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Do Bipolar Disorder Soft Signs Impact Outcomes Following Transcranial Magnetic Stimulation (TMS) Therapy for Depression?

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Abstract

Background: Transcranial Magnetic Stimulation (TMS) is not currently FDA approved for depressed patients with bipolar disorder (BD), but many unipolar depressed patients presenting for TMS have soft signs of bipolarity. It is not known whether or not these soft signs portend differential outcomes.

Objective: To investigate the relationship between BD soft signs and TMS treatment outcomes in a naturalistic treatment setting.

Methods: We conducted a retrospective chart review of MDD patients (n=105) treated with TMS. BD diathesis was defined by responses to a modified version of the Mood Disorder Questionnaire and family history.

Results: TMS response rates for the group with BD diathesis and the group without were equivalent using two self-report depression severity scales. Remission rate was significantly lower for the bipolar soft signs group (13.5% versus 30.2%; $p=0.04$) on one scale. This result does not hold when corrected for multiple comparisons. We did not observe switch to mania.

Limitations: These data are limited to patients diagnosed with unipolar depression with “soft” bipolar features defined by subthreshold symptoms. The results cannot be extrapolated to patients with a full bipolar diagnosis.

Conclusion: Bipolar diathesis in MDD is not a safety concern but may lead to somewhat lower remission rates when considering TMS treatment.

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Declaration of Interest

Dr. Carpenter has received consulting income from Magstim, and Butler Hospital has had clinical trials contracts with Janssen, Neuronetics, Cervel, and NeoSync.

Keywords

Major Depressive Disorder; Bipolar Disorder Risk; Transcranial Magnetic Stimulation; TMS clinical outcomes

Introduction

Depressed patients with a bipolar disorder diagnosis are currently excluded by insurance policies for coverage of standard “on-label” Transcranial Magnetic Stimulation (TMS) because the evidence base for efficacy and safety was derived largely from clinical trials that included only patients with unipolar major depressive disorder (MDD) (McClintock et al., 2017). Several randomized trials with bipolar depressed samples have failed to show efficacy (Fitzgerald et al., 2016; Hu et al., 2016), but others show promise for treating bipolar depression (Tavares et al., 2017; Mutz et al., 2018). There is some evidence that treatment-emergent hypomanic or manic episodes may be induced by repetitive TMS in patients with bipolar disorder (Rachid, 2017). Features of bipolarity exist along a spectrum, and the clinical history of some MDD patients referred for TMS therapy suggests a bipolar diathesis even when threshold diagnostic criteria for a bipolar affective disorder are not met.

The Mood Disorders Questionnaire (MDQ; (Hirschfeld et al., 2000) is a three-part, self-report questionnaire used by the TMS clinic at Butler Hospital to screen for bipolar disorder in patients referred for TMS therapy. MDQ part 1 consists of 13 items characterizing the lifetime presence or absence of hypomanic/manic symptoms. Part 2 queries whether bipolar symptoms occurred during the same period of time. Part 3 assesses for the severity of symptoms. Our TMS clinic utilizes a modified version of the MDQ including questions to assess for family history of bipolar disorder and past bipolar diagnosis.

To address the question of whether soft signs of bipolar disorder are relevant to TMS therapy clinical outcomes in MDD, we identified a subset of MDD patients treated in the TMS clinic who endorsed two or more co-occurring bipolar symptoms and/or reported a family history positive for bipolar disorder on the MDQ.

Methods

We conducted a retrospective chart review of 185 patients with MDD consecutively treated with TMS at the Butler Hospital TMS clinic between 2005 and 2015. All patients included in this subset were determined to have unipolar depression, and a full bipolar disorder diagnosis was ruled out on the basis of MDQ screening responses followed by clinical interview by a psychiatrist. Chart review and data extrapolation were approved by the Butler Hospital Institutional Review Board (IRB). Patients were included in the analysis if they received at least 5 TMS treatments initiated with the standard 10 Hz stimulation protocol and if the MDQ data from pre-TMS screening were available.

Bipolar disorder diathesis was characterized as presence of Bipolar “Soft Signs” (BSS) defined by the presence of 2 or more lifetime hypomanic/manic symptoms (out of 13 items in the MDQ part 1) that occurred during the same time period (i.e. MDQ part 2 positive),

and/or having a first-degree family member with bipolar disorder diagnosis. Application of these criteria comprised a subthreshold diagnosis which we hypothesized could reflect some shared biological features with threshold bipolar I and II disorders.

Clinical outcome variables included depression symptom severity assessed using the Patient Health Questionnaire-9 item scale (PHQ-9, (Kroenke et al., 2001) and the Inventory of Depressive Symptomatology, Self-Report scale (IDS-SR, (Rush et al., 1996) completed at baseline and following every 5 TMS treatments. Last observation carried forward (LOCF) scores were used if data were missing following the last treatment. Response was determined as 50% decrease between baseline and LOCF endpoint scores for each scale. Remission was defined as IDS-SR score of 14 or less (Rush et al., 1996) and/or PHQ-9 score of 4 or less (Kroenke et al., 2001). Concurrent medication use was characterized for each patient with two variables: “any antidepressant use” (yes/no) and “any antipsychotic or mood stabilizer use” (yes/no). BSS and patients not meeting bipolar risk criteria (Control Group; CTL) were compared with regard to demographic/clinical characteristics and clinical outcome variables using chi-square and independent t-test as appropriate. Significance was defined as $p < 0.05$ with two-tailed tests.

Results

Upon chart review, we gathered 105 of the 185 patients with MDD with viable MDQ data and at least 5 TMS treatments (10 Hz stimulation). Those in the BSS ($n=52$) were compared with CTL ($n=53$). No significant differences were seen between the two groups on clinical or demographic variables including age (BSS: 52.6 ± 13 versus CTL: 52.3 ± 13.3), gender (BSS: 75% versus CTL: 81.1% female), and number of TMS treatments received (BSS: 35.2 ± 6.7 versus CTL: 36 ± 8.4). 82.7% of the BSS were taking one or more antidepressant medications and 57.7% were taking antipsychotic medications or mood stabilizers, compared to 84.9% and 56.6% of the CTL group, respectively (not significantly different across groups). In the BSS, 73.1% had past hospitalizations and 44.2% had past ECT, compared with 62.3% and 30.2%, respectively, for the CTL patients (no significant difference). As expected, the BSS had significantly higher MDQ part 1 total scores (BSS: 3.9 ± 3 versus CTL: 1.4 ± 2.2 , $p=0.008$). Within the BSS, 51.9% reported family history of bipolar disorder.

The two groups did not differ on pre- or post-treatment mean IDS-SR or PHQ-9 scores (Figure 1A). Post-TMS response rates did not significantly differ for the two groups on either scale (Figure 1A). Significantly lower remission rate characterized the BSS clinical outcomes using IDS-SR (13.5% versus 30.2%; $p=0.04$) but not when using PHQ-9 criteria (23.5% vs. 27.5%, $p>.05$) (Figure 1B); the group difference in IDS-SR remission was no longer significant when the p-value was adjusted for multiple comparisons. While there is not perfect concordance between the two scales when categorical outcome criteria are applied, total scores on IDS-SR for our sample were significantly correlated with those on the PHQ-9 ($r=.66$, $p<.0001$). There was no significant effect of concurrent antidepressant or concurrent antipsychotic/mood stabilizer on any of the four treatment outcomes. There were three significant adverse events: one inpatient admission due to suicidality in CTL and two

inpatient admissions in the BSS (one due to suicidality and another due to onset of psychosis during TMS).

Discussion

The efficacy of TMS for bipolar depression has not been widely investigated, and some patients with unipolar MDD have soft bipolar signs which may indicate risk for differential outcome with standard TMS therapy. We found a somewhat lower remission rate in those with BSS on only one outcome measure (IDS-SR remission), but this finding did not survive correction for multiple comparisons. Patients in the BSS group were equally likely to respond to TMS treatment on both measures.

A number of open-label studies have shown positive effect of TMS (with a mixed range of parameters) in depressed patients with BD (Cohen et al., 2010; Dell’Osso et al., 2009; Harel et al., 2011), and similar, positive results were reported for several double-blind, sham-controlled studies (Dolberg et al., 2002; Tamas et al., 2007; Tavares et al., 2017). However, results are mixed, as several controlled trials have also shown no difference in TMS treatment outcomes for bipolar depression (Fitzgerald et al., 2016; Hu et al., 2016; Nahas et al., 2003). While the efficacy of TMS for BD remains to be clearly elucidated by large controlled trials using optimal stimulation parameters, our results expand upon the available literature by indicating that soft signs of bipolar disorder (in patients diagnosed with unipolar depression) do not significantly alter the outcomes of TMS treatment when compared to controls with no bipolar diathesis.

While the majority of studies report TMS is safe for bipolar depression (Fitzgerald et al., 2016; Hu et al., 2016; Nahas et al., 2003), some suggest TMS may induce mood destabilization (Dolberg et al., 2001), and we previously reported TMS-associated activation (emergence of insomnia, irritability, anxiety, or agitation) among patients with primary unipolar major depression (Philip et al., 2015). Additionally, there may be some risk of induced manic or hypomanic episodes in patients with bipolar disorder treated with repetitive TMS (Rachid, 2017). It therefore remains unclear whether standard high-frequency TMS protocols are safe for treating depression in patients with bipolar disorder.

Often a question of bipolar diagnosis is considered when assessing a patient presenting in a depressive episode. Overall, these data suggest that the presence of “soft” bipolar risk factors in MDD patients, such as positive family history and past occurrence of several co-occurring manic or hypomanic symptoms, should not raise safety concern when considering treatment with TMS therapy. Unfortunately, we do not have detailed information about how these bipolar soft signs change during treatment, as the MDQ was only administered at baseline and bipolar-specific symptom scales were not part of the routine assessment in our TMS clinic. However, treatment frequency was reduced to 5 Hz (a proxy for TMS-induced activation) in 57.7% of BSS cases, which is not dissimilar to the CTL group (51.6%), suggesting that these soft signs do not clearly portend elevated risk for adverse effects from TMS.

One limitation to our findings is the method we used to define soft signs of bipolar disorder. Pre-treatment endorsement of subthreshold symptoms on the MDQ (two or more co-occurring hypomanic/manic symptoms or a “yes” response to family history of bipolar disorder) was used to categorize the BSS group. It is possible that this self-report method and our subthreshold definition captured patients without meaningful bipolar diathesis. This limitation also speaks to the need for a more sensitive or better suited assessment tool that could be used to screen depressed patients and determine which ones were likely to develop hypomania or excessive activation with antidepressant treatments or TMS therapy.

These data cannot be extrapolated to patients with full bipolar diagnosis, and are limited to patients with MDD and “soft” (subthreshold) bipolar features as defined herein. We did not see activation in our subset of BSS patients, but those with full bipolar diagnosis could be at greater risk for these side effects and this should be considered when examining TMS outcomes in patients with a full bipolar diagnosis. Further research is warranted to examine the safety and efficacy of TMS treatment for patients in the bipolar spectrum.

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Highlights

- Bipolar disorder “soft signs” was defined by family history and MDQ response.
- Among depressed patients getting TMS, soft signs of bipolar disorder does not diminish response rate.
- A switch to mania was not seen in response to TMS in MDD patients with bipolar risk.

Figure 1.

Depression severity and TMS outcomes based on the PHQ-9 and IDS-SR. Mean (SD) baseline and post-TMS PHQ-9 and IDS-SR scores of depression severity (A). TMS response and remission outcomes for bipolar “soft signs” (BSS) and non-risk control patients (CTL) using PHQ-9 and IDS-SR criteria (B).