Data supplement for Grabski et al., Ketamine Adjunctive to Relapse Prevention–Based Psychological Therapy as a Treatment for Alcohol Use Disorder. Am J Psychiatry (doi: 10.1176/appi.ajp.2021.21030277)

Inclusion and Exclusion Criteria

Inclusion Criteria:

- 18 to 65 years old;
- Meet either a) DSM-5 criteria for moderate/severe alcohol use disorder or b) DSM-IV criteria for alcohol abuse/dependence within the last 12 months;
- Currently abstinent from alcohol (breathlyser BAC level 0.00) and negative urine drug screen (participants testing positive for THC who do not have a history or current cannabis dependency may be included; participants testing positive for benzodiazepines and who do not have a history or current dependency for benzodiazepines may be included);
- Capacity to give informed consent as defined by GCP guidelines;
- Willing to wear SCRAM-X bracelet for active treatment;
- Females of childbearing potential and males must be willing to use an effective method of contraception (hormonal or barrier method of birth control; True abstinence) from the time consent is signed until 6 weeks after treatment discontinuation and inform the trial if pregnancy occurs. For the purpose of clarity, True abstinence is when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence, spermicides only, withdrawal or lactational amenorrhoea method for the duration of a trial, are not acceptable methods of contraception;
- Females of childbearing potential must have a negative pregnancy test within 7 days prior to being registered for trial treatment and on day of first treatment.

Exclusion Criteria:

- Currently taking any other relapse prevention medication or anti-depressants;
- Current uncontrolled hypertension (systolic 140mm Hg or greater and diastolic 90mm Hg or greater);
- Currently has BMI outside normal limits <16 or > 35
- Any relevant mental or physical health issues as determined by medically qualified personnel, which may include:
    - Current or history of psychosis as identified by DSM-5 or DSM-IV SCID;
    - Current or historical diagnosis of schizophrenia in a first degree relative;
    - Current co-morbid psychiatric diagnosis excluding depression and anxiety;
    - Previous or current diagnosis of substance dependence / severe substance misuse disorder as confirmed by the participant's GP or if the participant has sought professional help for their dependence;
    - Clinically relevant history of neuropsychological difficulties. One or more previous medically confirmed seizures, including seizures witnessed by an appropriate clinician, documented evidence from an EEG or a history consistent with a diagnosis of an epileptiform illness;
    - Current suicidal ideation, as judged clinically.
- Any medication deemed, by the trial medical professionals, to pose risk combined with ketamine which may include daily prescribed use of;
    a. Barbiturates and/or narcotics
    b. Atracurium and tubocurarine
    c. Central nervous system (CNS) depressants (e.g. phenothiazines, sedating H1 – blockers or skeletal muscle relaxants)
    d. Thiopental
    e. Thyroid hormones
    f. Antihypertensive agents
    g. Theophylline and methylxanthines.

- Liver function tests that assess chronic liver damage (namely bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST)) > 3 times normal levels
- Where there are special warnings or precautions for use according to the SPC where the risk benefit ratio is not in favour of giving ketamine with assessment made by physical examination by medically qualified trial personnel, self-report or inspection of the medical notes. Current diagnosis of:
    a. Acute intermittent porphyria
    b. Dehydration or hypovolemia
    c. Hyperthyroidism
    d. Pulmonary or upper respitatory tract infection
    e. Severe Coronary artery disease, Cerebrovascular accident or cerebral trauma
    f. Known glaucoma or globe injuries
    g. Cirrhosis
    h. Epilepsy
    i. Intracranial mass lesions, hydrocephalus, or presence of head injury (i.e. evidence of lasting impact of head injury that is affecting everyday functioning)
- Not willing to use effective contraception or (females) take pregnancy test;
- Allergic reaction to ketamine;
- >10 previous inpatient detoxifications from alcohol;
- Pregnant or breastfeeding;
- Allergies to excipients of IMP or placebo;
- Use of another IMP that is likely to interfere with the study medication within 3 months of study enrolment.

List of measures and time points of assessment

	Pre-Screening	**Screening**	**Baseline**	**Treatment Phase**						**Follow Up**	
Visit #	-1	1	2	3	4	5	6	7	8	9	10
Timing	Within 12 weeks before visit 1	1-28 days before visit 2	1-28 days after visit 1	1-5 days after visit 2	4-21 days after visit 2	1-5 days after visit 4	4-21 days after visit 4	1-5 days after visit 6	4-21 days after visit 6	11-13 weeks after visit 2	23-25 weeks after visit 2
Informed Consent		X									
Medical History		X									
Physical [a]		X									
SCID		X								X	X
Vital Signs [b]		X	X	X	X	X	X	X	X		
Bloods [c, d]		X[c]	X[d]	X[d]	X[d]	X[d]	X[d]	x[d]	X[d]	X[d]	X[d]
Eligibility determination	X	X	X								
Urine Drug screen		X[e]	X[e]	X[f]	X[e]	X[f]	X[e]	X[f]	X[e]	X[e]	X[e]
Pregnancy Test I WOCBP		X	X		X		X				
Breathalyser		X	X	X	X	X	X	X	X	X	X
Randomisation			X								
SCRAM-X fitting		X[g]	X[g]								
IMP/Plac administration			X		X		X				
SCRAM-X checks			X	X	X	X	X	X	X		
Relapse-prevention based CBT			X	X	X	X	X	X	X		
Adverse Events review			X	X	X	X	X	X	X	X	X
Concomitant Medication review		X	X	X	X	X	X	X	X	X	X

Alcohol and Drug Use History		X							X	X	X
BDI		X	X		X		X		X	X	X
HAM-D		X	X	X	X	X	X	X	X	X	X
Columbia Suicide Severity Rating Scale		X									
POMS			X	X	X	X	X	X	X	X	X
STAI		X	X		X		X		X	X	X
ACQ-NOW		X	X	X	X	X	X	X	X	X	X
BPRS		X	X	X	X	X	X	X	X	X	X
PSI		X	X		X		X		X	X	X
Alcohol Timeline Follow Back		X	X		X		X		X	X	X
Drink diary									X	X	X
Fagerstrom Nicotine Dependence			X						X	X	X
Craving VAS			X	X	X	X	X	X	X	X	X
SF-12			X						X	X	X
Prose Recall			X	X	X	X	X	X	X	X	X
Delay Discounting			X						X	X	X
Stop Signal Reaction Time			X						X	X	X
Digit Span			X						X	X	X
Adverse effects VAS +			X	X	X	X	X	X	X	X	X
Pattern Recognition Memory Test			X		X		X		X	X	X

a) Physical assessed by trained medic – height, weight, an examination of cardiovascular, respiratory, GI and neurological function to a level of detail that would be expected for a patient due to receive anaesthesia.
b) Vital signs: oral/tympanic temperature, resting pulse, pulse oximetry and Blood Pressure.
c) Bloods (Screening) – FBC (haemoglobin, white cell count, platelets, mean red cell volume); Liver function (Bilirubin, ALT, AST, Total Protein, Alkaline Phos (ALP), Albumin, Globulin, gamma-glutamyl transpeptidase (GGT)), Biochemistry (urea, sodium, potassium, glucose, calcium, thyroid stimulating hormone).
d) Bloods (Study): BDNF; ketamine; Liver function (Bilirubin, ALT, AST, Total Protein, Alkaline Phos (ALP), Albumin, Globulin, gamma-glutamyl transpeptidase (GGT)).
e) Urine Drug screen (Screening, infusion days and F-UP visits) - (methamphetamine, cocaine, THC, benzodiazepines, tricyclic antidepressants, barbituates, phencyclidine,amphetamines, morphine, methadone, ketamine).
f) Urine Drug screen (Non-infusion days, treatment phase) – (methamphetamine, cocaine, THC, benzodiazepines, tricyclic antidepressants, barbituates, phencyclidine, amphetamines, morphine, methadone).
g) SCRAM-X device can be fitted at any one of these visits.

Sensitivity analysis 1: Relapse of alcohol use and percentage of days abstinent at 6 month follow-up: per protocol sample using observed data

Outcome	Ketamine (n=38)	Placebo (n=43)	PT (n=38)	PE (n=43)	Ketamine + PT (n=18)	Ketamine + PE (n=20)	Placebo + PT (n=20)	Placebo + PE (n=23)	Ketamine vs placebo OR[2] (95% CI)	Ketamine + PT vs Ketamine + PE OR[2] (95% CI)	Ketamine + PT vs placebo +PE OR[2] (95% CI)
Relapse[3]; n/N (%)	25/38 (66)	30/41 (73)	24/37 (65)	31/42 (74)	11/18 (61)	14/20 (70)	13/19 (68)	17/22 (77)	0.70 (0.27; 1.84)	0.67 (0.17; 2.59)	0.48 (0.12; 1.91)
									Ketamine vs placebo mean difference (95% CI)	**Ketamine + PT vs Ketamine + PE mean difference (95% CI)**	**Ketamine + PT vs placebo +PE mean difference (95% CI)**
Percentage days abstinent[4]; mean (SD); median [IQR] Timeline follow back	84.6 (17.7); 92 [43, 100]	72.3 (26.6); 75 [12, 100]	81.1 (24.2); 93 [12, 100]	75.3 (22.9); 78 [26, 100]	86.4 (18.1); 94 [48, 100]	83 (17.7); 87 [43, 100]	76.4 (28.3); 92 [12, 100]	68.7 (25.0); 71 [26, 100]	11.8 (1.8; 21.8)	3.4 (-8.5; 15.3)	16.9 (3.0; 30.9)

[1]Per protocol population defined as receiving at least three infusions of either ketamine or placebo.

[2]Adjusted for site.

[3]Including only participants with confirmed relapse status; relapse on 1 or more days from baseline to participant's final follow-up to a minimum of 159 days, maximum of 180 days; or no relapse and no days with missing data on alcohol use from baseline to participant's final follow-up to a minimum of 159 days, maximum 180 days.

[4]Denominator is number of days out of participant's total follow-up days (maximum 180) with observed data.

PE: Psychoeducation; PT: Psychotherapy.

