An exploratory, blinded, randomized, placebo-controlled study in subjects with depressive disorder to investigate the effect of minocycline on relapse after successful intravenous ketamine/minocycline-induced (partial) symptoms response

Published: 29-07-2013
Last updated: 22-04-2024

Primary ObjectiveThe primary objective of this study is to assess whether the antidepressant response to IV ketamine can be maintained by minocycline compared to placebo.Secondary ObjectivesThe secondary objectives of this study are:* To investigate...

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

Summary

ID

NL-OMON40601

Source
ToetsingOnline

Brief title
the effect of minocycline on relapse after ketamine/minocycline

Condition

- Mood disorders and disturbances NEC

Synonym
Bipolar Depression type II: depressive disorders, Major Depressiv Disorder

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Pharmaceutische industrie

Intervention

Keyword: depressive disorder, Ketamine, minocycline

Outcome measures

Primary outcome

Primary Endpoint

The primary efficacy endpoint will be the proportion of subjects who survive

relapse-free (among

responders) on Day 54 (Week 6) of the 6-week blinded treatment period.

A subject will be defined as *relapsed* if his/her MADRS total score has

returned to >= 30 after at least the

first dose administration of minocycline or placebo in the 6-week blinded,

treatment phase.

Secondary outcome

Major Secondary Endpoint

Ketamine non-responders: The change in MADRS total score from Day 12 (3 to 4

hours post dose) of the

12-day open-label treatment phase to end-of-study (Day 54).

Other Secondary Endpoints

* Change in the MADRS total score from baseline (Day 1 predose) during the IV

ketamine treatment phase (Days 1, 3, 5, 8, 10 and 12).

* Change in the MADRS total score from baseline (Day 1 predose) after the IV ketamine treatment phase (Days 20, 27, 34, 41, 48, and 54).

* Response (reduction >= 50% in MADRS total score relative to baseline) rate during the IV ketamine treatment phase (Days 1, 3, 5, 8, 10 and 12)

* Time to relapse (among responders) following completion of the IV ketamine infusion schedule.

* Effects on Columbia Suicide Severity Rating Scale (C-SSRS)

EXPLORATORY INFLAMMATORY MARKER EVALUATION

Venous blood samples (2 x 10 mL samples per time point) will be collected for the assessment of inflammatory markers (e.g., CRP, IL-6, IL-1β, TNF-α, MCP-1) at the time points specified in the Time and Events Schedule. At the same time-points, a venous blood sample (10 mL) will be collected for the extraction of messenger RNA (mRNA) for transcriptomics. RNA samples will not be used for genetic testing. Where appropriate consent is obtained, inflammatory marker samples and RNA samples will also be stored for future research related to inflammation and depression after the clinical study is completed (where local regulations permit).

SAFETY EVALUATIONS

Regular assessments of safety and tolerability of the study medication (i.e., ketamine, minocycline,

minocycline-matching placebo), and assessment of suicidal ideation and behavior

using the C-SSRS, will

be made during the study as outlined in the Time and Events Schedule.

TREATMENT COMPLIANCE

Venous blood samples (4mL) will be collected as per Time and Events schedule in

order to assess

treatment compliance for minocycline. Samples will only be analyzed in case of

doubt of treatment

compliance of a subject based on any abnormalities observed in the study data

collected.

STATISTICAL METHODS

Due to the exploratory nature of this study, no adjustments for multiple

testing will be applied.

