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Can a low dose of ketamine change how people with treatment-resistant depression remember their lives, deal with emotions, and make decisions?

Submission date
20/04/2023

Recruitment status
No longer recruiting

Registration date
05/05/2023

Overall study status
Completed

Last Edited
12/09/2024

Condition category
Mental and Behavioural Disorders

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

Plain English summary of protocol

Background and study aims
Clinical depression often involves a pessimistic view of things which have happened in the past and an impairment in the ability to experience pleasure or look forward to things. A licensed drug called ketamine affects the levels of glutamate, a chemical messenger in the brain, and has been used as a treatment, particularly for depression which hasn't got better with other types of medication. Glutamate plays a role in learning and memory so we are interested in understanding how ketamine can affect how people with depression remember past negative and positive memories. This project will help us understand what is the role of glutamate in depression and will expand our understanding of how ketamine can influence memory, the way people understand emotions and learn from rewards and punishments, and motivation.

Who can participate?
Adults with depression who have not improved with the standard antidepressant treatment

What does the study involve?
Study participants will undergo medical and psychiatric health screening, questionnaires and computer tasks before and after the administration of the study drug (a single infusion of ketamine or a dummy saline placebo), and an MRI scan a day after administration of the drug /placebo. MRI is a type of brain scan that allows us to see how the brain responds during, for example, memories of things which have happened in the past.

What are the possible benefits and risks of participating?
The study will not be of direct benefit to you, but it is hoped that the information obtained will help improve the treatment of depression. Possible risks from taking part involve answering questionnaires and completing memory and computer-based tasks, undergoing an MRI scan and receiving ketamine/placebo. These risks will be discussed with the participants prior to their

enrollment in the study. To minimise any harm or risks, participants will be carefully supervised and we will ensure that any risks are minimised by conducting a detailed medical and psychiatric screening and having 24-hour on-call availability for participants in the study.

Where is the study run from?
The Department of Psychiatry, University of Oxford (UK)

When is the study starting and how long it is expected to run?
October 2017 to January 2025

Who is funding the study?
Medical Research Council (UK)
Janssen Pharmaceutical (USA)
Wellcome Trust (UK)

Who is the main contact?
Professor Catherine Harmer (Principal Investigator), catherine.harmer@psych.ox.ac.uk (UK)

Contact information

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Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
302265

ClinicalTrials.gov number

Nil known

Secondary identifying numbers
IRAS 302265

Study information

Scientific Title
Does modulation of glutamate transmission in the brain using a sub-anaesthetic dose of ketamine affect
autobiographical memory, emotional processing and decision-making in treatment-resistant depression? - The Glutamate Emotion Memory Study (GEMS)

Acronym
GEMS

Study objectives
Primary: To investigate the effects of ketamine on negative emotional bias associated with autobiographical memory and the effects of ketamine on brain circuit associated with autobiographical memories
Secondary: To investigate the effects of ketamine on positive and non-emotional memories, on measures of emotional processing and emotional memory, on information processing and decision-making and on motivation and anhedonia

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 14/01/2022, South Central - Oxford C Research Ethics Committee (Health Research Authority (Bristol), Ground Floor, Temple Quay House, 2 The Square, BS1 6PN, UK; +44 (0)207 104 8241; oxfordc.rec@hra.nhs.uk), ref: 22/SC/0001

Study design
Randomized parallel-arm placebo-controlled experimental medicine study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
University/medical school/dental school

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Major depressive disorder

Interventions
Randomization
Participants are randomised using an online randomisation tool (www.sealedenvelope.com) to either placebo or ketamine arms. The randomisation code is drawn up by a researcher not involved in the remaining study visits. Randomisation is stratified for gender and order of conditions on the emotional processing task. The randomisation list containing the participant study ID and the allocation is updated when each new participant enters the randomised phase.

The study arms are as follows:
Study arm 1: Ketamine hydrochloride 0.5mg/kg diluted in 40mL of sodium chloride 0.9% and administered at a constant rate (60ml/h) over the course of 40 minutes
Study arm 2: 40mL of sodium chloride 0.9% administered at a constant rate (60ml/h) over the course of 40 minutes

Intervention providers:
Intervention preparation, administration and disposal are carried out by two unblinded staff members (dispenser and checker). The dispenser is a medically qualified clinician. The dispensing, administration and disposal are conducted under the supervision of a consultant psychiatrist who is on call and at the hospital site during the entire duration of the infusion. The checker can be another medically qualified clinician or nursing personnel. Participants undergo the infusion of ketamine/placebo at the Clinical Research Facility (CRF), Warneford Hospital, a facility that offers the resources and support needed for the close monitoring of participants during the administration of the study intervention.

