EXAMINING RUMINATION AND ANHEDONIA AS MECHANISMS OF KETAMINE TREATMENT FOR ALCOHOL USE DISORDERS

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Funding: This research has been funded by PhD scholarships to OMM by the Society for the Study of Addiction and University of Exeter College of Life and Environmental Sciences Global Excellence Scholarship. Funding for the Ketamine for the reduction of Alcoholic Relapse clinical trial came from the Medical Research Council (Grant number: L-023032).

Declaration of Interests: CJAM has consulted for Janssen Pharmaceuticals and has received research funding from Awakn Life Sciences. OMM has conducted research work funded by Awakn Life Sciences. All other authors declare no conflict of interest.

BACKGROUND

Ketamine is a drug known for its anaesthetic, analgesic, and strong dissociative effects.

Its clinical uses extend beyond anaesthesia and pain.

Ketamine has been shown to have rapid & sustained antidepressant effects (2) as well as increase abstinence and decreasing drugs use, craving and withdrawal symptoms (3)

In recent randomised placebo controlled blind clinical trials ketamine was associated higher abstinence rates as well as lower likelihood of alcohol use and heavy drinking (4, 5).

Several mechanisms have been proposed to underlie ketamine's therapeutic effects in alcohol use disorders (AUD) (6).

Other potential mechanisms include transdiagnostic processes of anhedonia and repetitive negative thinking which are frequently reported among populations with AUD.

BACKGROUND

Repetitive negative thinking and anhedonia have been linked to craving, withdrawal, alcohol consumption and relapse (7, 8).

Single dose of ketamine has been found to reduce repetitive negative thinking in a population with depression (9).

Ketamine was reported to lead to improved clarity of thought due to "reduced depressive ruminations" (10).

Single and repeated doses of ketamine have been found to consistently reduce anhedonia among populations with mood disorders and heroin use disorders (11-13).

Anti-anhedonic effects of ketamine were moderated by family history of AUD.

Family history of AUD has also been found to moderate subjective and antidepressant effects of ketamine (14-16).

This study aimed to:

a) explore repetitive negative thinking and anhedonia as a mechanisms of ketamine treatment for AUD

b) examine moderation of outcomes by family history of AUD

METHODS

Design: Randomised, placebo controlled, double blind phase II clinical trial: Ketamine for the reduction of alcoholic relapse trial (KARE) (5).

Participants: 96 individuals meeting criteria for alcohol use disorders (DSM-V) or alcohol dependence (DSM-IV)

-Those on relapse prevention medication or antidepressants, those with uncontrolled hypertension or with a history of psychosis were excluded (5).

Drug administration: Three ketamine infusions (0.8 mg/kg IV) or placebo (50 ml saline 0.9% IV) over three weeks

Psychotherapy or education: 7 sessions of relapse prevention based psychological therapy or alcohol education

METHODS

Statistical Analysis:

- Exploratory Factor Analysis (EFA) on baseline psychological measurements
- Based on EFA, factor score calculated for the end of treatment, 3 and 6 months follow-up
- For each factor, a Mixed ANOVA with Time and Drug Condition was conducted
- Moderated Mediations (Process Model 8) with Family History of Alcohol Use Disorders as Moderator, Drug Condition as Predictor, the factor as Mediator and the percentage of abstinence at 6 months follow-up as Outcome

RESULTS

Table 1: Participant Characteristics			
	Ketamine (N=48)	**Placebo (N=48)**	**Total**
Age M (SD)	42. 87 (10.18)	45.27 (11.79)	44.07 (10.59)
Gender N	31 (M) 17 (F)	30 (M) 18 (F)	61 (M) 35 (F)
Site N	25 (London) 23 (Exeter)	25 (London) 23 (Exeter)	50 (London) 46 (Exeter)
Inpatient detox history N	6 (Yes) 42 (No)	6 (Yes) 42 (No)	12 (Yes) 84 (No)
History of anxiety N	24	20	44
History of depression N	24	16	40
Family history of alcohol abuse (in any 1st degree relative) N	17	23	40
Alcohol consumption at screening (units per week) M (SD)	34.92 (33.92)	25.98 (24.04)	34.70 (34.29)
Heaviest regular alcohol use (units per week), M (SD)	124.83 (95.19)	137.77 (83.09)	128.43 (70.79)
Number of infusions received N			
3	38	43	81
< 3	10	5	15
Number of therapy/education sessions received			
7	38	43	81 (84)
< 7	10	5	15 (16)
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)

RESULTS

Exploratory Factor Analysis (EFA):

- 61 items from baseline questionnaires were entered into EFA
- Items with low communality scores (<0.2) removed
- Scree plot of eigenvalues was used to determine number of factors to extract for rotation
- 3 and 4 factors were extracted, 3 factor solution resulted in a clean factor structure
- 3 Factors: State Anxiety, Repetitive Negative Thinking, Anhedonia

RESULTS

Exploratory Factor Analysis (EFA):

Table 2: Total Variance Explained

	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings
Factor	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total
1	18.47	28.87	28.87	17.9	27.98	27.98	11.37
2	4.33	6.77	35.63	3.76	5.88	33.86	11.6
3	3.78	5.9	41.54	3.18	4.96	38.82	10.847

RESULTS

Table 3: Items loading to Factors 2 & 3

Factor 2	Factor Loading	Factor 3	Factor Loading
Guilty feelings [d]	0.775	You find activities less enjoyable than usual [c]	0.625
Self-criticalness [d]	0.716	Loss of Interest [d]	0.601
I feel guilty [b]	0.667	You find it more difficult than usual to start doing things [c]	0.589
I feel sorry for things done [b]	0.607	Work & Activities [f]	0.562
You feel that you need to be punished in some way [c]	0.598	Loss of pleasure [d]	0.557
Self-dislike [d]	0.551	Tiredness or Fatigue [d]	0.546
Past failure [d]	0.543	Loss of energy [d]	0.541
Punishment feelings [d]	0.534	I feel pleasant [a]	0.541
Do you feel nervous or apprehensive? [e]	0.530	You feel rather indifferent about things [c]	0.523

a: STAI: State-Trait Anxiety; b: POMS: Profile of Mood States, c: PSI: Psychotomimetic States Inventory d: BDI: Beck Depression Inventory, e: BPRS: Brief Psychiatric Rating Scale, f: HAMD: Hamilton Depression Rating Scale.

RESULTS

Mixed Measures ANOVA (Drug Condition & Time):

Factor 2 Repetitive Negative Thinking:

- Significant reduction in repetitive negative thinking in the ketamine group compared to placebo at 3 months follow-up [$F(1, 94)= 4.73$, $p=0.032$, $\eta_p^2=0.05$].
- No other significant differences at any other timepoints.

Factor 3 Anhedonia:

- Significant reduction in anhedonia in the ketamine group compared to placebo at 3 months follow-up [[$F (1, 94) =7.9$, $p=0.006$, $\eta_p^2=0.08$].
- No other significant differences at any other timepoints.

RESULTS

Moderated Mediation:

Factor 2 Repetitive Negative Thinking

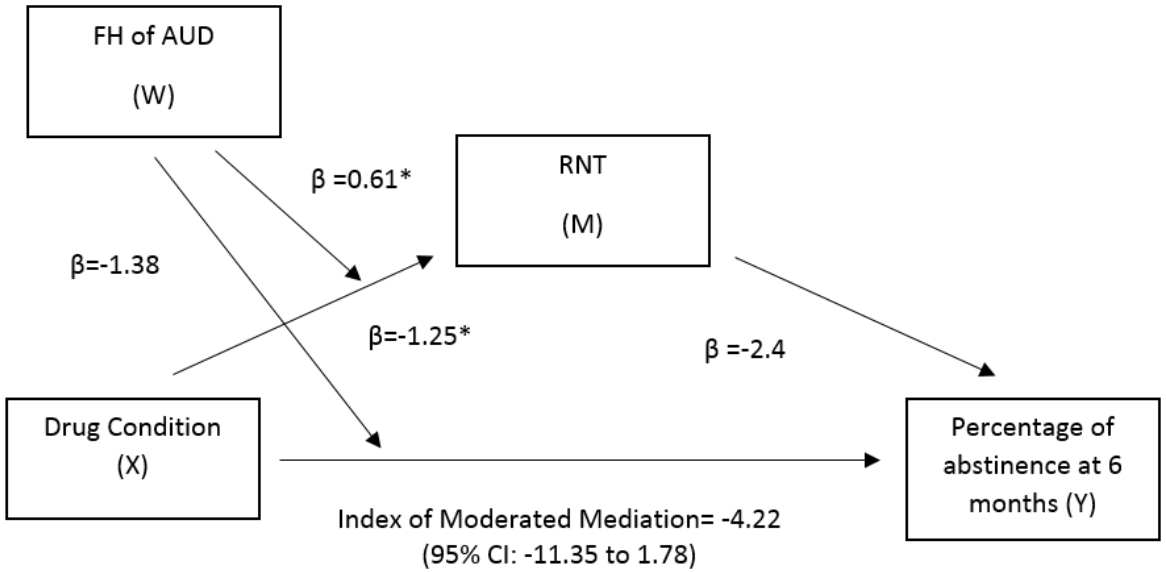

Fig1. *Moderated Mediation model*. The effect of Drug Condition (X) on Repetitive Negative Thinking (M) is moderated by Family History (FH) of AUD (W). The indirect effect of Drug Condition (X) on the percentage of abstinence at 6 months (Y) through Repetitive Negative Thinking is not moderated by Family History of AUD (W). Significant effect sizes are denoted by an asterisk (*).

RESULTS

Moderated Mediation:

Factor 3 Anhedonia

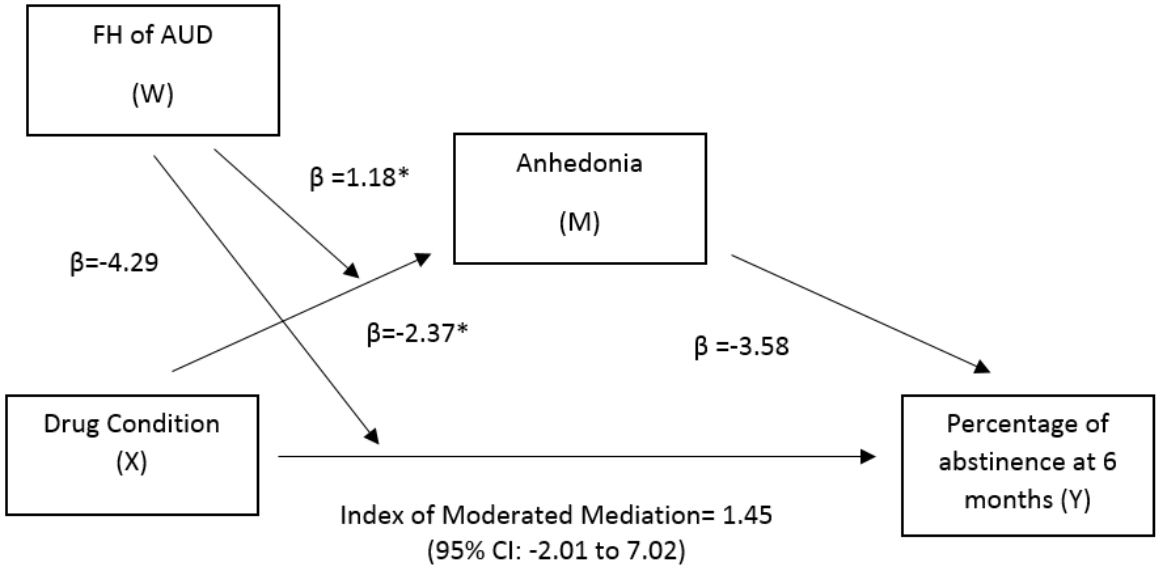

Fig2. *Moderated Mediation model*. The effect of Drug Condition (X) on Anhedonia (M) is moderated by Family History (FH) of AUD (W). The indirect effect of Drug Condition (X) on the percentage of abstinence at 6 months (Y) through Anhedonia is not moderated by Family History of AUD (W). Significant effect sizes are denoted by an asterisk (*).

DISCUSSION

Findings & Implications:

The findings extend previous research reporting reductions in anhedonia and repetitive negative thinking following ketamine infusions (9-13) to a population with AUD

Durability of the effects on anhedonia and repetitive negative thinking: patients may require booster sessions to maintain therapeutic benefits over longer follow-up

Consistent with research demonstrating ketamine's acute subjective effects and antidepressant effects are moderated by family history of AUD (11, 12, 14-16)

Mechanism of moderation by family history of AUD is not fully examined. Genetic variations in the NMDA receptor NR2A subunit which increase vulnerability to AUD may also increase sensitivity to the effects of ketamine as ketamine acts as a partial antagonist on this subunit (15, 17, 18)

DISCUSSION

Findings & Implications:

The lack of mediation by repetitive negative thinking may be explained by a number of methodological limitations: exclusion of those on antidepressant medications leading to a sample with minimal depression.

The timing of anhedonia measurement may explain the lack of mediation effect: previous studies measuring anhedonia during drug abstinence found no relationship to relapse (8) and anhedonia levels decrease with time following abstinence (19)

Previous studies have defined relapse in multiple ways (8). Different measures of relapse may be differentially sensitive to changes in anhedonia.

There may be unmeasured neurobiological or psychological mechanisms explaining ketamine's therapeutic effects in alcohol use disorders

DISCUSSION

Limitations & Future Directions:

Exploratory analysis & powered to detect the effect on primary outcomes	Power analysis to include mechanisms of interests
Strict exclusion criteria of the clinical trial (those on antidepressants or with poor liver function excluded)	Recruitment practices to consider generalisability of the trial sample to the population of interest
Repetitive negative thinking measured through relevant items of depressive mood, anxiety and worry questionnaires	Use validated measures of repetitive negative thinking such as the Ruminative Response Style Scale

THANKS FOR LISTENING. ANY QUESTIONS?

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