Sensitivity analysis 2: Relapse of alcohol use and percentage of days abstinent at 6 month follow-up: intention to treat population using observed and imputed data

Outcome	Ketamine (n=48)	Placebo (n=48)	PT (n=47)	PE (n=49)	Ketamine + PT (n=24)	Ketamine + PE (n=24)	Placebo + PT (n=23)	Placebo + PE (n=25)	Ketamine vs placebo OR[1] (95% CI)	Ketamine + PT vs Ketamine + PE OR[1] (95% CI)	Ketamine + PT vs placebo +PE OR[1] (95% CI)
Relapse; n (%)	-	-	-	-	-	-	-	-	0.73 (0.29; 1.83)	0.78 (0.23; 2.69)	0.49 (0.13; 1.90)
									Ketamine vs placebo mean difference (95% CI)	**Ketamine + PT vs Ketamine + PE mean difference (95% CI)**	**Ketamine + PT vs placebo +PE mean difference (95% CI)**
Percentage days abstinent at 6-month follow-up[2]; mean (SD); median [IQR]	79.2 (23); 87 [24, 100]	69.8 (27.5); 73 [12, 100]	77 (26.1); 88 [12, 100]	72.1 (25.3); 78 [19, 100]	79.3 (23.7); 89 [26, 100]	79.1 (22.7); 85 [29, 100]	74.6 (28.6); 87 [12, 100]	65.4 (26.2); 62 [22, 100]	10.1 (1.1; 19.0)	4.2 (-6.8; 15.2)	15.9 (3.8; 28.1)

[1]Adjusted for site.

[2]Denominator is number of days out of participant's total follow-up days (maximum 180) for participants with observed data for all days to final follow-up; imputed percentage otherwise.

PE: Psychoeducation; PT: Psychotherapy.

TABLE S1. Percentage of days abstinent at 6 month follow-up: intention to treat population using observed data

Outcome	Ketamine (n=48)			Placebo (n=48)			PT (n=47)			PE (n=49)			Ketamine + PT (n=24)			Ketamine + PE (n=24)			Placebo + PT (n=23)			Placebo + PE (n=25)			Ketamine vs placebo mean difference[1] (95% CI)			Ketamine + PT vs Ketamine + PE mean difference[1] (95% CI)			Ketamine + PT vs placebo +PE mean difference[1] (95% CI)		
Days alcohol use data collected[2]	M		SD	M		SD	M		SD	M		SD	M		SD	M		SD	M		SD	M		SD	M		SD	M		SD	M		SD
	147		51	157		43	150		50	155		45	144		56	150		47	156		44	159		43									
	Med	Min	Max	Med	Min	Max	Med	Min	Max	Med	Min	Max	Med	Min	Max	Med	Min	Max	Med	Min	Max	Med	Min	Max	Med	Min	Max	Med	Min	Max	Med	Min	Max
	164	1	180	167	1	180	167	1	180	167	1	180	165	1	180	164	1	180	167	1	180	167	1	180									
Percentage days abstinent[3]; Timeline follow-back	M		SD	M		SD	M		SD	M		SD	M		SD	M		SD	M		SD	M		SD	M		SD	M		SD	M		SD
Percentage days abstinent[3]; mean (SD); median [min, max] Timeline follow-back	84.4 (18.8); 92 [32, 100]		74.4 (26.0); 84 [12, 100]	82.4 (22.8); 93 [12, 100]			76.5 (23.3); 83 [26, 100]			86.4 (17.7); 94 [48, 100]			82.5 (20); 89 [32, 100]			78.3 (26.9); 92 [12, 100]			70.7 (25.1); 74 [26, 100]			10.1 (1.1; 19.0)			4.2 (-6.7; 15.2)			15.9 (3.8; 28.1)					
Percentage days abstinent[3, 4]; mean (SD); median [min, max] Timeline follow-back	-			-			-			-			-			-			-			-			9.7 (1.0; 18.4)			4.3 (-5.8; 14.5)			15.9 (3.9; 27.9)		

[1]Including only participants with confirmed relapse status; relapse on 1 or more days from baseline to participant's final follow-up to a minimum of 159 days, maximum of 180 days; or no relapse and no days with missing data on alcohol use from baseline to participant's final follow-up to a minimum of 159 days, maximum 180 days.
[2]Using observed data only from baseline until participant's final follow-up; follow-up capped at maximum of 180 days.
[3]Denominator is number of days out of participant's total follow-up days (maximum 180) with observed data.
[4]Adjusted for baseline alcohol consumption.
PE: Psychoeducation; PT: Psychotherapy; Med: Median; Min: Minimum; Max: Maximum

TABLE S2. Secondary alcohol related outcomes at 3 month follow-up: intention to treat population using observed data

