A randomised controlled trial of oral S-ketamine as add-on medication for patients with treatment-resistant major depressive disorder

Published: 29-08-2016
Last updated: 04-07-2024

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

Summary

ID

NL-OMON46103

Source
ToetsingOnline

Brief title
Oral S-ketamine for treating depression

Condition

- Mood disorders and disturbances NEC

Synonym
Depression, sadness

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: Ketamine, RCT, Treatment, Treatment resistant depression

Outcome measures

Primary outcome

The primary objective of this trial is to examine the antidepressant efficacy

of oral S-ketamine augmentation in patients with TRD. This will be measured by:

1) change in symptom severity, expressed as a change in total score on the

HDRS17;

2) response, defined as >= 50% decrease in total score on the HDRS17;

3) partial response, defined as 25-49% decrease in total score on the HDRS17.

Secondary outcome

1) To examine whether oral S-ketamine, compared to placebo, will:

- Have sustained effect on reducing the severity of depression after the

discontinuation of treatment, as measured with the HDRS17;

- Reduce self-reported severity of depression, as measured with the IDS-SR;

- Have a different effect in subgroups of patients, as measured with the HDRS17

and IDS-SR;

- Reduce the severity of symptom dimensions, as measured with the HDRS17 and

IDS-SR;

- Reduce the severity of suicidal ideation, as measured with the Beck Scale for

Suicide Ideation (BSS);

- Reduce the severity of anhedonia, as measures with the Snaith-Hamilton

Pleasure Scale (SHAPS) and the functional MRI (fMRI) Reward task;

- Improve general clinical impression, as measured with the Clinical Global Impression (CGI);
- Reduce anxiety symptoms, as measured with the BAI;
- Reduce pain, as measured with the Graded Chronic Pain Scale (GCPS);
- Reduce nicotine dependence, as measured with the Fagerström Test for Nicotine Dependence (FTND);
- Improve auto-biographical memory, as measured with the Autobiographical Memory Test (AMT);
- Improve health-related quality of life, as measured with the EuroQol-5D 5 Level (EQ-5D-5L);
- Increase brain activation in the prefrontal cortex, investigated with fMRI scanning;
- Reduce brain activation of limbic structures, insula, and the default mode network in responders, investigated with fMRI scanning;
- Alter the volume of the prefrontal cortex and limbic structures, investigated with MRI scanning;
- Alter glutamate and glutamine concentrations in the anterior cingulate cortex, investigated with Magnetic Resonance Spectroscopy (MRS) scanning;
- Alter cerebral blood flow, investigated with Arterial Spin Labelling (ASL) scanning;
- Change biomarkers patterns in blood and urine, pointing to changes in underlying disease mechanisms;
- Change gene expression patterns in white blood cells, which could point at changes in neuroplasticity;

- Induce side effects, as measured with the Systematic Assessment for Treatment Emergent Events (SAFTEE), the Iowa Sleep Disturbance Inventory (ISDI), the Questionnaire for Psychotic Experiences (QPE), the Dissociation Tension Scale (DSS), and by the monitoring of body weight, blood pressure and liver enzyme levels.

2) To conduct an economic evaluation that will assess cost-effectiveness and cost-utility of oral S-ketamine as compared to placebo from a societal perspective. Cost-effectiveness will be expressed as incremental cost per additional percentage point of patients recovered from depression as measured with the HDRS17. Cost-utility will be expressed as incremental cost per Quality Adjusted Life Year (QALY) gained, with health related quality of life scores assessed by means of the EQ-5D-5L and QALY*s calculated over the studies 10 weeks time horizon.

3) To conduct a Budget Impact Analysis (BIA) to inform decision-makers about the financial consequences of the adoption and diffusion of oral S-ketamine for TRD in the Dutch healthcare system.

4) To describe S-ketamine and norketamine pharmacokinetics after oral administration.

5) To explore the relationship between S-ketamine and norketamine pharmacokinetics and improvement on the HDRS17.

6) To determine the genotype of the CYP enzyme(s) involved in the metabolism of

S-ketamine.

Study description

Background summary

Major depressive disorder (MDD) is a common mental disorder with an impressive disease burden, for which currently available treatments (medication, psychotherapy and electroconvulsive therapy - ECT) unfortunately may be in effective. Around 30% of patients have therapy-resistant depression (TRD), defined as having no or only a partial response to a range of treatments. These patients often spend years in chronic depression, and there is a strong need to develop additional options to relieve this suffering.

A novel intervention that has shown rapid antidepressant effects is intravenous (IV) ketamine infusion. Ketamine currently is a well-known anaesthetic. Intravenous ketamine however has strong psychomimetic effects and is often given only once, leading to rapid relapse of depression. Oral ketamine administration is less invasive, may be provided for longer periods of time and current evidence shows a more benign side effect profile. Despite these potential benefits, the efficacy and tolerability of oral ketamine for TRD have not been sufficiently investigated.

Study objective

The proposed study aims to examine the antidepressant efficacy of oral S-ketamine augmentation in patients with TRD treated with regular antidepressants in a double-blind randomised controlled trial. Secondary questions involve the effects of oral S-ketamine on sleep, autobiographical memory, pain, anxiety, anhedonia, suicidal ideation, nicotine dependence, quality of life and consumption of medical care, as well as a detailed assessment of possible side effects caused by the ketamine treatment. Brain activation, brain blood flow and volume parameters, neuroplasticity, glutamate and glutamine concentrations in the brain, biomarkers, and the genotype of the CYP enzyme(s) involved in the metabolism of ketamine will be assessed, to develop a better understanding of the mechanisms of action and metabolism of S-ketamine. Furthermore, the study will also investigate the duration of effects after discontinuation of S-ketamine add-on treatment.

Study design

This study comprises a double-blind randomised placebo-controlled trial.

Participants will be assigned double-blind to one of the two treatment groups, and will receive either S-ketamine (50%) or placebo (50%). The effect of oral S-ketamine add-on treatment is investigated during ongoing and unchanged antidepressant therapy.

After inclusion (week 0), patients take medication 3 times per day for 6 weeks. After completion of this part of the study, a follow-up will be done after one (week 7), two (week 8) and four (week 10) weeks. Therefore, the total study duration is 11 weeks.

In the first week of treatment, oral S-ketamine and placebo will be administered at the study locations, in an inpatient setting. From week 2 on, patients can be discharged and use the study medication at home, if their treating psychiatrist decides it is clinically acceptable and convenient for the patient.

The questionnaires will be applied at the study locations in Groningen, Amsterdam, Rotterdam and Geldrop. The self-rating questionnaires can be filled in at home. Urine and blood will be collected at the study locations; neuroimaging scans will be performed in Groningen and Amsterdam.

Intervention

Subjects are randomly assigned to treatment with oral S-ketamine or placebo during 6 weeks. The tapering-in process consists of gradually increase dosages in the 4 first days of the treatment. The last day of the tapering-in process is day 4, which consists of 3 doses of 30 mg, leading to a total of 90 mg of S-ketamine. The tapering-off process consists of gradually decreasing dosages in the 3 last days of the treatment.

Study burden and risks

Participants will answer several questionnaires at several moments during the study. This is time consuming and it might be experienced as boring and/or annoying. Answering these questionnaires constitutes a negligible to mild burden.

In addition, venipunctures are involved in this study. Venipuncture to determine variables other than screening factors is optional for participants with needle phobia. Venipuncture is associated with negligible and known risks (e.g. skin irritation and bruising).

Of the 128 participants, 50 will undergo two MRI scan sessions of approximately one hour. During the scans, participants lie in a MR-scanner, which is a narrow space, and are required to lie still and perform some tasks. With regard to the MR-scanner noise, earplugs will be provided.

Participants will be hospitalized during the first week of the study, which is time-consuming, can be burdensome, and might interfere with daily activities. We do not expect that absence from work will be a problem in most of the cases, because we do not expect many participants to work on a regular basis, given the severity of their mental illness.

The physical examination that is part of the screening session, can make feel participants uncomfortable. This constitutes a negligible to mild burden.

The expected burden also consists of possible side effects of S-ketamine, such as nausea, dissociation, light-headedness, drowsiness and an increased heart rate. These side effects will be closely monitored during the treatment. The safety and well-being monitoring will be performed by physicians in such a frequency that actual risks will be identified swiftly and appropriately acted upon. Because the use of ketamine can impair driving, for example due to light-headedness, driving cars during the intervention period will be strongly discouraged.
Participants are allowed to object any or part of the assessments or investigations.

The study is intended to benefit one treatment group directly. Benefits to subjects and other patients are very well possible because the treatment is specifically tuned to reduce depression. However, they cannot be guaranteed.

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

- Male or female, age range: 18 to 80 years;
- Signed informed consent;
- Good understanding of spoken and written Dutch;
- DSM-5 diagnosis of Major Depresive Disorder, first or recurrent episode, ascertained by the Mini International Neuropsychiatry Interview (MINI-plus);
- Treatment Resistant Depression, defined as nonresponse to at least 3 different classes of antidepressants during lifetime, all given in an adequate dose (i.e. defined daily dose) for at least 4 weeks;
- At least moderately severe depression, defined by a score higher than 18 on HDRS17;
- Current treatment with an officially approved antidepressant medicine.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation:
- Bipolar depression or depression with psychotic features, according to the DSM-5;
- Previous or comorbid schizophrenia spectrum or other psychotic disorder according to the DSM-5, not including MDD with psychotic features;
- Comorbid severe personality disorder according to the DSM-5, that is the main reason for treatment;
- Previous or comorbid moderate or severe dependence of alcohol or drugs according to the DSM-5, not including tobacco-related and caffeine-related disorders;
- Recent (within the last 4 weeks) or current use of cannabis or any other non-prescribed psychoactive compounds, including Saint John*s wort;
- Relevant neurological disorder, such as dementia or epilepsy;
- Recent (within the last 4 weeks) change of antidepressant treatment;
- ECT sessions or any other antidepressant treatment change planned for the period of the study;
- Active suicidal intent, defined by scores higher than 2 on HDRS17 for suicidal ideation;
- (Suspected) pregnancy, insufficient contraception or lactation. If there is any doubt, a pregnancy test is performed;

- Recent (within the last 4 weeks) or current use of benzodiazepine and benzodiazepine-like agents (zolpidem, zopiclone) in excess of 2 mg lorazepam or an equivalent per day;
- Recent (within the last 4 weeks) or current use of somatic medication that commonly affects mood, like oral corticosteroids;
- Presence of any contra-indication for ketamine use, such as increased intracranial pressure, recent myocardial infarction or other relevant cardiac problems, severe hypertension, severe hyperthyroidism, severe liver problems, severe kidney problems, or the use of medication that ketamine interacts with on a major level, such as monoamine oxidase inhibitors;
- Vision or hearing problems that cannot be corrected and that interfere with the ability to comply with treatments and/or assessments;
- Mental incompetence to provide informed consent, based on the judgment of the general practitioner or treating psychiatrist of the participant;
- Inability to comply with treatments and/or assessments, based on the judgment of the general practitioner or treating psychiatrist of the participant.;For the MRI-scanning, there are additional exclusion criteria:
- MRI incompatible implants in the body, such as cochlear implants, insulin pumps or other metal implants;
- Any risk of having metal particles in the eye, for example due to manual work without proper eye protections;
- Tattoos containing red pigments;
- Claustrophobia;
- The refusal to be informed of structural brain abnormalities that could be detected during the experiment.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-02-2017

Enrollment:	128
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	S-ketamine
Generic name:	S-ketamine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	29-08-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-08-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-04-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-07-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-10-2020
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

ID: 24824
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2015-003957-16-NL
CCMO	NL55069.042.15

Study results

Date completed:	23-04-2021
Results posted:	26-05-2024
Actual enrolment:	113

First publication
25-03-2024