ISRCTN10138262 https://doi.org/10.1186/ISRCTN10138262

Can unhelpful drinking memories be destabilised and weakened by ketamine in heavy drinkers?

Submission date
14/02/2019

Recruitment status
No longer recruiting

Registration date
18/02/2019

Overall study status
Completed

Last Edited
27/11/2019

Condition category
Mental and Behavioural Disorders

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol

Background and study aims
Heavy drinking and alcohol use disorder (AUD) is a leading global cause of preventable mortality. Current treatment approaches unfortunately confer limited long-term efficacy in reducing reactivity to alcohol, craving and excessive drinking and rebound/relapse to previous drinking levels is the norm following treatment for AUD.

As heavy drinking and AUD/SUDs are fundamentally acquired or learned maladaptive behaviours1, learning an memory processes play a key role in their aetiology and persistence. Specifically, alcohol can usurp reward learning mechanisms to produce maladaptive reward memories (MRMs). These associative memories link alcohol-predictive environmental stimuli (e. g. the smell of beer) and to the rewarding effects of alcohol. These MRMs are why certain environmental trigger 'cues' can provoke craving, drug-seeking and consumption. Although MRMs play a central role in relapse to harmful drinking patterns, current treatments do not effectively target these memories. Problematically, once well-learned and 'stabilised' - into long-term memory storage, MRMs are extremely difficult to eradicate, explaining rebound and relapse even long after successful reduction or detoxification and abstinence.

Memory reconsolidation offers a potential means to directly rewrite MRMs, potentially reducing problematic drinking and relapse risk. During reconsolidation retrieved long-term memories are temporarily 'reactivated' and destabilise in order to update their contents before restabilising. Research in animals has shown that by blocking the N-Methyl D-Aspartate Receptor (NMDAR)-receptor, which is required to restabilise memories, one can interfere with their reconsolidation, meaning it is possible to selectively target and weaken memories. This temporary 'reconsolidation window' of memory instability following retrieval offers the only known mechanism to directly weaken MRMs , meaning it could form a key part of more effective former treatments for heavy drinking and AUD. Despite this, no studies currently exist demonstrating MRM weakening in heavy drinkers by interfering with their reconsolidation using an NMDAR blocker.

In this study, we therefore examine whether ketamine (an NMDAR antagonist) can weaken maladaptive alcohol memories in harmful/ hazardous drinkers by interfering with their reconsolidation. To the extent that are they are dependent upon these MRMs, successful weakening of these memories should reduce reactivity to alcohol and alcohol-related cues and excessive drinking.

Who can participate?
Participants can take part if they: Regularly consume > 40 (men) or >30 (women) UK units alcohol /week, primarily drink beer, drink alcohol ≥ 4 days/week, drinking >3 units on drinking days, are not seeking or undergoing treatment for any alcohol, drug or psychiatric disorder, are aged 18 – 60 years, are motivated to reduce their alcohol consumption, have a BMI of >18<35, score on the Alcohol Use Disorders Identification Test (AUDIT), as assessed by the experimenters during screening.

What does the study involve?
Participants complete three face-to-face testing sessions and four remote (web-based or telephone) follow ups. The face-to-face sessions take place at the Clinical Psychopharmacology Unit (CPU) at University College London.

On Session 1 (baseline): After ensuring participants have read the information sheet, understood the study and provided informed consent, they provide a breathalyser reading (Lion 500 Breathalyser, Lion Instruments, UK). Basic demographic details are then be recorded (age, gender, weight, height, highest education level, ethnicity), followed by details of family history of alcohol use. Questionnaire assessments related to alcohol consumption and mood are then completed followed by computer-based assessments. These involve 1) rating images of alcohol and drinking a small sample of beer 2) eye tracking in a visual probe task 3) performance during an alcohol 'bandit task'. During the latter three tasks, 64 channel EEG recordings are made. This involves fitting an electrode cap to participants' heads and using gel to improve conductance to the head. These procedures are all generally very comfortable and minimally invasive. Finally, a pain threshold will be assessed using pressure algometry. This involves pressing an electronic device on to the back of a participant's fingernail until they indicate that the pressure becomes 'painful'.

Before leaving the session, participants are given the opportunity to wash off the EEG electrode gel and given details about preparing for the next session. Particularly, they are all given 10mg domperidone to consume 1 hour before the session and are asked to confirm that they will not take solid foods in the 6 hr or clear liquids in the 2 hr prior to infusion.

