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Is Transcranial Magnetic Stimulation (TMS) an Effective Therapy in Reducing Depressive Symptoms in Adults with Bipolar Depression?

Emily M. Boylan
Philadelphia College of Osteopathic Medicine

Is Transcranial Magnetic Stimulation (TMS) an Effective Therapy in Reducing Depressive Symptoms in Adults with Bipolar Depression?

Emily M. Boylan, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not transcranial magnetic stimulation (TMS) is an effective therapy in reducing depressive symptoms in adults with bipolar depression.

STUDY DESIGN: Systematic review of three randomized controlled trials (RCTs) that were published in the English language between 2016 and 2019.

DATA SOURCES: Data sources included articles found using PubMed as the search engine and were selected based on their relevance to the research question as well as patient measured outcomes.

OUTCOMES MEASURED: Outcomes measured include changes in depression symptoms measured using the 17-item Hamilton Depression Rating Scale (HDRS-17) and Modified 24-item Hamilton Depression Rating Scale (HDRS).

RESULTS: Tavares et al. found that 48% of patients with bipolar depression receiving active TMS were treatment responders with a numbers needed to treat (NNT) of 5. Yang et al. showed no differences in HDRS scores between groups at baseline and follow-up as shown by $p=0.451$ and F-score of 0.577. Finally, Fitzgerald et al. demonstrated a mean change from baseline of 3.4 in the active group and mean change from baseline of 3.0 in the sham group. While both are significant changes, there is no significant change between treatment groups at the conclusion of the 4 week study.

CONCLUSIONS: Even though the study by Tavares et al.[1] showed a significant improvement with TMS in depressive symptoms in adults with bipolar depression, the other two studies by Yang et al.[2] and Fitzgerald et al.[4] demonstrated no difference between treatment groups. Based on these conflicting findings, the results from this systematic review are inconclusive. Thus, further research is needed that includes sufficiently larger sample sizes and longer treatment trials.

KEY WORDS: Bipolar Disorder, Transcranial Magnetic Stimulation

INTRODUCTION

Bipolar disorder is a highly disabling affective disorder characterized by mood swings and cognitive disturbances with limited therapeutic options.[1,2] The average age of onset is between 19 and 30 but ranges from 5 to 50 years old, and the prevalence of the disease is equal in both males and females.[3] Symptoms vary between individuals and type of bipolar disorder, but may include persistently elevated mood, irritability, extreme sadness, anxiety, impaired judgment, risky behavior, increased libido, racing thoughts, decreased need for sleep, weight loss/gain, and fatigue.[3] Even though the disorder is characterized by hypomania and mania episodes, depressive episodes exceed them in duration and frequency.[1] Bipolar depression, the depressive aspect of bipolar disorder, is associated with a twenty fold increased risk of suicide, and the duration of depressive episodes lasts three to five times as long as a manic or hypomanic episode.[4] Thus, reducing depressive symptoms in adults with bipolar depression is vital in providing these individuals with a better quality of life.

Bipolar disorder is a prevalent condition with a worldwide prevalence of around 2-3%, including both bipolar I and II subtypes.[1] During 2010 to 2011 in the United States, approximately 46,800 emergency room visits were made each year by persons older than 15 with a diagnosis of bipolar disorder, with an overall rate of 3.8 visits per 1,000 persons per year.[5] This statistic is likely even higher as the onset of bipolar disorder can begin prior to age 15. Since this disorder affects a significant amount of the population, it comes with a substantial economic cost. The total economic burden of bipolar disorder in the United States was $45 billion over a decade ago. Of that total, $7 billion was a result of direct costs of inpatient and outpatient care and nontreatment related expenditures, such as costs of criminal justice.[6] Individuals with bipolar disorder utilize health care services more frequently, and they have visits that are associated with much higher medical costs than those without the disorder.

The pathophysiology of bipolar disorder is unknown. However, it is known that both genetic and environmental factors play a role as it is highly inheritable and often triggered by traumatic life events. Because the exact pathophysiology is unknown, the treatment of bipolar depression is more complex and difficult than that of unipolar depression. There are limited first-line therapies for treating bipolar depression, but conventional medical therapies typically include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), atypical antipsychotics, anticonvulsants, and mood-stabilizing agents such as lithium. Psychotherapy, such as cognitive-behavioral therapy (CBT) and other approaches with a clinical psychologist or licensed professional counselor, have shown success in alleviating psychological symptoms. Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation therapy that has been proven to be effective in reducing depressive symptoms in those with unipolar depression.[1] It is hypothesized that TMS stimulates neurons in the region of the brain involved in mood control and depression. Since TMS has been shown to be effective in unipolar depression and there are limited effective first-line therapies for bipolar depression, TMS is being explored as an alternative treatment for bipolar depression because the therapy targets mood control neurons.

The exploration of TMS as a treatment option is critical to physician assistants and other medical providers who assess and treat bipolar disorder. It is imperative that they are aware of all treatment options, especially those outside of the standard treatment options and those that are noninvasive and well-tolerated, such as TMS. Bipolar disorder looks different for every individual; therefore, a provider's knowledge of available treatment options allows them to weigh all risks and benefits and develop the best treatment plan for each individual patient.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not transcranial magnetic stimulation is an effective therapy in reducing depressive symptoms in adults with bipolar depression.

METHODS

The studies selected for this EBM review were found using the search engine, PubMed, while using specific inclusion and exclusion criteria. All three RCTs were found in peer-reviewed journals and were published in the English language after 2009. Articles were selected based on their clinical relevance to the research question and whether or not they included patient oriented evidence that matters (POEM). The studies included three randomized controlled trials (RCTs) that reviewed adults over 18 years old diagnosed with bipolar disorder who were undergoing alternative treatment for their depressive symptoms. The intervention being observed in each of the three studies was TMS: Tavares et al.[1] used fifty five 18 hertz (Hz) trains delivered at 120% of the motor threshold (MT) intensity at 20 second intervals, Yang et al.[2] used fifty five 10 Hz trains delivered at 110% of the MT intensity at 30 second intervals, and Fitzgerald et al.[4] used twenty 10 Hz trains delivered at 110% of the MT intensity at 25 second intervals. All studies were compared to a sham transcranial magnetic stimulation that used sham coils that mimicked scalp sensations and the acoustic artifact of the active stimulation but without the neuronal activation. Outcomes measured in these studies included efficacy in reducing depressive symptoms in patients with bipolar depression measured using the 17-item Hamilton Depression Rating Scale (HDRS-17) and Modified 24-item Hamilton Depression Rating Scale (HDRS). All studies had patients rate their depression symptoms using these scales.

As stated above, specific inclusion and exclusion criteria were applied to all three articles. Inclusion criteria were randomized controlled trials that were published in English within the last 10 years and included adults 18 years and older. Exclusion criteria included no systematic reviews, articles published prior to 2009, or subjects less than 18 years old. Table 1 demonstrates all specific inclusion and exclusion criteria for each study analyzed in this review. Statistics reported for reduction in depressive symptoms included the following: Control Event Rate (CER), Experimental Event Rate (EER), Relative Benefit Increase (RBI), Absolute Benefit

Increase (ABI), Numbers Needed to Treat (NNT), F-score (F), p-value, and mean change from baseline.

