

Bipolar Disorder

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Current status of the utilization of antiepileptic treatments in mood, anxiety and aggression: drugs and devices.

[Barry JJ](#), [Lembke A](#), [Bullock KD](#).

Department of Psychiatry, Stanford University Medical Center, 401 Quarry Road MC 5723, Stanford, CA 94305, USA. jbarry@leland.stanford.edu

Interventions that have been utilized to control seizures in people with epilepsy have been employed by the psychiatric community to treat a variety of disorders. The purpose of this review will be to give an overview of the most prominent uses of antiepileptic drugs (AEDs) and devices like the Vagus Nerve Stimulator (VNS) and Transcranial Magnetic Stimulation (TMS) in the treatment of psychiatric disease states. By far, the most prevalent use of these interventions is in the treatment of mood disorders. AEDs have become a mainstay in the effective treatment of Bipolar Affective Disorder (BAD). The U.S. Food and Drug Administration has approved the use of valproic acid for acute mania, and lamotrigine for BAD maintenance therapy. AEDs are also effectively employed in the treatment of anxiety and aggressive disorders. Finally, VNS and TMS are emerging as possibly useful tools in the treatment of more refractory depressive illness.

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Low-field magnetic stimulation in bipolar depression using an MRI-based stimulator.

[Rohan M](#), [Parow A](#), [Stoll AL](#), [Demopoulos C](#), [Friedman S](#), [Dager S](#), [Hennen J](#), [Cohen BM](#), [Renshaw PF](#).

Brain Imaging Center, McLean Hospital, Belmont, MA 02478, USA.
mrohan@mclean.harvard.edu

OBJECTIVE: Anecdotal reports have suggested mood improvement in patients with bipolar disorder immediately after they underwent an echo-planar magnetic resonance spectroscopic imaging (EP-MRSI) procedure that can be performed within clinical MR system limits. This study evaluated possible mood improvement associated with this

procedure. **METHOD:** The mood states of subjects in an ongoing EP-MRSI study of bipolar disorder were assessed by using the Brief Affect Scale, a structured mood rating scale, immediately before and after an EP-MRSI session. Sham EP-MRSI was administered to a comparison group of subjects with bipolar disorder, and actual EP-MRSI was administered to a comparison group of healthy subjects. The characteristics of the electric fields generated by the EP-MRSI scan were analyzed. **RESULTS:** Mood improvement was reported by 23 of 30 bipolar disorder subjects who received the actual EP-MRSI examination, by three of 10 bipolar disorder subjects who received sham EP-MRSI, and by four of 14 healthy comparison subjects who received actual EP-MRSI. Significant differences in mood improvement were found between the bipolar disorder subjects who received actual EP-MRSI and those who received sham EP-MRSI, and, among subjects who received actual EP-MRSI, between the healthy subjects and the bipolar disorder subjects and to a lesser extent between the unmedicated bipolar disorder subjects and the bipolar disorder subjects who were taking medication. The electric fields generated by the EP-MRSI scan were smaller (0.7 V/m) than fields used in repetitive transcranial magnetic stimulation (rTMS) treatment of depression (1-500 V/m) and also extended uniformly throughout the head, unlike the highly nonuniform fields used in rTMS. The EP-MRSI waveform, a 1-kHz train of monophasic trapezoidal gradient pulses, differed from that used in rTMS. **CONCLUSIONS:** These preliminary data suggest that the EP-MRSI scan induces electric fields that are associated with reported mood improvement in subjects with bipolar disorder. The findings are similar to those for rTMS depression treatments, although the waveform used in EP-MRSI differs from that used in rTMS. Further investigation of the mechanism of EP-MRSI is warranted.

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Repetitive transcranial magnetic stimulation as an add-on therapy in the treatment of mania: a case series of eight patients.

[Saba G](#), [Rocamora JF](#), [Kalalou K](#), [Benadhira R](#), [Plaze M](#), [Lipski H](#), [Januel D](#).

Unite de recherche clinique, secteur III de Ville Evrard, 5, Rue du Dr Delafontaine, Saint-Denis, 93200 France. urcve@free.fr

The aim of this study is to assess the efficacy of repetitive transcranial magnetic stimulation (rTMS) as an add-on therapy in the treatment of manic bipolar patients. Eight patients were enrolled in an open trial. They received fast rTMS (five trains of 15 s, 80% of the motor threshold, 10 Hz) over the right dorsolateral prefrontal cortex (DLPFC). They were evaluated using the Mania Assessment Scale (MAS) and the Clinical Global Impression (CGI) at baseline and at day 14. All patients were taking medication during the treatment trial. There was a significant improvement of manic symptoms at the end of the trial. No side effects were reported. The results show a significant improvement of mania when patients are treated with fast rTMS over the right DLPFC. However, these results have to be interpreted with caution since they derive from an open case series and all the subjects were taking psychotropic medication during rTMS treatment. Double-

blind controlled studies with a sham comparison condition should be conducted to investigate the efficiency of this treatment in manic bipolar disorders.

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Newer treatment studies for bipolar depression.

[Gao K, Calabrese JR.](#)

NIMH Bipolar Research Center, Mood Disorders Program, University Hospitals of Cleveland/Case Western Reserve University School of Medicine, Cleveland, OH, USA.