Session 2 (Memory reactivation/ketamine administration: Session 1 + 48 hours):

Participants attend the anaesthetics department at UCLH for this session. Upon arrival, participants confirm compliance with instructions related to taking the domperidone, fasting from consuming food and drink prior to the session and provide a breathalyser reading. An IV cannula is then inserted into the non-dominant arm and a blood sample drawn. EEG and ECG equipment is attached while the participant is seated on a hospital trolley and completes baseline questionnaire measures of memory and mood. Thereafter 10 min baseline EEG/ECG recordings are taken. Participants then undergo the pressure algometry (pain threshold) task and then alcohol memory retrieval (RET) procedure or control (No RET) procedure, according to their random allocation to group. A brief set of working memory tests is then performed, after which ketamine or placebo infusion starts. The infusion continues for 30 minutes, during which time heart rate, blood pressure and EEG are monitored. Questionnaires concerning drug effects are collected mid-way through the infusion and again, 20 minutes after the infusion ends.

Participants are given ample time to recover following the infusion. A final blood-draw is taken and participants complete a series of basic competency tests before agreeing that they are fit to leave the hospital.

On Session 3 (session 2 + 7 days): Participants attend the CPU and repeat the drinking related self-report measures, physiological alcohol reactivity and computer-based tasks from Session 1 as well as repeating the pressure algometry assessment. Another blood draw is taken to assess any long-term effects of the infusion.

Before they leave session 3, the participants will be given instructions on completion of follow-up measures of mood, craving, attitudes and responses to alcohol in naturalistic drinking environments and drinking behaviour, collected remotely via a secured website (Qualtrics) or telephone assessment.

Follow-up reminders are sent at 2 weeks, 3 months, 6 months and 9 months and participants receive £5 for each completed follow-up.

What are the possible benefits and risks of participating?
Ketamine is an analgesic (pain-killing) and anaesthetic (sedative) drug that has been used for a long time in hospital settings, particularly in young children, as it is much safer than alternative anaesthetics. Ketamine has dissociative and sedative effects, meaning may feel sedated and 'detached; from their body or uncoordinated. The ketamine used in the study will be administered intravenously via a cannula in participants' arm. Participants should therefore not take part if they have a fear of needles or would be uncomfortable receiving intravenous ketamine.

Administration of ketamine or placebo will be undertaken by a trained anaesthetist in a clinical area in University College Hospital (UCH), London. We also collect some blood samples while the intravenous cannula is being prepared. These will be stored anonymously and analysed for levels of various blood chemicals related to ketamine's effects. Single dose ketamine is generally considered very safe and an expert team of anaesthetists perform all ketamine infusions.

Ketamine has some known significant side-effects that you should be aware of when deciding to take part:

1. In 10+% of cases: Increases in blood pressure, increases in heart rate, increases in intracranial pressure, tonic-clonic movements (muscular seizures), visual hallucinations, auditory hallucinations, vivid dreams, dissociation.
2. In 1-10% cases: Reductions in heart rate, changes in eye focus and movement (diplopia), reduction in blood pressure, increases in intraocular (eye) pressure, injection-site pain.
3. In < 1% cases: Anaphylaxis, irregular heartbeat (arrhythmia), depressed cough reflex, muscle twitches, increased salivation, increased metabolism, increased muscle tension, spasm of the larynx.

Due to these possible effects, participants must not take part if they have a personal or family history of psychosis or schizophrenia or other psychiatric disorder, or a medical condition affecting blood pressure, heart, lung, brain, liver or kidney function. Participants are encouraged to discuss this information with their general practitioner before deciding whether or not to take part.

By taking part in this research participants will be helping us to gain a clearer understanding of the biological basis of learning and memory about rewards, drinking patterns likes and dislikes

and how these stay the same or change over time. We think this information will be important for understanding drug and alcohol use disorders. Participants may experience some beneficial changes in their drinking, although the researchers make no claims or guarantees about this possibility.

Where is the study run from?
The study takes place at the clinical Psychopharmacology Unit, UCL, 1-19 Torrington Place, London, WC1E 7HB (sessions 1 and 3) and University College London Hospital (session 2).

When is the study starting and how long is it expected to run for?
The study started on 12/06/2015 and ran until 01/11/2018.

Who is funding the study?
The study was funded by the Medical Research Council (UK).

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

Protocol serial number
ReMIT

Study information

Scientific Title
ReMIT – Reconsolidation and Memory Interference Toolkit Study: Weakening Maladaptive Reward Memories in Hazardous/Harmful Drinkers by Pharmacologically Interfering with their Reconsolidation.

Acronym
ReMIT

Study objectives
1. Retrieval of maladaptive alcohol memories (RET), followed by an intravenous infusion of ketamine (RET+KET) will reduce reactivity to in vivo beer, as measured by self-rated urge to drink and enjoyment of beer. Such a reduction will not be seen when ketamine is administered following retrieval of control memories (No RET + KET) or when retrieval of maladaptive alcohol memories is followed by placebo infusion (RET +PBO).
2. Reductions in actual drinking (number of days per week, binges and quantitative alcohol consumption) will be observed following RET +KET manipulation, but not in RET +PBO. We hypothesise reductions in volume of alcohol consumption will also be seen in No RET + KET, due to previously demonstrated potential anti-drinking properties of ketamine per se. However, these reductions will be of a smaller magnitude than in RET+KET, as they will not be due to MRM weakening.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 12/06/2015, University College London Research Ethics Committee (Student and Registry Services, UCL, 2 Taviton Street, London, WC1H 0BT; +44(0)20 7679 8876; ethics@ucl.ac.uk), ref: 0760/004.

Study design
Randomised controlled trial, mechanistic study using mixed within/between subjects design, single centre

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Hazardous and harmful drinking behaviour

Interventions
The critical manipulation consists of the combination of alcohol memory retrieval procedure (RET) designed to destabilize maladaptive alcohol memories or control memory retrieval (No RET) plus 30 minutes IV infusion of 350ng/dl ketamine (KET) or saline placebo (PBO). The 'active' condition is retrieval+ ketamine (RET+KET). The two control conditions are No RET+KET and MRM retrieval followed by placebo (RET + PBO) saline placebo. These groups control for the effects of ketamine and effects of retrieval alone. Only their combination should interfere with memory reconsolidation. Group allocation is fully randomized with N = 30 per group.

There is one between-subjects factor (Group) with three levels, and a within-subjects factor with two levels (Time: Baselibne vs. post-manipulation or post-manipulation vs. follow-up) for primary outcomes.

Interventions are carried out on Day 3 (session 2) of the testing protocol. The retrieval/non-retrieval procedures take approximately 4 minutes. The subsequent infusions of drug or placebo last for 30 minutes. The end of the infusion marks the end of the intervention procedure. With pre and post-manipulation checks and post-infusion recovery time, the total time for the session is 80 minutes and is the same in all arms.

The follow-up assessments in all groups take place at 7 days, 2 weeks, 3 months, 6 months and 9 months following manipulation day. The first follow-up takes place in-lab and includes computerised assessments, questionnaires and debriefing/payment. In total this last 60 minutes. All subsequent follow ups are completed remotely via Qualtrics software and take 15-20 minutes to complete.

Randomisation was achieved via a code from random.org and was not stratified by any other variable. That is, participant all had an equal chance of being randomised to any given condition. Participants were randomised to condition following completion of baseline testing (Day 1).

Intervention Type
Drug

Phase
Not Applicable

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

Primary outcome(s)
Measured from baseline (pre-manipulation, Day 1) to post manipulation (Day 10):
1. Alcohol reactivity and priming; operationalized as self-rated urge to drink in-vivo alcohol (beer), urge to drink more beer post-consumption and anticipated/actual enjoyment of the beer

pre/post consumption.
2. Harmful drinking behavior, operationalized as number of drinking days and heavy drinking or 'binge' days per week and quantitative alcohol consumption, as assessed by the Timeline Follow-Back.
3. Perceived changes in drinking behaviour from Day 1 to Day 10, consisting of 5-point Likert scale items judging relative urge to drink, enjoyment of drinking and volume of drinking (anchored 'much less than usual' to 'much more than usual'). These are rated retrospectively on Day 10.

