

Deep Transcranial Magnetic Stimulation for treatment-resistant bipolar depression: A case report of acute and maintenance efficacy

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Deep Transcranial Magnetic Stimulation (dTMS) is currently being evaluated as a possible treatment for several neuropsychiatric disorders and has been demonstrated as a safe and effective procedure. This case presents a patient with bipolar depression that has been treated with 20 daily consecutive dTMS sessions and with one dTMS session every 2 weeks for the following 3 months. Depressive symptoms improved rapidly and response was maintained during the next 6 months; cognitive performances also improved. This report suggests that add-on dTMS may help overcoming drug-resistance in bipolar depression and protect from subsequent bipolar episodes of any polarity.

Keywords: Deep Transcranial Magnetic Stimulation; Treatment-resistant bipolar disorder; Bipolar depression; Prefrontal cortex; Maintenance treatment of bipolar disorder.

Bipolar Disorder (BPD) is a common, chronic, debilitating psychiatric illness, characterized by recurrent (hypo)manic and depressive episodes. Although the elevated mood during mania and hypomania characterizes BPD, depression is the predominant clinical condition (Judd & Akiskal, 2003). In fact, patients with BPD may spend at least half of their lives with some degree of depressive

symptomatology, which is a major cause of burden, functional impairment, and death among BPD patients (Altshuler et al., 2006; Kupka et al., 2007).

The treatment of bipolar depression is difficult because this disease is often confused with unipolar depression and treated as such. This results in incomplete or absent clinical response, and may even expose to the risk of phase switch or to

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We gratefully acknowledge the contribution of the Librarians of the School of Medicine and Psychology of Sapienza University, Drs. Mimma Ariano, Felicia Proietti, and Tiziana Mattei, in helping us localizing relevant literature.

rapid cycling. Current treatment guidelines are not helpful on this point, due to the lack of general consensus and to the divergences in the recommendation of antidepressants (Ghaemi, Ko, & Goodwin, 2002; Nivoli et al., 2011). Moreover, treatment-resistance is more frequent in bipolar depression than in unipolar depression; since the two disorders seem to be neurobiologically different, also the criteria for treatment-resistance should be different. Only recently there have been attempts to tackle this issue appropriately (Pacchiarotti et al., 2009).

Biological treatments, such as electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS), are considered like additional options for the treatment of treatment-resistant bipolar depression. ECT is considered to be an effective alternative for drug-resistant patients, but it requires general anesthesia, the induction of seizures, and may cause memory and learning impairments (Lukoyanov, Sá, Madeira, & Paula-Barbosa, 2004; Rami-Gonzalez et al., 2001; Zambello & Vaona, 2009). rTMS is a non-invasive technique already used to manage treatment-resistant unipolar and bipolar depression (Fitzgerald & Daskalakis, 2011; Zeeuws, Santermans, Baeken, & Vanderbruggen, 2010; Zeeuws et al., 2011); by means of an electromagnetic coil, placed above the patient's scalp, it sends magnetic pulses to the brain, thus inducing electrical activity in the underlying cortical tissue that can result in localized neuronal depolarization (George, Lisanby, & Sackeim, 1999). Neuroimaging studies have led to the imbalance hypothesis of Major Depressive Disorder (MDD), which postulates prefrontal asymmetry with relative hypoactivity in the left dorsolateral prefrontal cortex (DLPFC), along with relative hyperactivity in the right DLPFC (Drevets, 2000; Grimm et al., 2008). In fact, patients with unipolar depression have been found to benefit from excitatory high-frequency rTMS over the left DLPFC and inhibitory low-frequency rTMS over the right DLPFC (Burt, Lisanby, & Sackeim, 2002; Gershon, Dannon, & Grunhaus, 2003).

There is evidence that depression involves integrated neural pathways linking select cortical, sub-cortical, and limbic sites and related molecular mediators (Nemeroff, 2002; Nestler et al., 2002). These regions cannot be effectively stimulated utilizing standard rTMS technology (Nadeem, Thorlin, Gandhi, & Persson, 2003). For this reason, a new coil (H-coil) has been invented to allow safer stimulation of deeper brain regions (dTMS)

(Bersani et al., 2012; Roth et al., 2002; Zangen, Roth, Voller, & Hallett, 2005).

Several studies assessed the efficacy and safety of dTMS in patients with unipolar depression (Isserles et al., 2011; Levkovitz et al., 2009; Minichino et al., 2012; Rosenberg, Isserles, et al., 2011; Rosenberg, Shoenfeld, Zangen, Kotler, & Dannon, 2010; Rosenberg, Zangen, Stryjer, Kotler, & Dannon, 2010), but only one study of Harel et al. (2011) showed efficacy in bipolar depression. This study suggested a possible positive therapeutic effect of dTMS in patients with bipolar depression when used as adjuvant therapy, along with mood stabilizers and antidepressants. Despite these results are encouraging, the study did not investigate the long-term efficacy of the treatment. Dell'Osso, D'Urso, Castellano, Ciabatti, and Altamura (2011) already investigated the long-term efficacy of TMS, but in their study they used the superficial rTMS rather than the newer dTMS. Their results showed that the achievement of remission after acute rTMS was predictive of maintenance of response at 1 year and, however, the absence of acute rTMS response predicted the absence of subsequent response in the long term.

Our report aimed to assess efficacy and safety of daily add-on dTMS in relieving drug-resistant bipolar depression, and its ability to protect from episodes of either polarity during a 3-month maintenance period, with fortnightly sessions, and during another 3-month period, with no dTMS sessions and only continuation drug treatment.

MATERIALS AND METHODS

Deep TMS device

The dTMS stimuli were delivered using the Brainsway's H1-Coil Deep TMS System, composed by five main components: (i) an electromagnetic coil (H1-Coil), (ii) a TMS neurostimulator (Magstim Rapid or Rapid 2), (iii) a cooling system, (iv) a positioning device, and (v) a cart. The H1 coil is designed to effectively stimulate neuronal activation in medial and lateral prefrontal regions, including the orbitofrontal cortex, with a preference for the left hemisphere (Roth, Amir, Levkovitz, & Zangen, 2007; Roth, Padberg, & Zangen, 2007).

Deep TMS procedure

Prior to stimulation, patients were instructed to insert earplugs to mitigate any possible adverse

effects on hearing. Next, the H1 Coil were positioned over the patient's head at the appropriate location for abductor pollicis brevis (APB) stimulation, that was located by a suprathreshold intensity, and the resting motor threshold (MT) was established by gradually decreasing the stimulation intensity (using single pulse mode, applying one pulse every 5 seconds) while observing the patient's hand. MT was defined as the lowest stimulation intensity required to evoke a motor potential (MEP) of at least 50 μ V in 5 out of 10 stimulations. Subsequently, the coil was placed 6 cm anterior to the minimal APB MT location (i.e., the prefrontal cortex) and spatial coordinates were recorded with markings on a cap placed on the subject's head to ensure placement reproducibility. MT determination was repeated daily, and all treatments were delivered by one of four trained physicians (FSB, NG, LS, LM). Each dTMS session consisted of 2-second train duration with a 20-second inter-train interval. The total number of trains was 55 at 120% of the measured MT, at a frequency of 18 Hz. The complete cycle of the dTMS treatment consisted of five consecutive session days in a week for four consecutive weeks, for a total of 20 consecutive sessions.

Since the patient showed a significant response to treatment, we proposed a continued treatment with fortnightly dTMS sessions for the first 3 months after the 20th application, with the same parameters used in the acute phase (18 Hz for 2 seconds for 55 trains, at 120% of the MT). The patient was assessed at T0 (prior to 1st session), T1 (6th session), T2 (11th session), T3 (20th session), T4 (1 month after the 20th session), T5 (3 months after the 20th session, the last of continuation treatment),

and T6 (3 months after the end of continuation treatment) (Table 1).

Clinical measures

DSM-IV-TR Bipolar Disorder, Type-I diagnosis was confirmed through the Structured Clinical Interviews (SCID-I and SCID-II) for DSM-IV-TR criteria (First, Spitzer, Benjamin, Gibbon, & Williams, 1997; First, Spitzer, Gibbon, & Williams, 1996).

To assess clinical status we used the 21-item Hamilton Depression Rating Scale (HDRS-21; Hamilton, 1960), the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979), the Hamilton Anxiety Scale (HAM-A; Hamilton, 1959), the 18-item Brief Psychiatric Rating Scale (BPRS; Overall, 1974), and the Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978). To assess social and personal functioning we used the Global Assessment of Functioning (GAF; Bodlund, Kullgren, Ekselius, Lindstrom, & von Knorring, 1994). To assess possible cognitive and other side effects, we used the Mini Mental State Evaluation (MMSE; Folstein, Folstein, & McHugh, 1975) and the UKU Side Effects Rating Scale (UKU; Lingjærde, Ahlfors, Bech, Dencker, & Elgen, 1987) (Table 1).

Medications

dTMS was added-on the patient's drug treatment. During the stimulation period the patient was maintained on his current daily lithium

TABLE 1
Scores of clinical assessment scales

	T0 1st session	T1 6th session	T2 11th session	T3 20th session	T4 1 month after T3	T5 2 months after T4 (last session of maintenance treatment)	T6 3 months after T5
HDRS-21	23	10	6	4	5	5	4
MADRS	27	10	7	3	7	3	4
YMRS	9	8	5	5	6	6	6
HAM-A	20	7	7	3	5	4	2
BPRS	38	27	27	24	24	23	24
UKU	0	6	2	0	0	0	0
MMSE	27	29	28	30	28	30	30
GAF	51	61	65	81	81	85	85

(1200 mg/day), with plasma levels of 0.8 meq/L, and clonazepam (1 mg/day). Drug doses were stable during the dTMS period.

CASE REPORT

A 46-year-old drug-resistant (resistant to 2 consecutive antidepressant courses adequate for time and dosages) businessman with DSM-IV-TR Bipolar Disorder Type-I was referred to our center for a 3-month depressive episode. He was a very active person, he usually worked more than 10 hours a day, he spoke nine languages and travelled frequently for business or pleasure; he was married and had four children. The patient had no axis I or II comorbidities and had never manifested psychotic symptoms. The patient did not have any family history of psychiatric disorders.

Hypomanic onset occurred at age 18. He developed a first manic episode at age 30. He started a therapy with lithium 5 years later. His disorder showed a seasonal pattern, with manic episodes occurring within 1–2 days, mainly in spring and summer, while depressive episodes ran a slower course, occurring in 7–10 days, mainly during autumn and winter.

The index depressive episode in late August 2010 had a sudden onset. He complained about depressed mood, anhedonia, increased anxiety, sense of inadequacy and guilt, social withdrawal, initial and late insomnia and early awakening, and decreased appetite. He had also quit his job. In addition to lithium, he was treated with mirtazapine (45 mg/day) and immediate release oral quetiapine (200 mg/day) for the first 5 weeks; with bupropion (300 mg/day), immediate release oral quetiapine (200 mg/day) and clonazepam (1 mg/day) for the following 5 weeks. He refused ECT and reached our observation because of the persistence of the depressive symptoms despite medical prescriptions. Before starting dTMS, he was gradually withdrawn from bupropion and quetiapine over a period of 10 days; he provided written informed consent for the collection of his data for research, participation in the study, and subsequent publication.

The patient's motor threshold was 70% of the stimulator's capacity, hence he was administered dTMS at 100%, 105%, and 110% of the MT at the first, second, and third sessions, respectively. From the fourth session on, he was administered 120% of the MT, i.e., 84% of the stimulator's capacity.

RESULTS

The primary outcome was clinical response of depression, as assessed through the HDRS-21 and the MADRS. Secondary outcomes were scores on the BPRS, HAM-A, YMRS, MMSE, UKU, and GAF.

Depressive symptoms responded very rapidly. HDRS scores dropped from 23 at baseline to 10 at the 6th session, to 6 at the 11th session, and finally to 4 at the 20th session (Table 1).

YMRS scores dropped from 9 at baseline to 5 at the 2th session (Table 1).

MMSE scores progressively increased (showing improvement) from 27 at baseline to 30 at the 20th session, mainly due to improved orientation (Table 1).

During continuation sessions and 3 months after the completion of dTMS the patient was free from depression. He has shown no depressive relapse and no (hypo)manic switch.

DISCUSSION

This case shows that dTMS added on medication was followed by complete symptoms remission in a treatment-resistant bipolar depression episode; moreover, continuation dTMS was helpful in maintaining euthymia.

The patient had an unusually high MT; this may be a consequence of the use benzodiazepines, that are known to have increasing effects on MT (Paulus et al., 2008).

Depressive symptoms improved very rapidly; clinical remission was achieved after only 10 sessions (2 weeks). Unlike antidepressant drugs, which usually need 2–3 weeks for showing efficacy, this patient started improving by the first week of dTMS. Harel et al. (2011) showed a response rate of 63.2% (12 patients) and a remission rate of 52.6% (10 patients) in their 19 bipolar depressed patients after 20 dTMS add-on sessions; however, these patients were not treatment-resistant.

In addition to bipolar depression, in which this report is the first to show efficacy in treatment-resistance, dTMS showed effectiveness in treatment-resistant unipolar depression (Isserles et al., 2011; Levkovitz et al., 2009; Rosenberg, Isserles, et al., 2011; Rosenberg, Shoenfeld, et al., 2010; Rosenberg, Zangen, et al., 2010), treatment-resistant auditory hallucinations (Rosenberg Roth, Kotler, Zangen, & Dannon,

2011), treatment-resistant autism spectrum disorders (Enticott, Kennedy, Zangen, & Fitzgerald, 2011) and treatment-resistant negative symptoms of schizophrenia (Levkovitz, Rabany, Harel, & Zangen, 2011). Nevertheless, the small duration of the therapeutic effect is often the main weak point of the use of somatic therapies, and this issue has not been investigated in the previous dTMS study of bipolar depression (Harel et al., 2011). Our case showed that, after remission from an acute episode, fortnightly sessions of dTMS in addition to medication may be useful in avoiding relapses in the next 6 months. Furthermore, it is remarkable that all patients with bipolar depression treated with dTMS, i.e., our patient (Table 1) and Harel et al.'s (2011) 19 patients did not experience hypomanic or manic mood switches.

Our case also confirms the safety of dTMS, also in terms of cognitive improvements (Levkovitz et al., 2007); MMSE score increased from 27 to 30 after 4 weeks of therapy (Table 1). Although studies present in scientific literature so far showed that deep TMS is generally safe and tolerable, some side effects have been reported, such as scalp discomfort, migraine, dizziness, insomnia, and rare tonic-clonic seizures. No serious adverse events occurred during the trial we reported. The patient reported only mild and transient side effects, i.e., nausea, diaphoresis, and mild headache in the interval corresponding to the first three treatment sessions. Scalp discomfort, reported during the first days, disappeared within the first five session and scalp inspection revealed no skin lesions (Table 1).

In conclusion, this report suggests that dTMS can be useful in treatment-resistant bipolar depression and in preventing bipolar episodes of any polarity.

One limitation of this case report is the relatively short follow-up, another that we cannot attribute improvements only to dTMS, as the treatment was added on medications. However, given that the patient was drug-resistant, we may state that most of the change was due to the add-on dTMS. Given the successful results and the favorable tolerability profile of deep TMS, a systematic investigation with a larger cohort and a longer follow-up may be of great interest.

Original manuscript received 1 January 2012
Revised manuscript accepted 29 February 2012
First published online 24 July 2012

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