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# Repetitive transcranial magnetic stimulation in bipolar depression: Another puzzle of manic switch?

## Repetitivna transkranijalna magnetna stimuacija kod bipolarne depresije: još jedna zagonetka maničnog preokreta?

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### Introduction

Bipolar depression is common disorder characterized by substantial comorbidity, mortality, the highest suicide rate among psychiatric illnesses and severe social impairment, but is still often misdiagnosed.

The real prevalence of bipolar depression could be much higher than is thought, because the problem of misdiagnosis.

A percentage of undiagnosed bipolar patients is especially high in population of treatment resistant depression. These patients are most frequently misdiagnosed as having unipolar depression and treated with anitidepressant monotherapy, that result in worsening of the course of the illness and often lead to rapid cycling.

Two independent studies [1, 2] in population of 203 and 250 patients with major depression found 40–49% of bipolar disorder. In 1994, the results of survey of National Depressive and Manic-Depressive Association showed that 73% of 500 bipolar patients were misdiagnosed as having unipolar major depression [3]. Unfortunately, 10 years later the same association survey found that nothing has changed and that 69% of another 600 bipolar patients were misdiagnosed in this period of time [4].

Even when correctly diagnosed, treating bipolar depression can also be challenging, and after many treatment guidelines it is often much more difficult to manage bipolar depression than bipolar mania. In treatment of bipolar depression particularly delicate, often questionable, demanding "art and science", are treatment resistance (require high doses and combinations of antidepressants) *vs* risk of manic switch (sometimes happen even with the lowest doses of antidepressants in a first few days of treatment), but also problems of different treatment strategies in acute and maintenance therapy that often result in the problem of polypharmacy.

### Repetitive transcranial magnetic stimulation in affective disorders

During the last decade, the use of repetitive transcranial magnetic stimulation (rTMS) in treatment of pharmacoresistant major depressive disorder (MDD) applies increasingly.

rTMS is a neurostimulative technique, in which a magnetic stimulation coil is placed over a strictly defined positions of subjects head. The passage of current through the copper wire in the coil, leads to induction of magnetic field whose direction is perpendicular to the direction of current flow in the coil. Such a magnetic field leads to the induction of electric field in the surface layers of the cerebral cortex, which causes the activation of interneurons and pyramidal neurons, depending on the intensity of stimulation [5]. The application of a single magnetic pulse, as described above, leads to firing of several descendent potentials along the pyramidal tract, in case of stimulation of the motor cortex, with the possibility of recording short latency EMG response in the contralateral limb muscles (latency between 20 and 25 msec) [6]. However, using a series of magnetic stimuli with precisely defined frequency and intensity (usually lower than the threshold to cause motor response) is feasible to induce neuromodulatory effects, in

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terms of its effects last beyond the duration of stimulation [7]. This led to a concept of purposeful modulation of cortical activity in order to induce plastic changes [8]. This concept was confirmed in humans in the example of motor cortex plasticity induced by motor learning [9]. Low-frequency repetitive TMS (≤ 1 Hz) causes a consistent and lasting decrease in motor cortical excitability in healthy individuals in contrast to the "facilitatory" effects induced by high-frequency repetitive TMS (5–20 Hz) [10, 11]. The knowledge gained in the experiments on the motor cortex, moreover, as an analogy, used in the explanation of mechanisms of therapeutic effects of rTMS treatment of depression [12].

Efficacy of rTMS in major depression has been demonstrated in many randomized controlled trials [13–16]. However, only a few rTMS trials in bipolar depression have been published in the last 10 years with contradictory findings.

In 2002, the first rTMS study in bipolar depression [17] showed a significant rTMS efficacy compared to sham, Nahas [18] did not have a significant response in the group of 23 bipolar patients, but a recent trial showed also rTMS efficacy and safety in mixed episodes of bipolar disorder [19].

rTMS protocols in major depression predominantly used high frequencies of stimulation (≥ 5Hz) of the left dorsolateral prefrontal cortex (DLPFC) and only a few trials used low frequent (≤ 1Hz) rTMS of the right DLPFC [14, 20–22] where antidepressant efficacy was also shown, besides much better safety profile.

Generally, it is considered that major depression is related with the functional insufficiency of both left and right hemispheres, with lower excitability and metabolic hypoactivity in the left prefrontal cortex compared to higher right frontal cortical excitability. Use of rTMS in treatment of major depression is based on the opposite effects of high frequency (≥ 5 Hz) and low frequency (≤ 1 Hz) on cortical excitability [23], where low-frequency rTMS leads to reduced intracortical excitability, regional metabolism and blood flow [10, 24] and *vice versa* for high frequency rTMS [11, 25].

## Iatrogenic induction of hypomanic/manic switch – a form of bipolar illness?

Antidepressant associated manic switch was reported to be higher in bipolar type I disorder than unipolar depression [26, 27] or bipolar type II [28], and antidepressant induced mania during the treatment of unipolar depression is considered as a sign of latent bipolar disorder [29].

In unipolar depression, estimates of the rate of antidepressant associated mania have been in the range of 0–25% [26, 27, 30]. Higher rates of antidepressant-associated mania have been reported in bipolar disorder [26].

There is still no general consensus should antidepressant-induced mania be coded as a form of bipolar disorder. The International Classification of Diseases-10 (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) still do not code this state as a specific form of bipolar disorder. However, there is a widespread proposal, strongly supported by clinical evidences and many expert opinions, for antidepressant induced mania to be included in bipolar spectrum, provisionally with the categorization of bipolar III affective disorder [29] and it is also in consideration to be coded as bipolar affective disorder in DSM-V and ICD-11.

As with pharmacotherapy, iatrogenic induction of manic or hypomanic switch may occur during almost all other biological, non-pharmacological treatment for major depression, such as electroconvulsive therapy [31], vagus nerve stimulation [32], phototherapy [33] and therapeutic sleep deprivation [34, 35].

## Switch to hypomania/mania during rTMS treatment of major depression

Fitzgerald and Daskalakis [36], in an article addressed the issue of practical guidelines to use rTMS in depression, based both by review of the literature and experience these authors have in rTMS in the treatment of major depression more than 10 years found that the trials specifically of bipolar depression have been too limited at this stage to allow any conclusions, however rTMS could be reasonable treatment option. They suggest concurrent use of mood stabilizers during rTMS in these patients, even the risk of manic switch, in their opinion, is low.

In 2008, Xia et al. [37] published a review focused on treatment-emergent mania/hypomania (TEM) associated with rTMS (37). This review included 53 randomized controlled trials (RCTs) of rTMS in unipolar and bipolar depression, published until 2006, where in 10 trials a total of 13 cases of mania/hypomania were reported (3 cases in RCTs, other 10 in single or multiple case reports). They found that TEM occurrence rate in RCTs, in this sample of both unipolar and bipolar disorders was 0.84% for active treatment group, and 0.73% for sham group, which was not statistically different. In total of 65 bipolar patients the switching rate in the active rTMS group was 3.1% and for unipolar depression was only 0.34%, that all indicate that rTMS does not have a higher risk of manic switch than antidepressants pharmacotherapy.

Furthermore, this comprehensive review evaluated phenomenon of hypomanic/manic switch in rTMS trials in relation with diagnosis (unipolar and bipolar depression), the parameters of stimulation (laterality, frequency, intensity, duration of stimulus train and intertrain intervals, number of pulses per session, frequency of sessions), and found that switch was more often in bipolar depression, in patients who received two rTMS sessions per day, with no specific relation with laterality, frequency and duration of stimulus train.

As was mentioned above, in most rTMS studies of major depression high frequencies of stimulation were used, as in reported cases of switch to hypomania/mania but only a few studies using low frequencies of stimulation in depression reported switch to hypomania/mania. Ella [38] reported two cases of manic switch in patients previously thought to have unipolar depression during slow (1 Hz) rTMS treatment of the right DLPFC where number of stimuli per session they used was 1,200 stimuli/day; in one patient stimulation was applied during 2 weeks (10 sessions) and in another patient 3 weeks (15 sessions); in both cases the switch occurred few days after the last sessions.

In the first placebo-controlled, randomized trial of different frequencies of rTMS in posttraumatic stress disorder two cases of mania were reported – one in group stimulated with 1 Hz, another in group stimulated with 10 Hz, in both cases after only 3 days of stimulation [39]. Hausmann et al. [40] used bilateral rTMS (20 Hz, 100% of the resting motor threshold (RMT) over the left DLPFC and 1 Hz, 120% RMT over the right DLPFC) to enhance antidepressant outcome but patient switched to mania on day 7 of stimulation; in this study citalopram was also started on the first day of stimulation, and it's questionable was switch related to effect of rTMS, citalopram, or both. In this patient bipolar affective disorder was already diagnosed, so it's not clear why she received antidepressants without mood stabilizer.

Fitzgerald et al. [41] 2003 in double-blind, parallel design study reported one switch to mania with stimulation of 1 Hz, 100% RMT, 300 stimuli/session (in group stimulated with 10 Hz was no switch), but that particular patient was the only one diagnosed as bipolar among the unipolar depressed patients, and in 2006, the same author published parallel-crossover study with 1 and 2 Hz, where in 130 stimulated patients only one manic switch occurred (again, in patient with bipolar depression).

