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Ketamine-assisted psychological therapy to reduce alcohol relapse

Submission date
01/09/2023

Recruitment status
Recruiting

Registration date
03/11/2023

Overall study status
Ongoing

Last Edited
19/09/2024

Condition category
Mental and Behavioural Disorders

[X] 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
In the UK more than half a million adults have alcohol problems. Only 1 in 5 people with alcohol problems get treatment. Even of those who quit alcohol, 3 out of 4 will be back drinking heavily after a year. Alcohol-related harm is estimated to cost the UK NHS around £3.5 billion each year and wider UK society around £40 billion. Alcohol problems affect not only the individual but families, friends and communities. Alcohol-related deaths have increased still further since the pandemic and we urgently need new treatments. We previously ran a small phase II clinical trial in 96 people with severe alcohol problems. The treatment was 3 doses of ketamine given through a drip combined with 7 sessions of psychological therapy (KARE therapy). We found KARE therapy could reduce drinking 6 months after the start of treatment when compared to placebo. The study also found that giving psychological therapy combined with ketamine reduced drinking still further than when ketamine was given without psychological therapy. This phase III, multi-site study will build on our phase II trial and will run in up to 10 NHS sites across the UK.

Who can participate?
Adults with severe alcohol use disorder (AUD).

What does the study involve?
We will randomise 280 participants to receive 3 intravenous infusions of either a therapeutic or subtherapeutic dose of ketamine at weekly intervals. Participants will also be randomly allocated to receive either 7 sessions of psychological therapy or an alcohol education package. There will be 10 appointments over 6 months. At these visits medical assessments will be carried out including blood and urine samples analysis and psychological questionnaires will look at alcohol usage and mental health in the trial. We hope to collect enough evidence to establish if this treatment works, so that it may begin to be used in NHS settings.

What are the possible benefits and risks of participating?
We hope participating in the trial would help participants with their own aims to reduce or quit drinking alcohol. Participants are also offered the opportunity to wear an alcohol monitoring device which has been shown to help people stay abstinent from alcohol. Participants are also offered psychological support which can help participants reduce their drinking or remain sober.

Taking part can also lead to indirect benefits, leading to improvements in future understanding and treatment of alcohol use disorders, and help people remain abstinent for longer.
Ketamine is a safe and well-tolerated drug. However like all drugs, ketamine can cause effects on the body; most of these are mild and resolve quickly after the infusion of the drug is finished. In this trial we are using lower doses of ketamine than those used in anaesthesia. Ketamine has different effects on different people, however common side effects at this dose (affecting 1 in 10 people) are likely to include dissociative effects which may feel strange, like you are outside of your body, or have strange changes to hearing or vision. Some people can feel nauseous or be sick when they receive ketamine and their breathing, blood pressure and heart rate can quicken. Participants may also experience a mild rash or redness of the skin following infusion, which will resolve after the infusion stops. Participants are closely monitored throughout and after each infusion to check for any side effects. The effects are anticipated to only last for a short time and to wear off quickly after the infusion is stopped.

Where is the study run from?
University of Exeter (UK)

When is the study starting and how long is it expected to run for?
August 2023 to November 2026

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK).
AWAKN Life Sciences (Canada)

Who is the main contact?
Dr Stephen Kaar, stephen.kaar@gmmh.nhs.uk
Prof. Celia Morgan, celia.morgan@exeter.ac.uk

Study website
https://sites.exeter.ac.uk/morekare/

Contact information

Type(s)
Principal Investigator

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Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1008179

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
2022-23-16, IRAS 1008179, CPMS 58776

Study information

Scientific Title
A multi-centre investigation of increasing alcohol abstinence with ketamine-assisted psychological therapy in severe alcohol use disorder

Acronym
MORE-KARE

Study objectives
Primary objectives:
To assess whether KARE therapy impacts alcohol use (number of days heavy drinking) over six months (180 days) following the start of treatment in participants with severe alcohol use disorder compared to control.

Secondary objectives:
To determine whether or not treatment with KARE therapy (ketamine assisted psychological therapy) when compared to control impacts:
1. Continuous abstinence at six months (180 days) follow-up
2. Percentage days heavy drinking at 180 days follow-up
3. WHO risk drinking index

4. Social and role functioning
5. Depression and anhedonia
6. Craving and alcohol dependence
7. To establish methods for estimating intervention resource use and costs in a future cost-effectiveness analysis
8. To assess acceptability of health economic outcome measures
9. To assess continuing impact of KARE therapy on alcohol use, social functioning and mental health at 120 months (360 days) post randomisation.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 02/11/2023, London – London Bridge Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)2071048387; londonbridge.rec@hra.nhs.uk), ref: 23/LO/0800

Study design
Interventional double-blind randomized parallel-group controlled trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Efficacy

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
Severe alcohol use disorder

Interventions
In this double-blind trial, 280 participants will either receive three 40-minute intravenous infusions, one per week, of either 0.8 mg/kg or 0.05 mg/kg ketamine at a research facility. Participants will also receive seven sessions of psychological support, which could either be therapy or alcohol eductaion. Both therapy and education will be delivered by a therapist. The dose and type of psychological support will be randomly assigned by a computer using REDcap Academic software.

