimed at motivating subjects for behavioral changes and promoting the mastery of ZTEx. The consequence of physical inactivity (risk perception), self-efficacy of doing ZTEx, and the association between behavior and positive outcomes were covered. The group training of ZTEx was offered with examples. Subjects were invited to set realistic goals, plan possible actions and incorporate physical exercises into daily routine activities with the assistance of instructors (e.g., starting simple exercises while sitting or standing during waiting, watching TV, commuting or doing sedentary work). There were 10 different types of ZTEx such as simple stretching, and limb movements while sitting, standing or walking. During the second session (2 h; one week after the first session), the subjects shared experiences and barriers to doing ZTEx. Any positive changes were highlighted, and possible suggestions were discussed. The mastery of ZTEx by the subjects was inspected using a pre-designed checklist, and any discrepancy of technique was corrected. Sleep hygiene education and relaxation training: The treatment duration and frequency for the SHE group were the same as that of ZTEx training (two 2-hour sessions, one week apart. Each subject had a training handout (eight pages) about activity schedules and sleep hygiene instructions. The instructor introduced basic facts about sleep and insomnia; enhanced the understanding of personal sleep habits through the Sleep Hygiene Practice scale, Caffeine Knowledge quiz, the impact of poor sleep hygiene on maintaining sleep; and illustrated a role-model example of sleep-wake schedule. During the second session, the course content and home practice experience of subjects were reviewed. Local statistics regarding insomnia were shown, and the rationale of each instruction was discussed. Participants completed a “true/false” quiz regarding some facts of sleep for testing their understanding of sleep hygiene instructions. A course summary and Q&A session were arranged at the end of the session.

Study Quality

Using the AMSTAR instrument, we rated the quality of the review as low due primarily to the review authors not including a list of excluded studies with justification for their exclusion (see **Table 4** for the quality ratings). The authors of the review by Banno rated the RoB of the included RCTs as high using criteria from the Cochrane tool. The authors indicated that most of the studies did not blind patients, clinicians or outcome assessors. We rated the RoB of the D’Aurea trial as high due to lack of proper randomization and allocation concealment as well as lack of blinding of providers, and we rated the RoB of the Yeung trial as having some concerns due to lack of blinding of patients (see **Table 7** for the RoB ratings of the additional RCTs).

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 systematic review with 5 RCTs suggest there is no statistically significant difference between exercise and control in improving sleep onset latency or total sleep time (SOE: Low).

- Evidence from 1 systematic review with 4 RCTs suggest that there is no statistically significant difference between exercise and control in improving sleep efficiency (SOE: Low).
- Evidence from 1 systematic review with 2 RCTs suggest that exercise statistically significantly improves insomnia severity compared to control (SOE: Low).
- Evidence from 1 RCT suggests that overall there were no significant treatment differences between resistance exercise and stretching at 4 months follow-up. (SOE: Low)
- Evidence from 1 RCT suggests that resistance exercise and stretching led to significantly greater improvements in insomnia (ISI), actigraphic measures of sleep latency (SOL), wake after sleep onset (WASO), and sleep efficiency (SE) compared with control. Pittsburgh Sleep Quality Index (PSQI) global scores, and sleep duration also improved significantly following both experimental treatments compared with control, and PSQI-sleep efficiency improved significantly only after resistance exercise. (SOE: Low)
- Evidence from 1 RCT suggests no significant treatment differences using measure of the ISI, PSQI or actigraphy were found between resistance exercise and stretching post-intervention. (SOE: Low)
- Evidence from 1 RCT suggests no significant treatment differences were observed for mood (POMS), or quality of life measures (SF-36, 8 components) between groups. (SOE: Low)
- Evidence from 1 RCT suggests that Tension-anxiety (POMS) was significantly lower in the stretching group compared to control group, but no significant difference was observed between the resistance exercise and stretching groups. (SOE: Low)
- Evidence from 1 RCT suggests that zero-time exercise (ZTEx) statistically significantly improves severity of insomnia symptoms and related daytime impairments with a large between-group effect size compared to sleep hygiene education (SHE) at posttreatment and at 2, 4, 6 ,8 weeks follow-up. The difference became non-significant at week eight, suggesting a loss of efficacy two months after the training. (SOE: Low)
- Evidence from 1 RCT suggests that ZTEx cause no significant between-group treatment differences compared to SHE in sleep efficiency, sleep onset latency, total sleep time, and wake after sleep onset measured by sleep diary or actigraphy at posttreatment and at 2, 4, 6 ,8 weeks follow-up. (SOE: Very Low)
- Evidence from 1 RCT suggests that ZTEx cause no significant between-group differences compared to SHE in emotion, quality of life, fatigue, activity level, physical health, anxiety and depression at posttreatment and at 2, 4, 6 ,8 weeks follow-up. (SOE: Very Low)
- Evidence from 1 RCT suggests that ZTEx showed a significantly higher grip strength of the dominant hand than SHE with moderate effect size at week eight (ES= 0.56, P=0.04). (SOE: Very Low)
- Evidence from 1 RCT suggests that no significant differences between ZTEx and SHE groups for patient satisfaction in terms of the “confidence in effectiveness,” “confidence in recommending to

others," "perception of treatment rationale," and "likelihood of relieving other complaints". (SOE: Low)

Discussion

Overall, the findings of a single SR found that while exercise showed no significant difference when compared to control in improving sleep efficiency, sleep onset latency, or total sleep time, exercise was effective in improving insomnia severity. Two additional RCTs found no significant differences in stretching or resistance exercise after 4 months of treatment. There was a loss of efficacy two months after the training of zero-time exercise, but the effect was maintained with resistance exercise and stretching after the 4 months assessment. Resistance exercise and stretching were feasible and effective in treating insomnia symptoms at significant levels and led to significantly greater effect in improving insomnia symptoms, sleep parameters, mood and quality of life than in the control group at 4 months. Zero-time exercise also significantly improves severity of insomnia symptoms and related daytime impairments at 8 weeks, but no treatment difference was significant in sleep measures, mood or quality of life than the control group.

