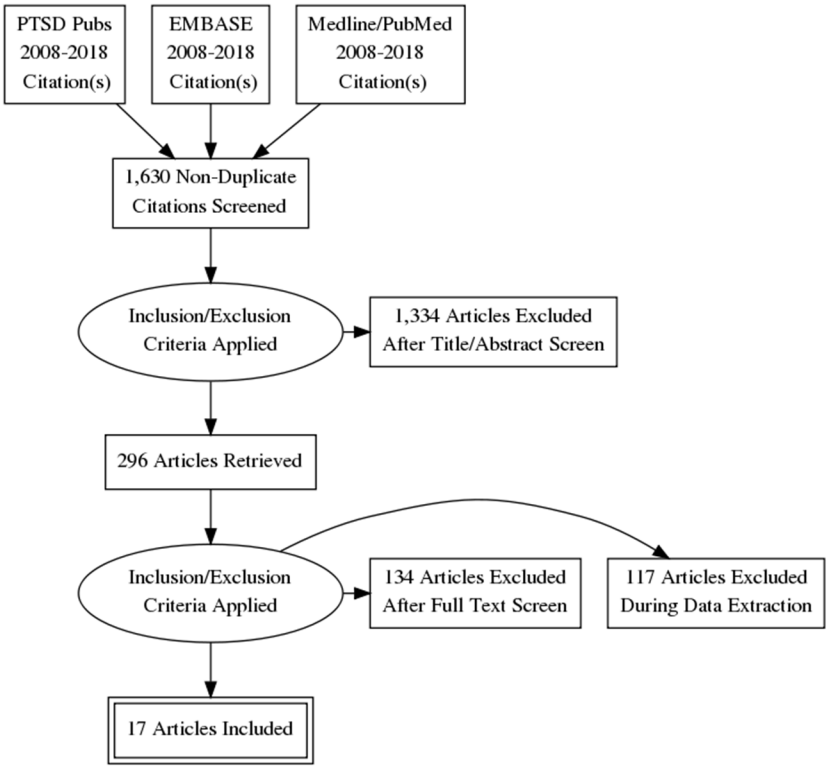
Chapter 1: Complementary and Integrative Health and other Non-Conventional Approaches for Treating Post-traumatic Stress Disorder (PTSD)

Results of the Literature Search for PTSD

Extensive literature searches identified 1,630 citations (after duplicates removed) potentially addressing the CIH interventions of interest for the treatment of PTSD. Of those, 1,334 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 296 full-length articles were retrieved for review (See Figure 1 for the PRISMA diagram). Of those, 134 were excluded due to having the wrong patient population (38 studies), the wrong study design (35 studies), the wrong intervention (31 studies), less than 20 patients (12 studies), duplicates (11 studies), wrong outcomes (4 studies), and more recent and/or comprehensive systematic review available (3 studies). An additional 117 studies were excluded during data abstraction. Reasons for these exclusions are listed in **Appendix B**.

Figure 1. Prisma Study Flow Diagram for PTSD



Overall, 17 studies were included in the systematic review for PTSD. **Table 1** presents a summary of the evidence (how many RCTs and/or SRs) for each CIH intervention.

Table 1. Overview of Evidence for CIH and other Non-Conventional Interventions to Treat Post-traumatic Stress Disorder

Intervention	Number and Type of Studies
Accelerated Resolution Therapy (ART)	1 RCT in 2 publications
Acupuncture	1 SR (with 7 RCTs)
Art therapy	0
Cannabinoids	0
Chiropractic care	0
Equine therapy	1 RCT
Exercise therapy (outdoor therapy)[1]	4 RCTs
Healing Touch	1 RCT
Hyperbaric Oxygen Therapy	0*
Massage therapy	0
Mind-Body therapies (includes meditation and yoga)	3 SRs (with 31 RCTs); 1 RCT
Music therapy	0
Tai chi	0
Therapeutic touch (Relaxation therapy)	2 RCTs
Training and caring for service dogs	0
Transcranial Magnetic Stimulation (TMS)	1 SR (with 11 RCTs); 2 RCTs
Total Studies	**17 studies (5 SRs with 49 RCTs and 12 additional RCTs)**

*We retrieved one SR (Peterson et al., 2018) with 2 RCTs that included patients with traumatic brain injury and co-occurring PTSD symptoms. However, the applicability of the findings from these RCTs to patients with PTSD was unclear because the prevalence of PTSD in these studies was only 36% to 65% and PTSD subgroups were not separately analyzed. Pooled findings of these RCTs suggest that there was no significant difference in PTSD score change between HBOT and controls.
PTSD: post-traumatic stress disorder; RCT: Randomized controlled trial; SR: systematic review

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

Accelerated Resolution Therapy (ART)

Evidence Base

Our searches of the literature identified one RCT published in two publications reporting on separate outcomes for the same population of patients who received ART for the treatment of PTSD symptoms (Kip et al. 2013; Kip et al. 2014). The overall strength of the evidence for all the reported outcomes of interest was rated low (**See Table 1**). This is largely due to the methodologic quality of the study and the small sample size.

Kip et al. conducted an RCT in which active duty service members and veterans were randomized to receive ART (n=29) or an active control (fitness and career counselling) (n=28). The mean age of the patients enrolled in the study was 41 years (38.9 ART; 44.0 AC) and most of the patients were male (80%). The authors recruited both active and retired service members. However, most of the enrolled patients were veterans (70%) compared to active duty service members (12%) and reservist (17%). **Table 3** presents more information about the characteristics of the enrolled patients. The primary outcomes of interest in the RCT were reduction in symptoms of PTSD, depression and pain and improved sleep quality.

ART typically consists of two components and bilateral eye movements. The first component involves "imaginary exposure" in which a patient is asked to recall the traumatic event while focusing on his/her emotions and physiological reactions. During this process, the patient is coached into a state of relaxation. Once relaxed, a trained clinician engages the patient in a series of bilateral eye movements intended to aid in diminishing any uncomfortable emotions and physical symptoms. The second component involves "imagery re-scripting" during which the patient replaces the traumatic memory with a neutral or positive image. ART was delivered to the patients enrolled in the Kip study in 2 to 5 sessions lasting about 60 to 75 minutes. Patients in the active control group received two, 1-hour sessions of fitness or career planning, as selected by the patient.

Study Quality

Using the Cochrane tool, we rated the RoB of the RCT as high primarily due to no blinding of patients, clinicians, or outcome assessors. See **Table 4** for individual 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 ART statistically significantly reduces PTSD symptoms immediately following treatment and at 3 months follow-up compared to active control. (SOE: Low)
- Evidence from 1 RCT suggests that ART statistically significantly reduces depression symptoms immediately following treatment and at 3 months follow-up compared to active control. (SOE: Low)
- Evidence from 1 RCT suggests that ART statistically significantly improves sleep quality at 3 months follow-up compared to active control. No significant difference was observed immediately following treatment. (SOE: Low)
- Evidence from 1 RCT suggests that ART statistically significantly reduces pain immediately following treatment compared to active control. (SOE: Low)

Discussion

Overall, the results of the Kip et al. RCT suggest that ART statistically significantly reduces symptoms of PTSD and depression compared to an active control immediately following treatment and at 3 months follow-up (Kip et al. 2013). It also appears to significantly improve sleep quality as measured by the Pittsburgh Sleep Quality Index compared to active control at 3 months follow-up. However, there was no observed statistically significant difference in sleep quality between ART and active control immediately following treatment. Finally, the results indicate that ART alleviates pain among veterans who reported experiencing neuropathic pain at baseline (Kip et al. 2014). See **Table 3** for more details about the results of the RCT. The overall strength of the evidence for all the reported outcomes of interest was rated low (**See Table 1**). This is largely due to limitations in the methodological quality of the study and the small sample size.

Table 1. Strength of Evidence for Accelerated Resolution Therapy (ART) to Treat PTSD

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
ART									
PTSD symptoms	1 RCT (Kip, 2013)	ART (n=29) vs. active control (n=28) 3 mos.	**Change on PCL-M** (mean [SD]): **Post-tx:** -15.4 (13.7); -2.1 (5.6); ES: 1.25, p<0.001; **3 mos. f/u:** -20.5, -25.0 to -16.0; ES 1.22, p<0.001; favors ART	Yes (-1)	No	No	Yes (-1); small sample size	NA	Low
Depression	1 RCT (Kip, 2013)	ART (n=29) vs. active control (n=28) 3 mos.	**Change in CES-D** (mean; 95% CI): **Post-tx:** -12.3, -17.1 to -7.5; 1.3, -1.6 to 4.2; ES: 1.27, p<0.001; **3 mos. f/u:** -11.8, -15.5 to -8.0; ES 0.85, p<0.001; favors ART	Yes (-1)	No	No	Yes (-1); small sample size	NA	Low
Sleep Quality	1 RCT (Kip, 2013)	ART (n=29) vs. active control (n=28) 3 mos.	**Change in PSQI** (mean; 95% CI): **Post-tx:** -2.4, -4.7 to -0.1; -0.1, -1.0 to 0.7; ES: 0.48, p=0.14; NS; **3 mos. f/u:** -5.7, -	Yes (-1)	No	No	Yes (-1); small sample size	NA	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
			7.8 to -3.6; ES 0.69, p<0.001; favors ART						
Pain	1 RCT (Kip, 2013)	ART (n=29) vs. active control (n=28) 3 mos.	**Change in POQ** (mean, [SD]): **Post-tx:** -14.0 (16.4); -0.5 (12.2); ES 0.08, p=0.006; favors ART	Yes (-1)	No	No	Yes (-1); small sample size	NA	Low

ART: Accelerated Resolution Therapy; CES-D: Center for Epidemiologic Studies Depression Scale; CI: confidence interval; CT: control group; ES: effective size; f/u: follow-up; mos.: months; NR: not reported; NS: not significant; PCL-M: PTSD Checklist (military version); POQ: Pain Outcomes Questionnaire; PTSD: post-traumatic stress disorder; PSQI: Pittsburgh Sleep Quality Index; RCT: randomized controlled trials; SD: standard deviation

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

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

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

Table 3. Evidence Table for RCTs on Accelerated Resolution Therapy (ART) to Treat PTSD

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Kip et al. (2014) and Kip et al. (2013) **Purpose:** To present the findings of the first RCT of ART conducted among U.S. service members and veterans. **Setting:** VA facilities in Tampa, FL; additional recruiting took place in Las Vegas, NV. **F/u:** 3 mos. **Funding source:** NR	**Number of patients:** 57; n=29 ART; n=28 AC **Inclusion criteria:** U.S. service member or veteran with prior deployment; age ≥18 yrs.; symptoms of psychological trauma including score of ≤40 on the PCL-M checklist and endorsement of PTSD items on the PDSQ; ability to read and speak English; denial of homicidal or suicidal ideation; and no evidence of psychotic behavior or psychological crisis. **Exclusion criteria:** Brain injury prohibiting speech, writing or purposeful action; major psychiatric disorder; currently undergoing treatment for substance abuse; previous diagnosis of eye movement disorder; and any medical condition judged to put individual at risk. **Pt. baseline characteristics (ART; AC):** Age (mean yrs.): 38.9 (11.5); 44.0 (13.4) Gender (% female): 17.2%; 21.4% Previous tx for PTSD (%): 65.5%; 71.4% Current military status (%): Active duty: 13.8%; 21.4% Reservist: 17.2%; 17.9% Veteran: 69.0%; 71.4% CES-D ≥16 (%): 75.9%; 75.0% PCL-M ≥50 (%): 69%; 60.7% Pain (% reporting): 93%; mostly neuropathic	**Intervention:** ART was delivered in 2 to 5, 60 to 75 min sessions that consisted of 2 components- first the pt is asked to recall the traumatic event while undergoing relaxation coaching followed by diminishment of uncomfortable emotions through clinician directed eye movements; the second involves replacing the traumatic memory with a neutral imagery. **Control:** Consisted of two, 1-hour sessions during which the pt received fitness and career counselling. **Outcomes of Interest:** PTSD symptoms (as measured by the PCL-M), depression (as measured by the CES-D), sleep quality (as measured by the PSQI), pain, and AEs	**Post-Intervention** **PTSD symptoms (ART; AC):** Pre/post change on PCL-M (mean [SD]): -15.4 (13.7); -2.1 (5.6); ES: 1.25, p<0.001; favors ART % responders (measured by % reliable change): 58.6%; 10.2%; RR: 5.47, 95% CI: 1.81 to 22.14, p=<0.001 **Depression (ART; AC)** Pre/post change in CES-D (mean; 95% CI): -12.3, -17.1 to -7.5; 1.3, -1.6 to 4.2; ES: 1.27, p<0.001 **Sleep Quality (ART; AC):** Pre/post change in PSQI (mean; 95% CI): -2.4, -4.7 to -0.1; -0.1, -1.0 to 0.7; ES: 0.48, p=0.14 **Pain (ART; AC):** Pre/post change in POQ (mean, [SD]): -14.0 (16.4); -0.5	**Conclusion:** Results suggest that ART therapy statistically significantly reduces symptoms of PTSD and depression compared to active control. It also appears to improve sleep quality and alleviate pain among veterans reporting experiencing neuropathic pain. **Limitations:** No blinding and limited follow-up **Study ROB:** High; due primarily to no blinding of patients, clinicians, and outcome assessors. **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
			(12.2); ES 0.08, p=0.006 **<u>3 mos. f/u (ART only; change from BL to f/u)</u>** PCL-M (mean, 95% CI): -20.5, -25.0 to -16.0; ES 1.22, p<0.001 CES-D (mean, 95% CI): -11.8, -15.5 to -8.0; ES 0.85, p<0.001 PSQI (mean, 95% CI): -5.7, -7.8 to -3.6; ES 0.69, p<0.001 Pain: NR **AEs (ART; AC):** n=7 (2 severe, 4 moderate, and 1 mild); n=0 4 AE's (2 nightmares, 1 anxiety, 1 sleep awakening) likely related to ART	

AC: active control; AEs: adverse events; ART: Accelerated Resolution Therapy; BL: baseline; CES-D: Center for Epidemiologic Studies Depression Scale; CI: confidence interval; ES: effect size; f/u: follow-up; mos.: months; NR: not reported; NS: not significant; PCL-M: PTSD Checklist (military version); POQ: Pain Outcomes Questionnaire; PTSD: post-traumatic stress disorder; PSQI: Pittsburgh Sleep Quality Index; RCT: randomized controlled trials; ROB: risk of bias; SD: standard deviation

Table 4. Cochrane Risk of Bias 2.0 Tool for RCTs on ART to Treat PTSD

Reference	Kip et al. (2013)
• Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	Yes
• Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization, concealed envelopes)?	NI
• Did baseline difference between study groups suggest a problem with randomization?	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?	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?	NA
• Could missingness in the outcome depend on its true value?	NA
• Do the proportions of missing outcome data differ between intervention groups?	NA
• Is it likely that missingness in the outcome depended on its true value?	NA
Overall ROB of Missing Data	**Low**
Measurement of the Outcome	
• Was the method of measuring the outcome inappropriate?	No
• Could measurement or ascertainment of the outcome have differed between intervention groups?	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	**High**
Selection of Reported Results	

Reference	Kip et al. (2013)
• 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, 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

Kip, K. E., Rosenzweig, L., Hernandez, D. F., Shuman, A., Sullivan, K. L., Long, C. J., …Diamond, D. M. (2013). Randomized controlled trial of accelerated resolution therapy (ART) for symptoms of combat-related post-traumatic stress disorder (PTSD). *Military Medicine, 178*(12), 1298-1309. doi: 10.7205/MILMED-D-13-00298

Kip, K. E., Rosenzweig, L., Hernandez, D. F., Shuman, A., Diamond, D. M. Girling, S. A., …McMillan, S. C. (2014). Accelerated resolution therapy for treatment of pain secondary to symptoms of combat-related posttraumatic stress disorder. *European Journal of Psychotraumatology, 5*. doi:10.3402/ejpt.v5.24066

Acupuncture

Evidence Base

Our searches of the literature identified one recently published SR that met inclusion criteria and addressed one or more of the key questions. The review published by Grant et al. (2017) assessed the impact of acupuncture on symptoms of PTSD, depression, anxiety and sleep quality among adults with clearly defined and diagnosed PTSD (Grant et al. 2017). The strength of the evidence for the reported outcomes ranged from low to very low due to methodological limitations of the included studies, between study heterogeneity, and lack of precision evidenced by wide confidence intervals surrounding the effect size estimates.

The evidence base for this review included 7 RCTs enrolling a total of 709 patients. The mean age of the enrolled patients was 39 years (range 18 to 65), and between 32% and 100% of patients were male. Follow-up ranged from immediately following treatment to 1 to 6 months post-treatment. See **Table 3** for more information about the patients and interventions assessed in the SRs addressing acupuncture.

Acupuncture was administered by placing thin or fine needles into known acupoints, either as adjunctive or monotherapy. Sessions ranged from 30 to 60 mins/session, 2 to 4 sessions per/week for 3 to 12 weeks. The control conditions included the following (2 studies had more than 1 arm):

- Key Question 1: Treatment as usual (3 RCTs), waitlist (1 RCT), and sham acupuncture (1 RCT)
- Key Question 2: Paroxetine (3 RCTs)
- Key Question 3: Cognitive behavioral therapy (CBT, 1 RCT)

Study Quality

Using the AMSTAR instrument, we rated the quality of the Grant review as high (See **Table 4** for more information on the review ratings). The authors of this review assessed the RoB of the RCTs using the Cochrane tool. The overall RoB of the trials included in the Grant review was moderate to high, primarily due to high attrition, unblinded participants, and no intent-to-treat analysis.

Key Findings

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

Acupuncture (fine needle)

- Combined evidence of 6 RCTS suggests that acupuncture statistically significantly reduces symptoms of PTSD compared to controls immediately following treatment. (SOE: Very low)
- Combined evidence of 4 RCTS suggests that acupuncture statistically significantly reduces symptoms of PTSD at 1 to 6 months follow-up. (SOE: Low)
- Evidence from 1 RCT suggests that acupuncture statistically significantly improves functional status compared to controls at 1 to 6 months follow-up. (SOE: Very low)
- Evidence from 1 RCT suggests no statistically significant difference between acupuncture and controls in improving quality of physical or mental health at 1 to 6 months follow-up. (SOE: Very low)

- Combined evidence from 4 RCTs suggests that acupuncture statistically significantly improves symptoms of depression compared to controls at 1 to 6 months follow-up. (SOE: Low)
- Evidence suggests no statistically significant difference between acupuncture and controls in reducing symptoms of anxiety (3 RCTs) or improving sleep quality (2 RCTs). (SOE: Very low)

Discussion

Overall, the findings of the Grant review suggest that fine needle acupuncture reduced PTSD symptoms both immediately following treatment (standardized mean difference [SMD]: 0.80, 95% [confidence interval] CI -1.59 to -0.01) and at 1 to 6 months follow-up (SMD: -0.46; 95% CI -0.85 to -0.06) compared to controls (Grant et al. 2017). It also improved functional status (SMD -0.97, 95% CI -1.53 to -0.42) and symptoms of depression (SMD: -0.56, 95% CI -0.88 to -0.23) compared to controls. However, no statistically significant differences were observed between fine needle acupuncture and controls for improving physical or mental health status, anxiety or sleep quality. The authors of the review indicated that meta-regression results suggest a significant difference in favor of acupuncture as monotherapy or adjunctive, for any type of acupuncture (e.g., full body, auricular acupuncture), and acupuncture compared to passive or active control. No serious adverse events were reported. The strength of the evidence for the reported outcomes ranged from low to very low due to methodological limitations of the included studies, between study heterogeneity, and lack of precision evidenced by wide confidence intervals surrounding the effect size estimates.

Table 1. Strength of Evidence for Acupuncture to Treat PTSD

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Acupuncture (fine needle)									
PTSD symptoms	**Post-tx:** 6 RCTs in Grant (2017)	ACU vs. any control (508);	SMD: -0.80, 95% CI -1.59 to -0.01; favors ACU	Yes (-1)	Yes (-1) Substantial heterogeneity	No	Yes (-1); wide 95% CIs	No	Very Low
	1 to 6 mos. f/u: 4 RCTs in Grant (2017)	ACU vs. any control (387)	SMD: -0.46; 95% CI -0.85 to -0.06; favors ACU	Yes (-1)	No	No	Yes (-1); wide 95% CIs	No	Low
Quality of Life (physical health, mental health and functional status	1 RCT in Grant (2017)	ACU vs any control (55) 1 to 6 mos.	**Physical health**: SMD: -0.47, 95% CI -1.01 to 0.07, NS **Mental health:** SMD: -0.33, 95% CI -0.87 to 0.21, NS **Functional status:** SMD -0.97, 95% CI -1.53 to -0.42,	Yes (-1)	No	No	Yes (-2); small sample size and wide 95% CIs	No	Very low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			favors ACU						
Depression symptoms	4 RCTs included in Grant (2017)	ACU vs. any control (387) 1 to 6 mos. f/u	SMD: -0.56, 95% CI -0.88 to -0.23), favors ACU	Yes (-1)	Yes (-1); substantial heterogeneity	No	No	No	Low
Anxiety symptoms	3 RCTs in Grant (2017)	ACU vs. any control (332) 1 to 6 mos.	SMD: -0.35, 95% CI -1.17 to 0.47, NS	Yes (-1)	Yes (-1); substantial heterogeneity	No	Yes (-1); wide 95% CI	No	Very Low
Sleep quality	2 RCTs included in Grant (2017)	ACU vs. any control (53) 1 to 6 mos.	SMD: -0.46, 95% CI -3.95 to 3.03, NS	Yes (-1)	No	No	Yes (-2); small sample size and wide 95% CIs	No	Very Low

ACU: acupuncture; CBT: cognitive behavioral therapy; CI: confidence interval; CT: control group; EMDR: Eye movement desensitization reprocessing; ES: effective size; mos.: months; NR: not reported; NS: not significant; PTSD: post-traumatic stress disorder; RCT: randomized controlled trials; SE: standard error; SMD: standardized mean difference; TAU: treatment as usual; 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 PTSD

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
Reference: Grant et al. 2017 **Organization/Country:** Rand Corporation, CA, USA **Purpose:** To estimate the effects of acupuncture on symptoms of PTSD, depression, anxiety, and sleep quality. **AMSTAR Rating:** High **Overall RoB of Included Studies:** Cochrane tool; moderate to high due to high attrition and lack of intent-to-treat analysis.	**Databases Searched:** PubMed, PsycINFO, AMED, CINAHL, Cochrane Database of Systematic Reviews, CENTRAL, Web of Science, EMBASE, PILOTS, Clinicaltrials.gov, and reference list of included studies **Dates Searched:** Inception to January 2016 **Inclusion/Exclusion Criteria:** Full-text RCTs with adult pts aged ≥18 yrs. with a clinical diagnosis of PTSD using valid diagnostic or screening measures. Studies must have assessed administration of thin or fine needles into known acupoints, either as adjunctive or monotherapy. Included studies of full acupuncture, auricular acupuncture, and other specific body sites. **Final Evidence Base:** 7 RCTs	**Diagnosis:** PTSD **Number of Patients:** 709 **Age:** Range 18 to 65; mean 39 yrs. for 5 of 7 studies **Gender:** 32% to 100% male	**Intervention:** Acupuncture sessions ranged from 30 to 60 mins/session, 2 to 4 sessions per/week for 3 to 12 weeks. **Comparators:** TAU (3 studies), WL (1 study), Sham (1 study), CBT (1 study), paroxetine (3 studies) *2 studies had 3 study arms **Follow-up:** post-intervention to 1 to 6 mos. **Outcomes:** PTSD symptoms, health-related quality of life, functional status, depressive and anxiety symptoms, sleep quality and AEs.	**PTSD symptoms (ACU vs. any control)** **Post-intervention:** 6 studies (n=508), SMD: -0.80, 95% CI -1.59 to -0.01; significantly favors ACU **Longer f/u:** 4 studies (n-387), SMD: -0.46; 95% CI -0.85 to -0.06; significantly favors ACU **QoL (ACU vs. any control)** Physical health at F/u: 1 study (n=55), SMD: -0.47, 95% CI -1.01 to 0.07, NS Mental health at F/u: 1 study (n=55), SMD: -0.33, 95% CI -0.87 to 0.21, NS Functional status at F/u: 1 study (n=56), SMD -0.97, 95% CI -1.53 to -0.42, significantly favors ACU **Depressive symptoms** (ACU vs. any control), f/u: 4 studies (n=387), SMD: -0.56, 95% CI -0.88 to -0.23), significantly favors ACU **Anxiety symptoms** (ACU vs. any control). f/u: 3 studies (n=332), SMD: -0.35, 95% CI -1.17 to 0.47, NS

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
				Sleep quality (ACU vs. any control), f/u: 2 studies (n=53), SMD: -0.46, 95% CI -3.95 to 3.03, NS Meta-regression results suggest significant difference in favor of ACU as monotherapy or adjunctive, for any type of ACU, and ACU compared to passive or active control. AEs: No serious AE's reported; some pts (number NR) reported minor needle pain, bleeding, and hematoma; refusal to continue due to needle pain (n=1); refusal to continue due to discomfort (n=1) and kidney pain (n=1). No evidence of publication bias **Limitations:** Limited to small number of RCTs with limited sample size and follow-up and unexplained heterogeneity

ACU: acupuncture; AEs: adverse events; APA: American Association of Psychology; CBT: cognitive behavioral therapy; CI: confidence interval; CT: control group; EMDR: Eye movement desensitization reprocessing; ES: effective size; I^2: % of heterogeneity between studies; mos.: months; NR: not reported; NS: not significant; PTSD: post-traumatic stress disorder; RCT: randomized controlled trials; SE: standard error; SMD: standardized mean difference; TAU: treatment as usual; WL: waitlist

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

Question	Grant et al., (2017)
Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
Did the review authors use a comprehensive literature search strategy?	Yes
Did the review authors perform study selection in duplicate?	Yes
Did the review authors perform data extraction in duplicate?	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	No
Did the review authors describe the included studies in adequate detail?	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
Did the review authors report on the sources of funding for the studies included in the review?	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? RCTs?	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No
Overall Quality	**High**

RoB: risk of bias

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

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

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

References

Grant, S., Colaiaco, B., Motala, A., Shanman, R. M., Sorbero, M. E., & Hempel, S. (2017). Needle acupuncture for posttraumatic stress disorder (PTSD): A systematic review. *RAND Corporation, RR-1433-OSD*. Available from: https://www.rand.org/pubs/research_reports/RR1433.html

Equine Therapy

Evidence Base

Our searches of the literature identified 1 RCT that met inclusion criteria and assessed the efficacy of therapeutic horse riding (THR) for reducing PTSD symptoms among veterans receiving treatment for PTSD at a VA medical center (Johnson, et al. 2018). The strength of the evidence for this outcome was rated very low primarily due to limitations in methodology of the study and the small sample size.

Johnson randomized 29 veterans no longer in active military service (e.g., as reservists) with a confirmed diagnosis of PTSD to receive 6 weeks of THR (n=15) or to a waitlist control (n=14). Most of the enrolled veterans were male (84%) with an average age of 54 years. The majority had served in the Army (44%), and the average number of deployments was 1.79 (ranging from 0 to 10).

During THR sessions, veterans learned the basics of horsemanship skills and completed tasks on horseback. Classes included grooming and interacting with the horse, placing the riding equipment (or tack) on the horse, riding the horse with a leader and 2 side-walkers, and cooldown exercises. THR sessions were led by 2 occupational therapists and 2 riding instructors. The sessions were held in an indoor/outdoor arena once a week for 6 weeks. Sessions lasted 1 to 2 hours depending on tasks. Veterans on the waitlist started THR after 6 weeks of being randomized in the study. Concurrent treatments were not reported in the study. See **Table 3** for more information about the study participants and interventions.

Study Quality

Using the Cochrane tool, we rated the RoB of the RCT as high primarily due to inappropriate randomization (study used veteran identification numbers instead of random numbers); no blinding of patients, clinicians, or outcome assessors; and attrition. 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 therapeutic horse riding statistically significantly reduces PTSD symptoms compared to waitlist control among veterans receiving treatment for PTSD at a VA medical center. (SOE: Very low)
- Evidence from 1 RCT suggests that there is no statistically significant difference in improvement in emotional skills between veterans who received 6 weeks of therapeutic horse riding or who served as a waitlist control. (SOE: Very Low)

Discussion

The findings of the RCT suggest that THR statistically significantly reduces PTSD symptoms as measured by the PTSD Checklist (military version) compared to waitlist control ($p<0.05$). However, the strength of the evidence for this outcome was rated very low. This is primarily due to limitations in methodology of the study and the small sample size. The study did not use a random numbers generator (e.g., coin toss, computer-generated random numbers table) to randomize patients to receive treatment or control. Instead, the authors used VA identification numbers to assign veterans to study groups. The study was also at high risk of bias for not blinding patients, treatment providers or outcome assessors and for

high overall attrition. No horse-riding or horse-related adverse events, such as falling or biting, were reported.

Table 1. Strength of Evidence for Equine Thearpy to Treat PTSD

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
PTSD symptoms	1 RCT Johnson et al, 2018	THR (15) vs WL (14) 6 weeks	**Mean PCL-M, [SD], b/w grp p-value):** THR: 47 (14.67); WL: 59.2 (14.2), p≤0.05, favors THR	Yes (-2)	No	No	Yes (-1)	No	Very low
Emotional coping skills	1 RCT Johnson et al, 2018	1 RCT Johnson et al, 2018 6 weeks	**Coping skills (mean CSES, [SD], b/w grp p-value):** THR: 130.2 (51.8); 115.0 (48.1); NS	Yes (-2)	No	No	Yes (-1)	No	Very low

CI: confidence interval; CSES: Coping Self-Efficacy Scale; NS: not significant; PCL-M: PTSD Checklist (military version); PTSD: post-traumatic stress disorder; RCT: randomized controlled trials; SD: standard deviation; THR: therapeutic horse riding; WL: waitlist control

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.

Evidence Category	Definition
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 Equine Thearapy to Treat PTSD

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Johnson et al. 2018 **Purpose:** To test the efficacy of a 6-wk therapeutic horseback riding program for decreasing symptoms of PTSD and increasing emotional coping skills among military veterans receiving treatment for PTSD at a VA medical center. **Setting: USA;** College of Veterinary Medicine in Missouri **F/u:** 6 weeks **Funding source:** Grant funded	**Number of patients:** 29; n=14 THR; n=15 WL **Inclusion criteria:** Veterans ≥18 yrs. no longer in active military service with a confirmed diagnosis of PTSD or PTSD with TBI using standard criteria; weight ≤220 pounds (to accommodate horses); and ability to walk 25 ft. without assistance **Exclusion criteria:** NR **Pt. baseline characteristics (All pts):** **Age (mean yrs., SD):** 54.3 (12.85) **Gender (% male):** 84% **Mean # deployments:** 1.79	**Intervention:** During THR sessions; veterans learned the basics of horsemanship skills and completed tasks on horseback; classes included grooming, riding, and cooldown. THR was led by 2 occupational therapists and 2 riding instructors and was held in an indoor/outdoor arena 1x/wk. for 6 weeks. Sessions lasted 1 to 2 hrs. depending on tasks and weather. **Control:** WL **Outcomes of Interest:** PTSD symptoms (measured using the PCL-M, lower scores better) and coping skills (measured by the CSES, higher scores better coping)	**6 wks.** **PTSD symptoms (mean PCL-M, [SD], b/w grp p-value):** THR: 47 (14.67); WL: 59.2 (14.2), p≤0.05, favors THR **Coping skills (mean CSES, [SD], b/w grp p-value):** THR: 130.2 (51.8); 115.0 (48.1); NS **AEs:** No reported AEs due to falls, kicking, biting, or other horse or horse riding-related injuries	**Conclusion:** The findings suggest that THR statistically significantly reduces PTSD symptoms compared to WL controls among veterans receiving treatment for PTSD at a VA medical center. THR does not appear to significantly increase coping skills. No horse riding-related AEs reported. **Limitations:** Small sample size, limited follow-up, self-reported outcome measures, and attrition **Study RoB:** High due to randomization procedures, lack of blinding of patients and outcome assessors, and attrition **Author conflict:** None reported

AEs: adverse events; CI: confidence interval; CSES: Coping Self-Efficacy Scale; f/u: follow-up; NR: not reported; NS: not significant; PCL-M: PTSD Checklist (military version); PTSD: post-traumatic stress disorder; RCT: randomized controlled trials; RoB: risk of bias; SD: standard deviation; TBI: traumatic brain injury; THR: therapeutic horseback riding; wks.: weeks; WL: waitlist

Table 4. Cochrane Risk of Bias 2.0 Tool for RCTs on Equine Therapy to Treat PTSD

Reference	Johnson et al., (2018)
➢ Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	No
➢ Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization, concealed envelopes)?	No
➢ Did baseline difference between study groups suggest a problem with randomization?	No
Overall RoB for Randomization Process	**High**
Deviation from Intended Intervention (Effect of Assignment)	
➢ Were participants aware of their assigned intervention during the trial?	Yes
➢ Were providers and people delivering treatment aware of assigned intervention during trial?	Yes
➢ Were there deviations from the intended intervention that arose because of the experimental context?	NI
➢ Were these deviations from intended intervention balanced between groups?	NA
➢ Were these deviations likely to have affected the outcome?	NA
➢ Was an appropriate analysis used to estimate the effect of assignment to intervention?	NI
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?	NI
➢ Could missingness in the outcome depend on its true value?	NI
➢ Do the proportions of missing outcome data differ between intervention groups?	No
➢ Is it likely that missingness in the outcome depended on its true value?	NA
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	**High**
Selection of Reported Results	

Reference	Johnson 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?	NI
Overall RoB of Reported Results	**High**
Overall Study ROB	**High**

*Responses: Y=Yes, PY=Probably Yes, N=No, PN=Probably No, 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

Johnson, R., Albright, D., Marzolf, J., Bibbo, J., Yaglom, H., Crowder, S., …Harms, N. (2018). Effects of therapeutic horseback riding on post-traumatic stress disorder in military veterans. *Military Medical Research, 5*(3), 1-13. doi: 10.1186/s40779-018-0149-6

Exercise

Evidence Base

Our searches of the literature identified 4 RCTs that assessed the impact of integrating exercise therapy[2] into standard care for the treatment of adults with PTSD (See **Table 3** for details on study characteristics). The strength of the evidence supporting the findings for exercise in reducing symptoms of PTSD was rated as low mainly due to methodological limitations of the included studies.

The most recent trial by Goldstein et al. (2018) randomized 47 U.S. veterans to receive either group exercise (EX, n=21) for 1-hour per day for 3 days a week over the course of 12 weeks or to a waitlist (WL, n=26) control (Goldstein et al. 2018). The exercise sessions included aerobic exercises, strength training, yoga and mindful breathing exercises. The average age of the patients enrolled in this trial was 46.8 years and about 40% of the patients were receiving medication therapy for PTSD, depression or pain. The primary outcomes assessed in the trial were change in PTSD symptoms and quality of life.