Key secondary outcome(s))

1. Maintenance of any post-manipulation changes in drinking behavior (according to the Timeline Follow-Back) at 9 month follow-up
2. Changes in liking and ‘urge to drink’ responses to visual images of beer, wine, soft drink (orange juice) and neutral images from Day 1 to Day 10. All ratings are on an 11-point scale.
3. Changes in the following measures of attitudes related to drinking: Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES), Comprehensive Effects of Alcohol (COEA) scale, Obsessive Compulsive Drinking Scale (OCDS), Alcohol Craving Questionnaire (ACQ-NOW) and Alcohol Use Disorders Identification Test (AUDIT). These are assessed at Day 1, Day 10, 2 week, 3-month, 6 month and 9-month follow-up time points.
4. Electronic pressure algometry as a measure of pain threshold, performed on Day 1, Day 3 and Day 10 will be collected to assess an exploratory learning model of pain and its possible disruption through memory mechanisms". This is operationalized as threshold pressure in Newtons.
5. The following measures are potentially important covariate or cofounding factors that we wish to assess for similarity between groups at baseline, but which are not outcomes for study. No specific predictions are made about changes or group differences in these measures: Family history of alcoholism, Lifetime cumulative drinking questionnaire, Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES), The Beck Depression Inventory (BDI), Barratt Impulsiveness Scale (BIS), Behavioural Inhibition/Activation Scale (BIS/BAS)4, Distress Tolerance Scale (DTS), Positive and Negative Affect Scale (PANAS), Alcohol Use Disorders Identification Test (AUDIT)
5.1. Acute responses to drug/placebo infusion as assessed by the Clinician Administered Dissociative States Scales (CADSS), Bodily Symptoms Scale (BSS), Drug Effects Questionnaire (DEQ) and Snaith-Hamilton Pleasure Scale (SHAPS). These are assessed pre-infusion, peri-infusion and post-infusion on Day 3
5.2. Attentional Bias to alcohol-relate cues as assessed by eye-tracking and in a visual dot-probe task performed on Day 1 and Day 10.
5.3. Performance and EEG responses on an alcohol 4-arm ‘bandit’ task, wherein participants must select an image associated with reward. Performance is defined as number of correct responses, total won, accuracy and latency to correct responses following a switch in the ‘pay-off’ image. EEG measures will be ERPs during the task on Day 1. This task is performed on Day 1 and Day 10.
5.4. EEG during the critical RET/No RET and drug procedures on Day 3. These exploratory measures will aim to assess electrophysiological predictors of responses to the critical manipulations using multivariate modelling to attempt to extract neural indices of memory destabilisation and subsequent interference that predict outcomes. They will consist of ERP, time-frequency and connectivity analyses.
5.5. Levels of self-rated surprise during the retrieval of MRMs on Day 3, rated on a -5 to +5 scale. Following the procedure outlined in Das et al (2018) JoVE, surprise or ‘prediction error’ is generated as part of the MRM retrieval procedure and this rating will serve as a manipulation check and exploratory moderator of treatment effects.

Completion date
01/11/2018

Eligibility

Key inclusion criteria
1. Scoring >8 on the Alcohol Use Disorders Identification Test (AUDIT)
2. Consuming > 40 (men) or >30 (women) UK units/week
3. Primarily drinking beer
4. Non-treatment seeking
5. Drinking ≥ 4 days/week
6. Drinking >3 units on drinking days
7. Aged 18-60
8. Endorsing a statement of being 'highly motivated to reduce' drinking
9. BMI >18<35

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
60 years

Sex
All

Total final enrolment
90

Key exclusion criteria
1. Diagnosis of alcohol or substance use disorder (AUD/SUD) or other psychiatric disorder
2. Undergoing or seeking treatment for alcohol use
3. Undergoing or seeking treatment for any psychiatric disorder
4. Use of recreational drugs (other than tobacco) > 1x/ month
5. Major physical health issues contraindicating ketamine
6. Blood pressure > 145/90, allergy/contraindication to ketamine
7. Pregnancy or breastfeeding

Date of first enrolment
01/03/2016

Date of final enrolment

01/03/2018

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University College London
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Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Government

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

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from Dr. Ravi Das by emailing ravi.das.ucl.ac.uk. Data will comprise primary outcome variables on pseudonymised data. These include primary alcohol reactivity, drinking, demographic and computerised task summary performance data. Data will only be made available upon reasonable request (under stipulations set out by GDPR) for scientific research purposes and will not be made available for commercial or third-party purposes.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/12/2019	27/11/2019	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes