Bipolar Disorders 2003: 5: 40–47

BIPOLAR DISORDERS
ISSN 1398-5647

Original Article

Left prefrontal transcranial magnetic stimulation (TMS) treatment of depression in bipolar affective disorder: a pilot study of acute safety and efficacy

Nahas Z, Kozel FA, Li X, Anderson B, George MS. 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. © Blackwell Munksgaard, 2003

Objectives: Repetitive transcranial magnetic stimulation (rTMS) has been shown to improve depressive symptoms. We designed and carried out the following left prefrontal rTMS study to determine the safety, feasibility, and potential efficacy of using TMS to treat the depressive symptoms of bipolar affective disorder (BPAD).

Methods: We recruited and enrolled 23 depressed BPAD patients (12 BPI depressed state, nine BPII depressed state, two BPI mixed state). Patients were randomly assigned to receive either daily left prefrontal rTMS (5 Hz, 110% motor threshold, 8 sec on, 22 sec off, over 20 min) or placebo each weekday morning for 2 weeks. Motor threshold and subjective rating scales were obtained daily, and blinded Hamilton Rating Scale for Depression (HRSD) and Young Mania Rating Scales (YMRS) were obtained weekly.

Results: Stimulation was well tolerated with no significant adverse events and with no induction of mania. We failed to find a statistically significant difference between the two groups in the number of antidepressant responders ($>50\%$ decline in HRSD or HRSD $<10-4$ active and 4 sham) or the mean HRSD change from baseline over the 2 weeks ($t=-0.22$, $p=0.83$). Active rTMS, compared with sham rTMS, produced a trend but not statistically significant greater improvement in daily subjective mood ratings post-treatment ($t=1.58$, $p=0.13$). The motor threshold did not significantly change after 2 weeks of active treatment ($t=1.11$, $p=0.28$).

Conclusions: Daily left prefrontal rTMS appears safe in depressed BPAD subjects, and the risk of inducing mania in BPAD subjects on medications is small. We failed to find statistically significant TMS clinical antidepressant effects greater than sham. Further studies are needed to fully investigate the potential role, if any, of TMS in BPAD depression.

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Key words: bipolar affective disorder, repetitive transcranial magnetic stimulation-rTMS – TMS-transcranial magnetic stimulation

Received 20 August 2002, revised and accepted for publication 29 October 2002

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Transcranial magnetic stimulation (TMS) involves placing an insulated coil of wire on the scalp. A very powerful current is sent through the coil to produce a magnetic field that passes unimpeded through the tissues of the head (1–3). The magnetic field, in turn, induces an electrical current in the brain (4, 5). The TMS uses the principle of inductance to convey electrical energy across the scalp and skull without the painful side-effects of direct percutaneous electrical stimulation. When the stimulation is given repeatedly, it is referred to as repetitive transcranial magnetic stimulation

(rTMS). There has been much interest recently in using rTMS as a treatment for depression. A number of open and double-blind studies have found that daily stimulation with a powerful electromagnet over the left prefrontal cortex can produce improvements in mood (6–9). There have been no published studies to date using TMS in a pure bipolar sample. Some bipolar patients, however, have been included in the group results of some trials [open (10, 11); randomized (12–16)]. Recent studies suggest that TMS may be equally as effective as electroconvulsive therapy (ECT) in non-psychotic depression (17–19).

The management of depression when it occurs in the setting of bipolar disorder, is a major clinical problem (20). Mood stabilizers such as the anticonvulsants carbamazepine and valproic acid are not particularly effective for the depressed phase of the illness, although there are reports of antidepressant properties (21, 22). The anticonvulsant lamotrigine does appear to have antidepressant effects (23, 24). Treatment of the depressed phase with conventional antidepressant pharmacotherapy can produce mania or increase a patient's cycle frequency (25, 26). Intermittent sleep deprivation and ECT are non-pharmacologic approaches to treating depression in patients with bipolar disorder. Sleep deprivation, however, is difficult to apply and is less effective than other methods, with relapse common after 1–2 days (27). ECT, although quite effective, requires general anesthesia and has significant cognitive side-effects (28). Building on earlier positive case studies (29–31), we organized the following pilot study to test whether rTMS was safe and feasible in bipolar affective disorder (BPAD) depression, and whether it might induce mania or prove effective as a treatment.

Materials and methods

Subjects

Diagnostic and Statistical Manual-IV defined BPAD subjects (bipolar types I and II), depressed or mixed phase, with Hamilton Rating Scale for Depression-28 (HRSD) (32) score > 18 were eligible. We excluded subjects with any comorbid axis I disorders (except simple and social phobia) or other significant medical, particularly neurologic, illnesses (seizures, head trauma and brain lesions). Subjects could not have mood cycles of < 30 days duration. Subjects could be taking carbamazepine or valproate alone or in combination, but the dose had to be stable for 2 weeks prior to beginning treatment, with persisting depression. All other psychotropic medications (especially antidepressants), were tapered over a 2-week washout (2 weeks longer for fluoxetine). Patients on lithium and lamotrigine, who could not taper these medications, were also excluded as these medications may have direct antidepressant properties in BPAD. Subjects were recruited from the Medical University of South Carolina (MUSC) Outpatient Psychopharmacology Clinic and other local referrals. There was no direct consumer advertising.

Evaluation

After signing written informed consent approved by the MUSC Institutional Review Board, the United States Food and Drug Administration, and in accordance with the Helsinki Declaration of 1975, subjects underwent a Structured Clinical Interview for DSM-IV (SCID-I) screening interview conducted by a trained clinician, and had their illness histories retrospectively defined and charted (33). Each week, subjects had the HDRS, the Young Mania Rating Scale (YMRS), Hamilton Anxiety Scale (HAM-A), Beck Depression Scale (Beck Scale) and Global Assessment of Functioning (GAF) administered by a trained and blinded clinician (BA).

In addition, subjects completed pre- and post-analog mood scales for each daily treatment session (NIMH Stanley Methods). The analog scale was a 100-mm line with a '0 – Worst Ever' at one end and a '10 – Best Ever' at the other end. Subjects indicated their present mood by placing an 'X' on the line. A quantitative number was obtained by measuring the distance from the beginning of the line to the 'X'.

The night prior to the first TMS treatment (sham or active) subjects were given a 1-mg dexamethasone tablet. In the morning (approximately 12 h after dexamethasone administration) and before the first treatment, serum levels of cortisol, thyroid-stimulating hormone (TSH) and prolactin were obtained. After the TMS treatment, serum levels of TSH and prolactin were obtained. This procedure was repeated for the tenth treatment.

At entry, subjects had a baseline structural magnetic resonance imaging scan (34).

rTMS parameters

Patients were assigned using an urn randomization based on age (<40 or ≥ 40 years) and gender to receive either daily left prefrontal rTMS [5 Hz, 110% motor threshold (MT), 8 sec on, 22 off, over 20 min] or placebo (lateral edge and posterior edge of the coil angled 45° off of the head with only the left anterior tip touching the skull) each weekday

morning for 2 weeks. We used a figure eight TMS coil with a solid core (Neotonus, Inc., Atlanta, GA, USA). Prior to each treatment (active and sham), subjects were questioned regarding the prior nights sleep (at least 6 h), recent caffeine use (less than three cups of coffee in the last 12 h), and any medication changes (started on medication known to significantly lower the seizure threshold like stimulants, buproprion, etc.). If the subjects were deemed safe for the TMS treatment, the MT was then determined before each treatment with the right thumb at rest using the method of limits as previously described (35). We then positioned the left prefrontal TMS coil 5 cm anterior and in a parasagittal line from the motor APB site. TMS was administered each day by a trained psychiatrist (XL) who purposefully had very limited verbal interaction with the subject.

Analysis

Subjective daily mood ratings To determine if there was an immediate (within day) change in subjective mood for the active versus the sham rTMS treatments, the visual analog scales were measured by an investigator blind to the treatment group. For each daily session, the premeasurement was subtracted from the postmeasurement to give an analog measurement difference of subjective change in mood. A positive number would therefore indicate an improvement in mood. The difference was averaged over the treatment days to obtain a mean for each subject. The mean difference was analyzed using a Student's *t*-test to compare the mean analog measurement difference for the active and the sham.

Motor threshold To see if a significant change in MT occurred for the active group over the course of the study, a paired *t*-test of the resting motor threshold (RMT) of day 10 versus treatment day 1 was performed for the active group. In addition, a paired *t*-test comparing the difference in RMT for the active and sham groups was calculated. To confirm this result, a repeated measures ANOVA was calculated with between-subject factors of active and placebo and with-in subject factors of treatment days 1 and 10.

Endocrine data Recent studies (36, 37) have shown that TMS can normalize the dexamethasone suppression test. Subjects with postdexamethasone cortisol levels of >5 μg/dL were considered non-suppressors. A chi-squared test was performed to determine if the number of non-suppressors converted to suppressors was different for the active versus sham group. To see if there was a significant difference for the active versus sham group in TSH from before the first treatment to before the tenth treatment, a paired *t*-test was performed. Elevation in serum prolactin has been identified as a marker for seizure activity (38). In an attempt to identify possible increases in prolactin associated with a TMS treatment, a paired *t*-test was performed for the difference in prolactin levels post- minus pretreatment for active versus sham.