Study description

Background summary

Better treatment paradigms for major depressive disorder (MDD) are needed. Ketamine, a racemate of R- (-)-ketamine and S-(+)-ketamine, is an approved medication for the induction of general anesthesia and for use in addition to other anesthetics. It is an anesthetic for diagnostic procedures and short-lasting surgery. A number of small, published studies suggest that intravenous (IV) ketamine may also have efficacy in subjects with treatment-resistant depression (TRD), with an onset of antidepressant effect within one day. However, after a single dose most subjects relapse within 1 week. The antidepressant response to ketamine can be prolonged by the administration of multiple doses.
However, ketamine is best used under healthcare supervision and frequent long-term use is associated with deleterious cognitive effects. Thus, ketamine

is difficult for regular and frequent administration. Therefore, it is important to identify other therapeutic options that can prolong the duration of symptom reduction induced by ketamine. Prior studies suggest that selective serotonin reuptake inhibitors (SSRIs), mood stabilizers, and the anti-glutamatergic drug riluzole are not sufficiently effective (Mathew et al 2010; Ibrahim et al., 2012). In this study, the aim is to investigate whether the tetracycline antibiotic drug, minocycline, can maintain IV ketamine-induced MDD symptom response. In all subjects, minocycline will be initiated at the same time as ketamine in the initial open-label treatment phase. This way, it is hoped that possible delays in the onset of effect of minocycline will not/minimally interfere with the timeto- relapse that is measured during the blinded treatment period.
Nonclinical and clinical studies suggest broad central nervous system (CNS) activities for minocycline: modulation of glutamate-induced excitotoxicity, antioxidant effects, and anti-inflammatory- and neuroprotective effects. Because of these broad CNS activities and the realization that the affected systems may play a role in the pathophysiology of depressive illness, several studies have been initiated to investigate the effect of minocycline in mood disorders. The CNS effects of minocycline resemble those of a novel class of brain-penetrating P2X7 antagonists, so that proof-of-concept (POC) in this study can guide the development of this class of compounds currently in non-clinical development

Study objective

Primary Objective
The primary objective of this study is to assess whether the antidepressant response to IV ketamine can be maintained by minocycline compared to placebo.

Secondary Objectives
The secondary objectives of this study are:
* To investigate the safety and tolerability of the administered study medications (i.e., ketamine and
minocycline);
* To investigate the effect of minocycline on symptoms of depression in ketamine non-responders.

Exploratory Objectives
The exploratory objective of this study is:
* To assess the relationship of inflammatory markers (e.g., C-reactive protein [CRP], interleukin
[IL]-6, IL-1β, TNF-α, monocyte chemotactic protein [MCP]-1) and/or changes in white blood
cell (WBC) RNA expression (transcriptomics) to response and relapse after ketamine infusion.

Study design

This is a placebo-controlled, blinded, randomized study being conducted in up to 80 male and female subjects, between 18 and 80 years of age (inclusive), with MDD or Bipolar Depression (BPD) Type II.
The study has four sequential phases:
1) A screening phase of up to 3 weeks,
2) A 12-day open-label treatment phase during which all subjects will receive ketamine and
minocycline,
3) A 6-week blinded OR optional open-label treatment phase:
a. For ketamine responders: A 6-week blinded treatment phase during which subjects will be randomly assigned to receive minocycline or placebo in a 1:1 ratio
b. For ketamine non-responders: An optional 6-week open-label treatment phase during
which subjects receive minocycline
4) A follow up phase: Subjects will have one End-of-Study visit.

The total study duration for each subject will be maximally 11 weeks. The end of the study is defined as the date of the last study assessment of the last subjects in the trial. Enrollment for the study will end when 42 eligible subjects respond to ketamine on Day 12 (of the 12-day open-label treatment phase) and are randomized to receive minocycline or placebo in the 6-week blinded treatment phase

Intervention

12-Day Open-Label Treatment Phase

Subjects will be admitted to the study site on Day 1, 3, 5, 8, 10, and 12 for study visits. Outpatient subjects may be discharged 4 hours after the start of the ketamine infusion (i.e., 4 hours postdose) if there are no safety concerns. Subjects cannot drive a car or operate machinery for 24 hours after receiving ketamine.
All subjects will receive ketamine 0.5 mg/kg IV infusion over 40 minutes while at the study site on Day 1, 3, 5, 8, 10, and 12, for a total of 6 doses (see Dosage and Administration). In the evening of Day 1 (i.e., Day 1 PM), subjects will orally self-administer minocycline 200 mg. Then,
starting the morning of Day 2 (i.e., Day 2 AM) through the morning of Day 12 (i.e., Day 12 AM), subjects will orally self-administer minocycline 100 mg bid.
A subject will be defined as a *ketamine responder* provided his/her MADRS total score on Day 12,
performed at 3 to 4 hours post dose, shows a * 50% decrease in comparison to baseline values (Day 1 predose). A subject will be defined as a *ketamine non-responder* provided his/her MADRS total score on Day 12, performed at 3 to

4 hours post dose, shows a < 50% decrease in comparison to baseline values (Day 1 predose).
Study procedures (e.g., efficacy, safety, biomarker) that will be performed during this treatment phase are described in the Time and Event Schedule.

6-Week Treatment Phase

Ketamine Responders (blinded, randomized)
Subjects that are *ketamine responders* will participate in a 6-week blinded, randomized treatment phase. Study visits will be conducted on Days 20, 27, 34, 41, and 48. Study procedures (e.g., efficacy, safety,treatment compliance) that will be performed at these visits are described in the Time and Event Schedule.
On Day 12 of the 12-day open-label treatment phase, 42 subjects will be randomly assigned in a 1:1 ratio to receive either minocycline 100 mg or placebo bid for 6 weeks. Subjects will orally self-administer minocycline 100 mg or placebo bid from the evening of Day 12 (i.e., Day 12 PM) through the morning of Day 54 (i.e., Day 54 AM) or until relapse, whichever comes first. A subject will be defined as *relapsed* if his/her MADRS total score has returned to >= 30 after at least the first dose administration of minocycline or placebo in this blinded phase. The subject and investigator will be blinded to treatment allocation through study completion. The Sponsor of the study, including dedicated sponsor personnel, will be unblinded.

Ketamine Non-Responders (optional, open-label)

Subjects that are *ketamine non-responders* will have the option to participate in a 6-week open-label treatment phase. Study visits will be conducted on Days 20, 27, 34, 41, and 48. Study procedures (e.g., efficacy, safety, treatment compliance) that will be performed at these visits are described in the Time and Event Schedule. Subjects will orally self-administer minocycline 100 mg bid from the evening of Day 12 (i.e., Day 12 PM) through the morning of Day 54 (i.e., Day 54 AM).

Study burden and risks

This is described in the patient information sheet at the section: "What are the possible side effects'
Side Effects from Ketamine
Like all medicines ketamine can cause side effects, although not everyone gets them. Side effects are normally dependent on the dose and how quickly the drug is administered.
Ketamine can sometimes cause allergic symptoms (*anaphylaxis*) such as breathing problems, swelling and rash and an increase in salivation. Some people have vivid dreams, feel confused or behave irrationally while recovering from anesthesia with ketamine.
The side effects of ketamine are classified on the basis of the frequency with which they occur, as follows:

• Very common: >=1/10 (>10%)
• Common: >=1/100 and < 1/10 (>1% and <10%)
• Uncommon: >=1/1000 and < 1/100 (>0.1% and <1%)
• Rare: >=1/10.000 and < 1/1000 (>0.01% and <0.1%)
• Very rare: < 1/10.000 (<0.01%)
• Unknown

Immune system disorders
Rare Allergic reaction
Psychiatric disorders

Common Vivid dreams, dream-like feeling, nightmares, out of body experience, feeling like you might pass out, and disrupted motor skills. These symptoms will go away when the administration is stopped.
Nervous system disorders

