Dutch-Depression Outcome trial comparing 5 day multi daily neuronavigated Theta burst sessions with 6 weeks standard rTMS

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Hypothesis: 5 day multi daily neuronavigated Theta burst sessions (developed by Stanford University and coined, SNT, i.e. Stanford NeuromdulaTion protocol) are more (cost-) effective than standard 10 Hz rTMS in patients with treatment resistant...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Mood disorders and disturbances NEC
Study type	Interventional

Summary

ID

NL-OMON56337

Source
ToetsingOnline

Brief title
DDOT

Condition

- Mood disorders and disturbances NEC

Synonym
depression, mood disorder

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC

Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: brain stimulation, depression

Outcome measures

Primary outcome

Clinical outcome is remission, which is defined as a score of 7 or lower on the clinician-rated HDRS-17 (Hamilton Depression rating Scale) measured directly after the last treatment session.

Secondary outcome

1) Health-related quality of life determined with the EuroQol-5D13 and Health care usage/costs, patients' and their family's out-of-pocket costs, and productivity losses owing to absenteeism measured with the Trimbos Institute and iMTA Cost questionnaire for Psychiatry (14).

2) Patient-reported outcome measures, i.e., positive mental health as measured with Mental Health Continuum-Short Form (15).

3) Percentual reduction of depressive symptoms as measured with self-rated HDRS-6 on each treatment day.

4) Relapse, at 5-, 10- and 25-weeks post-treatment. Relapse is defined as a HDRS-17 total score of 15 or higher for 2 consecutive assessments separated by 5 to 15 days or hospitalization for depression

5) Tolerability and safety of SNT and rTMS.

6) Factors that influence the implementation of SNT that are healthcare system-, clinician- or patient- related, in order to develop an implementation

plan.

Study description

Background summary

Novel therapies are necessary for patients with unipolar depression since more than 35% of these patients are medication-resistant. As a consequence, there is a high burden of illness for patients with depression*leading to increased suicide rates, inability to maintain proper work and/or social role functions, and reduced quality of life. A possible novel treatment strategy is an intensive five day course of intermittent Theta Burst, a form of transcranial magnetic stimulation (rTMS), which could lead to extremely high remission rates (79%) in patients with treatment resistant depression. However, it remains unknown whether this novel treatment strategy could be effective in depressed patients when compared to standard 10Hz rTMS (remission 30%).

Study objective

Hypothesis: 5 day multi daily neuronavigated Theta burst sessions (developed by Stanford University and coined, SNT, i.e. Stanford NeuromdulaTion protocol) are more (cost-) effective than standard 10 Hz rTMS in patients with treatment resistant depression.

Objective: To determine remission of depression and cost effectiveness using the SNT protocol, in patients with treatment resistant depression who did not respond to two or more evidence-based treatments.

Study design

This study comprises a multicentre, two-phase, randomized clinical trial. Phase 1 comprises a randomized controlled trial. In Phase 1, participants will be assigned to one of the two active treatment conditions, and will receive either treatment using the SNT protocol (5 days of 10 sessions/day, resulting in 50 sessions in total 90000 pulses) or standard 10 Hz left sided rTMS, provided once daily during 6 weeks (30 sessions in total, 90000 pulses). Phase 2 comprises three follow-up measurements, one at 5 weeks, one at 10 weeks and one at 25 weeks after the last treatment with SNT or 10 Hz standard rTMS. Finally, participants who were allocated to standard 10 Hz rTMS will be offered SNT after the end of the study (e.g. 25 weeks after the last rTMS session). Patients allocated to SNT can obtain 10 Hz standard rTMS after SNT has been completed.

Intervention

Intervention: 50 sessions using the SNT protocol in 5 days. We will target the region of the left DLPFC most anticorrelated with the subgenual anterior cingulate cortex (sgACC) in each participant based on subject-specific functional resting state MRI.

Comparison: 30 standard daily 10 Hz rTMS sessions in six weeks, targeting the left DLPFC based on standard measurement procedures of the skull.

Study burden and risks

Benefits: Possible increased remission compared to standard 10 Hz rTMS in patients with treatment resistant depression using the SNT protocol (average remission of 79% based on two small open label studies and a small RCT vs 30% remission in those receiving standard 10 Hz rTMS). We will also offer SNT after 25 weeks of follow-up, to participants who received standard 10 Hz rTMS. Knowledge gained from this study will allow adequate positioning of a possible novel treatment in the algorithm to treat patients with depression.

Burden and feasibility: The total time for study measurements for the participants allocated to SNT will be (180 plus 145 plus 3x 45) 460 minutes versus (180 plus 150 plus 3x45) 465 minutes for the participants allocated to standard 10 Hz rTMS. The total treatment time will be 5 days of 10 hours for the participants allocated to SNT and 6 weeks of daily (30 minute) sessions for the participants allocated to standard 10 Hz rTMS. Despite the high investment of patients, earlier studies have shown that an RCT, with rTMS is feasible with a drop out of approximately 7%.

Risk: rTMS and ITBS are proven safe treatments. rTMS and iTBS are widely used non-invasive brain stimulation technique, based on the principle of electromagnetic induction. During stimulation the participant will likely hear the clicks of the TMS pulses and experience stimulation of nerves and muscles of the head. The most common side effect is a light transient headache (~10% occurrence). A severe headache is uncommon (0.3-0.5% occurrence). In the current study patients will be stimulated with treatment a protocols that fall within the safety guidelines. All participants are screened for their relevant medical history and other TMS/iTBS safety aspects (e.g. presence of metal parts in the head).

Benefits: In this study, there will bet least the normal expected clinical benefit resulting in at least 25% remission for those receiving standard 10 Hz rTMS, whereas it is likely that remission in the SNT group is higher, and at least equal to the 25% remission for standard 10 Hz rTMS.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Adult patients with unipolar depression who did not respond to two or more evidence-based treatments for depression, in the current depressive episode, aged 18 years and over. In order to be eligible to participate in this study, a participant must meet all following criteria: - 18 years of age or older; - Sufficient level of spoken and written Dutch; - Ability to freely provide written informed consent; - Current DSM-5 diagnosis of a depressive episode, ascertained by the Mini International Neuropsychiatry Interview (MINI-S). - A Hamilton depression rating score (HDRS) of >16 points - have a treatment resistant depression, defined according to the criteria of Conway, that is, lack of remission for eight consecutive weeks after two different evidence-based treatments anti-depressant medication has to be adequately dosed. - Stable anti-depressant medication 6 weeks prior to study.

Benzodiazepines may be used up to a dosage equivalent of 3.0 mg lorazepam, and can be lowered over time during the study based on clinical judgement.

Exclusion criteria

Participants meeting any of the following criteria will be excluded from participation in this study - Bipolar disorder. - Current psychotic disorder* including psychotic depression, assessed by treating psychiatrist. - Suspected dementia, assessed with a dementia screening tool, i.e.i.e., the Montreal Cognitive Assessment (MOCA)(31), with a score of less than 20 points, or a clinical suspicion of dementia, or neuroimaging indication for neurodegeneration with a Fazekas > 1 and MTA >1. These cut-offs ensure exclusion of patients with (preclinical) dementia. - 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.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?* (32). - Metallic devices implanted above the neck, assessed at the baseline interview. - Patients diagnosed with epilepsy, by a neurologist, assessed at the baseline interview. - 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. - Inability to understand or comply with study requirements as judged by the investigators, assessed at the baseline interview. - Pregnancy

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-02-2024
Enrollment:	108
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	31-08-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-02-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-10-2024
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	NL83892.018.23