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Tavares et al., 2017[1]	RCT	50	18-65	Adults 18-65 years old diagnosed with bipolar disorders types I or II in an acute depressive episode	Presence of other neuropsychiatric conditions per DSM-IV criteria, such as unipolar depression, schizophrenia, substance dependence, dementia, TBIs, epilepsy, or personality disorders; pregnancy	7	Active deep transcranial magnetic stimulation vs sham transcranial magnetic stimulation once daily for 4 weeks, excluding weekends
Yang et al., 2019[2]	RCT	52	18-55	Adults 18-55 years old diagnosed with bipolar I or II disorder according to DSM-IV criteria on stable antipsychotic and mood stabilizing treatment	Patients who met criteria for diagnosis of substance/alcohol abuse, hx of neurologic illness (seizures, head trauma), EEG abnormalities, ECT or TMS within the last year, or significant unstable medical illness	No comment about losses	Active repetitive transcranial magnetic stimulation vs sham repetitive transcranial magnetic stimulation for 10 consecutive days
Fitzgerald et al., 2016[4]	RCT	46	18-70	Adults 18-70 years old diagnosed with bipolar affective disorder in a current episode of treatment resistant depression by DSM-IV criteria	Patients were excluded if they had unstable medical conditions, neurologic disorders, history of seizure disorder, or were pregnant or lactating	6	Active repetitive transcranial magnetic stimulation vs sham repetitive transcranial magnetic stimulation once daily for 4 weeks, excluding weekends

OUTCOMES MEASURED

Outcomes measured in all three studies included changes in depression symptoms measured using the 17-item Hamilton Depression Rating Scale (HDRS-17) and Modified 24-item Hamilton Depression Rating Scale (HDRS), which are two different versions of the same scale. All studies had patients answer the questions provided in these scales, and their answers were used to assess the severity of their depression and their progression throughout treatment. Scoring is based on a 17-item scale and scores of 0-7 are considered normal, 8-16 suggest mild depression, 17-23 suggest moderate depression, and scores over 24 indicate severe depression.

RESULTS

Tavares et al.[1] conducted a double-blind RCT to study the efficacy and safety of TMS in the treatment of bipolar depression patients. Their study involved 50 participants from the Clinics Hospital of the University of Sao Paulo ages 18 to 65 years old diagnosed with bipolar disorder types I or II according to the DSM-IV criteria, who were in an acute depressive episode with an HDRS-17 score of 17 or greater. The subjects needed to be free of any antidepressant drugs; however, they were allowed to be on low dose benzodiazepine, lithium, anticonvulsants or antipsychotic therapy. The subjects were stimulated on the left dorsolateral prefrontal cortex (DLPFC) every day for 4 weeks, except weekends, and they were clinically assessed every week using the HDRS-17 scale for a total of 8 weeks to include both the active phase and follow-up phase.[1] Therefore, their response to the treatment was determined using the HDRS-17 scale, looking for a 50% improvement from their baseline. In the experimental group receiving active TMS, the experimental event rate was 48% after 4 weeks of treatment, meaning they were considered responders to therapy.[1] Meanwhile, 24% were considered responders in the control group receiving sham TMS.[1] Their response to treatment proved TMS to be an effective therapy in reducing depressive symptoms when compared to the control group; however, these results

were not sustained after the group was re-assessed at week 8, which was 4 weeks after the discontinuation of TMS. The NNT in this study was 5; therefore, for every 5 patients, 1 more will benefit from treatment. These results are organized in Table 2.

Table 2. Treatment Responders Using HDRS-17 Scores

CER	EER	RBI	ABI	NNT
24%	48%	100%	24%	5

CER: Control Event Rate; EER: Experimental Event Rate; RBI: Relative Benefit Increase; ABI: Absolute Benefit Increase; NNT: Numbers Needed to Treat

Out of the 50 participants who entered the study, 43 finished the trial. There were two drop outs in the sham group due to missing consecutive visits, and there were five drop outs in the active group: two were dropped due to missing consecutive visits, two were dropped due to the severity of their depressive symptoms, and one was dropped due to the severity of the side effects, such as the burning scalp pain.[1] Thus, adverse events were considered in this study; however, scalp pain was the only event that was determined to be more prevalent in the active group compared to the sham group. Additional adverse events were considered, such as headache, neck pain, hearing difficulties, and concentration difficulties; however, those who experienced side effects were still included in the study.[1]