Common Dizziness
Uncommon Jerky arm movements, which resemble a seizure (as a result of increased muscle tension) and cross-eye.
Eye disorders
Common Blurred vision
Uncommon Double vision, increase in pressure in the eye
Heart / Vascular disorders
Common Increase in heart rate and blood pressure during administration period
Rare Irregular heart rate or decreased heart rate or low blood pressure
Respiratory, chest disorders
Common Increase pressure in the lungs and temporary slowing of breathing rate. These typically happen with high doses.
Skin and subcutaneous tissue disorders
Uncommon Rash
Gastrointestinal disorders
Common Nausea and vomiting, increased saliva production
General disorders and administration site conditions
Common Change in taste (metallic taste, bitter taste), nasal congestion, change in smell, sneezing
Uncommon nasal pain, bleeding, postnasal drip
Genitourinary Disorders
Rare pain or burning when you urinate
Investigations
Common Increase in blood pressure and increased heart rate (approx. 20% of the normal rate is usual) due to anxiety

Misuse of ketamine has been reported in the past. Reports have indicated that ketamine can cause various symptoms, including, but not limited to, flashbacks, hallucinations, euphoria or dysphoria (*unhappiness*), anxiety, insomnia (sleeplessness) or disorientation. Individuals with a history of drug misuse or dependence can develop a dependency on ketamine.

You should not drive or operate machinery for at least 24 hours after administration of the study drug. (See also under *What Do I Have To Do?*)
Side effects from Minocycline:
The following adverse reactions have been observed in patients receiving tetracyclines (Minocycline is part of the class of antibiotics called tetracyclines).

General Body as whole
Fever, discoloration of urine or stools or sweat

Allergic Reactions
(anaphylaxis, hypersensitivity): rash, blood spots,bruising and discolouring to the skin (purpura), shock, death, flaky skin(exfoliative dermatitis), increase in the number of white blood cells and oneor more of the following: inflammation of the liver (hepatitis), inflammation of the lungs caused by an infection (pneumonitis), inflammation of the kidneys, inflammation of the heart muscle (myocarditis) or membrane around the heart (pericarditis). Fever, swelling of the lymph nodes, swelling of the face, lips, tongue or throat.

Gastrointestinal disorders
feeling or being sick, diarrhoea, loss of appetite, underdevelopment of tooth enamel, inflammation of the tongue, mouth or intestines, difficulty swallowing, inflammation or ulceration of the gullet, indigestion, pseudomembranous colitis (watery diarrhoea, fever and cramps).

Nervous system disorders
dizziness, headache, tingling or pins and needles in the hands and feet, feeling of dizziness or spinning (vertigo), decreased sensitivity to touch, fits, drowsiness

Liver and Kidney
inflammation of the liver (hepatitis), kidneys or pancreas (pancreatitis), liver failure, jaundice (yellowing of theskin or whites of the eyes), abnormal liver function test results, acute kidney failure.

Heart disorders
inflammation of the heart muscle (myocarditis) or membrane around the heart (percarditis)

Blood disorders
increased levels of urea in the blood, blood vessel inflammation, changes in the numbers and types of your blood cells. If you notice increased bruising, nosebleeds, sore throats, infections, excessive tiredness, breathlessness on exertion or abnormal paleness of the skin, you should tell your doctor who may want you to have a blood test

Respiratory, chest disorders

inflammation of the lungs caused by an infection (pneumonitis), cough, increase in the number of white blood cells in the lungs

Skin and subcutaneous tissue disorders
a change in colour of the skin, nails, teeth, mucous membrane of the mouth, bones, thyroid, eyes, secretions including breast milk, tears or sweat (hyperpigmentation)

Immune system disorders
fever, itchy skin rash, rash, joint pain (arthralgia), inflammation (arthritis) stiffness or swelling of joints, increase in the number of white blood cells (serum sickness like syndrome). presence of antinuclear antibodies in the blood, joint pain (arthralgia), inflammation (arthritis) stiffness or swelling of joints and one or more of the following: fever, muscle pain (myalgia), inflammation of the liver (hepatitis), skin rash, inflammation of blood vessels

General disorders
fever, inflammation of the heart muscle (myocarditis) or membrane around the heart (percarditis), impaired hearing, ringing in the ears, thrush around your bottom, genital area or mouth, inflammation of male genitals, changes in thyroid function, systemic lupus erythematosus (SLE), if you already suffer from SLE Minocycline tablets may make your condition worse.

