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Sodium oxybate as a potential new treatment for catatonia in patients with depression, bipolar disorder or a psychotic disorder

Submission date
31/05/2024

Recruitment status
Recruiting

Registration date
03/06/2024

Overall study status
Ongoing

Last Edited
10/07/2024

Condition category
Mental and Behavioural Disorders

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Catatonia is a serious condition that can occur in people with depression, bipolar disorder, or psychotic disorders. If catatonia is not treated, it can lead to death in 10% of cases and cause other severe health problems such as kidney failure, muscle breakdown (rhabdomyolysis), pneumonia, blood clots (embolism), and permanent muscle stiffness (contractures). New treatments are needed for catatonia. Currently, the only drug available for catatonia is lorazepam, which is a benzodiazepine that increases the effects of a brain chemical called GABA. However, lorazepam does not work for about 25% of patients. For these patients, the only remaining option is electroconvulsive therapy (ECT). Many patients and their families are hesitant about ECT due to its invasive nature and potential memory side effects, but they often agree to it because there are no other options. ECT likely works in catatonia because it significantly boosts GABA levels in the brain. This has led researchers to wonder if other methods of increasing GABA could be new treatment options. One study found that sodium oxybate might help patients with catatonia. We believe sodium oxybate could be an alternative to ECT because it is a precursor of GABA and also stimulates GABA-B receptors, which should increase GABA activity in the brain and help patients with catatonia.

We want to find out if sodium oxybate is effective for psychiatric patients with catatonia who are in an acute psychiatric ward and have not responded to lorazepam treatment.

Our goal is to investigate whether sodium oxybate can be used as a new treatment for psychiatric patients with catatonia.

Who can participate?
Patients aged 18 years or older, with catatonia and a probable psychotic disorder, bipolar disorder or depressive disorder who do not respond to lorazepam, during 4 days of treatment with lorazepam.

What does the study involve?
The Laborit study combines two parts: a multicenter, prospective cohort study and a

randomized, controlled trial (RCT). The cohort study will follow patients with catatonia who are admitted to psychiatric hospitals. This part of the study helps in recruiting patients for the RCT and allows us to describe the characteristics and progress of patients with catatonia and identify possible contributing factors.
1. All patients with catatonia will first receive standard care, which involves gradually increasing the dosage of lorazepam to a maximum of 24 mg per day over 4 days, until their catatonia symptoms improve.
2. If a patient's catatonia symptoms do not improve with lorazepam, they will be randomly assigned to one of two groups for further treatment over the next 4 days:
Group 1: Continue with the high dose of lorazepam (21 patients).
Group 2: Switch to sodium oxybate (21 patients).

What are the possible benefits and risks of participating?
Possible benefits may be that the treatment is successful, and people therefore do not need to undergo ECT treatment. In the future, if the treatment is successful there will be more treatment options for the patients and their relatives to make an informed decision on.
Possible risks are the risk of side effects from the treatment with sodium-oxybate.

Where is the study run from?
Amsterdam UMC (Netherlands)

When is the study starting and how long is it expected to run for?
May 2023 to December 2028

Who is funding the study?
Hersenstichting (Netherlands)

Who is the main contact?
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Study website
https://laborit-studie.nl/

Contact information

Type(s)
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Additional identifiers

EudraCT/CTIS number
2021-004049-19

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
NL77938.018.23

Study information

Scientific Title
Sodium oxybate as a potential new treatment for catatonia in patients with depression, bipolar disorder or a psychotic disorder, a randomized controlled trial. The Laborit study

Acronym
Laborit

Study objectives
Sodium oxybate reduces catatonic symptoms significantly in patients that do not respond to lorazepam treatment.

Ethics approval required
Ethics approval required

Ethics approval(s)

Approved 22/05/2023, Medical Ethics Committee Amsterdam UMC (Meibergdreef 9, Amsterdam, 1105AZ, Netherlands; +31(0)205669111; metc@amsterdamumc.nl), ref: 2022.0080 - NL77938.018.23

Study design
Multicenter randomized controlled trial and cohort study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
To follow

Health condition(s) or problem(s) studied
Treatment of catatonia in adult patients with unipolar depression, bipolar disorder or psychotic disorders, that do not sufficiently benefit from treatment with lorazepam.

Interventions
The Laborit study combines a multicenter, cohort study on psychiatric patients with catatonia, enabling us to study the broad pallet of catatonia symptoms, course of catatonia, and their possible determinants, with an embedded randomized controlled trial, using sodium oxybate as a treatment for patients with catatonia. This study is conducted on acute clinical psychiatric wards as well as medical psychiatric units in multiple hospitals in the Netherlands. The patient, and if necessary, their legal representative, are provided with as much time as available, i.e. 4 days to determine if inclusion in the Laborit study is possible.