In addition, Nedjat and Folkerts [42] also reported transient hypomanic symptoms in a period of a day during high frequency rTMS of the left prefrontal cortex (PFC) in 3 of 50 healthy volunteers.

**How to manage hypomanic/manic switch if occurs during rTMS ?**

Most of the reported cases of switch to mania occurred within safety guidelines; the problem is that available guidelines focused on prevention of undesired seizures, but still do not consider prevention and management of manic switch.

This explains why the reported methods of managing hypomania/mania switches induced by rTMS in all published case reports were different.

In our case, hypomania has occurred at the end of the treatment when rTMS was already stopped as scheduled and we decided to keep antidepressant and carefully monitor patient during more frequent visits on outpatient clinic. During follow-up period symptoms of hypomania vanished in 2 weeks [43]. In this case, patients also continued to receive fixed dose of velafaxine during rTMS treatment associated with partial sleep deprivation (applied twice during two weeks), so in this patient hypomanic switch could be induced by synergistic effect of antidepressants treatment with rTMS and partial sleep deprivation as add-on therapy. In the above mentioned case reports in one patient after manic switch Ella [38] reported quick switch beck to depressive mood; valproate and sertraline were started and patient recovered in 5 weeks.

Sakkas et al. [44] in their study protocol used more aggressive stimulation with 20 Hz, 110% RMT, 1,600 stimuli/session, two sessions/day and reported one case of hypomania and one case of mania. They firstly tried to manage hypomania symptoms in one patient with discontinuation of antidepressant medication and continued rTMS treatment, but the patient became more manic; when rTMS was stopped the patient became depressed again and finally, euthymic after reintroduction of rTMS, this time stimulation was less aggressive – only once a day with concomitant use of mood stabilizers. This report definitely shows that mania-induced potential of rTMS correlates with the intensity of rTMS, but our protocol and above mentioned previous case reports [38, 40] with less intensive stimulation also result in switch to hypomania, that makes understanding of hypomanic/manic switch during rTMS much more unclear.

In contrary to Sakkas et al,[44] Cohen et al,[39] tried to manage mania during rTMS in posttraumatic stress disorder patients discontinuing firstly rTMS, then also antidepressant medication and manic symptoms abated in a 5 days. Hausmann et al. [40] decided to immediately stop both rTMS and antidepressant medication and started clozapine treatment; manic symptoms vanished in 5 days, but the patient switched back to depression and finally recovered after long lack of response on several antidepressants regimens in the next 3 months; this showed that rTMS treatment had even stronger antidepressant effect than all used medication. These authors also hypothesized that rTMS in combination with antidepressant medications might modulate kindling and sensitization phenomena, which enhance cycle acceleration in bipolar spectrum patients.

Dolberg et al. [45] used more intensive stimulation (10 Hz, 1,200 stimuli/day, 4 weeks) and reported two cases of manic switch that occurred even patients were on valproic acid during rTMS treatment; these authors decided to increase dose of mood stabilizer in one patient and added haloperidol in another patient, but in one of them manic symptoms lasted even 2 months.

In another case of manic switch during rTMS Ella et al. [38] first had enthusiastic try to stabilize a patient who switched during stimulation of right DLPFC with 1 Hz changing frequency of stimulation to 10 Hz at the same side, based on theories and neuroimaging findings of functional laterality of hemispheres in depression and mania and the opposite modulator effect of rTMS. This patient did not recover with this procedure, on the contrary, became more manic and recovered with valproate and risperidone treatment, but in the next few years a few case reports and controlled studies in mania were published, supporting efficacy of high frequency rTMS of right PFC in mania [19, 46, 47].

Use of mood stabilizers during rTMS treatment of bipolar depression was proposed to maximize safety, but that also did not completely stop switches during rTMS [37], similarly to use of mood stabilizers during antidepressant pharmacotherapy.

**Conclusion**

We want to highlight again that in cases of treatment resistant depression clinicians should always be aware of possible underlying bipolar disorder.

As another antidepressive biological treatments, rTMS also has a potential to induce hypomanic/manic switch.

Considering the fact that studies where hypomanic/manic switches were reported included patients with unipolar and but also bipolar depression, patients also often received antidepressants during rTMS and protocols of stimulation were different, further controlled studies with more specific inclusion criteria should give precise guidelines.

The idea of changing the frequency of stimulation if switch occurs looks elegant and already shown promising results. Further controlled studies of rTMS in mania are needed to answer if the riddle of manic switch during rTMS treatment of depression could be solved in a way with the same therapy.

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