Yang et al.[2] conducted a single-blind RCT that included 52 participants ages 18 to 55 years old diagnosed with bipolar disorder types I or II according to the DSM-IV criteria, who were outpatients at the First Hospital of Hebei Medical University and on stable antipsychotic or mood stabilizing therapy. The purpose of this study was to determine if TMS was effective and safe in improving depressive symptoms and cognitive function in bipolar disorder. The subjects were stimulated on the left DLPFC every day for 10 days, and they underwent baseline and follow up assessments using the modified 24-item HDRS scale. The data for emotional symptoms were analyzed using a 2 x 2 repeated-measures ANOVA, with treatment group (active TMS vs sham TMS) as the one factor and time of testing (baseline vs follow-up) as the other factor.[2] After 10 days of consecutive treatment, there were found to be no differences in HDRS

scores between baseline and follow up as demonstrated by an F-score of 0.577 and a p-value of 0.451.[2] Thus, this study failed to prove TMS as an effective therapy for those with bipolar depression. These results are displayed in Table 3.

Table 3. Analysis of HDRS Scores

Active TMS		Sham TMS		F-score	p-value
Baseline	Follow-up	Baseline	Follow-up	0.577	0.451
4.80 ± 2.784	3.20 ± 2.141	4.96 ± 2.919	3.81 ± 2.367		

There was no mention of any lost subjects in this study; therefore, without any confirmation about losses, it must be assumed that there were losses. Additionally, there were no serious adverse events that were reported during or after treatment with TMS, and there were no reported drop outs due to side effects. Three participants experienced dizziness during the first initial TMS treatment; one receiving active TMS and two receiving sham TMS.[2] Thus, dizziness was not a noteworthy adverse event related to the active treatment.

Fitzgerald et al.[4] conducted a double-blind RCT to explore the therapeutic benefit of TMS in the treatment of bipolar depression. The study included 46 participants ages 18 to 70 years old diagnosed with bipolar affective disorder in a current episode of treatment resistant depression as defined by the DSM-IV criteria, who also have a HDRS-17 score of 20 or greater.[4] The patients needed to be on stable antidepressant or psychoactive drugs without recent increases or initiation in the last 4 weeks, and they were all recruited by referral from both community and hospital based psychiatrists between January 2009 and May 2015.[4] They were stimulated on bilateral DLPFC, instead of a unilateral approach, every day between Monday and Friday over 4 weeks, and they were assessed using the HDRS-17 scale after two and four weeks of treatment. The results of the HDRS-17 scores were analyzed using a mean change from baseline calculation. At the beginning of the study, the mean baseline HDRS-17 score was 23.2 in the active group and 23.0 in the control group.[4] At the end of the 4 week study, the mean scores did

improve to 19.8 in the active group and 20.0 in the control group, creating a mean change from baseline of 3.4 and 3.0 respectively.[4] While there were significant reductions in the HDRS-17 scores, there was no difference between the treatment groups. See Table 3.

Table 4. Efficacy of TMS as Measured by Mean Change from Baseline

	Active TMS	Sham TMS
Baseline	23.2	23.0
End of Treatment (Week 4)	19.8	20.0
Mean Change from Baseline	3.4	3.0

There were six identifiable losses in this study. Of the 46 participants, four withdrew from the active group and two withdrew from the sham group. Of the four from the active group who withdrew, two were due to practical difficulties with attendance, one was due to withdrawn consent, and one was due to desire to access alternative treatment. Of the two from the sham group who withdrew, one was due to practical difficulties with attendance and the other was due to desire to access alternative treatment.[4] There were no comments about adverse events and data on safety was not reported in this study.

DISCUSSION

Despite all three RCTs having investigated TMS as an effective therapy in reducing depressive symptoms in bipolar depression, only one of the articles produced significant data to suggest it to be an effective therapy. Tavares et al.[1] was likely more successful since it followed the methods utilized by a notable study that used TMS for treatment of unipolar depression published by Levkovitz in 2015, including stimulation of the left DLPFC and an adequate trial of TMS of four weeks. While Tavares et al.[1] still showed significant improvement in depressive symptoms with four weeks of stimulation, it did not show a sustained response and remission at week 8. Thus, the study may have seen more substantial results if the duration of treatment was similar to Levkovitz's study of unipolar depression, where the brain was stimulated for 12 weeks.

Just as Tavares et al.[1] was limited by sample size and duration of treatment, the two studies that failed to produce significant data, Yang et al.[2] and Fitzgerald et al.[4], were also limited by those same two factors. None of the studies included more than 52 participants and none exceeded active treatment greater than four weeks. While Yang et al.[2] included the largest sample size (n=52) of the three studies, the study was limited by the duration of treatment, which was only 10 days of consecutive treatment. Even though treatment sessions vary in length, a typical course is four to six weeks.[7] Thus, this study falls significantly short of an adequate trial of TMS.

Fitzgerald et al.[4] also conducted their study over the course of four weeks; however, it included the smallest sample size (n=46) of the three studies, causing a lack of sufficient power to demonstrate advantage over the sham stimulation.[4] Once this study was complete, Fitzgerald et al.[4] had calculated a sample size that would have demonstrated a significant effect on the mean change in HDRS-17 scores, and it would require 157 participants in both the active and sham groups.[4] This suggests that an adequate sample size was not used for the study, and also suggests that it was not used in any of the three studies. Additionally, Fitzgerald et al.[4] stimulated both the left and right DLPFC. The study may have shown more significant results if it focused on stimulating just one side, specifically the left side which shows improvement with TMS in unilateral depression.

All three of the studies were conducted while the patients were on concurrent drug therapy, whether that was mood stabilizing drugs, anticonvulsants, or antidepressant drugs. These drugs could be confounding variables; thus, significantly impacting the results of these studies as TMS was not being assessed as monotherapy. The brain was already being altered by the effect of these drugs; therefore, the true effects of TMS could not be assessed.

Besides the limitations of the primary research, there were limitations specific to this systematic review. There are few existing articles from peer-reviewed journals that focus on

TMS as an intervention in reducing depressive symptoms in bipolar disorder; therefore, the pool of studies to analyze for this review was limited. The limitation in number made researching the intervention in question difficult, so three of the few articles that could be found were analyzed. Due to the small number of studies, the quality of the ones selected could be questioned. Additional studies need to be performed to further analyze the intervention for this specific patient population and provide a larger pool of quality studies.

Even though there is conflicting data to support TMS in this systematic review, additional research needs to be conducted since this noninvasive procedure is efficacious in previous unilateral depression studies. Additionally, TMS is widely available in many clinics and hospitals across the country.[7] The availability makes it a readily accessible treatment option once the proper research is conducted to support it as a regular treatment option. TMS is covered by most major commercial companies, such as United Healthcare, Cigna, Aetna, and BCBS.[8] However, in order to qualify for insurance coverage, a patient must be diagnosed with major depressive disorder, must have tried at least two to four different antidepressants without improvement, and/or must have tried psychotherapy without improvement.[8] Since it is generally well-tolerated, safe, and typically covered by insurance, providers, such as doctors, physician assistants, nurse practitioners, and more, should stay informed about the results of further studies using TMS as a therapy in reducing depressive symptoms in adults with bipolar depression.

CONCLUSION

Even though one RCT found TMS to be an effective therapy in reducing depressive symptoms in adults with bipolar depression, two RCTs did not produce any significant data to suggest it to be an effective therapy. Thus, this systematic review produces conflicting evidence to determine if TMS is an effective therapy in reducing depressive symptoms in adults with bipolar depression. According to this review, it cannot be determined if TMS is an effective therapy. This could be due to the methods used in each of the three studies, including sample

size, length of treatment, location of stimulation, and concurrent drug therapy use. All three of the RCTs are limited by sample size and treatment duration as they all consisted of less than 55 participants and none lasted longer than four weeks. Thus, TMS cannot be ruled out as an effective treatment option for bipolar depression. Further research is warranted that includes sufficiently larger sample sizes and longer treatment trials.

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