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RESEARCH REPORT

ADDICTION SSA

The psychoactive effects of repeated ketamine infusions and their mechanistic role in the treatment of alcohol use disorder: Secondary analysis of a randomised controlled trial

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Abstract

Background and aims: Ketamine assisted psychotherapy is a promising new treatment for alcohol use disorder (AUD). The psychoactive effects of repeated intravenous (IV) ketamine infusions in people with AUD and their mechanistic role in treating AUD are largely unknown. This study aimed to (1) quantify the subjective, psychoactive effects of IV ketamine in people with AUD, (2) investigate how these effects change over three dosing sessions and (3) test whether these effects mediate ketamine's therapeutic benefits in reducing alcohol consumption.

Design: Secondary analysis of the randomised, parallel-arm, double-blind, placebo-controlled, phase 2 'KARE' clinical trial.

Setting: Two clinical research facilities in England.

Participants: 96 adults (35 women) aged 18–64 years with moderate-to-severe AUD.

Intervention: Three weekly infusions of either ketamine (IV 0.8 mg/kg over 40 minutes) or placebo (saline solution).

Measurements: Psychoactive drug effects experienced were self-reported pre-, during- and post-infusion, every 20 minutes (eight times/infusion) on Likert scales (1–10), for: Effects of Drug, Liking of Drug, Altered Reality, Out of Body Experiences, Visual Distortion, Sound Distortion and Altered Time Perception. For each scale, we calculated area-under-the-curve (AUC) scores for each infusion and the AUC average across three infusions. The clinical outcome was percentage of days abstinent from alcohol in the 6 months after infusions.

Findings: Ketamine produced strong psychoactive effects on every scale, relative to placebo (all P values < 0.001). Ketamine's psychoactive effects were moderated by infusion number (infusion 2 vs. infusion 1) for: Liking of Drug ($P = 0.001$), Altered Reality ($P = 0.030$) and Out of Body Experiences ($P = 0.033$), with small-to-moderate effect sizes. The remaining four psychoactive effects were not statistically significantly changed by repeated dosing. No psychoactive effect statistically significantly mediated the relationship between drug treatment and percentage days abstinent (all P values = 0.075–0.935).

Conclusions: People with alcohol use disorder experience alterations in consciousness from 0.8 mg/kg intravenous ketamine administration. Ketamine's effects appear to be broadly consistent across three repeated infusions. Ketamine-related reductions in alcohol consumption do not appear to be mediated by the acute psychoactive effects of ketamine.

KEYWORDS
abstinence, alcohol use disorder, ketamine, psychedelic therapy, relapse prevention, subjective drug effects

INTRODUCTION

Alcohol consumption accounts for 5.1% of the global disease burden [1]. In the United Kingdom (UK), approximately 5% of the population drink more than 50 units of alcohol (400 g) per week, which puts them at higher risk [2], and more than 85 000 people in England receive treatment for an alcohol-only problem per year [3]. Numerous effective treatments for alcohol use disorder (AUD) exist [4]. However, there is a need to diversify treatment options, enhance response rates and improve long-term efficacy of treatments.

Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist with dissociative, psychotomimetic and antidepressant properties [5]. It has a favourable safety profile and has been recently approved as a treatment for treatment-resistant depression in the United States [6, 7]. Growing evidence suggests ketamine may be an effective treatment for AUD [8], as well as other substance use disorders (SUDs) [9–11]. In the 1990s, a non-randomised, unblinded, quasi-experiment from Russia demonstrated a single large dose of ketamine (2.5 mg/kg) increased abstinence from alcohol relative to a control treatment condition in people with AUD [12]. More recently, in a randomised control trial (RCT), a single 0.71 mg/kg intravenous (IV) ketamine infusion, combined with motivational enhancement therapy (MET), increased abstinence from alcohol and delayed relapse, relative to midazolam over 21 days [13]. Recently, in the KARE trial, Grabski and colleagues [14] demonstrated that three IV doses of 0.8 mg/kg ketamine increased the number of days abstinent from alcohol in people with AUD over 6 months. In this article, we are conducting a secondary analysis of this Grabski *et al.* [14] trial data.

In healthy people, ketamine has a distinct profile of subjective effects that include dissociative, mystical, ineffable, psychedelic and psychotomimetic effects (hallucinations and delusions) [15–18]. However, chronic alcohol use may blunt glutamate receptor sensitivity, leading to reduced drug-related subjective experiences and increased tolerance to ketamine [19–21]. Studies assessing acute subjective effects in people with AUD are scarce. However, one experiment investigated the dose-related subjective effects of ketamine in 20 male in-patients with severe AUD following detoxification and found that ketamine produced dose-related ethanol-like effects on each of the scales measured [22]. Additionally, a recent secondary analysis of participants in the ketamine arm (n = 12) of an AUD RCT found that participants experienced perceptual distortions, dissociations and multiple mystical and spiritual phenomena [23]. However, there remains a gap in the literature exploring these effects with a suitably large sample size, balanced gender and larger doses of ketamine. There is also a notable gap in the literature regarding how the acute subjective effects of ketamine change over multiple administrations, which has important clinical implications for repeated dosing regimens for ketamine in psychiatry [24]. Studies have suggested that multiple ketamine infusions yield a more durable and prolonged antidepressant response compared with a single infusion [24, 25], but may also pose potential risks [26]. It is, therefore, important to explore multiple ketamine infusions in the AUD population.

We do not understand how and why ketamine works as an effective relapse prevention treatment for AUD. Ketamine's acute psychoactive effects have been proposed as having an important therapeutic, mechanistic role [27–29]. Theoretically, this may be because strong mystical or dissociative effects may induce a lasting change in perspective toward the self, one's behaviour and connectedness to the world [30]. Classic serotonergic psychedelics, such as psilocybin, elicit somewhat similar subjective drug effects [31], and the strength of these psychoactive effects was related to a positive treatment response in depression [32], tobacco dependence [33] and AUD [34–36]. Importantly, dissociative effects of ketamine have predicted symptom improvements in people with depression [37]; mystical experiences mediated the therapeutic benefits of ketamine on cocaine use in people with cocaine use disorder [38, 39]; and mystical experiences mediated ketamine's impact on drinking outcomes in AUD [40], however, the overall pattern of findings is still mixed [27, 37]. Reviews highlight the promise of ketamine as a treatment for SUDs, but argue we do not yet have adequate high-quality data to conclude whether acute psychoactive effects mediate ketamine's therapeutic effect [27, 29].

In summary, three studies have specifically investigated ketamine's acute psychoactive effects in people with AUD [22, 23, 40]. One has explored whether acute psychoactive effects of ketamine mediate the therapeutic benefit of reduced alcohol consumption [40], but it had a smaller sample size (n = 40) and shorter follow-up period (21 days). Furthermore, none of these studies considered the impact of repeated ketamine infusions. If ketamine possesses therapeutic benefits because of its unique subjective psychoactive effects, or despite them, this will have implications for the development of ketamine and other NMDA receptor antagonists as psychiatric medicines.

Using data from the KARE clinical trial [14], which evaluated the clinical benefits of ketamine in 96 people with AUD who wanted to

abstain from alcohol, we aim to: (1) characterise the subjective psychoactive effects of IV ketamine in AUD; (2) investigate how these psychoactive effects change over three infusions; and (3) explore whether the strength of the psychoactive effects mediate the clinical, abstinence-promoting benefits. We hypothesised that people with AUD would experience strong ketamine-induced psychoactive effects and that these would mediate the clinical benefit of ketamine treatment.

METHODS

Participants

Full participant inclusion and exclusion criteria can be seen in the original article reporting the KARE trial [14]. To summarise, participants were recruited from the community via social media adverts, from primary care and from drug and alcohol services. Inclusion criteria were: 18 to 65 years old, Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5) moderate or severe AUD or DSM-IV alcohol abuse or dependence, currently abstinent from alcohol and aiming to abstain from alcohol. Exclusion criteria were contraindications for ketamine, personal or first-degree relative with a history of psychosis, current suicidal ideation and a past or current severe SUD to any other substance. See the Data S1 for a full list of eligibility criteria. All participants had been abstinent from alcohol for at least 24 hours at randomisation, and the objective of the clinical trial was to test whether ketamine assisted therapy could prolong abstinence.

Setting

The study was conducted at the National Institute for Health Research Exeter Clinical Research Facility and University College London Clinical Research Facility. Ethical approval was granted by the Southwest-Central Bristol Research Ethics Committee (reference 15/SW/0312) and received clinical trial authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA). The trial was registered at EudraCT (2015–000222-11) and ClinicalTrials.gov (NCT02649231).

Study design

The study was a randomised, between-subjects, double-blind, placebo-controlled trial. The trial was initially a 2 × 2 (drug by therapy) design and participants were randomised to one of four treatment arms:

1. ketamine + relapse prevention manualised therapy;
2. ketamine + alcohol education;
3. saline placebo + relapse prevention manualised therapy; and
4. saline placebo + alcohol education.

For this secondary analysis, we combined the manualised relapse prevention therapy and psychoeducation arms, comparing only ketamine vs. placebo groups (treatment arms 1 and 2 vs. 3 and 4 above).

Participants received three ketamine/placebo infusions. In this study, we collapsed across the therapy condition and did not analyse its impact. In our analyses, when investigating the subjective psychoactive effects as outcomes, the predictive factors were (1) drug: ketamine, placebo; and (2) infusion: first, second and third. Subsequently, we tested whether the strength of the psychoactive effects mediated the relationship between drug condition and the reduction in drinking.

Procedure

Participants attended 10 in-person visits. They received three ketamine or saline infusions, usually once per week for 3 weeks, with each infusion being a minimum of 4 days and a maximum of 21 days apart. They also received seven sessions of either manualised relapse prevention therapy (MT) or education about alcohol. Participants self-reported their drinking throughout the trial using a diary and the timeline follow-back method [41]. At the tenth visit (6 months) the primary clinical outcome measure of percentage days abstinent was calculated.

Infusions

A 40-minute IV infusion of either ketamine (0.8 mg/kg) or saline (0.9%) was administered by an anaesthetist. Before infusions, participants read a script explaining what to expect and encouraging reflection on a life without alcohol. A psychologist was present during all visits. Vital signs were monitored during and after infusion, and participants listened to instrumental music to facilitate relaxation. Participants completed the psychoactive Likert scales during pre-, during- and post-infusion.

Measures

Subjective psychoactive ketamine effects

The acute, subjective, psychoactive effects of ketamine were measured using Likert scales: effects of drug, liking of drug, altered reality, out of body experiences, visual distortion, sound distortion and altered time perception. The scales were not formally validated. However, very similar single-item Likert measures are widely used in psychopharmacology research to characterise acute psychoactive ketamine and other drug effects [15, 16, 42]. Participants rated each effect on a Likert scale from 1 (not felt at all) to 10 (strongly felt) 20 minutes pre-infusion, at the start of the infusion (0 minutes), during the infusion (20 minutes), at the end of the infusion (40 minutes) and then every 20 minutes up to 120 minutes post-infusion (60, 80, 100 and 120 minutes). This was done on all three infusion visits.

To quantify the totality of the drug's effects over time, we calculated the area-under-the-curve (AUC) value for each scale, and for each session [42, 43]. AUC was calculated using the R package *rstatix* and the function *area_under_curve*, with the trapezoid method. We

used these AUC values to explore the acute effects of ketamine (vs. placebo) and the impact of repeated infusions.

An average AUC score was calculated for each scale for each participant by averaging over the three infusions. If a participant did not complete all three infusions (20.9% in the ketamine group, 10.4% in the placebo group) (Table 1) then data from their completed infusions was averaged. In brief, two participants did not complete any infusions, 10 completed one infusion and missed the subsequent two, and three participants completed two infusions and missed the final one. If there was missing psychoactive effect data at any timepoint (11.5% data points were missing) (see Table S1) during the infusion then the participant's average score was calculated with present data only and included in analysis.

Alcohol use

Past alcohol use was quantified during the screening visit, including: DSM-5 AUD symptoms, current drinking at screening (units/week) and heaviest drinking period (units/week).

Participants self-reported their alcohol consumption during the trial using a diary and timeline follow-back method [41], which was checked at every visit. The primary outcome variable was the percentage of days abstinent over the 6-month (180 day) period. The numerator was the number of days abstinent, and the denominator was the number of total observed days (days with data reported). Days without data reported were ignored in analysis, with no assumption of relapse or abstinence for these missing days. See Table S2 for a summary of unreported days.

Data analyses

Statistical analyses were conducted using SPSS version 24 and R version 4.3.3.

Our first aim was to investigate the subjective psychoactive effects of 0.8 mg/kg IV ketamine versus placebo in people with AUD, not currently drinking and who were aiming to abstain from alcohol. Our second aim was to investigate how these effects change over three repeated infusions. To do this, we first visualised each psychoactive effect (ketamine vs. placebo) over every time point on each of the three infusions in Figure 1. Subsequently, we calculated AUC values for each scale at each infusion. Then, we conducted linear mixed models (LMMs), with the AUC values as the outcome, to investigate the effects of drug (ketamine vs. placebo) and infusion (first, second and third) and their interaction on psychoactive effects. The LMMs included a random intercept of participant, no random slopes and fixed effects of drug and infusion number. We used orthogonal Helmert

TABLE 1 Participant demographic, psychiatric and treatment information.

	Ketamine (n = 48)		Placebo (n = 48)		Total (n = 96)	
Characteristic	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	42.9	10.1	45.3	11	44.1	10.6
Alcohol consumption at screening (units/week)	38.0	38.3	30.5	29.0	34.7	34.3
Heaviest regular alcohol consumption (units/week)	125.6	45.4	131.3	89.2	128.4	70.8
No. of DSM-5 AUD symptoms	7.6	1.9	7.0	2.3	7.3	2.1
	n	**%**	***n***	**%**	***n***	**%**
Gender						
Male	30	62.5	31	64.4	61	63.5
Female	18	37.5	17	35.4	35	36.5
Site						
Exeter	23	50	23	50.0	46	47.9
London	25	52.1	25	52.1	50	52.1
Pre-randomisation psychedelic drug use (ever used)						
Ketamine	11	22.9	15	31.3	26	26.0
Psilocybin	22	45.8	25	52.1	47	49.0
LSD	17	35.4	25	52.1	42	43.8
No. of infusions						
0	2	4.2	0	0.0	2	2.1
1	6	12.5	4	8.3	10	10.4
2	2	4.2	1	2.1	3	3.1
3	38	79.1	43	89.6	81	84.4

Abbreviations: AUD, alcohol use disorder; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; LSD, lysergic acid diethylamide.

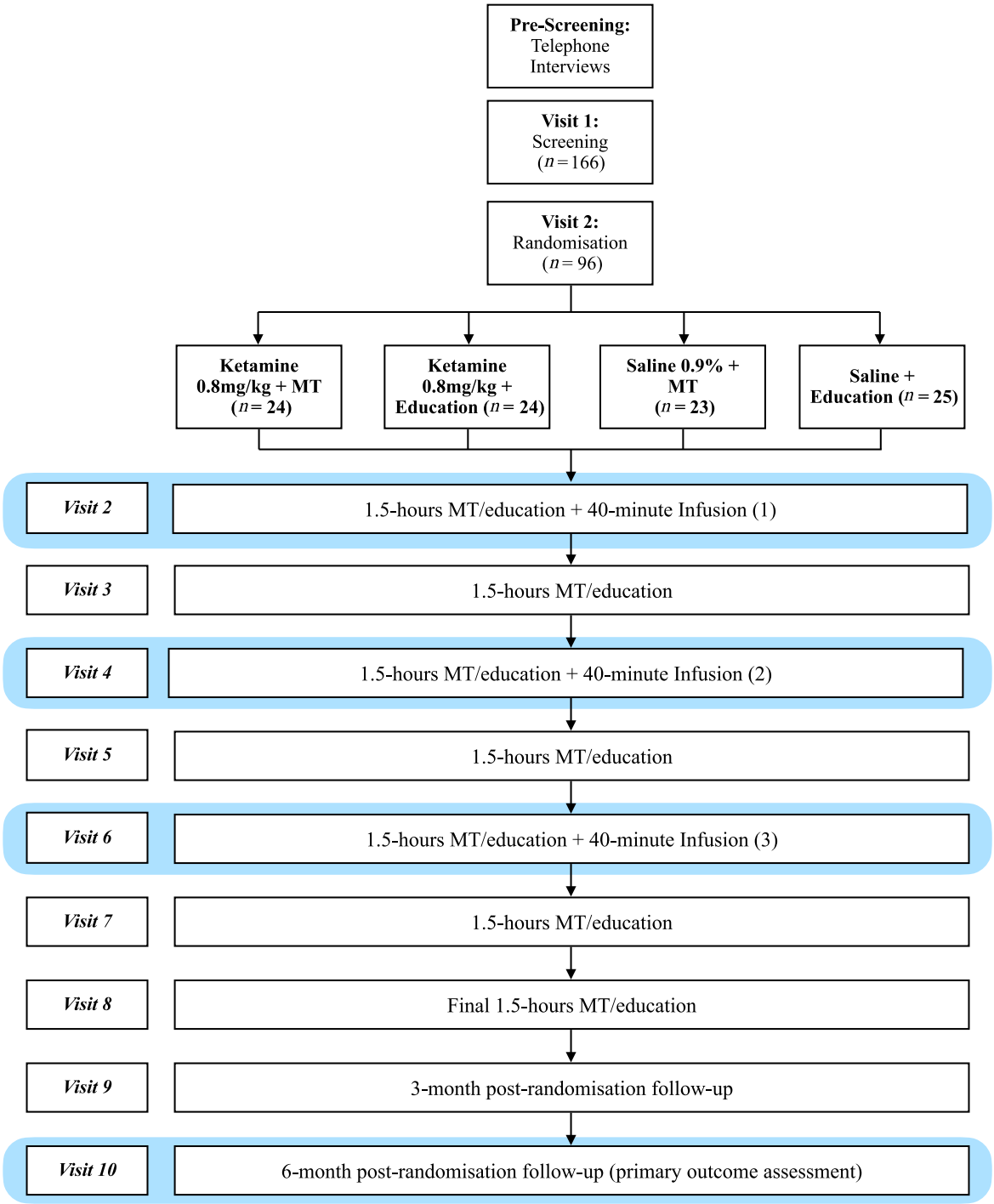

FIGURE 1 Study design, including all study visits. Only the visits that are highlighted in blue are relevant to this study. Infusions 1, 2 and 3 took place during visits 2, 4 and 6. MT, manualised relapse prevention therapy.

contrasts for drug (ketamine > placebo) and infusion number (H1: infusion 2 > infusion 1; and H2: infusion 3 > infusion 1 and 2). An orthogonal Helmert contrast is a statistical method for comparing means in an experiment, where the levels of a factor are ordered and successive contrasts are mutually independent (orthogonal). It compares the mean of each level against the mean of all previous levels [44]. Participants with at least one AUC value were included in our analysis, because LMMs handle missing data well with maximum likelihood estimation.

Our third aim was to explore whether the acute psychoactive effects of ketamine mediate the relationship between drug and percentage days abstinent. Mediation analyses were carried out with the Hayes method [45], using the SPSS PROCESS macro. The predictor variable was drug (i.e. treatment allocation) (X), the mediator was average AUC for each specific scale (M) and the outcome was percentage of days abstinent (Y). The mediation analysis first examines the total relationship between drug and the outcome: percentage days abstinent (Figure 2,

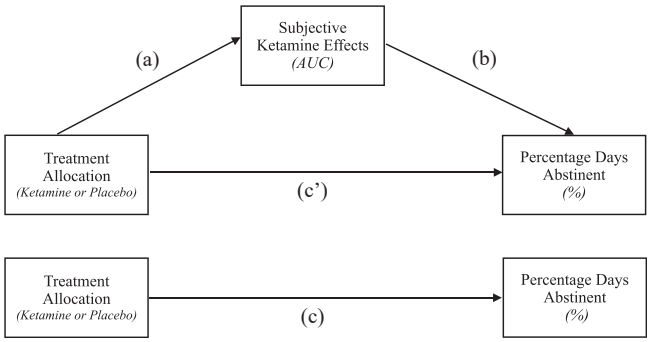

FIGURE 2 Expected mediation in which the relationship between treatment allocation (i.e. drug: ketamine vs. placebo) and percentage days abstinent is mediated by subjective ketamine effects [quantified using average area-under-the-curve (AUC) across all three infusions]. A mediation is found if: pathways a, b and c are significant ($P < 0.05$), and pathway c' is smaller than c or non-significant. Pathway a, indirect effect; pathway b, indirect effect; pathway c', direct effect; pathway c, total effect.

pathway c). Second, the analysis tests the relationship between the predictor and mediator (pathway a) and the mediator and outcome (pathway b). Third, it tests if the direct effect (pathway c') is reduced relative to the total effect. Significant indirect effects (pathways a and b), in combination with c' < c, would suggest that increased abstinence in the ketamine group is mediated by the psychoactive effects.

RESULTS

Participant characteristics

A summary of all 96 participant's demographic and infusion details is given in Table 1. More details can be found in the original article reporting the KARE trial [14]. A total of 81 participants completed all three infusions, two completed no infusions, 10 completed one infusion and three completed two infusions. In our analyses, participants with any psychoactive effect and any amount of alcohol timeline follow-back data were included.

An average of 153 drinking days were reported altogether, with a minimum of 1 day and a maximum of 205 days, although responses were capped at 180 days (6 months) in analysis. See Table S2 for details on missing alcohol timeline follow-back data. Further information specific to participants' alcohol use can be seen in Table 1.

Effect of drug allocation on percentage days abstinent from alcohol

As Grabski *et al.* [14] reported that ketamine increased percentage days abstinent from alcohol ($t_{94} = 2.18$, $P = 0.032$). Participants in the placebo group had 74.4% (SD = 26.0%) days abstinent, and participants in the ketamine group had 84.4% (SD = 18.8%) days abstinent. The group difference is 10.1% with 95% CI = 0.88%–19.3%.

Effect of drug and infusion number on ketamine effects scores

Graphs for all psychoactive effects can be seen in Figure 3. Average scores in the ketamine group increased substantially at the start of infusion (0 minutes), peaking at the end of infusion (40 minutes) before gradually declining again. Average scores in the placebo group remained around 1 (not felt at all) for most of the scales, apart from effects of drug and liking of drug, which showed increases during the infusion.

Table 2 shows the mean AUC score for each of the seven psychoactive scales, by drug condition and infusion. See Table S3 for the extent of missing AUC scores. Temporal reliability tests showed that psychoactive effects were reliable across infusions (see Tables S4 and S5).

Please see Table S6 or the full non-directional *F*-statistic LMM results and Table S7 for the directional β-statistic LMM results. In these models, we found a significant main effect of drug for every psychoactive effect (Table S6), indicating that those in the ketamine group experienced significantly stronger effects than those in the placebo group, regardless of infusion number.

There were significant interactions between drug (ketamine > placebo) and infusion H1-contrast (infusion 2 > infusion 1) for: out of body experiences, altered reality and liking of drug (see Table S6). For out of body experiences (−12.3) and altered reality (−9.2), the β for these interactions are negative (Table S7), indicating that the ketamine > placebo difference is smaller at infusion 2 than infusion 1, because the ketamine average is lower at infusion 2 (Table 2). For liking of drug (44.9), the β for this interaction is positive (Table S7), indicating that the ketamine > placebo difference is larger at infusion 2 than infusion 1. This is a consequence the liking AUC value in the ketamine group being higher at infusion 2 and the liking AUC value in the placebo group being lower at infusion 2 (Table 2). It is notable that even though these interactions were significant, the effect sizes for these moderation effects were small-to-moderate: out of body experiences (d = 0.26), altered reality (d = 0.39) and liking (d = 0.58). The proportional change in AUC value for ketamine, from infusion 1 to infusion 2, was only −9% for altered reality, −11% for out of body experiences and 29% for liking of drug.

For the other four psychoactive scales, there were no significant interactions between drug and infusion. Therefore, in combination with inspection of Figure 3 and Table 2 and Table S7, it is reasonable to conclude that the psychoactive effects of ketamine across three infusions were relatively stable.

Mediators of ketamine on abstinence

Subjective ketamine effects

We investigated whether average subjective ketamine effects AUC scores (Table 2) mediated the relationship between drug allocation

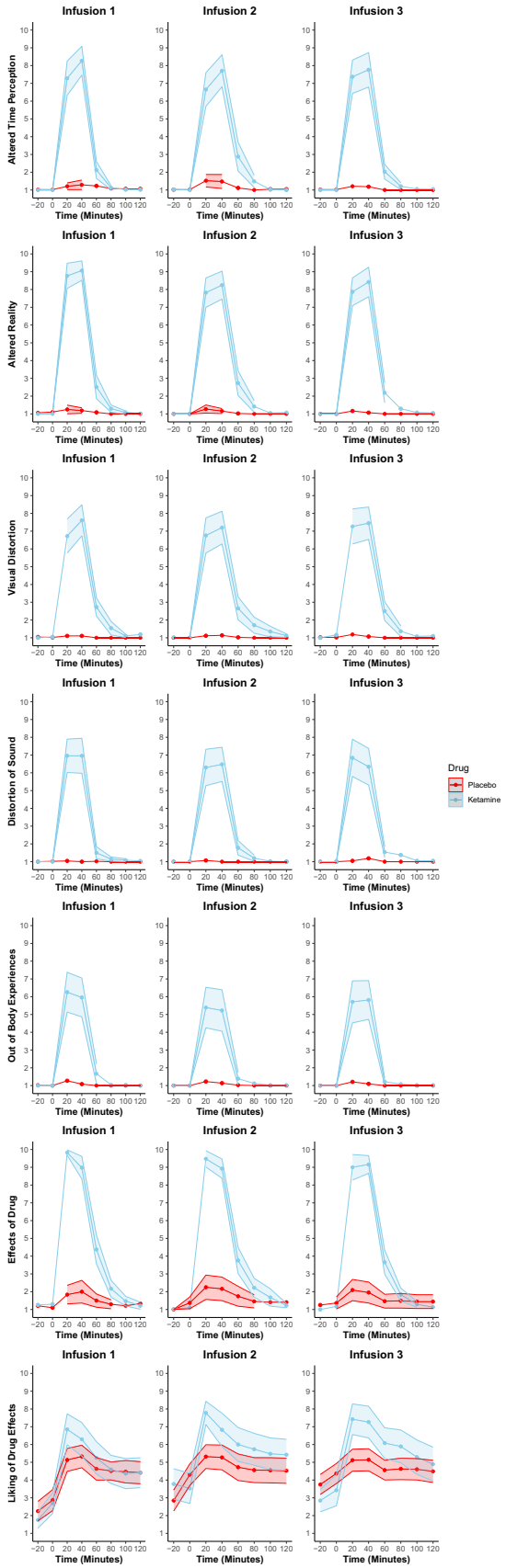

FIGURE 3 Psychoactive effects of ketamine (blue) versus placebo (red) over time for the three infusions. Each infusion begins at 0 minutes and ends at 40 minutes. Error bars show 95% CI.

and increased percentage days abstinent. The mediation pathway results can be seen in Table S8.

As stated above, allocation to the ketamine group increased percentage days abstinent from alcohol (pathway c: B = 10.07, P = 0.032). We also already know that randomisation to the ketamine group significantly increased the strength of psychoactive effects (pathway a: all B = 149.9–360.3, all P-values = <0.001–0.024). However, we found no evidence for significant mediation between drug and percentage days abstinent, via the psychoactive effects (pathway b: all B-values = −0.001 to 0.04, all P-values = 0.185–0.998; pathway c': all B-values = −1.01 to 12.1, all P-values = 0.075–0.935).

Correlations

The Pearson correlations between each psychoactive effect and percentage days abstinent, for the ketamine group, the placebo group and both combined are shown in Table S9. The scatterplots are shown in Figure S10. There are no significant correlations within either group, suggesting there is no relationship between psychoactive effect and reduced drinking in either ketamine or placebo groups.

Associations in the placebo group

We explored the relationship between subjective effects and percentage days abstinent in participants allocated to the placebo group. This was to explore whether participants who experienced a 'placebo effect', with noticeable subjective effects during the placebo infusion, had different clinical outcomes to those who reported no subjective effects. We divided the placebo group into those who reported any effect of drug at any point on any of the three infusions (the 'placebo effect group' n = 21), and those who never reported any effect of drug (the 'no placebo effect group' n = 28). There was no significant difference between the 'placebo effect group' (78.2%, SD = 22.9%) and the 'no placebo effect group' (71.4%, SD = 28.2%) on percentage days abstinent (t_{46} = 0.908, P = 0.369). Furthermore, within the 'placebo effect group', there were no significant correlations between any of the subjective effect scales and the percentage of days abstinent (all rs = 0.0–2.6, all P-values >0.24).

DISCUSSION

We conducted a secondary analysis of the KARE clinical trial data, which tested the effects of three doses of 0.8 mg/kg IV ketamine assisted psychotherapy on abstinence from alcohol, in people with moderate-to-severe AUD [14]. We showed that in people with AUD, ketamine produces the expected pattern of acute, psychoactive subjective effects. Second, we showed that these effects remain mostly similar across three ketamine infusions over 3 weeks, although there were small, but significant, reductions in altered reality and out of body experiences, as well as an increase in liking of drug, from the first

TABLE 2 Psychoactive ketamine effects split by drug and infusion with area-under-the-curve mean (SD) [min–max] {median (IQR)} data, rounded to nearest integer.

	Infusion 1		Infusion 2		Infusion 3		Total	
	Placebo	Ketamine	Placebo	Ketamine	Placebo	Ketamine	Placebo	Ketamine
Altered time perception	159 (69) [140–570] {140 (0)}	437 (114) [160–660] {480 (130)}	165 (66) [140–500] {140 (0)}	432 (145) [140–720] {420 (180)}	149 (25) [140–260] {140 (0)}	437 (112) [220–660] {500 (180)}	157 (45) [140–403] {140 (13)}	428 (97) [160–583] {440 (120)}
Altered reality	153 (28) [140–240] {140 (0)}	500 (87) [320–740] {500 (100)}	149 (24) [140–240] {140 (0)}	455 (112) [220–680] {480 (140)}	145 (20) [140–260] {140 (0)}	464 (126) [180–850] {500 (95)}	150 (22) [140–233] {140 (10)}	477 (89) [260–795] {478 (83)}
Visual distortion	145 (18) [140–260] {140 (0)}	436 (143) [140–770] {440 (190)}	146 (20) [140–240] {140 (0)}	427 (154) [140–940] {460 (220)}	146 (19) [140–240] {140 (0)}	444 (140) [140–750] {480 (180)}	146 (15) [140–213] {140 (0)}	432 (126) [140–735] {435 (127)}
Distortion of sound	142 (6) [140–160] {140 (0)}	396 (116) [140–640] {400 (180)}	141 (9) [140–200] {140 (0)}	376 (124) [140–640] {390 (175)}	145 (16) [140–220] {140 (0)}	386 (133) [140–650] {400 (200)}	142 (7) [140–173] {140 (0)}	378 (110) [140–637] {387 (107)}
Out of body experience	147 (28) [140–280] {140 (0)}	362 (160) [140–720] {380 (280)}	148 (36) [140–360] {140 (0)}	321 (154) [140–710] {320 (315)}	145 (25) [140–300] {140 (0)}	341 (146) [140–650] {320 (300)}	147 (25) [140–267] {140 (0)}	340 (135) [140–693] {335 (208)}
Effects of drug	203 (117) [140–570] {140 (55)}	589 (112) [380–900] {560 (120)}	219 (154) [140–800] {140 (80)}	570 (142) [240–1000] {545 (115)}	223 (201) [140–860] {140 (20)}	543 (117) [320–850] {540 (148)}	207 (128) [140–680] {140 (67)}	567 (104) [400–840] {530 (133)}
Liking of drug	594 (203) [140–1190] {590 (135)}	640 (259) [160–1130] {660 (370)}	561 (242) [140–1000] {660 (340)}	826 (342) [220–1400] {800 (500)}	640 (275) [140–1310] {700 (120)}	798 (329) [140–1310] {800 (490)}	584 (243) [140–1250] {650 (312)}	732 (306) [173, 1325] {742 (417)}

Note: A score of 140 indicates no effect.
Abbreviations: IQR, interquartile range; max, maximum; min, minimum.

infusion to the second infusion. Crucially, we found no significant evidence that any of these psychoactive effects mediated the clinical benefit of ketamine on reduced alcohol consumption. Last, within the placebo group, we found no significant evidence that the feeling of an acute drug effect predicted the clinical outcome.

Participants with AUD who received ketamine experienced marked subjective effects when compared to those who received placebo across our range of subjective psychoactive effect scales. A total of 0.8 mg/kg ketamine profoundly increased ratings for effects of drug, liking of drug, altered reality, out of body experiences, visual distortion, sound distortion and altered time perception. Chronic alcohol use leads to the upregulation of NMDA receptors [46], which could theoretically decrease the acute effects of ketamine [21, 47]. Our analysis adds to evidence suggesting that those with AUD experience marked subjective ketamine effects. Further research is needed to understand whether these are comparable in size to the subjective effects reported by healthy controls [15, 19].

We demonstrated that subjective effect scores reported during ketamine infusion remained largely consistent across the three visits, suggesting that participants did not develop measurable physiological tolerance or subjective alterations to the experience of ketamine over the three infusions. There were small, but significant, reductions from the first and second infusions for two scales: out of body experiences and altered reality. However, these reflected approximately a 10% drop and may be driven by the participants' apprehension and heightened novel experience during the first infusion. Repeated-measures psychopharmacology experiments often show stronger effects at the first session, when participants are in a novel environment, compared to subsequent sessions.

Our findings (Figure 2) show the pattern is broadly similar across all three infusions. There were no significant changes over three infusions in 4 other scales: visual distortion, sound distortion, altered time perception and effects of drug. Tolerance has been described in both anaesthetic and recreational use of ketamine, but this develops at substantially higher and more frequent ketamine dosing [48, 49] than we gave in our study. Patients are unlikely to become tolerant to the subjective effects after three IV 0.8 mg/kg doses of ketamine. Repeat administrations of ketamine have been shown to be beneficial in treating depression [24, 25] and heroin use disorder [10]. Further research is needed to determine optimal dosing schedules for SUDs and whether psychopharmacological tolerance appears with more frequent clinical ketamine dosing regimens.

Contrary to our hypothesis, we did not find evidence to suggest that more intense psychoactive effects mediated the relationship between ketamine treatment and clinical outcome (percentage days abstinent from alcohol). This is consistent with Olson's [50] proposal that the subjective effects of ketamine and classic psychedelics are not therapeutically relevant. Broadly, the subjective psychoactive effects of ketamine have predicted clinical response in previous SUD trials [27], however, our study, which is the largest to date, is the first to find no significant relationship between ketamine's psychoactive effects and reduced recreational substance use. Our results imply that

ketamine has relapse-preventing effects which are not explained by the altered state of consciousness that ketamine produces. Speculatively, this implies that ketamine's effects on neuroplasticity and functional brain changes, which do not acutely impact the conscious experience, may be more relevant in its therapeutic mechanism [28, 51]. A strong conscious-altering experience may not be necessary. The administration of ketamine during full anaesthesia, which blocks any subjective effect, to patients with depression, has produced both antidepressant [52–54] and null effects [55], leading to clinical scientists making claims on both sides of the argument. Future studies could potentially apply this study design to people with SUDs who are incidentally undergoing surgery. These discussions have implications for whether ketamine-analogue drugs, which do not produce psychoactive effects, should be developed and how therapy should be integrated into ketamine treatment procedures.

However, one major difference between our study and the previous trials that found an association between psychoactive effect and treatment response [11, 38, 40], is that they used the Hoods mysticism scale (HMS) to measure mystical effects during ketamine administration. Crucially, these studies did not find an association between dissociative effects and clinical response [11, 38, 40]. Our scales capture the dissociative effects (out of body experiences; altered reality), perceptual effects (distorted vision and sound) and strength of effect, however, they do not capture the spiritual or mystical effects. Therefore, future research must clarify if these mystical psychoactive effects (like the HMS) have clinical relevance, as well as further exploring the role of dissociation. The impact of a mystical experience, which may give lasting spiritual meaning to the event, may be quite different from the impacts of drug-induced dissociation.

There has been considerable discussion about positive expectations and placebo effects as the drivers of apparent clinical effects of psychedelic treatment [56, 57]. Our findings, specifically the null mediations and null associations within the placebo group, can partially speak to this debate. The subjective feeling of the drug predicted clinical response in neither the ketamine nor the placebo group, implying that the sense of being in the active condition was not significantly associated with treatment outcome.

Our study has a variety of strengths: the largest sample size (n = 96) in a study testing the psychological mechanisms of ketamine for SUD treatment; a longer duration of follow-up (6 months) compared to previous studies; and a randomised and placebo-controlled design. Limitations of our study include the fact that some participants did not complete all three infusions, the absence of the HMS and the use of saline placebo rather than an active control, like very low dose ketamine or a benzodiazepine like midazolam. Furthermore, as a result of our recruitment methods, our study sample does not represent the treatment-seeking AUD population, but the participants may in fact be more representative of the broader UK AUD population.

CONCLUSIONS

In summary, in a sample of people with moderate-to-severe AUD who want to abstain from alcohol, we found that administration of IV ketamine (0.8 mg/kg) causes marked psychoactive effects, including out of body experiences, altered reality and distortions of perceptions. These effects remain largely similar over three weekly infusions. Crucially, we did not find evidence that these psychoactive effects mediate the therapeutic effect of ketamine on reduced alcohol consumption. Future research into the therapeutic mechanism of ketamine in SUDs should concurrently evaluate the explanatory value of simple drug effects, mystical effects, markers of neural plasticity and functional brain alterations.

AUTHOR CONTRIBUTIONS

Cassie Bloy: Data curation; formal analysis; software; validation; visualization; writing—original draft; writing—review and editing. **Ananya Sarma**: Data curation; formal analysis; visualization; writing—original draft; writing—review and editing. **Bethan Marsh**: Investigation; project administration; writing—review and editing. **Lorna Hardy**: Investigation; project administration; writing—review and editing. **Meryem Grabski**: Writing—review and editing. **Merve Mollaahmetoglu**: Writing—review and editing. **Joshua Shotton**: Writing—original draft; writing—review and editing. **Shamhethan Bhaskaran**: Validation; writing—original draft; writing—review and editing. **Anne Lingford-Hughes**: Conceptualization; funding acquisition; methodology; supervision; writing—review and editing. **H. Val Curran**: Conceptualization; funding acquisition; methodology; supervision; writing—review and editing. **Celia Morgan**: Conceptualization; funding acquisition; investigation; methodology; project administration; resources; supervision; writing—review and editing. **Will Lawn**: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; software; supervision; validation; visualization; writing—original draft; writing—review and editing.

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DECLARATION OF INTERESTS

C.M. has consulted for Awakn Life Sciences and Sanna Science and received royalties from Awakn Life Sciences for the KARE therapy. W.L. has provided sporadic consultancy to the CRO AxialBridge and received royalties from Awakn Life Sciences for the KARE therapy. A.L.H. has received honoraria paid into her institutional funds for speaking and chairing engagements from Lundbeck, Lundbeck Institute UK, Janssen-Cilag, Pfizer, Servier as well as from British Association for Psychopharmacology for teaching addiction neurobiology and pharmacotherapy for management of alcohol dependence; has received research grants or support from Indivior, Lundbeck, GSK; has unrestricted funds support from Alcarelle for a PhD; consulted by Silence, NET Device Corps, Sanofi-Aventis, and also consulted by but received no monies from Britannia Pharmaceuticals, GLG, Opiant, Lightlake, Dobrin and Nodthera. She is Chair, Addiction Healthcare Goals Programme, Office of Life Sciences, UK

Government. B.M. received royalties from Awakn Life Sciences for the KARE therapy.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATEMENT

South West-Central Bristol Research Ethics Committee (reference number 15/SW/0312).

CLINICAL TRIAL REGISTRATION

The original trial was registered at ClinicalTrials.gov (NCT02649231) and EudraCT (2015–000222-11). This analysis was not pre-registered.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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