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Mechanisms of anti-depressant and anti-alcohol effects of ketamine in patients with alcohol use disorder

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Abstract

Ketamine is known to have anti-depressant effects and is suggested to reduce substance use. However, little is known about the mechanism of these effects.

Given evidence from studies in depression of a greater therapeutic effect in those with a family history of AUD, this latter factor was also investigated as a moderating factor. We used data from the KARE trial, a randomised triple-blinded controlled clinical trial, examining the efficacy of three infusions of ketamine each followed by psychological support as a treatment in people with AUD. State anxiety, anhedonia, repetitive negative thoughts (RNT) emerged as factors from a factor analysis of all the trial questionnaires. We replicated original trial analyses to show a significant reduction in percentage days abstinent and extended to demonstrate this survived including data on alcohol use from a time point before participants had

become abstinent from alcohol. Ketamine treatment was found to significantly reduce anhedonia and RNT at 3-months follow-up though not at 6-months. Family history of AUD was found to moderate the relationship between drug group and anhedonia and RNT at 3-months, with individuals with a family history of AUD reporting a greater effect of ketamine on anhedonia and RNT. Among people with a family history of AUD, ketamine reduced craving and this reduction then mediated its effects on percentage of abstinent days. This effect was not evident among those without AUD family history. . Neither anhedonia nor RNT scores at 3-months were found to mediate the effects of ketamine on abstinence at 6-months follow-up.

Family history of AUD emerged as an important patient characteristic to consider in the clinical use of ketamine in psychiatry.

Introduction

A promising novel pharmacological treatment for alcohol use disorder (AUD) is ketamine, a non-competitive antagonist of N-methyl D-aspartate (NMDA) receptor of glutamate. Following evidence of rapid and sustained antidepressant benefits (Krystal et al., 2019), ketamine has been reported to have therapeutic effects for substance use disorders (SUD) including cocaine, opiate and cannabis use disorders (Dakwar et al., 2014; 2017; 2019; 2020; Krupitsky et al., 2002; 2007). The early work in this area was conducted by Krupitsky and colleagues (1992; 1997) where substantial benefits of ketamine assisted therapy were found in AUD, which have been replicated in recent work (e.g., Dakwar et al., 2020; Grabski et al. 2022). Whereas these results need to be interpreted carefully considering the variations in dose, modes of administration, and adjunctive therapies, extant evidence provides signals that permit some observations.

Several neurobiological and psychological mechanisms have been proposed to explain ketamine's benefits in promoting abstinence, reducing craving and substance use among people with alcohol and SUD (Ezquerra-Romano et al., 2018); these mechanisms include ketamine's rapid antidepressant benefits. Depressive symptoms can be clustered into several transdiagnostic factors; two of which may be relevant for ketamine's therapeutic benefits for AUD repetitive negative or self-critical

thinking (RNT often called 'rumination') and anhedonia. RNT can be defined as a repetitive, passive and uncontrollable thinking process focusing on negative information (Ehring & Watkins, 2008). Importantly, a recent systematic review reported a strong positive relationship between RNT and alcohol use/alcohol related problems (Devynck et al., 2019). Multiple works (Selby et al., 2008; Selby & Joiner Jr, 2013; Selby et al., 2016) noted the indirect effects of RNT on alcohol consumption via amplifying negative emotions and reinforcing coping mechanisms linked to alcohol, leading to cravings.

In a qualitative study, patients have reported improved clarity of thought following ketamine treatment due to reductions in RNT (Lascelles et al., 2019). In one study, single dose of ketamine significantly reduced depressive rumination among patients with treatment resistant depression (Vidal et al., 2020). However, there is little quantitative evidence of the effects of ketamine on RNT among individuals with alcohol or SUD.

Anhedonia is characterised by a significant decrease or loss of interest or pleasure in usually enjoyable activities (Snaith et al., 1995). Individuals with alcohol and SUDs report increased levels of anhedonia (Garfield et al., 2014; Destoop et al., 2019), and their baseline anhedonia levels predict inability to quit drug use and increased likelihood of relapse at follow-up above and beyond overall depressive symptoms (Cook & al., 2010; Garfield et al., 2014; Leventhal et al., 2014; Leventhal et al., 2009; Nguyen et al., 2020; Piper et al., 2017; Crits-Christoph et al., 2018; Destoop et al., 2019; Nguyen et al., 2020). Single and repeated doses of ketamine were demonstrated to rapidly reduce anhedonia symptoms in individuals with depression or bipolar disorders with an effect as soon as 24 hours post-dose and up to 14 days (Ballard et al., 2017; Rodrigues et al., 2020; Wilkowska et al., 2021; Delfino et al., 2021), even among those with treatment resistance (Murrough et al., 2013; Lally et al., 2014; Lally et al., 2015, Zheng et al., 2021). Findings in populations with AUD and SUD similarly pointed to ketamine induced improvements in anhedonia (Krupitsky et al., 2002; Grabski et al., 2022). Moreover, improvements in depressive symptoms as well as reductions in anhedonia in depression appeared to be moderated by family history of AUD, with stronger effects among those with a positive family history of AUD (Lally et al., 2014), indicating that predisposition to AUD may be associated with improved anti-anhedonic response to ketamine.

Another mechanism of interest is craving. Craving is an important characteristic of alcohol and SUD as well as the focus of many AUD treatments. Among individuals undergoing treatment for AUD, craving levels measured at baseline, during and following treatment were found to independently predict relapse post-treatment (Monti et al., 1990; Flannery et al., 2003; Bottlender and Soyka, 2004; Gordon et al., 2006). Several studies have reported diminished craving for heroin and cocaine following ketamine administration (Dakwar et al., 2014; 2017 2019; Krupitsky et al., 2002; 2007). However, the effects of ketamine on alcohol craving have not been previously reported.

The current study aimed to investigate the transdiagnostic psychological mechanisms by which ketamine may be exerting its therapeutic effects in AUD, including anhedonia and RNT. We used data from a recently completed clinical trial in which detoxified individuals with AUD were randomly assigned to receive either three infusions of ketamine or placebo combined with relapse prevention focused psychological therapy or alcohol education. The primary outcomes of this trial are reported elsewhere, demonstrating increased percentage days abstinent from alcohol at 6-months follow-up in the ketamine group compared to placebo, with the greatest benefits observed when ketamine was combined with psychotherapy versus placebo combined with education (Grabski et al., 2022). This trial collected data on a wide battery of psychological measurements which measured overlapping concepts (e.g., depressive mood, anhedonia, anxiety/worry, RNT), therefore we used factor analytical techniques to combine similar items across different questionnaires. Based on previous research (e.g., Lascelles et al. 2019, Dakwar et al. 2019), it was hypothesised that ketamine would result in significant reductions in transdiagnostic psychological processes (e.g. anhedonia, RNT) as well as reductions in craving for alcohol, and that these changes would mediate ketamine's effects on the primary outcome (percentage of days abstinent at 6-months follow-up). Furthermore, based on the literature on family history of AUD moderating antidepressant and anti-anhedonic response to ketamine (e.g., Lally et al. 2014), it was expected that ketamine's impact on the primary outcome would be enhanced among individuals with positive family history of AUD compared to those without.

Method

Participants

96 participants were recruited from two study sites in London and Southwest England. In total, 1052 participants were assessed for eligibility at the pre-screening stage and out of these 166 were assessed for eligibility at a screening visit, with 70 of those being excluded and 96 being randomised. The primary inclusion criteria were: 18-65 years old, meeting the DSM V criteria for AUD or the DSM IV criteria for alcohol dependence within the last year, being abstinent from alcohol at the trial entry and having a negative urine drug screen (McAndrew et al., 2017). Exclusion criteria were: currently using medication for relapse prevention or antidepressants, uncontrolled hypertension (>140mm Hg systolic or >90mm Hg diastolic), body mass index <16 or >35, history of psychosis or psychosis in a first degree family member, previous/current diagnosis of substance dependence or severe SUDs, history of one or more confirmed seizures, and liver function tests >3 times normal levels (see McAndrew et al., 2017; Grabski et al. 2022 for further details).

Table 1: Demographic and clinical characteristics of participants at baseline

	Ketamine (N=48)	Placebo (N=48)	Total
Age M (SD)	42.87(10.18)	45.27(11.79)	44.07 (10.59)
Gender N (%)			
Males	31(64.5)	30(62.5)	61(64)
Females	17(35.5)	18(37.5)	35(36)
Site N (%)			
London	25(52)	25(52)	50(52)
Exeter	23(48)	23(48)	46(48)
Inpatient detox history N (%)			
Yes	6(12.5)	6(12.5)	12(12.5)
No	42(87.5)	42(87.5)	84(87.5)

History of anxiety N (%)	24(50)	20(66.7)	44(46)
History of depression N (%)	24(50)	16(33.3)	40(42)
Substance dependence history in a first degree relative (%)	2(4.2)	2(4.2)	4(4.2)
Family history of alcohol dependence (in any 1 st degree relative) (%)	17(35.4)	23(47.9)	40(41.6)
Alcohol consumption at screening following cutting down to start study (units per week) M (SD)	34.92 (33.92)	25.98(24.04)	34.70 (34.29)
Regular alcohol use (units per week) before cutting down to become abstinent, M (SD)	124.83 (95.19)	137.77(83.09)	128.43 (70.790)
Number of ketamine infusions received			
3	38	43	81(84)
2	2	1	3(3)
1	6	4	10(10)
< 1	2	0	2(2)
Baseline DSM V criteria met M (SD)	7.58(1.96)	6.98(2.27)	7.28(2.13)
Baseline STAI M (SD)	33.42(10.53)	33.52(10.8)	33.47 (10.61)
Baseline BDI M (SD)	11.62(7.94)	11.69(8.9)	11.65 (8.39)
Baseline ACQ-NOW M (SD)	3.22(1.19)	3.28(1.25)	3.25(1.21)

Table 2: Family history of AUD distribution across the four trial treatment groups

	Placebo+ Education	Placebo+ Therapy	Ketamine+ Education	Ketamine + Therapy	Statistics
Positive Family History	11	12	6	11	$X^2(3) = 3.63$, $p = 0.304$
Negative Family History	13	11	17	13	

Note: 1 participant in each of the placebo plus education group and the ketamine plus education group had missing data.

Design

The Ketamine for the reduction of Alcoholic Relapse (KARE trial) was a randomised, triple blinded, parallel group, placebo-controlled trial examining the effectiveness of ketamine treatment for AUDs (See McAndrew et al., 2017; Grabski et al. 2022). Participants were randomly allocated to one of the four study arms: ketamine (0.8mg/kg IV over 40 minutes), or placebo (50 ml saline 0.9% IV over 40 minutes) combined with either psychological therapy or education about alcohol. For the current analysis, comparisons were limited to the ketamine versus placebo group. The primary and secondary outcome data are reported elsewhere (Grabski et al., 2022) and the current study reports on a further analysis of the data from this trial examining mechanisms of the treatment effect. The trial was registered at ClinicalTrials.gov (NCT02649231) and EudraCT (2015-000222-11) (15).

Compliance with Ethical Standards

Ethics Approval: Ethical approval was granted by the South West–Central Bristol Research Ethics Committee (reference number 15/SW/0312) and the Medicines and Healthcare Products Regulatory Agency. **Consent to participate:** The study was conducted in accordance with the Declaration of Helsinki.

All participants gave written, informed consent.

Measures & Materials

The full list of measurements & materials completed at each visit can be found in the published protocol (McAndrew et al., 2017). Those included in the exploratory factor analysis (EFA) reported here were:

- Beck Depression Inventory (BDI) (Beck et al., 1961).
- Hamilton Depression Rating Scale (HAM-D): (Hamilton, 1960).
- State Trait Anxiety Inventory (STAI): (Spielberger et al., 1983).
- Brief Psychiatric Rating Scale (BPRS): (Overall & Gorham, 1962; 1988).
- Profile of Mood States (POMS): (McNair, Droppleman & Lorr, 1971).
- Psychotomimetic States Inventory (PSI): (Mason et al., 2008), with a specific subscale for anhedonia.

Treatment outcome Measures:

Alcohol Timeline Follow-back (TLFB) is a self-report measure of alcohol use which records retrospective daily report of units of alcohol consumed over a period of time (Sobell and Sobell, 1992). Alcohol TLFB was used to measure the primary outcomes of the clinical trial, percentage of abstinent days (meaning no alcohol consumed) over the 6 months following the first drug/placebo administration and relapse (defined as no heavy drinking days) (Grabski et al., 2022). Prescreening alcohol use was derived from data at the prescreening time point prior to cutting down from alcohol.

Alcohol Craving Questionnaire -Short Form Revised (ACQ-SF-R) is a 12 item self-report questionnaire measuring current alcohol craving symptoms, adapted from the 47 item ACQ-NOW questionnaire (Singleton et al., 1997).

Procedure (see Figure 1 and Grabski, et al., 2022 for further details)

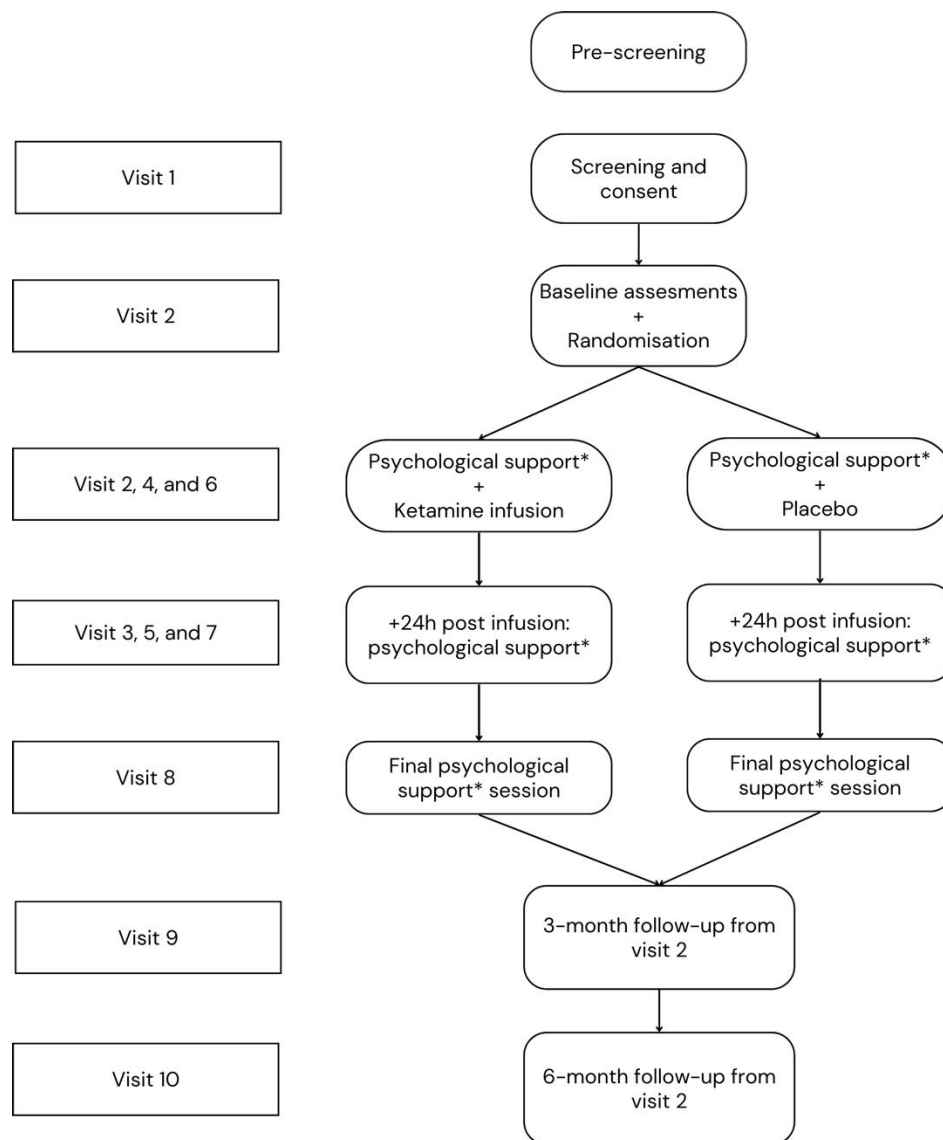


Fig1. Study visit timeline from enrolment to 6 months follow-up. Adapted from Grabski et al., 2022. “Psychological support*”: either alcohol education or psychological therapy; the two groups were collapsed for this analysis due to low power and even distribution across the groups. See also Table 2.

Baseline data were collected on demographic, psychological and physiological measures during the first treatment visit, prior to randomisation to treatment arm.

Drug administration

Participants received three IV Infusions of ketamine (0.8 mg/kg over 40 minutes) or placebo (0.9% saline over 40 minutes). The infusions were spaced by at least one

week and up to a maximum of 3 weeks. The higher ketamine dose (0.8 mg/kg vs 0.5 mg/kg most commonly) used in this study was determined based on the previously reported cross tolerance to ketamine among people with AUDs. The ketamine and placebo infusions were prepared by unblinded trial staff and administered by the anaesthetist through a cannula in the antecubital fossa. The therapists and the patients were blinded to the drug allocation. A therapist and a nurse were present throughout the infusion and regularly monitoring vital signs including blood pressure, heart rate and blood oxygen levels.

Participants remained at the clinical research facility for 2 hours for observation following the end of their infusion. They were also given psychological therapy or education about alcohol, but these groups were collapsed for this study (See McAndrew et al., 2017 for further details).

Statistical Analysis

Data analyses was conducted using SPSS IBM Version 28 and R Studio. The figures were produced on R Studio using afex package (Singmann et al., 2020) and the ggplot2 package (Wickham, 2016). All statistical tests were two-tailed. The statistical analysis plan for the main outcomes was pre-planned and registered (ClinicalTrials.gov Identifier: NCT02649231), however the analyses reported here were exploratory.

Exploratory Factor Analysis: For further details see the supplementary materials

We calculated factor scores based on 61 equally weighted items, items were included in a factor if the loading was statistically significant and over 0.40. We calculated the factor scores for the baseline, end of treatment, 3 months and 6 months follow-up timepoints by using the relevant item measurements taken at these timepoints. These factor scores then contributed to the ANOVA and mediation analyses.

ANOVAs

Assumptions of repeated measures and between subjects ANOVA were checked prior to analyses. Shapiro Wilks test was used to check normal distribution of DVs, when this assumption was not met, positively skewed data was transformed using logarithmic transformation. However, as the transformation did not result in a normal distribution of the data, the untransformed data were analysed. Missing values in the DVs were replaced with series mean. In case of sphericity violations, Huynh-Feldt corrections were reported. We used Bonferroni corrections for multiple comparisons. For each factor yielded by EFA, a mixed ANOVA with Drug Condition as between subjects IV (ketamine or placebo), Time as within subjects IV (baseline, end of treatment, 3 months follow-up, 6 months-follow-up) and the given factor as DV was conducted. Additionally, we repeated the mixed ANOVA with craving (measured using the total ACQ score) as the outcome. The DVs were checked for outliers by drug condition revealing no outliers for anhedonia, and six each for craving and RNT defined as more than three standard deviations from the mean.

Moderated Mediation Analyses

We conducted moderated mediation analyses to examine the hypothesis that changes in psychological mechanisms would mediate the effect of ketamine treatment on drinking outcomes. Analyses were performed using PROCESS version 3.5 on SPSS (Hayes, 2012) using Model 8, bootstrapping set to 5000 samples and with confidence intervals of 95%. Based on the results of EFA and ANOVAs, we conducted a moderated mediation analysis for each factor where there was a significant difference between the drug conditions at any of the follow-up timepoints (end of treatment, 3 months or 6 months follow-up). In these analyses, the predictor variable (X) was the Drug Condition (Ketamine vs Placebo) and the outcome (Y) variable was the percentage of abstinence at 6 months follow-up. The moderator (W) was the family history of alcohol dependence (Positive vs Negative). The mediators were respectively the RNT (Factor 2), Anhedonia (Factor 3), and Craving (measured using the ACQ-SF-R) at the 3 months follow-up in three separate moderated mediation analyses.

Results

Participants

The two treatment arms (ketamine vs placebo) were matched according to demographic and clinical characteristics (See Table 1). The majority of participants were male (N=61) and the mean age across the sample was 44.07. 10 participants had a history of at least one inpatient alcohol detox. At baseline, participants met on average 7.28 criteria on the DSM V for AUD, this was similar across the two treatment arms. 40 (41.6%) participants had a family history of alcohol dependence in a first degree relative (parent, child or sibling), this was distributed roughly evenly across the two treatment groups. Participants with a positive family history of alcohol dependence did not report more severe AUD symptoms as measured by number of DSM V criteria met at baseline [$F(1,92)=1.34$, $p=0.249$]. Respectively 46% and 42% of participants had a history of anxiety or depressive disorders. Current depressive symptoms were low, with mean BDI scores indicating minimal levels of depression.

Alcohol Use

To explore the change in alcohol use from the pre-screening time point (prior to cutting down alcohol use to enter the trial) linear mixed-effects model was fitted on the percentage of days abstinent, collapsed across intervention type (education/therapy), with drug group (ketamine, placebo) and timepoint (pre-screen, 3 months, 6 months) as fixed effects and a random intercept for participant. Type III tests of fixed effects with Satterthwaite's approximation for degrees of freedom were then used to evaluate the significance of the main effects and interaction. There was a significant main effect of drug group, $F(1, 95) = 6.42$, $p = .013$, a significant main effect of timepoint, $F(2, 190) = 1239.18$, $p < .001$, and a significant drug group $\times$ timepoint interaction, $F(2, 190) = 4.71$, $p = .010$ (Figure 1a). Illustrative data are presented for information by the original treatment allocation (Figure 1b)

An additional sensitivity analysis was conducted excluding participants with fewer than 159 days of available alcohol consumption data across the 6-month period.

There was a significant main effect of drug group, $F(1, 82) = 4.88$, $p = .030$, a significant main effect of timepoint, $F(2, 164) = 1014.37$, $p < .001$, and a significant drug group $\times$ timepoint interaction, $F(2, 164) = 4.26$, $p = .016$. These findings are consistent with the primary analysis including all participants.

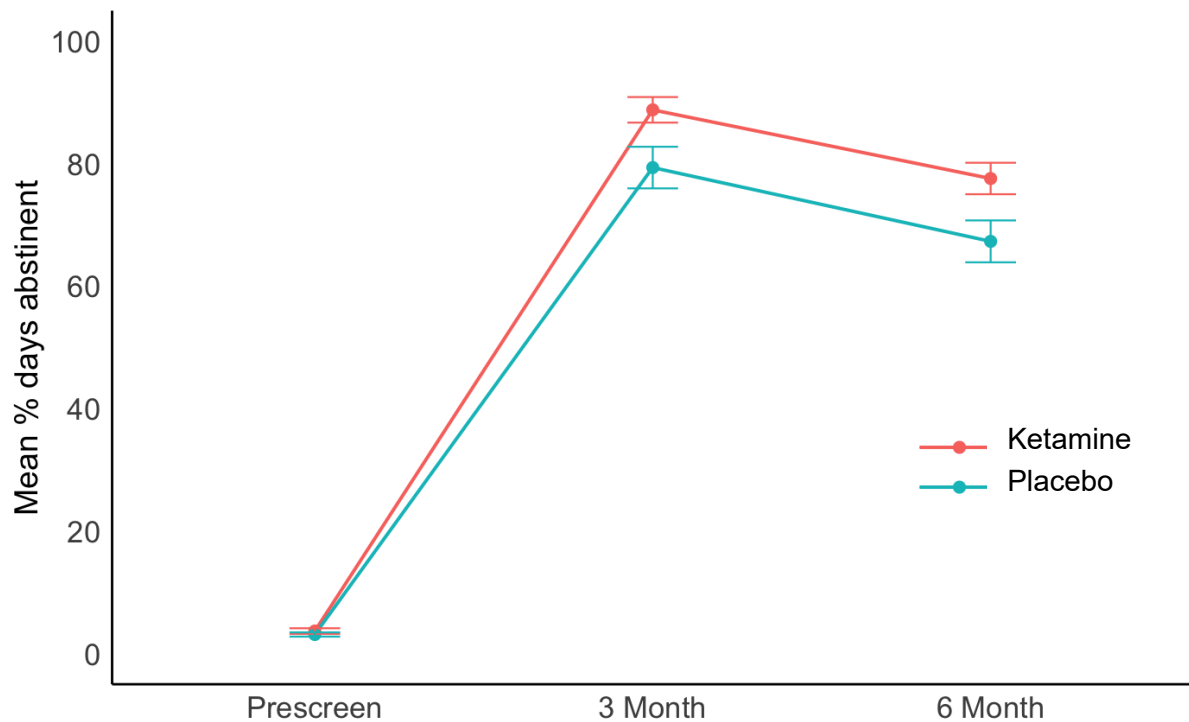


Figure 2a: Mean percent days abstinent for the ketamine and placebo group collapsed across intervention type (education/therapy). Error bars represent SEM

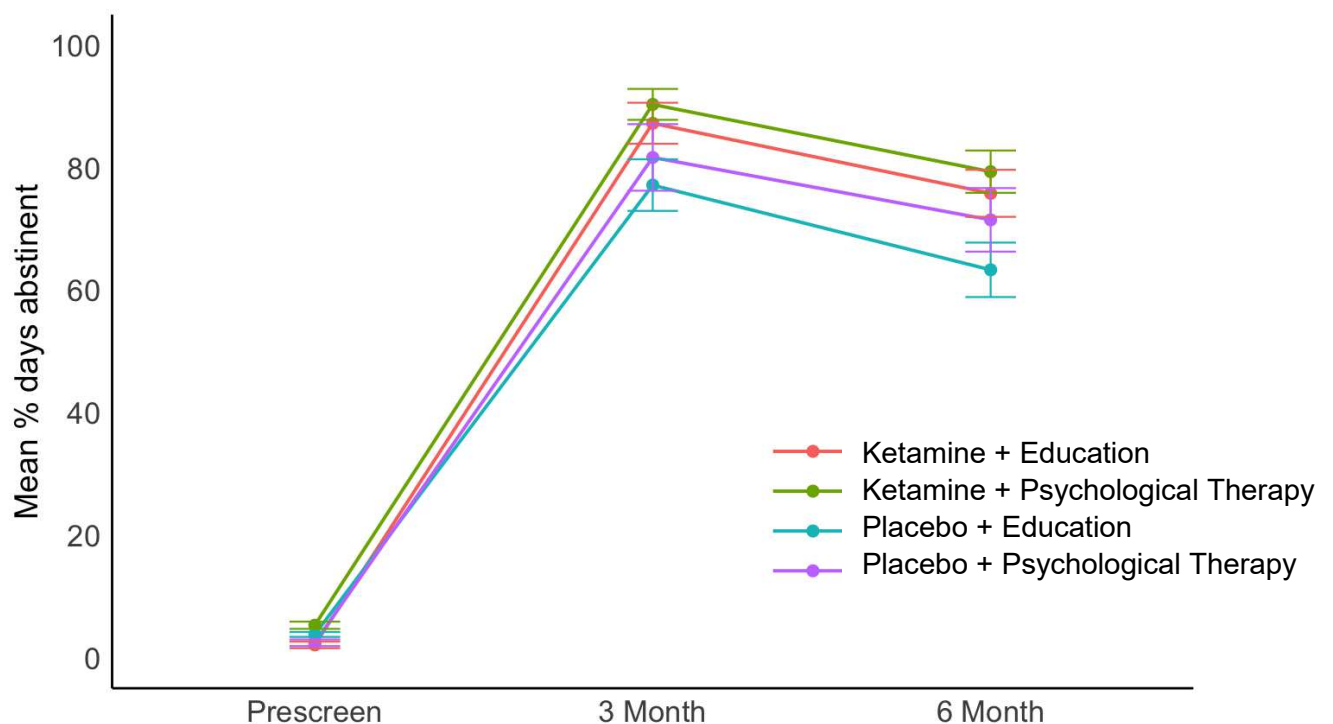


Figure 2b: Mean percent days abstinent for each group at each timepoint. Error bars represent SEM

Ketamine + Education
 Ketamine + Psychological Therapy
 Placebo + Education
 Placebo + Psychological Therapy

Main Analysis: Factor Labels

For details of the Exploratory Factor Analysis see supplementary materials. Following factor analysis three factors emerged from 61 initial questionnaire items. Factor 1 was interpreted as state anxiety given the items loading onto it (See Table 2 Supplementary materials) and the moderate-to-strong correlations between Factor 1 and items on the STAI and POMS relating to anxiety symptoms as seen in table 2 in the supplementary materials (e.g., POMS unease, restless, STAI worrying about possible misfortune, nervous). We interpreted Factor 2 as a form of repetitive negative thinking (RNT) as it was characterised by self-critical, guilty, past focused and anxious thinking as per the items highly loading onto this factor and items strongly correlated with this factor (See Table 2 in the Supplementary Materials). Factor 3 was labelled

as anhedonia as it was characterised by activities being less enjoyable/less pleasurable, loss of interest, loss of energy, feelings of indifference and difficulty in starting activities. Higher scores on Factor 1, 2, and 3 indicated respectively higher state anxiety, higher RNT and higher anhedonia. Histograms indicated that the factor scores were not normally distributed and had positive skews.

ANOVAs

We conducted a 4 (Time: T1, T2, T3, T4) x 2 (Condition: Ketamine, Placebo) Repeated measures ANOVA for each factor: anxiety, RNT, anhedonia and craving.

State Anxiety (Factor 1)

There was not a significant two-way interaction of Time*Drug Condition [$F(2.87, 269.87)=0.07$, $p=0.975$, $\eta_p^2<0.01$, $1-\beta=0.06$]. The main effects of Time [$F(2.87, 269.87)=10.68$, $p<0.001$, $\eta_p^2=0.1$, $1-\beta=0.99$] were statistically significant. However, there was no significant main effect of Drug Condition [$F(1, 94)=1.27$, $p=0.264$, $\eta_p^2=0.01$, $1-\beta=0.2$]

Repetitive Negative Thinking (Factor 2)

The two-way interaction between Time and Drug Condition was not statistically significant [$F(2.3, 202.41)=2.31$, $p=0.094$, $\eta_p^2=0.03$, $1-\beta=0.5$]. As the current trial was not powered to detect changes in mechanisms or interactions, we conducted simple effects analysis to compare the drug conditions at each level of time as we had a priori predictions about the effect of drug condition at the end of treatment. Bonferroni corrected simple effects ($0.05/4=0.0125$) analysis indicated a significant difference between the ketamine and placebo conditions at the 3 months follow-up timepoint [$F(1, 88)=7.51$, $p=0.007$, $\eta_p^2=0.08$, $1-\beta=0.77$], with the ketamine condition reporting lower RNT scores compared to placebo. There was no significant difference between the two conditions at other timepoints.

The main effect of Time [$F(2.3, 202.41)=42.78$, $p<0.001$, $\eta_p^2=0.33$, $1-\beta=1.0$] was significant, whereas the main effect of Drug Condition [$F(1, 88)=1.23$, $p=0.270$, $\eta_p^2=0.01$, $1-\beta=0.2$] was not significant.

Anhedonia (Factor 3)

Drug Condition had a significant main effect on anhedonia factor score [$F(1,94)=5.66$ $p=0.019$, $\eta_p^2=0.06$, $1-\beta=0.65$], with the ketamine condition reporting lower anhedonia scores than the placebo condition.

The two-way interaction between Time and Drug Condition was not significant [$F(2.75,269.68)=1.39$, $p=0.248$, $\eta_p^2=0.02$, $1-\beta=0.36$]. However, as we had a priori predictions about the effect of drug condition following the end of treatment, we conducted simple effect analysis to compare the drug conditions at each timepoint. The Bonferroni corrected simple effects ($0.05/4=0.0125$) analysis suggested that there was a significant difference between the two drug conditions on anhedonia at the 3 months follow-up time point [$F(1,94)=11.44$, $p=0.001$, $\eta_p^2=0.12$ $1-\beta=0.92$], with the ketamine condition reporting lower levels of anhedonia compared to the placebo condition. There were no other significant differences between the drug conditions at any other timepoint. There was a significant main effect of Time on Anhedonia Factor score [$F(2.87,269.68)=19.91$, $p<0.001$, $\eta_p^2=0.18$, $1-\beta=1.0$].

Craving

There was a significant main effect of Time on craving [$F(2.28,202.56)=67.41$, $p<0.001$, $\eta_p^2=0.43$, $1-\beta=1.0$]. Pairwise comparisons indicate that craving decreased significantly in both groups from baseline to end of treatment ($p<0.001$), no significant difference between end of treatment and 3 months follow-up ($p>0.999$), as well as no significant change from 3 months to 6 months follow-up ($p=0.924$).

The main effect of Drug Condition [$F(1,89)=5.17$, $p=0.025$, $\eta_p^2=0.06$, $1-\beta=0.61$] was significant, with placebo group reporting significantly higher craving than the ketamine group.

We found no evidence of a significant interaction between Time*Drug Condition [$F(2.28,202.56)=1.27$, $p=0.285$, $\eta_p^2=0.01$, $1-\beta=0.29$] on craving. Bonferroni corrected simple effects ($p=0.0125$) analysis suggested that there was a significant difference between the drug conditions at 3 months [$F(1,89)=6.93$, $p=0.010$, $\eta_p^2=0.07$, $1-\beta=0.74$] and 6 months [$F(1,89)=7.74$, $p=0.007$, $\eta_p^2=0.08$, $1-\beta=0.79$] follow-up.

Moderated Mediations

Repetitive Negative Thinking (Factor 2)

In the moderated mediation analysis, Drug Condition (X) was a significant predictor of RNT at 3 months (M) [$b=-2.27$, $t(90)=-3.43$, $p=0.009$]. Moreover, the moderator family history of AUD(W) [$b=-0.68$, $t(90)=-2.46$, $p=0.016$], as well as the interaction of Drug Condition and moderator [$b=1.22$, $t(90)=3.04$, $p=0.003$] were significant predictors of RNT (M). Among participants with a family history of AUD, ketamine was significantly associated with reductions in RNT at three months, [$b=-1.05$, $t(90)=-3.45$, $p=0.008$, 95% CI: -1.66 to -0.45]. However, for those with no family history of AUD there was no significant effect of Drug Condition on RNT at three months [$b=-0.17$, $t(90)=0.64$, $p=0.525$, 95% CI: -0.35 to 0.68] (See Figure 3a). Additionally, RNT(M) at three months was not a significant predictor of percentage of abstinence (Y) at six months [$b=-0.82$, $t(89)=-0.32$, $p=0.747$]. The interaction of family history of AUD (W) and Drug Condition (X) did not emerge as a significant predictor of the outcome either [$b=-1.08$, $t(89)=-0.11$, $p=0.916$]. We did not find significant conditional direct effects of Drug Condition (X) on outcome for people with [$b=10.1$, $t(89)=1.29$, $p=0.200$] and without family history of AUD [$b=11.18$, $t(89)=1.77$, $p=0.08$] (See Figure 3b). The index of moderation mediation [$b=-1.002$, 95% CI: -7.95 to 5.5] indicated that there was no evidence of a moderated mediation through family history of AUD since the 95% confidence interval included the null value of 0.

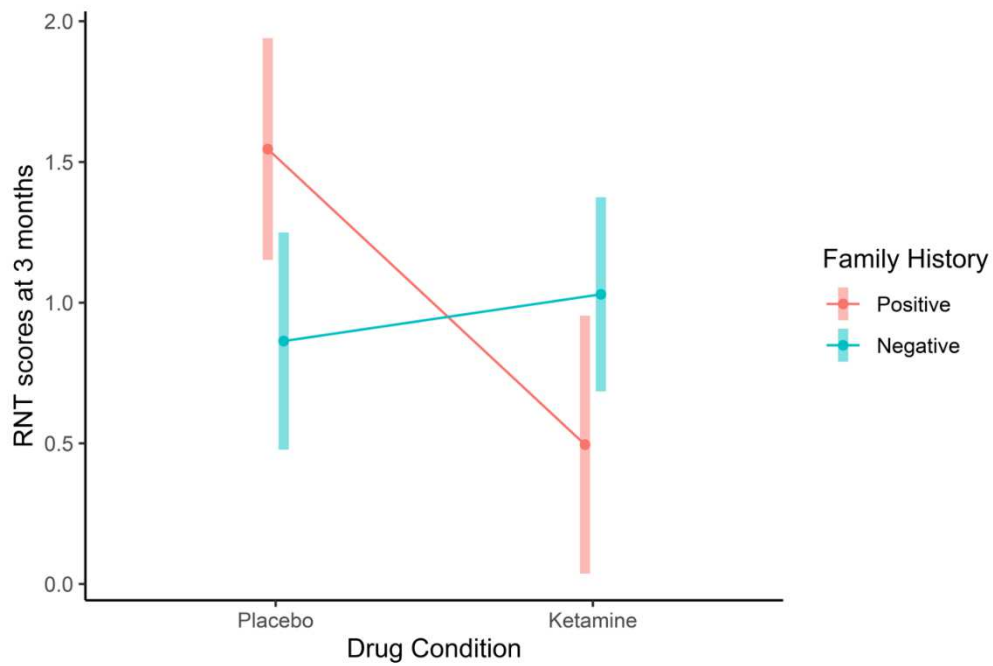


Fig3a. The simple slopes for the interaction of Drug condition and Family History of AUD on RNT scores at three months follow-up.

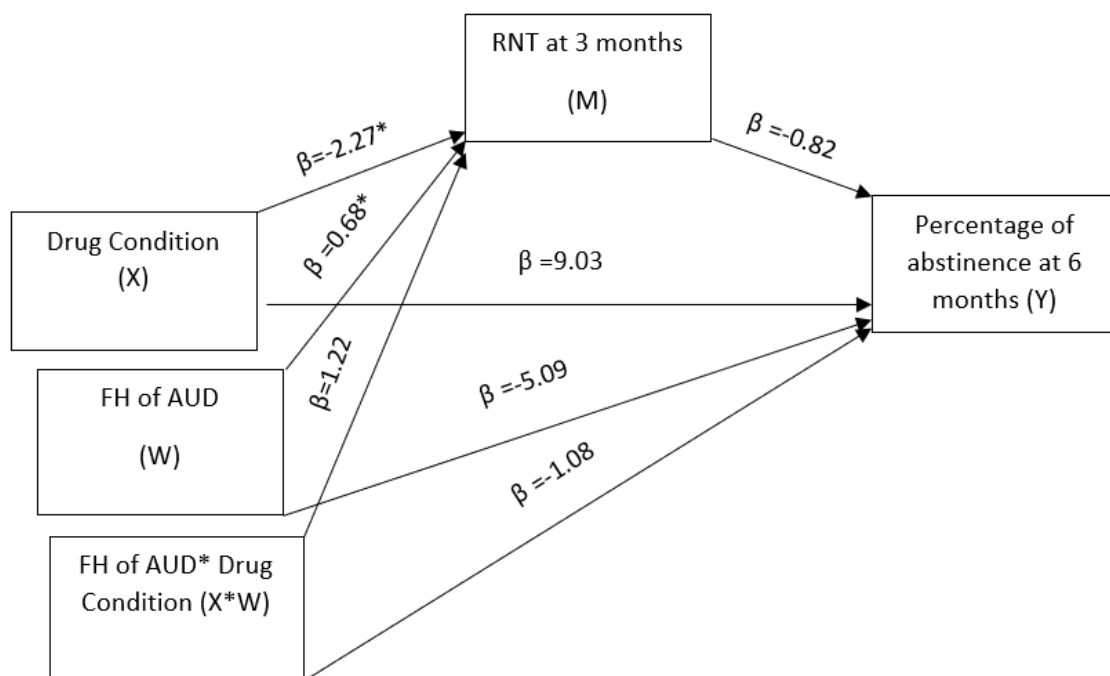


Fig3b. Moderated Mediation model demonstrating that the effect of Drug Condition (X) on RNT (M) is moderated by Family History of AUD (W). The indirect effect of Drug

Condition (X) on the percentage of abstinence at 6 months (Y) through RNT is not moderated by Family History of AUD (W).

Anhedonia (Factor 3)

Moderated mediation analysis indicated that Drug Condition (X) was a significant predictor of Anhedonia at 3 months (M) [$b=-3.76$, $t(90)=-4.25$, $p<0.001$]. The moderator (W) history of AUD in 1st degree relative was also a significant predictor of Anhedonia at 3 months (M) [$b=-1.06$, $t(90)=-2.87$, $p=0.005$]. Additionally, the interaction of Drug Condition and moderator was a significant predictor of the mediator [$b=1.82$, $t(90)=3.4$, $p=0.001$]. For individuals with a history of AUD in a 1st degree relative, ketamine was associated with significant reduction in anhedonia levels at three months follow-up compared to placebo [$b=-1.94$, $t(90)=-4.77$, $p<0.001$, 95 % CI: -2.75 to -1.13]. However, among people without a history of AUD in a 1st degree relative, ketamine did not significantly reduce anhedonia levels at three months compared to placebo [$b=-0.12$, $t(90)=-0.34$, $p=0.735$, 95% CI: -0.81 to 0.57] (See Figure 4a).

Moreover, the mediator Anhedonia at 3 months was not a significant predictor of the outcome percentage of abstinence at 6 months (Y), [$b=-2.28$, $t(89)=-1.21$, $p=0.231$]. Family history of AUD (W) [$b=-6.95$, $t(89)=0.1$, $p=0.321$] did not significantly predict the outcome, nor did it moderate the effect of Drug condition (X) [$b=4.23$, $t(89)=0.41$, $p=0.680$]. The conditional direct effects of Drug Condition (X) on the outcome were not significant for people with [$b=6.54$, $t(89)=0.80$, $p=0.406$] and without family history of AUD in a first degree relative [$b=10.77$, $t(89)=1.72$, $p=0.09$] (See Figure 4b). Moreover, there was no evidence of a moderated mediation [$b=-4.16$, 95% CI: -12.02 to 2.02] as the confidence interval for the index of moderated mediation included the null value of 0.

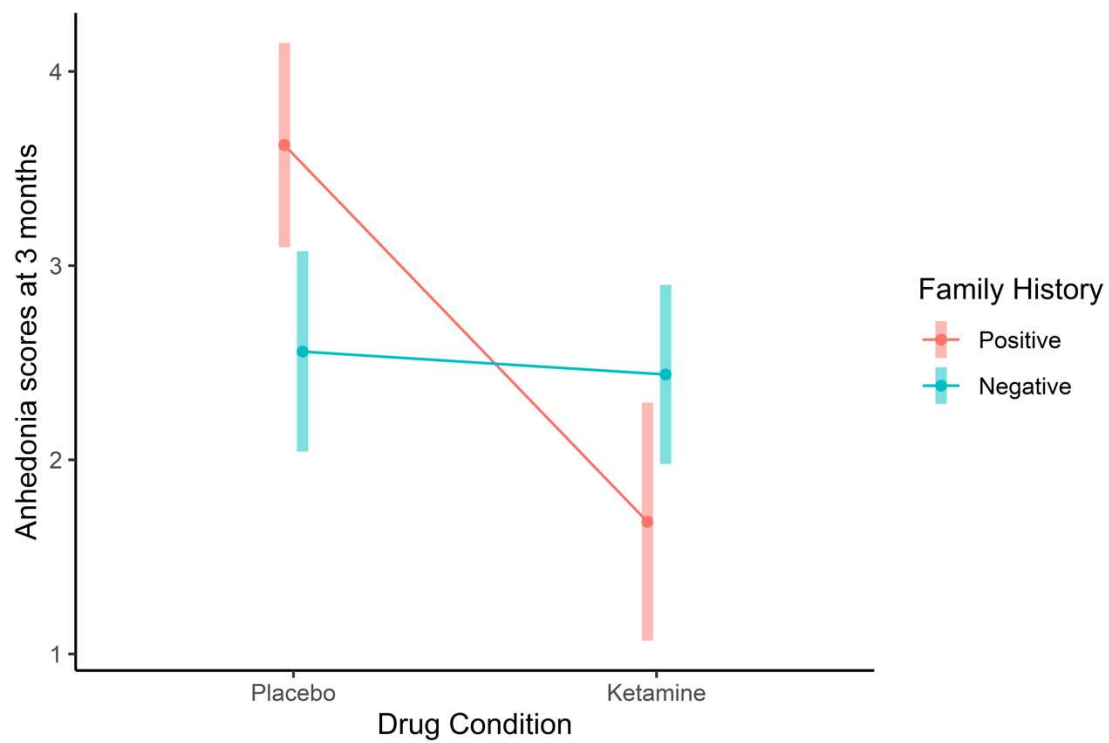


Figure 4a. The interaction of Drug Condition and Family History of AUD on Anhedonia scores at three months follow-up.

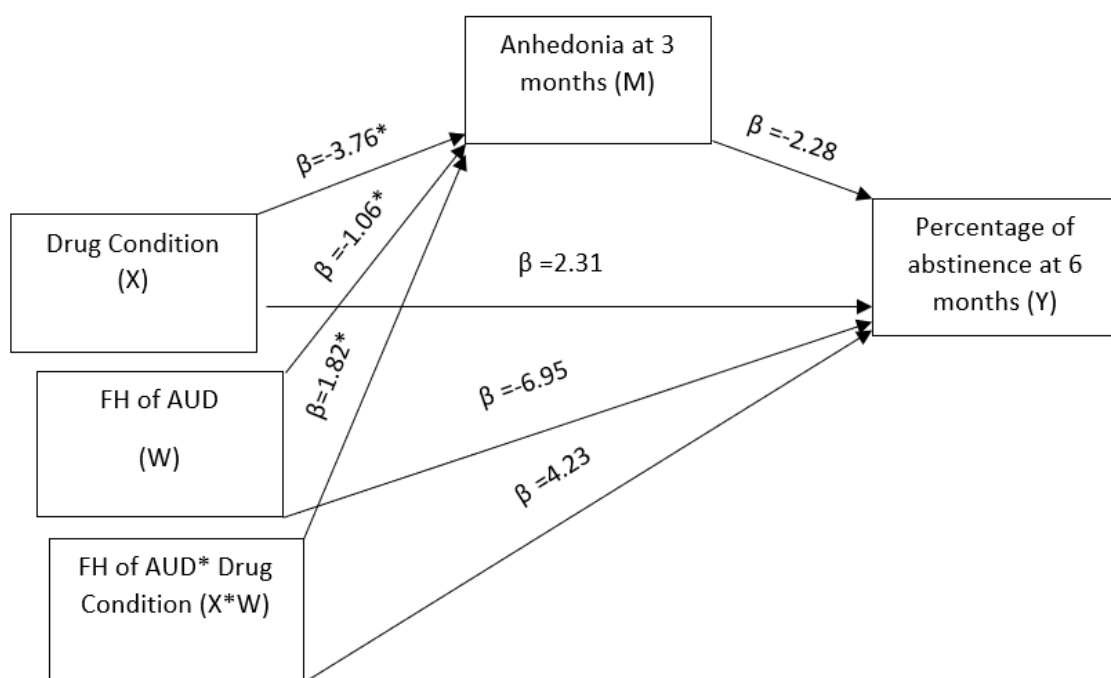


Figure 4b. *Moderated Mediation model demonstrating that the effect of Drug Condition (X) on Anhedonia (M) is moderated by Family History of AUD (W).* However, the indirect effect of Drug Condition (X) on the percentage of abstinence at 6 months (Y) through Anhedonia is not moderated by Family History of AUD (W).

Craving

In the moderated mediation analysis Drug Condition (X) significantly predicted craving at three months (M) [$b=-1.89$, $t(90)=-2.86$, $p=0.005$]. The moderator (W) history of AUD in 1st degree relative was also a significant predictor of craving at three months (M) [$b=-0.67$, $t(90)=-2.41$, $p=0.018$]. Moreover, the interaction of Drug Condition and moderator also significantly predicted the mediator [$b=1.05$, $t(90)=2.61$, $p=0.011$]. Among participants with a positive family history of AUD, ketamine was associated with significant reduction in craving levels at three months compared to placebo [$b=-0.85$, $t(90)=-2.78$, $p=0.007$, 95 % CI: -1.45 to -0.24]. However, among people without a family history of AUD, there was no significant difference in craving levels at three months between ketamine and placebo conditions [$b=0.2$, $t(90)=0.77$, $p=0.445$, 95% CI: -0.32 to 0.72] (See Figure 5a).

Moreover, the mediator significantly predicted the outcome percentage of abstinence at six months (Y), [$b=-10.27$, $t(89)=-4.47$, $p<0.001$]. However, the direct effect of Drug Condition (X) [$b=-8.56$, $t(89)=-0.57$, $p=0.572$] and the interaction of family history of AUD (W) and Drug Condition (X) were not significant predictors of the outcome [$b=10.83$, $t(89)=1.19$, $p=0.236$]. The conditional indirect effects of Drug Condition (X) on the outcome were significant for people with family history of AUD [$b=8.7$, 95% CI: 2.43 to 16.71] but not those without [$b=-2.05$, 95% CI: -7.4 to 2.72] (See Figure 5b). There was evidence for a moderated mediation [$b=-10.76$, 95% CI: -20.57 to -2.73] as the confidence interval for the index of moderated mediation (effect one -effect two) did not include the null value of 0 (See Figure 5c).

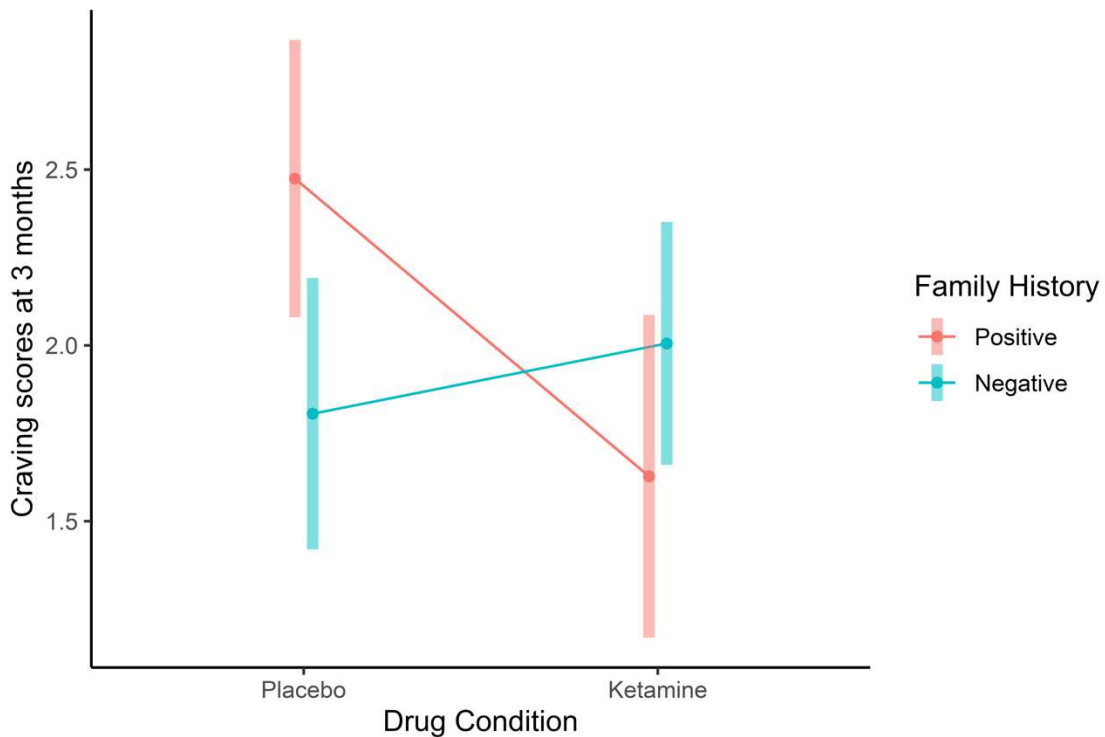


Figure 5a. The simple slopes for the interaction of Drug Condition and Family History of AUD on the Craving scores at Visit 9.

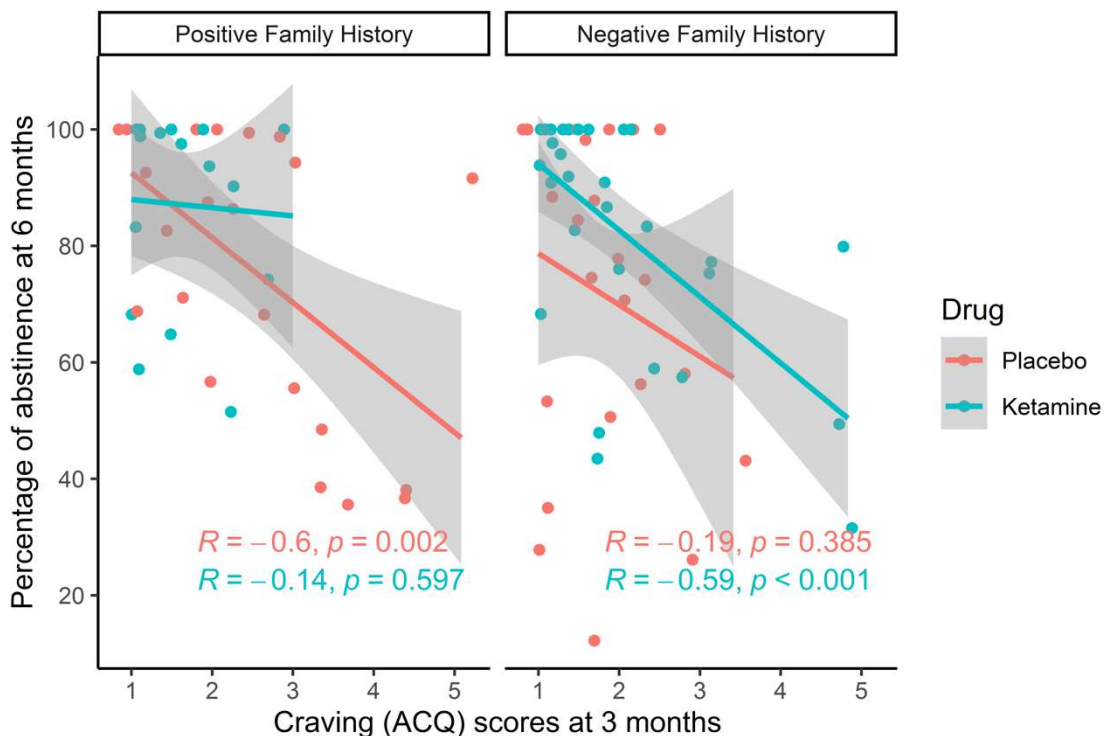


Figure 5b. Scatterplot of the relationship between craving scores at Visit 9 and the outcome percentage of abstinence at 6 months with regression line, as a function of Drug Condition and Family History of AUD. The indirect effect of Drug Condition on Percentage of Abstinence via Craving is moderated by family history of AUD.

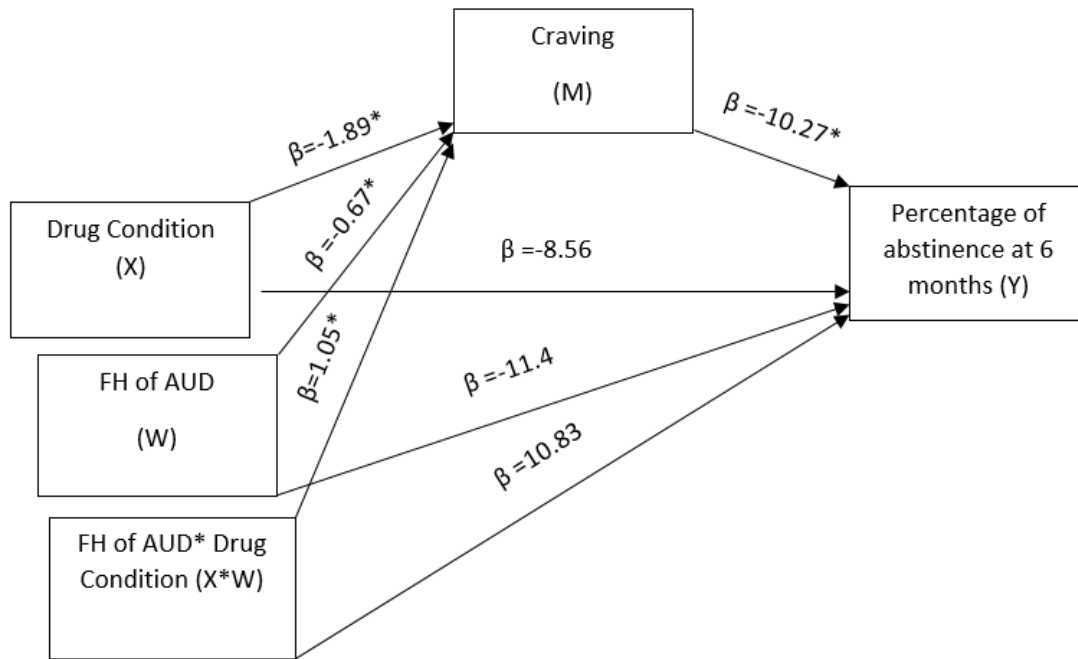


Fig 5c. Moderated Mediation model demonstrating that the effect of Drug Condition (X) on Craving (M) is moderated by Family History of AUD (W). Moreover, the indirect effect of Drug Condition (X) on the percentage of abstinence at 6 months (Y) through Craving is significantly moderated by Family History of AUD (W).

Discussion

This study explored the potential mechanisms mediating the therapeutic effects of ketamine for AUD. An additional analysis confirmed the significant differences in reduction in percentage days of abstinent reported in Grabski et al. (2022) but extended to include data prior to cutting down alcohol use to enter the trial. Exploratory factor analysis revealed three latent factors from 61 items across questionnaires measured at baseline: state anxiety, anhedonia, and RNT. We found that three ketamine infusions resulted in significant reductions in anhedonia and RNT symptoms at three months follow-up compared to placebo, though the reduction was no longer observed at six months follow-up. These effects appeared to be moderated by history of AUD in a first degree relative. However, ketamine was not associated

with reductions in anxiety symptoms at any time point. Moreover, in contrast with predictions, levels of anhedonia and RNT at 3-months' follow-up did not mediate ketamine's effects on increasing abstinence from alcohol at 6-months follow-up. Additionally, ketamine was found to reduce craving compared to placebo at 3- and 6-months follow-up. There was also evidence for a moderated mediation, whereby the effect of drug condition on percentage of days of abstinence via craving differed according to family history of AUD: among people with a family history of AUD, ketamine reduced craving and this reduction then mediated its effects on percentage of abstinent days. This effect was not evident among those without AUD family history.

We found that RNT was reduced in the ketamine group at 3 months follow-up only, which is in line with previous research (Ballard et al., 2018; Hasler et al., 2020; Vidal et al., 2020). Though RNT did not predict alcohol use in this study, previous research has demonstrated that higher levels of RNT predicts increased alcohol use, craving for alcohol, and odds of AUD (Caselli et al., 2008; Caselli et al., 2010; Smith & Book, 2010; Boschloo et al., 2013; Caselli et al., 2013; Devynck et al., 2016; Grynberg et al., 2016). This presents an interesting treatment path for AUD though craving and RNT were not significantly associated at 3- or 6-month follow-up in this study.

Fewer anhedonia symptoms were observed in the ketamine group in people with AUD compared to placebo at 3 months follow-up only, which has been similarly demonstrated in people with depression (Lally et al., 2014; 2015; Ballard et al., 2017; Ballard et al., 2018; Rodrigues et al., 2020; Hasler et al., 2020; Wilkowska et al., 2021; Delfino et al., 2021). Anhedonia is associated with higher risk of relapse in AUD and substance user groups due to its association with increased craving and withdrawal symptoms (Martinotti et al., 2008a; 2008b Janiri et al., 2005; Huhn et al., 2016; Cook et al., 2004; Leventhal et al., 2009), as such sustained anti-anhedonic effects of ketamine demonstrate clinical value for treating AUD. Benefits were observed at 3-month but not 6-month follow-up meaning the therapeutic effects may be short term.

In contrast to previous research which has demonstrated ketamine as an effective treatment for anxiety disorders, ketamine was not found to significantly reduce anxiety symptoms (Glue et al., 2017; 2018; 2020; Taylor et al., 2018; Bloch et al., 2012; Rodriguez et al., 2013). This could be because participants in this study had

no formal diagnosis of an anxiety disorder. Furthermore, as SSRIs are frequently prescribed for anxiety disorders and individuals using SSRIs were excluded from this study. It is likely that individuals with more severe anxiety symptoms were excluded, leading to a floor effect for anxiety. Finally, most previous studies reported short follow-up periods and since the effects of ketamine on anxiety appear to be transient with typical patient relapse observed within 2 weeks of finishing treatment (Glue et al., 2017; 2018) the longer follow-up periods of 3- and 6-months may explain why this effect was not observed.

Our findings that ketamine's effects on reducing anhedonia and RNT were moderated by family history of alcohol abuse are consistent with previous reports of greater antidepressant response among those with a family history of AUD (Luckenbaugh et al., 2012; Phelps et al., 2009). Whilst enhanced anti-anhedonic effects of ketamine among those with positive family history have been demonstrated (Lally et al., 2014; 2015), this is the first study to our knowledge to replicate this effect for RNT. Moreover, previous studies have reported moderating effects of family history of AUD on response to ketamine over shorter follow-up periods (ranging from 230 minutes to 28 days) and we extend these findings by demonstrating this effect over a three months' follow-up period.

Ketamine-induced reductions in craving for alcohol are also in line with previous reports of reduced craving for cocaine and heroin (Dakwar et al., 2014; 2017; Krupitsky et al., 2002; 2007). Additionally, we found a moderated mediation, whereby ketamine's indirect effects on abstinence via craving at 3-months were present for people with family history of AUD but not for those without. Contrary to predictions, RNT levels were not found to mediate the therapeutic effects of ketamine, which is in line with previous research in depression (Aust et al., 2019; Vidal et al., 2020). RNT has been found to worsen existing negative mood including depression, sadness, anxiety and anger only when individuals are already in a negative mood (Watkins & Roberts, 2020) which may mean that in the absence of depressive mood, the link between RNT and alcohol consumption may be diminished. As previously mentioned, people using SSRIs were excluded from this study which is likely to mean groups with more severe depressive symptoms - who are more likely to express this effect of RNT - would have been excluded, possibly explaining why this mediation was not found.

Anhedonia levels were also not found to mediate ketamine's therapeutic effects on alcohol abstinence. Previous research has shown mixed evidence regarding the link between levels of anhedonia and increased risk of relapse to substance use, with this discrepancy possibly due to timing of the anhedonia measurement; the evidence suggests that anhedonia levels during current substance use episode may be more closely linked to risk of relapse than anhedonia following detoxification (Garfield et al., 2014). This is not surprising given anhedonia significantly decreases in as soon as 30 days after detoxification for AUD (Martinotti et al., 2008b). Discrepancies in findings may also be explained by differences in defining relapse including any consumption (Nguyen et al., 2020; Powell et al., 2004; Snuggs & Hajek, 2013), continued use over a week (Cook et al., 2010), or meeting DSM criteria for dependence (Marra et al., 1998). In this study percentage of alcohol abstinent days at 6-months follow-up was used. Therefore, it is recommended that future research investigates the link between anhedonia and multiple measurements of relapse over long term follow-up and considers early improvements in anhedonia following ketamine treatment and how these might relate to drinking outcomes.

Limitations

The current design has several limitations. Firstly, as this was a proof-of-concept study, and this exploratory analysis capitalised on an existing dataset, it was only powered to detect the effect of ketamine on the primary outcomes (relapse rates and percentage of abstinence at 6 months); therefore, findings would benefit from replication in adequately powered studies (McAndrew et al., 2017). Indeed, observed power for these analyses was lower than the accepted minimum standard of 80% for several comparisons. This may explain the lack of significant mediation by the transdiagnostic processes explored here meaning that these results require replication in a study powered to detect these effects. Another limitation relates to the strict exclusion criteria of the clinical trial, whereby individuals with poor liver function were excluded due to the risks of ketamine to liver function. However, poor liver function is common among people with AUD, with increased alcohol consumption being strongly associated with alcohol related liver diseases such as liver cirrhosis (Roerecke et al., 2019). Additionally, individuals currently on antidepressant medications were excluded; however, individuals with AUD frequently experience comorbid depressive

disorders (Grant et al., 2004; Boschloo et al., 2011). Therefore, only including individuals with reasonable liver function who are not on antidepressants may have resulted in a sample with more mild AUD, limiting the generalisability of the results to affected AUD population in the community.

Furthermore, there were no validated questionnaires measuring RNT, instead relevant items from questionnaires of depressive mood and anxiety/worry were included in the exploratory factor analysis. There were limitations in the measurement of RNT used in the current study, with some core items of rumination not being captured here such as repetitiveness, passiveness, abstractness, and intrusiveness of these thoughts (Hummel et al., 2021; Rimes & Watkins, 2005; Segerstrom et al., 2004; Treynor et al., 2003; Wahl et al., 2019; Watkins, 2008; Watkins & Roberts, 2020). This factor was named RNT based on negative content, focus on the past, self-dislike, and self-criticism which overlap with RNT (Nolen-Hoeksema, 1987; 1991; Nolen-Hoeksema & Morrow, 1993; Ehrling & Watkins, 2008; Watkins, 2008). However, the items with the highest loadings were guilt and self-criticism. Guilt has been shown to be negatively associated with alcohol and substance use problems (Dearing et al., 2005; Treeby & Bruno, 2012) and hence may have confounded this analysis. This was similar for anhedonia, although there was one subscale of the PSI which was designed to measure anhedonia in schizophrenia/psychosis (Mason et al., 2008). In future clinical trials, use of validated measures such as Ruminative Response Scale Short Form (Treynor et al., 2003), and the Snaith-Hamilton Pleasure Scale (Snaith et al., 1995) for anhedonia are recommended to improve measurement of potential mechanisms of ketamine treatment. Moreover, the anhedonia factor in this study primarily relied on items focusing on consummatory anhedonia, inability to experience pleasure during activities, rather than anticipatory anhedonia, inability to anticipate pleasure from future activities. It would be interesting to assess in future studies whether ketamine has differential effects on distinct subtypes of anhedonia using measures such as the Temporal Experience of Pleasure Scale (TEPS) (Gard et al., 2006). Finally, family history of AUD was determined through self-report of family members receiving treatment for alcohol problems without validation through objective measurements such as diagnostic interviews or health records. However, confirming family history status through diagnostic interviews with family members would likely not be possible in a clinical trial due to practical constraints. Moreover, we did not

distinguish between individuals who had one or more first degree relatives with a history of AUD, it is possible that with accumulating numbers of relatives with AUD, vulnerability to AUD is increased. Since there were only 12 participants with more than one first degree relative with AUD history, it was not possible to assess the effect of cumulative risk.

Conclusions

We aimed to investigate transdiagnostic psychological processes which may underlie ketamine's therapeutic effects on increasing abstinence from alcohol using secondary data from the KARE trial, a randomised placebo-controlled pilot study. Using exploratory factor analysis, we identified three latent factors underlying items from numerous psychological measurements: state anxiety, RNT, and anhedonia. As predicted, ketamine was demonstrated to reduce anhedonia and RNT at three months' follow-up compared to placebo, though not at 6 months follow-up. We did not find differences in state anxiety between the ketamine and placebo conditions at any timepoint. Interestingly, ketamine's effects on RNT and anhedonia were moderated by family history of AUD: ketamine's therapeutic effects on RNT and anhedonia were found to be more pronounced among participants with a positive family history of AUD, consistent with previous research. This indicates that family history of AUD may be an important predictor of response to consider in future research on the use of ketamine in treatment settings.

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