The adverse events more commonly seen in overdose are dizziness, nausea, and vomiting.
No specific antidote for minocycline is known.
In case of overdosage, minocycline should be discontinued and patients treated symptomatically, with supportive measures. Minocycline is not removed in significant quantities by hemodialysis or peritoneal dialysis.
Side effects from tests:
• Blood draw: Taking blood may cause bruising at the place where the needle goes into the skin. Fainting, and in rare cases infection, may occur.
• ECG Risk: There is generally no risk with having an ECG. The sticky patches may pull your skin or cause redness or itching.
• An infusion may cause swelling of the vein by a blood clot. The study doctor and/or the study team is trained to treat such a reaction.

There may be risks with ketamine and Minocycline that are not yet known. Sometimes during a study, the Sponsor may learn new facts about the study drugs or treatments. It is possible that this information might make you change your mind about being in the study. If new information is discovered, your study doctor will tell you about it right away

Contacts

Public
Janssen-Cilag

dr. Paul Janssenweg 150
Tilburg 5026RH
NL
Scientific
Janssen-Cilag

dr. Paul Janssenweg 150
Tilburg 5026RH
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Diagnostic criteria for moderate to severe major depressive disorder (MDD), without mood incongruent psychotic features, or Bipolar Disorder Type II ;- Patients should have an Inventory of Depressive Symptomatology-Clinician Rated (IDS-C30) total score >= 34 at Screening and at Day 1 (predose) ;- Patients with major depressive disorder should have failed at least two adequate treatment courses (dose and duration) with antidepressant therapy, one of which is in the current episode ;- Patients should not have received electroconvulsive therapy (ECT) in the current episode but could be those for whom ECT is considered ;- Patients with bipolar depression (BPD) Type II must have been taking a stable dose of a mood-stabilizing medication (e.g., lithium, valproate, carbamazepine, lamotrigine, antipsychotic agents) for at least 4 weeks, dosed clinically to target the therapeutic range ;- Patients currently taking an antidepressant(s) must have received at least 2 weeks of stable antidepressant therapy at the time of Screening ;- Doses of current antidepressant therapies

should remain the same for the duration of the study ;- Women must be postmenopausal, surgically sterile, or if heterosexually active, practicing a highly effective method of birth control ;- Men who are heterosexually active with a woman of childbearing potential must agree to use a double barrier method of birth control and to not donate sperm during the study and for 3 months after receiving the last dose of study drug

Exclusion criteria

- Has a current DSM-IV axis I diagnosis other than MDD or BPD Type II at screening (except for co-morbid anxiety disorders) ;- Has a diagnosis of substance abuse or dependence within 6 months prior to screening evaluation (nicotine and caffeine dependence are not exclusionary) ;- Patient is currently taking > 4 psychotropic medications at Day 1 (predose) ;- Has an autoimmune disorder such as Crohn*s disease, rheumatoid arthritis, psoriasis currently treated with/requiring treatment with immunomodulatory therapies ;- Has any significant cardiovascular, respiratory, neurologic, renal, hepatic, endocrine, immunologic diseases, glaucoma, hypothyroidism or hyperthyroidism based on screening examination ;- Has uncontrolled hypertension (diastolic blood pressure >= 90 mmHg), despite diet, exercise or a stable dose of an allowed antihypertensive treatment, at Screening or Day 1 (predose) ;- Has planned vaccination within 2 weeks prior to the first dose of study medication through 2 weeks after the last dose of study medication ;- Has an active infectious disease/current infection ;- Has known allergies, hypersensitivity, or intolerance to minocycline or ketamine or its excipients ;- Has contraindications to the use of minocycline or ketamine per local prescribing information

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	01-08-2013
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ketamine
Generic name:	Ketamine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Minocyline
Generic name:	Minocycline
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	29-07-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-08-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-08-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-09-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	18-09-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-05-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-05-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2012-002954-21-NL
ClinicalTrials.gov	NCT01809340
CCMO	NL45242.056.13