Chapter 5: CIH and other Interventions identified in P.L. – 114-198 for Treating Patients at Risk of Suicide

Results of the Literature Search for Suicide

Extensive literature searches identified 5 RCTs* that met inclusion criteria and addressed the following interventions: exercise, relaxation training, and transcranial magnetic stimulation (TMS). The literature searches did not identify any publications meeting inclusion criteria for the following interventions: acupuncture, accelerated resolution therapy, cannabinoids, creative art therapy, chiropractic care, equine therapy, healing touch, hyperbaric oxygen therapy, massage therapy, meditation, music therapy, Tai Chi, Therapeutic Touch, training and caring for service dogs, or yoga. **Table 1** presents a summary of the evidence (how many RCTs and/or SRs) for each CIH intervention.

Table 1. Overview of Evidence for CIH Interventions to Treat Individuals at Risk of Suicide

Intervention	Number and Type of Studies for Suicide	Strength of the Evidence
Accelerated Resolution Therapy (ART)	0	NA
Acupuncture	0	NA
Art therapy	0	NA
Cannabinoids	0	NA
Chiropractic care	0	NA
Equine therapy	0	NA
Exercise therapy (outdoor therapy)[1]	1 RCT	Low
Healing Touch	0	NA
Hyperbaric Oxygen Therapy	0	NA
Massage therapy	0	NA
Meditation	0	NA
Music therapy	0	NA
Tai chi	0	NA
Therapeutic Touch	0	NA
Relaxation training	1 RCT	Very low
Training and caring for service dogs	0	NA
Transcranial Magnetic Stimulation (TMS)	3 RCTs	Low to Very low
Yoga	0	NA
Total Studies	**5 RCTs**	

[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.

RCT: Randomized controlled trial; SR: systematic review; *A pooled analysis of Blumberger 2012, 2016 is included in Weissman et al., 2018

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

Evidence Base

Our searches of the literature identified 5 RCTs that assessed the following: relaxation training (RT, 1 RCT), transcranial magnetic stimulation (TMS, 3 RCTs), and exercise (EX, 1 RCT).

Ward-Ciesielski et al. (2017) randomized 93 adults from the community who reported experiencing suicidal ideation in the last week to receive either brief dialectical behavior therapy (DBT) skills training or relaxation training (Ward-Ciesielski et al. 2017). The DBT intervention involved presenting participants with the following 5 skills: 1. Mindfulness (what to do with one's attention/mind and how to engage in mindfulness practices); 2. Mindfulness of current emotions (observing and describing emotional experiences; labeling emotions; observing physical sensations over time); 3. Opposite-to-emotion action (blocking the behaviors prompted by emotions and instead acting opposite to or inconsistently with emotional urges); 4. Distraction (distracting attention by thinking about or doing something else); and 5. Changing your body chemistry (applying ice water to the face, engaging in intense exercise, pacing one's breathing, and progressive muscle relaxation). Relaxation training was not introduced as a skill. Instead, the therapist moved into encouraging the participant to try a relaxation practice and then walked the participant through a sensory awareness relaxation activity. The sensory awareness activity involved the therapist reading a series of questions designed to prompt the participant to notice or pay attention to different sensations. Both interventions took place in one, 45 to 60-minute session.

George et al. randomized 41 adults admitted to an inpatient unit for suicidal crisis to receive either active TMS or sham TMS. Patients were recruited from two US based military hospitals. Patients in TMS group received high frequency TMS 3 times per day for 3 days (total 9 sessions). The primary outcomes measured in both studies included suicidal ideation and symptoms of depression and anxiety. Weismann et al., (2018) pooled data from 2 published RCTs (Blumberger et al., 2012; 2016) of TMS applied to the dorsolateral prefrontal cortex in adults with treatment-resistant depression (TRD). A total of 156 adults were included in the Weismann pooled analysis with participants being randomized into a unilateral TMS group (n=56), bilateral TMS group (n=52), and sham TMS (n=48). The High-Frequency Left (HFL) TMS group received 10 Hz. in 29 5-second trains with 30-second inter-train intervals. The bilateral TMS group received TMS at the right and left hemispheres of the dorsolateral prefrontal cortex (DLPFC) with 1 Hz over the right DLPFC followed by 10 Hz over the left DLPFC with 4 trains of 100 second duration and one train of 65 second duration for low-frequency right, with a 30 second inter-train interval, followed by HFL for 15 5-second trains with 30-second inter-train intervals. For the sham group, stimulation occurred over the site of active treatment, but with only the side-edge resting on the scalp, administered as HFL for 17 minutes, with the coil angled 45 degrees away from the skull in a single-wing tilt position to produce sound and some somatic sensation similar to those of active stimulation, but with minimal direct brain effects.

Abdollahi et al. (2017) randomized 70 adults with either mild or moderate depression to either a combined CBT and exercise group (n=35) or a CBT only group (n=35). Patients were recruited from two psychology clinics in Tehran, Iran. Both treatment groups received CBT once a week for 12 weeks with each session lasting for 90 minutes. Sessions were provided to groups of 4 to 6 participants and were led

by a doctorate level psychologist trained in CBT. The intervention group also received indoor exercise in a group setting as an adjunct treatment which was led by an exercise instructor with a doctorate in sport science. Exercise sessions occurred three times per week over 12 weeks and included a warm-up, cardio, walking, and a cool-down. The primary outcomes of interest included improvements in suicidal ideation and depression. See **Table 3** for more information about the patients and interventions in the included studies.