Outcome	Ketamine (n=48)	Placebo (n=48)	PT (n=47)	PE (n=49)	Ketamine + PT (n=24)	Ketamine + PE (n=24)	Placebo + PT (n=23)	Placebo + PE (n=25)	Ketamine vs placebo mean difference[1] (95% CI)
Days alcohol use data collected; mean (SD); median [min, max]; 90 days' alcohol use data collected (baseline to day 90); n %	80.7 (25.5); 35 (73)	83.8 (20.4); 40 (83)	81.1 (24.7); 38 (81)	83.3 (21.5); 37 (76)	78.7 (28.1); 17 (71)	82.7 (23.1); 18 (75)	83.7 (21); 21 (91)	83.9 (20.4); 19 (76)	-
Percentage days abstinent at 90 days[3] mean (SD), median [IQR]	88.8 (14.5); 96 [38, 100]	79.8 (23.2); 90 [18, 100]	86.1 (20.5); 97 [18, 100]	82.6 (19.1); 89 [38, 100]	90.3 (12.4); 97 [66, 100]	87.3 (16.4); 94 [38, 100]	81.7 (26.1); 97 [18, 100]	78.1 (20.7); 82 [38, 100]	9.0 (1.3; 16.7)
Percentage days abstinent at 90 days[3,4], mean (SD), median [IQR]									8.8 (1.2; 16.2)

[1]Adjusted for site.

[2]Using observed data only from baseline until follow-up capped at maximum of 90 days

[3]Adjusted for baseline alcohol consumption.

[4]Denominator is number of days out of participant's total follow-up days (maximum 90) with observed data.

PE: Psychoeducation; PT: Psychotherapy.

TABLE S3. Exploratory analysis I. Linear regression models including drug treatment and therapy treatment: intention to treat population using observed data.

	Model I		Model II	
	% days abstinent 90 days [3,4,5]	**% days abstinent 180 days [3,4,5]**	**% days abstinent 90 days [4,5,6]**	**% days abstinent 180 days [4,5,6]**
Ketamine[1]	8.9 (1.2; 16.6)	9.9 (1.0; 18.8)	9.0 (-1.9; 19.8)	11.5 (-1.0; 24.0)
Therapy[2]	3.5 (-4.2; 11.2)	6.0 (-2.9; 14.9)	3.6 (-7.4; 14.6)	7.6 (-5.1; 20.3)
Ketamine*Therapy	-	-	-0.2 (-15.7; 15.4)	-3.2 (-21.1; 14.7)

[1]Reference: placebo.
[2]Reference: psychoeducation.
[3]Denominator is number of days out of participant's total follow-up days (maximum 90) with observed data.
[4]Between group comparison reported as mean difference (95% confidence interval).
[5]Adjusted for site.
[6]Denominator is number of days out of participant's total follow-up days (maximum 180) with observed data.

TABLE S4. Questionnaire outcomes at Baseline, 3 and 6 months

	Ketamine	Placebo	PT	PE	Ketamine + PT	Ketamine + PE	Placebo + PT	Placebo + PE	Ketamine vs placebo[1]
SF-12 Mental									
Baseline	45.8 (9.9); 48	44.3 (12); 48	45.0 (11.3); 47	45.2 (10.8); 49	47.2 (8.9); 24	44.5 (10.9); 24	42.7 (13.2); 23	45.8 (10.8); 25	-
3 month	51.9 (8.3); 43	47.5 (12.1); 43	48 (11.4); 41	51.2 (9.6); 45	51.8 (7.9); 21	51.9 (8.9); 22	43.9 (13.1); 20	50.6 (10.4); 23	3.9 (-0.2; 8.0)
6 month	48.9 (10.8); 40	46.4 (11.2); 42	45.7 (12.2); 40	49.4 (9.6); 42	49.5 (12.0); 20	48.3 (9.8); 20	41.9 (11.4); 20	50.4 (9.6); 22	2.2 (-2.4; 6.7)
SF-12 Physical									
Baseline	51.4 (7.2); 48	52.3 (7.3); 48	50.1 (7.6); 47	53.5 (6.5); 49	48.0 (7.2); 24	54.8 (5.5); 24	52.3 (7.5); 23	52.2 (7.1); 25	-
3 month	52.5 (6.7); 43	54.1 (5.4); 43	52.2 (6.8); 41	54.3 (5.3); 45	49.9 (7.5); 21	54.9 (4.9); 22	54.7 (5.0); 20	53.7 (5.8); 23	-1.3 (-3.3; 0.8)
6 month	52.7 (6.5); 40	54.3 (5); 42	52.6 (6.5); 40	54.5 (4.9); 42	50.2 (7.4); 20	55.3 (4.3); 20	55.0 (4.6); 20	53.7 (5.4); 22	-1.4 (-3.6; 0.8)
PSI Subscale 1: Thought distortion									
Baseline	0.8 (1.6); 48	1.1 (1.8); 48	0.7 (1.5); 47	1.2 (1.9); 49	0.5 (0.8); 24	1.1 (2.2); 24	1.0 (2.0); 23	1.2 (1.7); 25	-
3 month	0.4 (1.0); 42	0.2 (0.6); 43	0.2 (0.7); 41	0.4 (0.9); 44	0.2 (0.9); 21	0.5 (1.0); 21	0.2 (0.5); 20	0.2 (0.7); 23	0.2 (-0.1; 0.5)
6 month	0.4 (1.2); 40	0.4 (1.1); 42	0.4 (1.2); 40	0.5 (1.1); 42	0.3 (0.8); 20	0.6 (1.4); 20	0.5 (1.5); 20	0.4 (0.7); 22	0.1 (-0.4; 0.5)
PSI Subscale 2: Perception/distortion									
Baseline	0.5 (1.4); 48	0.7 (1.6); 48	0.6 (1.5); 47	0.6 (1.5); 49	0.3 (1.1); 24	0.6 (1.7); 24	0.8 (1.9); 23	0.6 (1.3); 25	-
3 month	0.3 (1.0); 42	0.4 (0.8); 43	0.4 (0.9); 41	0.3 (0.9); 44	0.4 (1.2); 21	0.3 (0.7); 21	0.4 (0.7); 20	0.4 (1); 23	-0.1 (-0.4; 0.3)
6 month	0.1 (0.4); 40	0.5 (1.2); 42	0.5 (1.1); 40	0.2 (0.7); 42	0.1 (0.4); 20	0.1 (0.4); 20	0.8 (1.4); 20	0.2 (0.9); 22	-0.3 (-0.7; 0.0)
PSI Subscale 3: Cognitive disorganisation									
Baseline	5.6 (4.5); 48	5.2 (4.8); 48	5.2 (4.6); 47	5.6 (4.7); 49	5.3 (4.8); 24	5.9 (4.2); 24	5.1 (4.6); 23	5.3 (5.2); 25	-
3 month	3.0 (4.0); 42	3.7 (3.5); 43	3.5 (3.5); 41	3.3 (4.0); 44	2.8 (3.6); 21	3.2 (4.5); 21	4.2 (3.4); 20	3.3 (3.5); 23	-1.0 (-2.3; 0.2)
6 month	3.2 (4.0); 40	4.3 (5.0); 42	4.0 (4.3); 40	3.5 (4.8); 42	3.0 (4.4); 20	3.4 (3.7); 20	5.0 (4.0); 20	3.6 (5.7); 22	-1.3 (-3.1; 0.5)
PSI Subscale 4: Anhedonia									
Baseline	4.6 (3.6); 48	5.8 (4.2); 48	5.4 (4.1); 47	4.9 (3.7); 49	4.9 (3.6); 24	4.2 (3.5); 24	6.0 (4.6); 23	5.6 (3.9); 25	-
3 month	3.0 (3.2); 42	5.6 (3.8); 43	4.5 (3.7); 41	4.1 (3.8); 44	2.9 (2.5); 21	3.1 (3.8); 21	6.3 (4.0); 20	5.0 (3.6); 23	-1.8 (-3.1; -0.5)
6 month	4.0 (3.3); 40	5.4 (3.8); 42	5.0 (4.1); 40	4.3 (3.2); 42	3.4 (3.2); 20	4.5 (3.5); 20	6.7 (4.4); 20	4.2 (2.9); 22	-0.9 (-2.4; 0.5)
PSI Subscale 5: Manic experience									
Baseline	3.5 (1.9); 48	3.5 (2.3); 48	3.3 (2.0); 47	3.7 (2.1); 49	3.2 (1.8); 24	3.7 (2.0); 24	3.3 (2.3); 23	3.7 (2.3); 25	-
3 month	2.7 (1.9); 42	3.3 (1.8); 43	3.0 (1.6); 41	3.0 (2.0); 44	2.7 (1.6); 21	2.8 (2.2); 21	3.4 (1.6); 20	3.3 (1.9); 23	-0.6 (-1.3; 0.0)
6 month	3.4 (2.1); 40	3.4 (2.0); 42	3.6 (2.1); 40	3.2 (2.0); 42	3.3 (2.3); 20	3.5 (2.0); 20	3.9 (2.0); 20	2.9 (1.9); 22	-0.1 (-0.9; 0.8)
PSI Subscale 6: Paranoia									
Baseline	1.0 (1.7); 48	1.3 (2.5); 48	1.5 (2.4); 47	0.9 (1.9); 49	1.3 (2.2); 24	0.7 (1.1); 24	1.6 (2.6); 23	1.0 (2.4); 25	-
3 month	0.4 (1.0); 42	0.5 (1.4); 43	0.5 (1.5); 41	0.4 (1.0); 44	0.4 (1.0); 21	0.4 (1.1); 21	0.6 (1.9); 20	0.5 (0.9); 23	-0.1 (-0.6; 0.4)
6 month	0.5 (1.5); 40	0.9 (1.9); 42	0.8 (1.8); 40	0.6 (1.6); 42	0.5 (1.4); 20	0.6 (1.6); 20	1.2 (2.1); 20	0.7 (1.6); 22	-0.4 (-0.9; 0.2)
ACQ Total									
Baseline	2.7 (1.1); 48	2.6 (1.2); 48	2.8 (1.3); 47	2.6 (1.0); 49	2.9 (1.2); 24	2.6 (1.1); 24	2.8 (1.4); 23	2.5 (1.1); 25	-
3 month	1.9 (1.0); 43	2.1 (1.1); 43	1.9 (1.0); 41	2.0 (1.1); 45	1.8 (0.9); 21	1.9 (1.1); 22	2.1 (1.1); 20	2.1 (1.0); 23	-0.3 (-0.8; 0.1)
6 month	1.9 (0.8); 40	2.2 (0.9); 42	2.0 (1.0); 40	2.1 (0.8); 42	1.7 (0.9); 20	2.1 (0.6); 20	2.4 (1.0); 20	2.1 (0.9); 22	-0.4 (-0.7; 0.0)
FTND[2]									
Baseline	3.9 (2.4); 12	2.9 (1.9); 12	4.2 (2.2); 13	2.5 (1.8); 11	4.8 (2.4); 8	2.3 (1.0); 4	3.4 (1.5); 5	2.6 (2.1); 7	NP
3 month	2.7 (2.8); 10	3.0 (2.4); 11	4.1 (2.0); 10	1.7 (2.4); 11	4.2 (2.6); 6	0.5 (0.6); 4	4.0 (0.8); 4	2.4 (2.8); 7	NP
6 month	3.5 (3.1); 10	1.8 (1.6); 10	4.4 (2.4); 10	0.9 (1.0); 10	5.0 (3.0); 6	1.3 (1.3); 4	3.5 (0.6); 4	0.7 (0.8); 6	NP

[1]Adjusted for site and baseline score. [2]Includes participants who were smokers at baseline only. NR: Analysis not performed due to small numbers. Outcomes are mean (SD), n. PE: Psychoeducation; PT: Psychotherapy.

FIGURE S1. SCRAM data analysis
All 96 participants had a Secure Continuous Remote Alcohol Monitor (SCRAM) bracelet fitted at the beginning of the trial. On average participants wore the bracelet for 29.4 days (SD 20.53). The minimum amount that a participant wore the bracelet was 2 days and the maximum 176 days. Four participants cited not being able to tolerate the SCRAM bracelet as their reason from withdrawal from treatment.

SCRAM data of 79 participants that wore the bracelet until at least visit 7 were included in the analysis. SCRAM readings were available for 94% of the days between visit 2 up to visit 8 for these participants. The average amount of days the bracelet was worn in this time period was 19.54 days. For the following analysis of drinking days the half-hourly SCRAM readings were averaged across 24 hours of one day.

SCRAM and Alcohol Timeline-Followback (ATLF) data were available for 2026 days. For 94.4% of these days SCRAM and ATLF data matched on indication of alcohol use. More specifically for 90.7% of days SCRAM and ATLF data indicated no alcohol use in this time period and for 3.7% of days they indicated use of alcohol. On 2.8% of the days alcohol use was indicated by ATLF but not the SCRAM bracelet. Similarly, on 2.8% of the days alcohol was indicated by the SCRAM bracelet but not the ATLF. However, in this last case there were 9 days on which SCRAM and ATLF matched on alcohol use the day before, and it is likely that alcohol was still in the participant's system, thus picking a up a positive reading even though the actual drinking occasion was on the previous day. When correcting for those occasion the amount of days in which SCRAM data indicated alcohol consumption but the ATLF did not reduces to 2.5%.

A correlation between percentage of self-reported drinking days (mean 0.078%; SD 0.227) and percentage of SCRAM readings greater than 0 per day (mean 0.054%; SD 0.145) by participant between visits 2 and 8 was positive (r=0.75, df=78, p<0.001, 95% CI 0.63 to 0.83).

Correlation percentage of self-reported drinking days and percentage of SCRAM readings greater than 0 per day.

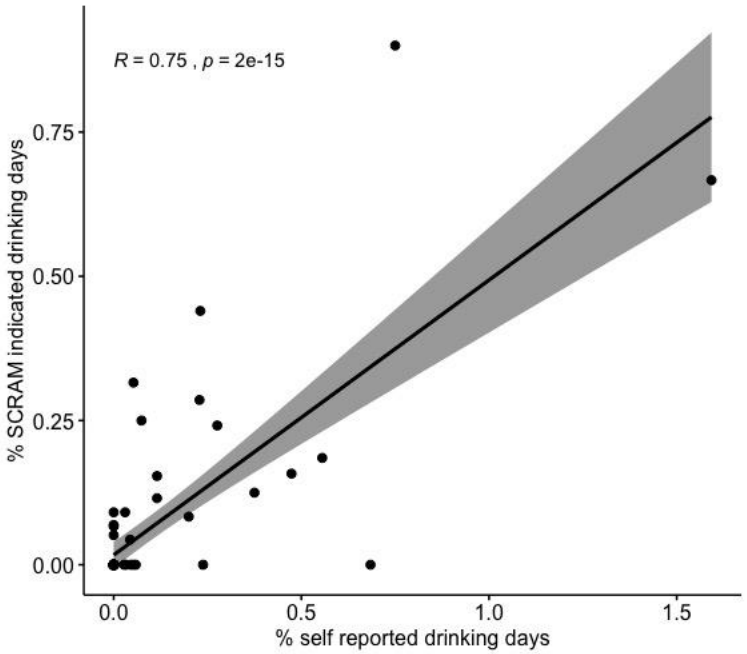
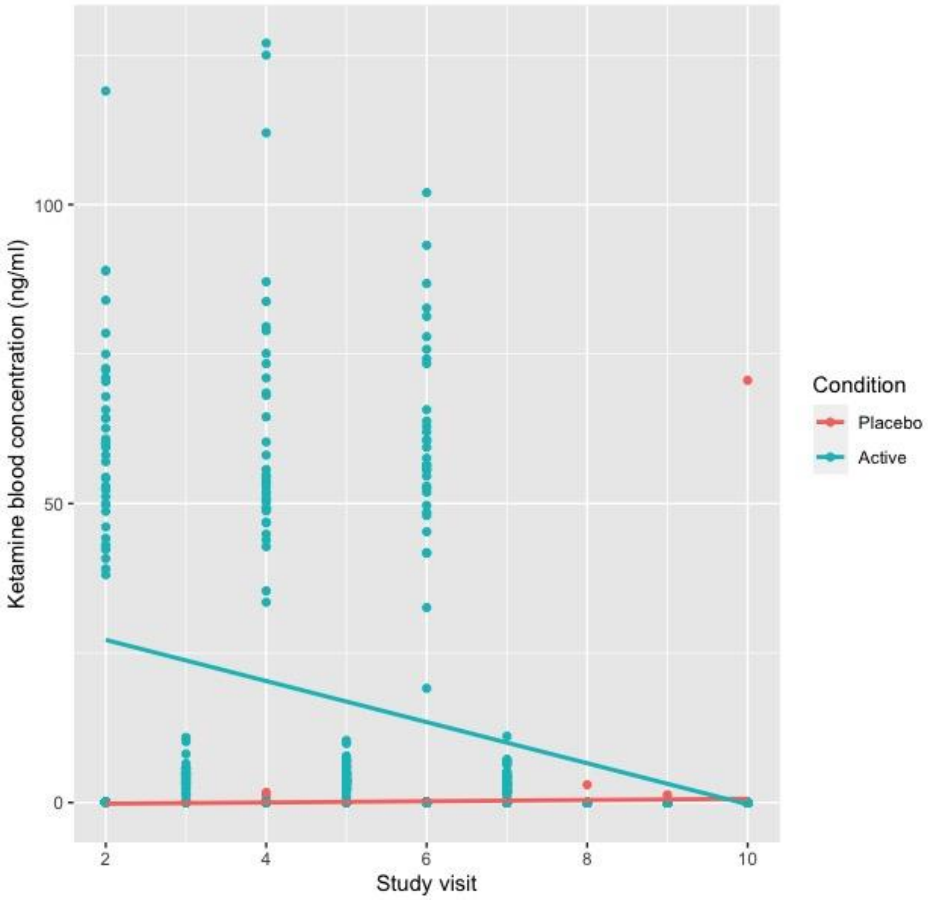


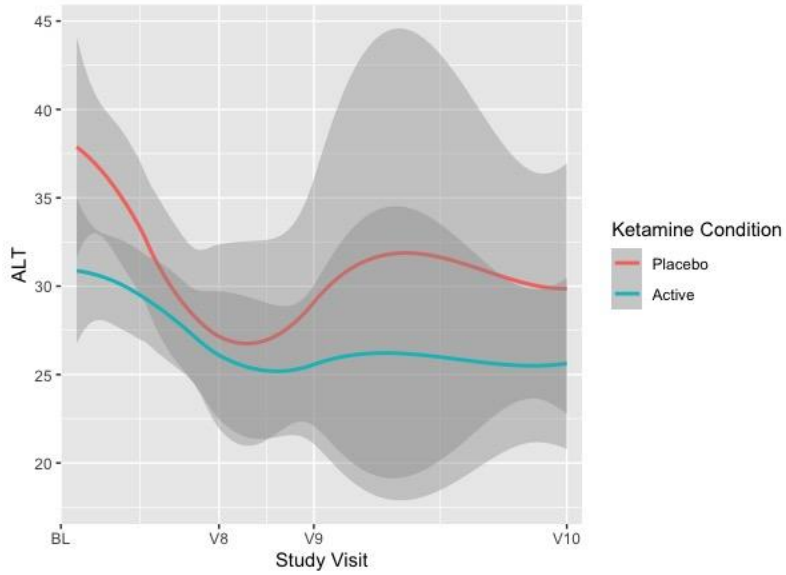
FIGURE S2. Average ketamine blood levels by drug condition



Infusions were administered at visits 2, 4 ,and 6. Positive ketamine readings in the placebo condition or outside the active treatment period were consistent with self-reported ketamine use.

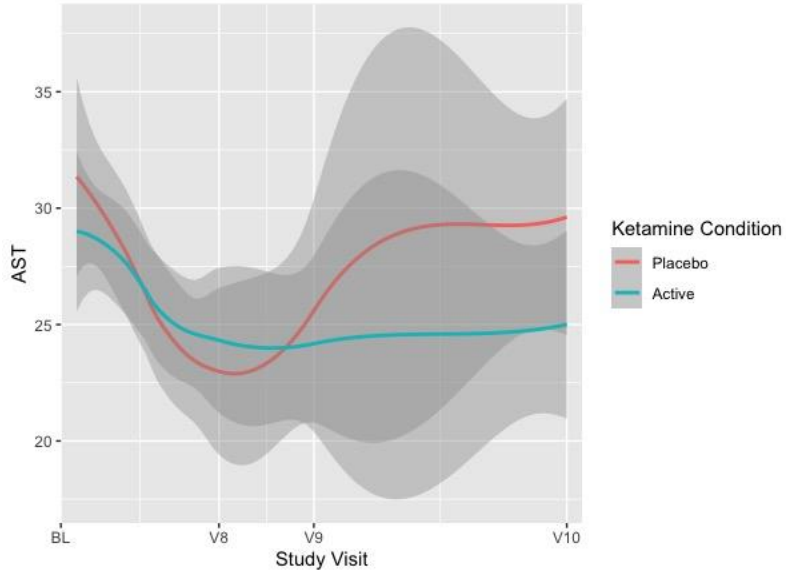
FIGURE S3. Liver function results

ALT by condition



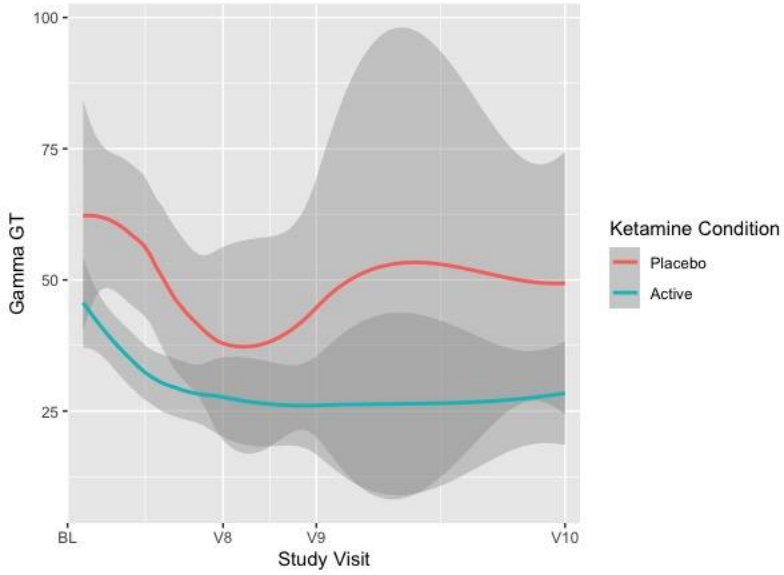
Lines fitted using LOESS curve smoothing

AST by condition



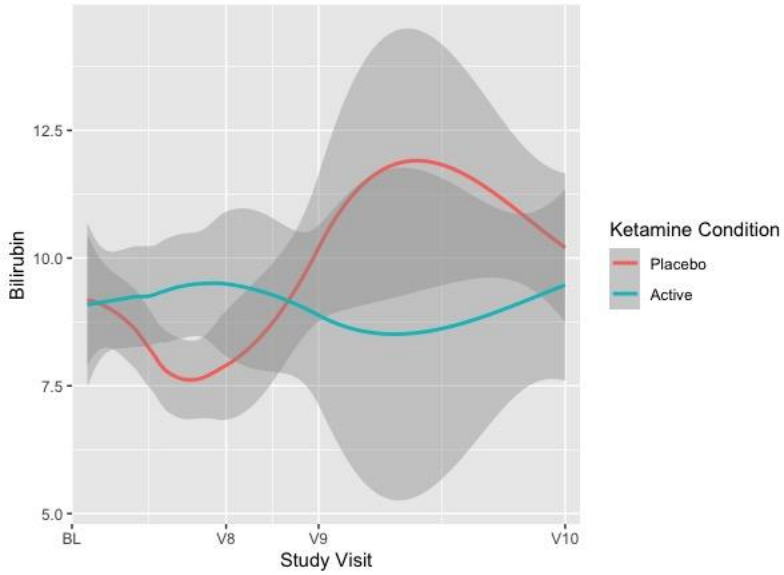
Lines fitted using LOESS curve smoothing

Gamma GT by condition



Lines fitted using LOESS curve smoothing

Bilirubin by condition



Lines fitted using LOESS curve smoothing

Subjective drug effects

Dizziness
Infusions 1, ketamine: mean=8.4, SD=3.5; placebo: mean=2.0, SD=0.1
Infusions 2, ketamine: mean=8.5, SD=3.4; placebo: mean= - , SD= -
Infusions 3, ketamine: mean=8.5, SD=3.5; placebo: mean= - , SD= -

Out of body experiences
Infusions 1, ketamine: mean=7.7, SD=3.8; placebo: mean=5.0, SD=0.6
Infusions 2, ketamine: mean=7.8, SD=4.0; placebo: mean=4.0, SD=0.7
Infusions 3, ketamine: mean=7.5, SD=3.8; placebo: mean=5.0, SD=0.6

Altered reality perception
Infusions 1, ketamine: mean=9.2, SD=1.9; placebo: mean=2.5, SD=0.5
Infusions 2, ketamine: mean=8.6, SD=2.7; placebo: mean=2.4, SD=0.5
Infusions 3, ketamine: mean=8.8, SD=2.9; placebo: mean=4.0, SD=0.5

Altered time perception
Infusions 1, ketamine: mean=8.8, SD=2.8; placebo: mean=3.3, SD=0.9
Infusions 2, ketamine: mean=8.4, SD=3.1; placebo: mean=3.6, SD=1.4
Infusions 3, ketamine: mean=8.8, SD=3.3; placebo: mean=3.0, SD=0.7