Mode of delivery:
Intravenous administration using an infusion pump over the course of 40 minutes

Outcome measures:
The primary outcomes include the change in the magnitude of negative and positive valence adjectives in the autobiographical memory task measured using a self-reported questionnaire. To investigate the effects of ketamine on negative emotional bias associated with autobiographical memories in TRD patients.
Each negative (guilty/ashamed, depressed/sad, angry/frustrated, upset, anxious/worried, worthless) and positive (grateful, energetic/motivated, hopeful, confident, loved, happy) valence adjectives. will be rated on a scale from 0 to 100. Change in magnitude will be assessed by calculating the difference in ratings of negative and positive adjectives using a self-reported questionnaire from baseline to after treatment
[Time Frame: -1 and 1 day after ketamine/placebo treatment]

Brain activation is measured by functional magnetic resonance in a network of areas related to autobiographical memories, including the medial prefrontal cortex and associated networks during the autobiographical memory task.
To investigate the effects of ketamine on: brain circuit associated with autobiographical memories
[Time Frame: 1 day after ketamine/placebo treatment]

The secondary outcome measures will investigate the effects of ketamine on:
1. Emotional processing such as emotional recognition the classification of positive and negative

descriptor words, recall of positive and negative descriptor words and recognition of positive and negative descriptor words
2. Reward processing
3. Brain circuit associated with reward processing
4. Choice behaviour in win and loss trials
5. Pupil dilation in the context of RL decision-making task
6. Motivation processing

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Ketamine hydrochloride 0.5 mg/kg, sodium chloride 0.9%

Primary outcome measure
1. Change in the magnitude of negative and positive valence adjectives in the autobiographical memory task measured using a self-reported questionnaire on day -1 and 1 day after ketamine /placebo treatment
2. Brain activation measured using functional magnetic resonance in a network of areas related to autobiographical memories, including the medial prefrontal cortex and associated networks during the autobiographical memory task 1 day after ketamine/placebo treatment

Secondary outcome measures
1. Accuracy measured using a computer-based task of facial expression recognition (FERT) on -1 day, and up to 2 hours after ketamine/placebo treatment
2. Reaction time measured using a computer-based task of facial expression recognition (FERT) on -1 day, and up to 2 hours after ketamine/placebo treatment
3. Accuracy to classify positive and negative descriptor words measured using the Emotional Categorisation Task (ECAT) up to 2 hours after ketamine/placebo treatment
4. Reaction time to classify positive and negative descriptor words measured using the Emotional Categorisation Task (ECAT) up to 2 hours after ketamine/placebo treatment
5. Number of positive and negative words correctly recalled (hits) and number of words incorrectly recalled (false alarms) measured using the Emotional Recall Task (EREC) up to 2 hours after ketamine/placebo treatment
6. Accuracy to correctly (hits) and incorrectly (false alarms) recognise positive and negative words measured using the Emotional Recognition Memory Task (EMEM) up to 2 hours after ketamine/placebo treatment
7. Reaction time to correctly (hits) and incorrectly (false alarms) recognise positive and negative words measured using the Emotional Recognition Memory Task (EMEM) up to 2 hours after ketamine/placebo treatment
8. Change in response choice during gain and loss measured using the Probabilistic Instrumental Learning Tasks (PILT) on 1 day after ketamine/placebo treatment
9. Brain activation measured using functional magnetic resonance imaging during the Probabilistic Instrumental Learning Tasks (PILT) in reward-related brain areas, including the ventral striatum and associated networks on 1 day after ketamine/placebo treatment
10. Explore performance on information processing and monetary win/loss reinforcement learning (RL) measured using decision-making tasks on 1 day after ketamine/placebo treatment
11. Explore performance on information processing and monetary win/loss reinforcement

learning (RL) measured using decision-making tasks using pupillometry on 1 day after ketamine /placebo treatment
12. Change in choice behaviour (effort and/or reward sensitivity) on accepted offers between sessions one and two measured using the Apples Gathering Task (AGT) up to 2 hours after ketamine/placebo treatment and 7 days after ketamine/placebo treatment

Overall study start date
01/10/2017

Completion date
06/01/2025

Eligibility

Key inclusion criteria
1. Male or female
2. Aged 20-60 years old
3. Willing and able to give informed consent for participation in the study
4. Sufficiently fluent English to understand and complete the tasks
5. Registered with a GP and consents to GP being informed of participation in the study
6. Participants need to meet a number of concurrent clinical criteria: Current criteria for Major Depressive Disorder, in a current major depressive episode, as determined by the SCID-5
7. Inadequate response to at least one and no more than three antidepressant treatments; Currently taking a licensed antidepressant at a therapeutic dose for at least four weeks
8. Pre-menopausal women and male participants engaging in sex with a risk of pregnancy must agree to use a highly effective method of contraception from Screening Visit until 30 days after receiving the study medication treatment
9. Male participants must not donate sperm until 30 days after receiving the study medication
10. Participants taking non-prescription/prescription medication may still be entered into the study, if, in the opinion of the Investigator, the medication received will not interfere with the study procedures or compromise safety
11. Willingness to refrain from driving, cycling, or operating heavy machinery, until the following morning or a restful sleep has occurred, whichever is later
12. Willingness to refrain from drinking alcohol for 3 days before the infusion visit and one day before any of the other visits throughout the study