Study Quality

Using the Cochrane tool, we rated the ROB of the George et al. RCT and Weismann et al. pooled analysis (Blumberger 2012; 2016) as having some concerns and the Ward-Ciesielski et al. RCT as high (See **Table 4** for ratings). The Ward-Ciesielski and Abdollahi RCTs was rated high due to >20% overall attrition, lack of reporting on allocation concealment, and not blinding the patients or providers.

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.

Relaxation Training

- Evidence from 1 RCT suggests that both brief dialectical behavioral therapy and relaxation training significantly reduced suicidal ideation and symptoms of depression and anxiety with no significant differences between interventions. (SOE: Very low)

High-Frequency (10 Hz) Transcranial Magnetic Stimulation (TMS) vs. Sham TMS

- Evidence from 3 RCTs suggest that there is no significant difference in suicidal ideation between active TMS and sham TMS at posttreatment (SOE: Very low).
- Evidence from 1 RCT suggests that there is no significant different in symptoms of depression or PTSD between active TMS and sham TMS 3 days posttreatment (SOE: Very low).

Bilateral (any frequency) Transcranial Magnetic Stimulation (TMS) vs. Sham TMS

- Evidence from 2 RCTs suggests that bilateral TMS is more effective than sham TMS in reducing suicidal ideation at posttreatment (SOE: Low).

Exercise

- Evidence from 1 RCT suggests that exercise as an adjunct to CBT yielded a greater decrease in suicidal ideation and depressive symptoms than CBT alone.

Discussion

Evidence from 1 RCT suggests that both relaxation training and brief dialectical behavioral therapy significantly reduced suicidal ideation and symptoms of depression and anxiety with no significant differences between interventions. The findings of the RCTs on High-Frequency TMS suggest that it is feasible and safe among inpatients admitted for suicidal crisis. Suicidal ideation and symptoms of depression and PTSD were significantly reduced for both patients who received active and sham rTMS with no significant difference between groups. Adverse events were minimal, with no differences in type

or severity between active or sham rTMS. Headache was the most frequently reported event. The findings of 2 RCTs found that suicidal ideation was more likely to resolve with bilateral TMS than with sham TMS.

Table 2. Strength of Evidence for CIH as Treatment for Individuals at Risk of Suicide

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
Relaxation Training									
Suicidal ideation	1 RCT Ward-Ciesielski et al. 2017	Brief dialectical behavior therapy skills training (DBT, 46) vs Relaxation training (RT, 47) 12 weeks f/u	Effect size from BL to follow-up was a SMD of 1.12 with no significant difference between groups between groups	Yes, (-2)	No	No	Yes, (1) due to no significant difference and limited information about measures of dispersion	NA	Very low
Depression/ Anxiety	1 RCT Ward-Ciesielski et al. 2017	Brief dialectical behavior therapy skills training (DBT, 46) vs Relaxation training (RT, 47) 12 weeks f/u	**Depression:** effect size from BL to follow-up was a SMD of 0.61 with no significant difference between groups **Anxiety:** effect size from BL to follow-up was a SMD of 0.59 with no significant	Yes, (-2)	No	No	Yes, (1) due to no significant difference and limited information about measures of dispersion	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
			difference between groups						
High-Frequency Transcranial Magnetic Stimulation									
Suicidal ideation	3 RCTs (George et al. 2014; Weissman et al., 2018 [Blumberger, 2012; 2016])	TMS (20) vs Sham (21) 3 days	Change in SSI score at 3 days; mean TMS; mean sham): -15.6; -15.3, NS	Yes, (-1)	No	No	Yes (-2); very small sample size and wide 95% CIs	NA	Very low
		TMS (56) vs. Sham (48) 3 to 6 weeks	Change in HDRS-17 at 3 to 6 weeks; OR, 95% CI, p: 1.59, 0.61 to 4.12, p=0.33; NS	Yes (-1)	No	No	Yes (-2); small sample size and wide 95% CIs	NA	Very low
Depression symptoms/ PTSD	1 RCT George et al. 2014	TMS (20) vs Sham (21) 3 days	No significant difference between rTMS and Sham on measures of depression and PTSD.	Yes, (-1)	No	No	Yes (-2); very small sample size and wide 95% CIs	NA	Very low
Bilateral Transcranial Magnetic Stimulation									
Suicidal ideation	2 RCTs (Weissman et al., 2018	TMS (52) vs. Sham (48)	Change in HDRS-17 at 3 to 6 weeks;	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
	[Blumberger, 2012; 2016])	3 to 6 weeks	OR, 95% CI, p): 3.03, 1.19 to 7.71, p=0.02; favors Bilateral TMS						
Exercise									
Suicidal ideation	1 RCT Abdollahi et al. 2017	CBT + exercise (35) vs. CBT (35)	Group-by-time interaction; *b*, 95% CI [SE]**:** -6.54, -7.68 to -5.37 (0.58), p≤.001; favors CBT + exercise	Yes (-1)	No	No	Yes (-1); very small sample size	NA	Low
Depression symptoms	1 RCT Abdollahi et al., 2017	CBT + exercise (35) vs. CBT (35)	Group-by-time interaction; *b*, 95% CI [SE]**:** -3.30, -6.00 to -0.50 (1.39), p≤.05; favors CBT + exercise	Yes (-1)	No	No	Yes (-1); very small sample size	NA	Low

BL: baseline; CI: confidence interval; CT: control group; ES: effective size; HDRS: Hamilton Depression Rating Scale; mos.: months; NR: not reported; NS: not significant; RCT: randomized controlled trials; SE: standard error; SMD: standardized mean difference; SSI: Beck Suicidal Scale Inventory

Table 3. GRADE Factors Used to Assess the Quality of a Body of Evidence

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

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

Table 4. Evidence Table for RCTs on CIH Interventions in the Treatment of Suicide

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Relaxation Training				
Reference: Ward-Ciesielski et al. 2017 **Purpose:** To compare the efficacy of a single-session dialectical behavior therapy (DBT) to relaxation training (RT) among adults at risk of suicide. **Setting:** Community mental health center **F/u:** 12 weeks **Funding source:** Grant funded	**Number of patients:** 93; n=46 DBT; n=47 RT **Inclusion criteria:** a) 18 years or older, b) experiencing suicidal ideation in the past week, c) having not received mental health treatment in the month prior to screening, d) living within commuting distance to the research office, and e) willing to consent to recording and assessment **Exclusion criteria:** a) non-English speaking and b) significant cognitive impairment. **Pt. baseline characteristics (RT; DBT):** **Age (mean yrs., SD): 41.8 (15.3); 38.6 (15.0)** **Gender (% male):** 62; 57 **Suicide attempt (% yes)** Lifetime: 66; 61 Past year: 26; 15 Past month: 4; 7 **NSSI (% lifetime):** 45; 72 **Mental health tx (% yes)** Past year: 30; 34 Never: 11; 11 **Medication (%):** 17; 15	**Intervention:** DBT Brief Suicide Intervention involved presenting participants with the following 5 skills: 1. Mindfulness (what to do with one's attention/mind and how to engage in mindfulness practices); 2. Mindfulness of current emotions (observing and describing emotional experiences; labeling emotions; observing physical sensations over time); 3. Opposite-to-emotion action (blocking the behaviors prompted by emotions and instead acting opposite to or inconsistently with emotional urges); 4. Distraction (distracting attention by thinking about or doing something else); and 5. Changing your body chemistry (applying ice water to the face, engaging in intense exercise, pacing one's breathing, and progressive muscle relaxation). **Control:** Relaxation training was not introduced as a skill. Instead, the therapist moved into encouraging the participant to try a relaxation practice and then walked the participant through a sensory awareness relaxation activity. The sensory awareness activity was based on a similar practice first developed by Goldfried and Davison and involves the therapist reading a series of questions	**Suicidal ideation:** effect size from BL to follow-up was a SMD of 1.12 with no significant difference between groups **Depression:** effect size from BL to follow-up was a SMD of 0.61 with no significant difference between groups **Anxiety:** effect size from BL to follow-up was a SMD of 0.59 with no significant difference between groups	**Conclusion:** The results suggest that both interventions led to significantly reduced levels of suicidal ideation, depression and anxiety with no significant differences observed between groups. **Limitations:** Very limited follow-up time, attrition, and concerns about overlap in content between DBT and RT. **Study RoB:** High due to concerns about allocation concealment, lack of blinding of patients and providers, and attrition (>20%). **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
		designed to prompt the participant to notice or pay attention to different sensations. Both interventions took place in one, 45 to 60-minute session. **Outcomes of Interest:** Suicide ideation (measured using the Scale for Suicidal Ideation), depression (measured using the Patient Health Questionnaire Depression Module), and anxiety (measured using the Beck Anxiety Inventory)		
Transcranial Magnetic Stimulation (TMS)				
Reference: George et al. 2014 **Purpose:** To examine if high dose TMS for suicidal inpatients is feasible and safe and improves suicidal thinking. **Setting:** 1 DoD and 1 VA military psychiatric hospital wards in the U.S. **F/u:** posttreatment (3 days) **Funding source:** U.S. Army Medical Research and Material Command	**Number of patients:** 41; 20 active TMS; 21 sham TMS **Inclusion criteria:** Inpatients admitted because of suicidal ideation (or attempt), aged 18 to 70 years, with a Beck Scale of Suicidal Ideation (SSI) score 12, and a score of at least 3 on Question #3 of the HRSD. Patients must have been in a depressive episode (unipolar or bipolar II, non-psychotic), as defined by DSM-IV. Because of the funding source and the desire to merge these data with other clinical trials within the consortium, they must also have had a diagnosis of PTSD, or mild TBI, or both. **Exclusion criteria:** Patients who had clinically unstable medical illnesses, metal in their head, a history of seizures, borderline personality disorder, or	**Intervention:** Repetitive TMS (rTMS) was delivered to the left prefrontal cortex, defined as a location 6 cm (cm) anterior to the right-hand motor thumb area. Trained treaters, who were not raters, delivered the treatments. rTMS was delivered with a figure-eight solid core coil at 120% motor threshold, 10 Hertz (Hz), 5 s (s) train duration, 10 s intertrain interval for 30 min (6000 pulses) 3 times daily for 3 days (total 9 sessions, 54,000 stimuli). These parameters are slightly greater than the published safety guidelines (10 Hz at 120% for only 4.2 s is within) **Control:** Sham Patients continued prescribed medications and participated in 'treatment as usual, which could include counseling, support and	**Suicidal thinking** (change in SSI score at 3 days; mean rTMS; mean sham): -15.6; -15.3, NS **Depression/PTSD:** No significant difference between rTMS and Sham on measures of depression and PTSD. **AEs:** 33 AEs overall (21 sham, 12 active), with 13 subjects experiencing at least one adverse event (6 sham, 7 active, P=0.74). The most commonly reported AE was headache with 9 incidents overall (5 rTMS; 4 sham) There were no suicide attempts and no serious adverse events in the acute phase.	**Conclusion:** The findings of the study suggest that high dose rTMS is feasible and safe among inpatients admitted for suicidal crisis. SSI scores declined significantly for both patients who received active and sham rTMS with no significant difference in scores between groups. Adverse events were minimal, with no differences in type or severity between active or sham rTMS. Headache was the most frequently reported event. **Limitations:** Very short follow-up time to measure longer-term efficacy or adverse events associated with TMS.