Table 1. Strength of Evidence for Exercise to Treat CID

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
Sleep onset latency	7 RCTs (5 RCTs in Banno, 2018; D'Aurea; Yeung)	Total (n=206) Exercise (NR); control (NR) F/u: 1 day to 6 mos.	**<u>Polysomnography and actigraphy</u>** MD: 1.90 (95% CI: -3.63 to 7.43), p=0.50; I^2=0%; **NS**	Yes (-1)	No	No	Yes (-1); wide 95% CI	No	Low
		Resistance (n=10); Stretching (n=10); Control (n=8) 4 mos. follow-up	**<u>PSQI</u>** Resistance: -47.5±15.0 Stretching: -37.9±25.3 Control: -15.6±18.4 **<u>Wrist actigraphy</u>** Resistance -7.1±4.6*; Stretching: -5.2±1.9*; Control: 2.2±2.1	Yes (-1)	No	No	Yes (-1)	No	Low
		ZTEx (n=18) vs. SHE (n=19) 2, 4, 6, 8 weeks follow-up	**<u>-Sleep Diary</u>** **Baseline** ZTEx : 50.2 ± 9.56; SHE: 60.6 ± 9.31; **Week 4** ZTEx : 30.6 ± 9.56; SHE: 48.5 ± 9.88; **p=0.56 (NS); Between-group ES (95% CI):** 0.43 (-0.23, 1.07)	Yes (-1)	No	Yes (-1)	Yes (-1)	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
			Week 8 ZTEx: 23.6 ± 9.56 SHE: 52.5 ± 9.92; **p=0.18 (NS);** Between-group ES (95% CI): 0.69 (0.01, 1.34) **-Actigraph** **Baseline** ZTEx : 15.6 ± 2.09 SHE: 20.0 ± 2.04; **Week 8** ZTEx: 17.7 ± 2.09; SHE: 17.5 ± 2.29; **p=0.14 (NS)** **Between-group ES (95% CI):** -0.02 (-0.67, 0.62)						
Total sleep time	7 RCTs (5 RCTs in Banno, 2018; D'Aurea; Yeung)	Total (n=206) Exercise (NR) vs control (NR) F/u: 1 day to 6 mos.	**Polysomnography and actigraphy** MD: 4.32 (95% CI: -9.19 to 17.84), p=0.53; I^2=0%; **NS**	Yes (-1)	No	No	Yes (-1); wide 95% CI	No	Low
		Resistance (n=10); Stretching (n=10); Control (n=8);	**Wrist actigraphy** Resistance 31.6±9.9; Stretching: 23.5±19.3; Control: -21.4±18.7	Yes (-1)	No	No	Yes (-1)	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
		4 mos. follow-up							
		ZTEx (n=18) vs. SHE (n=19) 2, 4, 6, 8 weeks follow-up	**<u>Sleep Diary</u>** Baseline ZTEx : 363.1 ± 16.10; SHE: 345.9 ± 15.68; **Week 4** ZTEx : 382.5 ± 16.10 SHE: 354.2 ± 16.57; p= 0.59 **(NS); Between-group ES (95% CI)**[d]: 0.40 (-0.26, 1.04); **Week 8** ZTEx : 391.5 ± 16.10; SHE: 372.5 ± 16.24; **p= 0.91 (NS);** **Between-group ES** (95% CI) [d] : 0.27 (-0.38, 0.91); **<u>Actigraph</u>** Baseline ZTEx: 389.2 ± 13.60; SHE: 403.8 ± 13.24; **Week 8**	Yes (-1)	No	Yes (-1)	Yes (-1)	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
			ZTEx: 379.2 ± 13.60 SHE: 394.5 ± 14.85; **p= 0.98 (NS);** **Between-group ES** (95% CI)[d]: -0.25 (-0.89, 0.40)						
Sleep efficiency	6 RCTS (4 RCTs in Banno, 2018; D'Aurea; Yeung)	Exercise (116) vs control (70) F/u: 1 day to 6 mos.	Mean difference (MD) was -0.56 (95% CI: -3.42 to 2.31), p=0.70; I^2=0%; **NS**	Yes (-1)	No	No	Yes (-1); wide 95% CI	No	Low
		Resistance (n=10); Stretching (n=10); Control (n=8); 4 mos. follow-up	**<u>PSQI</u>** Resistance: 19.5±3.9* Stretching: 13.3±6.3 Control: 2.1±4.3 **<u>Wrist actigraphy</u>** Resistance: 4.4±1.8* Stretching: 5.0±0.8* Control: -2.3±2.0	Yes (-1)	No	No	Yes (-1)	No	Low
		ZTEx (n=18) vs. SHE (n=19) 2, 4, 6, 8 weeks follow-up	**<u>Sleep Diary</u>** Baseline ZTEx: 76.4 ± 2.85; SHE: 70.3 ± 2.78; **Week 4** ZTEx: 78.4 ± 2.85; SHE: 75.3 ± 2.94; **p= 0.43 (NS);**	Yes (-1)	No	Yes (-1)	Yes (-1)	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
			Between-group ES (95% CI)[d]: 0.25 (-0.40, 0.89); **Week 8** ZTEx : 82.6 ± 2.85 SHE: 79.0 ± 2.97; **p= 0.56 (NS);** **Between-group ES** (95% CI)[d] 0.29 (-0.37, 0.93); **Actigraph** Baseline ZTEx: 83.3 ± 1.72; SHE: 83.1 ± 1.68; **Week 8** ZTEx: 83.3 ± 1.72 SHE: 83.7 ± 1.90; **p= 0.83 (NS);** **Between-group ES** (95% CI)[d] - -0.05 (-0.69, 0.59)						
Wake After Sleep Onset (WASO, min)	2 RCTs (Yeung et al. 2018; D'Aurea 2019)	Resistance (n=10); Stretching (n=10); Control (n=8); 4 mos. follow-up	**Wrist actigraphy** - Resistance -9.3±2.8*; Stretching: -7.1±3.0*; Control: 3.6±4.2	Yes (-1)	No	No	Yes (-1)	No	Low
		ZTEx (n=18) vs. SHE (n=19)	**Sleep Diary** Baseline ZTEx :	Yes (-1)	No	Yes (-1)	Yes (-1)	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
		2, 4, 6, 8 weeks follow-up	36.0 ± 6.73; SHE: 44.4 ± 6.55; **Week 4** ZTEx : 21.1 ± 6.73 SHE: 22.5 ± 7.07; **p= 0.53 (NS);** Between-group ES (95% CI)[d] 0.05 (-0.60, 0.69) **Week 8** ZTEx : 17.2 ± 6.73 SHE: 25.9 ± 7.05; **p= 0.98 (NS);** **Between-group ES** (95% CI)[d]: 0.29 (-0.36, 0.93) **-Actigraph** Baseline ZTEx: 41.5 ± 6.32; SHE: 48.7 ± 6.15; **Week 8** ZTEx: 39.7 ± 6.32 SHE: 34.4 ± 6.79; **p= 0.14 (NS);** **Between-group ES** (95% CI)[d]: -0.19 (-0.83, 0.46)						
Sleep duration (h)	1 RCT D'Aurea	Resistance (n=10); Stretching (n=10); Control (n=8);	**PSQI** Resistance:1.2±0.3 * Stretching: 1.6±0.6* Control: -0.1±0.2	Yes (-1)	No	No	Yes (-1)	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
		4 mos. follow-up							
Insomnia severity	4 RCTs (2 RCTs in Banno SR; 1 RCT Yeung; 1 RCT D'Aurea)	Exercise (32) vs control (34) F/u: 4 to 6 mos.	**ISI score** MD: -3.22 (95% CI: -5.36 to -1.07), p=0.003; I^2=0%; **favors exercise**	Yes (-1)	No	No	Yes (-1); small sample size	No	Low
		Resistance (n=10); Stretching (n=10); Control (n=8) 4 mos. follow-up	**ISI** **Mean change± standard error** Resistance: -10.5±2.3*; Stretching: -8.1±2.0*; Control: 2.3±1.8	Yes (-1)	No	No	Yes (-1)	No	Low
		ZTEx (n=18) vs. SHE (n=19) 2, 4, 6, 8 weeks follow-up	**ISI** **Mean change± standard error** **Baseline** ZTEx: 15.4 ± 1.10; SHE:16.0 ± 1.07; **Week 2** ZTEx: 10.2 ± 1.10; SHE: 14.6 ± 1.10; **p=0.001; Between-group ES (95% CI)[d] : 0.93 (0.23, 1.59);** **Week 4** ZTEx: 9.9 ± 1.10; SHE: 15.2 ± 1.13; **p=0.002; Between-**	Yes (-1)	No	Yes (-1)	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
			group ES (95% CI)[d] : 1.10 (0.39, 1.77); **Week 6** ZTEx: 9.2 ± 1.12; SHE: 14.5 ± 1.13; p**=0.008;** Between-group ES (95% CI)[d]: 1.09 (0.38, 1.76); **Week 8** ZTEx: 9.0 ± 1.10; SHE: 13.6 ± 1.12; **p=0.03;** Between-group ES (95% CI)[d]: 0.96 (0.26, 1.62)						
Global scores (PSQI: 0-21)	1 RCT D'Aurea	Resistance (n=10); Stretching (n=10); Control (n=8); 4 mos. follow-up	**(PSQI)** **Resistance:** -5.3±0.8*, Stretching: -3.9±1.5* vs. Control: -0.1±0.8	Yes (-1)	No	No	Yes (-1)	No	Low
Tension-anxiety (POMS score)	1 RCT D'Aurea	Resistance (n=10); Stretching (n=10); Control (n=8); 4 mos. follow-up	**<u>POMS</u>** Resistance: -1.8±1.6 Stretching: -6.8±1.3* Control: 0.9±2.4	Yes (-1)	No	No	Yes (-1)	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
HADS-Anxiety	1 RCT Yeung et al. 2018	ZTEx (n=18) vs. SHE (n=19) 2, 4, 6, 8 weeks follow-up	**HADS** **Baseline** ZTEx: 7.9 ± 0.97; SHE: 6.7 ± 0.95; **Week 4** ZTEx: 6.6 ± 0.97; SHE: 6.0 ± 0.98; **p= 0.42 (NS);** Between-group ES (95% CI -0.14 (-0.79, 0.51) **Week 8** ZTEx: 5.9 ± 0.97; SHE: 5.8 ± 0.99; **p=0.29 (NS);** Between-group ES 95% CI: -0.02 (-0.67, 0.62)	Yes (-1)	No	Yes (-1)	Yes (-1)	No	Very low
Depression (POMS score)	1 RCT D'Aurea	Resistance (n=10); Stretching (n=10); Control (n=8); 4 mos. follow-up	**POMS** Resistance: -3.5±2.8 Stretching: -5.9±2.7 Control: -1.2±1.4	Yes (-1)	No	No	Yes (-1)	No	Low
HADS-Depression	1 RCT Yeung et al. 2018	ZTEx (n=18) vs. SHE (n=19) 2, 4, 6, 8 weeks follow-up	**HADS** Baseline ZTEx: 6.8 ± 0.91; SHE: 5.3 ± 0.88; **Week 4** ZTEx: 5.9 ± 0.91; SHE: 5.6 ± 0.92; **p= 0.16 (NS);**	Yes (-1)	No	Yes (-1)	Yes (-1)	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
			Between-group ES (95% CI: -0.08 (-0.72, 0.57); Week 8 ZTEx: 5.8 ± 0.91; SHE:5.2 ± 0.92; **p=0.30 (NS)**; **Between-group ES** (95% CI: - 0.15 (-0.79, 0.50)						
Fatigue (POMS score)	1 RCT D'Aurea	Resistance (n=10); Stretching (n=10); Control (n=8); 4 mos. follow-up	**POMS** Resistance: -4.9±2.2 Stretching: -4.8±1.4 Control: -0.4±1.5	Yes (-1)	No	No	Yes (-1)	No	Low
20-item Multidimensional Fatigue Inventory (MFI-20)	1 RCT Yeung et al. 2018	ZTEx (n=18) vs. SHE (n=19) 2, 4, 6, 8 weeks follow-up	**MFI-20** **Baseline** ZTEx: 60.4 ± 2.69; SHE: 63.3 ± 2.61 **Week 4** ZTEx: 58.1 ± 2.69; SHE: 61.9 ± 2.73; **p=0.75 (NS)**; **Between-group ES** (95% CI: 0.33 (-0.33, 0.97) **Week 8** ZTEx: 53.4 ± 2.69; SHE: 60.0 ± 2.77; **p=0.30 (NS); Between-group ES**	Yes (-1)	No	Yes (-1)	Yes (-1)	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
			(95% CI: 0.56 (-0.11, 1.21)						
Physical functioning, SF-36 (0-100)	1 RCT D'Aurea	Resistance (n=10); Stretching (n=10); Control (n=8); 4 mos. follow-up	**SF-36** Resistance: 2.5±1.7 Stretching: 8.5±5.6 Control: -1.9±1.9	Yes (-1)	No	No	Yes (-1)	No	Low
Body pain, SF-36 (0-100)	1 RCT D'Aurea	Resistance (n=10); Stretching (n=10); Control (n=8); 4 mos. follow-up	**SF-36** Resistance: 13.4±11.1 Stretching: 8.0±7.8 Control: -0.1±9.4	Yes (-1)	No	No	Yes (-1)	No	Low
Social functioning, SF-36 (0-100)	1 RCT D'Aurea	Resistance (n=10); Stretching (n=10); Control (n=8); 4 mos. follow-up	**SF-36** Resistance: 17.5±11.2 Stretching: 29.0±9.5 Control: 5.9±5.7	Yes (-1)	No	No	Yes (-1)	No	Low
Mental health, SF-36 (0-100)	1 RCT D'Aurea	Resistance (n=10); Stretching (n=10);	**SF-36** Resistance: 20.2±7.3 Stretching: 21.2±8.2 Control:	Yes (-1)	No	No	Yes (-1)	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
		Control (n=8); 4 mos. follow-up	-2.5±4.9						
Patient Satisfaction	1 RCT Yeung et al. 2018	ZTEx (n=18) vs. SHE (n=19) 2, 4, 6, 8 weeks follow-up	No significant differences were found in the confidence in effectiveness in recommending to others," "perception of treatment rationale," and "likelihood of relieving other complaints" between ZTEx and SHE groups.	Yes (-1)	No	Yes (-1)	No	No	Low