Intervention Type
Drug

Pharmaceutical study type(s)

Pharmacoeconomic, Therapy

Phase
Phase III

Drug/device/biological/vaccine name(s)
Ketamine

Primary outcome measure
The number of days heavy drinking at six-month follow-up (Time Line Follow Back : TLFB, the most commonly used method in Alcohol Use Disorder clinical trials). TLFB data will be cross-referenced with self-report data using self-breathalyser data, BACtrack Skyn (continuous transdermal alcohol monitoring) and alcohol glucuronide urine dipstick and breathalyser at trial visits. A minimum of 180 days of data will be required with the measurement period capped at 187 days. Heavy drinking will be defined using EMA guidelines (60g/day for males, 40g/day for females).

Secondary outcome measures
1. Relapse (zero heavy drinking days, above 60g/day for males, 40g/day for females) is measured using the TimeLine Follow Back (TLFB) at baseline and at each trial visit during treatment as well as at 3- and 6-month follow-up.
2. Percentage of days abstinent from alcohol is measured using the TLFB at baseline and each study visit during treatment as well as at 3- and 6-month follow-up.
3. Clinical Global Impression (CGI Severity and CGI Improvement) is measured at baseline, visit 8 (end of treatment), as well as at 3- and 6-month follow-up.
4. Liver biomarkers (bilirubin, Gamma-GT, aspartate aminotransferase (AST) and alanine transaminase (ALT)) are measured at baseline, visit 4, visit 6, visit 8 (end of treatment), as well as at 3- and 6-month follow-up.
5. Percentage of heavy drinking days (above 60g/day for males, 40g/day for females) is measured using the TLFB at baseline and each study visit during treatment as well as at 3- and 6-month follow-up.
6. Reduction in WHO risk level for alcohol by at least two risk levels: from very high to moderate or high to low is measured at baseline, visit 8 (end of treatment), as well as at 3-, 6-, and 12-month follow-up.
7. Social functioning is measured using the SF-36 at baseline, visit 8 (end of treatment), as well as at 3-, 6-, and 12-month follow-up.
8. Depressive symptoms are measured by the Beck Depression Inventory (BDI) and Montgomery-Asberg Depression Rating Scale (MADRS) at baseline, visit 8 (end of treatment), as well as at 3- and 6-month follow-up. The BDI is also collected at 12-month follow-up.
9. Anhedonia is measured by the Snaith-Hamilton Pleasure Scale (SHAPS) at baseline, visit 4, visit 6, visit 8 (end of treatment), as well as at 3- and 6-month follow-up.
10. Craving is measured by the Alcohol Craving Questionnaire (ACQ-NOW) at baseline and each trial visit during treatment as well as at 3- and 6-month follow-up.
11. Alcohol dependence is measured by the Severity of Alcohol Dependence Scale (SADQ) at baseline, visit 8 (end of treatment), as well as at 3-, 6-, and 12-month follow-up.
12. Self-efficacy is measured by the alcohol abstinence self-efficacy scale at baseline, visit 8 (end of treatment), as well as at 3-, 6-, and 12-month follow-up.
13. Health economics: to establish methods for estimating intervention resource use and costs in a future cost-effectiveness analysis and assess the acceptability of health economic outcome measures. The EQ-5D-5L and ICECAP-A will be measured at baseline and 6-month follow-up.

Overall study start date
30/08/2023

Completion date
30/11/2026

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 28/06/2024:
1. 18 years old and over
2. Meet DSM-5 criteria for severe Alcohol Use Disorder
3. Abstinent from alcohol at randomisation (verified with withdrawal symptom checklist and breathalyser BAC level 0.00)
4. Seeking to reduce or quit alcohol long-term
5. Willing and able to consent and comply with trial procedure
6. People of childbearing potential and their sexual partners must be willing to use an effective method of contraception* (and must agree to continue for 6 weeks after the last dose of the IMP). Participants must be willing to inform the trial team if pregnancy occurs.
7. People of childbearing potential must have a negative pregnancy test within 28 days prior to being registered for trial treatment and on the day of first treatment.
* Highly effective contraception is defined as one of the following: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; vasectomised partner; practising true abstinence (when this is in line with the preferred and usual lifestyle of the subject). People of child-bearing potential could also be post-menopausal (no menses for 12 months without an alternative medical cause) or be surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

