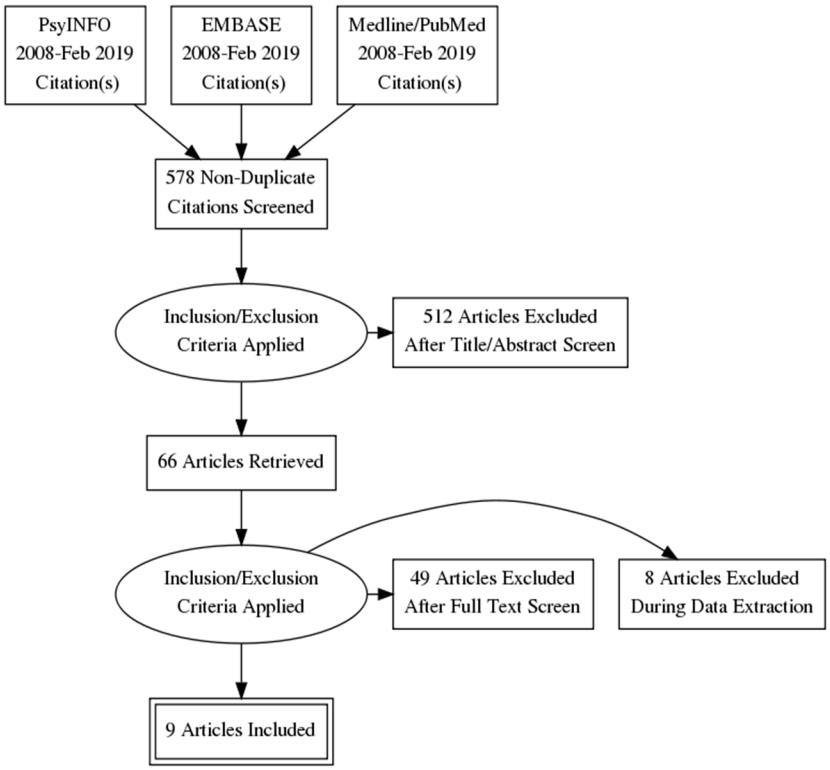
Chapter 8: Complementary and Integrative Health and other Non-Conventional Approaches for Treating Bipolar Disorder (BPD)

Results of the Literature Search for Bipolar Disorder

Extensive literature searches identified 578 citations (after duplicates removed) potentially addressing the CIH interventions of interest for the treatment of Bipolar Disorder. The studies in this SR included individuals with a diagnosis of Bipolar Disorders I and II but excluded individuals with unipolar depression. Of those studies, 512 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 66 full-length articles were retrieved for review. (See the PRISMA diagram). Of those, 49 were excluded due to having the wrong study design (17 studies), less than 20 patients (13 studies), the wrong comparator (7 studies), the wrong patient population (6 studies), the wrong intervention (2 studies), wrong outcomes (2 studies), and not English (2 study). An additional 8 studies were excluded during data abstraction. Reasons for these exclusions are listed in **Appendix B**.

Figure 1. Prisma Study Flow Diagram for Bipolar Disease



Overall, 9 studies were included in the systematic review for Bipolar Disorder. **Table 1** presents a summary of the evidence (how many RCTs and/or SRs) for each CIH intervention.

The literature searches did not identify any publications meeting inclusion criteria for the following interventions: acupuncture, accelerated resolution therapy, cannabinoids, 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 with Bipolar Disorder

Intervention	Number and Type of Studies	Strength of the Evidence (SOE)
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]	0	NA
Healing Touch	0	NA
Hyperbaric Oxygen Therapy	0	NA
Massage therapy	0	NA
Meditation	1	Very Low to Low
Music therapy	0	NA
Relaxation training techniques	0	NA
Tai chi	0	NA
Therapeutic touch	0	NA
Training and caring for service dogs	0	NA
Transcranial Magnetic Stimulation (TMS)	8 RCTs	Low to Moderate
Yoga	0	NA
Total Studies	**9 RCTs**	

RCT: Randomized controlled trial; SR: systematic review;

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

Mindfulness Meditation

Evidence Base

Our searches of the literature identified 1 RCT that met criteria and assessed the use of meditation in the treatment of adults with Bipolar Disorder. The study by Perich (b) et al 2013 assessed the effect of the quantity of mindfulness meditation practice on the psychiatric symptoms of adults following an eight (8) week course of Mindfulness-based Cognitive Therapy (MBCT). MBCT is a manualized group psychotherapy that combines the practices of mindfulness meditation with cognitive therapy. The patients attended 8 weekly group sessions and were expected to do homework assignments as well as have daily formal meditation practices. This study followed patients for 12 months and assessed whether the self-reported frequency (dose) of meditation practice during the follow-up period affected depression, mania or anxiety.

Participants had a DSM IV diagnosis of bipolar I or II disorder and were maintained on a stable dose of mood-stabilizing medication for the duration of the study period. Patients were initially randomized to MBCT or Treatment-As-Usual (TAU) for a study published separately as Perich (a) 2013. Perich (b) aimed to assess the relationship of mindfulness meditation practice to symptom improvements over a 12-month period following the completion of a course of MBCT. They hypothesized that individuals who practiced meditation for a minimum of 3 times/week would have lower depression and anxiety scores than those who practiced 2 times or less each week. After 8 weeks of MBCT, the study found that number of days in meditation practice was not significantly associated with self-reported or clinician-determined depression or anxiety. At 12 months follow-up, the number of days spent in mindfulness meditation practice was significantly inversely correlated with clinician-determined depression scores. At 12-month follow-up, when the sample was dichotomized into individuals who practiced mindfulness meditation once a day at least 3 or more times/week versus those who practiced it 2 or fewer times/week during MBCT, there was a significant difference between groups in clinician-determined depression. Those who meditated more frequently during treatment had lower scores for depression.

Study Quality

Using the Cochrane tool, we rated the RoB of Perich (b) (2013), as Some Concerns due to lack of participant blinding, outcome measurement and imprecision due to small sample size. (See **Table 2** 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 in patients with bipolar disease, mindfulness meditation (as part of MBCT) significantly improves depression and anxiety scores post-treatment (8 weeks) when practiced for one hour at least 3 times per week when compared to those who practiced $\leq$ 2 times per week. (SOE: Low)
- Evidence from 1 RCT suggests that in patients with bipolar disease, MBCT does not improve mania post-treatment. (SOE: Very low)
- Evidence from 1 RCT suggests that patients with bipolar disease who practice mindfulness meditation greater than or equal to 3 times per week, as part of an 8 week course of MBCT, may have more improvement in depression at 12 months than those who practice it 2 or fewer times /week (SOE: Low)

Discussion

The findings from Perich et al. are insufficient to recommend for or against mindfulness meditation-based intervention as a stand-alone self-administered adjunctive therapy to medication. At 12 months follow-up, the number of days practicing mindfulness meditation was significantly inversely correlated with clinician-determined depression scores in individuals who practiced mindfulness meditation once a day at least 3 or more times/week showing a significant improvement in clinician-determined depression. For patients treated with MBCT and pharmacotherapy, those who meditated more frequently during treatment had lower scores for depression.

The overall strength of the evidence for increased frequency of mindfulness meditation as part of a MBCT therapy was very low to low. In general, the strength of the evidence was limited due to limitations in the methodological quality of the RCT (e.g. lack of participant blinding, outcome measurement blinding and imprecision due to small sample size). Larger, more rigorously designed studies with longer follow-up of mindfulness meditation practice and more rigorous study of the quality of self-managed mindfulness meditation practice are needed.

Table 1. Strength of Evidence for Mindfulness Meditation to Treat Bipolar Disorder

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Depression	1 RCTs Perich(b) 2013	8 wks. Pharmacotherapy plus MBCT; 12-month F/U period with MM only	**Number of days practicing MM** At 8 weeks: MADRS: NS DASS: NS At 12 mon: MADRS: (r(16) = -5.559, p=.024 **Dichotomized ≥3MM sessions/wk. compared to 2/wk:** at 12 mon: MADRS z= -2.24, p=0.025) **statistically significant** DASS z= - 1.88, p=0.06 NS	Yes (-1)	Yes (-1)	No	No	No	Low
Anxiety	1 RCTs Perich(b) 2013	8 wks. Pharmacotherapy plus MBCT; 12-month F/U period with MM only Pre-/Post-Evaluation	Number of days practicing MM At 8 weeks: STAI: z = -2.43, p=0.015 Dichotomized ≥3MM sessions/wk. compared to 2/wk: at 12 mon: NS	Yes (-1)	Yes (-1)	No	No	No	Low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Mania	1 RCTs Perich 2013	8 wks. Pharmacotherapy plus MBCT ; 12 month F/U period with MM only	Number of meditation days at 8 weeks YMRS:NS	Yes (-1)	Yes (-1)	NA	Yes (-1)	No	Very low

CI: confidence interval; CT: control group; DASS: Depression Anxiety Stress Scale; ES: effective size; mos.: months; MADRS: Montgomery-Asberg Depression Rating Scale; MM: Mindfulness Meditation; NR: not reported; NS: not significant; PTSD: post-traumatic stress disorder; RCT: randomized controlled trials; STAI: State/Trait Anxiety Inventory; SE: standard error; SMD: standardized mean difference; rTMS: repetitive transcranial stimulation; TAU: treatment as usual; WL: waitlist; YMRS: Young Mania Rating Scale;

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

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

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

Table 3. Evidence Table for RCTs on Meditation to Treat BPD

Study Details	Study Population	Treatment	Results	Conclusion/ Limitations
Reference: Perich (2013b) **Purpose:** examine the impact of quantity of mindfulness meditation on BPD **Setting:** outpatient, Australia **Funding source:** National Medical Health and Medical Research Council (NHMRC) Program Grant no.222708 and Program Grant no.510135 and Rotary Australia	**Number of patients:** 34 MBCT **Inclusion criteria:** (i) met criteria for a lifetime DSM-IV diagnosis of bipolar I or II disorder, (ii) were able to be maintained on a mood stabilizing medication for the duration of treatment, (iii) were currently under the care of a GP or psychiatrist who would review medication as necessary, (iv) experienced at least one bipolar disorder episode (hypo/mania, depression, mixed episode) over the past 18 months, and (v) had a lifetime incidence of at least 3 bipolar episodes. **Exclusion criteria:** (i) currently experiencing a bipolar episode, (ii) had been given a diagnosis of schizophrenia or schizoaffective disorder, current substance abuse disorder, organic brain syndrome, antisocial or borderline personality disorder, (iii) had a concurrent significant medical condition which impeded their ability to participate, or (iv) were currently receiving other psychological therapy **Pt. baseline characteristics:** Thirty-four (70.8%) participants completed the MBCT program and 23 (67%) provided information regarding homework completion during the 8-week trial period. Seven (30%) participants were male and 16 (69%) were female. Mean age was 42 years	**Intervention:** Mindfulness-based Cognitive Therapy (MBCT) **Control:** Tx as usual (TAU) **Outcomes:** Young Mania Rating Scale (YMRS); Montgomery-Åsberg Depression Rating Scale (MADRS); Composite International Diagnostic Interview (CIDI) (WHO, 1997); Structured Clinical Interview for DSM-IV-TR Disorders (SCID-I) (First, Spitzer, & Williams, 2002) **F/u:** post-Tx & 12mo	Depression scores at 12-month follow-up were negatively correlated with the number of days meditated throughout the initial 8-week MBCT trial, suggesting that a deeper engagement with the MBCT program confers protection for depression symptoms over time. Those who continued to practice meditation throughout the 12-month follow-up period did not report any significant reductions in psychiatric symptomatology compared to those that had not Depression scores at 12-month follow-up were negatively correlated with the number of days meditated throughout the initial 8-week MBCT trial, suggesting that a larger dose of MM improves	**Limitations:** limited by small sample size and multiple comparison testing. Type of meditation practice was not examined. **Study ROB:** some concerns **Author conflict:** no conflict related to this study

Study Details	Study Population	Treatment	Results	Conclusion/ Limitations
			depression symptoms over time. **Number of days practicing MM** At 8 weeks: MADRS:NS DASS: NS At 12 mon: MADRS: (r(16) = -5.559, p=.024 Quantity of mindfulness meditation practiced throughout an MBCT program for bipolar disorder is related to lower depression scores at 12-month follow-up **Dichotomized ≥ 3MM sessions/wk. compared to 2/wk:** At 12 mon: MADRS z= -2.24, p=0.025) **statistically significant** DASS z= - 1.88, p=0.06 **NS** Quantity of MM meditation is related to lower anxiety scores at 8 weeks but not at 12-month follow-up **Number of days practicing MM** At 8 weeks: STAI: z = -2.43, p=0.015 **Dichotomized**	

Study Details	Study Population	Treatment	Results	Conclusion/ Limitations
			≥ 3MM sessions/wk. compared to 2/wk: At 12 mon: NS	

Table 4. Cochrane Risk of Bias 2.0 Tool for RCTs on Mindfulness Meditation to Treat BPD

Reference	Perich(a) 2013	Perich(b) 2013
• 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?	NA	NA
Overall RoB of Effect of Assignment	**Some concerns**	**Some concerns**
Missing Outcome Data		
• Were data for this outcome available for all, or nearly all, participants randomized?	Yes	PN
• Is there evidence that result was not biased by missing outcome data?	Yes	No
• Could missingness in the outcome depend on its true value?	NA	Yes
• 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	PN
Overall RoB of Missing Data	**Low**	**Some concerns**
Measurement of the Outcome		
• Was the method of measuring the outcome inappropriate?	Yes	Yes
• Could measurement or ascertainment of the outcome have differed between intervention groups?	Yes	No
• Were outcome assessors aware of the intervention received by study participants?	No	NI
• Could assessment of the outcome have been influenced by knowledge of intervention received?	Yes	Yes
• Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No	No

Reference	Perich(a) 2013	Perich(b) 2013
Overall RoB of Measurement of Outcome	**Some concerns**	**Some concerns**
Selection of Reported Results		
• Was the trial analyzed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?	Yes	Yes
Overall RoB of Reported Results	**Low**	**Low**
Overall Study RoB	**Some concerns**	**Some concerns**

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

References

Perich, T., Manicavasagar, V., Mitchell, P. B., Ball, J. R., & Hadzi-Pavlovic, D. (2013). A randomized controlled trial of mindfulness-based cognitive therapy for bipolar disorder. *Acta Psychiatrica Scandinavica*, *127*(5), 333–43.

Perich, T., Manicavasagar, V., Mitchell, P. B., & Ball, J. R. (2013b). The association between meditation practice and treatment outcome in mindfulness-based cognitive therapy for bipolar disorder. *Behaviour Research and Therapy*, *51*(7), 338–43.

Transcranial Stimulation

Evidence Base

Our searches of the literature identified 1 RCTs that met criteria and assessed the use of Direct Cranial Stimulation and 7 RCTs on the use of repetitive Transcranial Magnetic Stimulation (rTMS) in the treatment of adults with Bipolar Disorder.

The searches identified 1 RCT by Sampaio-Junior et al 2018 that met criteria. The investigators conducted a randomized, sham-controlled, double-blind trial involving 59 adult outpatients with type I or II bipolar disorder in a major depressive episode who were on a stable pharmacologic regimen. Participants were randomized to ten daily 30-minute, 2-mA, anodal-left and cathodal-right prefrontal sessions of active or sham tDCS on weekdays and then 1 session biweekly until week 6. Hamilton Depression Rating Scale (HDRS-17) scores were measured at baseline and at 2, 4 and 6 weeks. The investigators found that the cumulative response rates were higher in the active vs sham groups but not remission rates. Adverse events, including treatment-emergent affective switches, were similar between groups, except for localized skin redness that was higher in the active group. Active tDCS treatment did not result in an increase in hypomanic or manic episodes.

Our searches identified an additional 7 RCTS of Transcranial Magnetic Stimulation (TMS) that met inclusion criteria for this systematic review. We summarize each study here. Fitzgerald et al. (2015) studied 49 patients with bipolar disorder and a current episode if treatment resistant depression by DSM IV criteria. The RCT, evaluated the therapeutic efficacy of quetiapine plus sequential bilateral rTMS versus quetiapine alone in a two-arm randomized parallel design trial of active sequential bilateral stimulation versus sham. They found no significant difference in mean reduction of depressions scores or response rates.

Hu et al. (2016), performed a randomized trial in 38 bipolar II depressed patients. They randomly assigned patients to three arms: 1) left high frequency (12 pts.), 2) right low frequency (12 pts.), 3) sham treatment (12 pts.). Patients were evaluated at baseline and then weekly for 4 weeks. All three groups showed a decrease in HDRS-17, and MADRS over the study period but did not differ significantly among the three groups. This result indicated that active rTMS combined with quetiapine was not superior to quetiapine alone in improving depressive symptoms in patients with bipolar disorder.

Myczkowski et al. (2018) studies 43 patients diagnosed with bipolar disorder type I or II according to DSM IV criteria. Participants were randomized to receive 20 sessions (55 trains, 18 Hz, 120% resting motor threshold intensity) or sham rTMS. At baseline, 4 weeks and 8 weeks patients were tested with a battery of 20 neuropsychological assessments. Cognitive improvement was shown in all domains. It occurred in all intervention groups and was independent of depression improvement. No correlations with depression (baseline or during treatment) and cognitive improvement was found.

Praharaj et al. (2009) performed a prospective, hospital based, single blind randomized trial to evaluate the efficacy of adjunctive right prefrontal high-frequency suprathreshold rTMS compared to sham treatment in 41 bipolar disorder patients and mania (by ICD-10). All patients were receiving similar pharmacotherapy treatment as selected by the treatment team. The investigators found that rTMS was

well-tolerated and that the mania remission rate was higher for the active rTMS patients (100%) compared to sham treatment (65%, p=0.003). One of the active rTMS patients developed depression during the study while none of the sham patients developed clinical depression. The most common adverse events were transient pain, headache, or dizziness.

Rohan et al. (2014), performed a double blind, sham controlled trial to evaluate the effects of left frontomedial TMS in stable depressed patients with either BPD (41 patients) or major depressive disorder (22 patients). Subjects received a single, 20-minute treatment. Change in mood was assessed immediately afterward using a visual analog scale (VAS), the 17-item Hamilton Depression Rating Scale (HDRS-17), and the Positive and Negative Affect Schedule scales. Participants experienced non-significant improvement in mood, as measured by the VAS and the HDRS-17, following LFMS treatment as compared to sham treatment for bipolar disorder. It is important to note that the differences were not statistically significant in primary analyses of bipolar disorder and were only significant in secondary analyses combining data across both diagnostic groups (BPD and MDD).

Tavares et al. (2017) conducted a randomized sham-controlled trial to evaluate the efficacy and safety of deep Transcranial Magnetic Stimulation (dTMS) in 50 treatment-resistant bipolar patients on stable pharmacotherapy. Patients received 20 sessions of active or sham dTMS over the left dorsolateral prefrontal cortex (H1-coil, 55 18 Hz 2 s 120% MT trains). The primary outcomes was a change in the 17-item Hamilton Depression Rating Scale (HDRS-17) from baseline to endpoint (week 4). Secondary outcomes were changes from baseline to the end of the follow-up phase (week 8), as well as response and remission rates. Out of 50 patients, 43 finished the trial. There were 2 and 5 dropouts in the sham and active groups, respectively. Active dTMS was found to produce a greater reduction in depression than sham at the 4-week end point but not at follow-up. Remission rates were not statistically different. No TEMS episodes were observed.

Yang et al. (2019) conducted an RCT on 52 participants with bipolar disorder to evaluate the efficacy of rTMS. Participants randomized to active rTMS received high speed magnetic stimulation for 10 consecutive days for a total of 25,000 stimuli were applied over the left dorsolateral prefrontal cortex at 110% of the motor threshold. The sham group received corresponding sham stimulation. Clinical manifestations and cognitive functions were assessed using a modified 24-item Hamilton Depression Rating Scale (HDRS), the Young Mania Rating Scale (YMRS), and the MATRICS Consensus Cognitive Battery (MCCB). After ten days of treatment the active rTMS group had improved scores on the Wechsler Memory Scale-III Spatial Span, and the MCCB Category Fluency subtest, without intolerable adverse effects. No significant differences in HDRS or YMRS scores were found between active and sham group. The study was limited by lack of follow-up after the intervention.

Study Quality

Using the Cochrane tool, we rated the RoB of 1 study of tDCS as having “Some Concerns”. The RoB was judged to be “Low: for seven (7) RCTS on repetitive transcranial magnetic stimulation. (See **Table 5** 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 a single RCT suggests that tDCS treatment reduces depression and increases remission rates in patients with bipolar disease. (SOE: Moderate)
- Evidence from 7 RCTs provides insufficient evidence for or against the effectiveness of rTMS for treatment of depression in bipolar disorder. 5 RCTs showed no statistically significant change in depression symptoms while 2 RCTs demonstrated improvements in post-treatment depression scores. (SOE: Moderate)
- Evidence from 2 RCTs showed no change or improvement in cognition post-treatment with rTMS. (SOE: Low)

Discussion

Overall, the findings from this systematic review suggest that there is insufficient evidence to determine whether rTMS offered as an adjunctive therapy is effective for the treatment of the mania or depression symptoms in patients with bipolar disorder. It is important to note that the rTMS study methodology varied by frequency of stimulation (Hz), location and laterality of stimulation, intensity of stimulation and duration of treatment. The small number of patients treated and the inconsistent rTMS methodology make evaluation of the study results challenging. Further research is needed.

The overall strength of the evidence for mindfulness meditation-based interventions was very low. In general, the strength of the evidence was limited by the methodological quality of the RCTs (e.g. lack of blinding, unclear randomization process), small sample sizes, and very short follow-up periods. Larger, more rigorously designed studies with longer follow-up periods are needed.

Table 1. Strength of Evidence for Transcranial Stimulation (tDCS or rTMS) to Treat Bipolar Disorder

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Depression	1 RCT Fitzgerald (2016) 7 RCTs (Hu, 2016; Praharaj, 2009; Rohan, 2014; Sampaio-Junior, 2018; Tavares, 2017; Yang, 2019; Fitzgerald, 2016)	rTMS 23 (10M/13F) TAU 23 (10M/13F)	HAMD, IDS, YMRS at baseline and 4 wks. No significant differences between rTMS and SHAM. HAMD (rTMS=21.37 ±30.0%, Sham=15.07± 21.7%, p40.05) IDS scores groups (rTMS=22.27 ±30.1%, sham=17.37±21.2%, p40.05)	Yes (-1); Some concerns, evaluators unaware of group, however treatment clinicians knew.	No	No	No	No	Moderate
		Left rTMS 12 Right rTMS 13 SHAM 13	No significant difference at baseline and over the 4-week treatment (p>0.05). Mean score reduction (HDRS-17: F(2,32)=120.35, p<0.001; MADRS: F(2,32)=95.66, p<0.001; No	Yes (-1); Some concerns due to unknowns: Randomization Provider and assessor blinding.	No	No	No	No	Moderate

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			significant group effect (HDRS-17: F(2,32)=0.558, p=0.578; MADRS: F(2,32)=0.039 No significant difference in response rates (8/11 vs. 9/12 vs. 8/12, $\chi 2$=0.22, p=0.897) or remission rates (3/11 vs. 3/12 vs. 2/12, $\chi 2$=0.41, p=0.813)						
		rTMS: 21 pts; 29.76±6.80 yrs; 18M:3F Sham: 20 pts; 30.50±7.99 yrs; 17M:3F	CGI-S and YMRS scores showed a significant effect of treatment over time (repeated measures ANOVA). YMRS (ANOVA): (F=12.95, df=1.51/58.94, pb0.001, Greenhouse-	Yes (-1); Some concerns (randomization process not specified).	No	No	No	No	Moderate

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			Geisser corrected). CGI-S (ANOVA): (F=5.34, df=1.36/ 53.01, p=0.016, Greenhouse-Geisser corrected).						
		For the BPD group - LFMA 6M:15F; age 42.5 (SD 12.1) SHAM: 10M:10F; age 43.6 (SD 12.6) Second group of MDD was studied.	Assessment by self-rated VAS, PANAS, HDRS-17 VAS & PANAS differences were not statistically significant in the stratified analyses of the BPD group.	Yes (-1); Some concerns. Authors have patent interests and receive fees from Tal Medical. Blinding of treating staff and assessors was not specified.	No	No	Yes (-1)	No	Low
		tDCS 26 SHAM 26 Completed full 6 weeks	HDRS-17 at baseline, week 2, week 4, and the end point week 6 tDCS compared to sham:	none	none	none	none	none	High

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
			(βint = −1.68; number needed to treat, 5.8; 95% CI, 3.3-25.8; P = .01). Statistically significant Cumulative response rates (tDCS 67.6% vs sham 30.4%; NNT = 2.69; 95% CI, 1.84-4.99; P = .01). Statistically significant Remission rates (37.4% vs 19.1%; NNT = 5.46; 95% CI, 3.38-14.2; P = .18). Statistically significant Adverse events: similar between groups, except for localized skin redness						

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
			that was higher in the active group (54% vs 19%; P = .01). Statistically significant						
		rTMS 25 (17F:8M); 43.5 ± 12 Sham 25 (18F:7M); 41.2 ± 8.9 f/u at 4 & 8 wks	Trend for greater response rates in the active (48%) vs sham (24%) groups (OR = 2.92, 95% CI 0.87–9.78, p = 0.08) at week 4. However, response and remission at week 8 were not statistically significant. % Response @ 4 weeks (rTMS vs Sham) ITT 12 (48) vs 6 (24) 2.92 (0.87–9.78) p=0.08	None	None	None	None	None	High

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
			% Response @ 8 weeks (rTMS vs Sham) 8 (32) vs 6 (24) 1.49 (0.43–5.17) p=0.63						
		rTMS: 25 (12M:13F); age 28.64 ± 8.05 yrs SHAM: 17 (19M:8F); age 27.41 ± 7.08 yrs	No differences in HDRS scores (F1,50 = 0.577, p = 0.451) or YMRS scores (F1,50 = 0.657, p = 0.422) were found between groups at baseline and follow-up. rTMS improved cognitive function in BD participants in the WMS-III Spatial Span (F1,50 = 6.484, p = 0.014), and MCCB Category	Yes (-1); Some concerns (single blind study – researchers knew, method of randomization not specified.	Yes (-2)	No	No	No	Very low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			Fluency subtest (F1,50 = 4.853, p = 0.032).						
Cognition	2 RCTs (Myczkowski, 2018; Yang, 2019)	rTMS 20 Sham 23 rTMS 25 (17F:8M); 43.5 ± 12 Sham 25 (18F:7M); 41.2 ± 8.9 f/u at 4 & 8 wks	Cognition measures did not change with treatment, showing safety of rTMS.	Low risk	None	None	None	None	High
		rTMS: 25 (12M:13F); age 28.64 ± 8.05 yrs SHAM: 17 (19M:8F); age 27.41 ± 7.08 yrs	rTMS improved cognitive function in BD participants in the WMS-III Spatial Span (F1,50 = 6.484, p = 0.014), and MCCB Category Fluency subtest (F1,50 = 4.853, p = 0.032).	Yes (-2); single blind study – researchers not blinded; method of randomization not specified.	No	No	No	No	Low

BPD: Bi-Polar Disorder; CI: confidence interval; CT: control group; ES: effective size; DLPFC: dorsolateral prefrontal cortex; GCI-S: Clinical Global Impression Scores; HAMD: Hamilton Depression Rating Scale; HDRS-17: 17-item Hamilton Depression Rating Scale; HDRS: 24-item Hamilton Depression Rating Scale; HDRS-17: 17-item Hamilton Depression Rating Scale; IDS: Inventory of Depressive Symptomatology; MADRS: Montgomery-Asberg Depression Rating Scale; MCCB: MATRICS Consensus Cognitive Battery; MDD: Major

Depressive Disorder; mos.: months; MT: Motor Threshold for stimulation; NNT: number needed to treat; NR: not reported; NS: not significant; PANAS PA: self-administered Positive and Negative Affect Schedule; PSQI: Pittsburgh Sleep Quality Index; RCT: randomized controlled trials; SE: standard error; SIGH-D: 21-item Structured Interview Guide for the Hamilton Depression Scale; SMD: standardized mean difference; rTMS: repetitive transcranial magnetic stimulation; TAU: treatment as usual; tDCS: transcranial direct-current stimulation; VAS: Visual Analog Scale; WL: waitlist; YMRS: Young Mania Rating Scale

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

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

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

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

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
rTMS				
Reference: Fitzgerald (2016) **Purpose:** To evaluate the effectiveness of rTMS in the treatment of bipolar disorder **Setting:** Outpatients Recruited from range of hospital and community-based psychiatrists from January 2009 – May 2015. **Funding source:** PBF was supported by a Practitioner Fellowship grant from the National Health and Medical Research Council (NHMRC)	**Number of patients:** 49 **Inclusion criteria:** bipolar affective disorder and a current episode of treatment resistant depression by DSM IV criteria. **Exclusion criteria:** age outside range of 18–70unstable medical condition, neurological disorder, any history of a seizure disorder or who were pregnant or lactating; mixed symptoms on both clinical interview and rating with the Young Mania Rating Scale (YMRS) **Pt. baseline characteristics:** 29 female and 20 male; 18–70 (mean 47.97 +/- 11.9) years 23 rTMS (10M/13F) 23 TAU (10M/13F)	**Intervention:** rTMS **Control:** sham **Outcomes:** scores on the 17-item HAMD (Hamilton Depression Rating Scale - Hamilton 1967) from baseline to week 4 F/u:	T tests and χ2-squared tests were used, primary analysis were conducted with repeated measures analysis of variance (ANOVA) **No significant difference in response between the active and sham stimulation groups**	No significant benefit of sequential bilaterally applied rTMS in a group of patients with BD. **Limitations:** small sample size Study does not significantly inform the question as to whether other methods of administration of rTMS have effectiveness in BD (e.g. unilateral stimulation, including the more standard high-frequency left-sided stimulation) **Study ROB:** some concerns **Author conflict:** none reported

