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Repetitive Transcranial Magnetic Stimulation in the Treatment of Bipolar Disorder

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***Abstract*:** Bipolar disorder (BD) is a debilitating mood disorder marked by manic, hypomanic and/or mixed or depressive episodes. It affects approximately 1–2% of the population and is linked to high rates of suicide, functional impairment and poorer quality of life. Presently, treatment options for BD are limited. There is a strong evidence base for pharmacological (e.g., lithium) and psychological (e.g., psychoeducation) treatments; however, both of these pose challenges for treatment outcomes (e.g., non-response, side-effects, limited access). Repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique, is a recommended treatment for unipolar depression, but it is unclear whether rTMS is an effective, safe and well tolerated treatment in people with BD. This article reviews the extant literature on the use of rTMS to treat BD across different mood states. We found 34 studies in total ($N = 611$ patients), with most assessing bipolar depression ($n = 26$), *versus* bipolar mania ($n = 5$), mixed state bipolar ($n = 2$) or those not in a current affective episode ($n = 1$). Across all studies, there appears to be a detectable signal of efficacy for rTMS treatment, as most studies report that rTMS treatment reduced bipolar symptoms. Importantly, within the randomised controlled trial (RCT) study designs, most reported that rTMS was not superior to sham in the treatment of bipolar depression. However, these RCTs are based on small samples (NBD $\leqslant 52$). Reported side effects of rTMS in BD include headache, dizziness and sleep problems. Ten studies ($N = 14$ patients) reported cases of affective switching; however, no clear pattern of potential risk factors for affective switching emerged. Future adequately powered, sham-controlled trials are needed to establish the ideal rTMS treatment parameters to help better determine the efficacy of rTMS for the treatment of BD.

Keywords: bipolar disorder, depression, mania, repetitive transcranial magnetic stimulation, rTMS, treatment

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Introduction

Bipolar disorder (BD) is a chronic mood disorder often characterised by fluctuations in mood, energy, activity levels and functioning. Those affected suffer from debilitating, recurrent episodes of depression and (hypo)mania, with some people experiencing both mood episodes at the same time (referred to as mixed states).[1–3] BD affects approximately 1–2% of the population and is associated with significant functional impairment as well as high suicide and relapse rates.[4–8] Pharmacological interventions, including mood stabilisers (e.g., lithium) and atypical antipsychotics (e.g., quetiapine) are the recommended first-line treatments for BD.[9] However, these medications pose challenges for treatment, as they are associated with side effects (e.g., weight gain, metabolic dysregulation, sedation) and high levels (approximately 50%) of nonadherence.[10–13] Further, the use of traditional antidepressants (e.g., selective serotonin reuptake inhibitors) to treat BD depression remains a contentious issue, given the strong clinical concerns that antidepressants cause affective switching into (hypo)mania—now referred to as treatment emergent affective switch (TEAS).[14–16] Generally, the evidence supporting the use of antidepressants in BD is weak and conflicting.[17–20] Although there is growing evidence for the use of

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psychological therapies (e.g., cognitive behavioural therapy, psychoeducation, family interventions) alongside medication,[21] many BD patients fail to respond to these treatments,[22,23] emphasising the need for novel treatment approaches to be developed and tested.

A form of non-invasive brain stimulation, called repetitive transcranial magnetic stimulation (rTMS), has emerged as a potential line of investigation for the treatment of BD. In rTMS, an electromagnetic coil is placed over the patient's scalp, usually targeting the dorsolateral prefrontal cortex (DLPFC) region—an area that has been implicated in the regulation of mood and depression.[24] The coil delivers magnetic pulses that serve to alter neural circuits in the brain by non-invasively depolarising neurons. Different forms of TMS exist (e.g., single-pulse)[25]; however, it is the repetitive nature of these pulses, across short intervals, that distinguishes rTMS from other forms. The repetitive pulses are known to provoke long-lasting changes to the brain,[26] with high-frequency rTMS (>1 Hz) thought to have an excitatory effect, compared with low-frequency rTMS ($\leqslant 1$ Hz), which is thought to have an inhibitory effect on the cerebral cortex.[27] These frequencies can be applied alone or sequentially, either unilaterally or bilaterally. A newer form of rTMS has also emerged, called theta-burst stimulation (TBS). This differs from standard rTMS in that pulses are applied in a pattern known as theta bursts, delivering more stimulation within a shorter time-frame.[28]

rTMS is an effective and well-tolerated intervention in the treatment of unipolar depression [i.e. major depressive disorder (MDD)] in adults,[29] and there is a developing, yet promising, evidence-base for its use in adolescent depression.[30–32] For unipolar depression, it appears that both high-frequency rTMS applied to the left DLPFC (L-DLPFC) and low-frequency rTMS applied to the right DLPFC (R-DLPFC) are the protocols adopted most widely . However, meta-analyses report that high-frequency rTMS applied to the L-DLPFC is the protocol most associated with antidepressant properties (standardised mean difference $=-0.73$, $p<0.00001$).[33] However, it still remains unclear whether: (1) rTMS is an effective treatment for BD; (2) whether it is safe and; (3) especially, whether there is a risk of affective switching.[34]

A previous review on the effectiveness of rTMS in BD concluded that rTMS targeting the R-DLPFC, was effective at reducing symptoms of bipolar depression compared with sham.[18] In that work, the risk of TEAS was observed to be low, suggesting that rTMS is a safe and well-tolerated treatment for bipolar depression.[18] A more recent review by Gold *et al*, evaluated outcomes of rTMS in BD across different mood episodes (e.g, depressive and manic).[35] The authors searched the literature through to October 2018, investigating a variety of TMS procedures including rTMS, as well as deep TMS and conclude that TMS appears to be effective at reducing depressive symptoms.

In this review, we will extend the work by Gold *et al.* by focusing specifically on the use of rTMS in BD to provide an in-depth summary and critical analysis of the evidence to date.[35] We address two key research questions: (1) what is the effectiveness of rTMS in reducing depressive, mixed and manic episodes of BD?; and (2) what is the safety profile of rTMS in the treatment of BD? We also discuss areas for future research and clinical practice implications.

Methods

We searched both PubMed and PsycINFO databases up to June 2020, using the terms 'bipolar disorder' or 'mania' or 'depression' AND 'repetitive transcranial magnetic stimulation' or 'rTMS' or 'TMS' [see Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram]. We also searched ClincalTrials.gov to identify any current ongoing trial studies or completed but unpublished trials. We included any English language, peer-reviewed study [e.g., pre–post intervention, randomised controlled trials (RCTs), naturalistic studies, case series, case reports] that assessed the effects of rTMS in adult BD clinical samples. Case reports/series studies were included to help extract more detailed patient information (e.g., medication history) that may be associated with increased risk of affective switching. Where studies included a mixed sample (e.g., bipolar and unipolar depression), we only included those studies which assessed outcomes for bipolar and unipolar separately. We excluded studies that employed a non rTMS protocol (e.g., deep TMS) (for a summary of these studies see Gold *et al.*).[35] Following the searches, title and abstracts of all returned studies were screened to determine eligibility. Potential eligible studies then underwent full-text review.

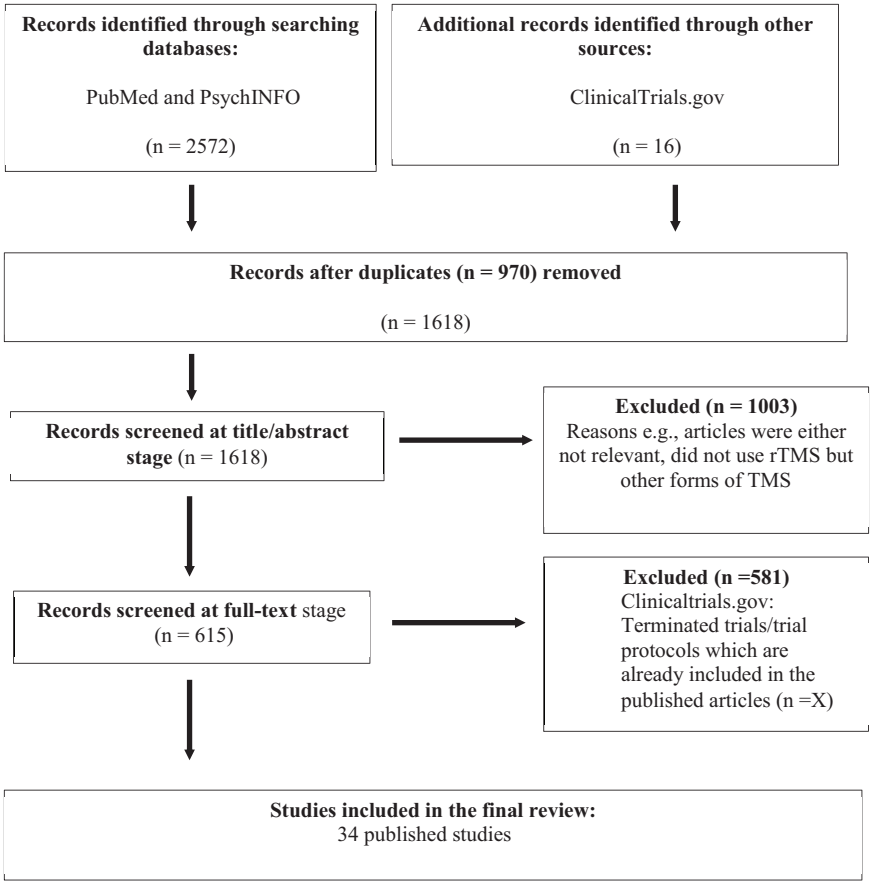

Figure 1. Systematic review process: PRISMA diagram.
PRISMA, preferred reporting items for systematic reviews and meta-analyses; rTMS, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation.

