Efficacy of repetitive transcranial magnetic stimulation in patients with medication-resistant bipolar depression. A multicenter, randomized, double-blind, sham-controlled study

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Objective: We want to determine the effectiveness of rTMS in patients with bipolar depression who did not respond to two or more adequately dosed medication trials, using an adequately powered pragmatic RCT. We hypothesize that active rTMS, compared...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Manic and bipolar mood disorders and disturbances
Study type	Interventional

Summary

ID

NL-OMON50802

Source
ToetsingOnline

Brief title
T-Bide

Condition

- Manic and bipolar mood disorders and disturbances

Synonym
bipolar depression, bipolar disorder

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: ZON-MW

Intervention

Keyword: bipolar depression, rTMS

Outcome measures

Primary outcome

Primary clinical outcome is determined by testing the treatment effect on the course of depression severity, measured by the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS) during 5 weeks of active or sham rTMS.

Secondary outcome

a) 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.

b) Response rate defined as 50% reduction of depressive symptoms, based on the SIGH ADS, directly after 25 active or sham rTMS sessions.

c) Remission rates directly after 25 active or sham rTMS sessions. Remission is defined as a Hamilton score (derived from the SIGH ADS) of 8 and lower.

d) The sustained response rate, i.e., those participants, who at 4 weeks and 12 weeks post-treatment, maintain a 50% reduction of depressive symptoms.

e) The sustained response rate after 21 weeks post-treatment (in real rTMS group).

f) Prevalence of side effects, including a possible switch to mania

g) Description of facilitators and barriers with regard to implementation.

h) Changes in negative and positive affect. Presence of negative mood (depressed mood) and anhedonia (lack of interest and pleasure) are considered core symptoms of depression, while absence of positive mood is not taken into account in questionnaires on assessing the severity of depression. The Leuven Affect and Pleasure Scale (LAPS) provides the opportunity to not only study changes in depressed mood, but also assesses changes in positive affect.

Other outcome parameters: We want to explore the possible effects of different patient characteristics, determined at baseline, on outcome of treatment in patients treated with rTMS. The following demographic and clinical factors, that have been studied in relation to the course of bipolar depression, have not been studied in relation to outcome in patients treated with rTMS: type of bipolar disorder, duration of index episode, age of onset of bipolar disorder, duration of bipolar disorder, number of previous mood episodes, family history of bipolar depression, psychiatric comorbidity. In addition, we want to explore the effects of metabolic and vascular risk factors on outcome of bipolar depression since these risk factors are strongly associated with onset and course of unipolar and bipolar depression. Again, these factors have not been studied in relation to outcome of treatment in bipolar patients treated with rTMS: height, weight, waist:hip ratio, ankle arm index (a measure to determine

peripheral atherosclerosis), CRP, triglyceride, HDL cholesterol, total cholesterol and HbA1c levels. We hypothesize that these risk factors influence outcome of bipolar depression. At last, we want to determine possible electrophysiological biomarkers using TMS-EEG measurements in bipolar depressive patients, compared to healthy controls.

Study description

Background summary

Background of the study: Bipolar disorder is a severe, chronic psychiatric disorder with patients suffering from recurrent depressive, (hypo)manic, and/or mixed episodes, and affects approximately 1.3% of the Dutch population. Depression is the predominant burden of illness in both bipolar I and bipolar II disorder, with patients suffering from depressive symptoms in more than 30% of their time. Suicide rates in patients with bipolar disorder are approximately 10-fold higher than that in the general population, especially during depressive episodes and mixed states. Bipolar depression is a challenging, unresolved condition with severe unmet needs that is far less studied compared to unipolar depression. More than 35% of patients with bipolar depression, despite receiving psychotherapy or medication, do not experience sufficient reduction in depressive symptoms. These patients are twice as likely to be hospitalized. Moreover, persistent depression can nearly double both direct and indirect employer costs. Only a limited number of effective treatments are available for depression in bipolar patients. The Dutch guideline on bipolar disorder suggests that there are three additional options for patients with bipolar depression who do not respond to two or more pharmacological interventions. First, two mood-stabilizing drugs can be used as combination therapy; second, a mood-stabilizing drug or antipsychotic can be used in combination with an antidepressant drug (including a monoamine oxidase inhibitor). However, by combining drugs, the risk of side effects increases, moreover, some of these drugs require strict monitoring or adhering to a strict diet. Third, for patients irresponsive to sequential medication, electroconvulsive therapy (ECT) remains the only possible biological treatment. Although ECT is an effective treatment for bipolar depression, it is not accepted or tolerated by a majority of patients. Most patients choose to refrain from ECT due to feared cognitive side effects, logistic difficulties (patients have to be observed by friends or relatives until 24 hours after ECT or have to be admitted to a psychiatric ward), or fear and stigma associated with ECT. There are no available data from large trials concerning the effect