Objective: Depressive symptoms of bipolar disorder have more negative impact on a patient's life than manic symptoms. This review focused on the emerging efficacy data for treatments in bipolar depression. Methods: English-language literature cited in Medline was searched with terms bipolar depression, clinical trial, and trial. Randomized, placebo-controlled trials of newer studies with older agents and all studies with newer or novel agents were prioritized. Open-label studies of novel agents presented at major scientific meetings were also included. Results: Olanzapine, olanzapine-fluoxetine combination (OFC), and quetiapine were superior to placebo in the acute treatment of bipolar depression. Lamotrigine only significantly reduced core symptoms of depression compared with placebo. Pramipexole, a dopamine D2/D3 receptor agonist and omega-3 fatty acids, a polyunsaturated fatty acid, augmentation to mood stabilizer (MS) had superiority to placebo in reducing depressive symptoms. Topiramate augmentation of an MS was equally as effective as Bupropion-SR. Patients treated with an MS responded well to the addition of agomelatine, a melatonin receptor agonist with 5-HT_{2C} antagonist properties. However, inositol and repetitive transcranial magnetic stimulation did not separate from placebo. Lamotrigine and olanzapine, and to a lesser extent, divalproex, are superior to placebo in preventing depressive relapses. All agents were relatively well tolerated. Conclusions: Olanzapine, OFC, and quetiapine are effective in the acute treatment of bipolar depression. Compared with lithium and divalproex, lamotrigine is more effective in preventing bipolar depression. Larger controlled studies of the other agents in the acute and maintenance treatment of bipolar depression are warranted.

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Treatment of bipolar mania with right prefrontal rapid transcranial magnetic stimulation.

[Michael N, Erfurth A.](#)

Mood Disorders Unit, Department of Psychiatry, University of Muenster, Albert-Schweitzer-Str. 11, 48129 Muenster, Germany.

BACKGROUND: Transcranial magnetic stimulation (TMS) has been suggested for the

treatment of a variety of CNS disorders including depression and mania. **METHODS:** Nine bipolar (I) in-patients diagnosed with mania were treated with right prefrontal rapid TMS in an open and prospective study. Eight of nine patients received TMS as add-on treatment to an insufficient or only partially effective drug therapy. **RESULTS:** During the 4 weeks of TMS treatment a sustained reduction of manic symptoms as measured by the Bech-Rafaelsen mania scale (BRMAS) was observed in all patients. **LIMITATIONS:** Due to the open and add-on design of the study, a clear causal relationship between TMS treatment and reduction of manic symptoms cannot be established. **CONCLUSIONS:** Our data suggest that right prefrontal rapid TMS is safe and efficacious in the add-on treatment of bipolar mania showing laterality opposed to the proposed effect of rapid TMS in depression.

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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](#).

Brain Stimulation Laboratory, Department of Psychiatry, Medical University of South Carolina, Charleston 29425, USA.

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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The Bech-Rafaelsen Mania Scale in clinical trials of therapies for bipolar disorder: a 20-year review of its use as an outcome measure.

[Bech P.](#)

Psychiatric Research Unit, WHO Collaborating Centre for Mental Health, Frederiksborg General Hospital, Hillerod, Denmark. pebe@fa.dk

Over the last two decades the Bech-Rafaelsen Mania Scale (MAS) has been used extensively in trials that have assessed the efficacy of treatments for bipolar disorder. The extent of its use makes it possible to evaluate the psychometric properties of the scale according to the principles of internal validity, reliability, and external validity. Studies of the internal validity of the MAS have demonstrated that the simple sum of the 11 items of the scale is a sufficient statistic for the assessment of the severity of manic states. Both factor analysis and latent structure analysis (the Rasch analysis) have been used to demonstrate this. The total score of the MAS has been standardised such that scores below 15 indicate hypomania, scores around 20 indicate moderate mania, and scores around 28 indicate severe mania. The inter-observer reliability has been found to be high in a number of studies conducted in various countries. The MAS has shown an acceptable external validity, in terms of both sensitivity and responsiveness. Thus, the MAS was found to be superior to the Clinical Global Impression scale with regard to responsiveness, and sensitivity has been found to be adequate, with the MAS able to demonstrate large drug-placebo differences. Based on pretreatment scores, trials of antimanic therapies can be classified into: (i) ultrashort (1 week) therapy of severe mania; (ii) short-term therapy (3 to 8 weeks) of moderate mania; (iii) short-term therapy of hypomanic or mixed bipolar states; and (iv) long-term (12 months) therapy of bipolar states. The responsiveness of MAS is such that the scale has been able to demonstrate that typical antipsychotics are effective as an ultrashort therapy of severe mania; that lithium and anticonvulsants are effective in the short-term therapy of moderate mania; and that atypical antipsychotics, electroconvulsive therapy (ECT) and transcranial magnetic stimulation seem to have promising effects in the short-term therapy of moderate mania. In contrast, the scale has been used to demonstrate that calcium antagonists (e.g. verapamil) are ineffective in the treatment of mania. MAS has also been used to add to the literature on the evidence-based effect of lithium as a short-term therapy for hypomania or mixed bipolar states and as a long-term therapy of bipolar states.