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	homelessness (at the Charleston site only, defined as having no address), those were committed to the hospital under court order, and those with schizophrenia or psychosis, bipolar disorder type I, or dementia. Subjects who had repeatedly abused or were dependent upon drugs within 6 days of study entry were excluded. **Pt. baseline characteristics (TMS; Sham):** **Age (mean yrs., SD): 38.7; 46.1** **Gender (% male): 9%; 81%** **Diagnosis (%):** mTBI only: 0%; 1% PTSD only: 35%; 48% mTBI and PTSD: 65%; 48% **Current substance abuse**: 46%; 11% **SSI total** (mean [SD]): 21.7 (5.7); 20.8 (5.3) **Length of stay before treatment (days)**: 2, range 2 to 3.75; 4, range 2 to 6	workup for electroconvulsive therapy (ECT) if indicated. **Outcomes of Interest:** Suicidal thinking (measured using SSI), depression (measured using HRSD); PTSD symptoms (measured using the CAPS); AEs		**Study RoB:** Some concerns due to lack of reporting about randomization procedures **Author conflict:** None reported
Reference: Weissman et al. 2018 (pooled data from Blumberger, 2012; Blumberger, 2016) **Purpose:** To examine the effects of TMS on suicidal ideation in patients	**Number of patients:** 156; 50 unilateral TMS; 52 bilateral TMS; 48 sham TMS **Inclusion criteria:** Voluntary and competent to consent; diagnosis of MDD (DSM-IV); aged 18 to 85; failed to achieve clinical response to at least 2 separate antidepressant trials of sufficient dose for at least 4 to 6 weeks, or	**Intervention:** High-Frequency Left (HFL) TMS – intensity: rTMS treatment intensity determined by using resting motor threshold (RMT). Subjects under age 65 had treatment delivered at 100% of the RMT; those over age 65 had treatment delivered at 120% of the RMT. Site of Stimulation: left hemisphere of DLPFC. Frequency:	**Suicidal ideation** (resolution, %): Bilateral (40.4); HFL (26.8); sham (18.8) Resolution of suicidal ideation between Bilateral and sham (OR, 95% CI, p): 3.03, 1.19 to 7.71, p=0.02; favors Bilateral TMS	**Conclusion:** Bilateral TMS of the DLPFC may be an effective treatment for suicidal ideation in patients with TRD when compared to sham. No significant difference was found between HFL TMS and sham.