of adhering to a sequenced medication algorithm on treatment response in patients with bipolar depression, contrary to the reports of previous studies in patients with unipolar depression. The STAR-D study showed that adhering to a sequenced medication algorithm is mainly effective in patients who received one or two antidepressant drugs, whereas those who required more than two sequential medication trials had the lowest response rates and the highest relapse rates. Expert opinion in the field of bipolar depression holds that similar response rate patterns are also observed in patients with bipolar depression. Findings from two small RCTs suggest that in bipolar depression addition of a mood stabilizing drug increases the response rate to approximately 20%. Adjunctive antidepressant treatment is controversial and has limited effect in patients with bipolar depression. These findings are in line with the results of observational studies, showing that 35% of patients with bipolar depression are medication resistant Therefore we argue that lack of sufficient response to two sequential medication trials is a predictor of poor prognosis in terms of efficacy, relapse, and future medication tolerance and warrants the use of novel treatment modalities with different mechanisms of action.

Repetitive transcranial magnetic stimulation (rTMS), a non-invasive neuromodulatory therapy, has recently been added to the treatment arsenal for unipolar depression. TMS is based on the principle of electromagnetic induction by applying magnetic pulses to the brain. This magnetic pulse induces an electrical current in the underlying neurons. When TMS pulses are applied repetitively (rTMS), this effect outlasts the time of stimulation and leads to enduring effects on cortical excitability. It is recognized as a valuable novel therapeutic option in medication-resistant unipolar depression. RCTs have consistently demonstrated the efficacy and safety of rTMS in medication-resistant unipolar depression, with response rates of 40%. Depending on the parameters of stimulation, rTMS can modulate cortical excitability in focal areas, with low-frequency rTMS being inhibitory and high-frequency rTMS usually excitatory. In unipolar depression, low-frequency rTMS over the right dorsolateral prefrontal cortex (DLPFC) is equally effective as high-frequency rTMS over the left DLPFC. Low-frequency rTMS is associated with a low risk of inducing epilepsy during rTMS and is easier to tolerate than high-frequency rTMS, therefore it is likely to be more accepable by patients. The risk of developing side effects is low; transient headache and localized scalp pain are the most common side effects and are eminently treatable with paracetamol.

There is preliminary evidence showing that rTMS is also effective in (medication-resistant) bipolar depression; however, to date, only a few underpowered studies have been performed. Two meta-analysis tried to determine the efficacy of rTMS in patients with bipolar depression. The first meta-analysis of 19 of these studies (consisting of 181 patients) showed that the overall treatment response rates were 44% in patients treated with active rTMS and 25% in those treated with sham rTMS. Findings from the second meta-analysis showed similar results (n=279). The findings of these

meta-analyses were hampered. First, the participating patients consisted of predominantly patients with unipolar depression and only few patients with bipolar depression. Second, the number of patients in the meta-analysis was small n=181 and n=279. Third, there were no data available on the number of medication-resistant patients. Finally, no follow-up data were available.

Therefore, a well-powered RCT is needed to determine the efficacy of rTMS in patients with medication-resistant bipolar depression according to the criteria of Hidalgo-Mazzei, i.e., lack of remission for eight consecutive weeks after two different adequate medication trials with at least two recommended monotherapy treatments or at least one monotherapy treatment and another combination treatment. In this RCT the choice for low-frequency rTMS rather than high-frequency rTMS was made because the data from the meta-analysis suggested that those receiving low-frequency rTMS had the highest response rates; 60% for those receiving active rTMS vs 7% in the sham rTMS group. However, the number of patients receiving low frequency rTMS was low (n=30). The second reason for choosing low-frequency rTMS is that it is easier to tolerate by patients, and because low-frequency rTMS is associated with a low risk of inducing epilepsy.
In addition, we will perform an explorative cost-effectiveness study and obtain data on implementation. Finally we want to further explore the effects of different patient characteristics on outcome of treatment, including, age, gender, type of depression, i.e. atypical or melancholic depression, duration of index episode, duration of bipolar disorder, number of previous mood episodes and presence of the cardiovascular risk factors We hypothesize that these patients characteristics including presence of cardiovascular risk factors contribute to a poorer outcome after rTMS treatment in patients with bipolar depression.

Clinical electrophysiological studies in patients with bipolar depression
Furthermore, we would like to investigate the electrophysiology (i.e., cortical excitability) of the patients suffering from bipolar depression. More specific, the direct changes in cortical excitation and inhibition following the administration of TMS pulses. This additional study is

Study objective

Objective: We want to determine the effectiveness of rTMS in patients with bipolar depression who did not respond to two or more adequately dosed medication trials, using an adequately powered pragmatic RCT. We hypothesize that active rTMS, compared to sham rTMS, will result in a greater difference in treatment effect on the course of depression severity, after 5 weeks of active or sham rTMS. Our RCT is of utmost importance since all RCTs in this field are underpowered and predominantly consist of patients with unipolar depression and relatively few patients with bipolar depression.

Study design

We will conduct a pragmatic multicentre double-blind randomized sham-controlled rTMS trial to determine the efficacy of rTMS in
166 patients with moderate to severe medication-resistant bipolar depression. In this study, medication-resistant bipolar depression is defined according to the criteria of Hidalgo-Mazzei, i.e., lack of remission for eight consecutive weeks after two different adequate medication trials with at least two recommended monotherapy treatments or at least one monotherapy treatment and another combination treatment. This study has 3 phases. In phase 1 participants will be randomly assigned to one of the two treatment groups, and will receive active or sham rTMS, for 25 rTMS sessions in 5 weeks. Monitoring takes place on a weekly basis. Phase 2 comprises of 12 weeks follow-up (17 weeks after the start of participation of the RCT) after treatment with active or sham rTMS. After 12 weeks of follow up, patients allocated to sham rTMS will be offered active rTMS. All patients will be followed for 21 weeks to determine sustained response rate, Phase 3. Alongside this RCT, we will also conduct an economic evaluation and evaluate facilitators and barriers related to implementation in the group of researcher and health care professionals involved in this study. The funding agency, i.e. ZonMw doelmatigheidsonderzoek, explicitly wants that the trial is based in normal care.

If patients agree on participating with the optional TMS-EEG measurement (in Amsterdam), this will take place before the start of the 25 rTMS treatments; after the screening (T0) and before the baseline measurements (T1). Participants will follow the METC approved TMS-EEG protocol of the randomized clinical trial named TIPICCO (TMS-induced plasticity improving cognitive control in OCD; dossier number NL67067.029.18). Which consists of two separate appointments:
1) Day one: Neuropsychological measurement & MRI scan session
2) Day two: TMS-EEG measurements
For this we will inform and include patients that are participating the T-BIDE study.

Intervention

Adults with current bipolar depression who meet the inclusion criteria will receive 25 rTMS sessions once daily five times a week, for five weeks, in adjunction to ongoing treatment as usual. If patients miss up to a maximum of 4 rTMS sessions during the five week treatment period, treatment will be extended to obtain the prescribed 25 rTMS sessions. If patients miss more than 4 sessions they will be registered as a drop out. Low-frequency rTMS will be applied at an intensity of 120% of the resting motor threshold to the right DLPFC: 1,500 pulses per session will be delivered continuously, with a treatment duration of 25 minutes. The localization of the right DLPFC target will be determined using the International 10-20 system, corresponding to the

F4 location. The International 10-20 system is a method that allows placement of electroencephalogram electrodes to be standardized. This system accounts for variability in patient skull size by using certain percentages of the circumference and distances between four basic anatomical landmarks of the skull. Beam developed a new, simpler, and faster way to find the F4 position in 2009, using only three skull measurements, allowing for easy and reliable use in clinical settings to target the right DLPFC. Because this is a pragmatic RCT, the five different study sites will use different rTMS machines, i.e. machines from the following manufacturers Mag and More, Magstim, Mag Venture en DeyMed.

Comparison
Adults with current bipolar depression who met the inclusion criteria will undergo 25 sham rTMS sessions once daily five times a week, for five weeks, in adjunction to ongoing treatment as usual. If patients miss up to a maximum of 4 sham rTMS sessions during the five week treatment period, treatment will be extended to obtain the prescribed 25 sham rTMS sessions. For sham rTMS, a sham coil will be used that delivers the same auditory effect, in order that the same procedural will be obtained.

TMS-EEG
Patients who agreed on participating TMS-EEG measurements shall receive the following intervention before the start of the rTMS treatments according to the T-BIDE protocol:
After determining the motor threshold, the set-up of the neuronavigation and preparing the 64-channel EEG cap on the participant*s head, a protocol existing of single and double pulse TMS will be administered at the right DLPFC, left DLPFC and the primary motor cortex (same spot as where the motor threshold was determined). The duration of the protocol is 12 minutes (times three brain areas).

Study burden and risks

Benefits: Treatment of depressive symptoms in bipolar patients with rTMS, initially in those receiving active rTMS. We will also offer active rTMS after 12 weeks of follow up, in participants who received sham rTMS. In the Netherlands, only a small numbers of unipolar depressed patients are treated annually, whereas virtually no bipolar patients are being treated with rTMS. Knowledge gained from this study will allow adequate positioning of rTMS treatment in the algorithm to treat bipolar depression. On a participant level, all participants will be treated with rTMS, i.e., those receiving sham rTMS will be offered active rTMS after a 12 week observation period. For the TMS-EEG appointments, if the patient decides to participate, they will receive an additional financial compensation.
Burden for participants: Total time for participants will be 23 hours and 5 minutes, including rTMS treatment
Risk: rTMS is a proven safe treatment, however it is associated with a low risk

to develop mania, a low suicide risk, a low risk to develop a seizure, and a moderate risk to develop transient headache. For the patients who decide to participate in the TMS-EEG study will have a total of two additional visits. Which means that we ask these patients a bit more of investment of their time.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Eligibility criteria:
- 18 years or older of age;
- Sufficient level of spoken and written Dutch;
- Ability to freely provide written informed consent;
- patients with bipolar I or II disorder, who have a medication-resistant bipolar depression, i.e., lack of remission for eight consecutive weeks after

two different adequate medication trials with at least two recommended monotherapy treatments or at least one monotherapy treatment and another combination
- A score > 16 points on the Hamilton depression rating scale for atypical depression (SIGH-ADS).
- A current DSM-5 diagnosis of bipolar depression, ascertained by the Mini International Neuropsychiatry Interview (MINI-plus).
- Or have tried at least two monotherapies in the previous depressive episode, which must have occurred within 12 months previous of the present episode but not more than three depressive episodes within these 12 months.
- Stable medication 4 weeks prior to study, including anti-manic medication, consisting of lithium, valproate, carbamazepine and all anti-psychotic drugs, in patients with bipolar I disorder. Patients with a bipolar 2 disorder using anti-depressant medication will also need to use anti-manic medication. 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.

Exclusion criteria

Partcipants meeting any of the following criteria will be excluded from participation in this study:
- A (hypo)manic episode within 3 months before the start of the trial.
- A Young Mania Rating Scale score > 12, before the start of the trial.
- Current psychotic disorder, including psychotic depression, assessed at the baseline interview.
- Dementia, assessed with a dementia screening tool, i.e. the Montreal Cognitive Assessment (34), assessed at the baseline interview.
- 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?".
- Metallic devices implanted above the neck, assessed at the baseline interview.
- Patients diagnosed with epilepsy, by a neurologist, assessed at the baseline interview.
- 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.
- 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.
- Pregnancy, If there is any doubt a pregnancy test is performed, at baseline.
- Known with rapid cycling.; e.g. more than 3 mood cycles per year.

- Inability to understand or comply with study requirements as judged by the investigators, assessed at the baseline interview.
- Earlier experiences with rTMS (as treatment or in a study)

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-05-2022
Enrollment:	166
Type:	Actual

Medical products/devices used

Generic name:	repetitive transcranial magnetic stimulation (rTMS)
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	13-01-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	02-01-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-09-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL77251.029.21