Study Details	Study Population	Treatment	Results	Conclusion/ Limitations
(1078567). KEH was supported by an NHMRC Career Development Fellowship (1082894). The study was supported by a project grant from the NHMRC (1041890). PBF has received equipment for research from Cervel Neurotech, Medtronic Ltd, MagVenture A/S and Brainsway Ltd and funds for research from Cervel Neurotech	**Withdrawal/Did not complete:** 49 recruited; 3 withdrew before randomization 6 withdrew during 1st 4wks of Treatment: 3 of these (2 active, 1 sham) related to practical difficulties with attendance, changes in life circumstance and 1 active participant due to withdrawn consent. In 2 patients (1 active, 1 sham) withdrawal related to a desire to access alterative treatment. Patients in either active or sham group did not guess their treatment group at a greater rate than would be expected by chance (48% active group, 61% sham group)			
Reference: Yang et al., 2019	**Number of patients:** 52 total; active rTMS	**Intervention:** rTMS given at left dorsolateral prefrontal	MCCB Post-tx f/u of 2 wks. (mean [SD], p value):	

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Purpose: To evaluate the effectiveness of rTMS on cognitive function in patients with BD **Setting:** Institution of Mental Health, Hebei Medical Univ.; Dept. of Psychiatry, First Hospital of Hebei Medical Univ. **Funding source:** National Science Foundation of China	(n=25); sham (n=27) **Inclusion criteria:** 18-55 years of age; diagnosis of bipolar I or II according to DSM-IV; stable antipsychotic and mood-stabilizing tx.; at least 3 mos. of clinical remission before randomization; Young Mania Rating Scale (YMRS) score ≤6; modified 24-item HDRS score ≤8 **Exclusion criteria:** patients with diagnosed substance or alcohol abuse; history of significant neurologic illness; EEG abnormalities; significant, unstable medical illnesses; ECT of rTMS within past year; participation in any structured psychological intervention within past 2 yrs.; comorbidities according to DSM-IV	cortex (DLPFC). Over 10 consecutive days, patients received 50 5-second, 10-Hz trains delivered at 110% of the motor threshold at 30-second inter-train intervals **Control:** Sham tx. was same except a false coil was placed in the same position as active tx. with same vibration as true stimulus but w/o magnetic field **Outcomes:** Cognitive function was measured using the MATRICS Consensus Cognitive Battery (MCCB) **F/u:** 2 wks.	Active rTMS; Sham Continuous Performance Test-Identical Pairs working memory, verbal: 2.830(0.760); 2.768(0.779), p=0.896; NS University of Maryland Letter-Number Span working memory, non-verbal: 24(3.926); 23.407(3.456), p=0.578; NS WMS-III Spatial Span verbal learning: 18.84(3.926); 18.814(4.123), p=0.014; favors rTMS Hopkins Verbal Learning Test, Revised visual learning: 29.64(5.685); 27.333(6.995), p=0.735; NS Brief Visuospatial Memory Test, Revised processing speed: 29.6(5.172);	

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	Pt. baseline characteristics (active rTMS; sham [mean, SD]): Gender (m/f): 12/13; 19/8 Age (yrs.): 28.64 (8.05); 27.41 (7.08)		26.444(6.612), p=0.105; NS Category Fluency: 25.080(4.864); 21.407(5.786), p=0.032; favors rTMS Trail Making A: 34.44(12.735); 35.963(11.227), p=0.412); NS BACS Symbol Coding reasoning and problem solving: 56.720(11.894); 55.741(11.782), p=0.297; NS NAB mazes social cognition: 14.24(5.988); 12.778(5.033), p=0.124; NS MSCEIT managing emotions: 9.44(2.063); 10(2.418), p=0.531; NS	
Reference: Hu (2016) **Purpose:** explore clinical efficacy and	**Number of patients:** 38 met criteria from 40 recruited **Inclusion criteria:** depressive	**Intervention:** repetitive transcranial magnetic stimulation (rTMS) Left	**F**/U: 4 weeks reduction in mean scores of HDRS-17 and MADRS (HDRS-17: F(2,32)=120.35,	No evidence that active rTMS in combination with quetiapine improved executive functioning compared with quetiapine monotherapy. **Limitations:** small sample size limited its statistical power; blinding effectiveness of mood raters was not assessed; antidepressant role of quetiapine

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
cognitive remediation of rTMS in a depressive episode of bipolar II disorder **Setting:** not specified **Funding source:** not specified	episodes in bipolar II disorder diagnosed by Structured Clinical Interview for DSM-IV axis I (SCID-I) **Exclusion criteria:** severe medical illnesses or neurologic disorders; comorbid psychiatric illness, any form of metal implants, or any history of suicide attempt, drug abuse, seizures, or medications known to lower seizure threshold. **Pt. baseline characteristics:** No significant difference was found among the three groups in age, gender, years of education, marital status, onset or duration of illness, or total number of episodes. Randomly assigned in a 1:1:1 ratio to 1 of 3	high frequency (12); Right high frequency (13) **Control:** Sham (13) ALL had + quetiapine **Outcomes:** baseline & weekly: 17-item Hamilton Depression Rating Scale (HDRS-17) and Montgomery-Asberg Depression Rating Scale (MADRS); Cognitive functioning was assessed before and after the study with the Wisconsin Card Sorting Test (WCST), Stroop Word-Color Interference Test (Stroop), and Trail Making Test (TMT) :	$p<0.001$; MADRS: $F(2,32)=95.66$, $p<0.001$; No significant group effect (HDRS-17: $F(2,32)=0.558$, $p=0.578$; MADRS: $F(2,32)=0.039$, $p=0.962$**; or group-by-time interaction** (HDRS-17: $F(2,32)=0.299$, $p=0.892$; MADRS: $F(2,32)=0.619$, $p=0.679$; **No significant difference in response rates** (8/11 vs. 9/12 vs. 8/12, $\chi2=0.22$, $p=0.897$) or remission rates (3/11 vs. 3/12 vs. 2/12, $\chi2=0.41$, $p=0.813$) was detected across the three groups. **No statistically significant difference in any factor scores of the HDRS-17 across the three groups,** including anxiety/somatization, cognition, sleep, weight, and retardation, at baseline and over the	might cover up the true effect of active rTMS on bipolar depression; relatively low stimulation intensity of 80% of motor threshold **Study ROB:** some concerns **Author conflict:** none reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	groups using a sequence number randomly generated for each participant by a computer and a randomization table was also generated. All three subject groups on quetiapine. 1. 12 pts - Left high-frequency 2. 13 pts. - Right high-frequency 3. 13 pts. - SHAM		4-week treatment ($p>0.05$).	
Reference: Myczkowski (2019) **Purpose:** Evaluate TMS for cognition & depression in BD. Test the cognitive safety of H1-coil TMS for BD patients. **Setting:** outpatient **Funding source:** This study was	**Number of patients:** 50 patients, 43 finished the study (20 rTMS ; 23 sham) **Inclusion criteria:** Fifty adult (18–65 years-old) patients diagnosed with type I or II bipolar disorder in an acute depressive episode were recruited. depressive episode of at least moderate severity corresponding to a Hamilton Depression Rating	**Intervention:** TMS **Control:** Sham **Outcomes:** Battery of neurocognitive tests, listed in Table 1 (vida infra). **F/U:**	No correlations between depression (at baseline or during treatment) and cognitive improvement were found. Deep (H1-coil) rTMS did not lead to change in cognitive impairment in patients with bipolar depression.	**Limitations:** 1) Absence of healthy control group. 2) The neuropsychological battery might have not been sensitive to detect specific cognitive improvements. **Study ROB:** low risk **Author conflict:** None

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
partially funded by Brainsway™.	Scale, 17-items (HDRS-17) ≥17 (Hamilton, 1960) **Exclusion criteria:** Only patients without concomitant antidepressant drug medication. Exclusion criteria included other psychiatric disorders (such as unipolar depression, schizophrenia, substance dependence, dementias and others); neurologic disorders (such as stroke, traumatic brain injury, epilepsy and others); severe personality disorders; presence of manic symptoms at baseline and/or a score on the Young Manic Rating Scale (YMRS) >12 points; presence of psychotic symptoms; acute suicidal symptoms; rapid-cycling bipolar disorder; pregnancy; and specific			

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	contraindications for H1-coil rTMS. **Pt. baseline characteristics :** rTMS 20 (5M:15F); 41.2 (SD 11.7) SHAM 23(5M:18F); 40.6 (SD 9)			
Reference: Praharaj (2009) **Purpose:** rTMS for BPD, mania **Setting:** hospital-based **Funding source:** Role of funding source Nothing declared.	**Number of patients:** 41 **Inclusion criteria:** diagnosis of bipolar disorder, mania according to Diagnostic Criteria for Research of ICD-10 **Exclusion criteria:** current neurological or any comorbid psychiatric disorders or history of drug abuse, past history of epilepsy, significant head injury or any neurosurgical procedure, with cardiac pacemakers or other metal parts in the body, or who have received ECT in past 6 months were excluded from the study. Patients were either drug-	**Intervention:** after one week of treatment of TAU (as inpatient?) "Randomized" to daily right prefrontal high frequency suprathreshold rTMS treatment in bipolar affective disorder, mania patients plus TAU or **Control:** sham stimulation plus TAU Baseline measurement (day 7), and after 5th and 10th rTMS **F/U:** 10 days	CGI-S and YMRS scores YMRS (ANOVA): (F=12.95, df=1.51/58.94, p=0.001, Greenhouse-Geisser corrected). CGI-S (ANOVA): (F=5.34, df=1.36/ 53.01, p=0.016, Greenhouse-Geisser corrected). **Significant effect of treatment over time**. **Adverse Events:** One patient receiving active rTMS developed mild depression during the study period No reports of any serious adverse effect of rTMS or sham treatment.	**Limitations:** The limitations of the study included lack of double blinding which could lead to rater bias during the assessment of symptoms. **Problems with Randomization:** Alternative assignment of the patients to either treatment group does represent true randomization is another limitation. Females were underrepresented in the study group. **Study ROB:** Some concerns (randomization process not specified). **Author conflict**: No conflict declared

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	naïve or drug-free for at least 2 months prior to the current study. **Pt. baseline characteristics :** rTMS: 21 pts; 29.76±6.80 yrs; 18M:3F Sham: 20 pts; 30.50±7.99 yrs; 17M:3F All the patients had received antipsychotic medications, which were converted to chlorpromazine equivalent per day (CPZ equivalent/day		The most common complaint of the patients receiving active treatment was pain during stimulation which improved spontaneously after completion of the session. Transient headache was reported by 6 pts. (28.57%) receiving active treatment following rTMS session, which lasted from < 1 hour – four hours. Dizziness and anxiety was also noted.	
Reference: Rohan (2014) **Purpose:** Testing LFMS for depression in MDD and BPD **Setting:** Outpatient **Funding source:** Stanley Medical Research	**Number of patients**: **Inclusion criteria:** Sixty-three patients ages 18 to 65 who met DSM-IV criteria for either BPD or MDD (35) and who were in a current episode of depression, defined as having a score greater than or equal to 17 on the 17-item Hamilton	**Intervention:** LFMA (Low Field Magnetic Stimulation) **Control:** SHAM **Outcomes:** primary outcome measures were a self-rated VAS, designed to be responsive to an immediate change in mood, and the	Improvements in both self-rated (VAS) and observer-rated (HDRS-17) mood were greater for active than sham treatment for all outcome measures and patient subgroups. These differences were <u>not</u> statistically significant in the stratified analyses, in which the treatment subgroups were	**Limitations:** Small sample, single Tx w/o follow-up of durability of improvement. Treating staff and assessor blinding was not specified. Assessment of participants knowledge of which TX recv'd was by asking - a week later - about the order of sham vs LFMS and may not be a valid assessment. **Study ROB:** some concerns **Author conflict:** Authors have patent interests and receive fees from Tal Medical Substantial improvement (10% of baseline) in mood was observed following LFMS treatment relative to sham treatment for both diagnostic subgroups for our primary outcomes, the VAS and the HDRS-17. Given the rapidity and magnitude of the mood-elevating effects of LFMS reported here, LFMS could serve as a valuable research tool.

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Institute 07TGS-1045.	Depression Rating Scale (HDRS-17) **Exclusion criteria:** Age outside of range? **Pt. baseline characteristics:** No significant differences between sham and treatment groups For the BPD group - LFMA 6M:15F; age 42.5 (SD 12.1) SHAM: 10M:10F; age 43.6 (SD 12.6)	observer-rated HDRS-17 **F/U:** None (assessment was 15 minutes after treatment/sham)	relatively modest in size. However, they reached significance when the data were combined across diagnostic groups. We observed a greater improvement in the self-rated PANAS PA scores (reflecting decreased ratings of depression) associated with active LFMS for both BPD and MDD patients. The difference was statistically significant for BPD patients alone and for the combined sample but not for MDD patients alone.	
Reference: Tavares (2017) **Purpose:** Deep (H1-coil) transcranial magnetic stimulation for BPD **Setting:** Outpatient	**Number of patients:** 50 started; 43 completed; 2 each group dropped due to missed sessions (4); 2 Tx group dropped for severity of depression; 1 Tx dropped for HA & burning scalp sensation	**Intervention:** dTMS 5 days/wk x 4 wks **Control**: Sham Outcomes: HDRS-17 (Hamilton, 1960) was the scale used for our primary efficacy	There was a trend for greater response rates in the active (48%) vs sham (24%) groups (OR = 2.92, 95% CI 0.87–9.78, p = 0.08) at week 4. Comparisons regarding response and remission at week 8 were not	**Limitations:** Small sample size limits results to "preliminary and hypothesis-driven" **Study ROB:** low risk **Author conflict:** none reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Funding source: Brainsway, which provided the dTMS devices and financial support	**Inclusion criteria:** All had treatment-resistant depression, 18 to 65 years old diagnosed with bipolar disorder types I or II in an acute depressive episode. main eligibility criterion was the presence of a depressive episode of at least moderate intensity, corresponding to a Hamilton Depression Rating Scale (17-items; HDRS-17)417 **Exclusion criteria:** other neuropsychiatric conditions per DSM-IV criteria (such as unipolar depression, schizophrenia, substance dependence, dementias, traumatic brain injury, epilepsy, and others—although anxiety disorders as comorbidities were included, provided the primary diagnosis was bipolar disorder);	outcome and also for defining response (⩾50% improvement from baseline), and remission status (HDRS-17 ⩽ 7) Secondary efficacy Outcomes included response and remission status at week 4, depression improvement from baseline to week 8, and response and remission status at week 8. Other outcomes included HAM-A and CGI-S improvement F/u: at 4 weeks	statistically significant: Trend for greater response rates in the active (48%) vs sham (24%) groups (OR = 2.92, 95% CI 0.87–9.78, p = 0.08) at week 4. However, response and remission at week 8 were not statistically significant. % Response @ 4 weeks (rTMS vs Sham) ITT 12 (48) vs 6 (24) 2.92 (0.87–9.78) p=0.08 % Response @ 8 weeks (rTMS vs Sham) 8 (32) vs 6 (24) 1.49 (0.43–5.17) p=0.63	

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	severe personality disorders; presence of (hypo)manic symptoms at baseline and/or a Young Manic Rating Scale (YMRS)412 points; rapid cycling bipolar disorder; acute suicidal ideation; pregnancy; specific contraindications to rTMS and motor threshold(MT)470% of maximum stimulator output assessed at the screening visit. **Pt. baseline characteristics:** 25 Tx (17F:8M); 25 Sham (18F:7M) both raters and patients were unable to identify the allocation group beyond chance			
tDCS				
Study: Sampaio-Junior **Purpose:** To determine the efficacy and safety of tDCS as an	**Number of Pts.:** 59 individuals with BD were randomly assigned to sham or active tDCS per a computer generated list, using random block sizes.	**Intervention:** Active tDCS (n = 30) versus **Control: Sham** (n = 29) Electrodes positioned over	19 active tDCS and 8 sham patients presented a sustained response. The cumulative survival rates at end point per Kaplan-Meier analysis were 67.6%	**Limitations:** Small sample size **Study ROB:** low risk **Author conflict:** none reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
adjunct treatment for BD. **Setting:** Outpatients at Academic Medical Center in Brazil **Funding Source:** NR	**Inclusion Criteria:** Included pts with BD who received a fixed pharmacologic regimen for 4weeks, which remained stable during the trial. **Exclusion Criteria:** Other psychiatric disorders, such as unipolar major depressive disorder, schizophrenia, substance dependence and abuse, and dementias; specific contraindications to tDCS. The only psychiatric comorbidities allowed were anxiety disorders. **Pt. Baseline Characteristics:** 24 women: 25 men Mean age: 45.7 (SD=10.3); Mean age at dx: 27.7 (SD=8)	the DLPFC bilaterally optimized for peak electric current densities over the DLPFC. Twelve 2-mA sessions (current density, 0.80 A/m2, ramp-up and ramp-down periods of 30 and 15 seconds, respectively) were applied for 30 minutes each day over 10 consecutive sessions daily from Monday through Friday, with weekends off, and 2 sessions were applied at weeks 4 and 6 (the study end point).	(95%CI, 50.1%-83.9%) and 30.4% (95%CI, 16.5%-51.8%). The Cox proportional hazards ratio associated with treatment group was 2.86 (SE, 1.22; 95%CI, 1.25-6.61; *P* = .01). The corresponding NTT was 2.69 (95% CI, 1.84-4.99 Similarly, 10 and 5 patients in the active and sham groups, respectively, presented sustained remission. The cumulative survival rates were 37.4% (95%CI, 22%-58.5%) and 19.1% (95% CI, 8.4%-40%). The Cox proportional hazards ratio was 2.07 (SE, 1.13; 95% CI, 0.71-6.06; *P* = .18). The NTT was 5.46 (95% CI, 3.38-14.2).	

BD: Bipolar Disorder; 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 4. Cochrane Risk of Bias 2.0 Tool for RCTs on Transcranial Stimulation to Treat BPD

Reference	Sampaio-Junior (2018)	Fitzgerald (2016)	Hu (2016)	Myczkowski (2018)	Praharaj (2009)	Rohan (2014)	Tavares (2017)	Yang (2019)
• Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	Yes	Yes	Yes	Yes	NI	Yes	Yes	NI
• Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization, concealed envelopes)?	Yes	Yes	NI	Yes	Yes	Yes	Yes	NI
• Did baseline difference between study groups suggest a problem with randomization?	No	No	No	No	No	No	No	Yes; education level differed, sham had 2x m: f, Tx group
Overall RoB for Randomization Process	**Low**	**Low**	**Some concerns**	**Low**	**Some concerns**	**Low**	**Low**	**Some concerns**
Deviation from Intended Intervention (Effect of Assignment)								
• Were participants aware of their assigned intervention during the trial?	No	No	NI	No	No	No	No	No
• Were providers and people delivering treatment aware of assigned intervention during trial?	No	No	NI	No	No	No	No	Yes
• Were there deviations from the intended intervention that arose because of the experimental context?	No	No	No	No	No	No	No	No

Reference	Sampaio-Junior (2018)	Fitzgerald (2016)	Hu (2016)	Myczkowski (2018)	Praharaj (2009)	Rohan (2014)	Tavares (2017)	Yang (2019)
• Were these deviations from intended intervention balanced between groups?	NA	Yes	NA	NA	NA	NA	NA	NA
• Were these deviations likely to have affected the outcome?	NA	No	NA	NA	NA	NA	NA	NA
• Was an appropriate analysis used to estimate the effect of assignment to intervention?	NA	Yes	Yes	NA	NA	Yes	NA	Yes
Overall RoB of Effect of Assignment	**Low**	**Some concerns**	**Some concerns**	**Low**	**Low**	**Low**	**Low**	**Some concerns**
Missing Outcome Data								
• Were data for this outcome available for all, or nearly all, participants randomized?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
• Is there evidence that result was not biased by missing outcome data?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
• Could missingness in the outcome depend on its true value?	NA	NA	NA	NA	NA	NA	NA	NA
• Do the proportions of missing outcome data differ between intervention groups?	NA	NA	NA	NA	NA	NA	NA	NA
• Is it likely that missingness in the outcome depended on its true value?	NA	NA	NA	NA	NA	NA	NA	NA
Overall RoB of Missing Data	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Measurement of the Outcome								
• Was the method of measuring the outcome inappropriate?	No	No	No	No	No	Yes	No	No

Reference	Sampaio-Junior (2018)	Fitzgerald (2016)	Hu (2016)	Myczkowski (2018)	Praharaj (2009)	Rohan (2014)	Tavares (2017)	Yang (2019)
• Could measurement or ascertainment of the outcome have differed between intervention groups?	No	No	Yes	No	No	No	No	No
• Were outcome assessors aware of the intervention received by study participants?	No	No	NI	No	No	No	No	Yes
• Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	Yes	PN	Yes	NA	NA	NA	Yes
• Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	No	NI	No	NA	NA	NA	NI
Overall RoB of Measurement of Outcome	**Low**	**Low**	**Some concerns**	**Low**	**Low**	**Some concerns**	**Low**	**Some concerns**
Selection of Reported Results								
• Was the trial analyzed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall RoB of Reported Results	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Overall Study RoB	**Low**	**Some concerns**	**Some concerns**	**Low**	**Some concerns**	**Some concerns**	**Low**	**Some concerns**

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

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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 Bipolar Disorder
- **Intervention (s):**
    - Complementary and integrative health (CIH) and other non-pharmacologic treatments: music therapy; equine therapy; training and caring for service dogs; yoga therapy; tai chi; acupuncture therapy; meditation therapy; outdoor sports therapy; hyperbaric oxygen therapy; accelerated resolution therapy; art therapy; magnetic stimulation therapy; massage; healing touch; therapeutic touch; cannabinoids; chiropractic care
    - Pharmacological treatments: SNRIs (bupropion, mirtazapine, nefazodone, venlafaxine); benzodiazepine; MAOIs; mood stabilizers (lithium, valproate, carbamazepine)
    - Psychological treatments: psychoanalytic/psychodynamic; dialectical behavior therapy; interpersonal and social rhythms therapy; CBT; behavioral activation; family therapy; psychoeducation
- **Outcomes:** quality of life; functional status; patient satisfaction; anxiety; insomnia; pain; manic symptoms; psychotic symptoms; depression; suicide; well-being; substance use
- **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 Bipolar Disorder.
- **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
Meditation	
Chiesa, A., & Serretti, A., 2011	Included in existing SR; Wrong intervention; Wrong population
Chu, C. S. et al., 2018	Wrong intervention
Transcranial Magnetic Stimulation (TMS)	
Donde, C. et al., 2017	Fewer than 20 patients
Mutz, J. et al., 2018	Wrong population
Ravindran, A. V. et al., 2013	Wrong population
Cannabinoids	
Khoury, J. M. et al., 2019	Fewer than 20 patients
Exercise	
Bauer, I. E. et al., 2016	Wrong study design
Mixed CIH	
Jarman, C. N. et al., 2010	Wrong intervention

References

Bauer, I. E., Gálvez, J. F., Hamilton, J. E., Balanzá-Martínez, V., Zunta-Soares, G. B., Soares, J. C., & Meyer, T. D. (2016). Lifestyle interventions targeting dietary habits and exercise in bipolar disorder: a systematic review. *Journal of Psychiatric Research*, *74*, 1–7.

Chiesa, A., & Serretti, A. (2011). Mindfulness based cognitive therapy for psychiatric disorders: a systematic review and meta-analysis. *Psychiatry Research*, *187*(3), 441–53.

Chu, C. S., Stubbs, B., Chen, T. Y., Tang, C. H., Li, D. J., Yang, W. C., ... & Tseng, P. T. (2018). The effectiveness of adjunct mindfulness-based intervention in treatment of bipolar disorder: a systematic review and meta-analysis. *Journal of Affective Disorders*, *225*, 234–45.

Donde, C., Amad, A., Nieto, I., Brunoni, A. R., Neufeld, N. H., Bellivier, F., ... & Geoffroy, P. A. (2017). Transcranial direct-current stimulation (tDCS) for bipolar depression: a systematic review and meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *78*, 123–31.

Jarman, C. N., Perron, B. E., Kilbourne, A. M., & Teh, C. F. (2010). Perceived treatment effectiveness, medication compliance, and complementary and alternative medicine use among veterans with bipolar disorder. *The Journal of Alternative and Complementary Medicine*, *16*(3), 251–55.

Khoury, J. M., Neves, M. D. C. L. D., Roque, M. A. V., Queiroz, D. A. D. B., Correa de Freitas, A. A., de Fátima, Â., ... & Garcia, F. D. (2019). Is there a role for cannabidiol in psychiatry? *The World Journal of Biological Psychiatry*, *20*(2), 101–16.

Mutz, J., Edgcumbe, D. R., Brunoni, A. R., & Fu, C. H. (2018). Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: a systematic

review and meta-analysis of randomized sham-controlled trials. *Neuroscience & Biobehavioral Reviews*, *92*, 291–303.

Ravindran, A. V., & da Silva, T. L. (2013). Complementary and alternative therapies as add-on to pharmacotherapy for mood and anxiety disorders: a systematic review. *Journal of Affective Disorders*, *150*(3), 707–19.

Appendix C

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

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

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

Figure 2. Bubble Plot of Findings for Depression Symptoms

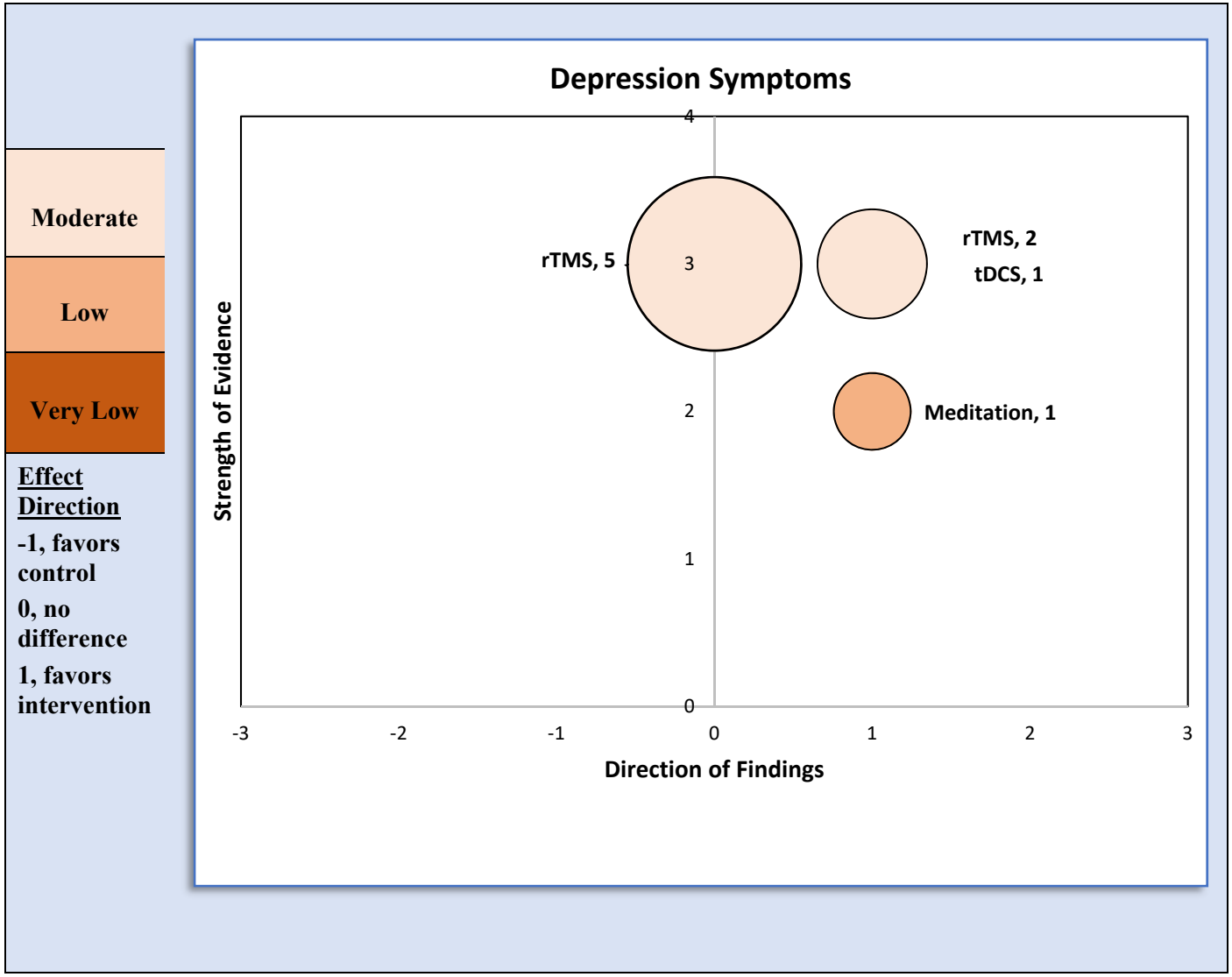

Figure 3. Bubble Plot of Findings for Anxiety Symptoms