Another trial by Park et al. (2015) randomized 31 adults with PTSD and head and neck pain to receive cervical exercises plus standard physical therapy (PT, n=15) or to standard PT alone (n=16) (Park et al. 2015). The exercise sessions in this study consisted of a 10-minute warm-up on the treadmill and guided stretching followed by 4 different head and neck exercises lasting 5 to 10 minutes each. The exercise sessions occurred 3 times per week over the course of 6 weeks. Patients in the control group received conventional PT pain management practices that included application of hot packs. The average age of patients in this trial was 60 years, and patients could continue their psychiatric medications provided there was no change in dose in the 2 months prior to the start of the study. The primary outcomes in this trial were pain, disability, and change in PTSD and other psychological symptoms.

Rosenbaum et al. (2015) randomized 81 patients hospitalized for PTSD to participate in an exercise program plus treatment-as-usual (TAU, n=39) or to TAU alone (n=42) (Rosenbaum et al. 2015). The exercise program involved 1-week of in-patient supervised exercise that included a variety of aerobic/strength-based exercises followed by 11-weeks of home-based exercises supplemented with a walking program. TAU involved psychotherapy, pharmaceutical interventions, and group therapy. All patients received in-patient care for up to 3 weeks followed by out-patient care lasting several months. The average age of patients was 49.5 years, and the primary outcomes measured were PTSD symptoms, depression, anxiety and sleep quality.

In the final RCT, Gelkopf et al. 2013 randomized 68 Israeli veterans with combat or military service-related PTSD to an adventure program (n=22) that primarily involved sailing as the physical activity or to a WL control (n=20) (Gelkopf et al. 2013). A total of 26 participants dropped out of the study after being randomized. The baseline characteristics of these participants were compared with those who continued in the study. No statistically significant differences were noted on key characteristics, such as age or symptom severity. The average age of participants in this trial was 37 years, and the primary outcomes assessed were PTSD symptoms, depression, quality of life and functioning.

Study Quality

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

We rated the RoB of the individual RCTs as some concerns to high due lack of information on allocation concealment, lack of blinding of patients, clinicians and outcome assessors, and attrition (see **Table 4** for the RoB 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 4 RCTs suggests that exercise therapy of any kind (e.g., aerobic, strength training, stretching, cervical exercises, and sailing) statistically significantly improves symptoms of PTSD compared to controls (e.g., WL, TAU, or other active treatment). (SOE: Low)
- Evidence from 2 RCTs suggest that exercise of any kind (e.g., aerobic, strength training, sailing) statistically significantly improves social and psychological quality of life compared to WL. (SOE: Low)
- Evidence from 2 RCTs suggest that there is no statistically significant difference between exercise and WL control in improving physical quality of life. (SOE: Very low)
- Evidence from 3 RCTs suggest that exercise of any kind (e.g., aerobic, strength training, sailing) statistically significantly improves depression compared to controls (e.g., WL, TAU, or other active treatment). (SOE: Low)
- Evidence from 2 RCTs suggest that exercise of any kind (e.g., aerobic, strength training, stretching) may reduce symptoms of anxiety compared to controls (e.g., WL, TAU, or other active treatment). (SOE: Very low)
- Evidence from 1 RCT suggests that cervical exercise among adults with PTSD and neck pain statistically significantly reduces pain compared to conventional physical therapy pain management practices (e.g., hot packs). (SOE: Very low)
- Evidence from 1 RCT suggests that there is no statistically significant difference in sleep quality between exercise therapy plus treatment as usual and treatment as usual alone. (SOE: Very low)

Discussion

Overall, the findings of the 4 RCTs that made up the evidence base for exercise suggest that exercise of any kind (e.g., aerobic, strength training, stretching, cervical exercise, sailing, or walking) used as an adjunct to medication and/or psychotherapy reduces symptoms of PTSD compared to controls (e.g., waitlist, TAU, or other active treatment). See **Table 1** for a summary of all the findings for exercise to treat adults with PTSD. The strength of the evidence supporting the findings for exercise in reducing symptoms of PTSD was rated as low mainly due to methodological limitations of the included studies. These limitations included lack of blinding of participants, clinicians and study staff, and outcome assessors and attrition. Low to very low-quality evidence also suggests that exercise may improve emotional or psychological quality of life (2 RCTs) and reduce symptoms of depression (3 RCTs), anxiety (1 RCT) and pain (1 RCT) compared to controls. However, limited evidence (1 RCT each)

suggest that there is no significant difference between exercise and controls in improving physical quality of life or sleep quality.

Table 1. Strength of Evidence for Exercise to Treat PTSD

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
Any Type of Exercise vs. Any Control									
PTSD symptoms	4 RCTs Goldstein 2018, Park 2015, Rosenbaum 2015, Gelkopf 2013	Exercise; includes aerobic, strength training, stretching, cervical exercises, and sailing (n=97) Control; includes WL, TAU, or standard PT (n=104)	Goldstein: Aerobic/strength vs WL: b/w grp ES: -0.90, 95% CI: -1.72 to -0.08 Park (cervical EX + PT vs. PT): b/w grp ES: -1.8, p=0.030 Rosenbaum (aerobic/strength vs TAU): b/w grp ES: -5.4, 95% CI, -10.5 to -0.3, p=0.04 Gelkopf (sailing and conditioning EX vs WL): 4.69, p=0.04	Yes (-2)	No	No	No	NA	Low
Quality of Life (social/ psychological)	2 RCTs Goldstein 2018, Gelkopf 2013	Exercise; includes aerobic/strength and sailing (n=43) Control: WL (n=46)	Goldstein: Aerobic/strength vs WL: b/w grp ES: 0.53, 95% CI 0.16 to 0.90 Gelkopf (sailing and conditioning EX vs WL): Social QoL, 5.9, p=0.01;	Yes (-2)	No	No	No	NA	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
			Emotional QoL, 5.8, p=0.02						
Quality of Life (physical)	2 RCTs Goldstein 2018, Gelkopf 2013	Exercise; includes aerobic/strength and sailing (n=43) Control: WL (n=46)	Goldstein: Aerobic/strength vs WL: b/w grp ES: 0.33, 95% CI -0.16 to 0.82	Yes (-2)	No	No	Yes (-1); wide 95% CIs	NA	Very Low
			Gelkopf (sailing and conditioning EX vs WL): 0.3; p=0.57						
Depression	3 RCTs Park 2015, Rosenbaum 2015, Gelkopf 2013	Exercise; includes aerobic, strength training, stretching, cervical exercises, and sailing (n=76) Control; includes WL, TAU, or standard PT (n=82)	Park (cervical EX + PT vs. PT): Post-tx mean -9.4; Post-tx mean -4.3, p=0.009	Yes (-2)	No	No	No	NA	Low
			Rosenbaum (aerobic/strength vs TAU): b/w grp ES: -7.0, 95% CI -11.9 to -2.1, p=0.006						
			Gelkopf (sailing and conditioning EX vs WL): 4.4, p=0.04						
Anxiety	2 RCTs Park 2015, Rosenbaum 2015	Exercise; includes aerobic, strength training, stretching,	Park (cervical EX + PT vs. PT): Post-tx mean -3.1; Post-tx mean -1.3, NS	Yes (-2)	No	No	Yes (-1); not significant	NA	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
		cervical exercises (n=54) Control; includes TAU, or standard PT (n=58)	Rosenbaum (aerobic/strength vs TAU): b/w grp ES: -6.3, 95% CI -10.3 to -2.3, p=0.003						
Pain	1 RCT Park et al. 2015	Cervical exercises+ PT (n=15) vs. PT alone (n=16)	Post-tx EX: -4.3; Post-tx CG: -1.0, p<0.00	Yes (-2)	No	No	Yes (-1); small sample size	NA	Very low
Sleep quality	1 RCT Rosenbaum 2015	Aerobic/strength (n=39) vs TAU (n=42)	Rosenbaum (aerobic/strength vs TAU): b/w grp ES: -1.6, 95% -3.5 to 0.3, p=0.1)	Yes (-2)	No	No	Yes (-1); wide 95% CI	NA	Very low

CG: control group; CI: confidence interval; ES: effect size; EX: exercise; f/u: follow-up; NR: not reported; NS: not significant; PT: physical therapy; PTSD: post-traumatic stress disorder; RCT: randomized controlled trials; RoB: risk of bias; SD: standard deviation; TAU: treatment as usual; WL: waitlist control

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.

Evidence Category	Definition
Precision of Evidence	Precision is the degree of certainty surrounding an estimate of effect with respect to an outcome. Precision is primarily assessed by examining the 95% confidence intervals around the summary effect size.

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

Table 3. Evidence Table for RCTs on Exercise to Treat PTSD

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Goldstein et al. 2018 **Purpose:** To evaluate the effects of IE to treat military veterans with PTSD. **Setting:** VA medical center in San Francisco **Funding source:** NR	**Number of patients:** 47 (n=21 IE; n=26 waitlist) **Inclusion criteria:** Veterans aged 18 to 69 yrs. with meeting standard diagnostic criteria for PTSD. **Exclusion criteria:** Veterans with a history of psychotic disorder, bipolar disorder, substance disorder in past year, pregnancy, serious neurological disorder, or physical or medical disability that precludes exercise. **Pt. baseline characteristics (all pts):** Age (mean yrs.): 46.8 yrs. Gender (% female): 80.8% Current medication for PTSD, depression or pain: 40% BL CAPS (mean [SD]): IE: 64.2; WL: 58.5, NS b/w groups % current depression: 34.7%	**Intervention:** Provided 1 hr., 3x per week with each session including aerobic exercise, strength training, yoga and mindful breathing exercises **Control:** WL lasted 12 weeks with pts completing the same assessments as IE group. **Outcomes:** PTSD symptoms as measured by the CAPS scale; quality of life as measured by the WHOQOL-BREF; and feasibility and acceptability of treatment (as measured by dropout rate) **F/u:** Post-tx at 12 weeks	**PTSD symptoms** CAPS (total score, mean [SD]): IE: 34.2 (19.62); WL: 44.2 (23.6), b/w grp ES: -0.90, 95% CI: -1.72 to -0.08 **Quality of life** WHOQOL psychological domain (b/w grp diff): ES: 0.53, 95% CI 0.16 to 0.90 WHOQOL physical domain (b/w grp diff): ES: 0.33, 95% CI -0.16 to 0.82 **Dropout** IE: n=5 (24%); WL: n=4 (15%); NS	Results suggest that IE statistically significantly reduces overall symptoms of PTSD and improves psychological quality of life compared to waitlist control. Attrition rates were similar between study groups. **Limitations:** Small sample size, limited follow-up, and inactive comparator **Study RoB:** Some Concerns, due to concerns about no patient or provider blinding and no information on allocation concealment **Author conflict:** None reported
Reference: Park et al. 2015 **Purpose:** To examine the effect of cervical exercises on neck pain, disability and psychosocial outcomes on pts with PTSD.	**Number of patients:** 31 (n=15 EX; n=16 CG) **Inclusion criteria:** Pts with confirmed diagnosis of PTSD who have experienced cervical (neck) pain for at least 3 mos. and have an NDI of <15. **Exclusion criteria:** History of cervical surgery within 3 mos., arthritis or cervical spine fracture, accompanying neurological	**Intervention:** Head and neck exercises plus conventional PT. The exercises consisted of a 10 min warm-up on the treadmill and guided stretching followed by 4 different head and neck exercises and stretches lasting 5 to 10 mins each. Each intervention session was conducted 3x/week for 6 wks. **Control:** Conventional PT (hot pack and ultrasound)	**6 weeks** (EX pre- post-tx mean; CG pre-post-tx mean; b/w grp p-value Pain (VAS): -4.3; -1.0, p<0.00 NDI: -3.9; -1.9, p=0.013 SCL-90 (depression): -9.4; -4.3, p=0.009 SCL-90 (anxiety): -3.1; -1.3, NS	Results suggest that cervical exercises among pts with PTSD and head and neck pain statistically significantly reduces pain and improves disability and psychological symptoms **Limitations:** Small sample size and limited follow-up **Study RoB:** High; due to lack of blinding of participants, study staff and outcome assessors

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Setting: University medical center, Korea **Funding source:** University grant	damage, malignant neoplasm or vascular disease, psychiatric problems with an inability to understand study questionnaires, or starting to receive psychiatric medication or undergoing a change in prescribed medication within 2 mos. of start of study. **Pt. baseline characteristics (EX; CG):** Age (mean yrs.): 57.5; 62.8 Gender (male/female): 13/2; 12/4 Duration of neck pain (mean mos. [SD]): 24.6 (12.1); 20.2 (10.1)	**Outcomes:** Pain (VAS), disability (NDI), PTSD symptoms (SCL-90; HSCL), depression and anxiety (SCL-90; HSCL) **F/u:** post-tx at 6 weeks	HSCL: -25: -5.3; -1.8, p=0030	**Author conflict:** None reported
Reference: Rosenbaum et al. 2015 **Purpose:** To assess the impact of a 12-wk exercise program in addition to TAU for pts hospitalized for PTSD. **Setting:** University of Sidney, Australia **Funding source:** NR	**Number of patients:** 81 (n=39 EX+TAU; n=42 TAU only) **Inclusion criteria:** Men and women aged ≥18 yrs. receiving in-patient care for confirmed PTSD diagnosed using standard criteria; medical clearance to participate in exercise program, and cognitively able to consent and participate. **Exclusion criteria:** Pts medically unfit to exercise; pregnant or women planning to become pregnant in the proceeding 12 mos.; and complex PTSD with trauma occurring in childhood only **Pt. baseline characteristics (EX; TAU):** Age (mean yrs.): 47.1; 52.0 Gender (% female): 8%; 24%	**Intervention:** 12 wks. of 1x/wk. supervised exercise, 2x/wk. in-home exercise, and a walking program facilitated with a pedometer and exercise diary + TAU **Control:** TAU involved psychotherapy, pharmaceutical interventions, and group therapy. The average length of pt. in-patient stay for all pts was 3 wks. followed by a less intensive outpatient program lasting several mos. **Outcomes:** PTSD symptoms (PCL-C); depression/anxiety (DASS), sleep quality (PSQI) and AEs **F/u:** Post-tx at 12-wks	**PTSD symptoms** (within grp difference from BL to post-tx; b/w grp difference): Ex: -9.8, 95% CI -13.7 to -6.0; TAU: -4.2, 95% CI -7.8 to -0.5; b/w grp: -5.4, 95% CI -10.5 to -0.3, p=0.04 **Depression/anxiety:** **Total DASS** (within grp difference from BL to Post)**:** EX: -22.2, 95% CI -32.5 to -11.9; TAU: -2.1, 95% CI -11.6 to 7.2; b/w grp: -17.4, 95% CI -28.9 to -6.0, p=0.004 **DASS Depression**: EX: -7.2, 95% CI -10.7 to -3.5; TAU: -0.8, 95% CI -3.8 to 5.3; b/w grp: -7.0, 95% CI -11.9 to -2.1, p=0.006 **DASS Anxiety:** EX: -7.1, 95% CI -10.7 to -3.6; TAU: -	Results suggest that exercise in addition to psychotherapy and pharmacological therapy statistically significantly reduces symptoms of PTSD, depression and anxiety compared psychotherapy and pharmacotherapy alone with no adverse physical events. Adding exercise to TAU did not significantly improve sleep quality. **Limitations:** Small sample size, missing data, and limited follow-up **Study RoB:** High; due to lack of blinding of pts and tx providers and high unexplained or accounted for attrition leading to missing data for primary outcomes. **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	Trauma experienced through job: 88%; 89% %PCL-C ≥45: 95%; 91%		0.8, 95% CI -3.9 to 2.4; b/w grp -6.3, 95% CI -10.3 to -2.3, p=0.003 **Sleep quality (PSQI total):** EX: -2.9, 95% CI -4.4 to -1.4; TAU: -1.1. 95% CI -2.9 to 0.6; b/w grp: -1.6, 95% -3.5 to 0.3, p=0.1) **AEs:** None related to exercise were reported	
Reference: Gelkopf et al. 2013 **Purpose:** To assess the impact of a weekly NAR program on Israeli veterans with chronic combat or service-related PTSD. **Setting:** Rehabilitation facility; Israel **Funding source:** NR	**Number of patients:** 68 (n=22 NAR; n=20 WL; n=26 DO) *The DO grp included 26 pts who dropped out prior to start of intervention **Inclusion criteria:** Pts with a confirmed diagnosis of combat or military service-related PTSD. **Exclusion criteria:** NR **Pt. baseline characteristics (NAR; WL; DO):** Age (mean yrs.): 39.1; 37.5; 34.7 Gender (% male): 100% across groups %Currently in tx: 81.8%; 80.0%; 84.6% PTSD severity (mean SASRQ [SD]): 116.4 (16.8); 111.2 (26.6); 104.7 (28.7)	**Intervention:** Sailing program delivered to small grp of 6 to 10 pts, 1x/week for 3 hours. The intent was to teach pts to sail; challenge their coping skills through sailing-related task and provide them with a haven to experience and discuss emotional responses to sailing challenges. Pts also participated in 2, 3-day outdoor camping trips. **Control:** WL **Outcomes:** PTSD symptoms (using the SASRQ), depression (using the BDI), functioning (using a scale that assessed 7 levels of functioning), and quality of life (using the HSS) **F/u:** Post-intervention at 12 mos.	**Post-Intervention (12 mos.)** b/w grp difference (F-statistic), p-value: PTSD: 4.69, p=0.04 Depression: 4.4, p=0.04 Functioning: 24.4, p<0.001 Lack of control of illness:8.2; p=0.007 Social QoL: 5.9, p=0.01 Emotional QoL: 5.8, p=0.02 Physical QoL: 0.3; p=0.57 Lack of hope: 12.1, p=0.001 No reported AEs	Results suggest that a 12-month nature adventure rehabilitation program led to statistically significant improvement in overall symptoms of PTSD and depression, functioning and social and emotional quality of life. Further regression analysis conducted by the authors suggest that these gains are the result of improvement in perceived control over illness. **Limitations:** Small sample size, waitlist control and all male study population **Study RoB:** High, due to no blinding of pts, providers and outcome assessors and high unexplained attrition. **Author conflict:** None reported

AEs: adverse events; BDI: Beck Depression Inventory; BL: baseline; CAPS: Clinician Administered PTSD Scale; CG: control group; CI: confidence interval; DASS: Depression Anxiety Stress Scale; DO: drop out; ES: effect size; EX: exercise; f/u: follow-up; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression scale; HSCL: Hamilton Symptom Checklist; HSS: Hamilton Service Scale; IE: integrated exercise; IPF: Inventory of Psychosocial Functioning; mos.: months; NAR: Nature adventure rehabilitation; NDI: Neck Disability Index; NR: not reported; NS: not significant; PCL-M: PTSD Checklist (military version); PSQI: Pittsburgh Sleep Quality Index; PT: physical therapy; PTSD: post-traumatic stress disorder; RCT: randomized controlled trials; RoB: risk of bias; SCL-90: Symptom Checklist-90; SASRQ: Stanford Acute Stress Reaction Questionnaire; SD: standard deviation; TAU: treatment as usual; VAS: Visual Analog Scale; WL: waitlist control

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

Reference	Goldstein et al., (2018)	Park et al., (2015)	Rosenbaum et al., (2015)	Gelkopf et al., (2013)
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)?	NI	NI	Yes	NI
➢ Did baseline difference between study groups suggest a problem with randomization?	No	No	No	No
Overall RoB for Randomization Process	**Some concerns**	**Some concerns**	**Low**	**Some concerns**
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	Yes	Yes	Yes
➢ Were there deviations from the intended intervention that arose because of the experimental context?	NI	NI	NI	NI
➢ Were these deviations from intended intervention balanced between groups?	NA	NA	NA	NA
➢ Were these deviations likely to have affected the outcome?	NA	NA	NA	NA
➢ 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?	Yes	Yes	No	No
➢ Is there evidence that result was not biased by missing outcome data?	NA	NA	No	No
➢ Could missingness in the outcome depend on its true value?	NA	NA	NI	Yes
➢ Do the proportions of missing outcome data differ between intervention groups?	NA	NA	No	NI
➢ Is it likely that missingness in the outcome depended on its true value?	NA	NA	NI	NI
Overall RoB of Missing Data	**Low**	**Low**	**High**	**High**

Reference	Goldstein et al., (2018)	Park et al., (2015)	Rosenbaum et al., (2015)	Gelkopf et al., (2013)
Measurement of the Outcome				
➢ Was the method of measuring the outcome inappropriate?	No	No	No	No
➢ Could measurement or ascertainment of the outcome have differed between intervention groups?	No	No	No	No
➢ Were outcome assessors aware of the intervention received by study participants?	No	Yes	No	Yes
➢ Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	NI	NA	NI
➢ Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NI	NA	NI
Overall RoB of Measurement of Outcome	**Low**	**High**	**Low**	**High**
Selection of Reported Results				
➢ Was the trial analyzed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?	Yes	NI	NI	NI
Overall RoB of Reported Results	**Low**	**Some concerns**	**Some concerns**	**Some concerns**
Overall Study RoB	**Some Concerns**	**High**	**High**	**High**

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

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

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

References

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Healing Touch

Evidence Base

Our searches of the literature identified 1 RCT that met inclusion criteria and assessed the efficacy of healing touch (HT) with guided imagery (GI) compared to treatment as usual (TAU) for treating PTSD (Jain et al. 2012). Jain randomized 123 active duty military personnel who had recently returned from a combat zone and were assessed as having PTSD symptoms to receive HT+GI and TAU (n=68) or TAU alone (n=55). The strength of the evidence for these outcomes was low due to an evidence base of only one study and to limitations in the methodological quality of the study that include lack of blinding of patients and self-reported outcome measures

HT is a type of biofield therapy that involves gentle, non-invasive touch by a trained practitioner, and GI utilizes visualization to induce a state of deep relaxation. The GI component of the intervention was provided through a CD recording specifically used in treating PTSD. The recording does not use imagined exposure but uses affirmations to enhance relaxation. Patients received 6 sessions of HT+GI over 3 weeks (2 sessions per week) with each session lasting 1-hour. Patients who were randomized to receive TAU continued to take prescribed medications for PTSD (medications were not specified in study). Patients in the HT+GI intervention also continued to take any prescribe medications for PTSD. See **Table 3** for more information about the patients and interventions assessed in this study.

Study Quality

Using the Cochrane tool, we rated the RoB of the RCT as Some Concerns due to patients not being blinded to treatment assignment and all outcomes measured using self-reported instruments. 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 healing touch plus guided imagery statistically significantly reduces PTSD symptoms compared to treatment as usual alone among active duty military personnel. (SOE: Low)
- Evidence from 1 RCT suggests that healing touch plus guided imagery statistically significantly reduces depression compared to treatment as usual alone among active duty military personnel. (SOE: Low)
- Evidence from 1 RCT suggests that there is no statistically significant difference between healing touch plus guided imagery and treatment as usual in improving physical or mental quality of life. (SOE: Low)

Discussion

The findings of the RCT suggest that healing touch plus guided imagery reduces symptoms of PTSD and depression compared to treatment as usual. However, it does not appear to have a significant impact on improving quality of life when compared to treatment as usual. The strength of the evidence for these outcomes was low due to an evidence base of only one study and to limitations in the methodological

quality of the study that include lack of blinding of patients and self-reported outcome measures. No adverse events were reported.

Table 1. Strength of Evidence for Healing Touch to Treat PTSD

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
PTSD symptoms	1 RCT Jain et al. 2012	HT+GI (68); TAU (55) F/u: 1 month	**Mean PCL-M, 95% CI, b/w grp p-value, ES:** HT+GI: 40.7, 37.0 to 44.2; TAU: 52.0, 48.0 to 56.0, p<0.001, SMD (Cohen's d): 0.85	Yes (-1)	No	No	Yes (-1); evidence from single study	NA	Low
Depression	1 RCT Jain et al. 2012	HT+GI (68); TAU (55) F/u: 1 month	**Mean BDI, 95% CI, b/w grp p-value, ES:** HT+GI: 16.4, 13.5 to 19.4; TAU: 23.9, 20.6 to 27.1, p<0.005, SMD (Cohen's d): 0.70	Yes (-1)	No	No	Yes (-1); evidence from a single study	NA	Low
Quality of Life	1 RCT Jain et al. 2012	HT+GI (68); TAU (55) F/u: 1 month	**Mean SF-36 PCS, 95% CI, b/w grp p-value, ES:** HT+GI: 49.9, 47.7 to 52.1; TAU: 47.2, 44.7 to 49.7, p=0.04, SMD (Cohen's d): 0.20	Yes (-1)	No	No	Yes (-1); wide 95% CIs	NA	Low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			Mean SF-36 MCS, 95% CI, b/w grp p-value, ES: HT+GI: 39.6, 36.5 to 42.6; 32.9, 29.5 to 36.3, p=0.002, SMD (Cohen's d): 0.58						

BDI: Beck Depression Inventory; BL: baseline; CI: confidence interval; f/u: follow-up; GI: guided imagery; HT+GI: healing touch plus guided imagery; NR: not reported; NS: not significant; PCL-M: PTSD Checklist (military version); PTSD: post-traumatic stress disorder; QoL: Quality of life; RCT: randomized controlled trials; RoB: risk of bias; SD: standard deviation; SF-36: Short-form 36; SMD: standardized mean difference; TAU: treatment as usual; wks.: weeks

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

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

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

Table 3. Evidence Table for RCTs on Healing Touch to Treat PTSD

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Jain et al. 2012 **Purpose:** To conduct an RCT to determine if HT+GI reduces PTSD symptoms compared to TAU in returning combat-exposed active duty military members with significant PTSD symptoms. **Setting:** Marine Corp base camp in Camp Pendleton, California, USA **Funding source:** NR	**Number of patients:** 123, n=68 HT+GI; n=55 TAU **Inclusion criteria:** Male or female active duty personnel age ≥18 yrs. who were recently post-deployed from a combat zone and were actively experiencing symptoms of PTSD. **Exclusion criteria:** Currently pregnant or nursing, currently using HT or GI from other sources, and not able to sign informed consent **Pt. baseline characteristics (HT+GI, TAU):** **Age (mean yrs., range):** 27.1 (20 to 42); 27.9 (20 to 48) **Gender (% male):** 89.7%; 92.7% **Mean # deployments:** 1.9; 2.0 **Mean military service yrs.:** 7.2; 7.9 **% Currently use medication for PTSD:** 56.9%; 51.9% **BL PCL-M (mean, 95% CI):** HT+GI: 54.0, 50.9 to 57.2; TAU: 55.6, 52.1 to 59.1 **BL BDI (mean, 95% CI):** HG+GI: 25.6, 22.9 to 28.4; TAU: 26.8, 23.7 to 29.8	**Intervention:** HT is a type of biofield therapy that involves gentle, non-invasive touch by a trained practitioner; GI utilizes visualization to induce a state of deep relaxation and was provided through a CD recording specifically used in treating PTSD. The recording does not use imagined exposure but uses affirmations to enhance relaxation. Patients received 6 sessions of HT+GI over 3 weeks (2 sessions per week) with each session lasting 1-hour. **Control:** TAU **Outcomes of Interest:** PTSD symptoms (PCL-M); depression (BDI); QoL (SF-36) **Follow-up:** Post-intervention; 3 weeks	**PTSD symptoms (mean PCL-M, 95% CI, b/w grp p-value, ES):** HT+GI: 40.7, 37.0 to 44.2; TAU: 52.0, 48.0 to 56.0, p<0.001, SMD (Cohen's d): 0.85 **Depression (mean BDI, 95% CI, b/w grp p-value, ES):** HT+GI: 16.4, 13.5 to 19.4; TAU: 23.9, 20.6 to 27.1, p<0.005, SMD (Cohen's d): 0.70 **QoL, physical (mean SF-36, 95% CI, b/w grp p-value, ES):** HT+GI: 49.9, 47.7 to 52.1; TAU: 47.2, 44.7 to 49.7, p=0.04, SMD (Cohen's d): 0.20 **QoL, physical (mean SF-36, 95% CI, b/w grp p-value, ES):** HT+GI: 39.6, 36.5 to 42.6; 32.9, 29.5 to 36.3, p=0.002, SMD (Cohen's d): 0.58 **AEs:** None reported	**Conclusion:** Results suggest that HT+GI and TAU statistically significantly reduces PTSD symptoms and depression and improves both physical and mental health QoL. No reported AEs. **Limitations:** Limited follow-up, no active control, self-reported outcomes. **Study RoB:** Some concerns; patients were not blinded to treatment assignment and all outcome measures were self-report. **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	BL SF-36-Physical (mean, 95% CI): HG+GI: 48.5, 46.1 to 50.1; TAU: 48.0, 45.5 to 50.6 **BL SF-36-Mental (mean, 95% CI):** HG+GI: 30.3, 27.6 to 33.1, TAU: 30.1, 27.1 to 33.3			

AEs: adverse events; BDI: Beck Depression Inventory; BL: baseline; CI: confidence interval; f/u: follow-up; GI: guided imagery; HT+GI: healing touch plus guided imagery; NR: not reported; NS: not significant; PCL-M: PTSD Checklist (military version); PTSD: post-traumatic stress disorder; QoL: Quality of life; RCT: randomized controlled trials; RoB: risk of bias; SD: standard deviation; SF-36: Short-form 36; SMD: standardized mean difference; TAU: treatment as usual; wks.: weeks

Table 4. Cochrane Risk of Bias 2.0 Tool for RCTs on Healing Touch to Treat PTSD

Reference	Jain et al. (2012)
• 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)?	No
• 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?	No
• Were these deviations likely to have affected the outcome?	No
• 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?	No
• Could missingness in the outcome depend on its true value?	No
• 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	**Low**
Measurement of the Outcome	
• Was the method of measuring the outcome inappropriate?	Yes
• Could measurement or ascertainment of the outcome have differed between intervention groups?	No
• Were outcome assessors aware of the intervention received by study participants?	Yes
• Could assessment of the outcome have been influenced by knowledge of intervention received?	NI
• Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NI
Overall RoB of Measurement of Outcome	**Some Concern**
Selection of Reported Results	

Reference	Jain 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?	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

Jain, S., McMahon, G., Hasen, P., Kozub, M., Porter, V., King, R., & Guarneri, E. (2012). Healing touch with guided imagery for PTSD in returning active duty military: A randomized controlled trial. *Military Medicine, 177*(9), 1015-1021.

Mind-Body Interventions (Meditation and Yoga)

Evidence Base

Our searches of the literature identified 2 SRs and 1 RCT that met inclusion criteria and assessed meditation-based interventions and 1 SR that assessed yoga. Due to similarities in the nature of the interventions, there is some overlap in the studies included in the SRs. In most studies, meditation or yoga were used as adjunctive therapies to treatment as usual (TAU) for PTSD. However, TAU was either not clearly defined in the studies or the authors simply noted that patients were able to continue taking their current medications for PTSD. The overall strength of the evidence for meditation-based interventions ranged from moderate to very low depending on the outcome. The strength of the evidence for yoga-based interventions was rated low due to limitations in the methodological quality of the included studies and unexplained heterogeneity.

Meditation

Gallegos et al (2017) conducted an SR that assessed the efficacy and safety of various forms of meditation used primarily as an adjunctive treatment for adults with PTSD (Gallegos et al. 2017). The evidence base for this SR included 17 RCTs that focused on meditation-based interventions: 10 focused specifically on mindfulness-based stress reduction (MBSR), 6 on other forms of meditation such as transcendental and mantra-based, and 1 focused on combination meditation practices. Overall, the RCTs in this review enrolled a total of 976 adult patients (≥18 years) with PTSD. Fourteen of the included studies assessed the impact of meditation on military populations. The control conditions included treatment as usual (TAU, 14 RCTs), waitlist (WL, 2 RCTs), and psychotherapy (1 RCT). Follow-up ranged from 2 to 16 weeks. The outcome of interest in this report was change in PTSD symptoms.

Hilton et al. (2017) also conducted a SR that assessed meditation-based interventions for treating PTSD. The evidence-base for this review included 7 RCTs that focused on meditation; 4 of these studies overlapped with studies in the Gallegos review. However, the Hilton review considered outcomes not assessed in the Gallegos review, such as quality of life, depression, and anxiety. We used the Hilton review to supply data on outcomes not reported in the Gallegos review. Overall, the RCTs in the Hilton review enrolled a total of 643 patients who were mostly males with a mean age range of 41 to 59 years. Five of the RCTs assessed MBSR and two assessed mantra-based meditation. The control conditions included the following TAU (7 RCTs), waitlist (WL, 5 RCTs), and present-centered therapy (PCT, 1 RCT). Several of the included RCTs had more than two study arms.

Finally, one RCT, published subsequent to the Gallegos and Hilton reviews, compared individually delivered mantra repetition therapy with another non-trauma-focused treatment for PTSD. Bormann et al. (2018) randomized 173 veterans (mean age 48.3 years) diagnosed with military-related PTSD to either the mantra group (n=89) or the present-centered therapy control group (n=84) (Bormann et al., 2018). Follow-up was 2 months and the primary outcome was change in PTSD symptom severity.

Yoga

Cramer et al. (2018) conducted a SR that assessed the evidence of yoga as an adjunctive treatment to pharmacotherapy or psychotherapy for reducing symptoms of PTSD. The evidence base consisted of 7 RCTs that enrolled a total of 284 adults diagnosed with PTSD. Most of the enrolled patients were male (72%) with a mean age range of 28.7 to 58.0 years (median 43.6). Four of the studies included only military personnel and/or veterans. The studies assessed various forms of yoga that included Sudarshan

Kriya (k=2), Kripalu (k=2), Kundalini (k=1), Satvananda (k=1), and trauma-informed (k=1). The median duration of the yoga interventions was 9.5 weeks and the median intensity was 1.75 hours/week. In 5 RCTs the comparator was waitlist and in 2 the comparator was an attention control condition that included time and attention from a therapist without a specific therapeutic component. Median follow-up across studies was 10 weeks.

Study Quality

Study Quality Ratings for SR and RCTs of Mind-Body Interventions

Reference	Quality Rating	Intervention	Comment
Systematic Reviews (AMSTAR Rating)			
Gallegos et al., (2017)	High Quality	Meditation	Included studies rated as Low RoB (8 studies), unclear RoB (5 studies), high RoB (3 studies) using Cochrane criteria. Primary reason for unclear or high RoB is unclear or lack of allocation concealment, no blinding and attrition
Hilton et al., (2017)	High Quality	Meditation	Included studies rated as poor (4 studies), fair (2 studies), and good (1 study) quality using USPSTF criteria; poor-quality studies failed to use ITT and had significant b/w group differences at baseline.
Cramer et al., (2018)	High Quality	Yoga	Included studies rated as moderate (k=1) to high (k=6) RoB using Cochrane criteria due to lack of allocation concealment and/or no blinding in most studies.
Individual RCTs (Cochrane RoB Rating)			
Borman et al., (2018)	Some concerns	Meditation	Rating due to some concerns about not blinding patients and clinicians; outcome assessors were blinding to group assignment.