CI: confidence interval; ES: effect size; f/u: follow-up; HADS: Hamilton Anxiety and Depression Scale; ISI: Insomnia Severity Index; MFI-20Multidimensional Fatigue Inventory (MFI-20); mos.: months; NA: not applicable; NR: not reported; NS: not significant; POMS: Profile of Mood States; RCT: randomized controlled trials; rTMS: repetitive TMS; SD: standard deviation; SF-6D: Short-Form Six-Dimension; SF-36: 36-item Short Form Survey; SHE: sleep hygiene education; SMD: standardized mean difference; TMS: transcranial magnetic stimulation; WASO: Wake After Sleep Onset; ZTEx: Zero-time exercise

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 CID

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
Reference: Banno 2018 **Organization/Country:** Japan **Purpose:** Meta-analysis to examine the efficacy of physical exercise as treatment for Chronic Insomnia Disorder and insomnia symptoms both as an independent intervention and as an adjunct intervention to medication **AMSTAR Rating:** Low **Overall RoB of Included Studies:** High	**Databases Searched:** Cochrane Central Register of Controlled Trials, MEDLINE, Embase, PsycINFO, World Health Organization International Clinical Trials Registry Platform, Clinicaltrials.gov **Dates Searched:** through 2017 **Inclusion/Exclusion Criteria:** **Inclusion:** RCTs of patients with primary (and secondary) insomnia; physical activity comprised of any body movement produced by skeletal muscle resulting in an increase in energy expenditure; exercise vs. non-exercise control; exercise plus medication vs. medication alone **Exclusion:** Patients with a sleep complaint and not diagnosed with insomnia; mindfulness meditation programs; massage therapy; breathing exercises w/o physical activity **Final Evidence Base:** 9 studies (6 studies included only patients w/ primary insomnia disorder)	**Diagnosis:** Insomnia (DSM-5 or ICD-3; insomnia symptoms) **Number of Patients:** 577 **Age:** 18 years or older (SR authors included pts. of any age in search, but only adults were in studies making up final evidence base) **Gender:** Male and female	**Intervention:** Aerobic Exercise **Comparators:** no treatment; adjunct to pharmacotherapy compared to pharmacotherapy alone **Follow-up:** variable but as long as 6 months **Outcomes:** Sleep efficiency; insomnia severity; sleep onset latency; total sleep time	**Sleep efficiency** 4 studies of 186 participants; all measured PSG and actigraphy; intervention period ranging from 1 day to 6 mos. Mean difference (MD) was -0.56 (95% CI: -3.42 to 2.31), p=0.70; I^2=0%; **NS** **Insomnia severity** 2 studies of 66 participants; all measured ISI; intervention period ranging from 4 to 6 mos. MD: -3.22 (95% CI: -5.36 to -1.07), p=0.003; I^2=0%; **favors exercise** **Sleep onset latency** 5 studies of 206 participants; all measured PSG and actigraphy; intervention period ranging from 1 day to 6 mos. MD: 1.90 (95% CI: -3.63 to 7.43), p=0.50; I^2=0%; **NS** **Total sleep time** 5 studies of 206 participants; all measured PSG and actigraphy; intervention period ranging from 1 day to 6 mos. MD: 4.32 (95% CI: -9.19 to 17.84), p=0.53; I^2=0%; **NS** **Adverse events**

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
				1 study reported an incident of a mild sprained ankle in exercise intervention group.

CI: confidence interval; ES: effect size; f/u: follow-up; HADS: Hamilton Anxiety and Depression Scale; ISI: Insomnia Severity Index; MFI-20Multidimensional Fatigue Inventory (MFI-20); mos.: months; NA: not applicable; NR: not reported; NS: not significant; POMS: Profile of Mood States; RCT: randomized controlled trials; rTMS: repetitive TMS; SD: standard deviation; SF-6D: Short-Form Six-Dimension; SF-36: 36-item Short Form Survey; SHE: sleep hygiene education; SMD: standardized mean difference; TMS: transcranial magnetic stimulation; WASO: Wake After Sleep Onset; ZTEx: Zero-time exercise

Table 4. Systematic Review Risk of Bias AMSTAR Checklist Table on Exercise to Treat CID

Question	Banno 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?	Yes
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?	No
Overall Quality	**Low**

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

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

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

Table 6. Evidence Table for RCTs on Exercise to Treat Chronic Insomnia Disorder (CID)

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: D'Aurea et al. 2019 **Purpose:** The aim of this study was to assess the effects of resistance exercise and stretching on sleep, mood, and quality of life in chronic insomnia patients. **Setting:** University Brazil**,** Arizona State University, Phoenix, USA **F/u:** Baseline (Preintervention); 4 months **Funding source:** Grants (NI)	**Number of patients:** Control (n=8) Stretching (n=10) Resistance (n=10) **Inclusion criteria:** 30 to 55 years old; insomnia complaints X 6 months; at least one daytime insomnia related complaint. **Exclusion criteria:** use of psychoactive drugs; history of psychiatric diseases; a shift work schedule; regular exercise in the last 6 months. **Pt. baseline characteristics:** **Age (years)** Resistance: 44.5±2.2 Stretching: 45.5±2.5 Control: 40.3±2.7 **BMI (kg/m2)** Resistance: 26.7±1.6 Stretching: 25.9±1.7 Control: 27.9±2.0 **Insomnia duration (years)** Resistance: 5.4±1.4 Stretching: 6.5±2.7 Control: 8.4±3.1 **Height** Resistance: 163.6±2.5 Stretching: 162.5±2.4 Control: 166.5±4.1	**Intervention:** **Resistance exercise training:** Sessions were scheduled three times a week for four months, 48 total sessions. **Stretching:** consisted of 48 stretching sessions, including 60 min of low intensity stretching, three times a week, from 5 to 6 p.m., for 4 months. **Outcomes of Interest:** Quality of life Functional status Anxiety Pain Depression Insomnia (insomnia severity index) Total sleep time (TST), sleep duration Wake after sleep onset (WASO) Sleep latency	-There were no significant baseline differences between Treatments. -Significant differences were observed in insomnia-related complaints (ISI) between groups (F2,24 = 7.27**; p = 0.003**). Analysis showed significant differences between the control group and both the resistance exercise and stretching groups. -Global PSQI scores also differed between groups (F2,24 = 6.08; **p=0.007**), as well as SE (F2,24 = 4.21; **p = 0.03**) and sleep duration (F2,24 = 4.81; **p = 0.02**), assessed using PSQI. Analysis showed significant differences between the control group and both the resistance and stretching groups for global PSQI score and sleep duration. -Compared with the control group, PSQI-sleep efficiency improved only after resistance exercise. - No significant differences in ISI or PSQI were found between resistance exercises and stretching. -There were significant differences in actigraphy data between groups for sleep latency (F2,24 = 4.16; **p = 0.03**), SE (F2,24 = 5.46; p = **0.01**) and WASO (F2,24 = 5.94**; p = 0.008**). Post-hoc analysis	The results suggest no significant differences between 4-month resistance exercise vs. stretching for improving insomnia severity and objective and subjective sleep in patients with chronic insomnia. However, both the resistance exercise and stretching treatments led to significantly greater effects than in the control group. Both the resistance exercise and the stretching interventions decreased insomnia severity (ISI), and improved sleep quality (PSQI) and actigraphic measures of home sleep (SOL, WASO, and SE) compared to the control group. Stretching also reduced tension-anxiety, but no other significant treatment differences were observed for mood or quality of life. **Limitations:** 1. Small sample size 2. Participants were non-randomly assigned to control group. 2. Fewer participant-researcher interactions in the control group could have resulted in greater

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
			showed significant differences between the control group and both the resistance exercise and stretching group for all above-described sleep variables. However, there were no significant post-intervention differences between the resistance exercise and stretching groups for actigraphic sleep. -Significant improvements were observed between groups in tension-anxiety as assessed with the POMS scale (F2,24 = 4.41; **p = 0.02**). Post-hoc analysis showed significant differences between the control and stretching groups, but not between the resistance exercise and stretching groups. No significant correlations were observed between changes in tension-anxiety and sleep improvements.	improvements in the experimental treatments, including expectancy, demand, and Hawthorne effects. **Study ROB**: High **Author conflict:** None reported
Reference: Yeung et al. 2018 **Purpose:** To evaluate the feasibility and clinical effects of a lifestyle-integrated exercise, namely zerotime exercise (ZTEx), on improving insomnia in inactive adults	**Number of patients:** 37 patients, ZTEx (n=18); SHE (n=19) **Inclusion criteria:** (1) adults aged 18-65 years; (2) were Chinese Hong Kong residents capable of Cantonese or Putonghua communication; (3) who fulfilled the DSM- 5 diagnostic criteria of insomnia disorder (primary insomnia) according to a	**Intervention:** Subjects in zero-time exercise (ZTEx group, n=18) attended two 2-hour training lessons in small groups of 5-7. to learn ZTEx which they then practiced daily for eight weeks. Subjects in the SHE group (n =19) attended two lessons of the same schedule and duration. **Sleep hygiene education and relaxation training (n=19):** The treatment duration and frequency	**Primary outcome of insomnia symptom severity**: Compared with the SHE group, the ZTEx group had a significantly greater reduction of insomnia symptom severity with a large effect size at all four assessment time points (week two: ES= 0.93, **P =0.001**; week four: ES =1.10, P =0.002; week six: ES = 1.09, **P = 0.008**;	**Conclusions:** The simple and brief ZTEx training showed high acceptability and exercise compliance and the first evidence of efficacy in reducing insomnia severity in inactive adults with insomnia disorder. Patients were equally satisfied with both the treatments. **Limitations:** 1. Since the study recruited inactive

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
with insomnia disorder. **Setting:** School of Nursing, Hong Kong Polytechnic University. **F/u:** 2, 4, 6, 8 weeks **Funding source:** NI	validated diagnostic tool, the Brief Insomnia Questionnaire (BIQ) (including difficulties in falling asleep, difficulties in staying asleep, or early morning awakening associated with clinically significant impairment in daily living for at least three months); (4) who scored at least 10 points on the ISI (5) were willing to provide informed consent and comply with the trial protocol; (6) were ambulatory and independent in daily activities; and (7) had less than 150 min of moderate physical activity or 75min of vigorous physical activity per week, or an equivalent combination of both **Exclusion criteria:** (1) their insomnia might be due to specific medical conditions, side effects of medication intake, or other sleep disorders; (2) they used medication or psychotherapy for insomnia or other psychiatric disorders; (3) they had psychiatric disorders identified by DSM-IV structured clinical interviews, including generalized anxiety disorder, major depressive disorder, posttraumatic stress disorder, and psychosis; (4) they had impaired cognitive functioning for providing consent or understanding instructions (scored <22 in Hong Kong	for the SHE group were the same as that of ZTEx. **Telephone F/U**: Twice a week in both groups **Outcomes:** Severity of insomnia symptoms and the associated daytime impairment (ISI), handgrip strength assessed with a hand dynamometer, severity of depressive and anxiety symptoms evaluated by the Hospital Anxiety and Depression Scale (HADS), the severity of fatigue assessed by Multidimensional Fatigue Inventory (MFI-20), quality of life assessed by Short-Form Six-Dimension (SF-6D) and physical movements assessed by the Actigraphy measured that estimate wake and sleep states like the total time in bed (TIB), sleep-onset latency (SOL), wake after sleep onset (WASO), and total sleep time (TST), sleep efficiency (SE), and self-reported moderate and vigorous intensity physical activities (MVPA)	week eight: ES = 0.96, P = **0.03**). The differences remained significant after Bonferroni correction for multiple time comparison points (**P < 0.0125**), **<u>except at week eight.</u>** **-Secondary outcomes: Sleep diary and actigraphy:** No significant between-group difference was observed between the ZTEx and SHE groups in SOL, WASO, TST, and SE measured by sleep diary or actigraph in all study visits. **-Emotion, quality of life, fatigue, activity level, physical health,** **and BMI:** shows no significant between-group difference in HADS anxiety and depression scores, MFI-20, SF-6D utility score, time spent on moderate and vigorous intensity activities, and BMI throughout in all study visits. The ZTEx group showed a significantly higher grip strength of the dominant hand than the SHE group with moderate effect size at week eight (ES =0.56, **P =0.04**). There were high rates of treatment acceptability, fidelity,	people, subjects were highly motivated 2. Sample consisted of a high proportion of female subjects (91.9%), and it also excluded psychiatric comorbidities, both of which may limit the generalizability of the results. Conversely, we did not assess subjects' menopausal status which might have affected their sleep; 3. The study was limited by the lack of an objective measure of activity level; 4. We did not use polysomnography for excluding participants who might be potential sufferers of sleep apnea and other possible sleep disorders **Study ROB:** Some concerns **Author conflict:** Authors report no conflicts.

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	Montreal Cognitive Assessment); (5) they were shift workers; (6) their body mass index was 27.5 or above; and (7) they had unsafe medical conditions and were not recommended for exercising by physicians. **Pt. baseline characteristics:** recruited subjects were mainly female (91.9%) with a mean age of 49.9 years (SD = 13.6) and a BMI of 22.1 (SD = 2.8). The mean duration of insomnia was 7.3 (SD = 7.5) years. Only a few of them had used exercise as an intervention for insomnia (8.1%) before participation. The average duration of their moderate-to-vigorous activities was 22.0 min (SD = 41.0) weekly. The mean score of ISI was 15.7 (SD = 3.9), and about half of the subjects had moderate-to-severe insomnia (ISI scored -15; 54.1%). The ZTEx group did not substantially differ from the SHE group, except for education.		and treatment compliance (Patient satisfaction): The ZTEx group rated an average of 8.6 (SD =1.1) out of 10 for the acceptability of ZTEx training. They had high treatment compliance (15 of 18 subjects in the ZTEx group completed the two sessions).	

CI: confidence interval; ES: effect size; f/u: follow-up; HADS: Hamilton Anxiety and Depression Scale; ISI: Insomnia Severity Index; MFI-20Multidimensional Fatigue Inventory (MFI-20); mos.: months; NA: not applicable; NR: not reported; NS: not significant; POMS: Profile of Mood States; RCT: randomized controlled trials; rTMS: repetitive TMS; SD: standard deviation; SF-6D: Short-Form Six-Dimension; SF-36: 36-item Short Form Survey; SHE: sleep hygiene education; SMD: standardized mean difference; TMS: transcranial magnetic stimulation; WASO: Wake After Sleep Onset; ZTEx: Zero-time exercise

Table 7. Cochrane Risk of Bias 2.0 Tool for RCTs for Exercise to Treat CID

Reference	D'Aurea et al. 2019	Yeung et al.
➢ Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	No	Yes
➢ Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization, concealed envelopes)?	No	Yes
➢ Did baseline difference between study groups suggest a problem with randomization?	No	No
Overall RoB for Randomization Process	**Some concerns**	**Low**
Deviation from Intended Intervention (Effect of Assignment)		
➢ Were participants aware of their assigned intervention during the trial?	NI	No
➢ Were providers and people delivering treatment aware of assigned intervention during trial?	Yes	Yes
➢ Were there deviations from the intended intervention that arose because of the experimental context?	No	No
➢ Were these deviations from intended intervention balanced between groups?	NA	NA
➢ Were these deviations likely to have affected the outcome?	NA	NA
➢ Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	Yes
Overall RoB of Effect of Assignment	**Some concerns**	**Some concerns**
Missing Outcome Data		
➢ Were data for this outcome available for all, or nearly all, participants randomized?	Yes	Yes
➢ Is there evidence that result was not biased by missing outcome data?	PY	No
➢ Could missingness in the outcome depend on its true value?	NA	NA
➢ Do the proportions of missing outcome data differ between intervention groups?	NA	No
➢ Is it likely that missingness in the outcome depended on its true value?	NA	No
Overall RoB of Missing Data	**Low**	**Low**
Measurement of the Outcome		
➢ Was the method of measuring the outcome inappropriate?	No	No
➢ Could measurement or ascertainment of the outcome have differed between intervention groups?	No	No
➢ Were outcome assessors aware of the intervention received by study participants?	No	No
➢ Could assessment of the outcome have been influenced by knowledge of intervention received?	No	No
➢ Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No	No
Overall RoB of Measurement of Outcome	**Low**	**Low**
Selection of Reported Results		

Reference	D'Aurea et al. 2019	Yeung et al.
➢ Was the trial analyzed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?	PY	Yes
Overall RoB of Reported Results	**Low**	**Low**
Overall Study RoB	**High**	**Some concerns**

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

References

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Music Interventions

Evidence Base

Our searches of the literature identified 1 systematic review (SR) and 1 randomized controlled trial (RCT) that assessed the role of music-based interventions for the treatment of chronic insomnia disorder. The SR, by Feng et al., (2018) set out to compare and rank music interventions and no-music controls for its impact for patients with insomnia. This SR identified 20 studies, both randomized and non-randomized, with a total of 1,339 patients, with about half receiving music-based interventions and the rest controls. The comparison between listening to music and usual care was the most common and characteristic of ten (out of twenty) studies. Other music interventions in the studies were: listening to music and acupuncture, listening to music and language induction, listening to placebo music, music-assisted relaxation with/ without stimulus control, music with exercise. The primary outcome was the Pittsburgh Sleep Quality Index (PSQI), a subjective assessment of sleep quality and insomnia severity. Secondary outcomes included sleep onset latency (SOL) and sleep efficiency.

The single RCT by Huang et al., (2017) identified that was not included in the SR by Feng et al, was published in 2017 but past the search date of the SR of May 2017. This trial compared listening to music to a music video intervention for its impact on both subjective and objective sleep parameters among 71 adults with sleep disturbances (PSQI > 5). A non-music control group was also included. The content of both the music and the music videos were based on Buddhist principles and teachings.

Study Quality

Using the AMSTAR instrument, we rated the SR as being of moderate to low quality primarily because the risk of bias of the individual studies wasn't clearly integrated into the interpretation of the results. The duration of the interventions and the follow-up time for the outcome assessments were also not reported. Otherwise the SR itself followed rigorous methodologies and included a relatively large number of studies with diverse music-based interventions and found relatively consistent results. The single RCT by Huang et al., was well-designed and thus rated highly (low risk of bias), yet the study itself was so small, of short duration, and specific in terms of the content of the interventions, generalizability is likely low.

Key Findings

Below, we describe the key findings for the outcomes of interest with the GRADE strength of the evidence (SOE) rating regarding the effectiveness of music-based interventions compared to different control interventions for the treatment of primary chronic insomnia disorder. See Table 1 for factors that influenced the SOE ratings.

- Evidence from 1 SR (including 20 clinical trials) suggests that music-based interventions are effective in improving sleep quality among patients with chronic insomnia disorder (SOE: Moderate)
- Evidence from 1 SR (including 20 clinical trials) suggests that listening to music and music-based relaxation improves sleep quality compared to usual care (no music) among patients with chronic insomnia disorder (SOE: Moderate to Low)
- Evidence from 1 RCT suggests that neither listening to music nor music videos impact objective measures of sleep and sleep quality among patients with sleep disturbances (SOE: Moderate)

- Evidence from 1 RCT suggests that listening to music may improve subjective assessments of total sleep time among patients with sleep disturbances (SOE: Moderate)

Discussion

Overall, the findings of the 20 studies from the SR and the additional RCT suggest that music-based interventions improve sleep and sleep quality according to subjective measures but may not impact objective assessments of sleep among patients with chronic insomnia disorder. Because design of included music-based interventions varied widely—type of music, activities while listening to music, amount of time for the music intervention and proximity to sleep time, etc. –the research showing some benefit for a diverse group of interventions is promising. However, more research is needed to understand the mechanism by which music impacts sleep and how to optimize music interventions to maximize the impact. Because music is so accessible and has essentially no adverse effects, even modest benefits suggest that further study is warranted.

Table 1. Strength of Evidence for Music Interventions to Treat CID

Primary Outcomes	Quantity and Type of Evidence	Intervention (n)/ Control (n)	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Pittsburgh Sleep Quality Index (PSQI)/ overall sleep quality	1 SR with 20 studies (RCTs and non-RCTs) (Feng, et al., 2018)	Music-based interventions (n=684)/ non-music and other music-based interventions (n=655)—f/u not reported	Music interventions vs. usual care: SMD: -0.61, 95% CI: -1.01- -0.20), music-associated relaxation vs. usual care (-0.28, -0.48 to -0.08).	Yes (-1)	No	No	No	No	Moderate
Sleep parameters: Sleep onset latency (SOL), sleep efficiency (SE)	1 SR with 20 studies (RCTs and non-RCTs) (Feng, et al., 2018)	Music-based interventions (n=684)/ non-music and other music-based interventions (n=655)—f/u not reported	**SOL:** Music associated relaxation and listening to music vs. controls: (SMD: -0.26, -0.64- -0.09 and -0.28, -0.53 to -0.02). **Sleep efficiency:** listening to music and music with exercise showed a ns tendency to improve SE	Yes (-1)	No	No	No	No	Moderate

Objective sleep parameters (via EEG): TST, SOL, SE, sleep stages, REM sleep, WASO and number of awakenings.	1 RCT (Huang, et al., 2017).	N=71 (24 with music, 23 with music video and 24 with no music controls), f/u day 6 (after 4 days of intervention)	Neither music nor music video had any impact on objective sleep outcomes.	No	No	No	Yes (-1) due to small sample size	No	Moderate
Subjective sleep parameters: Total Sleep time (TST), SOL, daytime fatigue	1 RCT (Huang, et al., 2017).	N=71 (24 with music, 23 with music video (MV) and 24 with no music controls), f/u day 6 (after 4 days of intervention)	Music group had subjectively longer TST than MV or control groups: 404.21 min (SE 11.95) vs. 365.28 (11.45) vs. 386.58 (9.00).	No	No	No	Yes (-1) due to small sample size	No	Moderate

CI: confidence interval; CID: chronic insomnia disorder; CG: control group; EEG: electroencephalogram; ES: effect size; F/u: Follow-up; ISI: MD: mean difference; MV: music video; NR: not reported; NS: not significant; PCT: QoL: Quality of Life; PSQI: Pittsburgh Sleep Quality Index; RoB: Risk of Bias; RCT: randomized controlled trials; SE: standard error; SOL: Sleep onset latency; SMD: standardized mean difference; SM: self-monitoring; SR: systematic review; ss; statistically significant; Tx: treatment; TAU: treatment as usual; TST: total sleep time; TWT: total wake time; WASO: Wake after sleep onset; WL: waitlist

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 Review on Music Interventions to Treat Chronic Insomnia Disorder

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
Reference: Feng et al, 2018 **Organization/Country:** The 302nd Hospital of Chinese PLA, Beijing, China. Most included studies took place in Asia. **Purpose:** to compare and rank music interventions and no-music controls for primary insomnia patients. **AMSTAR Rating:** *High* **Overall RoB of Included Studies:** Risk of bias tool was the Physiotherapy Evidence Database (PEDro) scale score and the Critical Appraisal Skills Program (CASP).	**Databases Searched:** 4 English and Chinese databases including: PubMed, Embase, the Cochrane Library, and China National Knowledge Infrastructure Library (CNKIL) **Dates Searched:** Inception to May 2017 **Inclusion/Exclusion Criteria:** clinical trials (random or not randomized) of adults with primary insomnia in the community or clinical settings. Other study designs (narrative reviews, etc.) excluded. **Outcomes:** Primary outcome was sleep quality as measured by the PSQI overall and the sleep quality subscale of the PSQI. Secondary outcomes were sleep onset latency (SOL) in minutes, and sleep efficiency (%). Sleep efficiency was the total sleep time divided by the total recording time (analogous to time in bed).	**Final Evidence Base:** 20 trials **Number of Patients:** 1,339 (684 to music intervention and 655 to no-music controls) in 20 studies total, mean sample size=67 range (14-145). **Baseline characteristics:** Control and intervention arms did not differ from one another in terms of age, gender, marital status, duration of insomnia, education level, PSQI score at baseline. Baseline characteristics (means, etc.) not shown in SR.	**Interventions:** 12 interventions assessed including: listening to music, listening to music and acupuncture, listening to music and language induction, listening to placebo music, music-assisted relaxation with/ without stimulus control, music with exercise, stimulus control (avoid daytime napping, e.g.) usual care (sleep education, etc.). Half of the trials compared music intervention to usual care. **Comparators:** Half of the trials compared listening to music intervention to usual care, other comparators were acupuncture, western medicine, language induction, stimulus control, usual care muscle relaxation.	**PSQI: Listening to music vs. usual care:** All music interventions were ss more effective than usual care, with listening to music the most effective. (SMD: -0.61, 95% CI: -1.01- -0.20). **Overall sleep quality: Music interventions vs. usual care:** music-associated relaxation was ss more effective compared to usual care (-0.28, -0.48 to -0.08). **SOL: Music interventions vs. controls:** music-associated relaxation and listening to music were ss better than controls: (-0.26, -0.64- -0.09 and -0.28, -0.53 to -0.02). **Sleep efficiency: Music interventions vs. controls:** listening to music and music with exercise showed a tendency (ns) to improve sleep efficiency. **Limitations:** limited to adults, included studies had small sample sizes, limited to 4 databases, substantial heterogeneity between pairwise outcomes, inclusion of non-randomized trials.

CI: confidence interval; CID: chronic insomnia disorder; mos.: months; MD: mean difference; NR: not reported; NS: not significant; PSQI: Pittsburgh Sleep Quality Index; RoB: Risk of Bias; RCT: randomized controlled trials; SE: standard error; SOL: Sleep onset latency; SMD: standardized mean difference; SR: systematic review; ss; statistically significant; TST: total sleep time; WASO: Wake after sleep onset.

Table 4. Systematic Review Risk of Bias AMSTAR Checklist Table on Music to Treat CID

Question	Feng 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?	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?	No
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 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?	No
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

Table 6. Evidence Table for RCT on Music Interventions to Treat Chronic Insomnia Disorder (CID)

Study Details	Study Population	Treatment	Results	Conclusion/ Limitations
Reference: Huang et al., 2017 **Purpose:** To compare the effects of music and music video interventions on objective and subjective sleep quality. **Setting:** I-Shou University, Kaohsiung City, Taiwan **Funding source:** National Science Council, Taiwan	**Number of patients:** 71 (24 with music, 23 with music video and 24 with no music controls). **Inclusion criteria:** PSQI >=5, SOL> 30 minutes, TST <= 6.5 hours/ night over the last month, aged 20 or older. **Exclusion criteria:** neurological or psychiatric problems, pregnant or nursing, history of drug or alcohol abuse. **Pt. baseline characteristics (all pts):** Age (mean yrs.): 41.06 Gender (male/female): 79 % female, 55% married, Education: 49.3% > high school; 36.6% Buddhist, baseline PSQI: 9.48; 12.93% with depression. Baseline subjective TST(mean) = 379.23 (SD 81.78). No significant differences between intervention groups except more depression in music video group so this was covariate for the data analysis.	**Interventions: Music listening:** 3 peaceful Buddhist songs (30 minutes) to be listened for 4 days at bedtime. **Music video (MV):** 30-minute music video of seven peaceful religious Buddhist films (to be watched in full at one sitting) at least 2 hours before usual bedtime for 4 consecutive days. **Control:** no music or music videos during the study period. **Outcomes: Objective:** single-channel portable EEG used to assess TST, SOL, sleep efficiency, sleep stages, REM sleep, WASO and number of awakenings. **Subjective:** subjective Total Sleep time (TST), SOL, daytime fatigue. **Other:** affinity/ patient preference for music and MV assessed.	**Objective:** Neither music nor music video had any impact on objective sleep outcomes. **Subjective outcomes:** music group had subjectively longer TST than MV or control groups: 404.21 min (SE 11.95) vs. 365.28 (11.45) vs. 386.58 (9.00). **Dropouts:** 0 Adverse effects: 1 mild AE of patient worrying about losing EEG.	**Conclusions:** Neither music nor music video intervention had positive effect on objective sleep parameters. Listening to music increased subjective total sleep time in adults with sleep disturbances. **Limitations:** Small sample size, lack of impact could be related to specific music and music videos chosen, short duration of intervention and follow-up, subjective measurements may be unable to discern changes. **Study RoB:** Low risk of bias. Although participants were aware of their intervention assignment, intervention affinity did not differ between groups nor seem to affect result. **Author conflict:** Reported no conflicts.

CI: confidence interval; CID: chronic insomnia disorder; CG: control group; EEG: electroencephalogram; ES: effect size; F/u: Follow-up; ISI: MD: mean difference; MV: music video; NR: not reported; NS: not significant; PCT: QoL: Quality of Life; PSQI: Pittsburgh Sleep Quality Index; RoB: Risk of Bias; RCT: randomized controlled trials; SE: standard error; SOL: Sleep onset latency; SMD: standardized mean difference; SM: self-monitoring; SR: systematic review; ss; statistically significant; Tx: treatment; TAU: treatment as usual; TST: total sleep time; TWT: total wake time; WASO: Wake after sleep onset; WL: waitlist

Table 7. Cochrane Risk of Bias 2.0 for RCT on Music Interventions to Treat CID

Reference	Huang et al., (2017)
➢ 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)?	Yes
➢ Did baseline difference between study groups suggest a problem with randomization?	No
Overall RoB for Randomization Process	**Low**
➢ Were participants aware of their assigned intervention during the trial?	Yes
➢ 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**
➢ 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?	No
➢ 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?	No/ NA
Overall RoB of Missing Data	**Low**
➢ Was the method of measuring the outcome inappropriate?	No
➢ Could measurement or ascertainment of the outcome have differed between intervention groups?	No
➢ Were outcome assessors aware of the intervention received by study participants?	No
➢ Could assessment of the outcome have been influenced by knowledge of intervention received?	Yes
➢ Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No
Overall RoB of Measurement of Outcome	**Low**
➢ Was the trial analyzed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?	Yes
Overall RoB of Reported Results	**Low**
Overall Study RoB	**Low**

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

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

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

References

Feng, F., Zhang, Y., Hou, J., Cai, J., Jiang, Q., Li, X., … Li, B. A. (2018). Can music improve sleep quality in adults with primary insomnia? a systematic review and network meta-analysis. *International Journal of Nursing Studies*, *77*(May 2017), 189–196. https://doi.org/10.1016/j.ijnurstu.2017.10.011

Huang, H. T., Lin, S. L., Lin, C. H., & Tzeng, D. S. (2017). Comparison between acupuncture and biofeedback as adjunctive treatments for primary insomnia disorder. *Alternative Therapies in Health & Medicine*, *23*(4), 8–15.

Table 1. Summary of Finding of CIH for CID

	Sleep Quality			Insomnia Severity			Total Sleep Time			Wake After Sleep Onset			Sleep Latency		
Intervention	**EB**	**Findings**	**SOE**	**EB**	**Findings**	**SOE**	**EB**	**Findings**	**SOE**	**EB**	**Findings**	**SOE**	**EB**	**Findings**	**SOE**
ACU vs. Active control	23 RCTs	+	L	1 RCT	-	L	9 RCTs	+	VL				1 RCT	+	L
ACU vs. Sham	4 RCTs	+	M	2 RCTs	+	M	7 RCTs	+	L						
Cannabinoids	1 RCT	NS	VL												
Exercise				4 RCTs	+	L	1 SR (k=5)	NS	L	1 RCT	+	L	1 SR (k=5)	NS	L
Massage				1 RCT	+	L	1 RCT	NS	VL				1 RCT	NS	VL
Meditation	2 RCTs	+	M	3 RCTs	+/NS*	M	3 RCTs	+	M	2 RCTs	NS	L	3 RCTs	+	M
Music	1 SR (k=20)	+	M				1 RCT	+	M				1 SR (k=20)	+	M
Relaxation															
TMS							1 RCT	+	VL						
Tai Chi	2 RCTs	+	VL												
Yoga				1 RCT	+	VL									

+ 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
*Meditation showed no statistically significant difference compared to TAU (pharmacotherapy w/ sleep hygiene, however meditation was more effective than inactive controls (self-monitoring or education).

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 Chronic Insomnia Disorder
- **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: antihistamine (diphenhydramine); tricyclic antidepressants (doxepin); sedative-hypnotics (eszopiclone, zaleplon, zolpidem IR, zolpidem CR, zolpidem CR); benzodiazepine (temazepam); melatonin agonists (ramelteon); orexin receptor antagonists (suvorexant); atypical antidepressants (trazodone); tricyclic antidepressant (amitriptyline); tetracyclic antidepressant (mirtazapine)
    - Psychological treatments: CBT-I; sleep restriction; paradoxical intention; biofeedback therapy; BBTI
- **Outcomes:** quality of life, functional status, patient satisfaction, anxiety, pain, PTSD, depression, insomnia (general, such as insomnia severity index), total sleep time (or sleep duration), wake after sleep onset, sleep latency, sleep quality
- **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 CID.
- **Wrong language:** Study in language other than English.
- **Wrong or no intervention:** CIH treatments other than those listed in inclusion criteria; medications other than those listed in inclusion criteria; psychological treatments other than those listed in inclusion criteria
- **Wrong comparator:** CIH treatments other than those listed in inclusion criteria; medications other than those listed in inclusion criteria; psychological treatments other than those listed in inclusion criteria

- **Wrong outcome(s):** Any study that does not have at least one of the included outcomes of interest. Any subjective outcome (e.g. symptoms; quality of life) not measured using a validated instrument.

Appendix B

Table 1. Studies Excluded at Data Abstraction Level

Authors	Reason for Exclusion
Acupuncture	
Zhang, Y. F. et al., 2010	Wrong comparator
Yeung, W. F. et al., 2018	Wrong intervention
Yeung, W. F. et al., 2009	Study included in Shergis et al., 2016 SR
Yeung, W. F. et al., 2012	Wrong intervention
Yeung, W. F. et al., 2009b	More recent/comprehensive SR exists
Vieira, A. et al., 2018	More recent/comprehensive SR exists
Waits, A. et al., 2018	Wrong intervention
Tu, J. H. et al., 2012	Included in a previous SR
Sjöling, M., Rolleri, M., & Englund, E., 2008	Included in a previous SR
Nordio, M., & Romanelli, F., 2008	Wrong intervention
Li, L. F., & Lu, J. H., 2010	Wrong intervention
Lee, M. S. et al., 2008	More recent/comprehensive SR exists
Kalavapalli, R., & Singareddy, R., 2007	Older than 2008
Huang, W., Kutner, N., & Bliwise, D. L., 2009	More recent/comprehensive SR exists
Cheuk, D. K. et al., 2012	More recent/comprehensive SR exists
Huo, Z. J., Guo, J., & Li, D., 2013	Wrong comparator
Huang, L. S. et al., 2009	Wrong intervention
Huang, H. T., Lin, S. L., Lin, C. H., & Tzeng, D. S., 2017	Wrong comparator
He, W. et al., 2018	Wrong population
Hachul, H. et al., 2012	Fewer than 20 patients enrolled in study
Guo, J. et al., 2013	Included in a previous SR
Gao, X. Y. et al., 2014	Wrong intervention
Gao, X. et al., 2013	Wrong comparator
Ernst, E., Lee, M. S., & Choi, T. Y., 2011	More recent/comprehensive SR exists
Chung, K. F. et al., 2018	Wrong comparator
Chung, K. F. et al., 2014	Wrong population
Chen, J. et al., 2018	Protocol only
Chen, H. Y. et al., 2007	Older than 2008
Cao, H. et al., 2009	More recent/comprehensive SR exists
Bergdahl, L. et al., 2017	Wrong population

Authors	Reason for Exclusion
Cannabinoids	
No studies were excluded.	
Massage Therapy	
No studies were excluded.	
Relaxation Therapy	
No studies were excluded.	
Transcranial Magnetic Stimulation (TMS)	
No studies were excluded.	
Tai Chi	
Zou, L. et al., 2018	More recent/comprehensive SR exists
Raman, G. et al., 2013	More recent/comprehensive SR exists
Jiang, Y. H., Tan, C., & Yuan, S., 2017	Wrong intervention
Yoga	
No studies were excluded.	
Meditation	
Zhang, J. X. et al., 2015	Wrong intervention
Wang, X. et al., 2019	Wrong population
Rusch, H. L. et al., 2018	Wrong population
Ong, J. C. et al., 2018	Wrong outcome(s)
Garcia, M. C. et al., 2018	Duplicate
Gross, C. R. et al., 2011	Wrong intervention
Gong, H. et al., 2016	More recent/comprehensive SR exists
Garland, S. N. et al., 2015	Wrong population
Black, D. S. et al., 2015	Included in a previous SR
Exercise	
Yang, P. Y. et al., 2012	More recent/comprehensive SR exists
Wang, J. et al., 2015	Wrong intervention
Tan, X. et al., 2016	Wrong population
Sharif, F. et al., 2015	Wrong population
Rubio-Arias, J. Á. et al., 2017	More recent/comprehensive SR exists
Pasos, G. S. et al., 2012	More recent/comprehensive SR exists
Montgomery, P., & Dennis, J. A., 2002	Older than 2008
Lowe, H. et al., 2019	More recent/comprehensive SR exists
Hartescu, I., Morgan, K., & Stevinson, C. D., 2015	Included in a previous SR; Duplicate study
Baron, K. G. et al., 2013	Abstract only
Alessi, C., & Vitiello, M. V., 2015	More recent/comprehensive SR exists
Music Interventions	
Wang, Q. et al., 2016	Included in a previous SR
Jespersen, K. V. et al., 2015	More recent/comprehensive SR exists

Authors	Reason for Exclusion
Huang, C. Y., Chang, E. T., & Lai, H. L., 2016	Wrong comparator
Harmat, L., Takács, J., & Bodizs, R., 2008	Wrong population
De Niet, G. et al., 2009	More recent/comprehensive SR exists
Chang, E. T. et al., 2012	More recent/comprehensive SR exists
Mixed CIH Interventions	
Sarris, J., & Byrne, G. J., 2011	More recent/comprehensive SR exists
Brasure, M. et al., 2015	More recent/comprehensive SR exists
Melo, F. D. L. et al., 2018	Included in a previous SR

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Appendix C

See **Figures 2, 3, 4, 5 and 6** below for bubble maps. Bubble maps provide a visual overview of the distribution of evidence for the complementary and integrative health and other interventions included in these systematic reviews. The bubble maps display information about the research meeting the inclusion and exclusion criteria (see Appendix A) for these reviews and include the following:

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

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

Figure 2. Bubble Plot of Findings for CID Sleep Quality

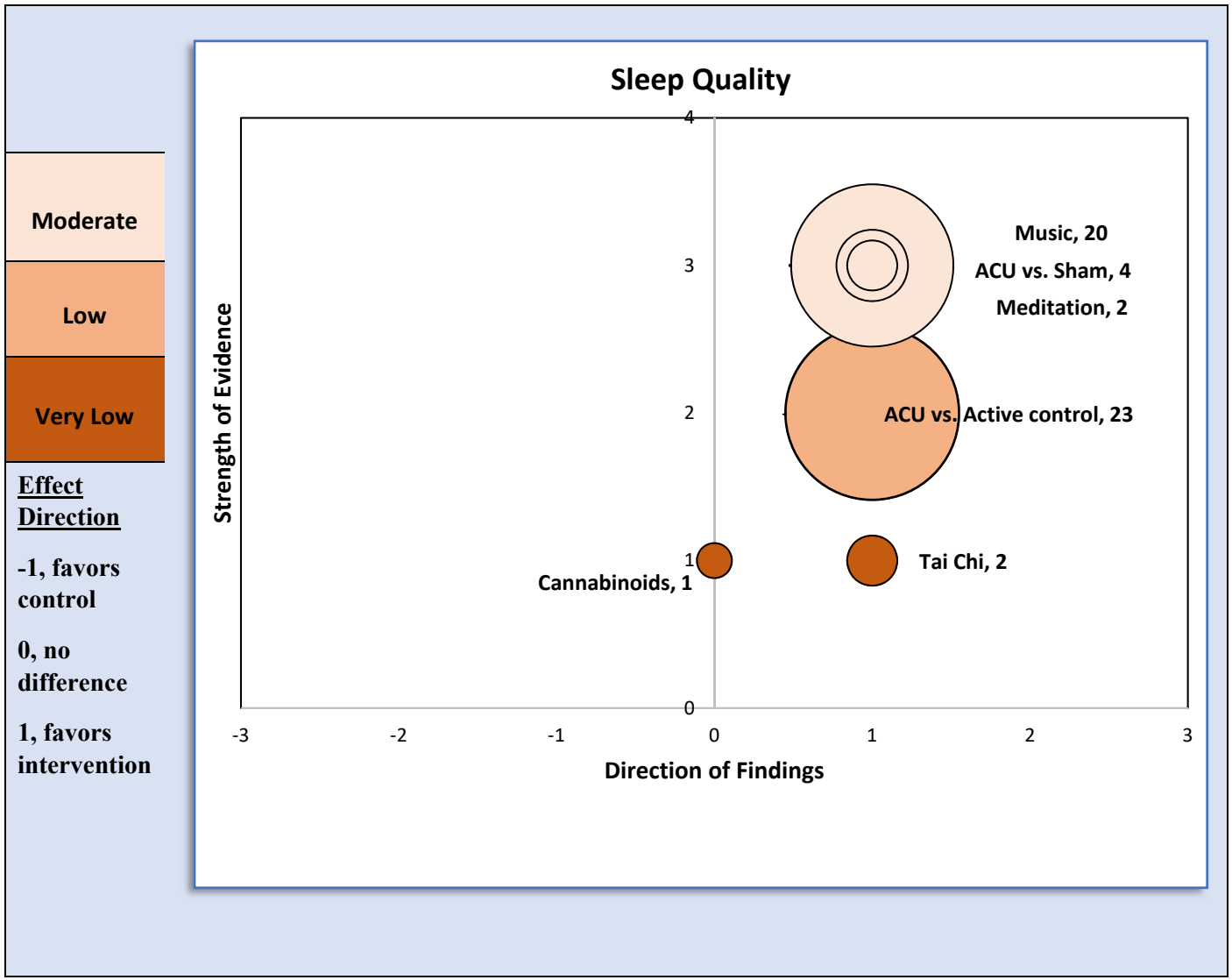

Figure 3. Bubble Plot of Findings for CID Insomnia Severity

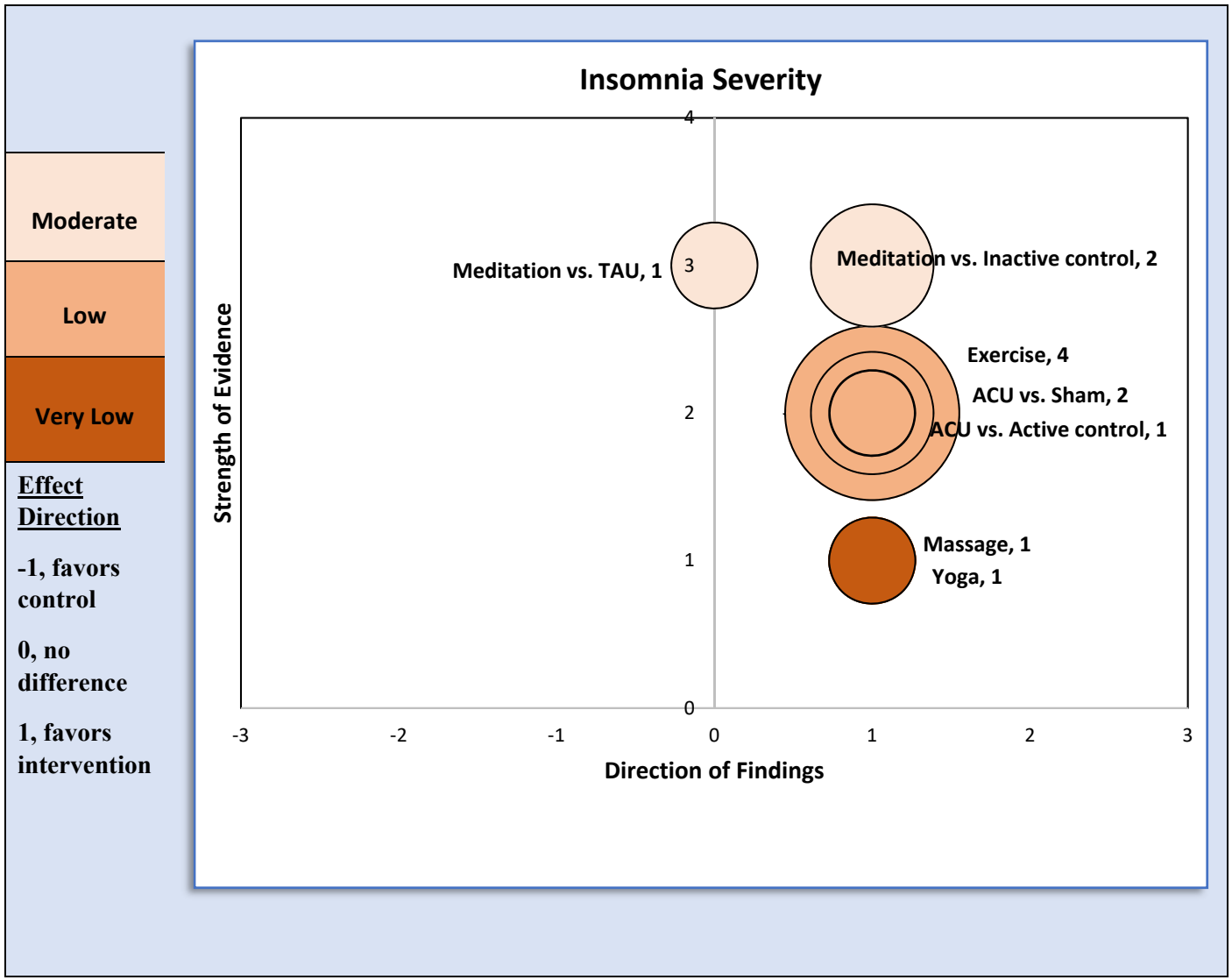

Figure 4. Bubble Plot of Findings for CID Total Sleep Time

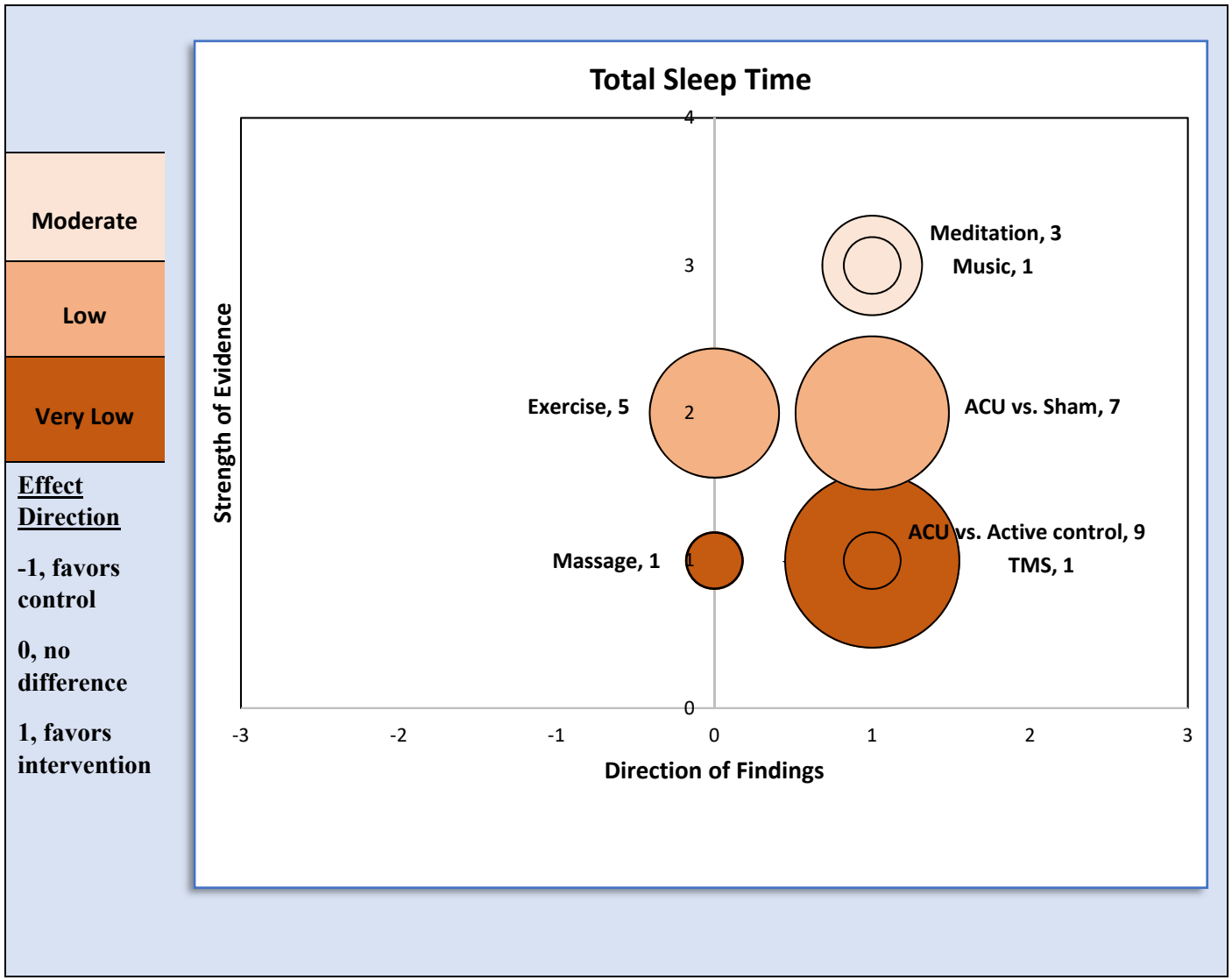

Figure 5. Bubble Plot of Findings for CID Wake After Sleep Onset

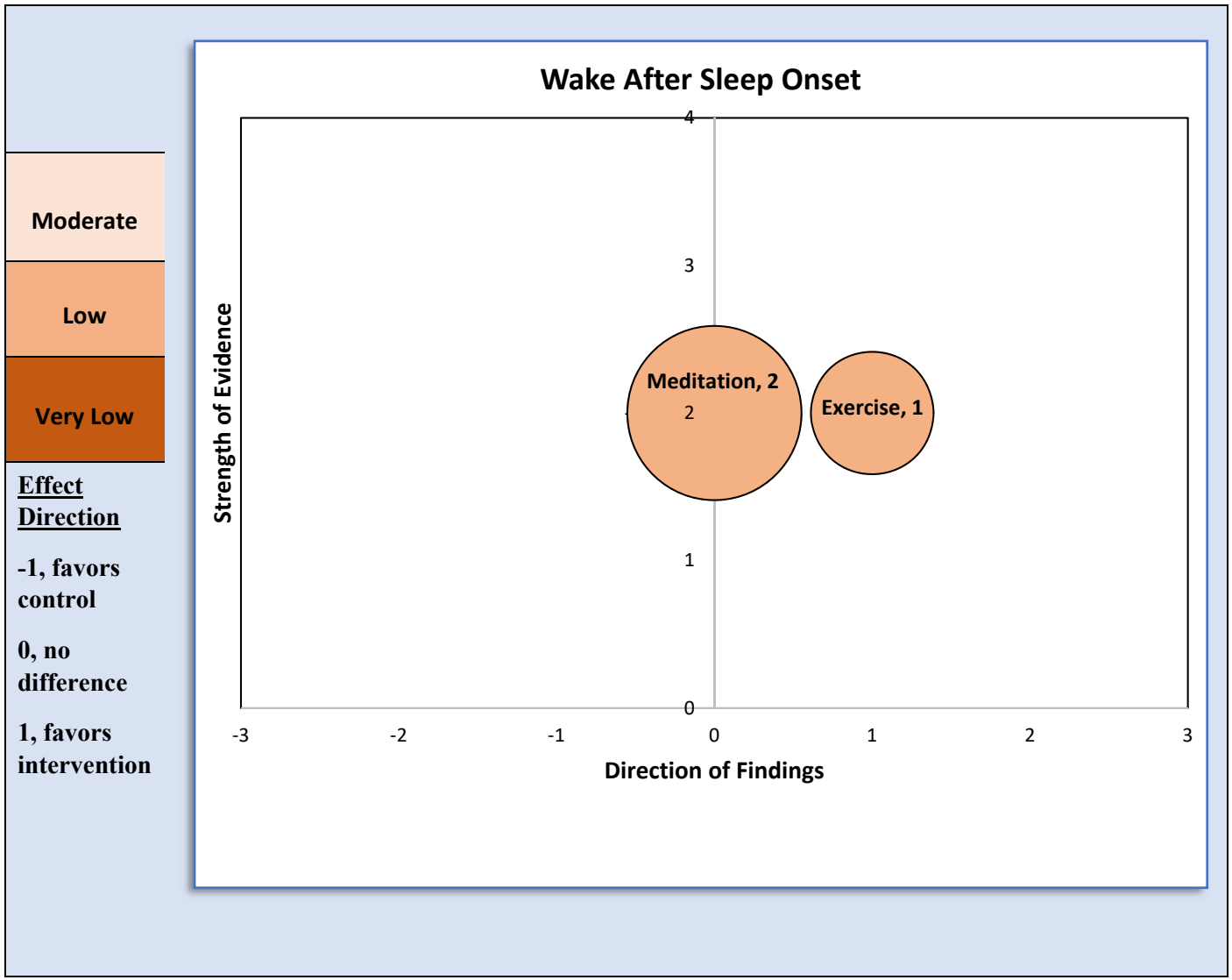

Figure 6. Bubble Plot of Findings for CID Sleep Onset Latency