TRAMBID

Study protocol

i. Study design

A single-center, double-blind, randomized, three-arm parallel-group, sham-controlled study comparing efficacy and safety of 10 Hz rTMS at the right ventrolateral cortex (RVL rTMS) with the left dorsolateral 10 Hz rTMS (LDL rTMS), and the sham rTMS as an add-on treatment in patients with bipolar I and II disorder, currently with the major depressive episode (BDE).

The study is composed of an initial screening phase (up to 2 weeks), a four-week double-blind treatment phase with daily rTMS (active or sham), and a four-week open-label follow-up phase for those who responded to acute treatment.

Enrollment of patients takes place at the National Institute of Mental Health, Klecany, Czech Republic (NIMH-CZ)

All study procedures will be carried out according to the Declaration of Helsinki, approved by the Institutional Review Board of the National Institute of Mental Health, and reviewed by the State Institute of Drug Control (CZ). The study is supported by a grant from Czech Health Research Council, registration No. 16-31380A.

ii. Participants

Both inpatients and outpatients with bipolar disorder I and II, currently in the major depressive episode (BDE) are eligible for study participation. The patients will be diagnosed according to DSM-IV-TR criteria confirmed by Mini International Neuropsychiatric Interview (MINI), Czech version 5.0.0 (Sheehan et al. 1998). The patients must meet the following inclusion criteria at screening and at baseline visit to be enrolled into the study: females or males aged 18 to 70 years; moderate to severe depression based on the Montgomery-Åsberg Depression Rating Scale (MADRS) score ≥ 20; a current BDE lasting at least 4 weeks but no more than 12 months; taking mood stabilizers (lithium, valproate, lamotrigine) or second-generation antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone) at a steady dosage for at least 4 weeks before screening and it is clinically appropriate to continue during the trial period; failed to respond to at least one adequate antidepressant trials in the current BDE; being able and willing to provide written informed consent; and right-handedness.

Patients will be excluded if one of the following conditions is present: psychotic symptoms during the current BDE; hypomanic, manic, or mixed features at screening or at baseline visit (the Young Mania Rating Scale (YMRS) > 11); significant risk of suicidal behavior based upon MINI or MADRS item 10 (suicidal thoughts) ≥ 4 at screening or baseline visit; eight or more episodes of BD within 12 months prior to study enrollment; history of any DSM-IV Axis I diagnosis other than bipolar disorder I and II, with exception of anxiety disorders; history of substance use disorders (except nicotine addiction) in the last year; personality disorder that makes participation in the trial difficult in the opinion of the investigator; pregnancy or breast-feeding; contraindication for rTMS therapy or MRI scanning (a history of epilepsy or any medical condition likely to increase risk of seizure, mass brain lesions, cerebrovascular accident, a history of major head trauma with unconsciousness, metal implants or fragments in the head, pacemaker or other electronic devices); electroconvulsive therapy within the last six months.

Written informed consent will be obtained from each patient who meets inclusion and exclusion criteria and agreed to participate in the study.

iii. Study protocol

The screening phase lasts for a minimum of 4 days, but no longer than 14 days. Within this period eligibility criteria will be assessed, and informed consent is obtained. The blood level of mood stabilizers (lithium, valproate) will be checked to confirm an adequate range for maintenance treatment. For lamotrigine and antipsychotics minimum daily doses are defined as follows: lamotrigine 200mg, aripiprazole 10mg, olanzapine 10mg, quetiapine 300mg, and risperidone 2mg. If the lower blood level of mood stabilizers or the dose of other agents will be found the screening period was prolonged to enable dose adjustment. After a week clinical status and eligibility criteria will be re-assessed. If patients use antidepressants there will be a possibility to taper off.

Upon completion of the screening period, subjects will undergo T1-weighted MRI scanning, EEG recording, and psychiatric scales and self-assessment rating within three days before the baseline visit. A day before baseline visit patients will be randomly allocated (1:1:1) according to permuted block design with a fixed block size of 6 to one of the three treatment arms:

a) RVL rTMS: active 10Hz rTMS applied to the left DLPFC (BA 46), 100% of motor threshold, 2s on, 8s off, 10 minutes duration; 1200 pulses per session; 20 session;

b) LDL rTMS: active 10Hz rTMS applied to the right VLPFC (BA 47), 100% of motor threshold, 2s on, 8s off, 10 minutes duration; 1200 pulses per session; 20 session

c) sham rTMS with a sham coil applied randomly to left DLFPC or right VLPFC; 20 session

Concomitant medication allowed in case of insomnia or anxiety is z-hypnotics (zolpidem up to 10mg, or zopiclone 7.5mg at night), hydroxyzine (25mg, 50mg dose per day, and clonazepam (0.5mg per dose, 1mg per day). Otherwise, medication at baseline will remain unchanged over the acute phase of the study.

Patients will be clinically assessed at baseline and weekly during the four-week double-blind phase using Montgomery and Åsberg Rating Scale (MADRS), Young Mania Rating Scale (YMRS), Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR-16), and the Clinical Global Impressions Scale for use in bipolar illness (CGI-BP). Raters are blind to patients´ group assignment.

Follow-up phase

Subjects who will not respond in the acute phase of the study terminate participation and will be treated as usual according to their psychiatrists. The patients who will complete the acute phase of the study (regardless of group assignment) and achieve response (50% or more reduction from baseline in MADRS score), continue (if agreed) to the 4-week, open-label, follow-up. Patients will be assessed biweekly with the same clinical scales as during the acute phase. In case of relapse (MADRS score ≥ 20), follow-up is terminated and appropriate pharmacotherapy is provided.

iv. RTMS and MRI

rTMS will be delivered using the MagPro R30 stimulator (MagVenture, Denmark) and Cool-B65 A/P coil with both an active and a placebo side, enabling the rTMS operator to stay blinded. To empower the masking process, we will use surface electrodes connected to the electric stimulator for all treatments to mimic scalp sensation accompanying active rTMS. When sham rTMS is applied, the coil

will be oppositely oriented and simultaneously shielded magnetic stimulation pulses, and electrodes will be placed following active rTMS depending on the site.

Before rTMS, the individual resting motor threshold (RMT) will be determined according to standards: a single TMS pulse is delivered to the motor cortex (left M1 area), specifically to the site corresponding to the somatotopic location of the right thenar. RMT is defined as the lowest intensity of rTMS device output that elicits five or more electromyographic responses (EMG MagPro R30 equipment) ≥50 μV within ten trials.

Individual MRI scans will be obtained on 3T Siemens Prisma scanner (Siemens, Erlangen, Germany). We acquired high-resolution T1-weighted three-dimensional (3D) anatomical images using magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequence with the following parameters: TR = 2400 ms, TE = 2.34 ms, Flip Angle = 8 deg, 64-channel head coil, Pixel Bandwith = 210 Hz/Px, FOV = 224 x 224 mm, Voxel Size = 0.7 mm isotropic.

The position of the coil will be guided by the Brainsight Frameless Neuronavigation System (Rogue Research Inc., Montreal, Canada). First, we will identify the coordinates for cortical hotspots at the left Brodmann area (BA) 46 in LDL group and at the right BA 47 in RVL. Then, we will mark the hotspot for the exact coil position corresponding to the selected cortical hotspot in each MRI. Finally, we will co-register the individual image data with the patient's head to target the coil hotspot (center of the coil) on the subject's head. Correct coil position will be checked regularly by measuring from the marked point on the cap to several anatomical regions.

v. Outcome measures

The primary outcome measure is the mean change in total scores on the Montgomery–Åsberg Depression Rating Scale (MADRS) from the baseline to week 4. The secondary efficacy measures are mean change in QIDS-SR (self-assessment) and CGI-BD scores over the study period, and the response (50% reduction in MADRS total scores) and remission (score of 10 or less in the MADRS total scores) rates at the end of treatment. The dropout rates and adverse events rates are additional secondary outcome parameters.

vi. Statistics

Baseline demographic and clinical characteristics will be analyzed by one-way analysis of variance, Kruskal-Wallis test, or chi-square test as appropriate. Efficacy and safety analyses will be based on a modified intention-to-treat (mITT) approach that includes all randomized patients who received at least one rTMS application. The primary outcome measure of change from baseline to week 4 in MADRS score will be analyzed using a mixed-effects model for repeated measures (MMRM). Post hoc pairwise comparisons of least-square means will be corrected using the Holm-Bonferroni method. For the secondary efficacy parameter, we will analyze the change from baseline at the endpoint with an MMRM as the primary parameter. Categorical secondary parameters will be compared using the chi-square test and a logistic regression model. Statistical tests will be done with a two-sided α-level of 0.05 for statistical significance and performed with statistical software STATA (StataCorp.).