RoB: Risk of bias

Key Findings

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

Meditation

- Combined evidence from 15 RCTs suggests that meditation-based interventions, including mindfulness-based stress reduction and mantra-based meditation, statistically significantly reduce symptoms of PTSD compared to controls (TAU:14 studies; WL:1 study). (SOE: Moderate)
- Combined evidence from 8 RCTs suggests that meditation-based interventions statistically significantly reduce symptoms of depression compared to controls (TAU/WL:7 studies; Psychotherapy:1 study). (SOE: Low)
- Combined evidence from 3 RCTs suggest that there is no statistically significant difference between meditation-based interventions and controls in improving symptoms of anxiety. (SOE: Low)
- Combined evidence from 5 RCTs suggest that there is no statistically significant difference between meditation-based interventions and controls in improving mental or physical quality of life. (SOE: Low)

- Evidence from 1 RCT suggests that MRP is statistically significantly more effective than present-centered therapy in reducing insomnia immediately following treatment and at 2 months follow-up (SOE: Low)

Yoga

- Combined evidence from 5 RCTs suggests that yoga as an adjunctive therapy is statistically and clinically more effective than waitlist control at reducing symptoms of PTSD at 10 weeks follow-up. (SOE: Low)
- Combined evidence from 2 RCTs suggests that there is no significant difference between yoga and attention control in reducing symptoms of PTSD. (SOE: Low)

Discussion

Meditation

Overall, the findings of the Gallegos review suggest that meditation-based interventions offered as adjunctive therapy to TAU reduce PTSD symptoms (MBSR: standardized mean difference [SMD]: 0.33, 95% confidence interval [CI]: -0.48 to -0.18; other forms of meditation: SMD: 0.37, 95% CI: -0.60 to -0.13). The findings of the Borman RCT suggest that meditation is more effective than person-centered psychotherapy in reducing symptoms of PTSD and insomnia. Further findings from the Hilton review suggest that meditation interventions also improve symptoms of depression (SMD: -0.34, 95% CI -0.59 to -0.08) compared to controls. However, no statistically significant differences were observed in the Hilton review between meditation and controls for improving anxiety or quality of life. The authors of both reviews did additional analysis to see if the observed effects of meditation varied depending on type of meditation, comparator, trauma, study quality or dosage. The findings in each review do not indicate that these moderators have any significant impact on the overall effect of meditation. Due to the limited number of monotherapy studies, the authors stated it was not possible to determine if there was a difference in favor of meditation as monotherapy compared to it as an adjunctive treatment. No serious adverse events were reported among participants randomized to the meditation group; however, one person in the control condition attempted suicide.

The overall strength of the evidence for meditation-based interventions ranged from moderate to very low depending on the outcome. In general, the strength of the evidence was limited due to limitations in the methodological quality of the RCTs (e.g., lack of blinding, attrition) and statistical imprecision of the findings. Larger, more rigorously designed studies with longer-follow up periods are needed to fully assess the efficacy of meditation therapies in the treatment of PTSD.

Yoga

Overall, the findings from the Cramer review suggest that yoga as an adjunctive therapy is effective in reducing PTSD symptoms compared to waitlist control (SMD: -1.10, 95% CI -1.72 to -0.47, I2=72%). However, the strength of the evidence for this comparison was rated low due to limitations in the methodological quality of the included studies and unexplained heterogeneity. Further findings from this review suggest that there is no statistically significant difference between yoga and attention control conditions in reducing symptoms of PTSD. No adverse events were reported in any of the included RCTs.

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

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
Meditation									
PTSD symptoms	1 SR with 17 RCTs (Gallegos 2017); 1 RCT (Borman 2018)	MBSR (8 RCTs; n=345) vs control (n=334); 2 to 16 wks.	**Gallegos:** SMD: -0.33, 95% CI: -0.48 to -0.18; I^2: 0.01%; favors MBSR	Yes (-1)	No	No	No	No	Moderate
		Other MED (7 RCTs; n=140) vs control (n=148); 2 to 16 wks.	**Gallegos:** SMD: -0.37, 95% CI: -0.60 to -0.13, I^2: 0.0%, favors MED **Borman: CAPS**: ES: 0.49, p=0.006, favors MED; **PCL-M:** ES: 0;43, p=0.04, favors MED	Yes (-1)	No	No	No	No	Moderate
		Combo MED (18) vs control (14); 8 wks.	**Gallegos:** SMD: 0.46, 95% CI: -	Yes (-1)	No	No	Yes (-2); wide 95% CI and very	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
			0.25 to 1.17; NS				small sample size		
Depression	1 SR with 8 RCTs (Hilton et al. 2017); 1 RCT (Borman et al. 2018)	MED vs control Total n=628 4 to 8 wks.	**Hilton:** SMD: -0.34, 95% CI -0.59 to -0.08), significantly favors MED **Borman:** (PHQ-9): SMD: 0.21, btw grp diff: -1.26, 95% CI 0.74 to -3.26, p=0.49	Yes (-1)	Yes (-1); findings of newer RCT inconsistent with SR findings	No	No	No	Low
Anxiety	1 SR with 3 RCTs (Hilton et al. 2017)	MED vs control Total n=264 4 to 8 weeks	SMD: -0.14, 95% CI: -0.63 to 0.36, I^2=0%	Yes (-1)	No	No	Yes (-1); wide 95% Cis	No	Low
Quality of life	1 SR with 4 RCTs (Hilton et al. 2017); 1 RCT (Borman et al. 2018)	MED vs control Total n=337 4 to 8 wks.	**Hilton:** mental health only, 4 RCTs, SMD: 0.52, 95% CI -0.24 to 1.28, I^2=64%,	Yes (-1)	No	No	Yes (-1); wide 95% CIs	No	Low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			NS; physical health only, 3 RCTs, 0.54, 95% CI -1.02 to 2.11, I^2=73%, NS						
Insomnia	1 RCT (Bormann, 2018)	MRP (89) vs. active control (84) 2 mos. f/u	SMD: 0.69, mean b/w grp difference: -4.81, 95% CI -2.30 to -7.32, p=0.004	Yes (-1)	No	No	Yes (-1); 1 small study	No	Low
Yoga									
PTSD symptoms	5 RCTs in 1 SR Cramer et al. 2018	Yoga (111) vs WL (95)	SMD: -1.10, 95% CI -1.72 to -0.47, I^2=72%	Yes (-1)	Yes (-1); due to high unexplained heterogeneity	No	No	NR	Low
	2 RCTs in 1 SR Cramer et al. 2018	Yoga (52) vs Attention CT (50)	SMD: -0.31,95% CI -0.84 to 0.22, I^2=43%	Yes (-1)	No	No	Yes (-1); wide 95% CIs	NR	Low

CI: confidence interval; CT: control group; ES: effective size; F/u: Follow-up; I^2: % of heterogeneity between studies; MBSR: mindfulness-based stress reduction; MED: meditation; mos.: months; NS: not significant; PCT: Present-centered therapy; PTSD: post-traumatic stress disorder; Quality of Life: QoL; RCT: randomized controlled trials; SE: standard error; SMD: standardized mean difference; Tx: treatment; TAU: treatment as usual; USPSTF: US Preventive Services Task Force; 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 Mind-Body Interventions to Treat PTSD

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
Meditation				
Reference: Gallegos et al. 2017 **Organization/Country:** University of Rochester, Medical Center, USA **Purpose:** To conduct a meta-analysis to assess the effect of meditation and yoga on PTSD outcomes in adult patients. **AMSTAR Rating:** High **Overall RoB of Included Studies:** Cochrane tool, Low (8 studies), unclear (5 studies), high (3 studies); overall RoB moderate	**Databases Searched:** Medline, PsycINFO, and Clinicaltrials.com **Dates Searched:** Inception to May 2016 **Inclusion/Exclusion Criteria:** RCTs with a minimal of 10 adult pts as minimum sample size with a clinical diagnosis of PTSD using valid diagnostic or screening measures. Studies must have evaluated the effect of a meditation intervention either as an adjunctive or monotherapy. Interventions included: mindfulness meditation, other meditation, or yoga. **Final Evidence Base:** 17; 10 RCTs for MBSR; 6 RCTs for meditation interventions; 1 RCT combination mindfulness and meditation *We only abstracted data for mindfulness and meditation-oriented interventions; See Cramer et al. 2018 for evidence on yoga.	**Diagnosis:** PTSD **Number of Patients:** Med n=485; CG n=491 **Age:** ≥18 yrs. **Gender:** NR 14 of the included studies assessed military population	**Intervention:** MBSR is a manualized group intervention that includes breathing exercises, hatha yoga, walking meditations, and meditative body scan; other meditation includes transcendental meditation, Sudarshan Kriya yoga, and mantra-based meditation. Meditation interventions were carried out over 2 to 22 sessions lasting between 1 to 2 hours over the course of 2 to 16 weeks. **Comparators:** Active (mostly TAU, k=14); WL (k=2) **Follow-up:** post-intervention ranging from 2 to 16 weeks **Outcomes:** PTSD symptoms as measured by CAPS, PCL or other PTSD outcome measure	**PTSD symptoms (post-intervention)** **MBSR vs controls (10 RCTs)** SMD: -0.33, 95% CI: -0.48 to -0.18; I^2: 0.01% **Other MED vs controls (6 RCTs)** SMD: -0.37, 95% CI: -0.60 to -0.13, I^2: 0.0% **Combination vs controls (1 RCT)** SMD: 0.46, 95% CI: -0.25 to 1.17 No evidence of publication bias. Results of moderator analyses assessing type of meditation, outcome measures, veteran status, and type of control suggests no appreciable differences in effect size. However, studies with smaller sample sizes (<30) had slightly larger effect sizes **Limitations:** Limited number of RCTs with small sample sizes, limited follow-up of included RCTs; and high or unclear RoB for half of included trials due largely to

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
				unclear or no allocation concealment, lack of blinding of outcome assessor and attrition.
Reference: Hilton et al. 2017 **Organization/Country:** Rand Corporation, CA, USA **Purpose:** To estimate the efficacy and safety of meditation interventions on symptoms of PTSD, depression, anxiety, health-related quality of life, functional status, and adverse events **AMSTAR Rating:** High **Overall RoB of Included Studies:** USPSTF criteria; poor to good due to lack of intent-to-treat analysis statistically significant differences among potential confounders at baseline	**Databases Searched:** PubMed, PsycINFO, AMED, CINAHL, Cochrane Database of Systematic Reviews, CENTRAL, Database of Abstracts of Reviews of Effect, PILOTS **Dates Searched:** Inception to November 2015 **Inclusion/Exclusion Criteria:** RCTs with adult pts with a clinical diagnosis of PTSD using valid diagnostic or screening measures. Studies must have evaluated the effect of a meditation intervention either as an adjunctive or monotherapy. **Final Evidence Base:** 7 RCTs We only abstracted data for mindfulness and meditation-oriented interventions for the outcomes of depression and quality of life; See Cramer et al. 2018 for evidence on yoga; See Gallegos et al. 2017 for data on PTSD outcomes.	**Diagnosis:** PTSD **Number of Patients:** 643 **Age:** Mean age range 41 to 59 **Gender:** 0% to 100% male All included studies assessed combat related trauma	**Intervention:** Meditation sessions ranged from 26 to 150 mins/session, 1 to 2 sessions per/week for 4 to 12 weeks. **Comparators:** TAU/WL (7 studies), PCT (1 study), *1 study had 3 study arms **Follow-up:** post-intervention to 4 to 32 weeks. **Outcomes:** PTSD symptoms, health-related quality of life, functional status, depressive and anxiety symptoms, adverse events.	**Depressive symptoms (MED vs. any control):** 8 RCTs, SMD: -0.34, 95% CI -0.59 to -0.08), significantly favors MED **Anxiety: (MED vs any control):** 3 RCTs, SMD: -0.14, 95% CI: -0.63 to 0.36, I^2=0% **QoL (MED vs. any control):** mental health only, 4 RCTs, SMD: 0.52, 95% CI -0.24 to 1.28, I^2=64%, NS; physical health only, 3 RCTs, 0.54, 95% CI -1.02 to 2.11, I^2=73%, NS Meta-regression results did not suggest significant differences among intervention types, comparators, trauma type, dosage, or study quality. Not possible to determine differential effects of offering meditation as adjunctive or monotherapy due to lack of monotherapy studies. **AEs:** No AE's reported among pts randomized to intervention group; 1 AE,

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
				reported in PCT control group (suicide attempt) No evidence of publication bias. **Limitations:** Only self-reported measures for depression, anxiety, QoL. Potential bias due to lack of participant blinding, lack of ITT analysis and differences at baseline.
Yoga				
Reference: Cramer et al. 2018 **Organization/Country:** University of Duisburg-Essen, Germany **Purpose:** To assess the evidence of yoga for reducing symptoms of PTSD **AMSTAR Rating:** High **Overall RoB of Included Studies:** Cochrane tool; moderate (k=1) to high (k=6) RoB due to lack of allocation concealment, no blinding in most studies and high overall attrition	**Databases Searched:** PubMed, PsycINFO, AMED, CINAHL, Cochrane Database of Systematic Reviews, CENTRAL, Database of Abstracts of Reviews of Effect, PILOTS **Dates Searched:** Inception to July 2017 **Inclusion/Exclusion Criteria:** RCTs with adult pts with a clinical diagnosis of PTSD using valid diagnostic or screening measures. Studies were included regardless of type yoga style, frequency or length of session. Types of control could include no tx or attention control (separate meta-analysis conducted for different control types). Only included assessing PTSD with validated measures. Studies involving pts with comorbid physical or mental disorders were included. **Final Evidence Base:** 7 RCTs	**Diagnosis**: PTSD **Number of Patients**: 284 **Age**: Mean age range 28.7 to 58.0 (median 43.6) **Gender**: 73% male 4 RCTs included only military personnel and/or veterans	**Intervention:** The studies assessed various forms of yoga that included Sudarshan Kriya (k=2), Kripalu (k=2), Kundalini (k=1), Satvananda (k=1), and trauma-informed (k=1). The median duration was 9.5 wks. and the median intensity was 1.75 hrs./wk. **Comparators:** WL (5 RCTs), attention control (2 RCTs) which include time and attention from therapist w/out a specific therapeutic component. **Follow-up:** Median 10 wks. **Outcomes:** PTSD symptoms as measured by CAPS, PCL, PSS and SCID	**Yoga vs WL (5 RCTs):** SMD: -1.10, 95% CI -1.72 to -0.47, I^2=72% Mean difference on the PCL reached clinical significance of ≥10 pts: MD=-13.11, 95% CI -17.95 to -8.27 **Yoga vs Att. CT (2 RCTs):** -SMD: 0.31,95% CI -0.84 to 0.22, I^2=43% Retention was comparable b/w yoga and WL (p=0.75) and yoga and att. CT (p=0.67) No AEs reported **Limitations:** Only self-reported measures for PTSD; small number of included studies, and methodological limitations of included studies that includes lack of allocation

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
				concealment, lack of blinding and attrition.

AEs: adverse events; CAPs: Clinician Administered PTSD Scale; CI: confidence interval; CT: control group; ES: effective size; F/u: Follow-up; I^2: % of heterogeneity between studies; MBSR: mindfulness-based stress reduction; MED: meditation; mos.: months; NS: not significant; PCL: PTSD checklist; PCT: Present-centered therapy; PSS: PTSD Symptom Scale; PTSD: post-traumatic stress disorder; Quality of Life: QoL; RCT: randomized controlled trials; SCID: Structured Clinical Interview for DSM-IV-TR; SE: standard error; SMD: standardized mean difference; Tx: treatment; TAU: treatment as usual; USPSTF: US Preventive Services Task Force; WL: waitlist

Table 4. Systematic Review Risk of Bias AMSTAR Checklist Table on Mind-Body Interventions to Treat PTSD

Question	Gallegos et al., (2017)	Hilton et al., (2017)	Cramer et al., (2018)
Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	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?	Yes	Yes	Yes
Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes
Did the review authors use a comprehensive literature search strategy?	Yes	Yes	Yes
Did the review authors perform study selection in duplicate?	Yes	Yes	Yes
Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	No	No	No
Did the review authors describe the included studies in adequate detail?	Yes	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	Yes
Did the review authors report on the sources of funding for the studies included in the review?	No	No	Yes
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? RCTs?	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	Yes
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	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	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	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No	No	Yes
Overall Quality	**High**	**High**	**High**

RoB: risk of bias

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

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

Table 6. Evidence Table for RCTs on Mind-Body Interventions to Treat PTSD

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Borman et al. 2018 **Purpose:** To compare mantrum therapy to person-centered trauma therapy for adults with PTSD. **Setting:** VA Medical Centers in San Diego, CA and Bedford, MA **Funding source:** VA supported study	**Number of patients:** 173; n=89 MRP; n=84 PCT **Inclusion criteria:** Veterans ≥18 yrs. with at least 1 military-related traumatic experience and met DSM-IV criteria for PTSD with a symptom severity cutoff off score of ≥4f5 on the CAPS and ≥50 on the PCL-M. **Exclusion criteria:** NR **Pt. baseline characteristics (MRP; PCT):** Age (mean, yrs.): 48.3 (14.6); 49.5 (14.5) Gender (% male): 82%; 88% % Currently on medication for PTSD: 66%; 64% % Discontinued pharmacological tx: 22%; 14% Mean BL CAPS score: 77.4 (16.5); 75.6 (16.8)	**Intervention:** MRP involves silently repeating a mantram, usually a spiritually related word or phrase, to initiate relaxation and practice the skills of slowing down and focusing attention on the present. **Control:** PCT is a manualized person-centered psychotherapy. It focuses on current events in the patient's life and uses techniques such as mirroring and problem-solving to help patients with current stressors. Both MRP and PCT were delivered on a one-to-one bases for 1-hour sessions weekly sessions over the course of 8-weeks. Each treatment condition used a manualized approach with a trained instructor. All pts asked to refrain from participating in other psychotherapy but could continue to take medications. **Outcomes:** PTSD symptoms (CAPS, PCL-M); insomnia (ISI); Depression	**2 mos. f/u (SMD, b/w grp mean change, 95% CI, p-value):** **CAPS:** 0.46, -9.34, 95% CI -1.50 to -17.18, p=0.04 **PCL-M:** 0.33, -4.51, 95% CI 0.70 to -9.72, p=0.25 **Insomnia (ISI):** 0.69, -4.81, 95% CI -2.30 to -7.32, p=0.004 **Depression (PHQ-9):** 0.21, -1.26, 95% CI 0.74 to -3.26, p=0.49 **Quality of life (WHOQOL):** 0.24, 3.01, 95% CI 7.36 to -1.34, p=0.45	Results suggest that MRP is more effective than PCT in reducing PTSD symptom severity and insomnia among a sample of veterans with PTSD. **Limitations:** Small sample size and limited follow-up. **Study ROB:** Moderate; due to lack of blinding of patients and participants **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	Mean BL PCL-M score: 59.2 (12.09); 57.6 (11.5)	(PHQ-9); Quality of life (WHOQOL-brief form) **F/u:** 2 mos.		

CAPS: Clinician Administered PTSD Scale; CI: confidence intervals; ISI: Insominia Severity Index; mos: months; MRP: Mantram repitition program; PCL-M: PTSD checklist-military version; PCT: Person-centered therapy; PHQ-9: Patient Health Questionnaire; PTSD: post-truamatic stress disorder; RoB: risk of bias; SMD: standarized mean difference; WHOQOL: World Health Quality of Life Brief Form

Table 7. Cochrane Risk of Bias 2.0 Tool for RCTs on Mind-Body Interventions to Treat PTSD

Reference	Bormann et al. (2018)
Randomization Process	
➢ 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?	No information
➢ 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 information
➢ 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 information
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?	No
➢ 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?	NA
Overall RoB of Missing Data	**Low**
Measurement of the Outcome	
➢ Was the method of measuring the outcome inappropriate?	No
➢ Could measurement or ascertainment of the outcome have differed between intervention groups?	Probably not
➢ 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?	NA
➢ Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Overall RoB of Measurement of Outcome	**Low**

Reference	Bormann et al. (2018)
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
Overall RoB of Reported Results	**Low**
Overall Study RoB	**Some concerns**

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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Relaxation Techniques

Evidence Base

Our searches of the literature identified 2 RCTs that met inclusion criteria and assessed the efficacy of relaxation therapy (RT). One compared RT to eye movement desensitization and reprocessing (EMDR) an evidence based treatment, in the treatment of PTSD among patients with multiple sclerosis (Carletto et al. 2016), and the other compared RT to a culturally adapted form of cognitive behavior therapy (CA-CBT) among Latino women with treatment-resistant PTSD (Hinton et al. 2011).

In the first RCT, Carletto randomized 50 patients with relapsing and remitting or progressive multiple sclerosis and co-occurring PTSD to receive either RT (n=25) or EMDR (n=25). RT in this study included a series of relaxation techniques performed by two trained therapists that included diaphragmatic breathing, muscle relaxation, visualization, cue-controlled relaxation, and rapid relaxation. EMDR was administered in accordance to Shapiro's protocol and was provided by 3 experienced clinicians. The first session involved training patients in stabilization techniques and the remaining sessions involved imaginary exercises about the traumatic event along with eye movement reprocessing until the trauma no longer evoked distress. Each intervention group received 10, 60-minute long treatment sessions delivered over the course of 12 to 15 weeks. The primary outcomes included proportion of patients no longer meeting the diagnosis of PTSD at six months follow-up and change in symptoms of PTSD, depression, anxiety and quality of life. To be included in this study, patient had to suspend all concomitant psychological treatments and psychotropic medications at least one month prior to start of study.

In the other RCT, Hinton randomized 24 Latino women with treatment resistant PTSD to a culturally adapted version of CBT (n=12) or to applied muscle relaxation therapy (n=12). CBT in this study was delivered using culturally appropriate language, prompts, imagery and exposure visualizations. CBT was manual-based and delivered by a trained therapist over the course of 12 to 14 weekly sessions lasting one hour. RT involved applied muscle relaxation techniques provided by a trained therapist or the patient. The treatment also consisted of psychoeducation about PTSD and how it produces anxiety and somatic symptoms. RT was also provided over the course of 12 to 14 weekly sessions lasting one hour. Patients in each therapy group were permitted to take their prescribed medications for PTSD and continue with any supportive therapy they were receiving. The primary outcomes in this study were change in symptoms of PTSD and anxiety. See Table 2 for more information about the patients and interventions included in the RCTs for relaxation therapy.

Study Quality

Using the Cochrane tool, we rated the RoB of the RCT by Carletto as Moderate due to concerns about the lack of blinding of patients and treating clinicians. The RoB of the RCT by Hinton 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 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 EMDR was associated with a slightly higher proportion of patients with multiple sclerosis who no longer met the diagnosis of PTSD at follow-up compared to relaxation therapy. (SOE: Low)
- Evidence from 1 RCT suggests that EMDR and relaxation therapy alone led to similar improvement on measures of PTSD, anxiety, depression, and quality of life among patients with multiple sclerosis and co-occurring PTSD with no statistically significant difference between treatments (SOE: Low)
- Evidence from 1 RCT suggests that culturally adapted CBT statistically significantly reduces PTSD symptoms and anxiety compared to relaxation therapy among Latino women with treatment resistant PTSD. (SOE: Low)

Discussion

The evidence from one RCT suggests that relaxation therapy alone led to similar improvement on measures of PTSD symptoms, depression, anxiety, and quality of life as EMDR among patients with multiple sclerosis and co-occurring PTSD. However, EMDR was associated with a higher proportion of patients who no longer met the diagnosis of PTSD at 6 months follow-up (100% vs 77%, p=0.049). The strength of the evidence was rated low due to the limited evidence base (1 RCT with 50 patients) and some concerns with the methodological quality of the study (lack of patient and clinician blinding). See **Table 1** for the more information about the strength of evidence ratings. Evidence from another RCT indicated that a culturally adapted version of CBT was more effective than relaxation therapy alone in reducing symptoms of PTSD and anxiety among Latino women with treatment-resistant PTSD. The strength of the evidence from this RCT was rated very low due to the very small sample size (n=24 patients) of the study and methodological limitations that include no information about the randomization process and lack of blinding of patients, clinicians and outcome assessors. This study also only included self-reported measures of change in PTSD symptoms. No adverse events were reported in either of the RCTs included as evidence for relaxation therapy.

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

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
PTSD symptoms	1 RCT Carletto et al 2016	EMDR (25) vs RT (25) 6 months	Mean F/u CAPS: EMDR: 16.6 (10.1); RT: 19.5 (15.6); NS btw grp difference Mean F/u IES-R: EMDR: 28.25 (18.26); RT: 28.68 (19.39); NS btw grp difference	Yes (-1)	No	No	Yes (-1); single, small study with no significant difference	No	Low
Anxiety	1 RCT Carletto et al 2016	EMDR (25) vs RT (25) 6 months	Mean F/u HADS-anxiety: EMDR: 7.40 (3.93); RT: 7.64 (6.19); NS btw grp difference	Yes (-1)	No	No	Yes (-1); single, small study with no significant difference	No	Low
Depression	1 RCT Carletto et al 2016	EMDR (25) vs RT (25) 6 months	Mean F/u HADS-depression: EMDR: 7.20 (3.93); RT:m7.73 (4.73); NS btw grp difference	Yes (-1)	No	No	Yes (-1); single, small study with no significant difference	No	Low
Quality of life	1 RCT Carletto et al 2016	EMDR (25) vs RT (25) 6 months	FAMS-total: EMDR: 102.7 (39.4); RT: 109.8 (35.9); NS btw grp difference	Yes (-1)	No	No	Yes (-1); single, small study with no significant difference	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
PTSD symptoms	1 RCT Hinton et al. 2011	Culturally adapted CBT (12) vs. AMR (12)	Mean PCL, SD, b/w grp p-value, ES): CBT: 36.4 (12.7); AMR: 58.9 (14.7); p<0.01; SMD: 1.6	Yes (-2)	No	No	Yes (-1); single study with a small sample	No	Very low
Anxiety	1 RCT Hinton et al. 2011	Culturally adapted CBT (12) vs. AMR (12)	Mean SCL, SD, b/w grp p-value, ES): CBT:1.4 (0.6); AMR: 2.1 (0.8); p<0.01; SMD: 1.1	Yes (-2)	No	No	Yes (-1); single study with a small sample	No	Very low

AEs: adverse events; AMR: Applied muscle relaxation; BL: baseline; CBT: cognitive behavioral therapy; CI: confidence interval; EMDR: Eye movement desensitization and reprocessing; FAMS: Functional Assessment in Quality of Life in MS; f/u: follow-up; HADS: Hamilton Anxiety or Depression Scale; IES-R: Impact of Event Scale-Revised; MS: Multiple Sclerosis; NR: not reported; NS: not significant; PCL: PTSD Checklist; PTSD: post-traumatic stress disorder; QoL: Quality of life; RCT: randomized controlled trials; RoB: risk of bias; RT: relaxation therapy; SCL: Symptom Checklist; SD: standard deviation; SMD: standardized mean difference; 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

Evidence Category	Definition
	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 PTSD

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Carletto et al. 2016 **Purpose:** To compare the efficacy of EMDR to relaxation therapy for PTSD among patients with MS. **Setting:** University Hospital, Turin, Italy **Funding source:** NR	**Number of patients:** 50; n=25 in EMDR; n=25 in RT **Inclusion criteria:** Diagnosis of relapsing/remitting and primary or secondary progressive MS disease (disease in inactive phase); between 18 and 65 years; diagnosis of PTSD using clinical assessment; presence of PTSD symptoms for at least 3 months; fluent in Italian; able to provide consent; and willingness to suspend psychotropic medication and other therapy for PTSD 1 month prior to start of study. **Exclusion criteria:** Presence of severe psychiatric disorder, medical disease other than MS; substance abuse; suicide attempts; overt dementia; or corticosteroid shot in the past 30 days. **Pt. baseline characteristics (EMDR; RT):** **Age (mean yrs., SD):** 39.5 (1.68); 40.6 (10.0) **Gender (% male):** 25%; 13% **Years since MS dx:** 7; 7	**Intervention:** EMDR was administered in accordance to Shapiro's protocol and was provided by 3 experienced clinicians. The first session involved training pts in stabilization techniques and the remaining 10 sessions involved imaginary exercises about the traumatic event along with eye movement reprocessing until the trauma no longer evoked distress. **Control:** RT included a series of relaxation techniques performed by 2 trained therapists that included diaphragmatic breathing, muscle relaxation, visualization, cue-controlled relaxation, and rapid relaxation. Each intervention group received 10, 60 min long treatment sessions delivered over the course of 12 to 15 wks. **Outcomes of Interest:** PTSD symptoms (measured by CAPS, IES and proportion of pts meeting PTSD diagnosis after tx), anxiety and	**Responders (proportion who no longer met PTSD dx):** Post-tx (12 wks., EMDR, RT): 85%; 72.7%; btw/grp p-value: NS F/u (6 mos., EMDR; RT): 100%; 77.3%; btw/grp p=0.049 **Symptoms at 6 mos. f/u** (EMDR, RT, mean score, SD, and b/w grp p-value): CAPS: 16.6 (10.1); 19.5 (15.6); NS IES-R: 28.25 (18.26); 28.68 (19.39); NS	**Conclusion:** The findings suggest that both EMDR and RT led to significant improvement in PTSD symptoms, depression, anxiety and quality of life from pre-treatment to follow-up with no significant difference between treatments on any symptom outcomes. EMDR was associated with a slightly higher proportion of pts who no longer met the diagnosis of PTSD at follow-up. No adverse events were reported. **Limitations:** Small sample size and methodological limitations in study conduct. **Study RoB:** Some Concerns; due primarily to lack of blinding of patients and clinicians **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	Mean number of previous traumas: 3.5 (6); 5 (7) **Mean CAPS-total BL:** 44.5 (14.1); 44.4 (11.13) **IES-R-total BL:** 53.05 (12.87); 51.36 (9.58) **HADS-Anxiety BL:** 12.1 (3.95); 11.32 (3.76) **HADS-Depression BL:** 10.15 (3.38); 10.36 (4.09) **FAMS-total BL:** 88.8 (34.3); 96.7 (31.5)	depression (measured by HADS), and quality of life (measured by FAMS) **Follow-up:** 6 months	HADS-anxiety: 7.40 (3.93); 7.64 (6.19); NS HADS-depression: 7.20 (3.93); 7.73 (4.73); NS FAMS-total: 102.7 (39.4); 109.8 (35.9); NS There was significant pre to posttreatment improvement on all symptom outcomes in both groups (p<0.001). AEs: None reported	
Reference: Hinton et al. 2011 **Purpose:** To compare the efficacy of a culturally adapted form of CBT to AMR for Latino women living in the U.S. with treatment-resistant PTSD. **Setting:** U.S. based community outpatient clinic that provides specialized	**Number of patients:** 24, n=12 CBT: n=12 AMR **Inclusion criteria:** **Exclusion criteria:** Inability to give informed consent; psychosis in the past year; not having Spanish as preferred language; active substance abuse; and male gender **Pt. baseline characteristics (CBT; AMR):** **Age (mean yrs., SD):** 47.6 (8.2); 51.4 (5.9) **Gender (% male):** 100% female **Country of origin:** n=14 Puerto Rico; n=10 Dominican Republic **Time living in U.S.:** >10 yrs.	**Intervention:** CBT was delivered using culturally appropriate language, prompts, imagery and exposure visualizations. CBT was manual-based and delivered by a trained therapist over the course of 14 weekly sessions lasting 1 hour. **Control:** AMR involved applied muscle relaxation techniques provided by a trained therapist or the patient. The treatment also consisted of psychoeducation about PTSD and how it produces anxiety and somatic symptoms. AMR was also provided over the course of 14 weekly sessions lasting 1 hour. Patients in each therapy group were permitted to take their prescribed	**<u>12 wks. f/u</u>** **PTSD symptoms (mean PCL, SD, b/w grp p-value, ES):** 36.4 (12.7); 58.9 (14.7); p<0.01; SMD: 1.6 **Anxiety (mean SCL, SD, b/w grp p-value, ES):** 1.4 (0.6); 2.1 (0.8); p<0.01; SMD: 1.1 **AEs:** None reported	**Conclusion:** Results suggest that culturally adapted CBT statistically significantly improved symptoms of PTSD and anxiety among Latino women with treatment resistant PTSD compared to relaxation therapy alone with no reported AE's. **Limitations:** Small sample size and methodological limitations **Study RoB:** High; unclear randomization procedures; lack of blinding of patients, clinicians and outcome assessors, and self-reported outcomes. **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
services to Latino patients. **Funding source:** NR	**BL PCL (mean, SD; CBT; AMR):** 69.8 (6.5); 71.1 (7.9) **BL SCL (mean, SD; CBT; AMR):** 2.5 (0.5); AMR (0.6)	medications for PTSD and continue with any supportive therapy they were receiving. **Outcomes of Interest:** PTSD symptoms (measured using PCL), anxiety (measured using SCL), and AEs **Follow-up:** 12 wks.		

AEs: adverse events; AMR: Applied muscle relaxation; BL: baseline; CI: confidence interval; Dx: diagnosis; EMDR: Eye movement desensitization and reprocessing; FAMS: Functional Assessment in Quality of Life in MS; f/u: follow-up; HADS: Hamilton Anxiety or Depression Scale; IES-R: Impact of Event Scale-Revised; MS: Multiple Sclerosis; NR: not reported; NS: not significant; PCL: PTSD Checklist; PTSD: post-traumatic stress disorder; QoL: Quality of life; RCT: randomized controlled trials; RoB: risk of bias; RT: relaxation therapy; SCL: Symptom Checklist; SD: standard deviation; SMD: standardized mean difference; Tx: treatment; wks.: weeks

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

Reference	Carletto et al., (2016)	Hinton et al., (2011)
➢ Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	Yes	NI
➢ Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization, concealed envelopes)?	Yes	NI
➢ Did baseline difference between study groups suggest a problem with randomization?	No	No
Overall RoB for Randomization Process	**Low**	**Some Concerns**
Deviation from Intended Intervention (Effect of Assignment)		
➢ Were participants aware of their assigned intervention during the trial?	Yes	Yes
➢ Were providers and people delivering treatment aware of assigned intervention during trial?	Yes	Yes
➢ Were there deviations from the intended intervention that arose because of the experimental context?	No	No
➢ Were these deviations from intended intervention balanced between groups?	NA	NA
➢ Were these deviations likely to have affected the outcome?	NA	NA
➢ Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	Yes
Overall RoB of Effect of Assignment	**Some Concerns**	**Some Concerns**
Missing Outcome Data		
➢ Were data for this outcome available for all, or nearly all, participants randomized?	Yes	Yes
➢ Is there evidence that result was not biased by missing outcome data?	NA	NA
➢ Could missingness in the outcome depend on its true value?	NA	NA
➢ Do the proportions of missing outcome data differ between intervention groups?	NA	NA
➢ Is it likely that missingness in the outcome depended on its true value?	NA	NA
Overall RoB of Missing Data	**Low**	**Low**
Measurement of the Outcome		
➢ Was the method of measuring the outcome inappropriate?	No	No
➢ Could measurement or ascertainment of the outcome have differed between intervention groups?	No	No
➢ Were outcome assessors aware of the intervention received by study participants?	No	Yes
➢ Could assessment of the outcome have been influenced by knowledge of intervention received?	No	NI
➢ Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No	NI

Reference	Carletto et al., (2016)	Hinton et al., (2011)
Overall RoB of Measurement of Outcome	**Low**	**High**
Selection of Reported Results		
➢ Was the trial analyzed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?	Yes	NI
Overall RoB of Reported Results	**Some Concerns**	**Some Concerns**
Overall Study RoB	**Some concerns**	**High**

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

Carletto, S., Borghi, M., Bertino, G., Oliva, F., Cavallo, M., Hofmann, A.,…Ostacoli, L. (2016). Treating post-traumatic stress disorder in patients with multiple sclerosis: A randomized controlled trial comparing the efficacy of eye movement desensitization and reprocessing and relaxation therapy. *Frontiers in Psychology, 7*(526). doi: 10.3389/fpsyg.2016.00526

Hinton, D., Hofmann, S., Rivera, E., Otto, M., & Pollack, M. (2011). Culturally adapted CBT (CA-CBT) for latino women with treatment-resistant PTSD: A pilot study comparing CA-CBT to applied muscle relaxation. *Behaviour Research and Therapy, 49*, 275-280. doi: 10.1016/j.brat.2011.01.005

Transcranial Magnetic Stimulation (TMS)

Evidence Base

Our searches of the literature identified 1 SR and 2 RCTs that assessed the efficacy of TMS or repetitive (r) TMS used as an adjunctive treatment for treating adults with PTSD (key question 2 and 3). The review published by Yan et al. (2017) included 11 RCTs that assessed the efficacy and safety of TMS at varying frequencies compared to sham TMS (Yan et al. 2017). The strength of the evidence supporting the findings for TMS for symptoms of PTSD was rated as moderate to low due to methodological limitations of the included studies and between study heterogeneity.

The RCTs included in the review enrolled a total of 377 patients (n=217 TMS; n=160 sham) with a diagnosis of PTSD according to standard diagnostic criteria. Four of the RCTs enrolled veterans with combat related PTSD. The average age of the patients was 39.7 years. The primary outcomes assessed in this review were PTSD symptoms, depression, anxiety, sleep quality, and adverse events. In 6 of the included RCTs, TMS was used as an adjunct to drug and/or psychological therapy. The authors of these studies indicated that previously used drugs or psychological interventions were not discontinued or changed during the 3 weeks prior to the start of the study or during the study. Patients received TMS either bilaterally or unilaterally in the right or left dorsolateral prefrontal cortex (DLPFC). The authors of the review conducted subgroup analysis of studies that administered TMS at frequencies greater than 1 Hz. Sham TMS was delivered in a manner that provided a similar sound and scalp sensation as the actual treatment.

One RCT, published subsequent to the Yan review, compared the efficacy and safety of bilateral TMS and unilateral TMS. Ahmadizadeh et al. (2018) randomized 58 Iranian veterans between the ages of 42 and 69 years (mean age 50 years) with a confirmed diagnosis of PTSD to receive either bilateral TMS (n=19), unilateral TMS (n=19) or sham TMS (n=20) (Ahmadizadeh et al. 2018). All enrolled patients were stable on their current psychosocial or psychotropic treatment for 2 months prior to the start of the study. Follow-up was 4 weeks and the primary outcomes were change in PTSD symptoms and adverse events.

The other RCT, published by Kozel et al. (2018), compared active TMS immediately followed by cognitive processing therapy (CPT) to sham TMS followed by CPT (Kozel et al. 2018). This study randomized 103 female and male U.S. veterans diagnosed with combat-related PTSD (See Table 4). The average age of the enrolled patients was 32.4 years. Patients could continue to take prescribed medications for PTSD, depression, or pain. Overall, 53% of patients were taking medication. TMS was delivered over the right DLPFC at 1 Hz for 30 minutes for a total of 1800 pulses per day immediately followed by a 60-minute CPT session. Follow-up was 6 months and the primary outcomes were change in PTSD symptoms, depression and psychosocial functioning. See **Table 3 and Table 6** for more information about the patients and interventions assessed in this studies that made up the evidence base for TMS.

Study Quality

Using the AMSTAR instrument, we rated the quality of the review as moderate due primarily to the review authors not explicitly stating if the review methods were established prior to conducting the review (see **Table 4** for the quality ratings). The authors of the review by Yan rated the RoB of the

included RCTs as moderate to high using criteria from the Cochrane tool. The authors indicated that some of the studies did not blind patients, clinicians or outcome assessors. The authors also found that overall the TMS group had significantly higher baseline symptoms of PTSD and depression than patients in the control group, suggesting the presence of potential selection bias in some studies. We rated the RoB of the Ahmadizadeh trial as having some concerns due to lack of blinding of the clinician who provided treatment, and we rated the RoB of the Kozel trial as high due significant unexplained attrition (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.

Bi-lateral or Uni-lateral TMS (any frequency) vs. Sham TMS

- Combined evidence from 11 RCTs suggests that active TMS statistically significantly reduces PTSD symptoms compared to sham TMS. (SOE: Low)
- Combined evidence from 5 RCTs suggest that there is no statistically significant difference in clinician assessed PTSD symptoms between active TMS and sham TMS. (SOE: Very low)
- Combined evidence from 6 RCTs suggests that active TMS statistically significantly reduces anxiety compared to sham TMS. (SOE: Low)
- Combined evidence from 5 RCTS suggests that there is no statistically significant difference between active TMS and sham TMS for reducing depression. (SOE: Low)

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

- Combined evidence from 8 RCTs suggests that high frequency TMS statistically significantly reduces PTSD symptoms compared to sham TMS. (SOE: Low)
- Combined evidence from 3 RCTs suggest that there is no statistically significant difference in clinician assessed PTSD symptoms between high frequency TMS and sham TMS. (SOE: Very low)
- Combined evidence from 6 RCTs suggests that high frequency TMS statistically significantly reduces anxiety compared to sham TMS. (SOE: Low)
- Combined evidence from 4 RCTS suggests that there is no statistically significant difference between active TMS and sham TMS for reducing depression. (SOE: Low)

Low Frequency Bi-lateral or Uni-lateral TMS (<1 Hz) vs. Sham TMS

- Combined evidence from 3 RCTs suggests that low frequency TMS statistically significantly reduces PTSD symptoms compared to sham TMS. (SOE: Low)
- Combined evidence from 3 RCTs suggests that high frequency TMS statistically significantly reduces depression compared to sham TMS. (SOE: Low)

- Combined evidence from 3 RCTS suggests that there is no statistically significant difference between active TMS and sham TMS for reducing anxiety. (SOE: Low)

TMS + Cognitive Processing Therapy vs sham TMS + Cognitive Processing Therapy

- Evidence from 1 RCT suggests that active TMS + CPT is statistically significantly more effective than sham TMS + CPT in reducing PTSD symptoms. (SOE: Moderate)
- Evidence form 1 RCT suggests that there is no statistically significant difference between active TMS + CPT and sham TMS + CPT in reducing depression or improving psychosocial functioning. (SOE: Low)

Discussion

Overall, the findings of the RCTs that made up the evidence base for TMS suggest that active TMS at any frequency used as an adjunct to medication and/or psychotherapy reduces symptoms of PTSD compared to sham TMS. The strength of the evidence supporting the findings for TMS for symptoms of PTSD was rated as moderate to low due to methodological limitations of the included studies and between study heterogeneity. The evidence suggests that there is no statistically significant difference between active TMS at higher frequencies (≥1 Hz) and sham TMS for symptoms of depression. However, the combined evidence from 3 RCTs suggests that TMS at lower frequencies may reduce symptoms of depression (standardized mean difference [SMD]: -0.92, 95% confidence interval [CI] 0.11 to 1,72, p=0.03) compared to sham TMS. The strength of the evidence for this finding was low due to methodological limitations of the included studies and between study heterogeneity. Finally, the combined evidence from 6 RCTs suggests that active TMS at frequencies ≥ 1Hz statistically significantly reduces symptoms of anxiety compared to sham TMS (SMD: -0.89, 95% CI -1.50 to -0.29, p=0.01). The strength of the evidence was rated low. Headache was the most commonly reported adverse event among patients receiving active TMS. However, the duration of treatment and length of follow-up of most of the studies that made up the evidence base for TMS were insufficient to determine adverse events associated with repeated exposures or follow-up periods longer than 6 months.

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

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Bi-lateral or Unilateral rTMS (Any Frequency) vs Sham									
PTSD symptoms	11 RCTs (10 in Yan, 2017; Ahmadizadeh, (2018)	rTMS (236); sham (180) 4 weeks reported in Ahmadizadeh, 2018	**Change in PCL**: **SR**: (10 RCTs): SMD: -2.38, 95% CI -3.30 to -1.45, p=0.00; I^2=89% **RCT:** mean (SD): bi-rTMS, 45.8 (4.67); uni-rTMS, 49.4 (6.58); sham, 66.9 (10.3); significant difference b/w active tx and sham (p=0.001); NS b/w bi and unilateral TMS.	Yes (-1)	Yes (-1); substantial unexplained heterogeneity	No	No	No	Low
Depression	5 RCTs in Yan, 2017	rTMS (NR) vs sham (NR) F/u: NR	**Change in HAM-D:** SMD: -0.07, 95% CI -0.43 to 0.29,	Yes (-1)	No	No	Yes (-1); wide 95% CI	No	Low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			p=0.71; I^2=0.0%						
Anxiety	6 RCTs in Yan, 2017	rTMS (NR) vs sham (NR) F/u: NR	**Change in HAM-A:** SMD: -0.89, 95% CI -1.50 to -0.29, p=0.01; I^2=66%	Yes (-1)	Yes (-1); substantial unexplained heterogeneity	No	No	No	Low
Bi-lateral or Unilateral rTMS (HIGH Frequency ≥1 Hz) vs Sham									
PTSD symptoms	8 RCTs in Yan, 2017	rTMS (NR) vs sham (NR) F/u: NR	**Change in PCL**: SMD: -2.83, 95% CI -3.84 to -1.82, p=0.00; I^2=88%	Yes (-1)	Yes (-1); substantial unexplained heterogeneity	No	No	No	Low
Depression	4 RCTs in Yan, 2017	rTMS (NR) vs sham (NR) F/u: NR	**Change in HAM-D:** SMD: -0.07, 95% CI -0.45 to 0.32, p=0.74; I^2=0.0%	Yes (-1)	No	No	Yes (-1); wide 95% CI	No	Low
Anxiety	6 RCTs in Yan, 2017	rTMS (NR) vs sham (NR) F/u: NR	**Change in HAM-A:** SMD: -1.07, 95% CI -1.66 to -0.48, p=0.00; I^2=60%	Yes (-1)	Yes (-1); substantial unexplained heterogeneity	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
Bi-lateral or Unilateral rTMS (Low Frequency <1 Hz) vs Sham									
PTSD symptoms	3 RCTs in Yan, 2017	rTMS (NR) vs sham (NR) F/u: NR	**Change in PCL**: SMD: -0.92, 95% CI 0.11 to -1.72, p=0.03; I^2=59%	Yes (-1)	Yes (-1); substantial unexplained heterogeneity	No	No	No	Low
Depression	3 RCTs in Yan, 2017	rTMS (NR) vs sham (NR) F/u: NR	**Change in HAM-D:** SMD: -0.54, 95% CI 0.08 to 0.1.00, p=0.02; I^2=0.0%	Yes (-1)	No	No	Yes (-1); wide 95% CI	No	Low
Anxiety	3 RCTs in Yan, 2017	rTMS (NR) vs sham (NR) F/u: NR	**Change in HAM-A:** SMD: 0.32, 95% CI -0.14 to 0.77, p=0.17; I^2=0.0%	Yes (-1)	No	No	Yes (-1); wide 95% CI	No	Low
rTMS+CPT vs sham rTMS+ CPT									
PTSD symptoms	1 RCT Kozel (2018)	rTMS+CPT (n=54); sham rTMS+CPT (n=49)	Mean [SD] score: rTMS+CPT; sham rTMS+CPT, p-value): **CAPs:** 27.5 (4.04); 37.5 (4.49), p=0.023	Yes (-1)	No	No	No	NA	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
			PCL: 30.8 (2.1); 38.0 (2.4), p=0.017 **M-PTSD:** 78.9 (3.1); 90.5 (3.4), p=0.004						
Depression and psychosocial function	1 RCT Kozel (2018)	rTMS+CPT (n=54); sham rTMS+CPT (n=49)	Mean [SD] score: rTMS+CPT; sham rTMS+CPT, p-value): **QIDS:** 4.98 (0.84); 8.12 (0.93); NS **IPF:** 2.7 (0.16); 3.09 (0.18); NS	Yes (-1)	No	No	Yes (-1); p-values indicate NS or overlapping CIs)	NA	Low

CI: confidence interval; CAPS: Clinician Administered PTSD Scale; CPT: cognitive reprocessing therapy; f/u: follow-up; HAM-A: Hamilton Anxiety scale; HAM-D: Hamilton Depression scale; IPF: Inventory of Psychosocial Functioning; M-PTSD: Mississippi Scale for Combat Related PTSD; mos.: months; NA: not applicable; NR: not reported; NS: not significant; PCL: PTSD Checklist (military version); PTSD: post-traumatic stress disorder; QIDS: Quick Inventory of Depressive Symptomology; RCT: randomized controlled trials; rTMS: repetitive TMS; SD: standard deviation; SMD: standardized mean difference; TMS: transcranial magnetic stimulation

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

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

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

Table 3. Evidence Table for Systematic Reviews on Transcranial Magnetic Stimulation (TMS) to Treat PTSD

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
Reference: Yan et al. (2017) **Organization/Country:** China **Purpose:** To conduct a SR to assess the effectiveness of rTMS delivered at different frequencies for treating PTSD. **AMSTAR Rating:** Moderate **Overall RoB of Included Studies:** Moderate to high; some studies did not blind pts, clinicians or outcome assessors, and review authors found that the rTMS group had significantly higher PTSD and depression scores than the sham group.	**Databases Searched:** PubMed, The Cochrane library, EMBASE, PsychInfo, ISI Web of Knowledge, and Chinese specific databases **Dates Searched:** Inception to August 1, 2016 **Inclusion/Exclusion Criteria:** Pts aged 18 to 75 yrs. with a diagnosis of PTSD according to DSM-IV; study could be of any research design provided the aim was assess TMS or rTMS treatment for PTSD symptoms. **Final Evidence Base:** 18 studies (11 RCTs) *only reported findings for pooled analysis of RCTs	**Diagnosis:** PTSD; 4 studies reported stressor related to combat; NR in remaining studies **Number of Patients:** 377 (n=217 TMS; n=160 sham) **Age:** Mean 39.7 yrs. **Gender:** 51% female In all studies; TMS was an augmentative to drug therapy (k=18); and to both drug and psychotherapy in 1 study.	**Intervention:** Bilateral or right or left DLPFC TMS **Comparators:** Sham TMS delivered through a coil that provided a similar sound and scalp sensation as the actual treatment. **Follow-up:** NR **Outcomes:** PTSD, depression and anxiety symptoms, sleep quality and AEs	**TMS at any Frequency** **PTSD symptoms (PCL-C):** **Self-reported (10 RCTs):** SMD: -2.38, 95% CI -3.30 to -1.45, p=0.00; I^2=89% **Clinician reported (5 RCTs):** SMD: -0.66, 95% -1.58 to 0.26, p=0.16; I^2=73% **Depression (HAM-D, 5 RCTs):** SMD: -0.07, 95% CI -0.43 to 0.29, p=0.71; I^2=0.0% **Anxiety (HAM-A, 6 RCTs):** SMD: -0.89, 95% CI -1.50 to -0.29, p=0.01; I^2=66% **Sleep (1 RCT):** n=10 pts in TMS reported improvement vs. 1 in the sham control **TMS at High Frequency (>1Hz)** **PTSD symptoms (PCL-C):** **Self-reported (8 RCTs):** SMD: -2.83, 95% CI -3.84 to -1.82, p=0.00; I^2=88% **Clinician reported (3 RCTs):** SMD: -1.09, 95% CI -2.66 to 0.47, p=0.17; I^2=82% **Depression (HAM-D, 4 RCTs):** SMD: - 0.07, 95%

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
				CI -0.45 to 0.32, p=0.74; I^2=0.0% **Anxiety (HAM-A, 6 RCTs):** SMD: -1.07, 95% CI -1.66 to -0.48, p=0.00; I^2=60% **Sleep (1 RCT):** NR **<u>TMS at Low Frequency (<1 Hz)</u>** **PTSD symptoms (PCL-C):** **Self-reported (3 RCTs):** SMD: 0.92, 95% CI 0.11 to 1.72, p=0.03; I^2=59% **Depression (HAM-D, 3 RCTs):** SMD: 0.54, 95% CI 0.08 to 1.00, p=0.02; I^2=0.0% **Anxiety (HAM-A, 3 RCTs):** SMD: 0.32, 95% CI -0.14 to 0.77, p=0.17; I^2=0.0% **AEs:** Headache was the most commonly reported AE No evidence of publication bias and meta-regression results suggest that none of the assessed co-variates (High or low frequency; >1,000 pulse/day; study design; history of PTSD; number of tx sessions; or receiving more than 1 SSRI) had an impact on the overall tx effect.

Study Details	Search Strategy/Evidence Base	Patients	Interventions/Comparators	Results
				Limitations: Unexplained heterogeneity of included studies; significant difference in severity of PTSD in some studies, with pts receiving rTMS having more severe PTSD than sham pts; limited number of studies and small sample size.

AE: adverse events; CI: confidence interval; DLPFC: dorsolateral prefrontal cortex; HAM-A: Hamilton Anxiety scale; HAM-D: Hamilton Depression scale; I^2: % of heterogeneity between studies; mos.: months; NR: not reported; NS: not significant; PTSD: post-traumatic stress disorder; RCT: randomized controlled trials; RoB: risk of bias; SMD: standardized mean difference; rTMS: repetitive TMS; TMS: transcranial magnetic stimulation

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

Question	Yan et al., (2017)
Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
Did the review authors use a comprehensive literature search strategy?	Yes
Did the review authors perform study selection in duplicate?	Yes
Did the review authors perform data extraction in duplicate?	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	No
Did the review authors describe the included studies in adequate detail?	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
Did the review authors report on the sources of funding for the studies included in the review?	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? RCTs?	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	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

Table 6. Evidence Table for RCTs on Transcranial Magnetic Stimulation (TMS) to Treat PTSD

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Ahmadizadeh et al. 2018 **Purpose:** Randomized trial to compare the efficacy of bilateral and unilateral rTMS for PTSD. **Setting:** Behavioral science research center, Tehran, Iran **Funding source:** NR	**Number of patients:** 58 (n=19 bilateral; n=19 unilateral; n=20 sham) **Inclusion criteria:** Veterans aged 42 to 69 years with combat-related PTSD diagnosis meeting DSM-IV criteria and having a PCL-M score of >50 and no change in psychosocial tx or psychotropic medication in past 2 mos. **Exclusion criteria:** Pts with Axis 1 psychiatric diagnosis or personality disorder, pts with significant neurological or medical condition, pts with pace maker, implantable medication pump or metal objects (including dental work) in or around head that could not be safely removed for rTMS tx. **Pt. baseline characteristics (all pts):** Age (mean, yrs.): 50.45 yrs. Gender (male: female): 58:0.0 Currently on medication: 44% Failed previous psychological tx: 18% Failed previous pharmacological tx: 45% Time since trauma (yrs.): 25.7	**Intervention:** bilateral rTMS at 1200 pulses per session at 20 Hz right DLPFC followed by 1200 pulses per session at 20 Hz left DLPFC per session; unilateral rTMS at 2400 pulses per session at 20 Hz right DLPFC Tx sessions include 3, 30 min sessions per week for 1st 2 weeks; 2, 30 min sessions on the 3rd and 4th week **Control:** Sham bilateral rTMS using similar equipment but without active stimulation for 10 daily sessions. **Outcomes:** PTSD symptoms as measured by PCL-M and AEs **F/u:** 4 weeks	**End of Tx (10 sessions):** **Responders (% bi-TMS, uni-TMS, and sham):** 62.5%, 41.2%, and 0%; active tx significantly higher than sham (p=0.001); NS between bi and unilateral TMS Responder defined as % pts with 2 or more SDs above BL PCL-M **Mean PCL-M (SD) score** (bi-TMS, uni-TMS, and sham; lower scores better): 45.8 (4.67); 49.4 (6.58); 66.9 (10.3); significant difference b/w active tx and sham (p=0.001); NS b/w bi and unilateral TMS. **AEs:** 2 pts in bilateral grp reported headache (both withdrew); 1 reported discomfort (pt. withdrew), and 1 pt. in unilateral grp reported warmth sensation; no AEs reported in sham grp.	Results suggest that active rTMS statistically significantly reduced symptoms of PTSD compared to shame rTMS after 10 sessions of treatment with few reported AEs. **Limitations:** No blinding of treating clinicians/outcome assessors and limited follow-up. **Study ROB:** Moderate; due to no blinding of clinicians/outcome assessors and unclear allocation concealment **Author conflict:** None reported
Reference: Kozel et al. 2018 **Purpose:** Randomized trial to test if rTMS just prior to CPT would	**Number of patients:** 103 (n=54 rTMS+CPT; n=49 sham rTMS+CPT) **Inclusion criteria:** Male/female veterans, ages 18 to 60 yrs. with a current dx of combat related PTSD.	**Intervention:** rTMS + CPT; rTMS delivered over right DLPFC at 1 Hz for 30 min for a total of 1800 pulses per day immediately followed by	**6 mos. f/u** (mean [SD] score: rTMS+CPT; sham rTMS+CPT, p-value): CAPs: 27.5 (4.04); 37.5 (4.49); p=0.023	Results suggest that PTSD symptoms improved from BL to follow-up in both study groups, but patients in the rTMS+CTP group experienced significantly

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
improve clinical outcomes compared to sham for veterans with PTSD. **Setting:** University of Texas, Dallas, TX **Funding source:** Department of Defense and Texas Health and Human Services Commission	Pts allowed to cont. current medications, but encouraged to keep dose, etc. stable. **Exclusion criteria:** Hx of significant neurological or medical or using medication thought to contradict pt. safety (e.g., stimulant); serious psychiatric comorbidity; pregnant or breast feeding; and unable to speak or understand English. **Pt. baseline characteristics (all pts):** Age (mean yrs.): 32.4 yrs. Gender (% female): NR; authors state that most pts were male Current medication for PTSD, depression or pain: 53% Previous tx for PTSD (%): 40% previous psychotherapy **Current military status (%):** Active duty: 6.8%	60 min CPT session. Tx took place 1 day/week for 12 weeks. **Control:** Sham rTMS + CPT; same as above without active stimulation **Outcomes of Interest:** PTSD symptoms as measured by the CAPS, PCL, M-PTSD, QIDS, and IPF **F/u:** 6 mos.	PCL: 30.8 (2.1); 38.0 (2.4); p=0.017 M-PTSD: 78.9 (3.1); 90.5 (3.4); p=0.004 QIDS: 4.98 (0.84); 8.12 (0.93); NS IPF: 2.7 (0.16); 3.09 (0.18); NS **AEs:** No reported seizures; 3 headaches (2 active rTMS, 1 sham), 1 reported alcohol dependence	more improvement than patients in the sham rTMS+CTP group. **Limitations:** Attrition and limited follow-up **Study ROB:** High, due to high overall attrition (41%) **Author conflict:** None reported

AEs: adverse events; BL: baseline; CAPS: Clinician Administered PTSD Scale; CI: confidence interval; CPT: cognitive processing therapy; DLPFC: dorsolateral prefrontal cortex; f/u: follow-up; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression scale; IPF: Inventory of Psychosocial Functioning; M-PTSD: Mississippi Scale for Combat Related PTSD; mos.: months; NR: not reported; NS: not significant; PCL-M: PTSD Checklist (military version); PTSD: post-traumatic stress disorder; QIDS: Quick Inventory of Depressive Symptomology; RCT: randomized controlled trials; ROB: risk of bias; rTMS: repetitive transcranial magnetic stimulation; SD: standard deviation; TMS: transcranial magnetic stimulation

Table 7. Cochrane Risk of Bias 2.0 Tool for RCTs on TMS to Treat PTSD

Reference	Ahmadizadeh et al., (2018)	Kozel et al., (2018)
➢ Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	Yes	Yes
➢ Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization, concealed envelopes)?	No	Yes
➢ Did baseline difference between study groups suggest a problem with randomization?	No	No
Overall RoB for Randomization Process	**Some Concerns**	**Low**
➢ Were participants aware of their assigned intervention during the trial?	No	No
➢ Were providers and people delivering treatment aware of assigned intervention during trial?	Yes	Yes
➢ Were there deviations from the intended intervention that arose because of the experimental context?	No	No
➢ Were these deviations from intended intervention balanced between groups?	NA	NA
➢ Were these deviations likely to have affected the outcome?	NA	NA
➢ Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	NA
Overall RoB of Effect of Assignment	**Some Concerns**	**Some Concerns**
➢ Were data for this outcome available for all, or nearly all, participants randomized?	Yes	No
➢ Is there evidence that result was not biased by missing outcome data?	Yes	Probably Yes
➢ Could missingness in the outcome depend on its true value?	NA	NI
➢ 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	NA
Overall RoB of Missing Data	**Low**	**High**
➢ 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?	NA	NA
➢ Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NA
Overall RoB of Measurement of Outcome	**Low**	**Low**

Reference	Ahmadizadeh et al., (2018)	Kozel 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	Yes
Overall RoB of Reported Results	**Some Concerns**	**High**
Overall Study RoB	**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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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 PTSD
- **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: SSRIs (fluoxetine, paroxetine, and sertraline); SNRIs (venlafaxine); other second-generation antidepressants (nefazodone); tricyclic antidepressants (imipramine); monoamine oxidase inhibitors (phenelzine)
    - Psychological treatments: prolonged exposure therapy; cognitive processing therapy; eye movement desensitization and reprocessing; trauma-focused CBT; brief eclectic psychotherapy; narrative exposure therapy; written narrative exposure therapy; stress inoculation training; present-centered therapy; and interpersonal therapy.
- **Outcomes:** improvement in global PTSD severity, adverse events; loss of diagnosis; remission; self-reported PTSD symptom improvement; comorbid symptoms; quality of life; functional status; patient satisfaction; anxiety; insomnia; and pain
- **Timing:** no minimum follow-up
- **Setting(s):** primary care; specialty care; general mental health care

Exclusion Criteria:

- **Wrong publication type**: narrative review article, case reports editorial, commentary, protocol of randomized trial without results, any article without original data, abstract alone.
- **Wrong study design:** Observational study (for example, cohort study, case control study, cross-sectional study); treatment study without randomization, randomized study with less than 20 patients (10 per study group).
- **Wrong population**: animal studies, children or adolescents less than 18 years of age (studies must have enrolled a patient population in which at least 80% of patients were diagnosed with PTSD.
- **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
Accelerated Resolution Therapy (ART)	
Waits, Marumoto, & Weaver, 2017	Wrong study design (narrative review)
Acupuncture	
Church & Feinstein, 2017	More recent/comprehensive SR available
Sebastian & Nelms, 2017	Wrong intervention
Church, Sparks, & Clond, 2016	Included in Sebastian, 2017
King, Spence, Hickey, Sargent, Elesh, & Connelly, 2015	Included in Grant, 2018
Church, 2014	Included in Sebastian, 2017
Engel, Cordova, Benedek, Liu, Gore, Goertz, Ursano, 2014	Included in Grant, 2018
Kip, Rosenzweig, Hernandez, Shuman, Diamond, Girling, McMillan, 2014	Wrong intervention
Kim, Heo, Shin, Crawford, Kang, & Lim, 2013	Included in Grant, 2018
Prisco, Jecmen, Bloeser, McCarron, Akhter, Duncan, Reinhard, 2013	Included in Grant, 2018
Ernst, Snyder, Dunlop, 2012	Wrong population
Wang, Hu, Wang, Pang, Zhang, 2012	Included in Grant, 2018
Karatzias, Power, Brown, McGoldrick, Begum, Young, Adams, 2011	Included in Sebastian, 2017
York, Crawford, Walter, Walter, Jonas, Coeytaux, 2011	Wrong population
Zhang, Feng, Xie, Xu, Chen, 2011	Included in Grant, 2018
Equine Therapy	
Charry-Sanchez, Pradilla, & Talero-Gutierrez, 2018	Wrong study design
O'Haire, Guerin, & Kirkham, 2015	Wrong study design
Exercise	
LeBouthillier & Asmundson, 2017	Wrong patient population
Mehling, Chesney, Metzler, Goldstein, Maguen, Geronimo, Neylan, 2017	Wrong outcomes
Rahman, Werfalli, & Lehmann-Waldau, 2017	Wrong study design
Stubbs, Vancampfort, Rosenbaum, Firth, Cosco, Veronese, Schuch, 2017	Wrong study design
Hall, Gregg, Bosworth, Beckman, Hoerster, Sloane, & Morey, 2016	< 20 patients
Vancampfort, Richards, Stubbs, Akello, Gbiri, Ward, & Rosenbaum, 2016	Wrong study design
Whitworth & Ciccolo, 2016	Wrong study design
Fetzner & Asmundson, 2015	Wrong comparator
Poulsen, Stigsdotter, & Refshage, 2015	Wrong study design

Authors	Reason for Exclusion
Rosenbaum, Vancampfort, Steel, Newby, Ward, & Stubbs, 2015	Wrong intervention (includes mostly yoga studies)
Caddick & Smith, 2014	Wrong study design
Kim & Burge, 2012	Wrong patient population
Lawrence, De Silva, & Henley, 2010	Cochrane in which no studies met inclusion criteria
Liedl, Muller, Morina, Karl, Denke, & Knaevelsrud, 2011	Wrong patient population
Healing Touch	
No studies were excluded at the full-text level.	
Mind-Body Interventions	
Macy, Jones, Graham, & Roach, 2018	More recent/comprehensive SR available
Nguyen-Feng, Clark, & Butler, 2018	More recent/comprehensive SR available
Rice, Liu, & Schoeder, 2018	Wrong study design
Brom, Stokar, Nuriel-Portat, Ziv, Lerner, & Ross, 2017	Wrong intervention
Kelly & Phillips, 2017	Other (not a full-text article)
Sciarrino, DeLucia, O'Brien, & McAdams, 2017	More recent/comprehensive SR available
Barnes, Monto, Williams, & Rigg, 2016	Wrong study design
Duan-Porter, Coeytaux, McDuffie, Goode, Sharma, Mennella,…Williams, 2016	More recent/comprehensive SR available
Heffner, Crean, & Kemp, 2016	Wrong study design
Nolan, 2016	More recent/comprehensive SR available
Rhodes, Spinazzola, & van der Kolk, 2016	Wrong study design
Wahbeh, Goodrich, Goy, & Oken, 2016	Wrong outcome(s)
Jindani, Turner, & Khalsa, 2015	Other
Quinones, Maquet, Velez, & Lopez, 2015	Other
Bergen-Cico, Possemato, & Pigeon, 2014	Wrong outcome(s)
Dick, Niles, Street, DiMartino, & Mitchell, 2014	Wrong outcome(s)
Mitchell, Dick, DiMartino, Smith, Niles, Koenen, Street, 2014	Other
Reddy, Dick, Gerber, & Mitchell, 2014	Wrong outcome(s)
Seppala, Nitschke, Tudorascu, Hayes, Goldstein, Nguyen, Davidson, 2014	Other
van der Kolk, Stone, West, Rhodes, Emerson, Suvak, & Spinazzola, 2014	Other
Carter, Gerbarg, Brown, Ware, D'Ambrosio, Anand, Katzman, 2013	Other
Crawford, Wallerstedt, Khorsan, Clausen, Jonas, & Walter, 2013	Wrong patient population
King, Erickson, Giardino, Favorite, Rauch, Robinson, & Liberzon, 2013	Wrong study design
Reddy, Dick, Gerber, & Mitchell, 2013	Duplicate
Reddy, Dick, Gerber, & Mitchell, 2013	Duplicate
Kearney, McDermott, Malte, Martinez, & Simpson, 2012	Wrong study design

Authors	Reason for Exclusion
Stoller, Greuel, Cimini, Fowler, & Koomer, 2012	Wrong patient population
Telles, Singh, & Balkrishna, 2012	More recent/comprehensive SR available
Relaxation Therapy	
Markowitz et al. 2016	Wrong study design
Transcranial Magnetic Stimulation (TMS)	
Guo & Wang, 2017	Wrong study design
Yadollahpour, Rashidi, & Kunwar, 2017	More recent/comprehensive SR available
Trevizol, Barros, Silva, Osuch, Cordeiro, & Shiozawa, 2016	More recent/comprehensive SR available
Bogdanova, Gilbert, Kark, Ho, Yee, Brown, & Pascual-Leone, 2015	< 20 patients
Berlim & van den Eynde, 2014	More recent/comprehensive SR available
Karsen, Watts, & Holtzheimer, 2014	More recent/comprehensive SR available
Isserles, Shalev, Roth, Peri, Kutz, Zlotnick, & Zangen, 2013	More recent/comprehensive SR available
Watts, Landon, Groft, & Young-Xu, 2012	More recent/comprehensive SR available
Boggio, Rocha, Oliveira, Fecteau, Cohen, Campanha, Fregni, 2010	More recent/comprehensive SR available

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Appendix C

See **Figures 4 and 5** 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 PTSD Symptoms

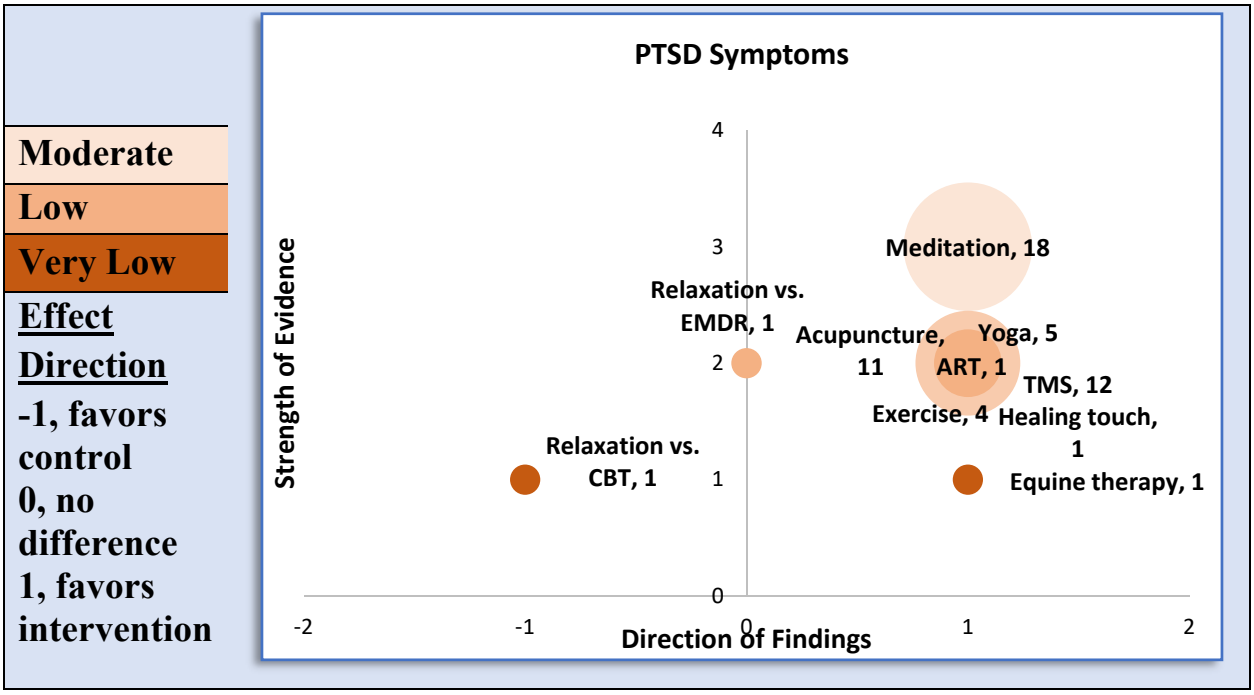

Figure 3. Bubble Plot of Findings for Depression