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Transcranial magnetic stimulation in the treatment of bipolar depression

Submission date
04/06/2021

Recruitment status
No longer recruiting

Registration date
27/05/2022

Overall study status
Completed

Last Edited
04/06/2024

Condition category
Mental and Behavioural Disorders

[ ] Prospectively registered
[X] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol

Background and study aims
Bipolar disorder (BD) is a severe mental disorder with a recurrent course. Manic episodes are a prominent feature of BD, but the burden of major depression episodes (bipolar depression [BDE]) is even more substantial. However, treatment of BDE is still limited, and only a few medications have shown definite effectiveness. Repetitive transcranial magnetic stimulation (rTMS) belongs to non-invasive brain stimulation (NIBS) methods and is approved to treat major depression, but its importance to BDE is not yet fully understood. This study aims to evaluate the effectiveness and safety of rTMS in treating patients with bipolar depression. The study lasts 4 weeks and is designed as randomized with three different rTMS procedures, including placebo stimulation.

Who can participate?
Patients with bipolar disorder aged between 18 to 70 years who are currently in depression and existing treatment does not help them sufficiently.

What does the study involve?
The study involves 20 rTMS sessions (one session every weekday) during the 4 weeks. Participants are randomly allocated to one of three different rTMS interventions: two of them are real rTMS, and one is placebo stimulation. Depression severity and its change are assessed weekly using objective and self-assessed scales. In addition, for safety reasons and the rTMS coil targeting, electroencephalogram (EEG) and magnetic resonance imaging (MRI) examinations are scheduled before and at the end of the study.

What are the possible benefits and risks of participating?
Participating could benefit the alleviation of depressive symptoms. The risk of participation includes side effects such as headache, facial muscles twitching, hearing difficulties, or mood change/swinging, which are mild and transient in most cases.

Where is the study run from?
National Institute of Mental Health, Klecany (Czech Republic)

When is the study starting and how long is it expected to run for? (what are the overall start and end dates?)
May 2015 to January 2021

Who is funding the study?
Czech Health Research Council (Czech Republic)

Who is the main contact?
Dr Tomas Novak
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Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Protocol serial number
AZV no. 16-31380A

Study information

Scientific Title
High-frequency MRI-guided repetitive transcranial magnetic stimulation as an add-on treatment in bipolar I or II depression: a randomized, sham-controlled, double-blind, parallel study

Acronym
TRAMABID

Study objectives

The primary objective of the proposed project is to compare the efficacy and tolerability of high-frequency (HF) repetitive transcranial magnetic stimulation (rTMS) to the left dorsolateral prefrontal cortex (LDL) and the right ventrolateral prefrontal cortex (RVL) with sham TMS in the treatment of bipolar depression.
The mean change in total scores on the Montgomery–Åsberg Depression Rating Scale (MADRS) from the baseline to week 4 is the primary outcome measure. The secondary efficacy measures are mean change in QIDS-SR (self-assessment) and CGI-BD scores over the study period, and the response and remission rates, as defined by a 50% or greater reduction in MADRS total scores and as a score of 10 or less in the MADRS total scores at the end of treatment. The dropout rates and adverse events rates are additional secondary outcome parameters.
H1: The reduction of depressive symptoms is higher in both active rTMS groups (LDL, RVL) compare to sham rTMS at the end of the 4-week study period.
H2: The number of responders is higher in both active rTMS groups compare to sham rTMS at the end of the 4-week study period.
H3: The number of subjects who dropped out from the acute phase of the study for any reason is not different across treatment groups.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 17/06/2015, Ethics Board (Commission) of National Institute of Mental Health (Topolova 748, 250 67 Klecany, Czech Republic; +420 (0)283088312; ek@nudz.cz), ref: 78/15

Study design
Four-week randomized sham-controlled double-blind three-group parallel study with 4-week open-label follow-up

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Bipolar I or II disorder, current episode depressive, moderate to severe, without psychotic symptoms

Interventions
Patients are randomly allocated according to permuted block design with a fixed block size of 6 to one of the three intervention groups:
1. Active 10 Hz rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) (BA 46), 100% of motor threshold, 2 s on, 8 s off, 10 minutes duration; 1200 pulses per session; 20 sessions
2. Active 10 Hz rTMS applied to the right ventrolateral prefrontal cortex (VLPFC) (BA 47), 100% of motor threshold, 2 s on, 8 s off, 10 minutes duration; 1200 pulses per session; 20 sessions
3. Sham rTMS with a sham coil applied either to left DLFPC or to right VLPFC (randomly per ten subjects); 20 sessions

Intervention Type
Device

Phase
Phase III/IV

Drug/device/biological/vaccine name(s)
MagPro R30 stimulator (MagVenture, Denmark) and Cool-B65 A/P coil

Primary outcome(s)
Depression severity is measured using the Montgomery–Åsberg Depression Rating Scale (MADRS) from baseline to week 4

Key secondary outcome(s))
1. Depression severity is measured using the Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR) and overal psychopathology related to bipolar disorder is measured using the Clinical Global Impression-Bipolar (CGI-BP) scores from baseline to week 4
2. Response and remission rates, as defined by a 50% or greater reduction in MADRS total scores and as a score of 10 or less in the MADRS total scores at the end of treatment
3. Dropout rates and adverse events rates measured using the Adverse Effects Questionnaire at weeks 1, 2, 3, and 4

Completion date
30/01/2021

Eligibility

Key inclusion criteria
1. Both inpatients and outpatients with bipolar disorder I and II, currently in the major depressive episode (BDE) diagnosed according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria
2. Females or males
3. Age 18 to 70 years
4. Moderate to severe depression based on the Montgomery-Åsberg Depression Rating Scale (MADRS) score ≥20
5. Current BDE lasting at least 4 weeks but no more than 12 months
6. 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
7. Failed to respond to at least one adequate antidepressant trial in the current BDE
8. Being able and willing to provide written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
60

Key exclusion criteria
1. Psychotic symptoms during the current BDE
2. Hypomanic, manic, or mixed features at screening or at the baseline visit (the Young Mania Rating Scale (YMRS) >11)
3. Significant risk of suicidal behavior based upon MINI or MADRS item 10 (suicidal thoughts) ≥4 at screening or baseline visit
4. Eight or more episodes of BD within 12 months prior to study enrollment
5. History of any DSM-IV Axis I diagnosis other than bipolar disorder I and II, with exception of anxiety disorders
6. History of substance use disorders (except nicotine addiction) in the last year
7. Personality disorder that makes participation in the trial difficult in the opinion of the investigator
8. Pregnancy or breastfeeding
9. Contraindication for rTMS therapy or MRI scanning (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)
10. Electroconvulsive therapy within the last 6 months

Date of first enrolment
01/01/2017

Date of final enrolment
30/11/2020

Locations

Countries of recruitment
Czech Republic

Study participating centre
National Institute of Mental Health
Topolova 748
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25067

Sponsor information

Organisation
National Institute of Mental Health

ROR
https://ror.org/05xj56w78

Funder(s)

Funder type
Research council

Funder Name
Agentura Pro Zdravotnický Výzkum České Republiky

Alternative Name(s)
Czech Health Research Council, AZV ČR

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
Czech Republic

Results and Publications

Individual participant data (IPD) sharing plan
Data of primary and secondary measurements will be shared upon reasonable request (additional analyses, meta-analyses). Data will be provided as fully anonymized. Contact for access to the dataset: Tomas Novak (tomas.novak@nudz.cz).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		25/05/2024	04/06/2024	Yes	No
Participant information sheet			05/05/2022	No	Yes
Protocol file			05/05/2022	No	No