Step 1, Days 1-4: Patients with catatonia will receive care as usual by titrating the dose of lorazepam to a maximum of 24mg/day in 4 days, until response of catatonia symptoms occurs (response., defined as 50% reduction measured with the Bush Francis Catatonia Rating Scale [BFCRS] compared to baseline).
Step 2, Days 5-10: If no response occurs, patients will be randomized between the following: continuation of high dose lorazepam for an additional 4 days OR administration of sodium oxybate, after a 60 % dose-reduction of lorazepam, on days 5 and 6. Sodium oxybate will be given on day 7 to 10 and will be titrated up to a maximum of 27 gr daily, i.e. 4,5 gr every 4 hours. The dose of 27g/day is based on the finding that the maximal dosage for narcolepsy is 4.5 g twice a night; moreover, this maximal dosage of 27 g/day is similar to the findings from the only study to date using sodium oxybate in catatonia. If response occurs with a dose lower than 27 g /day, this dosage will be continued, which is an approach similar to the titration of lorazepam in catatonia. It is necessary to treat catatonia within a maximum of 10 days because the morbidity and mortality of untreated catatonia is high.
Patients and staff administering medication are aware of the treatment given. However,

independent raters that determine the effect of sodium oxybate or lorazepam, are unaware of the allocated treatment. If during this RCT the patient deteriorates, i.e., catatonia worsens, defined as no intake of fluids, or there is an increase in autonomic dysregulation or fever combined with moderately severe to severe muscle rigidity, the patient treating psychiatrist has to decide to stop the RCT and start ECT.

Randomisation will be conducted through data management software Castor and will be operated by an independent researcher. Block randomisation will be used with random block sizes of 2, 4 or 6. The researcher that is doing the measurements in the trial is unaware of the treatment the patient receives.

Intervention Type
Drug

Pharmaceutical study type(s)
Pharmacodynamic, Dose response

Phase
Phase III

Drug/device/biological/vaccine name(s)
Sodium Oxybate (Xyrem)

Primary outcome measure
The response rate after four days of treatment in both groups (lorazepam and sodium oxybate) as measured by difference in BFCRS scores. Response is defined as a 50% reduction in symptoms based on the BFCRS.

Secondary outcome measures
1. Remission based on differences in BFCRS score after four and ten days of treatment. Remission is defined as a BFCRS score lower than 3 points or not fulfilling DSM 5 criteria for catatonia, i.e. 2 out of 12 classification criteria for catatonia
2. Occurence of side effects in both treatment groups (high dose lorazepam and sodium oxybate) measured using patient records thoroughout
3. Prevalence of retarded type catatonia versus excited type catatonia as measured by clinical factors that are scored in the BFCRS after four and ten days of treatment

Overall study start date
22/05/2023

Completion date
01/12/2028

Eligibility

Key inclusion criteria
1. Adult patients (age 18 years and over)
2. Admition to an acute psychiatric ward for the treatment of catatonia, not responedingto usual care (i.e., increasing doses of lorazepam to a maximum of 24 mg during 4 days).
3. DSM-5 classification of either unipolar depressive disorder, bipolar disorder or a psychotic

disorder
4. Catatonia is present for a maximum of eight weeks.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
42

Key exclusion criteria
1. Not able to take drugs orally, i.e., subjects who actively resist treatment, and are thus not able /or want to take oral sodium oxybate
2. Somatic disorder underlying catatonia
3. Use of anti-psychotic drugs if patients prior to the development of catatonia either had an increase or change in anti-psychotic medication. Patients that have been treated with a stable dose of antipsychotics for a longer period of time should be allowed to be treated further with anti-psychotic medication if the patient's treating psychiatrist deems this necessary and catatonia is mild, i.e. BFRCS <9
4. Known heart failure or renal impairment due to significant amounts of sodium in the sodium oxybate
5. Known sleep apnoea.
6.1. Use of GABAergic drugs including gabapentin, pregabalin and clonidine
6.2. Use of GHB dehydrogenase inhibitors, including valproate, phenytoin and ethosuximide
6.3. Use of opioids, except tramadol
7. Presence of alcohol use disorder
8. Presence of malignant catatonia (as is indicated by autonomic dysregulation, item 23 of the Bush Francis Catatonia rating scale, scoring 3 combined with moderately severe to severe muscle rigidity, item 11 of the Bush Francis Catatonia rating scale, scoring 2 or higher) or development of malignant catatonia during the study
Patients with malignant catatonia need to receive treatment with ECT as soon as possible since mortality in those with untreated catatonia ranges between 10 and 40%

Date of first enrolment
01/09/2024

Date of final enrolment
01/07/2028

Locations

Countries of recruitment

Netherlands

Study participating centre
Amsterdam UMC
Meibergdreef 5
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Netherlands
1105AZ

Study participating centre
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Amstelveenseweg 589
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Netherlands
1081JC

Study participating centre
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Laan van de Heelmeesters 2
Hilversum
Netherlands
1211MS

Study participating centre
Arkin
Vlaardingenlaan 5
Amsterdam
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Study participating centre
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Maasstadweg 96
Rotterdam
Netherlands
3079DZ

Study participating centre

Rijnstate
Wagnerlaan 55
Arnhem
Netherlands
6815AD

Study participating centre
Leids Universitair Medisch Centrum (LUMC)
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Sponsor information

Organisation
Amsterdam UMC Location VUmc

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Sponsor type
Hospital/treatment centre

Website
https://www.amsterdamumc.nl/nl.htm

ROR
https://ror.org/00q6h8f30

Funder(s)

Funder type
Charity

Funder Name
Hersenstichting

Alternative Name(s)
Hersenstichting Nederland, Nederlandse Hersenstichting

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Netherlands

Results and Publications

Publication and dissemination plan
Planned publication in a peer-reviewed journal

Intention to publish date
01/12/2029

Individual participant data (IPD) sharing plan
The dataset generated during and/or analysed during the current study are expected to be made available. The exact data sharing plan will be made available at a later date.

IPD sharing plan summary
Not expected to be made available, Data sharing statement to be made available at a later date