DOI:
10.1176/appi.ajp.2021.21030277

Document Version
Peer reviewed version

Ketamine adjunctive to relapse prevention based psychological therapy as a treatment for alcohol use disorder

[a]Grabski, Meryem., PhD[1,2], [a]McAndrew, Amy., PhD[1], Lawn, Will., PhD[2], Marsh, Beth., BSc[1,2], Raymen, Laura., MSc[1], Stevens, Tobias., PhD[1], Hardy, Lorna., PhD[1], Warren Fiona., PhD[3], Bloomfield, Michael., PhD[2,4], Borissova, Anya., MD[2], Maschauer, Emily.[1], Broomby, Rupert., MD[5], Price, Robert., MD[5], Coathup, Rachel., MD[6], Gilhooly, David., MD[6], Green, S.F., MD[6], Palmer, Edward. M.D [1], Gordon-Williams, Richard., MD[6], Iskandar, Georges., MD[6], Hill, Robert., PhD[7], Harris, Jen., DClinPsych[7], Mollaahmetoglu, M., MSc.[1], Curran H.Valerie., Prof [2], Brandner, Brigitta., MD[6], Lingford-Hughes, Anne., M.D. Prof [8], Morgan, Celia .J.A, Prof[1].
*co-first authors

1. Psychopharmacology and Addiction Research Centre, University of Exeter, UK
2. Clinical Psychopharmacology Unit, University College London, UK
3. College of Medicine and Health, University of Exeter, UK
4. Translational Psychiatry Research Group, University College London, UK
5. Royal Devon and Exeter NHS Foundation Trust, UK
6. University College London Hospitals NHS Foundation Trust, UK
7. South London and Maudsley NHS Foundation Trust, UK
8. Faculty of Medicine, Department of Brain Sciences, Imperial College London, UK

Word count:
Abstract: 289
Main text: 4572

Corresponding author:
Celia Morgan,
Psychopharmacology and Addiction Research Centre, University of Exeter,
Washington Singer Laboratories, University of Exeter, Perry Road, Prince of Wales Road, Exeter, EX4 4QG, UK,
Email: Celia.Morgan@exeter.ac.uk, phone: 01392 724649

Previous presentation: Presented at Royal College of Psychiatrists' Meeting Sept 8th 2020, Online

Disclosure of Competing interest: CJAM and HVC have consulted for Janssen Pharmaceuticals, CJAM has a research grant from Awakn Life Sciences, all other authors report no financial relationships with commercial interests

Acknowledgements: Funding for this trial from the Medical Research Council to CJAM, ALH and HVC (Grant number: L-023032) is registered at ClinicalTrials.gov (ID: NCT02649231).We would furthermore like to thank Dr. Evgeny Krupitsky for his pioneering research into ketamine as a treatment and his input into the design of the study. This paper is dedicated to the memory of our colleague Dr. David Gilhooly.

Abstract

Objective: Early evidence suggests that ketamine might be an effective treatment to sustain abstinence from alcohol. This study aimed to investigate the safety and efficacy of ketamine compared to placebo to reduce relapse in patients diagnosed with AUD. An additional aim was to pilot ketamine combined with mindfulness-based relapse prevention therapy compared to ketamine and alcohol education (as a therapy control).

Methods: In this double-blind placebo-controlled phase II clinical trial 96 patients with severe alcohol use disorder were randomised to one of four conditions: i) three weekly ketamine infusions (0.8 mg/kg IV over 40 minutes) plus psychological therapy (mindfulness based relapse prevention) ii) three saline infusions plus psychological therapy, iii) three ketamine infusions plus alcohol education iv) or three saline infusions plus alcohol education. The primary outcomes were self-reported percentage of days abstinent and confirmed alcohol relapse at 6 months follow-up in the ketamine versus saline condition.

Results: Ninety-six participants (35 women, mean age [SD], 44.07 [10.59]) were included in the intention to treat analysis. The treatment was well tolerated – no serious adverse events associated with the study drug were recorded. Although confidence intervals were wide, consistent with a proof of concept study, there were a significantly greater number of days abstinent from alcohol in the ketamine versus the placebo group at 6 months follow-up, however there was no difference in relapse rates between the ketamine versus the placebo group.

Conclusions: This study demonstrated that three infusions of ketamine were well tolerated in patients with alcohol use disorder and increased the number of days of abstinence from alcohol at six months follow up. The findings suggest a beneficial effect of adding psychological therapy alongside ketamine treatment that requires further investigation in a fully powered clinical trial.

Introduction

Harmful use of alcohol causes more than 5% of the disease burden worldwide (1), but a great proportion of individuals with alcohol use disorder (AUD) do not respond to currently available pharmacological and behavioural treatments, with more than 70% of those entering treatment relapsing within one year (2). The N-methyl-d-aspartate receptor (NMDA-R) antagonist ketamine is a promising candidate therapy in AUD for several reasons. Firstly, substantial evidence supports the anti-depressant properties of subanaesthetic doses of ketamine (3), leading to the recent FDA and EMA approval of esketamine, an enantiomer of ketamine, for use in treatment resistant depression. Depressive symptoms are common in individuals entering treatment for AUD, and the likelihood of alcohol relapse is increased in patients with such symptomatology (4, 5). Ketamine may support alcohol abstinence by temporarily alleviating depressive symptoms during the high-risk relapse period in the weeks post detoxification.

Furthermore, ketamine might aid alcohol abstinence by providing a window during which psychological therapies can be more effective. Evidence from pre-clinical studies suggests that ketamine increases synaptogenesis and neurogenesis, known to be disrupted following addiction (6, 7). Learning and planning are impaired in patients with AUD and these deficits likely underpin the limited effectiveness of therapy in patients suffering from AUD (8, 9). Ketamine may provide a temporary boost to synaptogenesis and neurogenesis which may allow psychological therapies and new strategies for managing addiction to embed more readily (10). There is little empirical evidence on the effectiveness of psychological therapy additional to ketamine treatment, but one study suggested that 10 weeks of cognitive behavioural therapy alongside ketamine infusions might prolong ketamine-induced symptom reduction in treatment resistant depression (11). The subjective experiences that accompany ketamine infusions may provide a new perspective that may be helpful in psychological therapy. Ketamine induces a sense of dissociation and disembodiment that has been described as facilitating an ‘observer state’ similar to that described in mindfulness, which may be helpful for allowing patients to consider thoughts and emotions from a more removed perspective (12).

Several studies have directly investigated the effect of ketamine on patients with problematic alcohol use: An early, non-randomised study found that three subanaesthetic doses of ketamine (2.5 mg/kg intramuscular:IM) adjunctive to psychodynamic psychotherapy led to a one year abstinence rate (at outpatient follow-up) of 66% in a group of inpatient AUD patients following detoxification compared to a 24% abstinence rate in an untreated control group (13). The positive impact of ketamine on AUD has been corroborated recently in 40 outpatients, randomized to a single infusion of either ketamine

(0.71 mg/kg intravenous) or the active placebo midazolam alongside motivational enhancement therapy in both conditions. At 21 days, 47% in the ketamine group reported using alcohol compared with 59% in the midazolam group. (12). Furthermore, in participants with hazardous drinking patterns (but no clinical diagnoses), one intravenous ketamine infusion combined with a memory reactivation protocol, but no therapy intervention, was associated with reduced alcohol use at 6 months (14). Given the heterogeneity in the literature on the effect of ketamine on AUD in terms of study design, dosing regimen, use of additional therapy and type of therapy, further research is needed specifically given the dearth of current treatments for AUD.

Given the antidepressant properties of ketamine, very early evidence that it might aid psychological therapy and a few studies showing initial benefits of ketamine as a treatment for AUD, the current study set out to investigate the safety and feasibility of ketamine infusions versus saline infusions on percentage days abstinent at 6 months follow-up. In the current study three ketamine infusions were administered weekly, as this has shown to be effective in earlier research (13)[a].

We furthermore aimed to pilot ketamine combined with mindfulness-based relapse prevention therapy (henceforth: therapy) compared to ketamine plus alcohol education (as a therapy control). This type of psychological therapy was chosen as it has shown to be effective and the ketamine experience can be considered to potentially promote engagement in mindfulness practise by giving experiential insights. Thus, in the current phase II clinical trial we are comparing 4 treatment conditions: 1) ketamine (active) and therapy (active), 2) ketamine (active) and alcohol education (control), 3) saline (control) and therapy (active) and, 4) saline (control) and alcohol education (control). We hypothesised that the ketamine plus therapy group (active plus active) would be most effective in sustaining abstinence, with the lowest abstinence rates in the placebo plus education group (control plus control).

Methods

Participants.

Participants were recruited from primary care and secondary care drug and alcohol services as well as from the community through social media, newspaper and radio advertisements.
All participants had to achieve initial abstinence at randomization, meaning they had to be abstinent for at least 24 hours and have an alcohol breathalyzer reading of 0.0 at the baseline visit. This allowed us to investigate the impact of ketamine on prolonging abstinence. During an initial telephone screening (AM, WL, MG, BM, LR, LH, CJAM) the current level of alcohol use of the participant was assessed. Alcohol abstinent participants were immediately invited to a screening visit. Those drinking at levels that meant they could safely cut down to abstinence within four weeks were asked to do so and then scheduled for a screening visit. Alternatively, participants were encouraged to undergo a

supervised detoxification in primary care or through their current treatment provider and once initial abstinence had been achieved they were invited for a screening visit.At the screening visit, after written informed consent was gained, eligibility was determined by the study physician, taking the patient's medical history, physical examination, mental health assessments, blood and urine analysis, and breath alcohol tests. At the end of the study participants were remunerated financially to compensate them for the time spent in the study at a level correspondent to the national living wage.

Eligible participants had to be 18-65 years old, meet DSM-5 criteria for moderate/ severe alcohol use disorder or DSM-IV criteria for AUD, have a good command of the English language, to be currently abstinent from alcohol and have a negative urine screen for all drugs apart from cannabis and benzodiazepines. This was due to the long half-life of both drugs and the fact that cannabis is comorbid with AUD and benzodiazepines are a commonly prescribed drug in AUD for sleeping problems. Current or historic dependence on either of these drugs was an exclusion criterion.

Key exclusion criteria were uncontrolled hypertension (systolic blood pressure 140mm Hg or greater and diastolic blood pressure 90mm Hg or greater), the use of antihypertensives or antidepressants, current suicidal ideation, a diagnosis of any current or past psychiatric disorder (except for depression, anxiety or alcohol use disorder/dependence), or of substance dependence (except for AUD) or ever seeking professional help for dependence on an illicit substance. Study applicants who had more than ten previous inpatient alcohol detoxifications or a history of harmful ketamine use were also excluded (a full list of the inclusion/ exclusion criteria can be found in SA1).

All procedures and patient visits took place at either NIHR Exeter Clinical Research Facility or NIHR UCLH Clinical Research Facility. The trial was registered at clinicaltrials.gov (NCT02649231) and under the following EudraCT number: 2015-000222-11 (15). Ethical approval was granted by South West – Central Bristol Research Ethics Committee (reference number 15/SW/0312) and the Medicine's and Health Regulatory Authority (MHRA) UK. All analysis were pre-planned and registered at EudraCT (2012-000222-11) and clinicaltrials.gov unless indicated otherwise.

Design. In this double-blind phase II clinical trial, recently detoxified adults with AUD were randomly assigned to one of four treatment arms:1) ketamine (active) and therapy (active), 2) ketamine (active) and alcohol education (control), 3) saline (control) and therapy (active) and, 4) saline (control) and alcohol education (control). Participants were invited to attend ten study visits (see Figure 1). Self-reported drinking events were recorded at every visit using an Alcohol Timeline-Followback. Participants were provided with an alcohol diary to record their alcohol use between visits 8 and 9 and 9 and 10 (see Figure 1). A Secure Continuous Remote Alcohol Monitor (SCRAM, Alcohol Monitoring Systems, Inc.) bracelet for continuous alcohol monitoring (every 30 minutes) was

attached before randomization at visit 1 or 2 and removed at visit 8 (end of treatment), to corroborate self-reported Alcohol Timeline Followback outcomes.

Randomisation and masking. Participants were randomized in a 1:1:1:1 ratio using a block design stratified by treatment site to one of the four treatment arms at the beginning of visit 2. All staff except for pharmacy, who had no contact with participants, were blinded to drug treatment allocation and all except the therapists were blind to the therapy/education allocation.

Therapy and alcohol education control. At visit two and the subsequent six visits participants received either manualised therapy or alcohol education as a placebo control for therapy. Both were administered by trained psychologists – with all therapists delivering both types of treatment. The sessions were timed so that the infusion was always preceded by a therapy or alcohol education session and followed by another therapy or alcohol education session about 24 hours later.

The aim of the seven therapy sessions based on manualised mindfulness-based relapse prevention was to support the participants to develop an enjoyable and meaningful life without alcohol (16). Each session was designed to last 1.5 hours and contained one topic related to each of the two overarching themes of the therapy: relapse prevention and the promotion of well-being. In between these two main themes, a different relaxation or mindfulness exercise was introduced in each session. The sessions covered a range of relapse prevention techniques including dealing with high risk situations, activity scheduling and problem solving alongside dealing with thinking biases (CBT-based) mindfulness practise and techniques such as urge surfing. Patients were also required to reflect on resources needed for a meaningful life without alcohol. Between sessions patients used journals to record and reflect on their experiences and completed a number of exercises, alongside mindfulness practise. All therapy sessions were recorded and an independent consultant clinical psychologist reviewed recordings to check adherence to the treatment protocol on a weekly or biweekly basis. The therapy manual was incorporated into a step by step scripted ‘guidebook’ for the participant and therapist that was designed to be prescriptive to facilitate adherence to the therapy protocol.

The seven alcohol education sessions were also designed to last 1.5 hours so that interpersonal interaction time matched the therapy, to act as a control for the therapy condition. During these sessions the focus was on educational topics including the driving forces of addiction, the biological effects of alcohol, and ways to improve healthy living and nutrition. In contrast to the psychological therapy these sessions had no formal psychological components relating to personal relapse prevention strategies, mindfulness or the promotion of personal well-being.

Drug administration: Ketamine (0.8 mg/kg) or placebo (0.9% saline) of the same volume were administered as intravenous infusions. The dose was higher than depression studies based on findings of possible cross-tolerance to ketamine in people with alcohol use disorder (17). The infusions were administered at visits 2, 4, and 6. These visits were spaced apart a minimum of one and a maximum of three weeks and lasted for 40 minutes. This dose roughly equates to the lowest effective intramuscular dose (1.2mg/kg IM) in alcohol dependent patients used in previous research (Krupitsky, personal communication, 2012). The lowest dose of ketamine is preferable to minimise psychotomimetic effects which may reduce treatment tolerability and increase risk of drop-out. The route of administration was intravenous infusions as this is considered the best method to control ketamine blood levels, was associated with fewer adverse effects than intramuscular dosing and has been by now established as the conventional method for administering ketamine for therapeutic purposes. Saline was used instead of an active placebo as upon starting this was the first study in this patient group since the early work in Russia (13), and we were concerned that an active placebo benzodiazepine may have unintended therapeutic consequences (18).

Before each infusion patients were prepared in terms of potential ketamine experiences by the therapist (see also Mollaahmetoglu et al. (19) for further details) and how they might reflect on the previous therapy session during the drug experience, including directions to use the relaxation or mindfulness techniques learned prior to the infusion during the experience. Patients were asked where possible to bring to mind their intention for a life without alcohol. A therapist was present and available throughout the infusion should the patient require reassurance.

The infusion was administered by an anaesthetist through a cannula in the antecubital fossa. Blood pressure, heart rate and blood oxygen levels were measured and a psychologist and a nurse were present during the infusion. During the infusion participants listened to instrumental music through headphones in a single bed hospital room to facilitate relaxation and minimise distraction from external stimuli. A therapist was available throughout the infusion should the patient require reassurance. Participants rated potential side effects at -20 minutes, 0 minutes (start of infusion), 20 minutes (mid-infusion), 40 minutes (end of infusion), and at 60, 80, 100 and 120 minutes after the infusion. These were assessed by a research nurse or psychologist.

Primary outcomes. The co-primary outcomes were self-reported percentage days abstinent and confirmed alcohol relapse at 6 months after first infusion, both measured using the Alcohol Timeline-Followback self-report questionnaire. Confirmed relapse for this study was defined as one or more days of heavy use; heavy use was defined as more than 64.8 g of pure alcohol for men (8.1 standard UK units) and more than 52.0 g for women (6.5 standard UK units) per day. (20). Abstinence was defined as no alcohol consumption.

Secondary outcomes. Alcohol-related secondary outcomes were self-reported relapse and percentage days abstinent at 3 months. Other secondary outcomes included depression, measured using Beck's Depression Inventory [BDI (21)] and the Hamilton Rating Scale for Depression [HAMD (22)], general health, measured by the 12 Item Short Form Survey [SF-12 (23)], psychotomimetic experiences (assessed before drug administration as included to index any protracted psychotic like effects of ketamine and not as an indicator of acute effects), measured by the Psychotomimetic States Inventory [PSI (24)], level of cigarette dependence, measured by the Fagerstrom Test of Cigarette Dependence [FTCD (25)], alcohol craving, measured by the Alcohol Craving Questionnaire [ACQ (26)], and SCRAM alcohol readings. The assessment time-points of each measure as well as other measures not presented here can be found in supplementary materials (SA2).

Subjective drug effects. Other safety measures included acute subjective effects of ketamine assessed by the researcher through a VAS scale of common ketamine effects , vital signs, alcohol breath monitoring, laboratory tests of liver function and ketamine as well as urine screens for pregnancy and drug use (27).

Blood sample analysis. Ketamine blood concentration was measured at each visit after randomization and twice on infusion visits: shortly before and two hours after infusion.

Statistical analysis. The main analysis method for all analyses was intention to treat (ITT; participants were analysed according to their treatment allocation) and used observed data only. All inferential analyses (for both primary and secondary outcomes) included adjustment for treatment site. For the primary outcomes, further sensitivity analyses were performed, including imputation of missing data and participants who received the full treatment. The current study was not powered to assess an interaction between the drug and the therapy condition.

Self-reported alcohol relapse status and percentage days abstinent from randomisation to 6-month follow-up were reported descriptively by treatment arm. Only participants with a minimum of 159 days of completed drinking self-report data were included in the main ITT analysis of alcohol relapse status as this was the shortest duration of time before any participant completed the 6 month (23-25 week) follow up in the study. Reporting time was capped at 180 days, but further sensitivity analyses were conducted with imputed data (multiple imputation method) and a per protocol analysis of only participant who received the full treatment. Logistic regression modelling was used to compare the ketamine group with the placebo group (combined across therapy and alcohol education). Further models compared ketamine plus therapy versus ketamine plus education, and ketamine plus therapy versus placebo plus alcohol education. Self-reported percentage days abstinent at 3 months and

longest abstinent spell within 3 months were also reported descriptively and analysed using linear regression modelling, with the only sensitivity analysis being adjustment for baseline alcohol use.

Other secondary outcomes were reported descriptively at baseline, 3 months and 6 months. Inferential analyses using linear regression with adjustment for site and baseline scores were used to compare the combined ketamine and combined placebo group at 3 months and 6 months. Repeated measures analyses using hierarchical linear modelling with a random effect on participant was used to investigate the effects of ketamine versus placebo for questionnaire outcomes across baseline, 12 days, 90 days and 6 months, including all participants with data for at least one of these timepoints. Analyses for FTCD included only participants who were smokers at baseline.

For continuous data, effect sizes were calculated as standardised mean differences with associated 95% confidence intervals.I If confidence intervals cross zero this can be interpreted as a non-significant effect (α=0.05). The size of the value indicates the magnitude of the difference (28). For dichotomous data odds ratios were calculated, which can be interpreted as percentage reduction if negative and percentage increase if positive.If CIs do not include 1 then this can be interpreted as a significant difference (α=0.05).

An exploratory analysis was conducted that was not in the original statistical analysis plan: the interaction between the ketamine and therapy conditions on percentage days abstinent at 3 and 6 months was tested using logistic regression modelling in the intention to treat population.

All analyses were performed using Stata v.16; the statistician was blind to treatment group for the analyses of the primary outcomes and alcohol related secondary outcomes.

Results

Demographics (Table 1). The first patient was recruited on 09/22/2016 and the last on 07/23/2019. A total of 166 applicants attended a screening visit, of whom 96 met the eligibility criteria and were randomized to one of the four treatment arms (35 women, mean age [SD], 44.07 [10.59]) (Figure 2). Most participants (95%) were recruited from the community through social media, newspaper and radio advertisements. The remainder were recruited from primary care and secondary care drug and alcohol services. The treatment groups were similar in demographic and baseline clinical characteristics. Length of ketamine treatment (randomization to visit 6) averaged 17.1 $\pm$ 4.7 days (min 12, max 35, N=81). Length of completed participation in the trial (randomization to visit 10) averaged 190 $\pm$ 31 days (min 163, max 369, N=81). 45% of participants had had a lifetime diagnosis of an anxiety disorder and 40% of depression.

Ten participants reported having received inpatient detoxification at least once. Participants met on average 7.29 ± 2.13 DSM-5 criteria for AUD – this was relatively evenly distributed across treatment groups. At screening participants reported an average of 34.5 ± 34.4 UK standard units per week and 8.2 ± 16.3 quit attempts. At randomisation, the average alcohol use had reduced to 1.7 ± 2.9 UK standard units per week (Table 1). Drug experimentation was common in this sample, as would be expected amongst a group with severe alcohol use disorder and whilst participants were not permitted to have a comorbid substance use disorder, 26% had tried ketamine (up to ten times previously); 49% had tried magic mushrooms and 44% Lysergic acid diethlyamide (LSD) although none were regular users.

Primary outcomes. Based on the ITT analysis there were a significantly greater percentage of days abstinent at 6 months follow up in the ketaminein the ketamine versus the placebo group, pooled across the therapy conditions (mean difference 10.1, 95% CI 1.1 to 19.0) (Figure 3, Table ST1). Similar results were observed across sensitivity analyses, one including only participants who completed all treatment visits and one with missing data imputed (ST1). No significant difference was found for relapse (recurrent heavy use) within 6 months. (Table 2).

Secondary outcomes. When comparing the ketamine + therapy condition to the saline + education condition the results favoured ketamine on percentage days abstinent (mean difference=15.9 95%; CI 3.8 to 28.1 [ST1]) but there was no significant difference for odds of relapse (OR=0.46; 95% CI 0.12 to 1.74 [Table 2]). When comparing the ketamine + therapy condition with the ketamine + education condition the results were not significant for percentage days abstinent (mean difference=4.2; 95% CI -6.7 to 15.2[ST1]) or odds of relapse (OR=0.75; 95% CI 0.21 to 2.65 [Table 2]). There were more days abstinent and lower odds of relapse in the ketamine + therapy condition, but the CI included the null (ST1 & Table 2).

The ITT analysis indicated a significant effect of ketamine versus placebo for percentage days abstinent from alcohol at 3 months (mean difference 9.0, 95% CI 1.3 to 16.7) (Figure 3 and Table ST2). A significant reduction was found in BDI depressive symptoms in the ketamine compared with the placebo group at 3 months (mean difference -2.6, 95% CI -4.9 to -0.4) (Table 2). However, at 6 months no significant difference in mean BDI between ketamine and placebo condition emerged (mean difference -1.1, 95% CI -3.7 to 1.6) (Table 2). On the HAMD, differences in depressive symptoms at both 3 and 6 months were non-significant (see Table 2).

Of the six Psychomimetic States Inventory (PSI) subscales, anhedonia showed a significant reduction at 3 months in the ketamine versus the placebo group with a 95% CI that did not include the null effect (mean difference -1.8, 95% CI -3.1 to -0.5), but not at 6 months (mean difference -0.9, 95% CI

-2.4 to 0.5) (Table ST4). There were no differences in SF-12 mental and physical health subscales, and alcohol craving (Table ST4).

A correlation between percentage of self-reported drinking days on TLFB (0.078%, SD 0.227) and percentage of SCRAM readings greater than 0 (M 0.054%, SD 0.145) per participant between visits 2 and 8 was positive ($r=0.75$, $p<0.001$, 95% CI 0.63 to 0.83) (see supplementary materials SF1).

Adverse events. Overall, 53 adverse events in 20 participants were rated by medical staff as either definitely (N=7), probably (N=3) or possibly (N=43) related to the study drug. None of these were rated as serious adverse events. The majority of these were rated as mild. Four adverse events in 3 participants were rated as severe (ie. significant symptoms that prevent normal daily activity), all in the active drug condition (low mood, hypertension, tachycardia and euphoria). Two participants in the active drug condition withdrew due to not tolerating the treatment. Six participants reported using ketamine on a single occasion during the follow up period of the trial, of these three were allocated to placebo and three to the active drug treatment. All of these participants had used ketamine recreationally prior to participation in the trial.

Subjective drug effects. When asked whether they felt they had been given the drug, 100% percent of patients in the ketamine group, and 27% in the placebo condition reported that they had after the first infusion, 95 % for the ketamine group and 34 % for placebo group for the second infusion and 100 % for ketamine and 23% for placebo in the third infusion**.** Subjective effects of dizziness, out of body experiences, altered reality perception, and altered time perception were not in the statistical analysis plan but have been descriptively reported in the supplementary materials showing a profile consistent with ketamine administration (SA3). Several indices of liver function indicated an improvement over the course of the trial. A LOESS fitted curve indicated a more linear improvement in participants in the ketamine group, whereas the placebo group showed a u-shaped response (SF3).

Blood sample analysis. Average ketamine blood levels, taken two hours after infusion, were similar across infusions 1, 2 and 3 (M 60.3 ng/ml, SD 18.7; M 66.5 ng/ml, SD 31.6; M 66.1 ng/ml, SD 31.6, respectively) (SF2).

Exploratory analyses outcomes. The interaction between the drug and therapy conditions on days abstinent was not significant at 3 or 6 months follow-up (Table ST3).

Discussion

This proof of concept study set out to examine the effect of ketamine alongside manualised mindfulness-based relapse prevention therapy on alcohol intake and relapse in currently abstinent patients with AUD over 6 months. The results showed that ketamine increased the number of days abstinent from alcohol at 3 and 6 months compared to placebo. The greatest difference in percentage of days abstinent from alcohol was between patients given ketamine and therapy and those given placebo and education. Overall relapse did not differ significantly between groups.

The longevity of the effect on percentage days abstinent was impressive, being maintained at 6 months following entry into the study after only three infusions. To our knowledge this is the first phase II clinical trial to examine the therapeutic effects of ketamine in addiction over this long follow up period. The long-lasting nature of the therapeutic effect we saw here for alcohol use is consistent with other research in groups with alcohol use disorder (12) but contrasts with studies in depression, where changes in symptoms are maintained for only around two weeks following infusion (29). The overall beneficial effect of alcohol abstinence and the participants' adherence to the abstinence protocol was confirmed by the observation that liver function improved over the course of the trial. The impact of ketamine on alcohol abstinence was only evident for percentage days abstinent, not for relapse, which might be because binary outcome variables are less sensitive to detecting differences than more granular, continuous variables.

To our knowledge this is the first study in clinical research with ketamine to include ketamine combined with psychological therapy alongside ketamine combined with a comparison 'psychological' placebo. Alcohol education was used here as a therapy control and was less effective than the relapse prevention. Whilst the sample size was small, these data suggest the possibility of a beneficial effect between ketamine and psychological therapy that warrants further investigation. Whereas in the early work in AUD by Krupitsky and colleagues ketamine was given alongside psychotherapy, the contemporary literature on treatment approaches in depression have largely given ketamine alone (13). Ours and other emerging data (11) tentatively suggest that adding therapy may be fruitful avenue for prolonging the clinical benefits of ketamine in both substance use disorders and depression. Recently, Dakwar and colleagues combined ketamine with motivational enhancement therapy for AUD, based on ketamine's effects on motivation to quit cocaine (Dakwar et al., 2014) combining these two interventions was expected to increase motivation to achieve and maintain abstinence. Along with the current study, Dakwar and colleagues have also demonstrated mindfulness based approaches to be effective in substance use disorders, and intuitively this therapeutic approach is a good fit with ketamine where the drug experience can act to bridge and bring added insights to early stage mindfulness practise (12). Original work by Krupisky et al. (13) used transpersonal therapy approaches incorporating elements of aversive therapy to facilitate aversion towards alcohol; thisseemed to produce more pronounced effects, however, studies were conducted under vastly

different conditions when compared to more recent work. Participants were recruited from Russian alcohol and drug inpatient treatment settings. The dose and administration route in the current study also differed from previous research that administered a single higher dose of ketamine (2.5-3 mg/kg) via intramuscular route (IM) (Krupitsky et al., 1992; Krupiskty et al., 1997). IM was chosen in the latter study due to its longer acting acute effects compared to intravenous administration, (Krupitsky et al., 1992; Krupiskty et al., 1997). The current dose and administration route resemble Dakwar and colleagues' recent RCT for AUD, though this consisted of a single dose (0.7mg/kg IV) given to people meeting criteria for mild alcohol use disorder who were currently drinking. The present study adds to the literature by demonstrating that repeated doses of ketamine are safe and efficacious in prolonging abstinence from alcohol in people with severe alcohol use disorder, who had stopped drinking prior to treatment .Dose ranging studies have not been conducted, but it is important to establish the minimum effective dose, as ketamine treatment studies in AUD have on the whole opted for higher doses than are used in treatment resistant depression Future work should consider conducting dose ranging studies.

An effect of ketamine on depressive symptoms at 3 months was found when assessed with the self-rated BDI, but not the clinician - rated HAM-D. Generally, the HAM-D is believed to place emphasis on somatic symptoms whereas the BDI focuses on depressive cognitions (30, 31). It should also be noted that depression scores in this sample were on average low, likely due to the use of antidepressants being an exclusion criterion therefore caution is warranted before any interpretation of changes in depressive symptoms. One explanation for our findings might be that ketamine specifically affects anhedonia (32), as in this study we found anhedonia to be reduced at 3 months as assessed by the PSI anhedonia subscale, consistent with research in depression.

That ketamine can reduce both alcohol use and depression in alcohol use disorder is encouraging therapeutically. Whilst a clear link between depression and alcohol use disorder is acknowledged, alcohol and mental health services still struggle to meet the needs of dual diagnosis patients (33) so ketamine may represent a solution to this long-standing comorbidity. Transdiagnostic factors common across depression and substance use disorders that may be common targets for ketamine, for example alterations in reward sensitivity and anhedonia, are important to identify to advance the use of ketamine in dual diagnosis.

There were no serious adverse events associated with the trial drug, and adverse events were generally mild, suggesting that this treatment is well tolerated in this population. Ketamine in anaesthesia is indicated for use with caution in people with AUD in the Summary of Product Characteristics, however the results of this study suggest that at a subanaesthetic dose it is a well-tolerated treatment

in this group, and that concurrent alcohol use problems need not be an exclusion from ketamine treatment in other psychiatric settings such as depression (34).

This study had a number of limitations, notably that the generalisability of the study findings which is limited by the rigid enrolment criteria, such as for example the prohibition of antidepressant use. Furthermore, the blinding of both study conditions (psychotherapy and ketamine) was challenging, especially if participants had had prior experience with either ketamine or psychological therapy. Saline was used instead of an active placebo as upon starting this was the first study in this patient group since the early work in Russia (13), and we were concerned that an active placebo benzodiazepine may have unintended therapeutic consequences (18). Subsequently, studies have emerged demonstrating that midazolam does not have unintended treatment consequences and indeed is associated with reduced engagement with treatment (12). The challenge of blinding to ketamine effects is a limitation of the study, which whilst not entirely circumvented by midazolam, particularly in a group that are not naïve to benzodiazepines or ketamine, are certainly reduced. Around one third of patients in the placebo group believed they have been given the active drug, , however nearly all of the patients in the ketamine group thought they had been given the active drug, which could impact their self-perceived efficacy in alcohol use. Therefore, future studies should use active placebos to better maintain the blind (35). Due to the functional unblinding component associated with ketamine, future studies should systematically ensure that all assessments are conducted by a person who has not observed any part of the drug treatment.

We included a group that included some individuals who had prior experience of ketamine, which may have compounded functional unblinding issues. Individuals with more positive expectations of ketamine based on previous experiences may have been more likely to volunteer to take part in the trial, though the majority of participants (73%) reported no previous ketamine use. Whilst including this group may be seen as a weakness, the absence of subsequent problematic ketamine use suggests that this therapy may be suitable for those with such experimental recreational ketamine experiences. Ketamine use rates are high in the UK where the study is conducted with lifetime rates at 1.9% (EMCDDA, 2020), and amongst a group with alcohol use disorder, rates are still higher amongst 16-24 year olds therefore excluding individuals with any prior ketamine experience may become increasingly problematic.

Nearly half of our sample reported experimental use of magic mushrooms or LSD; individuals' previous experiences with other psychedelic substances may have influenced expectations from ketamine treatment, though this may also reflect openness to new experiences.

A formal assessment of the effect of therapeutic alliance would be a further important addition to future studies. The use of the mystical experience questionnaires was not considered at the time of designing the study as this did not relate to our hypotheses, and we made the decision to not use the CADSS to keep the measures that participants were doing under the influence of ketamine to a minimum, however in retrospect it would have been helpful to include these, and they would be an important addition to future studies Given heterogeneity in baseline alcohol use, future studies might consider using more individualised markers of drinking such as total number of drinks consumed or multiple event approaches such as number of days of heavy drinking, however this was not part of the pre-planned analysis of the current study. Lastly a dose-finding study might be an important avenue for future research, given the dearth of ketamine in AUD.

In conclusion, this trial demonstrated that three subanaesthetic infusions of ketamine support abstinence from alcohol, and that abstinence may possibly be further enhanced when ketamine treatment was combined with therapy. Overall, this treatment was well-tolerated. The data presented here, along with emerging data from other studies of ketamine in alcohol use disorder suggest that a further definitive trial is warranted.

References

1. World Health Organization. Global status report on alcohol and health 2018: World Health Organization; 2019.

2. Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. Jama. 2006;295(17):2003-17.

3. Zarate CA, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Archives of general psychiatry. 2006;63(8):856-64.

4. Greenfield SF, Weiss RD, Muenz LR, Vagge LM, Kelly JF, Bello LR, et al. The effect of depression on return to drinking: a prospective study. Archives of general psychiatry. 1998;55(3):259-65.

5. Brière FN, Rohde P, Seeley JR, Klein D, Lewinsohn PM. Comorbidity between major depression and alcohol use disorder from adolescence to adulthood. Comprehensive psychiatry. 2014;55(3):526-33.

6. Chambers RA. Adult hippocampal neurogenesis in the pathogenesis of addiction and dual diagnosis disorders. Drug and alcohol dependence. 2013;130(1-3):1-12.

7. Mandyam CD, Koob GF. The addicted brain craves new neurons: putative role for adult-born progenitors in promoting recovery. Trends in neurosciences. 2012;35(4):250-60.

8. Bates ME, Buckman JF, Nguyen TT. A role for cognitive rehabilitation in increasing the effectiveness of treatment for alcohol use disorders. Neuropsychology review. 2013;23(1):27-47.

9. Birch AM, McGarry NB, Kelly ÁM. Short-term environmental enrichment, in the absence of exercise, improves memory, and increases NGF concentration, early neuronal survival, and synaptogenesis in the dentate gyrus in a time-dependent manner. Hippocampus. 2013;23(6):437-50.

10. Ezquerra-Romano II, Lawn W, Krupitsky E, Morgan C. Ketamine for the treatment of addiction: Evidence and potential mechanisms. Neuropharmacology. 2018;142:72-82.

11. Wilkinson ST, Rhee TG, Joormann J, Webler R, Lopez MO, Kitay B, et al. Cognitive Behavioral Therapy to Sustain the Antidepressant Effects of Ketamine in Treatment-Resistant Depression: A Randomized Clinical Trial. Psychotherapy and Psychosomatics. 2021;90(5):318-27.

12. Dakwar E, Levin F, Hart CL, Basaraba C, Choi J, Pavlicova M, et al. A single ketamine infusion combined with motivational enhancement therapy for alcohol use disorder: a randomized midazolam-controlled pilot trial. American Journal of Psychiatry. 2020;177(2):125-33.

13. Krupitsky E, Grinenko A. Ketamine psychedelic therapy (KPT): a review of the results of ten years of research. Journal of psychoactive drugs. 1997;29(2):165-83.

14. Das RK, Gale G, Walsh K, Hennessy VE, Iskandar G, Mordecai LA, et al. Ketamine can reduce harmful drinking by pharmacologically rewriting drinking memories. Nature communications. 2019;10(1):1-10.

15. McAndrew A, Lawn W, Stevens T, Porffy L, Brandner B, Morgan CJ. A proof-of-concept investigation into ketamine as a pharmacological treatment for alcohol dependence: study protocol for a randomised controlled trial. Trials. 2017;18(1):1-9.

16. Chawla N, Collins S, Bowen S, Hsu S, Grow J, Douglass A, et al. The mindfulness-based relapse prevention adherence and competence scale: development, interrater reliability, and validity. Psychotherapy Research. 2010;20(4):388-97.

17. Petrakis IL, Limoncelli D, Gueorguieva R, Jatlow P, Boutros NN, Trevisan L, et al. Altered NMDA glutamate receptor antagonist response in individuals with a family vulnerability to alcoholism. American Journal of Psychiatry. 2004;161(10):1776-82.

18. Lejoyeux M, Solomon J, Adès J. Benzodiazepine treatment for alcohol-dependent patients. Alcohol and Alcoholism. 1998;33(6):563-75.

19. Mollaahmetoglu M, Keeler J, Ashbullby KJ, Argyri EK, Grabski M, Morgan CJA. "This is something that changed my life": a qualitative study of patients' experiences in a clinical trial of ketamine treatment for alcohol use disorder. Manuscript under review. 2021.

20. Garbutt JC, Kampov-Polevoy AB, Gallop R, Kalka-Juhl L, Flannery BA. Efficacy and safety of baclofen for alcohol dependence: a randomized, double-blind, placebo-controlled trial. Alcoholism: Clinical and Experimental Research. 2010;34(11):1849-57.

21. Beck A, Steer R, Brown G. BDI-II, Beck depression inventory: manual: Psychological Corp. San Antonio, TX. 1996.

22. Hamilton M. A rating scale for depression J Neurol Neurosurg Psychiatry 23: 56–62. View Article. 1960.

23. Ware Jr JE, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Medical care. 1996:220-33.

24. Mason OJ, Morgan CJ, Stefanovic A, Curran HV. The psychotomimetic states inventory (PSI): measuring psychotic-type experiences from ketamine and cannabis. Schizophrenia research. 2008;103(1-3):138-42.

25. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom K. The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. British journal of addiction. 1991;86(9):1119-27.

26. Singleton EG, Tiffany ST, Henningfield JE. Development and validation of a new questionnaire to assess craving for alcohol. Problems of Drug Dependence, 1994. 1995:289.

27. Morgan CJ, Rossell SL, Pepper F, Smart J, Blackburn J, Brandner B, et al. Semantic priming after ketamine acutely in healthy volunteers and following chronic self-administration in substance users. Biological psychiatry. 2006;59(3):265-72.

28. Sedgwick P, Marston L. Meta-analyses: standardised mean differences. Bmj. 2013;347.

29. Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biological psychiatry. 2013;74(4):250-6.

30. Brown C, Schulberg HC, Madonia MJ. Assessment depression in primary care practice with the Beck Depression Inventory and the Hamilton Rating Scale for Depression. Psychological Assessment. 1995;7(1):59.

31. Schneibel R, Brakemeier E-L, Wilbertz G, Dykierek P, Zobel I, Schramm E. Sensitivity to detect change and the correlation of clinical factors with the Hamilton Depression Rating Scale and the Beck Depression Inventory in depressed inpatients. Psychiatry research. 2012;198(1):62-7.

32. Lally N, Nugent A, Luckenbaugh D, Ameli R, Roiser J, Zarate C. Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression. Translational psychiatry. 2014;4(10):e469-e.

33. IAS. Alcohol and Mental Health: Policy and Practice in England. Factsheet Series. Insitute of Alcohol Studies, London. 2018.

34. Medicines.org.uk. Ketamine 50 mg/ml Injection. 2020.

35. van Egmond K, Wright CJ, Livingston M, Kuntsche E. Wearable Transdermal Alcohol Monitors: A Systematic Review of Detection Validity, and Relationship Between Transdermal and Breath Alcohol Concentration and Influencing Factors. Alcoholism: Clinical and Experimental Research. 2020;44(10):1918-32.