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
with treatment-resistant major depression (TRD) who failed to respond to at least 2 medication trials **Setting:** NR **F/u:** posttreatment (3 to 6 weeks) **Funding source:** No funding specific to this study received	could not tolerate at least 2 weeks of antidepressant medication; have score ≥ 22 on 17-item HAM-D **Exclusion criteria:** History of DSM-IV substance dependence or abuse in last 6 months; self-harm behavior in past 6 months; concomitant major, unstable medical or neurologic illness, or history of seizures; acutely suicidal; pregnant; metal implants; currently or in last 4 weeks taking more than 2 mg/day or equivalent of lorazepam, monoamine oxidase inhibitors, and/or bupropion due to its associated increased risk for seizures **Pt. baseline characteristics (unilateral TMS; bilateral TMS; Sham):** **Age (mean yrs., SD):** 47.4 (13.8); 49.4 (13.4); 47.1 (12.2) **Gender (n, female):** 40; 28; 29 **HDRS-16 baseline score (m, SD):** 24.3 (3.4); 22.7 (3.5); 24.3 (3.2) **Suicide item baseline score (m, SD)**: 24.3 (3.4); 22.7 (3.5); 24.3 (3.2) **Active medication <u>during</u> Blumberger (2016) study (%):** Benzodiazepine: 40; 50; 39 Atypical antipsychotic: 25; 30; 31.7	10 Hz. Duration: 29 - 5 second trains with 30 second inter-train interval. Intervention: Device: Repetitive Transcranial Magnetic Stimulation. Most patients continued taking their medications while receiving this intervention treatment. <u>Bilateral TMS</u> - intensity: rTMS treatment intensity determined by using resting motor threshold (RMT). Subjects under age 65 had treatment delivered at 100% of the RMT; those over age 65 had treatment delivered at 120% of the RMT. Sites of Stimulation: right and left hemispheres of the DLPFC. Frequency: 1 Hz over the right DLPFC followed by 10 Hz over the left DLPFC. Duration: i) low-frequency right: 4 trains of 100 second duration and one train of 65 second duration, with a 30 second inter-train interval, followed by ii) HFL: 15 - 5 second trains with 30 second inter-train interval. Intervention: Device: Repetitive Transcranial Magnetic Stimulation. Most patients continued taking their medications while receiving this intervention treatment. **Control:** Sham Stimulation occurred over the site of active treatment, but with only the side-edge resting on the scalp,	Resolution of suicidal ideation between HFL and sham (OR, 95% CI, p): 1.59, 0.61 to 4.12, p=0.33; NS **AEs:** Reported in Blumberger, 2012: 1 patient in bilateral grp. withdrew after myocardial infraction, 2 patients experienced suicidality requiring hospitalization (1 in unilateral grp., 1 in sham), 1 patient in unilateral grp. withdrew due to insomnia, 1 patient in both bilateral and unilateral grps. withdrew prior to pre-defined end-point due to missing 4 consecutive treatments Reported in Blumberger, 2016: 1 patient in bilateral grp. withdrew after being hospitalized for anxiety and subsequently receiving mediation prohibited by study; 3 patients in unilateral grp. withdrew due to increased anxiety; 2 patients in bilateral grp. and 2 patients in unilateral grp. withdrew due to inability to tolerate treatment	**Limitations:** Neither RCT in study were designed or powered to test specific hypothesis of effect of TMS on suicidal ideation; suicidal ideation was measured with suicide item from HDRS-17 rather than a more comprehensive suicide scale such as BSIS; study did not include patients w/ severe, emergent suicidality as measured by a score of 4 on the HDRS-17 suicide item which limits generalizability to emergent forms of suicidality or suicidal ideation; baseline HDRS-16 scores were statistically different between sham and bilateral, suggesting that response to bilateral TMS for suicidal ideation may be confounded by bilateral grp. having lower baseline HDRS-16 scores; both RCTs were from same research center, reducing external validity **Study RoB:** Some concerns due to lack of reporting about allocation concealment **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	Antidepressant-antipsychotic combo: 22.5; 30; 29.3 Antidepressant and lithium: 0; 7.5; 2.4 Two antidepressants: 47.4; 50; 43.9 No antidepressant: 10; 0; 4.9 **Active medication <u>during</u> Blumberger (2012) study (%):** SSRI: 36.4; 23.1; 15 SNRI: 13.6; 38.5; 25 Tricyclic antidepressant: 22.7; 11.5; 15 Mirtazepine: 9.1; 11.5; 5 Trazodone: 9.1; 7.7; 5 Lithium augmentation: 0; 0; 5 Atypical antipsychotic augmentation: 9.1; 19.2; 5 Med combination: 27.3; 30.8; 30 Benzodiazepine use: 40.9; 23.1; 35	administered as HFL for 17 minutes, with the coil angled 45 degrees away from the skull in a single-wing tilt position to produce sound and some somatic sensation (e.g., contraction of scalp muscles) similar to those of active stimulation, but with minimal direct brain effects. Intervention: Device: Repetitive Transcranial Magnetic Stimulation **Outcomes of Interest:** Resolution of suicidal ideation, defined as a decrease from any non-zero score at baseline to a score of zero post-treatment on the HDRS-17 suicide item		
Exercise				
Reference: Abdollahi et al. 2017 **Purpose:** To evaluate the effects of exercise as an adjunct to CBT for suicidal ideation and depression **Setting:** NR **F/u:** Posttreatment	**Number of patients:** 70; 35 CBT + exercise; 35 CBT **Inclusion criteria:** Sedentary; able to understand and sign written informed consent; formal diagnosis of major depressive episode **Exclusion criteria:** Inability to do exercise due to medical problems **Pt. baseline characteristics (CBT + exercise; CBT):**	**Intervention:** CBT + exercise. CBT provided once per week for 12 weeks for 90 min. in groups of 4-6. Exercise sessions conducted under supervision of trained instructor and consisted of warm-up, cardio, walking, and cool-down. Exercise sessions occurred 3 times per week for 12 weeks. **Control:** CBT alone	**Suicidal ideation** (group-by-time interaction; *b*, 95% CI [SE]**:** -6.54, -7.68 to -5.37 (0.58), p≤.001; favors CBT + exercise **Depression** (group-by- time interaction; *b*, 95% CI [SE]**:** -3.30, -6.00 to -0.50 (1.39), p≤.05; favors CBT + exercise **AEs:** NR	**Conclusion:** The findings of the study suggest that, while both exercise as an adjunct to CBT and CBT alone are both effective in reducing suicidal ideation and depression, the combination of exercise and CBT yielded a greater decrease in suicidal ideation and depressive symptoms than CBT alone.

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Funding source: NR	**Age (mean yrs., SD):** 50.91 (7.43); 48.43 (6.83) **Gender (male, %):** 60; 45.7	**Outcomes of Interest:** Suicidal ideation measured using BSSI; depressive symptoms measured using BDI-II		**Limitations:** Exercise was not studied in isolation; no follow-up. **Study RoB:** High due to high attrition, lack of reporting on allocation concealment, lack of blinding, and no ITT analysis. **Author conflict:** NR

AEs: adverse events; CBT: Cognitive Behavioral Therapy; ECT: Electroconvulsive Therapy; HDRS: Hamilton Depression Rating Scale; HFL TMS: High-frequency left TMS; Hz: Hertz; RMT: Resting Motor Threshold; ROB: risk of bias; rTMS: repetative transcranial magnetic stimulation; SD: standard deviation**;** SSI: Beck Suicidal Scale Inventory; TMS: transcranial magentic stimulation;

Table 5. Cochrane Risk of Bias 2.0 Tool for RCTs on CIH for Suicide

Reference	Ward-Ciesielski et al. 2017	George et al. 2014	Abdollahi et al., 2017	Weissman et al., 2018 (Blumberger, 2012; 2016)
• Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	Yes	NI	Yes	Yes
• Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization, concealed envelopes)?	NI	NI	NI	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**	**Some concerns**	**Some concerns**
• Were participants aware of their assigned intervention during the trial?	Yes	No	NI	No
• Were providers and people delivering treatment aware of assigned intervention during trial?	Yes	Yes	NI	Yes
• Were there deviations from the intended intervention that arose because of the experimental context?	PN	No	PN	PN
• Were these deviations from intended intervention balanced between groups?	PN	No	NA	NA
• Were these deviations likely to have affected the outcome?	PN	No	NA	NA
• Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	No	No	Yes
Overall RoB of Effect of Assignment	**Some concerns**	**Low**	**Some concerns**	**Low**
• Were data for this outcome available for all, or nearly all, participants randomized?	No	Yes	No	Yes
• Is there evidence that result was not biased by missing outcome data?	No	No	No	NA
• Could missingness in the outcome depend on its true value?	PN	No	PN	NA
• Do the proportions of missing outcome data differ between intervention groups?	PN	No	PN	NA
• Is it likely that missingness in the outcome depended on its true value?	PN	No	PN	NA
Overall RoB of Missing Data	**High**	**Low**	**High**	**Low**
• 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	No	NI	No
• Could assessment of the outcome have been influenced by knowledge of intervention received?	No	No	No	No
• Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No	No	No	No
Overall RoB of Measurement of Outcome	**Low**	**Low**	**Low**	**Low**

Reference	Ward-Ciesielski et al. 2017	George et al. 2014	Abdollahi et al., 2017	Weissman et al., 2018 (Blumberger, 2012; 2016)
• Was the trial analyzed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?	Yes	Yes	NI	Yes
Overall RoB of Reported Results	**Low**	**Low**	**Some concerns**	**Low**
Overall Study ROB	**High**	**Some concerns**	**High**	**Some concerns**

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

Table 6. 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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George, M. S., Raman, R., Benedek, D. M., Pelic, C. G., Grammer, G. G., Stokes, K. T., … Stein, M. B. (2014). A two-site pilot randomized 3 day trial of high dose left prefrontal repetitive transcranial magnetic stimulation (rTMS) for suicidal inpatients. *Brain Stimulation*, *7*(3), 421–431. https://doi.org/https://dx.doi.org/10.1016/j.brs.2014.03.006

Ward-Ciesielski, E. F., Tidik, J. A., Edwards, A. J., & Linehan, M. M. (2017). Comparing brief interventions for suicidal individuals not engaged in treatment: A randomized clinical trial. *Journal of Affective Disorders, 222*, 153–161. https://doi.org/https://dx.doi.org/10.1016/j.jad.2017.07.011

Weissman, C. R., Blumberger, D. M., Brown, P. E., Isserles, M., Rajji, T. K., Downar, J., … Daskalakis, Z. J. (2018). Bilateral repetitive transcranial magnetic stimulation decreases suicidal ideation in depression. *Journal of Clinical Psychiatry*, *79*(3).

Summary of Evidence of CIH and Other Interventions for Patients at Risk for Suicide

This systematic review assessed the efficacy of specific CIH approaches, and other interventions used in the treatment of individuals at risk of suicide. The overall evidence base included 5 RCTs that met inclusion criteria and addressed relaxation training (RT, 1 RCT), transcranial magnetic stimulation (TMS, 3 RCTs), and exercise (EX, 1 RCT). The literature searches did not identify any publications meeting inclusion criteria for the following interventions: acupuncture, accelerated resolution therapy, cannabinoids, creative art therapy, chiropractic care, equine therapy, healing touch, hyperbaric oxygen therapy, massage therapy, meditation, music therapy, Tai Chi, training and caring for service dogs, or yoga.

Evidence from 1 RCT suggests that both relaxation training and brief dialectical behavioral therapy significantly reduced suicidal ideation and symptoms of depression and anxiety with no significant differences between interventions. The findings of the RCTs on High-Frequency TMS suggest that it is feasible and safe among inpatients admitted for suicidal crisis. Suicidal ideation and symptoms of depression and PTSD were significantly reduced for both patients who received active and sham rTMS with no significant difference between groups. Bilateral TMS was found to be more effective in reducing and/or resolving suicidal ideation than sham TMS. Adverse events were minimal, with no differences in type or severity between active or sham rTMS. Headache was the most frequently reported event. Evidence from 1 RCT suggests that exercise as an adjunct to CBT led to significantly greater improvements in suicidal ideation and depression compared to CBT alone.

The strength of the evidence for RT was rated very low and TMS was rated low to very low due primarily to limitations in the methodological quality of the studies (lack of blinding, attrition), small number of studies, small sample sizes, lack of precision surrounding the estimated effect sizes, and limited follow-up. The strength of evidence for exercise was rated low due primarily to limitations in the methodological quality of the study (lack of blinding, attrition), small number of studies, small sample size and lack of follow-up. **Table 7** below provides an overview of the evidence and findings for RT and TMS used in the treatment of individuals at risk of suicide.

Table 7. Summary of Finding of CIH for Suicide

	Suicidal Ideation			Depression			Anxiety		
Intervention	**EB**	**Findings**	**SOE**	**EB**	**Findings**	**SOE**	**EB**	**Findings**	**SOE**
DBT vs. RT	1 RCT	NS	VL	1 RCT	NS	VL	1 RCT	NS	VL
HF TMS vs. Sham	3 RCTs	NS	VL	1 RCT	NS	VL	1 RCT	NS	VL
Bilateral TMS vs. Sham	2 RCTs	+	L						
EX + CBT vs. CBT	1 RCT	+	L	1 RCT	+	L			

+ favors intervention; - favors control; NS: no significant difference between intervention and control; CBT: Cognitive Behavioral Therapy; DBT: dialectical behavior therapy; EB: evidence base; Exercise: exercise; HF: High-frequency; L: Low strength of evidence; MOD: Moderate strength of evidence; NR: not reported; RCT: randomized controlled trial; RT: relaxation training; SOE: strength of evidence; SR: systematic review; TMS: transcranial magnetic stimulation; VL: very low strength of evidence

Appendix A

Inclusion Criteria:

- **Publications type:** Systematic reviews (SRs) and randomized controlled clinical trials (RCTs) published in English language in peer reviewed journals.
- **Search date:** 01/01/2008 to present
- **Population:** Adults 18 years or older at risk for suicide.
- **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: lithium, ketamine
    - Psychological treatments: cognitive therapy, problem solving therapy
- **Outcomes:** suicide attempts, suicide deaths, suicide ideation, overdose, readmissions, health status, symptomology, quality of life, functional status, patient satisfaction, anxiety, insomnia, pain
- **Timing:** no minimum follow-up
- **Setting(s):** primary care; specialty care; general mental health care

Exclusion Criteria:

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

Appendix B

Table 1. Studies Excluded at Full-text Level

Authors	Reason for Exclusion
Exercise	
Neunhauserer et al., 2013	Wrong outcomes
Sturm et al., 2012	Wrong study design
Relaxation Training	
Ward-Ciesielski et al., 2016	Study protocol (not a complete study)
Yoga	
Nyer et al., 2018	Wrong comparator

SR: systematic review

References

Neunhauserer, D., Sturm, J., Baumgartlinger, M. M., Niederseer, D., Ledl-Kurkowski, E., Steidle, E., … Niebauer, J. (2013). Hiking in suicidal patients: Neutral effects on markers of suicidality. *American Journal of Medicine*, *126*(10), 927–930. https://doi.org/https://dx.doi.org/10.1016/j.amjmed.2013.05.008

Nyer, M., Gerbarg, P. L., Silveri, M. M., Johnston, J., Scott, T. M., Nauphal, M., … Streeter, C. C. (2018). A randomized controlled dosing study of Iyengar yoga and coherent breathing for the treatment of major depressive disorder: Impact on suicidal ideation and safety findings. *Complementary Therapies in Medicine*, *37*, 136–142. https://doi.org/https://dx.doi.org/10.1016/j.ctim.2018.02.006

Sturm, J., Ploderl, M., Fartacek, C., Kralovec, K., Hitzl, W., Niebauer, J., …Faracek, R. (2012). Physical exercise through mountain hiking in high-risk suicide patients. A randomized crossover trial. *Acta Psychiatrica Scandinavia, 126*, 467-475.

Ward-Ciesielski, F., Jones, C., Wielgus, M., Wilks, C., & Linehan, M. (2016). Single-session dialectical behavior therapy skills training versus relaxation training for non-treatment-engaged suicidal adults: A randomized controlled trial. *BMC Psychology, 4*(13), 1-7.

Appendix C

See **Figures 1, 2 and 3** below for bubble maps. Bubble maps provide a visual overview of the distribution of evidence for the complementary and integrative health and other interventions included in these systematic reviews. The bubble maps display information about the research meeting the inclusion and exclusion criteria (see Appendix A) for these reviews and include the following:

