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Trans cranial magnetic stimulation in bipolar depression

Submission date
15/01/2022

Recruitment status
No longer recruiting

Registration date
31/01/2022

Overall study status
Completed

Last Edited
20/01/2022

Condition category
Mental and Behavioural Disorders

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Bipolar depression causes extreme mood swings that include emotional highs and lows). New treatments are necessary for patients with bipolar depression since more than 35% of these patients are medication-resistant. As a consequence, there is a high burden of illness for patients with bipolar depression, leading to increased suicide rates, inability to maintain proper work and /or social role functions, and reduced quality of life. A possible new treatment strategy is repetitive transcranial magnetic stimulation (rTMS), which is effective in patients with unipolar depression. However, it is unknown whether it is also effective in those with bipolar depression. The aim of this study is to determine whether rTMS is effective in patients with bipolar depression who did not respond to two or more adequately dosed medication trials.

Who can participate?
Patients aged 18 years and over with bipolar depression who did not respond to two or more adequately dosed medication trials, in the current depressive episode.

What does the study involve?
In Phase 1, participants will be assigned to one of the two treatment groups and will receive active or sham rTMS for 25 rTMS sessions (i.e. 5 weeks). Phase 2 comprises of two follow-up measurements, one at 4 weeks and one at 12 weeks after treatment with active or sham rTMS. After the 12 weeks of follow-up patients allocated to sham rTMS will be offered active rTMS. In Phase 3 all patients will be followed for 21 weeks to determine the sustained response rate to treatment

What are the possible benefits and risks of participating?
rTMS is a safe treatment with few side effects. Participants could benefit from rTMS treatment but the current study is necessary to determine if it is an effective treatment in patients with bipolar depression.

Where is the study run from?
Amsterdam UMC Location VUmc (Netherlands)

When is the study starting and how long is it expected to run for?
January 2022 to February 2025

Who is funding the study?
ZonMw (Netherlands)

Who is the main contact?
E van Exel
tbide@ggzingeest.nl

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
NL77251.029.21

Study information

Scientific Title
Efficacy of repetitive Transcranial magnetic stimulation in patients with medication-resistant BIpolar DEpression: a multicenter, randomized, double-blind, sham-controlled study

Acronym
TBIDE

Study objectives
Active repetitive transcranial magnetic stimulation (rTMS), compared to sham rTMS, will result in a larger reduction of depressive symptoms, in patients with treatment-resistant bipolar depression

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 13/01/2022, Medical Ethical Committee Amsterdam UMC, location VUmc (De Boelelaan 1109
1081 HV Amsterdam, The Netherlands; +31 204444444; Metc@vumc.nl), ref: 2021.0414

Study design
Pragmatic multicentre randomized clinical trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Treatment-resistant bipolar depression, i.e. patients with bipolar depression who did not respond to two or more adequately dosed medication trials

Interventions
Active repetitive transcranial magnetic stimulation (rTMS, low frequent 1Hz rTMS, targeting the right right dorsolateral prefrontal cortex), compared to sham rTMS.

In Phase 1, participants will be assigned to one of the two treatment groups and will receive active or sham rTMS for 25 rTMS sessions (i.e. 5 weeks). Phase 2 comprises of two follow-up measurements, one at 4 weeks and one at 12 weeks after treatment with active or sham rTMS. After the 12 weeks of follow-up patients allocated to sham rTMS will be offered active rTMS. In Phase 3 all patients will be followed for 21 weeks to determine the sustained response rate to treatment.

Patients will be randomly allocated to the active rTMS or sham rTMS group. Stratified across sites, we will use block randomization, using random sequences of block size 4 and 6. This approach ensures treatment assignment balance within each complete block and minimizes the imbalance of group sizes within clinical centers, thus correcting for confounding from possible differences between treatment sites (such as differences in experience with rTMS). Block randomization will be done using Castor.