Results

Summary of included studies

The search revealed 34 studies in total, and most were assessing rTMS for bipolar depression ($n=26$; Table 1), but evidence on bipolar mania ($n=5$; Table 2), bipolar mixed states ($n=2$; Table 3) and no active current episode ($n=1$) was also available. The overall mean age range across all studies was 29.76–62.00 years. The most common measure used to assess depressive symptoms was the Hamilton Depression Rating Scale (HAM-D) ($n=16$), followed by the Montgomery-Åsberg Depression Rating Scale (MADRS) ($n=5$), the Beck Depression Inventory (BDI) ($n=3$) and the Quick Inventory of Depressive Symptomology (QIDS) ($n=2$).[36–39] The Young Mania Rating Scale (YMRS) was most often employed to assess manic symptoms ($n=4$).[40]

In the bipolar depression studies, a total of 470 bipolar patients received rTMS (mean age range = 27.40–60.00 years). This literature included case reports ($n=8$), naturalistic studies ($n=3$), open-label trials/follow-up studies ($n=3$), RCTs comparing active treatments ($n=3$) and sham-controlled RCTs ($n=9$). rTMS protocols varied (see Table 1), with most studies employing standard rTMS using high-frequency only ($n=9$), followed by low-frequency only ($n=4$), sequential rTMS (low + high-frequency) ($n=4$), low *versus* high-frequency ($n=3$), TBS ($n=3$) and low *versus* sequential rTMS ($n=2$). One study failed to state the rTMS protocol.[58] Across these studies, there was a total of 32 different active rTMS treatment protocols being investigated with: 12 of these targeting the L-DLPFC alone (similar to the unipolar depression literature), 11 targeting the R-DLPFC, 6 targeting both the R- and L-DLPFC sequentially. Three studies failed to report the target location for stimulation.

Table 1. Summary of bipolar depression studies ($n = 26$).

Study	Sample size (n)	rTMS sessions (n)	rTMS location	rTMS motor threshold (%)	rTMS frequency (Hz)	rTMS protocol	Depression symptom outcomes
Case report/series ($n = 8$)							
Garcia-Toro[41]	1	10	Unknown	90%	High (20 Hz)	30 trains, 2 s duration with a 30 s interval	Symptoms reduced throughout treatment
Dolberg *et al.*[42]	2	20	Unknown	Unknown	High (10 Hz)	20 trains, duration 6 s, with 30 s between each	Not reported
Hausmann *et al.*[43]	1	7	L-DLPFC + R-DLPFC	100% + 120%	High (20 Hz) + Low (1 Hz)	10 trains of 10 s + 20 min of low	Symptoms reduced throughout treatment
Li *et al.*[44]	1	40	L-DLPFC	120%	High (10 Hz)	5 s train and 10 s interval	Symptoms reduced throughout treatment
Zendjidjian *et al.*[45]	1	40	L-DLPFC	120%	High (10 Hz)	5 s train, 25 s interval	Symptoms reduced throughout treatment
Brunelin *et al.*[46]	1	20	L-DLPFC	110%	High (5 Hz)	8 s on and 22 s off, repeated every 30 s	Symptoms reduced after 15 sessions
Huang *et al.*[47]	1	3	L-DLPFC	100%	High (5 Hz)	8 s train, 40 trains per day	Symptoms reduced with three rTMS sessions
Kaster *et al.*[48]	1	12	L-DLPFC	120%	Theta-burst (50 Hz)	2 s on and 8 s off for a total of 600 pulses	Symptoms reduced throughout treatment—up to session 10
Naturalistic studies (n = 3)							
Cohen *et al.*[49]	56	>30	L-DLPFC	<100%	High (20 Hz)	Unclear	rTMS treatment improved symptoms
			R-DLPFC	100%	Low (1 Hz)	Unclear	
Carnell *et al.*[50]	50	18–20	R-DLPFC	110%	Low (1 Hz)	15 min	rTMS treatment improved symptoms
			R-DLPFC	110%	Low (1 Hz)	30 min	
			R-DLPFC + L-DLPFC	110%	High (10 Hz) + Low (1 Hz)	5 s interval with a 25 s intertrain for 15 min + continuous low-frequency rTMS	
Philips *et al.*[51]	17	30	L-DLPFC	120%	High (10 Hz)	3000 pulses per session	rTMS treatment improved symptoms

(Continued)

Table 1. (Continued)

Study	Sample size (*n*)	rTMS sessions (*n*)	rTMS location	rTMS motor threshold (%)	rTMS frequency (Hz)	rTMS protocol	Depression symptom outcomes
Open-label trials (n = 3)							
Dell'Osso *et al.*[52,53]	11	15	R-DLPFC	110%	Low (1 Hz)	300 stimuli per day	Reduction in depression scores from baseline to post treatment
Kazemi *et al.*[54]	20	10	R-DLPFC + LDLPFC	120% + 100%	Low (1 Hz) + High (10 Hz)	10 s train, 2 s interval and 150 pulse trains + 5 s, 10 s interval and 75 pulse trains	Reduction in depression scores from baseline to post treatment
RCTs comparing active treatments (n = 3)							
Fitzgerald *et al.*[55]	25	10–20	R-DLPFC	110%	Low (1 Hz)	15 min, 900 pulses	Significant effect of time on depression scores. 12 patients receiving 2 Hz and 5 patients receiving 1 Hz achieved a clinical response
					Low (2 Hz)	15 min, 1800 pulses	
Dell'Osso *et al.*[56]	19	20	1. R-DLPFC	110%	Low (1 Hz)	Seven trains of 60 s, interspersed by 1 min pause	Significant reduction in HAM-D scores across all diagnostic groups
			2. R-DLPFC	110%	Low (1 Hz)	Continuous 15 min of treatment	
			3. L-DLPFC	80%	High (10 Hz)	15 trains of 5 s, 25 s interval	
Kazemi *et al.*[57]	30	20	1. R-DLPFC	120%	Low (1 Hz)	10 s, 2 s interval, 250 trains	Both groups demonstrated a reduction in depression symptoms from pre to post. No significant between group differences.
			2. R-DLPFC + L-DLPFC	100%	Low (1 Hz) + High (10 Hz)	10 s, 2 s interval, 150 trains + 5 s, 10 s interval, 75 trains	
Sham-controlled RCTs (n = 9)							
Dolberg *et al.*[58]	20	20	Not stated	Not stated	Not stated	Not stated	rTMS group demonstrated significant improvement in depression symptoms
Nahas *et al.*[59]	23	10	L-DLPFC	110%	High (5 Hz)	8 s on, 22 s off, over 20 min	No significant differences between groups for depression symptoms

(Continued)

Table 1. (Continued)

Study	Sample size (*n*)	rTMS sessions (*n*)	rTMS location	rTMS motor threshold (%)	rTMS frequency (Hz)	rTMS protocol	Depression symptom outcomes
Fitzgerald *et al.*[60]	8	10+	R-DLPFC + L-DLPFC	110% + 100%	Low (1 Hz) + High (10 Hz)	Three trains, 140 s, 30 s interval + 15 trains, 5 s duration, 25 s interval	Some evidence that rTMS had an effect: 2/4 patients in the sequential rTMS group showed improvements, compared with 1/4 in the sham
Tamas *et al.*[61]	5	8	R-DLPFC	95%	Low (1 Hz)	100 consecutive stimuli	rTMS group showed greater symptom improvement compared with sham, but there was no significant group differences in depression scores throughout the first 4-weeks of treatment
Beynel *et al.*[62]	12	10+	L-DLPFC	80%	Theta-burst (50 Hz)	Applied twice a day, 5 days a week for 1–3 weeks. 2 s train of bursts, 3 pulses at 50 Hz was repeated at 200 ms every 10 s	A reduction in symptoms noted in both groups, but no difference between sham or TBS group post-treatment
Hu *et al.*[63]	38	20	1. L-DLPFC	80%	High (10 Hz)	30 trains, 4 s stimulation, 12 s off	No significant difference in depression scores over the trial, across the three groups
			2. R-DLPFC	80%	Low (1 Hz)	120 trains, 10 s stimulation, 2 s off	
Fitzgerald *et al.*[64]	49	20	R-DLPFC + L-DLPFC	110% + 110%	Low (1 Hz) + High (10 Hz)	1000 pulses + 20 trains, 5 s duration with 25 s interval	Results showed that both groups reported a significant reduction in depression symptoms over time. However, there were no significant between group differences in depression scores found
Yang *et al.*[65]	52	10	L-DLPFC	110%	High (10 Hz)	5 s, 30 s intervals	No significant improvement in symptoms were found for the active rTMS *versus* sham
Bulteau *et al.*[66]	26	30	L-DLPFC	80%	TBS (50 Hz)	iTBS applied twice daily with a 3-h interval. 990 pulses per session, 2 s train containing 3 pulses at 50 Hz	Both groups demonstrated a reduction in symptoms over time, but no significant differences in depression scores or the number of patients who achieved remission, were found between active TBS and sham

iTBS, intermittent theta-burst stimulation; L-DLPFC, left dorsolateral prefrontal cortex; R-DLPFC, dorsolateral prefrontal cortex; TBS, theta-burst stimulation; rTMS, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation.

Table 2. Study of bipolar mania studies ($n = 5$).

Study	Sample size (n)	rTMS sessions (n)	rTMS location	rTMS motor threshold (%)	rTMS frequency (Hz)	rTMS protocol	Manic symptom outcomes
Open-label trials (n = 2)							
Michael and Erufurth[67]	9	16	L-DLPFC	80%	High (20 Hz)	20 trains, 2 s per train, interval of 1 min	Symptoms reduced from baseline to treatment end
Saba *et al.*[68]	8	10	R-DLPFC	80%	High (10 Hz)	Trains of 15 s, with 20 s interval	Symptoms reduced from baseline to treatment end
RCTs comparing active treatments (n = 1)							
Grisaru *et al.*[69]	16	10	R-DLPFC	80%	High (20 Hz)	20 trains, 2 s per train and 1 min interval	Significant improvement in symptoms in the right-sided rTMS group
			L-DLPFC	80%	High (20 Hz)	20 trains, 2 s per train and 1 min interval	
Sham-controlled RCTs (n = 2)							
Kaptsan *et al.*[70]	19	10	L-DLPFC	80%	High (20 Hz)	20 trains, 2 s per train, 1 min interval	No significant difference between groups
Praharaj *et al.*[71]	41	10	R-DLPFC	110%	High (20 Hz)	20 trains, 2 s train, 10 s interval	A greater improvement in symptoms for the active rTMS *versus* sham

L-DLPFC, left dorsolateral prefrontal cortex; R-DLPFC, dorsolateral prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation.

For bipolar mania, five studies were found (see Table 2), which included a total of 93 bipolar patients (mean age range = 29.76–62.00 years). These studies included open-label trials ($n = 2$), RCTs comparing active treatments ($n = 1$) and sham-controlled RCTs ($n = 2$). All studies investigated high-frequency rTMS (10–20 Hz) and, unlike the results for bipolar depression, more of the mania studies targeted the R-DLPPFC (R-DLPFC only $n = 2$; both L- and R-DLPFC separately $n = 1$; L-DLPFC only $n = 2$). No studies investigated sequential rTMS.

For bipolar mixed states, two studies ($N = 42$; mean age range 44.90–52.00 years) were found (see Table 3). The case report investigated high-frequency rTMS applied to the L-DLPFC, whereas the open-label trial investigated low-frequency rTMS applied to the R-DLPFC.

Finally, one case series study by Li *et al.* investigated whether rTMS could be used as a maintenance treatment in BD.[74] Here, seven patients who had responded to rTMS, received weekly rTMS sessions for more than 1 year (thus, at the time of treatment they were not currently in an active depressive or manic episode). This study applied high-frequency rTMS to the L-DLPFC.

Evidence for the use of rTMS for treating bipolar depression

Case reports/series

Most case reports/series investigated the effects of high-frequency rTMS,[41,42,44–48] with all but one reporting that rTMS helped to reduce patients' depression symptoms.[42] Some ($n = 2$)

Table 3. Study of bipolar mixed states ($n = 2$).

Study	Sample size (n)	rTMS sessions (n)	rTMS location	rTMS motor threshold (%)	rTMS frequency (Hz)	rTMS protocol	Depression and/or manic symptom outcomes
Case reports/series (n = 1)							
Zeeuws *et al.*[72]	1	20	L-DLPFC	120%	High (20 Hz)	Unknown	Symptoms reduced throughout treatment
Open-label trials (n = 1)							
Pallanti *et al.*[73]	40	15	R-DLPFC	110% intensity	Low (1 Hz)	140 s trains, 30 s interval	Both depression and mania symptoms reduced throughout treatment

L-DLPFC, left dorsolateral prefrontal cortex; R-DLPFC, dorsolateral prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation.

of these studies highlight the risk of affective switching in bipolar patients (for a detailed outline see the results section '*What is the safety profile of rTMS in BD?*'). Only one case report investigated sequential rTMS,[43] reporting a reduction in depression symptoms after seven sessions of rTMS, but also a manic switch. More recently, Kaster *et al.* reported the beneficial effects of TBS at reducing depression symptoms following 10 sessions in one patient, but again there was a reported manic switch.[48]

Naturalistic studies

Cohen *et al.* investigated pred.[49] Authors report that age, refractoriness, baseline depression severity and number of prior depressive episodes were all associated with a need for a longer duration of rTMS treatment.

Using data ($N = 240$, BD = 50) from an Australian private rTMS clinic comparing treatment responses by diagnostic group, Carnell *et al.* examined an rTMS treatment response among a mixed sample of unipolar and bipolar depression.[50] Participants received one of three rTMS protocols (see Table 1), each employing the '5 cm rule' to target the prefrontal cortex. All patients completed 18–20 treatment sessions over 4–6 weeks (for specific details of the methods used for this data see Galletly *et al.*).[75,76] Results showed that all patients demonstrated an improvement in depression symptoms (HAM-D) from baseline to post treatment [bipolar sample baseline mean (M) = 20.26, standard deviation (SD) = 5.97 *versus* post treatment M = 12.38, SD = 7.31]. Further, 17/50 bipolar patients met treatment response criteria (>50% reduction in HAM-D) and 13/50 met remission criteria (post-treatment HAM-D score of ⩽7).

A second naturalistic study conducted by Philips *et al.* analysed patient records of those who had been treated with rTMS (>30 sessions) for either treatment-resistant unipolar ($n = 54$) or bipolar ($n = 17$) depression.[51] The main outcome here was the QIDS, which was assessed at baseline and after every five treatment sessions and post intervention. Both unipolar and bipolar patients demonstrated an equal response (>50% reduction in QIDS scores) over the 30 treatment sessions, with 11/17 (65%) of bipolar patients specifically. Remission (QIDS score ⩽5) was also achieved equally in both groups, with 6/17 (35%) bipolar patients. Overall, bipolar patients' mean depression scores significantly reduced from baseline to post treatment.

Open-label trials

One 3-week open-label trial examined the effectiveness of low-frequency rTMS.[52] This was also the first open-label rTMS trial to adopt the use of neuro-navigation techniques [magnetic resonance imaging (MRI)] to target the R-DLPFC, as earlier RCT trials had adopted the '5 cm rule' for example Fitzgerald *et al.* and Nahas *et al.*[55,59] Depression measures included the HAM-D and MADRS, which were assessed at baseline and after each week of treatment (time 1, 2, 3). All patients ($N = 11$) completed the trial. Results showed a significant reduction in HAM-D scores from baseline to time 2 (mean difference = −6.9) and in MADRS scores from baseline to time 3

(mean difference = −10.1). This cohort of participants was then followed prospectively up to 1 year later in a second study, to determine the long-term effects of rTMS treatment.[53] They found that four patients had maintained symptomatic improvement at the 1-year follow up.

The first open-label bipolar depression trial to investigate sequential bilateral (low and high-frequency).[54] All patients received 10 sessions of bilateral rTMS and depression symptoms, as measured *via* the BDI, were measured at baseline and treatment end. Authors found a significant reduction in depression scores from pre (M = 30.15, SD = 10.05) to post (M = 15.25, SD = 8.37) treatment, $p < 0.0001$.

RCTs comparing active treatments

One study explored two different forms of low-frequency rTMS (1 Hz *versus* 2 Hz) in a mixed sample (MDD $n = 105$, BD $n = 52$).[55] Patients were also offered an additional 2 weeks of treatment (10 sessions) if they demonstrated a treatment response following the first 10 sessions (defined as >20% reduction in HAM-D scores). After 4 weeks of treatment, 12/13 BD patients in the 2 Hz group and 5/12 patients in the 1 Hz group achieved remission.

Dell'Osso *et al.* were the first to examine the effectiveness of both low *versus* high-frequency rTMS applied to both the R- and L-DLPFC, respectively.[56] This randomised 4-week trial used a mixed sample of unipolar ($n = 14$) and bipolar ($n = 19$) patients, who were assigned randomly to receive one of three rTMS protocols (see Table 1). Depression symptoms significantly reduced for all patients over 4 weeks, irrespective of rTMS protocol or diagnostic group.

The effects of bilateral *versus* unilateral rTMS stimulation was explored by Kazemi *et al.*[57] They investigated the use of beta wave activity [*via* electroencephalography (EEG)] to understand whether it correlated with depression symptoms throughout rTMS treatment. Results showed a significant difference in treatment responses (BDI > 50% reduction from baseline) between the bilateral (12/15 patients) and the unilateral (7/15 patients), $p < 0.005$, but no differences in remission (BDI < 8 post-treatment) or response were found (bilateral = 6/15 *versus* unilateral 6/15, $p > 1.00$). Lastly, changes in BDI scores were compared at baseline and post treatment for both groups; however, no significant differences were found.

Sham-controlled RCTs

Dolberg *et al.* conducted the first RCT (double-blind) with an exclusive sample of bipolar patients experiencing a depressive episode ($N = 20$).[58] This study found that patients in the active rTMS group had significantly lower depression scores at treatment end (M = 15.7, SD = 4.80), compared with the sham (M = 21.3, SD = 5.3) ($p < 0.05$). However, the type of rTMS or sham condition is not described and sample size was small.

Following this work, Nahas *et al.* conducted a separate RCT focusing on high-frequency (5 Hz) rTMS.[59] Although the rTMS treatment appeared to be well tolerated by patients (i.e. no withdrawals or reported adverse cognitive effects), the authors found no significant differences in the number of treatment responders between groups (4/11 in the active rTMS group and 4/12 in the sham). The mean percentage change for HAM-D scores from baseline to treatment end did not differ significantly between groups ($p = 0.83$).

Fitzgerald *et al.* conducted an RCT, whereby a mixed sample of unipolar depression ($n = 42$) and bipolar patients ($n = 8$) were recruited.[60] Clinical response was defined as a 50% reduction in MADRS scores and, for the bipolar sample, there was some evidence that the rTMS treatment had a beneficial effect at reducing depression scores, as 2/4 rTMS patient's *versus* 1/4 sham patients demonstrated a treatment response.

Adopting a slightly different rTMS protocol, Tamas *et al.* assigned participants to receive either low intensity (1 Hz) rTMS applied to the R-DLPFC ($n = 4$) or sham rTMS ($n = 1$),[61] with treatments scheduled twice a week for 4 weeks. Outcomes were assessed *via* the HAM-D and the YMRS. Compared with sham, at the end of treatment, those who received active rTMS demonstrated significantly fewer depression symptoms. Notably, contrary to Dolberg *et al.*,[58] improvement in depression symptoms was found only at 2 weeks post treatment.

Beynel *et al.* investigated TBS in a 3-week pilot study and randomly assigned patients to either intermittent TBS (iTBS) ($n = 5$) or sham ($n = 7$).[62] Here, following treatment, 4/5 patients from the active rTMS group *versus* 4/7 from the sham met

clinical response criteria (>50% reduction in MADRS scores). However, analysis of post-treatment MDRS between groups showed no significant difference ($p=0.92$), nor was there any significant difference in the improvement of MDRS scores between groups (active rTMS improvement score M=60.00, SD=18.00 *versus* sham improvement score M=56.00, SD=29.00), $p=0.81$.

Hu *et al.* examined the effectiveness of rTMS in bipolar patients who were also taking quetiapine medication.[63] This 4-week trial examined the clinical efficacy of rTMS (i.e., on reducing depression symptoms) as well as the cognitive functioning of patients following treatment. The authors found that active rTMS (both low and high-frequency) alongside quetiapine was no more effective at reducing depression symptoms compared with the quetiapine sham stimulation condition. Further, there were no statistically significant differences in cognitive outcomes across the three groups, either before or after rTMS treatment.

In an RCT ($N=49$), Fitzgerald *et al.* investigated sequential rTMS (low and high-frequency stimulation) *versus* sham and found that both groups reported a significant reduction in depression symptoms over time ($F=15.00$, $p<0.001$), with no differences in scores by treatment group.[64] Further, there were no significant differences in the mean reduction of HAM-D scores between the active (M=21.30, SD=30.0%) *versus* sham (M=15.00, SD=21.70%) groups, $p>0.005$, and neither was there any significant difference in the number of patients meeting response/remission criteria (p's >0.05).

Yang *et al.* have conducted the largest (published) bipolar depression rTMS trial to date.[65] This RCT recruited BD patients who had at least 3 months of clinical remission before randomisation. The main outcome measures were cognitive functioning, as measured *via* the MATRICS Consensus Cognitive Battery (MCCB), and clinical symptoms (e.g. depression/mania) measured *via* a modified version of the HAM-D (24-item) and the YMRS. These were assessed at baseline and at follow up (2 weeks after the last rTMS treatment). There were no significant differences in HAM-D or YMRS scores between groups at follow up ($p>0.42$). However, the data did show that rTMS improved cognitive functioning, specifically the Spatial Span and Category Fluency items on the MCCB.

Another recent TBS study was conducted by Bulteau *et al.*[66] This 3-week trial investigated the efficacy of intermittent TBS (iTBS) ($n=12$) *versus* sham ($n=14$), with the number of patients entering remission (BDI score <10) at treatment end as the primary outcome. Patients from both the active iTBS treatment group ($n=7/12$) and the sham ($n=5/14$) achieved remission response post intervention, with no significant difference between treatment groups found ($p=0.43$).

Evidence for the use of rTMS for treating bipolar mania

Open-label trials

The two open-label trials found both investigated high-frequency rTMS. Michael and Erfurth's 4-week trial reported that manic symptoms – assessed *via* the Bech-Rafaelsen Mania Scale – significantly reduced post treatment (M=6.90, SD=6.81), compared with baseline (M=22.22, SD=5.90. Most (8/9) patients were also taking psychotropic medication.[67,77] Similarly, Saba *et al.* found that manic symptoms improved from baseline (M=23.25, SD=6.67) to treatment end (M=11.00, SD=4.7), $p=0.02$ (10 sessions).[68] In this study, all patients were taking psychotropic medication during rTMS treatment.

RCTs comparing active treatments

Grisaru *et al.* were the first to investigate rTMS for manic symptoms in BD.[69] After 2 weeks of treatment, patients who had rTMS applied to the L-DLPFC, *versus* R-DLPFC, demonstrated a significant improvement in manic symptoms from baseline to post treatment.

Sham-controlled RCTs

The first sham-controlled RCT for rTMS in the treatment of mania showed that both the active rTMS and sham groups reported significant improvements in manic symptoms over time.[70] However, no significant main effect for treatment group, or time × treatment interaction effect was found (Fs <0.8, p values >0.5). The authors propose that this could be due to the illness severity of patients in this sample (noted to be more severe compared with the results of Grisaru *et al.*) or that a more intensive (e.g. greater duration) treatment is possibly required to target symptoms of mania.[69]

The largest study to date to assess rTMS for the treatment of manic symptoms was conducted by

Praharaj *et al.*[71] Results revealed a significant treatment × time interaction effect ($F = 12.95$, $p < 0.001$, eta squared = 0.25), demonstrating significant differences between groups at post treatment (day 10), with lower manic symptoms in the active rTMS group (M = 5.76, SD = 3.26) *versus* the sham (M = 11.05, SD = 6.86).

Evidence for the use of rTMS for treating mixed state bipolar

Case reports/series

Zeeuws *et al.* report a 52-year old woman who had previously tried, and been resistant to, electroconvulsive therapy (ECT).[72] She was treated with 20 sessions high-frequency rTMS and demonstrated a significant decreased in depression symptoms from baseline to post treatment (i.e. 50% reduction in HAM-D scores).

Open-label trials

Pallanti *et al.* conducted a 4-week trial whereby low-frequency rTMS was applied to the R-DLPFC to all patients.[73] Analysis of both HAM-D and YMRS showed a significant main effect of time, with significant differences found between baseline and after 10 (p's < 0.05) and 15 stimulations (p's < 0.01).

Evidence for the use of rTMS for treating bipolar (no current mood episode)

Case reports/series

Only one study investigated the effectiveness of rTMS as a maintenance treatment in BD patients not currently in a mood episode.[74] Responders ($n = 7$) from a previous trial were offered maintenance rTMS for up to 1 year.[59] Out of seven patients, three completed a full 1 year of weekly rTMS treatment and demonstrated an average HAM-D score of 13 (SD = 5.9).

Current ongoing trials

A search of ClinicalTrials.gov revealed 16 registered trials, of which 9 were excluded as they were either terminated, not relevant to this review or the trial status was unknown; this left 7 trials ($n = 6$ completed trials and $n = 1$ ongoing trial).

From the completed trials ($n = 6$), only one was published and already included in this review and the rest appeared to be completed, but unpublished, studies.[52] Two completed studies – both open-label trials–reported results: one looked at the effectiveness of low-frequency (1 Hz) rTMS applied to the R-DLPFC in treatment resistant bipolar depression ($N = 28$). The results suggest that the rTMS reduced depressive symptoms in this sample [ClinicalTrials.gov identifier: NCT00186485]. Another open-label trial investigated a 3-week intervention of high-frequency rTMS for bipolar depression ($N = 15$), with results suggesting that rTMS reduced depressive symptoms [ClinicalTrials.gov identifier: NCT00699218]. Other completed studies included a randomised study comparing bilateral high-frequency rTMS *versus* unilateral low-frequency rTMS [ClinicalTrials.gov identifier: NCT01932749] and two RCTs: (1) investigating theta-burst stimulation *versus* sham in bipolar depression [ClinicalTrials.gov identifier: NCT00186758] and (2) investigating rTMS *versus* sham on depression, mania and cognitive functioning outcomes [ClinicalTrials.gov identifier: NCT03207048].

The search revealed one ongoing study that relevant to this review [ClinicalTrials.gov identifier: NCT02749006] that is being conducted in Canada. This randomised double-blind study plans to investigate the effects of TBS *versus* sham on depressive symptoms in an acute bipolar sample ($N = 100$). Primary outcome measure is depressive symptoms as measured *via* the MADRS, and secondary outcomes include manic symptoms, cognitive functioning and quality of life ratings.

What is the safety profile of rTMS in BD?

Table 4 outlines the reported side effects and risk of induced mania found from the included studies. A total of 19 studies reported that patients experienced no side effects. However, from the studies that did report side effects, these included: headache, scalp pain, sleep problems (e.g. insomnia), dizziness, nausea, fatigue and anxiety. Notably, induced seizure from rTMS treatment was not reported in any of these studies. In studies that utilised one active rTMS treatment arm, it is clear that headache and scalp pain are two side effects reported across different all rTMS protocols (i.e. both high and low-frequency applied to L- and R-DLPFC. Interestingly, the two TBS trial studies both reported no side effects.[62,66]

A total of 10 studies ($n = 5$ case series/reports, $n = 5$ trial studies) reported instances of affective switching (see Tables 4 and 5). Focusing on these 10 studies, we extracted information on

Table 4. Summary of reported side effects across all studies (*N* = 34).

Study	Headache	Scalp pain	Nausea	Fatigue	Sleep problems	Dizziness	Anxiety	Patients reported none of these side effects	Side effects not reported	Frequency of sample whom reported side effects	Did active rTMS induce affective switching in any of the sample? (yes/no/not reported)
Grisaru *et al.*[69]								✓		N/A	No
Garcia-Toro[41]								✓		N/A	Yes
Dolberg *et al.*[58]								✓		N/A	Not reported
Dolberg *et al.*[42]					✓					1/2 (50%)	Yes
Nahas *et al.*[59]								✓		N/A	No
Kaptsan *et al.*[70]	✓									1/19 (5.26%)	No
Michael and Erufurth[67]								✓		Unclear. Article reports there were 'little subjective side effects'	No
Saba *et al.*[68]								✓		N/A	No
Hausmann *et al.*[43]								✓		N/A	Yes
Li *et al.*[74]								✓		N/A	No
Fitzgerald *et al.*[55]								✓		Unclear. Article reports there were 'no significant adverse events'	Yes
Fitzgerald *et al.*[60]	✓		✓							8/25 (active group) however, it is unclear whether these were BD patients or unipolar	No
Tamas *et al.*[61]	✓			✓	✓[a]	✓				Frequency information not reported	No
Praharaj *et al.*[71]	✓					✓	✓			Frequency information not reported	Yes
Dell'Osso *et al.*[52,53]	✓				✓[b]					3/11 (27.27%)	No
Brunelin *et al.*[46]								✓		N/A	No
Cohen *et al.*[49]	✓				✓					11/56 (19.64%)	Yes
Zeeuws *et al.*[72]								✓		N/A	No

(Continued)

Table 4. (Continued)

Study	Headache	Scalp pain	Nausea	Fatigue	Sleep problems	Dizziness	Anxiety	Patients reported none of these side effects	Side effects not reported	Frequency of sample whom reported side effects	Did active rTMS induce affective switching in any of the sample? (yes/no/not reported)
Li *et al.*[44]								✓		N/A	Not reported
Beynel *et al.*[62]								✓		N/A	Not reported
Pallanti *et al.*[73]	✓	✓			✓[b]					5/40 (12.5%)	No
Huang *et al.*[47]								✓		N/A	Yes
Zendjidjian *et al.*[45]								✓		N/A	No
Dell'Osso *et al.*[56]	✓	✓			✓[b]					7/29 however, it is unclear whether these were BD patients or unipolar	Yes
Hu *et al.*[63]	✓									Three patients (one from each protocol) withdrew from the study due to headaches	Yes
Fitzgerald *et al.*[64]								✓		N/A	Not reported
Carnell *et al.*[50]	✓	✓		✓						Frequency information not reported[c]	No
Kazemi *et al.*[57]								✓		N/A	No
Kazemi *et al.*[54]								✓		N/A	Not reported
Yang *et al.*[65]					✓[b]	✓				4/52 (7.69%)	No
Bulteau *et al.*[66]								✓		N/A	No
Philips *et al.*[51]		✓								Frequency information not reported	Not reported
Kaster *et al.*[48]					✓					1/1 (100%)	Yes

[a]Defined as 'sleep disturbances'.
[b]Defined as insomnia.
[c]Reported side effects are documented in Galletly *et al.*[76]
BD, bipolar disorder; rTMS, repetitive transcranial magnetic stimulation.

Table 5. Themes for reported risk of induced switching ($n = 10$).

Study	% of sample reported to experience affective switching	Type of affective switching	rTMS frequency	Number of rTMS sessions before affective switch	Baseline depression severity information	Concurrent medication during rTMS treatment			
						Antidepressants	Antipsychotics	Anticonvulsants	Mood stabilisers
Garcia-Toro[41]	100% (1/1)	Manic	High (20 Hz)	1	Baseline HAM-D: 31		✓	✓	
Dolberg *et al.*[42]	100% (2/2)	Manic	High (10 Hz)	Patient 1: 15	Patient 1: 15-year history of BD			✓	
				Patient 2: 20	Patient 2: one depressive episode 15 years prior				
Hausmann *et al.*[43]	100% (1/1)	Manic	High (20 Hz) + Low (1 Hz)	7	Baseline HAM-D: 23	✓			
Fitzgerald *et al.*[55]	One patient a developed hypomanic episode soon after phase I (but doesn't specify whether this was a BD or MDD patient)	Hypomanic	Unclear—either low 1 Hz *versus* 2 Hz	10	Not stated	✓[a]			✓[a]
Praharaj *et al.*[71]	(1/41) 2.43%	Depression	High (20 Hz)	10	Not stated	Patients in the trial were drug free for at least 2 months			
Cohen *et al.*[49]	4/56 (7.14%)	Hypomanic	Unclear whether they received low (1 Hz) or high (20 Hz)	Not stated	Not stated	Not stated	Not stated	Not stated	
Huang *et al.*[47]	1/1 (100%)	Manic	High (5 Hz)	3	Baseline HAM-D: 22	✓		✓	
Dell'Osso *et al.*[56]	1/19 (5.26%)	Manic	Low (1 Hz)	10	Not stated	Not stated	Not stated	Not stated	
Hu *et al.*[63]	1/38 (2.63%)	Manic	High (10 Hz)	15			✓		
Kaster *et al.*[48]	1/1 (100%)	Manic (with psychosis)	Theta (50 Hz)	12	Three prior episodes of mania with psychosis		✓	✓	

[a]Unclear if the patient who experienced switching was on these medications during the treatment, but article reports that most patients were taking these alongside treatment.
BD, bipolar disorder; HAM-D, Hamilton depression rating scale; MDD, major depressive disorder; rTMS, repetitive transcranial magnetic stimulation.

potential risk factors to affective switching across the studies (see Table 5). From this data, it is clear that affective switching was not only limited to patients whom were also taking antidepressants, as previously suggested,[78] but it has also occurred in patients taking antipsychotic and anticonvulsant medication also. From the studies that report affective switching, most employed high-frequency rTMS protocols (including TBS) ($n = 6$), *versus* low-frequency ($n = 2$), sequential low *versus* high ($n = 1$) and one where the protocol was unclear. Based on the limited available evidence, it appeared that the number of rTMS sessions conducted before evidence of affective switching emerged ranged from 1 to 15 ($M = 10.30$, $SD = 5.70$, median = 10) and those who did experience affective switching had a long history of depression and/or high current depressive symptoms.

Discussion

Effectiveness of rTMS to treat BD

When reviewing the naturalistic studies, open-label trials and randomised studies, there appears to be a detectable signal of efficacy for rTMS treatment, as all of these studies report that rTMS treatment reduced symptoms of depression to varying extents. However, the extent to which evidence from RCTs support the efficacy of rTMS is unclear. Out of the nine sham-controlled RCTs investigating rTMS in bipolar depression, three reported that rTMS was superior to sham.[58,60,61] However, all three studies are limited by their low sample sizes ($n < 20$). Specifically, in Tamas *et al.* there was only one patient allocated to the sham condition and Dolberg *et al.* fail to report the type of rTMS treatment used.[58,61] This is in contrast to the evidence of RCTs within unipolar depression literature, and is consistent with the view that bipolar depression and unipolar depression may require different paradigms for treatment. For instance, in the unipolar depression literature, double-blind RCTs (sham-controlled) of low-frequency rTMS have shown that rTMS was superior to sham.[79] Similarly, the meta-analysis by Gaynes *et al.* evaluated the efficacy of rTMS in treatment-resistant depression[80]; they assessed sham-controlled trials and concluded that rTMS produced meaningful reductions in depression symptoms compared with sham.

It is worth noting that the type of sham treatment used in these studies also varies. Three studies failed to report details on the sham,[58,61,66] whereas in others, the sham involved similar stimulation parameters to the active rTMS treatment but where the coil was angled away from the head (e.g. 45 degrees).[59,60,63,64] This is thought to produce a weak degree of stimulation and to produce a similar sensation on the scalp as the active treatment. However, Yang *et al.* were the only study to employ a false coil sham, but using the same procedure, possibly representing the optimal sham design.[65]

For the bipolar mania studies there was two RCTs and only one reported that rTMS was superior to sham,[71] suggesting that high-frequency rTMS may be effective at reducing manic symptoms; however, further RCTs, with larger samples, are needed before firm conclusions can be drawn. In terms of the sham conditions adopted, both studies utilised a sham that tilted the coil at an angle (e.g. 45 degrees).

Safety profile of rTMS in bipolar disorder

Based on our included studies, the reported side effects found (not including affective switching) are similar to those documented in the rTMS unipolar depression studies.[81] These are generally considered to be 'mild' and known to subside throughout treatment. Risk of seizure is a serious adverse effect documented in the unipolar depression literature,[81,82] but the current review found no evidence for this in existing BD studies.

Based on the included studies, risk of affective mania switching was low, similar to previous reviews.[34] However, detailed information on the cases who did switch was lacking, thus it remains unclear what the predictors of affective switching are. Early BD case reports were the first to document affective switching within rTMS treatment,[42] and previous reviews have investigated this topic. For example, Xia *et al.* reported rates of affective switching among unipolar ($n = 455$) *versus* bipolar depressed patients ($n = 65$) and found risk to be higher among the bipolar (3.1%) *versus* the unipolar sample (0.34%)[34] Another review conducted by Rachid searched the literature for published studies (from 1966 to 2015) documenting treatment-emergent mania during rTMS treatment[78]; 19 patients, diagnosed with either unipolar or bipolar depression, were found to have experienced treatment-emergent mania during rTMS treatment. The author concludes that rTMS in monotherapy, or alongside antidepressant medication, could possibly induce

(hypo)manic episodes, with both high- and low-frequency rTMS demonstrating and association with induced mania. They recommend that BD patients undergoing rTMS treatment also be prescribed a mood stabiliser to combat help combat the risk of induced mania.

In the current review, we note that patients who were taking other types of medication (e.g. antipsychotics/anticonvulsants) were also known to experience affective switching, suggesting that it is not just those who are also taking antidepressant medication who are at risk. Out of the 10 studies that reported affective switching (patients $N=14$), 50% (7/14) received high-frequency rTMS, 14.29% (2/14) received low-frequency rTMS, 7.14% (1/14) received both high and low-frequency (sequential) rTMS and in 28.57% (4/14) the exact rTMS protocol for those whom switched was unclear (either high 20 Hz or Low 1 Hz).[49] Most of these switches were found among case series/report studies ($N=5$), followed by uncontrolled studies ($N=3$, e.g. randomised studies/naturalistic studies) and sham-controlled RCTs ($N=2$). However, due to the limited patient information available on those who experience affective switching, it is still unclear whether these variables pose significant risk factors. We do not fully understand the rate of affective switch, but it looks to be uncommon or rare. In order to design a trial to detect a very small difference between groups (rTMS *versus* treatment as usual or sham control), and allowing for the rate of baseline affective switch associated with mood disorders in general, it is likely to require a very large sample size within an RCT design. We would suggest more data are needed from observational (and controlled) studies to understand the affective switch rate, and what factors are associated with switch before an RCT could be designed to fully understand the risk of affective switch.

Future research and clinical practice guidance

Based on the reviewed evidence, we make several recommendations for future research. First, one limitation of the included studies is that they all have small samples ($<N=52$), thus, adequately powered, sham-controlled RCTs are necessary to determine the efficacy of rTMS in the treatment of BD. Given the current evidence, and therapeutic need, these RCTs should focus on the treatment of bipolar depression currently. Second, future work might also seek to employ more TBS protocols instead of standard rTMS, given its potential for greater treatment efficiency, reduction in participant burden and associated treatment costs. Third, we note many studies reported a lack of any side effects of the treatment. It is unclear whether these represent an omission to collect the data or some other form of bias, but it is unlikely that any effective treatment will not have any side effects, given the side effect burden in even placebo conditions. Fourth, research on the use of rTMS in the treatment of manic symptoms and those with mixed states BD, is still in its infancy. Future RCTs are necessary to understand how effective rTMS is, but also which protocols are best suited for this affective state; this remains unclear (e.g. low *versus* high-frequency, rTMS applied to the L- *versus* R-DLPFC). Fifth, there is a strong clinical need to better understand those at risk of affective switching following rTMS treatment. Future research trials should offer detailed information on the patients who do experience induced mania from treatment. Specific details such as the types of medications currently prescribed, previous number of manic episodes and descriptions of depressive and/or manic symptoms are critical and would be an important step to help guide clinical decision making. Similarly, more information on patients who demonstrate a response (i.e. significant reduction in symptoms) from RCT trials would be important, especially in the context of an adequately powered RCT. For instance, in unipolar depression, predictors of rTMS treatment response cover a range of neurobiological (e.g. hormonal), neuroimaging (e.g. higher baseline metabolic activity) and treatment parameter (e.g. number of pulses) factors.[83] Lastly, the mechanisms behind rTMS treatment remain largely unclear. A recent review of the potential mechanisms of rTMS unipolar depression has been conducted,[84] but whether these apply to bipolar depression and mania is unknown and remains a future research priority.

Conclusion

There is growing interest in the use of rTMS as a treatment for BD, with studies separately investigating the effects of rTMS on both depressive and manic symptoms. Based on the literature to date, there appears to be a possible signal of efficacy for rTMS in treating bipolar depression and mania. However, when compared with sham treatments, most RCTs reported no significant differences in symptoms, but there is a lack of any adequately

powered trial. There is also a crucial need to establish the ideal rTMS treatment parameters to help better determine the efficacy of rTMS in the treatment of BD.

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References

1. Goodwin FK and Jamison KR. *Manic-depressive illness: bipolar disorders and recurrent depression*. New York: Oxford University Press, 2007.
2. Strejilevich S, Martino DJ, Murru A, *et al.* Mood instability and functional recovery in bipolar disorders. *Acta Psychiatr Scand* 2013; 128: 194–202.
3. Rowland TA and Marwaha S. Epidemiology and risk factors for bipolar disorder. *Ther Adv Psychopharmacol* 2018; 8: 251–269.
4. Pini S, de Queiroz V, Pagnin D, *et al.* Prevalence and burden of bipolar disorders in European countries. *Eur Neuropsychopharmacol* 2005; 15: 425–434.
5. van der Voort TY, van Meijel B, Hoogendoorn AW, *et al.* Collaborative care for patients with bipolar disorder: effects on functioning and quality of life. *J Affect Disord* 2015; 179: 14–22.
6. Marwaha S, Durrani A and Singh S. Employment outcomes in people with bipolar disorder: a systematic review. *Acta Psychiatr Scand* 2013; 128: 179–193.
7. Baldessarini RJ, Tondo L, Pinna M, *et al.* Suicidal risk factors in major affective disorders. *Br J Psychiatry* 2019; 215: 621–626.
8. Solomon DA, Keitner GI, Miller IW, *et al.* Course of illness and maintenance treatments for patients with bipolar disorder. *J Clin Psychiatry* 1995; 56: 5–13.
9. Fountoulakis KN, Grunze H, Vieta E, *et al.* The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for bipolar disorder in adults (CINP-BD-2017), part 3: the clinical guidelines. *Int J Neuropsychopharmacol* 2017; 20: 180–195.
10. Kemp DE. Managing the side effects associated with commonly used treatments for bipolar depression. *J Affect Disord* 2014; 169(Suppl. 1): S34–S44.
11. Keck PE Jr and McElroy SL. Outcome in the pharmacologic treatment of bipolar disorder. *J Clin Psychopharmacol* 1996; 16(2 Suppl. 1): 15S–23S.
12. Scott J and Pope M. Self-reported adherence to treatment with mood stabilizers, plasma levels, and psychiatric hospitalization. *Am J Psychiatry* 2002; 159: 1927–1929.
13. Miasso AI, Carmo BPD and Tirapelli CR. Bipolar affective disorder: pharmacotherapeutic profile and adherence to medication. *Rev Esc Enferm USP* 2012; 46: 689–695.
14. El-Mallakh RS, Vöhringer PA, Ostacher MM, *et al.* Antidepressants worsen rapid-cycling course in bipolar depression: a STEP-BD randomized clinical trial. *J Affect Disord* 2015; 184: 318–321.
15. Gitlin MJ. Antidepressants in bipolar depression: an enduring controversy. *Int J Bipolar Disord* 2018; 17: 278–283.
16. Tohen M, Frank E, Bowden CL, *et al.* The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. *Bipolar Disord* 2009; 11: 453–473.
17. Sidor MM and MacQueen GM. An update on antidepressant use in bipolar depression. *Curr Psychiatry Rep* 2012; 14: 696–704.
18. McGirr A, Karmani S, Arsappa R, *et al.* Clinical efficacy and safety of repetitive transcranial magnetic stimulation in acute bipolar depression. *World Psychiatry* 2016; 15: 85–86.
19. McGirr A, Vöhringer PA, Ghaemi SN, *et al.* Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. *Lancet Psychiatry* 2016; 3: 1138–1146.
20. Vázquez GH, Tondo L, Undurraga J, *et al.* Overview of antidepressant treatment of bipolar depression. *Int J Neuropsychopharmacol* 2013; 16: 1673–1685.
21. Swartz HA and Swanson J. Psychotherapy for bipolar disorder in adults: a review of the evidence. *Focus* 2014; 12: 251–266.

22. Geddes JR and Miklowitz DJ. Treatment of bipolar disorder. *Lancet* 2013; 381: 1672–1682.

23. Reinares M, Sanchez-Moreno J and Fountoulakis KN. Psychosocial interventions in bipolar disorder: what, for whom, and when. *J Affect Disord* 2014; 156: 46–55.

24. Pandya M, Altinay M, Malone DA, *et al.* Where in the brain is depression? *Curr Psychiatry Rep* 2012; 14: 634–642.

25. Mishra BR, Sarkar S, Praharaj SK, *et al.* Repetitive transcranial magnetic stimulation in psychiatry. *Ann Indian Acad Neurol* 2011; 14: 245–251.

26. Banerjee J, Sorrell ME, Celnik PA, *et al.* Immediate effects of repetitive magnetic stimulation on single cortical pyramidal neurons. *PLoS One* 2017; 12: e0170528.

27. Wassermann EM and Lisanby SH. Therapeutic application of repetitive transcranial magnetic stimulation: a review. *Clin Neurophysiol* 2001; 112: 1367–1377.

28. Mendlowitz AB, Shanbour A, Downar J, *et al.* Implementation of intermittent theta burst stimulation compared to conventional repetitive transcranial magnetic stimulation in patients with treatment resistant depression: a cost analysis. *PLoS One* 2019; 14: e0222546.

29. Slotema CW, Dirk Blom J, Hoek HW, *et al.* Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. *J Clin Psychiatry* 2010; 71: 873–874.

30. Hett D, Rogers J, Humpston C, *et al.* Repetitive transcranial magnetic stimulation (rTMS) for the treatment of depression in adolescence: a systematic review. *J Affect Disord* 2020; 278: 460–469.

31. Croarkin PE and MacMaster FP. Transcranial magnetic stimulation for adolescent depression. *Child Adolesc Psychiatr Clin N Am* 2019; 28: 33–43.

32. Magavi LR, Reti IM and Vasa RA. A review of repetitive transcranial magnetic stimulation for adolescents with treatment-resistant depression. *Int Rev Psychiatry* 2017; 29: 79–88.

33. Teng S, Guo Z, Peng H, *et al.* High-frequency repetitive transcranial magnetic stimulation over the left DLPFC for major depression: session-dependent efficacy: a meta-analysis. *Eur Psychiatry* 2017; 41: 75–84.

34. Xia G, Gajwani P, Muzina DJ, *et al.* Treatment-emergent mania in unipolar and bipolar depression: focus on repetitive transcranial magnetic stimulation. *Int J Neuropsychopharmacol* 2008; 11: 119–130.

35. Gold AK, Ornelas AC, Cirillo P, *et al.* Clinical applications of transcranial magnetic stimulation in bipolar disorder. *Brain Behav* 2019; 9: e01419.

36. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23: 56.

37. Montgomery SA and Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979; 134: 382–389.

38. Beck AT, Steer RA and Brown GK. *BDI-II: Beck Depression Inventory* (2nd ed.). San Antonio, TX: The Psychological Corporation, 1996.

39. Rush AJ, Trivedi MH, Ibrahim HM, *et al.* The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry* 2003; 54: 573–583.

40. Young RC, Biggs JT, Ziegler VE, *et al.* A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 1978; 133: 429–435.

41. Garcia-Toro M. Acute manic symptomatology during repetitive transcranial magnetic stimulation in a patient with bipolar depression. *Br J Psychiatry* 1999; 175: 491–491.

42. Dolberg OT, Schreiber S and Grunhaus L. Transcranial magnetic stimulation-induced switch into mania: a report of two cases. *Biol Psychiatry* 2001; 49: 468–470.

43. Hausmann A, Kramer-Reinstadler K, Lechner-Schoner T, *et al.* Can bilateral prefrontal repetitive transcranial magnetic stimulation (rTMS) induce mania? A case report. *J Clin Psychiatry* 2004; 65: 1575–1576.

44. Li X, Fryml L, Rodriguez JJ, *et al.* Safe management of a bipolar depressed patient with prefrontal repetitive transcranial magnetic stimulation (rTMS) over 7 years and >2 million stimuli. *Brain Stimul* 2014; 7: 919–921.

45. Zendjidjian XY, Lodovighi MA, Richieri R, *et al.* Resistant bipolar depressive disorder: case analysis of adjunctive transcranial magnetic stimulation efficiency in medical comorbid conditions. *Bipolar Disord* 2014; 16: 211–213.

46. Brunelin J, Maklouf WB, Nicolas A, *et al.* Successful switch to maintenance rTMS after maintenance ECT in refractory bipolar disorder. *Brain Stimul* 2010; 4: 238–239.

47. Huang CC, Su TP and Shan IK. A case report of repetitive transcranial magnetic stimulation-induced mania. *Bipolar Disord* 2004; 6: 444–445.

48. Kaster TS, Knyahnytska Y, Noda Y, *et al.* Treatment-emergent mania with psychosis in bipolar depression with left intermittent theta-burst rTMS. *Brain Stimul* 2020; 13: 705–706.

49. Cohen RB, Brunoni AR, Boggio PS, *et al.* Clinical predictors associated with duration of repetitive transcranial magnetic stimulation treatment for remission in bipolar depression: a naturalistic study. *J Nerv Ment Dis* 2010; 198: 679–681.

50. Carnell BL, Clarke P, Gill S, *et al.* How effective is repetitive transcranial magnetic stimulation for bipolar depression? *J Affect Disord* 2017; 209: 270–272.

51. Phillips AL, Burr RL and Dunner DL. Repetitive transcranial magnetic stimulation in the treatment of bipolar depression: experience from a clinical setting. *J Psychiatr Pract* 2020; 26: 37–45.

52. Dell'Osso B, Mundo E, D'Urso N, *et al.* Augmentative repetitive navigated transcranial magnetic stimulation (rTMS) in drug-resistant bipolar depression. *Bipolar Disord* 2009; 11: 76–81.

53. Dell'Osso B, D'Urso N, Castellano F, *et al.* Long-term efficacy after acute augmentative repetitive transcranial magnetic stimulation in bipolar depression: a 1-year follow-up study. *J ECT* 2011; 27: 141–144.

54. Kazemi R, Rostami R, Khomami S, *et al.* Bilateral transcranial magnetic stimulation on DLPFC changes resting state networks and cognitive function in patients with bipolar depression. *Front Hum Neurosci* 2018; 12: 356.

55. Fitzgerald PB, Huntsman S, Gunewardene R, *et al.* A randomized trial of low-frequency right-prefrontal-cortex transcranial magnetic stimulation as augmentation in treatment-resistant major depression. *Int J Neuropsychopharmacol* 2006; 9: 655–666.

56. Dell'Osso B, Oldani L, Camuri G, *et al.* Augmentative repetitive Transcranial Magnetic Stimulation (rTMS) in the acute treatment of poor responder depressed patients: a comparison study between high and low frequency stimulation. *Eur Psychiatry* 2015; 30: 271–276.

57. Kazemi R, Rostami R, Khomami S, *et al.* Electrophysiological correlates of bilateral and unilateral repetitive transcranial magnetic stimulation in patients with bipolar depression. *Psychiatry Res* 2016; 240: 364–375.

58. Dolberg O, Dannon P, Schreiber S, *et al.* Transcranial magnetic stimulation in patients with bipolar depression: a double blind, controlled study. *Bipolar Disord* 2002; 4: 94–95.

59. Nahas Z, Kozel FA, Li X, *et al.* Left prefrontal transcranial magnetic stimulation (TMS) treatment of depression in bipolar affective disorder: a pilot study of acute safety and efficacy. *Bipolar Disord* 2003; 5: 40–47.

60. Fitzgerald PB, Benitez J, de Castella A, *et al.* A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatry* 2006; 163: 88–94.

61. Tamas RL, Menkes D and El-Mallakh RS. Stimulating research: a prospective, randomized, double-blind, sham-controlled study of slow transcranial magnetic stimulation in depressed bipolar patients. *J Neuropsychiatry Clin Neurosci* 2007; 19: 198–199.

62. Beynel L, Chauvin A, Guyader N, *et al.* What saccadic eye movements tell us about TMS-induced neuromodulation of the DLPFC and mood changes: a pilot study in bipolar disorders. *Front Integr Neurosci* 2014; 8: 65.

63. Hu S-H, Lai J-B, Xu D-R, *et al.* Efficacy of repetitive transcranial magnetic stimulation with quetiapine in treating bipolar II depression: a randomized, double-blinded, control study. *Sci Rep* 2016; 6: 1–7.

64. Fitzgerald PB, Hoy KE, Elliot D, *et al.* A negative double-blind controlled trial of sequential bilateral rTMS in the treatment of bipolar depression. *J Affect Disord* 2016; 198: 158–162.

65. Yang L-L, Zhao D, Kong L-L, *et al.* High-frequency repetitive transcranial magnetic stimulation (rTMS) improves neurocognitive function in bipolar disorder. *J Affect Disord* 2019; 246: 851–856.

66. Bulteau S, Beynel L, Marendaz C, *et al.* Twice-daily neuronavigated intermittent theta burst stimulation for bipolar depression: a randomized sham-controlled pilot study. *Neurophysiol Clin* 2019; 49: 371–375.

67. Michael N and Erfurth A. Treatment of bipolar mania with right prefrontal rapid transcranial magnetic stimulation. *J Affect Disord* 2004; 78: 253–257.

68. Saba G, Rocamora JF, Kalalou K, *et al.* Repetitive transcranial magnetic stimulation as an add-on therapy in the treatment of mania: a case series of eight patients. *Psychiatry Res* 2004; 128: 199–202.

69. Grisaru N, Chudakov B, Yaroslavsky Y, *et al.* Transcranial magnetic stimulation in mania: a controlled study. *Am J Psychiatry* 1998; 155: 1608–1610.

70. Kaptsan A, Yaroslavsky Y, Applebaum J, *et al.* Right prefrontal TMS versus sham treatment of mania: a controlled study. *Bipolar Disord* 2003; 5: 36–39.

71. Praharaj SK, Ram D and Arora M. Efficacy of high frequency (rapid) suprathreshold repetitive transcranial magnetic stimulation of right prefrontal cortex in bipolar mania: a randomized sham controlled study. *J Affect Disord* 2009; 117: 146–150.

72. Zeeuws D, De Rycker K, De Raedt R, *et al.* Intensive high-frequency repetitive transcranial magnetic stimulation treatment in an electroconvulsive shock therapy-resistant bipolar I patient with mixed episode. *Brain Stimul* 2011; 4: 46–49.

73. Pallanti S, Grassi G, Antonini S, *et al.* rTMS in resistant mixed states: an exploratory study. *J Affect Disord* 2014; 157: 66–71.

74. Li X, Nahas Z, Anderson B, *et al.* Can left prefrontal rTMS be used as a maintenance treatment for bipolar depression? *Depress Anxiety* 2004; 20: 98–100.

75. Galletly C, Gill S, Clarke P, *et al.* A randomized trial comparing repetitive transcranial magnetic stimulation given 3 days/week and 5 days/week for the treatment of major depression: is efficacy related to the duration of treatment or the number of treatments? *Psychol Med* 2012; 42: 981–988.

76. Galletly CA, Clarke P, Carnell BL, *et al.* A clinical repetitive transcranial magnetic stimulation service in Australia: 6 years on. *Aust N Z J Psychiatry* 2015; 49: 1040–1047.

77. Bech P, Rafaelsen O, Kramp P, *et al.* The mania rating scale: scale construction and inter-observer agreement. *Neuropharmacology* 1978; 17: 430–431.

78. Rachid F. Repetitive transcranial magnetic stimulation and treatment-emergent mania and hypomania: a review of the literature. *J Psychiatr Pract* 2017; 23: 150–159.

79. Berlim MT, Van den Eynde F and Daskalakis ZJ. Clinically meaningful efficacy and acceptability of low-frequency repetitive transcranial magnetic stimulation (rTMS) for treating primary major depression: a meta-analysis of randomized, double-blind and sham-controlled trials. *Neuropsychopharmacology* 2013; 38: 543–551.

80. Gaynes BN, Lloyd SW, Lux L, *et al.* Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. *J Clin Psychiatry* 2014; 75: 477–489.

81. Rossi S, Hallett M, Rossini PM, *et al.* Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009; 120: 2008–2039.

82. Loo CK, McFarquhar TF and Mitchell PB. A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. *Int J Neuropsychopharmacol* 2008; 11: 131–147.

83. Kar SK. Predictors of response to repetitive transcranial magnetic stimulation in depression: a review of recent updates. *Clin Psychopharmacol Neurosci* 2019; 17: 25–33.

84. Zhengwu P, Cuihong Z, Shanshan X, *et al.* Mechanism of repetitive transcranial magnetic stimulation for depression. *Shanghai Arch Psychiatry* 2018; 30: 84–92.