Outcome The primary clinical outcome variable was the percentage change in HRSD at 2 weeks compared with day 1 of treatment (clinical response defined as $>50\%$ decline in HRSD or <10). In addition, YMRS, HAM-A, Beck Depression Scale, and GAF were analyzed using Student's *t*-tests for significant differences between active and sham groups.

Following the last day of the 2 weeks and after the final ratings were obtained, the blind was broken for each subject. Those initially randomized to sham treatment were offered the option of 2 weeks of active treatment at the same parameters. Treatment responders to either the active or later open TMS phase were offered the option of weekly maintenance TMS treatments over the next year.

Results

Subjects

Subjects included 23 adults with 11 subjects being randomized to receive active daily left prefrontal TMS for 2 weeks (see the Table 1 for demographics).

Integrity of the blind

All subjects were asked prior to breaking the blind what they thought they had received, and whether there had been anything on the part of study personnel that influenced their decision. All subjects guessed their status based on their clinical response. That is, all responders guessed they were receiving active TMS. All clear non-responders guessed sham. There were no cases of study personnel compromising the blinding of allocation to treatment group.

Safety and tolerance

There were no adverse cognitive effects of the TMS as measured by subjective complaints. In addition, there were no drop-outs from the study. Previous studies have shown that TMS can induce mania in BPAD patients (39). We were thus concerned

Table 1. Demographics of study population

	Active rTMS	Sham rTMS
Number (men)	11 (4)	12 (5)
Mean age in years (SD)	42.4 (7.3)	43.4 (9.3)[a]
Mean baseline HRSD (SD)	32.5 (4.3)	32.8 (7.6)
Mean baseline YMRS (SD)	1.7 (2.6)[b]	0.6 (1.0)
Mean baseline HAM-A (SD)	18.1 (1.6)[b]	16.4 (1.2)[d]
Mean length of illness in years (SD)	22.6 (8.1)[c]	19.3 (11.2)[d]
Mean length of present episode in months (SD)	18.6 (18.4)[b]	23.5 (24.5)[e]
Subjects on mood stabilizers	7	7
Bipolar type – I depressed, II depressed, I mixed	5, 6, 0	7, 3, 2

The data is not available as it was not recorded at the time of the study.

[a]Available for 11 sham subjects.

[b]Available for 10 rTMS subjects.

[c]Available for 9 rTMS subjects.

[d]Available for 10 sham subjects.

[e]Available for 8 sham subjects.

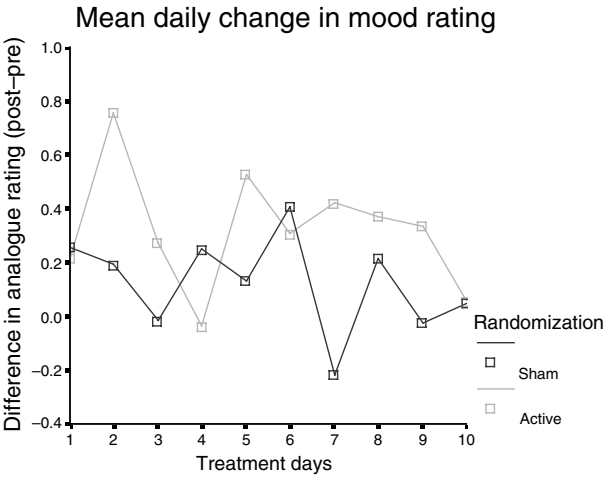

Fig. 1. The immediate mean change in subjective mood ratings (post- minus pre-TMS treatment) for subjects receiving active and sham is graphed by treatment day. There does not appear to be a trend for change in immediate mood differences across the treatment days.

about inducing mania with TMS. No subjects stopped the study as a result of hypomania or mania and active rTMS did not cause a statistically significant within-group increase in the YMRS ($t = -0.73$, $p = 0.49$).

Subjective daily mood ratings

For the 20 subjects with available data (one active and two sham missing), there was only a trend for a statistically significant improvement in subjective mood from daily baseline on the day of treatment for the active versus the sham rTMS ($t = 1.58$, $p = 0.13$). We then plotted the group change in daily subjective mood ratings for each of the 10 days to determine whether the within-day effects were greater at the beginning or end of the 2 weeks. There was no clear pattern (Fig. 1).

Motor threshold

There were no statistically significant within (active – difference treatment day 10 – treatment day 1 = 5.9, SD 12.2; $t = 1.60$, $p = 0.14$) or between-group changes (active versus placebo; $t = 1.11$, $p = 0.28$) in MT comparing treatment day 1 to treatment day 10. The repeated measures ANOVA confirmed that there was no significant main effect by treatment group ($F = 0.14$, $p = 0.717$).

Endocrine data

There were only three subjects who met criteria for dexamethasone non-suppression (1 active and 2 placebo) which precluded any meaningful statistical analysis. Descriptively, the one non-suppressor who received active treatment continued to non-suppress (active non-responder). A suppressor who received active treatment became a non-suppressor but was a clinical responder. One of the two non-suppressing subjects who received sham converted to a suppressor (placebo non-responder). There was no statistically significant difference between the sham and active groups for change in TSH ($t = 0.98$, $p = 0.35$) over the course of the 2 week treatment. The change in prolactin levels from pre-TMS treatment to post-TMS treatment was not significantly different ($t = 0.60$, $p = 0.56$) for active versus sham TMS, providing evidence that no seizure activity had occurred.

Blind randomized mood ratings

There were four of 11 active TMS responders and four of 12 sham TMS responders. Each group had one remitter. Using paired versus unpaired *t*-tests did not produce meaningful differences in results for all measures analyzed. There was no significant difference between the two groups in HRSD change from baseline over the 2 weeks ($t = -0.22$, $p = 0.83$). The mean percentage change in HRSD was 25% (SD 32%) for the active TMS and 25% (SD 31%) for the sham TMS. In addition, there were no significant differences between the active and sham groups for the YMRS ($t = -0.96$, $p = 0.35$), HAM-A ($t = -0.06$, $p = 0.95$), Beck Depression Scale ($t = 0.55$, $p = 0.59$) and GAF ($t = 0.64$, $p = 0.52$). Interestingly, of the four

active responders, three were on anticonvulsants and/or benzodiazepines. Due to the small numbers, limited conclusions can be made from this result, but clearly these medications cannot completely prevent a significant response.

Discussion

We have demonstrated that left prefrontal TMS can be safely administered to BPAD depressed subjects for 2 weeks (many of whom were taking antimanic medications) without a significant increase in manic symptoms as measured by the YMRS. Unlike others who have used prefrontal TMS in BPAD patients (39), we did not induce mania in any subjects. Contrary to an earlier report (40), there was only a trend and not a statistically significant improvement in subjective mood from pre-TMS to post-TMS for active compared with sham. There was unfortunately some missing data that makes any firm conclusions in this small sample very tenuous. We found no significant change in MT over 2 weeks of treatment for the active rTMS. With this small sample and these particular TMS parameters, we also failed to find a statistically significant difference in depressive symptom response between those receiving active and sham rTMS. The percentage of active responders (four of 11 or 36%) was consistent with previous studies (12, 14, 15), but was not significantly different from the percentage of sham responders (four of 12 or 33%).

There are many factors that need to be considered in interpreting the results of this pilot study. First, this study was small and could only detect extremely large effects. The failure to find differences between active and sham with a small sample should not be confused with showing that there is no difference. This would require a much larger study. Conceivably, however, left prefrontal TMS at these parameters does not have antidepressant effects in BPAD-depressed subjects. Interestingly, over the same years of this trial, our group at MUSC found evidence for TMS antidepressant effects using similar parameters, the same raters, TMS administrators, and recruitment patterns, in a mixed unipolar and bipolar depression study (13) and in a geriatric depressed cohort (41). This study had less power than the George et al. (2000) study to detect a difference in terms of sample size, and there were other key differences in TMS administration and study design that are particular to studying BPAD depression. Specifically, most of the subjects in the George et al. (2000) study were medication free and those likely to worsen with medication taper were not enrolled.

Secondly, the area of treatment parameters with rTMS has significantly advanced since this study was conceived and carried out. Since this trial was designed, data has emerged that only 2 weeks of treatment with rTMS may be inadequate, with at least 3 weeks of treatment needed for optimum response (16–18, 42). On the other hand, both the duration and number of stimuli were likely adequate to test if depressive symptoms can be significantly improved with rTMS. We delivered 1600 stimuli/day (16 000 total stimuli). This appears to be near the average for most studies. The intensity (110% MT) and frequency of stimulation were also in the realm of other recent studies where active TMS was significantly superior to sham.

This study highlights many of the problems inherent in studying bipolar depression. Many have argued that bipolar disorder has been understudied relative to general depression (43). The management of bipolar depression is both difficult to research, as well as challenging to manage clinically. In order to meet recruitment at our sight, we had to mix BPI and BPII subjects, although they are clearly different clinically. There is also the issue of medications. Although a medication-free study would have been stronger scientifically, we felt this was ethically unwise given the potential for inducing manias with TMS, and the clear cases of treatment refractoriness following discontinuation of mood stabilizers (44). We thus compromised by allowing continuation of some, but not all, mood stabilizers. The relatively rapid 2-week taper was likely insufficient to establish a stable baseline, and may have contributed either to the lack of effectiveness, or to the relatively high placebo rate. We suggest that future studies of TMS in BPAD depression employ a slower washout, and have at least 4 weeks of baseline prior to study entry. There is also a theoretical concern about whether certain medications, particularly anticonvulsants or benzodiazapines, might block the antidepressant effects of TMS. This has been a particular concern in the ECT literature (45). Some clinical studies have found TMS response in the setting of concomitant medications (42), although these were not consistently anticonvulsants in a BPAD-depressed sample.

Another consideration is that for the sham TMS we positioned the TMS coil with the left anterior tip touching the scalp. This angle may still result in about 40–50% of current induced in the brain (C. Epstein, personal communication), and potentially have some biologic effects. Future studies in our laboratory and others are now using a form of sham TMS coil with a sheet of metal inserted between the coil and the person's head, which

blocks the magnetic field but has much the same noise and feel as a real coil.

Although immediate improvement in mood did not reach statistical significance (possibly due to missing data points), active TMS did produce a trend toward subjectively improving mood immediately after a treatment compared with placebo. This trend replicates work by George (1994) (46), and Szuba (1999) (40), that left rTMS can induce an immediate subjective improvement in mood. These subjective mood changes are immediate and not necessarily consistent. The lack of significant change in the subjective Beck Depression Scale suggests that these results do not necessarily indicate a lasting subjective change in mood.

One concern in the literature is that prefrontal rTMS can induce a change in the MT over time (47). We, however, found no difference comparing the MT from treatment day 1 to treatment day 10 either within the group of subjects receiving active stimulation or the difference in MT between the groups of active and sham. The reason for this difference could be related to differences in population, methods to determine the MT or statistical methods employed, but is largely unknown. Further study with well-defined methods to determine MT are needed to clarify this issue.

Since our cohort had only three dexamethasone non-suppressors, we could not perform any meaningful analysis. Interestingly, we had so few non-suppressors, and one of the subjects who became a non-suppressor actually clinically responded to active TMS. The lack of significant change in prolactin prior to treatment to post-treatment is reassuring data that we were not inducing seizures. The lack of change in TSH was also interesting but difficult to interpret as dexamethasone also suppresses TSH as well as cortisol (48). A final consideration is that dexamethasone itself may have somehow impacted on the clinical rating scale results of this study.

The management of depression in the setting of bipolar disorder is a vexing problem. On the one hand, we have demonstrated that prefrontal TMS is safe in this population, without an overwhelming risk of inducing mania. On the other hand, we failed to find even a trend toward an antidepressant effect in this pure BPAD-depressed group. Thus, for now, TMS is in the class of antidepressant treatments where there is clear evidence of its effectiveness in UP depression (6–9) but where double-blind demonstration of effectiveness in BPAD has not been shown. The lack of statistically significant difference in placebo in this study is probably more related to study design (too short medication washout and baseline assessment), higher than expected placebo response, and small sample size than there being a fundamental difference in response for bipolar verses unipolar depression.

We have identified several areas that should be changed in future TMS antidepressant trials in this population. Increased number of days of treatment, more stable medication washout, and a different measurement of depressive symptoms should be strongly considered in future trials. More research is needed to determine whether left prefrontal TMS over several weeks has an antidepressant effect in this population.

Acknowledgements

Support: The bulk of this study was funded by a grant to Dr George from the Stanley Foundation. The BSL is also supported in part by research grants from the National Alliance for Research on Schizophrenia and Depression (NARSAD), the Borderline Personality Disorders Foundation (BPDRF), NINDS grant RO1-AG40956, and the Defense Advanced Research Projects Agency (DARPA). The BSL has also received grant support from Cyberonics (VNS) and Neotonus (Neuronetics) (TMS) for clinical trials.

The authors would like to thank Carol Hanback, Minnie Dobbins, Poya Moghadam and Alyssa Melson for administrative help. None of the authors have equity or financial conflicts.

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