Intervention Type
Device

Phase
Not Applicable

Primary outcome(s)

Depressive symptoms measured by the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS) at baseline and 5 weeks

Key secondary outcome(s))
1. Economic evaluation based on the general principles of a cost-effectiveness (utility) analysis, which will be performed alongside the intervention by comparing patients treated with active rTMS with those receiving sham rTMS. Patient-reported outcome measures (i.e., quality-adjusted life years) will be determined. Additionally, societal costs and health consumption will be assessed for the economic evaluation at baseline and 12 weeks post-treatment
2. Response rate defined as 50% reduction of depressive symptoms, based on the SIGH ADS, directly after 25 active or sham rTMS sessions
3. Remission rates directly after 25 active or sham rTMS sessions; remission is defined as a SIGH ADS score of 8 and lower
4. Sustained response rate, i.e., those participants, who at 4 weeks and 12 weeks post-treatment, maintain a 50% reduction of depressive symptoms
5. Sustained response rate after 21 weeks post-treatment, in those who received active rTMS, in those who only received sham rTMS, and in those who initially received sham rTMS and later opted to receive active rTMS
6. Prevalence of side effects, including a conversion to mania using the Young Mania rating scale and the rTMS side effects questionnaire, at baseline and during 6 weeks of active or sham rTMS.

Completion date
01/02/2025

Eligibility

Key inclusion criteria
1. 18 years of age or older
2. Sufficient level of spoken and written Dutch
3. Ability to freely provide written informed consent
4. Current DSM-5 diagnosis of a depressive episode in bipolar I or II disorder, ascertained by the Mini International Neuropsychiatry Interview (MINI-plus)
5. A Hamilton depression rating score (HDRS) of >16 points: this score will be obtained from the SIGH-ADS, a depression rating scale able to determine the HDRS score and a score for atypical depression
6. Have a medication-resistant bipolar depression, defined according to the criteria of Hidalgo-Mazzei, that is, lack of remission for 8 consecutive weeks after two different medication trials, at adequate therapeutic doses, with at least two recommended monotherapy treatments or at least one monotherapy treatment and another combination
7. Stable medication 4 weeks prior to the study, including anti-manic medication, consisting of lithium, valproate, carbamazepine and all anti-psychotic drugs, in patients with bipolar I disorder. Dosages of anti-manic medications will be determined between the participant/patient and his /her psychiatrist. Stable medication also includes stable use of benzodiazepines up to a dosage equivalent of 3.0 mg lorazepam

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. A (hypo)manic episode within 3 months before the start of the trial
2. A Young Mania Rating Scale score >12, before the start of the trial
3. Current psychotic disorder including psychotic depression, assessed by treating psychiatrist
4. Dementia, assessed with a dementia screening tool, i.e. the Montreal Cognitive Assessment (MOCA), assessed at the baseline interview. Scoring below 20 points is an indication of the presence of dementia, this score below 20 points will be used as an exclusion criterium
5. Active suicidal thoughts and intent to act on it, assessed at the baseline interview and before the start of the trial. This assessment is based on the Columbia suicide severity rating scale, i.e. question 5 is answered positive “Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?”
6. Metallic devices implanted above the neck, assessed at the baseline interview
7. Patients diagnosed with epilepsy, by a neurologist, assessed at the baseline interview
8. Patients with bipolar II disorder who use anti-depressant medication without anti-manic medication or patients with bipolar I disorder, not using anti-manic medication
9. Substance abuse 4 weeks prior to the study, including high dosage of benzodiazepine, a dosage equivalent higher than 3.0 mg lorazepam, assessed at the baseline interview
10. Pregnancy, if there is any doubt a pregnancy test is performed at baseline
11. Previous treatment with rTMS
12. Inability to understand or comply with study requirements as judged by the investigators, assessed at the baseline interview

Date of first enrolment
01/02/2022

Date of final enrolment
01/02/2024

Locations

Countries of recruitment
Netherlands

Study participating centre
Amsterdam UMC, location VUmc
Amsterdam
Netherlands
1081 HV

Study participating centre
GGZinGeest
Amsterdam
Netherlands
1081 JC.

Study participating centre
PSQ
Rotterdam and the Hague
Netherlands
2512 VA

Study participating centre
Altrecht
Utrecht
Netherlands
3512 PG

Study participating centre
Radboud UMC
Nijmegen
Netherlands
6525 GA

Study participating centre
ProPersona
Nijmegen
Netherlands
6534 AM

Study participating centre
UMC Groningen
Groningen
Netherlands
9713 GZ

Sponsor information

Organisation
Amsterdam UMC Location VUmc

ROR
https://ror.org/00q6h8f30

Funder(s)

Funder type
Research organisation

Funder Name
ZonMw

Alternative Name(s)
Netherlands Organisation for Health Research and Development

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
Netherlands

Results and Publications

Individual participant data (IPD) sharing plan
Data are available on request: E.vanexel@ggzingeest.nl

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes