A randomised non-inferiority trial of esketamine versus electroconvulsive therapy in treatment-resistant depression

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Phase 1:The primary objective of this trial is to investigate whether oral esketamine is non-inferior to ECT after eight weeks of individually optimized treatment, in participants with NTRD.Phase 2:To compare the efficacy of maintenance oral…

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

Summary

ID

NL-OMON51415

Source
ToetsingOnline

Brief title
RESET-TRD

Condition

- Mood disorders and disturbances NEC

Synonym
sadness, Treatment-resistant depression

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Zorginstituut Nederland

Intervention

Keyword: depression, ECT, esketamine, non-inferiority

Outcome measures

Primary outcome

To investigate whether oral esketamine is non-inferior to ECT, the short term effectiveness is measured by the percentage of patients with response to treatment at change from baseline in MADRS total score (defined as >=30% reduction or MCID) to 8 weeks of treatment, in patients with NTRD.

Secondary outcome

Secondary objectives and endpoints include:

1. To investigate whether oral esketamine is non-inferior to ECT in patients with NTRD on the short term in depression symptom severity, suicidality, clinical impression, functioning, and quality of life, measured by:

a) Change in depressive symptom severity, defined as a reduction in IDS-SR total score between baseline and 8-weeks of treatment.

b) Change in suicidal ideation, defined as a reduction in Columbia Suicide Severity Rating Scale (C-SSRS) scores between baseline and 8-weeks of treatment.

c) Change in general clinical impression, defined as a reduction in the Clinical Global Impression (CGI) score, the Clinical Global Impression Severity scale (CGI-S) score, and an increase in the Clinical Global Impression Improvement scale (CGI-I) score between baseline and 8-weeks of treatment.

d) Change in functioning, defined as a reduction in the WHO Disability Assessment Schedule (WHODAS) total score between baseline and 8-weeks of

treatment.

e) Change in health-related quality of life, defined as a reduction in the 5-level Euroqol-5D (EQ-5D-5L) total score between baseline and 8-weeks of treatment.

2. To explore long-term effectiveness of oral esketamine treatment compared to ECT treatment in participants who respond to initial treatment, as measured by:

a) Remission rates, defined as MADRS total score <= 9 at the follow-up visits, and including both sustained remission (remission achieved <= 8-weeks of treatment and sustained during follow-up), and delayed remission (remission achieved > 8 weeks of treatment and sustained during 1-year follow-up);

b) Relapse (within 6 months of remission) and recurrence (after 6 months of remission) rates, defined as:

• Meeting the MADRS criteria for depressive disorder (total score >= 19) for at least two consecutive measurements, OR;

• Worsening of symptoms requiring treatment policy change, OR;

• Readmission to hospital, OR;

• Suicide attempt.

c) Comparing the differences in course of depression during the 52 weeks of follow-up between the two conditions, based upon the monthly MADRS and IDS-SR total scores.

d) Change in depressive symptom severity, defined as a reduction in IDS-SR total score between 8-weeks of treatment and 1-year-follow-up.

e) Change in suicidal ideation, defined as a reduction or preservation of initial reduction in C-SSRS scores between 8-weeks of treatment and follow-up.

f) Change in general clinical impression, defined as a reduction or preservation of initial reduction in the CGI score, CGI-S score, and improvement as measured with the CGI-I between 8-weeks of treatment and 1-year follow-up.

g) Change in functioning, defined as a reduction or preservation of initial reduction in the WHODAS total score between 8-weeks of treatment and 1-year follow-up.

h) Change in health-related quality of life, defined as a reduction or preservation of initial reduction in the EQ-5D-5L total score between 8-weeks of treatment and 1-year follow-up.

i) The comparable or more narrow profile of additional treatments received during follow-up, derived from the Treatment Inventory of Costs in Psychiatric Patients (TIC-P) questionnaire.

3. To investigate whether oral esketamine is more patient friendly than ECT with respect to treatment burden, side effects, tolerability and risk of abuse during treatment and at follow-up, as measured by:

a) Systematic Assessment for Treatment Emergent Events (SAFTEE);

b) Ketamine Side Effect Tool (K-SET);

c) 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC);

d) Cognitive tests: Dutch Adult Reading Test (DART); Dutch Rey Auditory Verbal Learning Test (D-RAVLT); Montreal Cognitive Assessment (MoCA); Trail making Test A and B; Subjective Assessment of Memory Impairment (SAMI); Columbia Autobiographical Memory Interview (CUAMI);

e) Body weight, blood pressure, heart rate, kidney function and liver enzyme

levels.

f) Exploring participants* experiences with treatment with oral esketamine or ECT, by interviewing a subset of participants (optional in informed consent).

4. To investigate whether oral esketamine treatment is more cost-effective compared to ECT, as expressed by incremental costs per Quality Adjusted Life Year (QALY) gained. Costs will be measured from a societal perspective, including productivity costs using the TIC-P. QALYs will be assessed with utility scores derived from the EQ-5D-5L using the validated Dutch tariff. A Budget Impact Analysis (BIA) will be conducted to inform decision-makers about the financial consequences of the adoption and diffusion of oral esketamine treatment for NTRD in the Dutch healthcare system.

5. To investigate predictors and working mechanisms of successful oral esketamine and ECT treatment, by:

a) Assessing demographical, clinical staging, and profiling characteristics, including: gender, age, depression subtypes (as assessed by the MINI-plus at screening), level of treatment resistance (as assessed by the Dutch Method for Staging TRD (DM-TRD)), previous depressive treatments (especially ECT and IN esketamine), dissociative experiences (as assessed by the 5D-ASC), treatment expectancy (as assessed by the Credibility and Expectancy Questionnaire (CEQ)), personality traits (as assessed by the Standardized Assessment of Personality - Abbreviated Scale (SAPAS)), and childhood trauma (as assessed by the Jeugd Trauma Vragenlijst (JTV), a Dutch version of the Childhood Trauma Questionnaire (CTQ)).

b) Assessing neurobiological markers covering major pathophysiological

mechanisms involved in mood disorders (optional in informed consent):

a. blood and urine biomarkers;

b. gene expression patterns in white blood cells;

c) Assessing the pharmacokinetic profile of oral esketamine, by measuring plasma levels of esketamine and its metabolites, and by exploring the relationship between these and our primary outcome.

d) Exploring potential pharmacodynamic characteristics of oral esketamine, by exploring the relationship between the pharmacokinetic profile of oral esketamine and:

a. The genotype of the CYP enzyme(s) involved in the metabolism of oral esketamine (in a subgroup of 12 participants);

b. Body Mass Index (BMI);

c. The concurrent use of antidepressants and benzodiazepines;

d. Ethnic origin.

6. To explore participants* subjective experiences with treatment with oral esketamine or ECT, as measured by a Dutch individual semi-structured interview questioning a subset of participants devired from both treatment arms about their personal experiences of the treatment and procedures. Also, the interview will address how participants relate to their illness and their personal circumstances. Asking permission to participate will be asked at inclusion, the semi-structured interview will be conducted at the end of phase 1.

Study description

Background summary

Depression is one of the most impactful medical conditions worldwide, a leading cause of disability, and a major contributor to the overall global burden of disease. Unfortunately, response to treatment is rather unpredictable, slow in onset, and incomplete in success rate. Stepwise protocolled treatment with different antidepressants and psychotherapies fails to achieve a clinically meaningful response in approximately 30% of patients.
Professional guidelines advise electroconvulsive therapy (ECT) as the final treatment step for patients with Treatment Resistant Depression (TRD), but ECT entails certain disadvantages: the procedure requires repeated anesthesia and clinical admission, there is a risk of persistent and significant cognitive side effects, and 40% of patients relapse within 6 months. Hence, there is a pressing need for efficacious alternatives for patients with TRD. This is even more so in patients with Non-psychotic Treatment Resistant Depression (NTRD), for whom ECT is overall less effective than in patients who have depression with psychotic features.
A novel intervention that has shown rapid and robust antidepressant effects is ketamine treatment, either as intravenous (IV), intranasal (IN) or oral formulation, all of which were shown to be effective in patients with NTRD. IV esketamine appears to have the most robust immediate results on the reduction of depressive symptoms, but direct comparisons between the different applications have not been done, and at 4 to 8 weeks the differences in effects between the different forms of applications appear to be very limited. Furthermore, not much is known about how to sustain the antidepressant effect after successful initial esketamine treatment. Looking at patient burden, IV clearly is the most invasive variant, followed by IN dosing that needs to be applied in the clinic at every dose and oral esketamine that may safely be used for longer periods of time, including at home. These advantages make generic oral esketamine a patient-friendly treatment compared to the other formulations. Furthermore, oral esketamine is much cheaper than IN esketamine and also less costly than ECT. Given its promising effects and presumed advantages, an important question is whether oral esketamine or a combination of oral and IV esketamine, may serve as effective and acceptable alternatives to ECT for NTRD patients.
This study is funded by a grant from ZonMw together with Zorg Instituut Nederland (ZINL) under the program *Veelbelovende Zorg*. If outcomes are positive, ZINL will facilitate subsequent implementation and reimbursement of low-cost generic oral esketamine for the treatment of patients with NTRD in the Netherlands. This could lead to an additional, affordable, reimbursed esketamine variant on the market.

Study objective

Phase 1:
The primary objective of this trial is to investigate whether oral esketamine

is non-inferior to ECT after eight weeks of individually optimized treatment, in participants with NTRD.

Phase 2:
To compare the efficacy of maintenance oral esketamine treatment versus ECT to prevent relapse, during one year follow-up, in participants who responded to initial treatment in phase 1.

Secondary objectives include: 1) To investigate whether oral esketamine is non-inferior to ECT in patients with NTRD on the short term including depressive symptom severity, suicidal ideation, clinical impression, functionality, and quality of life; 2) To explore long-term effectiveness of oral esketamine treatment compared to ECT treatment in participants who respond to initial treatment; 3) To investigate whether oral esketamine is more patient friendly than ECT with respect to treatment burden, side effects, tolerability and risk of abuse; 4) To investigate whether oral esketamine is more cost-effective compared to ECT; 5) To explore predictors and working mechanisms of successful oral esketamine and ECT treatment; 6) To explore participants* subjective experiences with treatment with oral esketamine or ECT.

Study design

This study comprises a multicentre, randomized clinical non-inferiority trial with long-term follow-up, with two parallel 1:1 treatment arms: oral esketamine versus ECT. Phase 1 comprises the randomized non-inferiority part of the trial in which the efficacy of the two treatments is compared. In phase 1 participants will be assigned to one of the two treatment arms, and will receive either oral esketamine or ECT twice a week for eight weeks, titrating the dosages. Phase 2 comprises the long-term follow-up of both study conditions, for one year in total. This phase is more naturalistic and describes whether the two conditions are successful in maintaining initial response. In phase 2, both conditions will be tapered down on individual basis.

Intervention

Participants will be provided either oral esketamine or ECT twice a week. Both conditions are individually tailored for optimal effectiveness. The esketamine arm will start with an initial dose of 0.5 mg/kg oral esketamine. Dosages are then titrated, based on individual tolerability and clinical effect, to a maximum dose of 3.0 mg/kg.
ECT is also performed twice a week, according to standard care consistent with the Dutch national ECT guideline. ECT is individually tailored, as seizure threshold levels are determined for each patient to choose the amount of charge (dosage) of the stimulus offered.
If results are suboptimal after 6 weeks, ECT is switched from right unilateral to (potentially more potent) bilateral application.

All participants who have shown a Minimally Clinically Important Difference (MCID), MCID is established as a >=30% reduction on MADRS total score, at 8 weeks of treatment (phase 1) are offered continuation of treatment in phase 2. Frequency is tapered depending on clinical outcome following a fixed protocol, aiming to keep responders stable and prevent depression relapse or recurrence. In both conditions, participants will also use regular antidepressant medication, in order to further reduce the chance of relapse. This is the standard procedure for both ECT and oral esketamine follow-up treatments.

Study burden and risks

The study is intended to benefit participants directly, because the treatments are specifically aimed at reducing depressive symptoms. Since blinding is impossible to achieve in the comparison between ECT and oral esketamine, and withholding treatment in this severely ill patient group is unethical, there is no placebo arm and all participants receive an active treatment. Participation in this trial implies that participants contribute to the development of medical knowledge that may also be of benefit for future patients.
The health risks attached to participation will be limited. There is ample experience with oral esketamine as an anaesthetic and analgesic agent, that is used in a wide range of medical settings and indications, including NTRD. In addition, recent studies have also demonstrated safety of esketamine for NTRD patients. Known side effects of esketamine are usually mild and self-limiting. Side effects will be closely monitored during and after treatment sessions. Actual risks, for example increase in blood pressure, will be identified swiftly and appropriately acted upon. The health risks and treatment burden in the ECT arm are not different from regular ECT treatment, which is standard guideline-based practice in psychiatry.
Participants will be asked to answer or fill out questionnaires at several moments during the study. This Routine Outcome Monitoring is broadly implemented in mental healthcare, and standard practice in clinical psychiatry for all forms of depression treatment. However, for study purposes additional questionnaires are added. Completing questionnaires take time and could sometimes be experienced as boring and/or annoying. The interviews could also distress participants to some degree, considering the personal and emotional content. However, we have found in earlier studies that patients often appreciate this as careful attention that is paid to their burdensome situation. Venipuncture is associated with negligible risks, and negligible to mild burden. Physical examination is associated with negligible to mild burden. Participants are allowed to object to any or part of the assessments or investigations during study participation.
Given the limited additional patient burden in the current trial compared to routine treatment, and the possible positive outcome for participants themselves as well as for future patients, we believe that offering study participation to patients that fit the inclusion criteria is well justified.

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

• 18 years or older of age at screening;
• Sufficient level of spoken and written Dutch;
• Ability to freely provide written informed consent prior to study participation;
• Current DSM-5 diagnosis of MDD without psychotic symptoms, ascertained by the Mini International Neuropsychiatry Interview (MINI-plus);
• At least moderate to severe depression, defined by a MADRS total score >= 20;
• Indication for ECT treatment for the treatment of the current depressive episode.
• TRD, defined as non-response to (or established non-tolerability of) treatment with at least two different antidepressants plus an augmentation step such as lithium, mirtazapine or quetiapine during lifetime, all prescribed in

an adequate dose (i.e. defined daily dose) for at least four weeks;
• Patients agree with initial clinical admission and subsequent daycare/outpatient treatment.

Exclusion criteria

• Prior or current bipolar disorder, schizophrenia spectrum, other psychotic disorders, current MDD with psychotic features (previous MDD with psychotic features is allowed if the current episode is non-psychotic). All diagnoses according to DSM-5, assessed with MINI-plus interview at screening;
• Current use of a MAOI in excess of a daily dose of 60 mg;
• The presence of current moderate or severe dependence of alcohol or drugs at screening according to the DSM-5, not including tobacco-related and caffeine-related disorders, ascertained by the MINI-plus;
• Recent (within the last four weeks of screening) or current use of cannabis or any other non-prescribed psychoactive compounds, including Saint John*s wort, assessed at screening;
• Relevant neurological disorders, such as dementia or epilepsy;
• Recent (within the last four weeks of screening) change of treatment with antidepressants;
• Planned changes in antidepressant treatment during phase 1 of the study, not being part of the standard practice of ECT treatment like change in lithium or anti-epileptics;
• Active suicidal plans, defined by a score higher than 5 (explicit plans for suicide when there is an opportunity or active preparations for suicide) on the MADRS*s item for suicidal ideation;
• (Suspected) pregnancy, lactation, or insufficient contraception. If there is any doubt, a pregnancy test is performed;
• Current use of benzodiazepine and benzodiazepine-like agents (zolpidem, zopiclone) in excess of 3 mg lorazepam or an equivalent per day;
• Recent (within the last four weeks of screening) start or change in the use of somatic medication that commonly affects mood, like corticosteroids;
• Previous treatment with ECT or esketamine during the current depressive episode;
• Presence of any contra-indication for esketamine use, such as increased intracranial pressure, cerebrovascular accident, cerebral trauma, glaucoma, recent myocardial infarction (<6 months), or other relevant cardiac problems like unstable angina pectoris or myocardial disease, aneurysmal vascular disease, severe hypertension, severe hyperthyroidism, severe liver problems, severe kidney problems, the use of medication that esketamine interacts with on a major level, such as monoamine oxidase inhibitors and xanthine derivates (aminophylline, theophylline) or previous hypersensitivity to esketamine or its components; While not exclusion criteria, enrolling a potential participant who meets any of the relative contra-indications for esketamine use according to the Summary of Product Characteristics (SPC), like clinically significant

respiratory conditions, will be decided based on a per patient assessment of potential risk;
• Presence of any contra-indication for ECT according to the Dutch Richtlijn Electroconvulsietherapie (2010) (appendix A). While not exclusion criteria, enrolling a potential participant who meets any of the relative contra-indications for ECT according to the Richtlijn Electroconvulsietherapie will be decided based on a perpatient assessment of potential risk;
• Mental incompetence to fully understand the informed consent of this study, based on the judgment of the general practitioner or treating psychiatrist of the participant;
• Inability to understand or comply with study requirements, as judged by the investigator(s);
• Use of other investigational drugs within 4 weeks of screening.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2022
Enrollment:	180
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Esketamine
Generic name:	Esketamine hydrochloride

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	05-07-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-02-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-06-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EudraCT	EUCTR2021-001326-21-NL
CCMO	NL80223.042.22