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

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

Figure 1. Bubble Plot of Findings for Suicidal Ideation

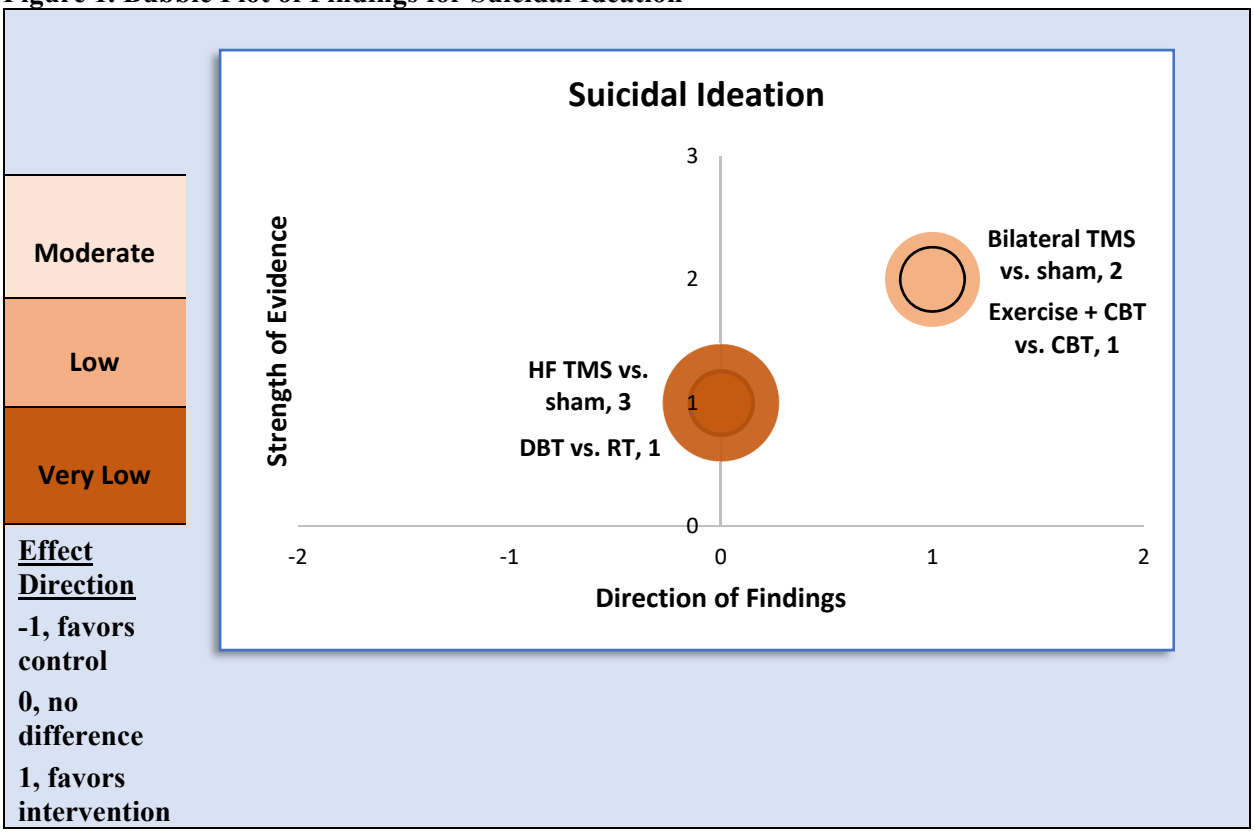

Figure 2. Bubble Plot of Findings for Depression

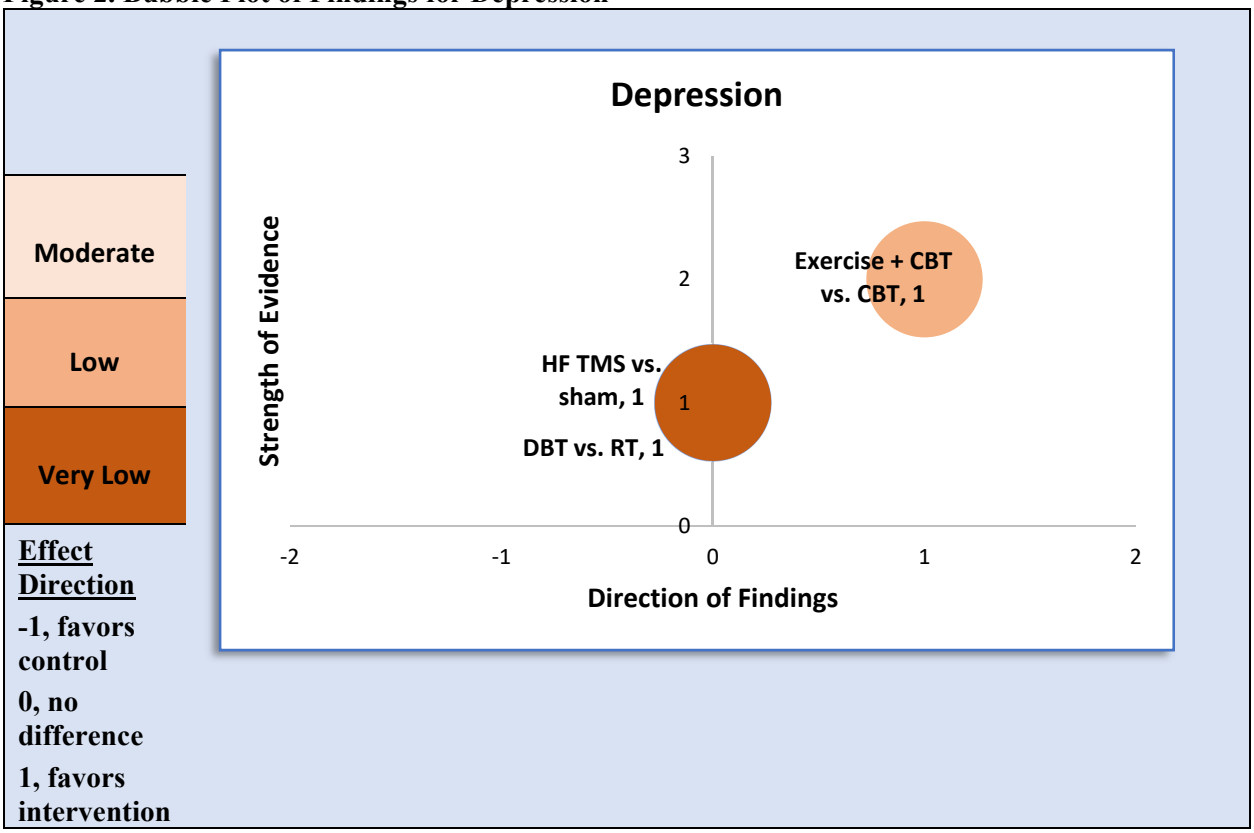

Figure 3. Bubble Plot of Findings for Anxiety