Participant type(s)
Patient

Age group
Adult

Lower age limit
20 Years

Upper age limit
60 Years

Sex
Both

Target number of participants
60

Key exclusion criteria
1. History of /or current DSM.5 bipolar disorder, schizophrenia or emotionally unstable personality disorder [co-morbid anxiety disorders (including agoraphobia, generalized anxiety disorder, social anxiety disorder and panic disorder) and Posttraumatic Stress Disorder (PTSD) are allowed]
2. Participants who fulfill current criteria for other comorbid disorders may still be entered into the study, if, in the opinion of the Investigator, the psychiatric diagnosis will not compromise safety or affect data quality
3. Diagnosis of a major cognitive disorder or evidence of cognitive impairment
4. Clinically significant risk of suicide
5. Participants undergoing or who have undergone electroconvulsive therapy for the treatment of the current episode of depression
6. Substance or alcohol use disorder over the past 6 months
7. Regular alcohol consumption of more than 21 units a week or excessive alcohol consumption up to three days before any of the in-person study visits or inability to abstain from alcohol for more than 3 days
8. Moderate cigarette use (> 10 cigarettes per day)
9. History of, or current general medical conditions that in the opinion of the Investigator may interfere with the safety of the participant or the scientific integrity of the study
10. Current pregnancy (as determined by urine pregnancy test), breastfeeding, planning a pregnancy, or unwillingness to practice birth control during the study
11. Clinically significant abnormalities of laboratory tests, physical examination, or ECG. A participant with a clinical abnormality or parameters outside the reference range for the population being studied may be included only if the Investigator considers that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures
12. Current or history of heart rhythm disorders
13. Clinically significant untreated hypertension
14. Any contraindication to MRI including claustrophobia, any trauma or surgery which may have left magnetic material in the body, magnetic implants or pacemakers, and inability to lie still for 1 hour or more
15. Previous participation in a study using the same, or similar, emotional processing tasks in the last three months
16. Previous lifetime use of ketamine or phencyclidine
17. Participants with planned medical treatment within the study period that might interfere with the study procedures
18. Participant who is unlikely to comply with the clinical study protocol or is unsuitable for any other reason, in the opinion of the Investigator.

Date of first enrolment
20/04/2022

Date of final enrolment
30/12/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University of Oxford
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Study participating centre
NIHR Oxford cognitive health Clinical Research Facility
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Sponsor information

Organisation
University of Oxford

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Sponsor type
University/education

Website
https://researchsupport.admin.ox.ac.uk/clinical-trials-research-governance

ROR

https://ror.org/052gg0110

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Wellcome Trust

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

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

Location
United Kingdom

Funder Name
Janssen Pharmaceuticals

Alternative Name(s)
Janssen Pharmaceutica NV, JANSSEN-CILAG NV, Janssen Belgium, Janssen, Janssen Pharmaceuticals

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Belgium

Results and Publications

Publication and dissemination plan
The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines and other contributors will be acknowledged.

Intention to publish date
30/12/2025

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Prof Catherine Harmer, catherine.harmer@psych.ox.ac.uk. Data which has been fully de-identified may be shared with other academic and commercial organisations in the future, including those outside of the EU, to allow for large meta-analyses or international collaborations. Participants will be informed of this. All research data will be archived on the Department of Psychiatry network drive and the other University of Oxford servers for 10 years, after which it will be securely destroyed. All paper CRFs, ICFs and TMFs will be archived in the University storage facility with a date for destruction.

Consent is required and obtained from study participants as part of the informed consent form. The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database, with the exception of the consent and contact forms (which will be stored securely in a locked filing cabinet in the Neuroscience Building, Department of Psychiatry, University of Oxford) and the prescription and randomisation forms which will be stored securely in a locked cabinet at the Clinical Research Facility (CRF), Oxfordhealth Foundation Trust. All documents will be stored securely and will be only accessible to study staff and authorised personnel. The study will comply with the UK General Data Protection Regulation (UK GDPR) and Data Protection Act 2018, which require data to be anonymized as soon as it is practical to do so.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No