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2. Meet DSM-5 criteria for severe Alcohol Use Disorder
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5. Willing and able to consent and comply with trial procedure
6. People of childbearing potential and their sexual partners must be willing to use an effective method of contraception* (and must agree to continue for 6 weeks after the last dose of the IMP). Participants must be willing to inform the trial team if pregnancy occurs.
7. People of childbearing potential must have a negative pregnancy test within 7 days prior to being registered for trial treatment and on the day of first treatment.
* Highly effective contraception is defined as one of the following: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; vasectomised partner; practising true abstinence (when this is in line with the preferred and usual lifestyle of the subject). People of

child-bearing potential could also be post-menopausal (no menses for 12 months without an alternative medical cause) or be surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
280

Key exclusion criteria
Current participant inclusion criteria as of 28/06/2024:
1. Currently taking any other alcohol relapse prevention medication
2. Current uncontrolled hypertension (systolic ≥150 mmHg or diastolic ≥100 mmHg)
3. Being actively treated for a current co-morbid substance use disorder (SUD) or having been treated in the past 12 months. If the participant is currently in treatment for a comorbid SUD but is abstinent from any substance use and has a negative urine drug screen (except cannabis and benzodiazepine) participant could be included at the discretion of the investigator.
4. History of ketamine use disorder as assessed by the SCID.
5. Pregnant or breast-feeding
6. Not willing to use effective contraception or (people of child-bearing potential) take pregnancy test.
7. Use of another experimental IMP that is likely to interfere with the trial medication within 3 months of trial enrolment.
8. Known allergies to ketamine or excipients of IMP.
9. Meets current criteria for or has a history of any psychotic illness including substance induced psychosis.
10. Current suicide risk as judged clinically and using CSSR or a history of a suicide attempt within the past year.
11. BMI < 16 or > 35 kg/m²
12. Positive urine drug screen for ketamine.
13. Where there are “Special warnings and precautions for use for ketamine infusion” according to the SmPC.
14. Where risk vs benefit ratio is not in favour of giving ketamine, with assessment made by physical examination by medically qualified trial personnel, self-report, or inspection of the medical notes.
15. Received any previous ketamine treatment.

Previous participant exclusion criteria:
1. Currently taking any other alcohol relapse prevention medication
2. Current uncontrolled hypertension (systolic >140 mmHg or diastolic >90 mmHg)
3. Being actively treated for a current co-morbid substance use disorder (SUD) or having been

treated in the past 12 months. If the participant is currently in treatment for a comorbid SUD but is abstinent from any substance use and has a negative urine drug screen (except cannabis and benzodiazepine) participant could be included at the discretion of the investigator.
4. History of ketamine use disorder as assessed by the SCID.
5. Pregnant or breast-feeding
6. Not willing to use effective contraception or (people of child-bearing potential) take pregnancy test.
7. Use of another experimental IMP that is likely to interfere with the trial medication within 3 months of trial enrolment.
8. Known allergies to ketamine or excipients of IMP.
9. Meets current criteria for or has a history of any psychotic illness including substance induced psychosis.
10. Current suicide risk as judged clinically and using CSSR or a history of a suicide attempt within the past year.
11. BMI < 16 or > 35 kg/m²
12. Positive urine drug screen for ketamine.
13. Where there are “Special warnings and precautions for use for ketamine infusion” according to the SmPC.
14. Where risk vs benefit ratio is not in favour of giving ketamine, with assessment made by physical examination by medically qualified trial personnel, self-report, or inspection of the medical notes.

Date of first enrolment
25/06/2024

Date of final enrolment
31/12/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
NIHR Exeter Clinical Research Facility
Barrack Road
Exeter
United Kingdom
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Study participating centre
Oxford Health NHS Foundation Trust
Powick
Headington
Oxford

United Kingdom
OX4 1PD

Study participating centre
Surrey and Borders Partnership NHS Foundation Trust
Two Bridges, Guildford Street
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Study participating centre
NIHR Brighton & Sussex Clinical Research Facility
University of Sussex
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Sussex
United Kingdom
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Study participating centre
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Sponsor information

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res-sponsor@exeter.ac.uk

Sponsor type

University/education

Website
http://www.exeter.ac.uk/

ROR
https://ror.org/03yghzc09

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
AWAKN Life Sciences

Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Conference presentation
Publication on website
Other publication
Submission to regulatory authorities
Other
Trial documents will be archived for a minimum of 10 years after the end of the trial in line with the University of Exeter policies. After 10 years, all personal identifiable data will be securely

destroyed upon authorisation from the Sponsor. The anonymised dataset will be stored indefinitely in a repository under controlled access by the University of Exeter for the purposes of future ethically approved research. Requests for access to trial data will go through the University of Exeter.

Intention to publish date
30/11/2027

Individual participant data (IPD) sharing plan
repository TBC. All trial data excluding personal identifiable information will be made available indefinitely. Consent from participants will be obtained for data to be stored for the purposes of other ethically approved research in the future and that data will be shared anonymously.

IPD sharing plan summary
Stored in publicly available repository