Ketamine as a potential intervention for alcohol withdrawal and benzodiazepine deprescribing in patient suffering from major depressive disorders

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Abstract English

Background:

Alcohol and benzodiazepine / Z-drugs (BZDR) can easily lead to dependence but can be challenging to discontinue. The neurophysiologic state underlying BZDR withdrawal syndromes overlap significantly with alcohol withdrawal, and classically presents in patients who have discontinued their medications or alcohol after long-term use. Few pharmacological interventions have evidence for facilitating BZDR discontinuation, and none in patients actively suffering from Treatment Resistant Depression (TRD). Recent clinical evidence in alcohol use disorders and pre-clinical evidence in benzodiazepine dependence suggests that ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, may be an effective intervention to treat benzodiazepine withdrawal. In this thesis, we present two papers: 1) a systematic review of ketamine for alcohol use disorders and withdrawal in humans and 2) a cohort study on the potential therapeutic effects of ketamine on long-term BZDR discontinuation in patients suffering from TRD.

Methods:

Paper # 1 : We initially conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines on studies using ketamine to treat harmful alcohol use and withdrawal states in humans given the shared neurophysiologic state underlying BZDR and alcohol withdrawal.

Paper # 2: We then conducted an ambi-directional cohort study where discontinuation of long-term (>6 month) BZDRs was attempted in 22 patients with severe unipolar or bipolar TRD receiving a course of six subanesthetic ketamine infusions over four weeks. We investigated the

rates of successful BZDRs deprescription, trajectories of acute psychological withdrawal symptoms, and subsequent BZDRs abstinence during a mean follow-up of 1 year (primary outcome). Clinically significant deteriorations in depression, anxiety, sleep, and/or suicidality during the acute BZDR discontinuation phase were measured by repeated standardized scales and analyzed by latent growth curve models and percent correct classification analysis.

Results:

Paper # 1: Eight full-text articles investigated the impact of ketamine on alcohol use and withdrawal. Three studies looked specifically at the effect of adding ketamine to conventional treatment of withdrawal symptoms in participants admitted to intensive care units for severe alcohol withdrawal. The studies found that ketamine reduced withdrawal symptoms.
Paper #2: In our cohort study, of the 22 eligible patients, all agreed to enroll. Ninety-one percent (20/22) of participants successfully discontinued all BZDRs by the end of the 4-week ketamine intervention, confirmed by urinary analyses. Less than 25% of discontinuers experienced any significant worsening of anxiety, depression, sleep difficulties, or suicidality during treatment. During follow-up (mean [range] duration, 12 [3–24] months), 64% (14/22) of patients remained abstinent from any BZDRs.

Conclusions:

These results suggest that ketamine infusions may potentially facilitate the treatment of alcohol use disorders and deprescription of BZDRs, even in patients with active treatment resistant depression and significant comorbidity. Further investigation is warranted into this potential novel application of ketamine.

Résumé (en français)

Contexte :

L'alcool et les benzodiazépines / Z-Drug (BZDR) sont des substances entrainant rapidement un état de dépendance, et sont donc difficile à arrêter. L'état neurophysiologique qui sous-tend le syndrome de sevrage des BZDR se superpose de manière significative au sevrage d'alcool et se manifeste classiquement chez les patients qui ont cessé de prendre leurs médicaments dans le cadre d'une utilisation à long terme. Peu d'interventions pharmacologiques ont démontré leur utilité à faciliter l'arrêt des BZDR, et aucune chez des patients souffrant activement d'une dépression résistante au traitement (DRT). Des données précliniques récentes suggèrent que la kétamine, un antagoniste non-compétitifs des récepteurs NMDA dont les bénéfices cliniques ont été rapportés dans le sevrage alcoolique, pourrait être une intervention efficace pour aider à la discontinuation des BZDR. Dans cette thèse, nous présentons deux articles : 1) une revue systématique de l'utilisation de la kétamine dans les troubles liés à la consommation d'alcool et le sevrage chez l'humain et 2) une étude de cohorte sur l'effet thérapeutique potentiel de la kétamine sur l'arrêt du BZDR chez des patients souffrant de DRT.

Méthodes :

Article #1 : Nous avons d'abord procédé à une revue systématique de la littérature, conformément aux directives PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), des études utilisant la kétamine pour traiter la consommation nocive d'alcool et les états de sevrage chez l'humain.

Article #2 : Nous avons ensuite mené une étude de cohorte ambi-directionnelle chez 22 patients souffrant de dépression unipolaires ou bipolaires ayant tenté de discontinuer leur médication BZDRs alors qu'ils recevaient un traitement de six infusionss subanesthésiques de kétamine reçu

sur quatre semaines. Nous avons étudié les taux de déprescription réussie des BZDR, les trajectoires des symptômes psychologiques aigus de sevrage et l'abstinence ultérieure des BZDR au cours d'un suivi moyen d'un an (résultat primaire). Les détériorations de la dépression, de l'anxiété, du sommeil et/ou de la suicidalité pendant la phase aiguë d'arrêt des BZDR ont été mesurées par des échelles standardisées répétées et analysées par des modèles de courbe de croissance latente et une analyse de classification correcte de pourcentage.

Résultats :

Article #1 : 8 articles étudiant l'impact de la kétamine sur la consommation d'alcool et/ou le sevrage ont été identifiés. Trois études ont examiné spécifiquement l'effet de la kétamine sur les symptômes de sevrage alcoolique chez des participants admis en unité de soins intensifs pour un sevrage sévère. Les résultats étaient variables d'un essai à l'autre, mais globalement prometteurs.
Article # 2 : En ce qui concerne les résultats de l'étude de cohorte, sur les 22 patients éligibles, tous se sont inscrits à l'étude et 91% ont réussi à arrêter leur médication BZDR à la fin de l'intervention de 4 semaines avec la kétamine, ce qui a été confirmé par des analyses urinaires. Moins de 25 % des patients ayant discontinué leur traitement ont connu une aggravation significative de l'anxiété, de la dépression, des troubles du sommeil ou de la suicidalité pendant le traitement. Au cours du suivi (durée moyenne [intervalle], 12 [3-24] mois), 64 % des patients sont restés abstinent.

Conclusions :

Ces résultats suggèrent que les infusions de kétamine pour la DRT peuvent faciliter le traitement du trouble d'usage d'alcool et la déprescription des BZDR, même chez des patients présentant des symptômes dépressifs actifs et des comorbidités psychiatriques importantes. Cette nouvelle application potentielle de la kétamine mérite d'être étudiée plus avant.

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Preface & Contribution of Authors:

Nicolas Garel designed the studies, conducted the screening phase of the systematic review, coordinated ethics approval, recruited patients, collected, and analyzed data, was the lead in preparing the two manuscripts included, and formatted the text into a manuscript-based thesis. Kyle Greenway designed the study, coordinated ethics approval, recruited patients, collected, and analyzed data, and reviewed all drafts of manuscripts critically for intellectual content. Christina MaCnaulty conducted the screening phase of the systematic review and reviewed all drafts of manuscripts critically for intellectual content. Dr Paul Lespérance, Dr JP Miron and Dr Gustavo Turecki reviewed all drafts of manuscripts critically for intellectual content. Julien Thibault-Levesque recruited patients and collected data. Dr. Lê-Anh L. Dinh-Williams analyzed data and reviewed all drafts of manuscripts critically for intellectual content. Dr Didier Jutras-Aswad supervised study design and reviewed all drafts of manuscripts critically for intellectual content. Dr Soham Rej supervised study design and reviewed all drafts of manuscripts critically for intellectual content. Dr Stephane Richard-Devantoy supervised study design, research ethics process, and reviewed all drafts of manuscripts critically for intellectual content.

Overview - Overall Rationale and Objectives

Alcohol and benzodiazepine can easily lead to dependence but can be challenging to discontinue [1,2]. Both benzodiazepines and alcohol act in similar ways in the central nervous system, including by the enhancement of the effects of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [2,3]. The neurophysiologic states underlying BZDR withdrawal syndromes overlap significantly with alcohol withdrawal and classically presents in patients who have discontinued their medications or alcohol after long-term use [2,4]. Withdrawal symptoms include physiological reactions of tachycardia, elevated blood pressure, diaphoresis, nausea, vomiting, and diarrhea. Neurological symptoms include paresthesia, visual disturbances and perceptual distortions, cognitive and memory disturbances and, in the most severe cases (sudden discontinuation), seizures, delirium tremens, and death [5,6]. Psychological symptoms include anxiety, agitation, panic attacks, depression, irritability, and insomnia [5,6]. Those symptoms result from a loss of inhibitory effect at the GABAergic level and from glutaminergic overstimulation [5,7]. Drugs that modulate glutamine may thus hold therapeutic potential – indeed, recent clinical evidence in alcohol use disorders and pre-clinical evidence in benzodiazepine dependence suggests that ketamine, a non-competitive inhibitor of the glutaminergic N-methyl-D-aspartate (NMDA) receptors, may hold promise as a novel treatment of these conditions [7,8,9].

In this thesis, we present two papers:

- 1) a systematic review of ketamine for alcohol use disorders and withdrawal in humans and
- 2) A cohort study on the potential therapeutic effect of ketamine on BZDR discontinuation with patient suffering from Treatment Resistant Depression.

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Manuscript 1: Efficacy of ketamine intervention to decrease alcohol use, cravings, and withdrawal symptoms in adults with problematic alcohol use or alcohol use disorder: a systematic review and comprehensive analysis of mechanism of actions.

1. Introduction

Unhealthy alcohol use, encompassing the spectrum of alcohol use resulting in negative health consequences, is extremely common [1,2]. Nearly 30% of adults in the United States use alcohol in an unhealthy manner that requires some form of intervention, 14% meet criteria for current alcohol use disorder (AUD), and 29% meet criteria for AUD in their lifetime [3]. Most people with problematic alcohol use do not have access to treatment, and of those engaged in treatment, a large number do not respond to available medications or behavioral interventions [3,4]. Even with treatment response, estimated long-term relapse rates are between 20% and 80% [5,6]. More effective pharmacotherapy and psychotherapy options, particularly of novel mechanisms, are thus needed [4,7-9]

Chronic and heavy alcohol use has many repercussions on brain homeostasis [10]. Adverse neurobiological adaptations in the context of chronic alcohol use involve many neurotransmitter systems, including glutamate and, notably, the N-methyl-D-aspartate receptors (NMDAR), one of the three types of ionotropic glutamergic receptors of the central nervous system [10,11]. Upregulation and changes in NMDAR function during chronic alcohol exposure are implicated in prefrontal circuit alterations, neurotoxicity, withdrawal, increased reactivity to substance cues, and cravings [12]. Ketamine is a non-competitive inhibitor of NMDAR. In recent years, numerous randomized clinical trials and meta-analyses of ketamine have demonstrated potent antidepressant effects of ketamine even in patients resistant to conventional treatments[13].

Ketamine's effects are thought to be at least partly related to its capacity to normalize cortical glutamate homeostasis and to induce neuroplasticity [13,14], thereby facilitating the learning of new coping mechanisms and behaviors [7]. These effects could prove beneficial in multiple chronic mental health conditions, like substance use disorders, as diminished plasticity and decreased glutamatergic synaptic transmission are thought to play key roles in the genesis and chronicity of these disorders [15].

Indeed, there is recent evidence that ketamine may be an effective intervention in the treatment of certain addictions, like cocaine and opioid use disorders [16]. Emerging data also suggest that ketamine interventions can decrease alcohol use and help control withdrawal symptoms [17,18]. These preliminary findings have generated significant academic and public interest and controversy, driven in part by ketamine's diverse therapeutic applications and its status as a drug of abuse [19]. In order to better characterize the current state of the evidence on the use of ketamine for alcohol use disorder, we undertook a systematic review of this intervention's role in decreasing alcohol use, craving and withdrawal symptoms.

2. Methodology

This systematic review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20]. The systematic review protocol was registered on PROSPERO in August 2021, an international database of systematic reviews (registration #273241).

2.1 Data source and search strategy

The search strategy, created and validated by the research team and an experienced librarian (DZ), was first validated for Medline (Ovid) and adapted subsequently for four other databases (CINAHL Complete [EBSCOhost], PsycINFO [Ovid], EBM Reviews [Ovid] and EMBASE [Ovid]). For completion, a search on Google Scholar was additionally performed. The search strategies were peer reviewed by another senior information specialist prior to execution using the Peer Review of Electronic Search Strategies (PRESS) Checklist [21]. Reference lists of included articles were manually screened to identify additional studies. The comprehensive literature search was initially conducted on 25 August 2021 and is reported in the Electronic Supplementary Material in the Appendix.

2.2 Eligibility criteria

The Population, Intervention, Comparator, Outcome, and Time (PICOT) approach was used to determined eligibility criteria. Studies were included in this review if they 1) were written in English, French, or Spanish languages; 2) were empirical studies of any methodology (e.g., experimental, observational, etc.) published in peer-reviewed journals; 3) were conducted with or without control groups; 4) tested ketamine administration (single or multiple dosing) with or without the combination of psychotherapeutic or other pharmacological interventions; 5) reported one or more of the main outcomes – alcohol use outcomes (i.e. quantity, frequency, relapse, abstinence), craving (cue-induced or not), and/or withdrawal (i.e. withdrawal symptoms, severity, benzodiazepine requirements to control symptoms); and 6) tested these outcomes in a population of adult males and females (aged 18 years and older) with AUD, hazardous alcohol use, heavy drinking, or alcohol withdrawal syndromes.

2.3 Article selection

Records were screened for eligibility based on titles and abstracts by two researchers (NG and CM). To increase the reliability of the screening process, a coding manual for exclusion reasons was used (Appendix 2). The coding manual was pilot tested by NG and CM using 100 references to clarify the criteria and standardize coding. Each researcher then independently coded in Excel the entire set of references. Results were then compared, disagreements were mediated, and the final decisions were reached for phase two inclusion. In phase two, full-text articles were read independently by the same two researchers (NG and CM) and assessed based on the eligibility criteria using a second coding manual (Appendix 3). Reasons for exclusion were carefully documented to include details about the reason. Disagreements were resolved by a senior researcher (DJA). In cases of ambiguous information in manuscripts, study authors were contacted.

2.4 Data extraction and analysis

A list of variables of interest, including the main outcomes of interest, was determined and validated *a priori* by the research team during the study protocol phase. Data extraction was performed by NG and CM from included studies. Study authors were contacted to clarify key information. Data for variables of interest were extracted into standardized tables, and disagreements were resolved through discussions which included the senior researcher. The extracted data corresponded to one of four categories: 1) study characteristics; 2) primary outcomes (i.e., alcohol use, cravings, withdrawal symptoms); 3) secondary outcomes; and 4) risk of bias. A narrative synthesis method was then used for data analysis.

2.4.1 Study characteristics

Study characteristic variables included descriptive information, such as trial design, sample characteristics, and funding sources. Data pertaining to sample sizes, gender, and dropout rates were also included. Additionally, we extracted descriptive information about the intervention and comparison conditions when present.

2.4.2 Main outcomes and related outcomes

Our main outcomes of interest were alcohol use, craving, and withdrawal symptom severity. We defined alcohol use outcomes as those assessing quantity and frequency of alcohol use, abstinence rates, and relapse rates. Alcohol craving outcomes included both standard and cue-induced craving measures. Withdrawal outcomes were defined as those relating to withdrawal symptoms/severity or quantities of benzodiazepine required for withdrawal management.

When available, we extracted related outcomes that provided additional information about the benefits and harms of ketamine interventions, such as psychiatric clinical outcomes (e.g., anxiodepressive symptoms), motivation to reduce alcohol consumption, functioning, quality of life and well-being, length of intensive care unit (ICU) stay, vital signs, tolerability, safety and adverse events (e.g., hemodynamic changes, neuropsychiatric and physical symptoms, etc.), and relevant biomarkers.

2.4.3 Risk of bias assessment

For all included studies, we assessed the risk of bias using specific critical appraisal tools: the Risk Of Bias In Non-randomized Studies (ROBINS-1) tool [22] for non-randomized trials and the Cochrane Collaboration's tool 2.0 (RoB-2) for randomized controlled trials (RCT) [23] . We contacted study authors to obtain further information when details were lacking. We considered

incomplete data for all outcomes. Disagreements between the two researchers were mediated by a senior researcher (DJA).

3. Results

3.1 Search results

A total of 1922 citations were retrieved from the six databases after duplication removal in EndNote, performed by the librarian (DZ), using the method of W. Bramer [24]. After the first screening phase, 1900 studies were excluded, and full-text review was carried-out for 22 studies. Eight of these studies were included, as demonstrated by the PRISMA flow chart (Figure 1).

3.2 Study characteristics

The characteristics of the eight studies included in this review are detailed in Table 1. Four of these studies were undertaken in the United States [25-28], one in the United Kingdom [18], two in Russia [29,30], and one in France [31]. Three studies utilized a RCT design [18,28,30] and three studies employed a cohort design [26,27,29], two of which included control groups [26,29]. The other two studies were a retrospective case series [31] and a small open-label pilot study [25], both without control groups. Study duration ranged from 1 day to 3 years follow-up.

Three studies examined the addition of ketamine administrations to the usual management of withdrawal symptoms in patients admitted to the ICU for severe alcohol withdrawal (SAW) [26,27,31]. The other five studies investigated the impact of ketamine on alcohol use and/or cravings and/or withdrawal in outpatient settings [18,25,28-30]. Ketamine administration protocols varied significantly across the five studies. Given this heterogeneity, each study's

ketamine treatment paradigm and therapeutic model (psychedelic-assisted-psychotherapy, control of withdrawal symptoms, normalization of neural deficits, etc.) are detailed in Table 1.

Sample sizes varied between n=5 and n=211 participants, with a total sample size of n=634 unique participants for all eight trials. Participants' mean age was 38 years across the eight studies. One hundred two (16%) participants were admitted to the ICU for SAW, 442 (70%) participants were treatment-seeking AUD patients, and 90 (14%) of participants were not treatment-seeking hazardous/harmful drinkers. The one study of hazardous/harmful drinkers (without a formal diagnosis of alcohol use disorder) reported very high mean scores on the Alcohol Use Disorders Identification Test (AUDIT) in their sample, including on heaviness and frequency of drinking and bingeing, injuries, guilt, and blackout items [18]. Average alcohol consumption in this study sample – equivalent to 5.9 US standard drinks and 5.6 drinking days in the week preceding enrolment – was similar to the AUD population of the only other study reporting daily alcohol consumption prior to ketamine treatment [28]. Given these similarities, and the lack of clear cut-offs between this study's definition of at-risk drinkers and AUD, we discussed these two populations as one.

The funding sources were public/governmental agencies or unknown. Statistical analysis ranged from simple descriptive statistics to more complex linear mixed models.

3.3 Primary outcomes

Of the eight studies included in this review, four studies assessed alcohol use outcomes, three studies assessed craving outcomes, and four studies assessed withdrawal outcomes. Within each primary outcome categories, results in the text and tables were organized by study design.

Principal measures of interest for the main outcomes varied significantly amongst the studies. Specific results are detailed in Table 2.

3.3.1 Alcohol use

Alcohol use outcomes were assessed by reported quantities of alcohol consumption, frequency of drinking days and heavy drinking days, and rates of abstinence/relapse in variable follow-up periods from 10 days to 3 years. Quantity, frequency, abstinence, and relapses of alcohol use were assessed using the timeline follow back method (TLFB) in two studies [18,28] and by monthly structured clinical evaluations in two studies [29,30].

3.3.1.1 Randomized-controlled trials

In one of the three RCT assessing alcohol use outcomes, 40 treatment-seeking adults with alcohol dependence were randomly assigned to receive one intravenous (IV) infusion of ketamine (0.71 mg/kg) or an active control (midazolam infusion) in the second week of a 5-week outpatient program of motivational enhancement therapy (MET) [28]. The study reported a significant difference between groups in proportion of abstinence, proportion of heavy drinking days, and time to relapse, all favoring the ketamine group compared to the control group during a 21-day follow-up period. No group differences were found for the time to first use or time to first heavy drinking day during the same follow-up period. A major difference in group abstinence was maintained at 6 months, though there was a significant level of attrition (52.5%).

In the second RCT, a single ketamine infusion was combined with a procedure designed to destabilize Maladaptive Reward Memories (MRMs), which are thought to be involved in the

maintenance of substance use disorders [18]. Ninety participants were randomized to one of three groups, and the trial was designed to assess the specific effects of ketamine on memory retrieval. Ketamine (or placebo) was administered on the third day of the study targeting a plasma concentration of 350 ng/ml for 30 min. Linear mixed models on TLFB-rated number of drinking days/week found a significant reduction in the intervention group receiving ketamine infusion after retrieval of alcohol-MRMs versus the control groups at 10 days. The intervention group also showed a highly significant reduction of 23.5 UK units/week in general alcohol consumption from baseline to post-manipulation. A significant reduction was also seen in the group receiving ketamine without alcohol-MRMs (13.6 UK units/week) but not in the group receiving placebo infusion. Only the ketamine + alcohol-MRMs group reported significantly fewer weekly binges. After the first phase of the study, reversion to heavy drinking was assessed by comparing drinking across a follow-up period of 9 months, which revealed reductions in weekly alcohol consumption in all three groups, with no group differences.

The third study, completed in Russia in 1992, evaluated the combination of ketamine with psychedelic and aversive therapy approaches ("the Affective Contra Attribution Method"), with the aim of creating links between alcoholism and its negative life consequences [30]. The participants were randomized to either ketamine (86 participants) or treatment-as-usual (100 participants). The participants randomized to ketamine received a single intramuscular administration of ketamine (3 mg/kg) in combination with bemegride and aethimizol. The anxiogenic properties of bemegride were thought to increase the negative emotional valence of the hallucinatory experience induced by ketamine, and aethimizol was thought to promote the integration of this experience in long-term memory. At the peak of hallucinatory experience,

participants smelled and tasted alcohol while interacting with the therapist, creating associations between the challenging hallucinatory experiences and alcohol use. The dosing session was followed by group therapy to facilitate the integration of the experiences. Seventy percent of participants in the ketamine group remained abstinent compared to 24% in the control group at 1 year follow-up.

3.3.1.2 Prospective cohort study

The fourth study evaluating the impact of ketamine on alcohol use outcomes was a prospective cohort study by the same Russian group from 1997 [29]. Following a 3-month inpatient detoxification, 211 treatment-seeking adults with alcohol dependence were assigned to receive one intramuscular administration of ketamine (2.5 mg/kg) associated with existential psychotherapy or to conventional psychotherapy without ketamine. The study found significantly more patients reporting abstinence at 1 year in the ketamine versus the control group: 66% versus 24%. Only the ketamine group was followed up to 2- and 3-years post-intervention with reported abstinence in 33 of 81 patients (41%) and in 14 out of 42 patients (33%) at 2 and 3 years, respectively. Though conclusions are limited by the lack of a control group, the authors argue that these rates of remission are higher than those seen with standard treatments.

3.3.2 Craving

Craving outcomes were assessed in three studies by different measures, including the Obsessive and Compulsive Drinking Scale (OCDS) [18,25], the Craving and Arousal visual analog scale [28], the Alcohol Craving Questionnaire (ACQ-NOW) [18], and different self-constructed Likert rating scales [18].

3.3.2.1 Randomized-controlled trials

In the trial assessing ketamine's impact in conjunction with memory retrieval destabilization/reconsolidation, participants were asked to rate their cravings in a complex method at the beginning and at the end of the active phase of the study [18]. Baseline and post-manipulation (i.e., Day 1 and Day 10) cravings were assessed by asking participants to rate the effects of having a beer placed in front of them on a scale of -5 (greatly reduces urge) to +5 (greatly increases urge). After then consuming the beer, participants rated their post-consumption urges to consume more alcohol using the same scale. Three other craving measures were collected on Day 1 and Day 10: the ACQ-NOW, the OCDS, and a single-item Likert scale examining participants' "urge to drink" relative to before the intervention day (-2 = much less, 0 = about the same, +2 = much more). The group receiving ketamine after alcohol-MRMs showed significantly reduced cue-induced urges to drink the beer provided and subsequent urges to drink more alcohol, compared to the two control groups. Changes in subjective impressions of cravings showed significant group effects, driven by reductions in the group receiving ketamine after alcohol-MRMs. No group differences were found on the OCDS, and the results of the ACQ-NOW were not reported in the article nor in the supplementary documents.

No effect on cravings was found in the RCT of Dakwar and colleagues, which reported no significant group differences on the Craving and Arousal visual analog scale [28].

3.2.2.1 Single-group cohort study

An 8-week open-label study of five patients with concurrent major depressive disorder and AUD evaluated the effects of four weekly ketamine administrations (0.5 mg/kg) in conjunction with

injectable naltrexone [25]. Eighty percent (4 of 5) of patients reported improvements in alcohol cravings and consumption, as measured by the OCDS at the end of the study.

3.3.3 Withdrawal

Withdrawal outcomes were assessed in four studies: three retrospective studies conducted in ICU settings with a combined sample of 103 patients suffering from delirium tremens (DT) [26,27,31], as well as in the RCT study combining MET and ketamine in AUD outpatients [28]. Withdrawal outcomes measures included detailed case descriptions of agitation reported by intensivists [31], withdrawal symptom severity assessed by the risk of intubation [26] or by the Clinical Institute Withdrawal Assessment (CIWA) tool [26-28], and the time to achieve withdrawal symptom control after ketamine initiation as measured by the CIWA-Ar or by the Motor Activity Assessment Scale (MAAS) in intubated patients [27]. Mean doses of benzodiazepines required to control withdrawal symptomatology were also reported in two studies [26,27].

3.3.3.1 Randomized-controlled trial

The only RCT reporting withdrawal outcomes, the study of Dakwar and colleagues, was conducted in an outpatient setting with alcohol-dependent patients free from SAW symptoms. No significant group differences were observed using the CIWA [28].

3.3.3.2 Retrospective cohort studies

Pizon and colleagues conducted a retrospective cohort study including 63 patients admitted to the University of Pittsburgh Medical Center ICU before and after ICU treatment guidelines

changed to incorporate ketamine for DT [26]. The pre-guidelines group (January 2008 to March 2011) were treated in a symptom-triggered fashion with benzodiazepines and/or phenobarbital. The post-guideline group (April 2011 to January 2015) received IV ketamine from admission until delirium resolution, in addition to the same symptom-triggered management.. The authors found that the ketamine group had a lower probability of intubation (odds ratio, 0.14; $p < 0.01$; 95% CI, 0.04– 0.49). They also reported that ketamine patients were administered significantly less benzodiazepines relative to the control group by 1016.6 mg of diazepam equivalents,

In the same year, another group reported the SAW symptom control and lorazepam requirements of a retrospective cohort of 30 patients admitted to the ICU receiving adjunctive continuous ketamine infusions (initial dose of 0.5 mg/ kg/h; maximum dose of 4.5 mg/kg/h; maximum average daily dose of 1.6 mg/kg/h). Before ketamine initiation, patients received symptom-triggered boluses of lorazepam and phenobarbital, and eventually a lorazepam infusion if the bolus regimen proved inadequate for controlling symptoms. Symptom control was assessed with the CIWA-Ar or, for the 22 intubated patients (73% of the cohort), the MAAS. All patients achieved symptom control within 1 hour of ketamine initiation. Numeric decreases in lorazepam infusion rates from baseline were observed 1 hour after initiation of ketamine and became statistically significant at 24 hours (−4 mg/h; $p = 0.01$).

3.3.3.3 Case series

The first study using ketamine in alcohol withdrawal was a case series in 1972 of nine patients whose delirium agitation was successfully controlled within minutes of a flexible regimen of intramuscular and IV ketamine added to conventional treatment [31].

3.3 Secondary outcomes

Secondary outcomes varied significantly between studies, yielding 16 different measures within three broad categories: Psychiatric and psychological outcomes, length of ICU and hospital stays, and adverse and common side effects. Result descriptions are summarized in Table 3 and described below in these three domains.

3.3.1 Psychiatric and psychological outcomes

Mood outcomes and various measures of cognition, behavior, psychological traits/states, and attitudes related to substance use disorder were assessed with multiple scales, detailed in Table 3.

In the small open-label study evaluating naltrexone and ketamine in five patients suffering from comorbid major depressive episode and AUD, 100% of the participants experienced an antidepressant response (defined by a 50% reduction scores at 4 hours post-infusion on the Montgomery-Åsberg Depression Rating Scale (MADRS)) by the fourth infusion [25]. Krupitsky and Grizenko also observed a significant pre-post decrease in the depression subscale of the Minnesota Multiphasic Personality Inventory (MMPI) for the participants treated with the combination of ketamine and existential psychotherapy [29]. A significant decrease in hypochondria, anxiety, hysteria, psychasthenia, schizophrenia sensitivity, and repression subscales of the MMPI were also found, while a significant increase in the ego-strength subscale was reported [29].

For the other psychiatric and psychological secondary outcomes/scales, the interaction of time by treatment group was not significant in any of the statistical models [18,28].

3.3.2 Length of ICU and hospital stay

In the only controlled ICU study, the post-guideline group treated with ketamine showed a significant decrease in ICU length of stay and trended towards decreased hospitalization length compared to the pre-guidelines group [26]. Another study specifically examining this outcome lacked a control group, which prevented comparisons [27].

3.3.3 Adverse and common side effects

Adverse and common side effects were retrieved from medical charts, prospectively self-reported or recorded by the research team using the Clinician Administered Dissociative States Scale (CADSS). In all eight studies, the interventions were globally well tolerated. No serious or persistent adverse events were reported. Transient hypertension and tachycardia occurred in a minority of patients [27,31]. No emergent neuropsychiatric symptoms, except dissociative symptoms, developed in any patients even in the setting of ketamine doses up to 4.5 mg/kg/h. In the two RCTs that measured dissociative symptoms using the CADSS, a significant difference between the ketamine and placebo groups was observed with higher scores in the ketamine groups [18,28].

3.4 Risk of bias assessment

Risk of bias assessments are summarized in Figure 2.1 for RCT studies and in Figure 2.2 for non-RCT studies. Each primary outcome measure was assessed independently. The overall risk

of bias was considered high or critical across all outcomes in the three RCTs, except for the primary outcome (abstinence) in the study by Dakwar and colleagues, whose risk was rated at "some concerns." Regarding the included RCTs, the domains that were at the highest risk of bias were missing outcome data and measurement of the outcomes, mainly related to the potential of unblinding due to the psychoactive effects of ketamine. The overall risk of bias was also considered high or critical across all non-RCT studies. The risk assessment of non-RCTs was adapted according to study design.

4. Discussion

4.1 Overview of findings and study methodologies

This systematic review examined evidence on ketamine interventions to decrease alcohol use, craving, and withdrawal symptoms in adults with problematic alcohol use or AUD. Eight studies met the inclusion criteria and assessed at least one of our primary outcomes of interest. Results were mixed within and across trials, especially for craving; alcohol use and withdrawal severity outcomes were more consistent, but the latter suffered from more methodological flaws. A specific and thorough assessment of outcomes found the studies to be at high or critical risk of bias. Despite the limited evidence, methodological flaws, heterogenous administration routes and doses, small sample sizes, and variable outcome criteria, the available studies provide key preliminary findings to guide future research efforts.

4.2 State of the evidence, critiques, and potential mechanism of actions

The current state of evidence prohibits any definitive conclusions about the efficacy of ketamine in alcohol use and withdrawal, though various forms of ketamine interventions appear to be

generally safe. The study results presented in this review require sound replication with well-designed and larger clinical trials.

4.2.1 Alcohol use and cravings

The four studies that examined alcohol consumption, including the three RCTs with the most rigorous trial designs, reported positive impacts of ketamine on drinking quantity, frequency, and/or periods of sobriety. Interestingly, the four studies administered ketamine in very different models of care and contexts, corresponding to different but interrelated views of the potential mechanisms of action of ketamine in substance use disorder (SUD).

According to different pre-clinical and human studies that examined the effect of ketamine in SUD, experts have argued that ketamine may block reconsolidation of drug-related memories [32,33], provoke peak or mystical-type experiences that enhance psychotherapeutic process and lead to profound perspective shifts [34-36], offer antidepressive effects (potentially beneficial given the high comorbidity of depression and SUD) [7] [13], and/or increase neuroplasticity/neurogenesis thus facilitating learning [14,37,38]. Enhanced learning is proposed to reverse drug-related neural adaptations, accelerate the benefits of psychotherapy, and generally facilitate the acquisition of new adaptative behaviors.

This latter hypothesis underpinned Dakwar and colleagues' method of administration, which combined ketamine with a psychotherapeutic intervention (MET) in patients suffering from alcohol dependence. The treatment rationale was based on the hypothesis that the behavioral-psychological intervention would act synergistically to consolidate the transient motivational and

neuroplastic benefits of ketamine into more sustained change, as supported by the promising results the authors have observed previously with ketamine in cocaine use disorder [38]. Indeed, this study found a lower likelihood of all alcohol use and of heavy alcohol use and a longer time to relapse over the study period with the addition of a single ketamine infusion to MET. A strength of this study is the use of an active placebo (midazolam) to reduce the functional unblinding associated with ketamine's psychoactive effects. However, the significant difference in CADSS group scores highlight how midazolam is an imperfect comparator, and thus the ketamine group may have experienced increased placebo responses and/or measurement biases. A potentially related source of bias is that while completion rates were 100% in the ketamine arm of this study, more than 25% of participants in the control condition dropped out. Furthermore, the sample of the study was small, homogeneous and free of other psychiatric/addictive comorbidities, significantly affecting external validity. It is worth mentioning that Dakwar and colleagues demonstrated in a recent article that the improvements in drinking behaviors were mediated by the mystical-type psychoactive effects of ketamine [39], rather than other perceptual effects such as dissociation. This finding is in line with the therapeutic framework of the previous "psychedelic" investigations by Krupitsky and colleagues in the late 1990's [34-36].

The psychedelic model emphasizes the importance of the subjective ketamine experiences, in line with the early research of the 1960's using psychoactive drugs like LSD and psilocybin to treat alcoholism [40] In this framework, the experiences generated by ketamine are posited to increase awareness of unconscious processes that sustain addiction, produce aversions to alcohol, enhance self-compassion, generate insight-bestowing "breakthrough" realizations, modify worldviews, and/or increase feelings of "connectedness" with self and beyond – all of which

may enhance chances of overcoming addiction [29,34,35,41]. Psychedelic treatment protocols embed the drug experiences in psychotherapy, being preceded by preparatory and followed by integrative sessions [42]. Krupitsky and colleagues reported that this approach yields clear benefits: in the first study, 24% of the control group remained abstinent after 1 year versus 70% of the group receiving the combination of ketamine with psychedelic and aversive approaches. Similarly, in the second study 24% of the control group remained abstinent after 1 year versus 66% of the ketamine psychedelic existential therapy group. While impressive at first glance, the studies lacked important components of modern pharmacological trials such as participant/researcher blinding and rigorously randomized allocation to study groups. Bias arising from group allocation by physician or patient choice precludes the drawing of any firm conclusions. Furthermore, important differences in the treatment and comparison interventions make it impossible to disentangle the contribution of ketamine to the observed outcomes.

Another potentially beneficial effect of ketamine in SUD is its posited capacity to rewire memories under certain conditions [43]. Meta-analytic evidence from pre-clinical studies suggest that NMDAR antagonism can alter memory reconsolidation, the process by which existing memories are stored again after activation [33]. Activated memories are susceptible to modification and re-organization, and several lines of evidence have suggested that ketamine (likely through its synaptogenetic effects) can enhance the encoding of changes during reconsolidation processes. For example, ketamine has been shown to accelerate the post-retrieval extinction of traumatic memories in patients suffering from post-traumatic stress disorder [44]. In addictions, ketamine may similarly disrupt maladaptive drug and alcohol reward memories,

reducing reactivity to drug cues and thereby reducing cravings [45-47]. The weakening of such "relapsogenic memories" may therefore reduce the risk of relapse.

This theoretical framework led Das and colleagues to generate a complex retrieval task involving activation of maladaptive alcohol memories (or neutral memories) before administering a ketamine infusion (or a placebo infusion), as described in the results section. They found that the intervention group, who received a ketamine infusion immediately after undergoing a task designed to retrieve alcohol memories, had less alcohol consumption and drinking days compared to controls who received only ketamine or the alcohol memory retrieval. Ketamine without the alcohol-retrieval task produced a reduction in alcohol consumption to a lesser degree, which the study authors interpret as confirming synergistic benefits of the study's two components. Of note, baseline alcohol consumption was higher in the intervention group than the two control groups, which raises the possibility of regression to the mean as contributing to the intervention's greater decrease in alcohol consumption observed in that group.

Though promising, the intervention group only showed significant reductions in the self-constructed Likert craving scales, and no group differences were seen on the OCDS, a more conventional and psychometrically validated scale of cravings [48]. In addition, no information was provided on another more standard measure of cravings, the ACQ-NOW, despite the total scores being referenced in the pharmacokinetic model results. This raises concerns of another negative association and, accordingly, a reporting bias. Finally, as for the studies described above, the nature of the ketamine-induced dissociative state raises important methodological questions. All 60 participants in the ketamine group correctly guessed their group randomization,

undermining blinding and potentially leading to important measurement biases. Indeed, de-blinding generated by ketamine's psychoactive effect and potential high levels of response expectancy are a source of major concern in ketamine studies, described by experts as a source of intervention effect over-estimation [49].

Craving was also examined by Yoon and colleagues, who found a reduction in the OCDS, but this cannot be interpreted and separated from the antidepressant effects of ketamine or the effects of the co-administered naltrexone.

4.2.2 Withdrawal

Alcohol withdrawal largely results from decreased inhibitory GABAergic effects and from glutaminergic overstimulation by NMDAR upregulation [50]. Benzodiazepines are the mainstay treatments of alcohol withdrawal but, given the modifications in glutaminergic transmission, antagonizing NMDAR with a molecule like ketamine is a plausible intervention [50]. In animal models, consumption of alcohol during withdrawal states results in operant conditioning (negative reinforcement) of AUD via reduction of withdrawal discomfort, increasing the chance of compulsive alcohol seeking behaviors and relapse when withdrawal symptoms are experienced [51]. Ketamine could thus help to decrease this risk by decreasing withdrawal symptoms. The first-ever reported use of ketamine in alcohol withdrawal was the 1972 case series by Condi and colleagues. The next scientific publication on ketamine in alcoholic withdrawal appeared 43 years later when Wong and colleagues reported positive effects of ketamine in 23 patients admitted to the ICU for DT [17]. This study was not included in the review because the data reported in the article were incorporated 3 years later in the larger study

conducted by Pizon and colleagues [26]. The three reviewed studies in SAW demonstrated that ketamine can potentially reduce withdrawal severity and decrease the lorazepam needed to control withdrawal symptoms. However, the retrospective nature of those studies, the small sample sizes, the lack of rigorous confounding analysis, and the fact that ketamine was given and initiated at the discretion of the medical team (with heterogenous dosing, timing, and variable use of adjunctive medications) undermine the confidence in these results. Furthermore, the decreased benzodiazepine requirements in the uncontrolled study by Shah and colleagues and the rapid control of the symptoms in the study by Condi and colleagues are difficult to discriminate from the effects of the other pharmacological agents and/or the natural course of the withdrawal state, knowing by example that the mean time to initiation of ketamine relative to lorazepam treatment was 41.4 hours in the study of Shah et al. The only study on SAW with a control group did not match participants according to withdrawal severity. Another critical aspect of these retrospective observational studies is that data were collected over long timeframes (up to 7 years [26]), which may have introduce multiple confounding variables, such as evolution in medical practices (outside the variable use of adjunctive medications). Furthermore, in using clinician-rated scales to evaluate withdrawal severity, which in turns was determining the initiation of ketamine treatment, differences in scoring by different practitioners overtime could have introduced a lot of measurement errors.

The only study reporting withdrawal outcome In patients who were not admitted to the ICU due to withdrawal severity found negative results. All the studies were determined to be at critical risk of bias.

4.2.3 Safety data and related outcomes

Very few of the safety outcomes differed between the ketamine and non-ketamine study groups. Notable safety concerns regarding ketamine at lower doses are categorized as cardiovascular and respiratory effects, central nervous system reactions (emergent reaction such as confusion, delirium, dreamlike/dissociative states, excitement, agitation, hallucinations, vivid imagery), genitourinary symptoms, and abuse liability [13] . In all eight studies, no serious or persistent adverse events were reported. A significant difference was seen in the level of dissociation in patients receiving ketamine, which subsided rapidly. As three studies employed a single ketamine administration and three studies were conducted in severely ill patients unable to withdraw from the intervention, limited information is available on the tolerability of repeated dosing. The small sample size of the studies also limits any conclusions about the risk of adverse effects that may be serious but less frequent.

Concerning the studies done in ICU, the adverse effects of ketamine (including central nervous system effects) were documented by nursing staff during the intervention and may not have been differentiable from alcohol withdrawal symptoms or other medication effects. All patients were treated concurrently with high doses of benzodiazepines, which are known to mitigate the emergent reactions caused by ketamine [52,53].

The five prospective studies did not report any iatrogenic ketamine misuse, a significant concern for this intervention in this clinical population. Additionally, the abundant literature from more than 20 years of study of ketamine in treatment-resistant depression is generally reassuring – no new onset of drug or alcohol misuse has been reported – but patients with a history of SUD were generally excluded from these studies [13]. Nevertheless, ketamine acts on the opioid system and has clear psychological addictive properties [54-56]. There is thus a need to carefully select,

accompany, monitor, and support patients in ketamine interventions against addiction to avoid iatrogenic harms, particularly in outpatient and repeated-dosing contexts [28,45].

4.3 Putative mechanisms of action

As described above, numerous possible mechanisms of action for ketamine against problematic alcohol use have been raised in the eight included articles. These include pharmacological effects that reduce withdrawal symptoms (which may reduce the drive to consume alcohol to mitigate the associated distress and discomfort), neural effects that encompass rewiring of maladaptive memories (which may diminish pathological reward memories and decrease the risk of craving and relapse) and increased neuroplasticity (which may create a critical window of enhanced learning capacity), antidepressive effects (which may decrease the use of alcohol as self-medication for anxiodepressive symptoms), and psychedelic mechanisms that lead to enhanced insight and motivation (which may increase capacities to alter maladaptive behaviours). An additional possible mechanism of ketamine is its capacity to improve executive cognitive functions such as decision making and planning. These effects could all theoretically facilitate psychotherapeutic progress and potentially interact synergistically.

4.4 Review strengths and limitations

This review is the first systematic assessment of the efficacy of ketamine in AUD and withdrawal. This review used a well-defined protocol and rigorous methodology with multiple sources of information including direct communication with more than half of the included study authors. The main strength is that the reported outcomes were each rigorously evaluated using validated bias tools, adding nuance to the interpretation of the results. In terms of limitations, this

review only assessed articles written in French, English or Spanish, potentially missing studies published, for example, in Russia where pioneering work has been performed. The inclusion of several types of outcomes and study designs complicated the narrative synthesis and resulted in the evaluation of several related but distinct clinical entities. The withdrawal studies included were more consistent with the anesthesiology literature and used much larger doses of ketamine than those used in addictions, decreasing the relevance for more common and prevalent mild to moderate withdrawal syndromes. The outcome heterogeneity also precluded meta-analysis, decreasing the strength of the findings.

5. Conclusion

In conclusion, various ketamine interventions appear to be safe and possibly effective for alcohol consumption, cravings, and withdrawal. However, our systematic review demonstrates that despite significant media coverage and excitement in the general and scientific community about ketamine for such alcohol related conditions, the current evidence is limited. Significant research is ongoing – indeed, a recent RCT assessing the efficacy and safety of ketamine in increasing abstinence in AUD was published after our literature search [57], and at least 3 clinical trials assessing ketamine in alcohol disorders in the USA are currently recruiting (NCT02461927; NCT04084860; NCT04562779).

Given the current scientific excitement for ketamine treatments outside of anesthesiology, including in SUD, it is imperative that research and RCTs replicate and expand the current findings, while informing on the possible underlying mechanisms of action. Many questions remained that could be answered by future trials of higher methodological quality. Future studies

should investigate the acute and lasting effects of ketamine, psychotherapeutic interventions, and their intersection. Designs that include multiple arms with varied protocols of ketamine administration and psychotherapy sessions would help elucidate their relative contributions. Longer-term follow-up may identify important inflection points that may guide clinicians in determining optimal lengths of treatment. Functional imaging and neuropsychological assessments could clarify hypothesized therapeutic mechanisms of ketamine-psychotherapy combinations such as improved cognitive abilities and enhanced learning. Lastly, the use of active comparators and the routine assessment of unblinding and expectancy are important steps towards addressing concerns about potential inflated effect sizes seen in ketamine trials. Those type of studies will help determine if ketamine is indeed an effective treatment of AUD and, if so, in which intervention protocol

Tables and figures Manuscript 1.

Table 1. Study characteristics evaluating ketamine interventions for alcohol use disorders and severe withdrawal syndromes organized by study design

Authors, year (country) & Study design	Diagnosis/ population (mean age)	Sample size (% male)	Ketamine utilization / therapeutic model	Duration	Intervention (N)	Control (N)	Dropouts (N)	Statistical analysis	Funding sources
Dakwar et al., 2020 (USA) **Double-blind RCT**	Treatment-seeking alcohol dependent patients (DSM-IV criteria) with ≥ daily use and ≥ 4 heavy drinking days/week or 35 drinks/week (men) and 28 drinks/week (women) (53,0 y.o.)	40 (48%)	Combined ketamine and mindfulness psychotherapy intervention to prevent relapse	5 weeks psychotherapy (ketamine infusion on week 2) and 6 months of follow-up post-intervention	5 weeks of MET + IV ketamine infusion (0.71 mg/kg) (N=17)	5 weeks of MET + IV midazolam (0,025 mg/kg) (N=23)	Intervention = 0 Control = 6	Longitudinal logistic mixed-effects model with a logit link and a random intercept	NIDA
Das et al., 2019 (UK) **Single-blind RCT**	Non treatment-seeking volunteers with hazardous/harmful drinking patterns (AUDIT score > 8 and: not meeting	90 (61%)	Combined ketamine-behavioural intervention to disrupt memory consolidation (Reorganization of synaptic architecture of maladaptive long-term memories)	10 days (experimental manipulation on day 3) and 9 months of follow-up (2 weeks, 3, 6, and 9 months) post-manipulation	Ketamine infusion (targeting blood concentration of 350 ng/ml for 30 min) +retrieval of alcohol-MRMs (RET + KET) (N= 30)	Two control conditions: (1) ketamine infusion (targeting blood concentration of 350 ng/ml for 30 min) + No retrieval of alcohol-MRMs (No-	None during the 10 day-testing protocols Attrition during remote 9-month follow-up: RET + KET = 13; No-RET + KET = 11;	Mixed-Anova 2x3 (time x group); linear mixed models for long-term follow-up	MRC

	SCID criteria for AUD, consuming > 40 (men) or > 30 (women) UK units/week, drinking ≥ 4 days/week, or drinking >3 units on drinking days) (27,5 y.o)					RET + KET) (N=30) (2) IV saline solution (placebo) + retrieval of alcohol-MRMs (RET + PBO) (N=30)	Ret + PBO = 10; (total = 34)		
Krupisky et al., 1992 (Russia) **RCT**	Treatment-seeking alcohol dependent patients who failed to maintain sobriety during a 3-months follow-up in OPD (36.1 y.o)	186 (100%)	Psychedelic-assisted psychotherapy	One-year follow-up	Psychedelic and aversive therapy + single dose of IM ketamine (3,0 mg/Kg) with IM aethimizol (3 ml 1,5%) and IV bemegride (10 ml 0,5%)	Treatment as usual (Aversive emetic therapy, pharmacological treatment of craving, and individual and group therapy)	Intervention = 2	Descriptive statistics	Unknown

Krupitsky and Grizenko, 1997 (Russia) **Prospective cohort study**	Treatment-seeking alcohol dependent patients (37.4 y.o)	211 (100%)	Psychedelic assisted psychotherapy	One-year follow-up with control group 3 years follow-up without control group	3-month inpatient detoxification + single dose of IM ketamine (2.5 mg/Kg) and existential psychotherapy (N=111)	3-month inpatient detoxification and conventional psychotherapy (N=100)	Intervention = 8 Control = 7 at one-year	Descriptive statistics T-tests for demographic differences	Unknown
Pizon et al., 2018 (USA) **Retrospective cohort study**	Patients admitted to ICU diagnosed with Delirium Tremens by DSM-*V* criteria (49,9 y.o)	63 (81%)	Biomedical intervention to decrease withdrawal symptoms and benzodiazepine requirements	From admission to hospital discharge	Symptom-triggered treatment (i.e., control group) + IV ketamine infusion (0.15–0.3 mg/kg/hr) until delirium resolution (N=34)	Symptom-triggered treatment with BZD and/or phenobarbital until delirium resolution (N=29)	Nil	Multivariable linear regression analysis for the outcomes of ICU days and hospital days; Multivariable logistic regression for intubation; Student t tests for benzodiazepine requirements	None
Shah et al., 2018 (USA) **Retrospective cohort study**	Patients admitted to ICU for SAW despite continuous infusion of	30 (82%)	Biomedical intervention to decrease withdrawal symptoms and benzodiazepine requirements	1, 4, 8, 24, and 48 hours post-ketamine initiation	IV ketamine infusion (0.5 mg/kg/h to maximum of 4.5 mg/kg/h) added to a continuous infusion of	No control	Nil	Descriptive statistics; Student t tests for BZD requirement	None

	lorazepam (45,6 y.o.)				lorazepam +/- lorazepam bolus (N = 30)				
Yoon et al., 2019 (USA) **Open-label trial**	Outpatients with comorbid depression and AUD (49,2 y.o.)	5 (80%)	Biomedical intervention to treat depressive state in comorbid AUD	8 weeks (4 weeks of treatment phase and 4 weeks of follow-up phase)	Injectable-naltrexone (380mg) + 4 weekly IV ketamine doses (0.5mg/Kg) (N=5)	No control	1	Descriptive statistics	USDVA
Condi et al., 1972 (France) **Retrospective case series**	Patients admitted to ICU and diagnosed with Delirium Tremens (42,0 y.o)	9 (89%)	Biomedical intervention to decrease withdrawal symptoms	Observations during whole length of ICU stay, from 1 to 7 days	Flexible dose of ketamine, IV (4-6 mg/Kg) or IM (5-20 mg/Kg), added to BZD, pentobarbital, meprobamate (N=9)	No control	Nil	Nil	Unknown

AUD: Alcohol Use Disorder; AUDIT: Alcohol Use Disorders Identification Test; BZD: Benzodiazepine; ICU: Intensive Care Unit; IM: Intramuscular; IV: Intravenous; KET : Ketamine; Kg:Kilogram; MET : Motivational enhancement interviewing ; Mg: Milligram; Ml: Milliliter; Ng: Nanogram; MRC: Medical Research Council ; MRMs: Maladaptive Reward Memories; NIDA : National Institute of Drug Abuse; OPD: Outpatient department; PBO: Placebo; RET: Retrival; RCT: Randomized clinical trial; UK: United Kingdom; USDVA: United-State Department of Veterans Affairs; SAW: Severe alcoholic withdrawal

Table 2. Alcohol use, cravings, and withdrawal results of studies evaluating ketamine interventions for alcohol use disorders and severe withdrawal syndromes organized by study design

Authors	Baseline alcohol use (mean)	Outcomes category	Outcome measures	Results*	Authors' interpretation
Dakwar et al., 2020 **Double-blind RCT**	Average number of drinks per day (7 days before consent) = 6.6 Average number of heavy drinking days (7 days before consent) = 5.1	Craving	Craving and arousal (measured by visual analog scale)	No significant difference between groups	No improvement
		Alcohol Use	Abstinence (measured by TLFB-21 days, confirmed by urine ethyl glucuronide testing)	Proportion of abstinence remained stable in the ketamine group while decreasing significantly in the control group (time-by-treatment interaction ($F = 25.1$, $df = 1, 797$, $p < 0.001$))	Improvement
			Abstinence at 6 months post-trial (measured by one telephone interview)	Numerically more participants in the ketamine group reported abstinence (N = 6, 75%), compared to the midazolam group (N = 3, 27%)	Improvement (statistical analysis not performed)
			Time to relapse (measured by TLFB-21, defined by drop-out or first heavy drinking day)	Longer time to relapse in ketamine group compared to control group ($x^2 = 4.2$, $p = 0.04$) based on the log-rank test	Improvement
			Time to first use (measured by TLFB-21)	No significant differences between groups based on the log-rank test	No improvement
			Time to first heavy drinking day (measured by TLFB-21)	No significant differences between groups based on the log-rank test	No improvement
			Heavy drinking days (measured by TLFB-21)	Proportion of heavy drinking days decreased significantly in the ketamine compared to the control group (time-by-	Improvement

				treatment interaction (F = 12.34, df = 1, 798, p < 0.001))	
		Withdrawal	CIWA	No significant difference between groups	No improvement
Das et al., 2019 **Single-blind RCT**	Average number of drinking days (14 days before consent) = 11.11 Average number of heavy drinking days (14 days before consent) = 3.62 Mean daily consumption = 10.26 UK Alcohol Units	Craving	Cue-induced urges, pre- and post-consumption (self-reported Likert scale)	Significant reduction in RET + KET group only, in pre- ($F(1.87) = 19.703$, $p < 0.001$, $n_p^2 = 0.185$) and post-consumption urges ($F(1,87) = 24.46$, $p < 0.001$, $n_p^2 = 0.219$)	Improvement in RET + KET
			Change in general urges to drink (not cue-induced) (self-reported Likert scale)	Significant group effects ($F(2,87) = 5.071$, $p = 0.008$, $\eta 2 = 0.1$) due to greater reduction in RET + KET compared to RET + PBO ($t(59) = 3.183$ $p = 0.001$, $r = 0.3$)	Improvement in KET + RET
			OCDS	No significant differences across group	No improvement
			ACQ-NOW	NI	NI
		Alcohol Use	Weekly alcohol consumption (UK Alcohol Units) (measured by TLFB-10)	Significant reduction in RET + KET group only ($F(1,89.17) = 19.55$, $p < 0.001$, $n_p^2 = 0.14$)	Improvement in RET + KET
			Weekly drinking days (measured by TLFB-10)	Significant reductions in RET + KET ($F(1,89.17) = 19.55$, $p < 0.001$, $n_p^2 = 0.14$) and No-RET + KET groups ($F(1,89.17) = 6.527$, $p = 0.012$, $n_p^2 = 0.052$)	Improvement in RET + KET and No-RET + KET

			Weekly heavy drinking days (measured by TLFB-10)	Significant reductions in RET + KET group only ($F(1,88.95) = 15.821$, $p < 0.001$, $\eta_p^2 = 0.116$)	Improvement in RET + KET
			Long-term weekly alcohol consumption (UK Alcohol Units) at 9 months follow-up (measured by TLFB-10)	No significant difference between groups (Group × Time ($F(2,81.54 = 0.091$, $p = 0.913$))	Equivalent improvement in all three groups
			Self-perceived changes in volume of drinking retrospective Likert-scale	Significant group effects ($F(2,87) = 3.164$, $p = 0.047$, $\eta^2 = 0.07$) due to greater reductions in RET + KET than RET + PBO ($t(59) = 2.366$, $p = 0.05$, $r = 0.29$)	Improvement in RET + KET
		Withdrawal	NA	NA	NA
Krupitsky et al., 1992 **RCT**	Unknown	Craving	NA	NA	NA
		Alcohol use	Abstinence at one year evaluated by monthly structured clinical interviews	Abstinence observed in 69.8% (60/86) of the KPT group vs 24% (24/100) of the control group	Improvement
		Withdrawal	NA	NA	NA
Krupitsky and Grizenko, 1997	Unknown	Craving	NA	NA	NA
		Alcohol use	Abstinence at one year evaluated by monthly structured clinical interviews	Abstinence observed in 65.8% (73/111) of the KPT group vs 24% (24/100) of the control group	Improvement

Prospective cohort study			Abstinence at 2 years evaluated by yearly structured clinical interview	Abstinence observed in 40.7% (33/81) of the KPT group (no control group)	Sustained Improvement
			Abstinence at 3 years evaluated by yearly structured clinical interview	Abstinence observed in 33.3% (14/42) of the KPT group (no control group)	Sustained improvement
		Withdrawal	NA	NA	NA
Pizon et al., 2018 **Retrospective cohort study**	Unknown	Craving	NA	NA	NA
		Alcohol use	NA	NA	NA
		Withdrawal	Withdrawal severity (risk of intubation)	Decreased likelihood of intubation in ketamine vs control group (OR 0.14; $p < 0.01$; 95% CI, 0.04–0.49)	Improvement
			Mean benzodiazepine requirement based on WAS (mg of diazepam equivalent)	Decreased benzodiazepine requirements in ketamine vs control group (2525.1 mg vs 1508.5 mg (T-test, $P = 0.02$))	Improvement
Shah et al., 2018 **Retrospective cohort study**	Unknown	Craving	NA	NA	NA
		Alcohol Use	NA	NA	NA
		Withdrawal	Time to initial symptom control (defined as CIWA-Ar score < 20 or MAAS score < 4 if intubated)	Initial symptom control obtained within 1h of ketamine initiation for all patients; No statistical analysis	Improvement
			Lorazepam requirements at 1, 4, 8, 24, and 48 hours after ketamine initiation (infusion rate mg/h)	Decreased requirement of lorazepam at 24h post ketamine initiation (− 4 mg/h, $p = 0.01$). No differences at other time point	Improvement

Yoon et al ., 2019 **Open-label trial**	Unknown	Craving	OCDS	80% of patients reported improvement in alcohol craving and consumption post-ketamine	Improvement
		Alcohol Use	NA	NA	NA
		Withdrawal	NA	NA	NA
Condi et al., 1972 **Retrospective case series**	Unknown	Craving	NA	NA	NA
		Alcohol Use	NA	NA	NA
		Withdrawal	Description of cases	Delirium agitation controlled in all participants 2-3 minutes post-ketamine	Improvement

*Statistical tests and effect sizes reported as presented in the articles

ACQ-Now: Alcohol Craving Questionnaire; CIWA: Clinical Institute Withdrawal Assessment; CIWA-Ar: Clinical Institute Withdrawal Assessment Revised; KPT: ketamine psychedelic therapy; MAAS: Motor Activity Assessment Scale; mg: milligram; NA: not assessed; NI: no information; OCDS: Obsessive Compulsive Drinking Scale; OR: odds ratio; PBO: placebo; RET: retrieval; TLFB: Timeline Follow Back; UK: United Kingdom; USA: United States of America; WAS: Withdrawal Assessment Scale

Table 3. Related outcome domains of studies evaluating ketamine interventions for alcohol use disorders and severe withdrawal syndromes organized by study design				
Author and Study design	**Related outcome domains**	**Outcomes measures**	**Result**	**Authors' interpretation**
Dakwar et al., 2020 **Double-blind RCT**	Dissociation	CADSS	Significant increase in the ketamine group (median score: 19 vs 2, x^2=7.87, p=0.005)	Significant increase in ketamine group
	Stress sensitivity	PSS	No difference	No group differences
	Impulsivity	BIS	No difference	No group differences
	Self-efficacy	AASES and DTCQ	No difference	No group differences
Das et al., 2019 **Single-blind RCT**	Dissociation	CADSS	Significant increase in RET + KET and No-RET + KET F(4, 172) = 35.281, p < .001, η_p^2 = .451) and no change in RET + PBO	Significant increase in groups receiving ketamine vs PBO group with rapid normalization post-infusion
	Depressive symptoms	BDI	Significant reduction in all groups (F(1, 86) = 18.423, p < .001, η_p^2 = .175)	No group differences
	Impulsivity	BIS	NI	NI
	Distress tolerance	DTS	NI	NI

	Affect	PANAS	Significant reduction in negative affect in RET + KET (F (1, 87) = 9.106, p= .003, ηp^2 = .095). No significant differences in positive affect	Improvement in negative affect in RET + KET group
	Motivation	SOCRATES	Significant reduction in all groups on "taking steps" subscale (F(1, 86) = 17.561, p <.001, ηp^2 = .17.).No significant changes in ''ambivalence'' F(1, 86) = .061, p= .806, ηp^2 = .001) or ''recognition'' F(1, 86) = 1.628, p=.205, ηp^2 = .019	No group differences
		BIS/BAS	No difference between group	
	Common adverse effects	Side effects in the ketamine group (vs control)	Sedation 47% (vs 52%); headache 35% (vs 17%); mild agitation 12% (vs 0%)	No serious adverse effects
Krupitsky and Grizenko, 1997 **Prospective cohort-study**	Psychological traits	MMPI (results only for the intervention group)	Significant decreases: hypochon-dria, depression, anxiety, hysteria, psychasthenia, Scz, SR. Significant increase: ego-strength (Student t-test = p < 0.001 to p < 0.05)	Improvement
Pizon et al., 2018	ICU length of stay	Number of days	Significant decrease in the ketamine group of 2.83 days (95% CI, –5.58 to –0.089 d; p = 0.043)	Improvement

Retrospective cohort study	Hospital stay	Number of days	Non-significant trend toward decrease in the ketamine group of 3.66 days (95% CI, –8.40 to 1.08 d; p = 0.13)	No difference between groups
	Adverse events	Neuropsychiatric symptoms	Oversedation in 1 patient	No serious adverse events
Shah et al., 2018 **Retrospective cohort study**	ICU length of stay	Number of days	8.2 days	Equivocal (No control group)
	Adverse effects	Neuropsychiatric side-effects	None	No development of neuropsychiatric side effects
		Hemodynamic (BP and heartrate)	Hypertension occurred in two patients (6.7%)	No serious hemodynamic event
Yoon et al., 2019 **Open-label trial**	Depressive symptoms	MADRS (antidepressant response defined by a 50% reduction at 4 hours post-infusion)	60% of patients after 1st infusion and 100% by the 4th infusion	Significant improvement
Condi et al., 1972 **Retrospective case series**	Adverse effects	Hemodynamic (BP and heartrate)	BP stable, mean increased heartrate of 10-15 bpm in half of the patients	General hemodynamic stability
		Neuropsychiatric side-effects	None	No development of neuropsychiatric symptoms

Alcohol Abstinence Self-Efficacy Scale; BDI: Beck Depression Inventory; BIS: Barratt Impulsiveness Scale; BISBAS: Behavioral Inhibition/ Behavioral Activation Scale; BP: blood pressure; bpm: beats per minute; DTCQ: Drug Taking Confidence Questionnaire; DTS: Distress Tolerance Scale; KPT: Ketamine Psychedelic Therapy; MADRS: Montgomery-Åsberg Depression Rating Scale; MMPI : Minnesota Multiphasic Personality Inventory; NI: no information; PANAS: Positive and Negative Affect Scale; PSS: Perceived Stress Scale; SCZ: Schizophrenia; SES: Self-Efficacy Scale; SOCRATES: Stages of Change Readiness and Treatment Eagerness Scale; SR: Sensitivity Repression

Figure 1. PRISMA Flow diagram

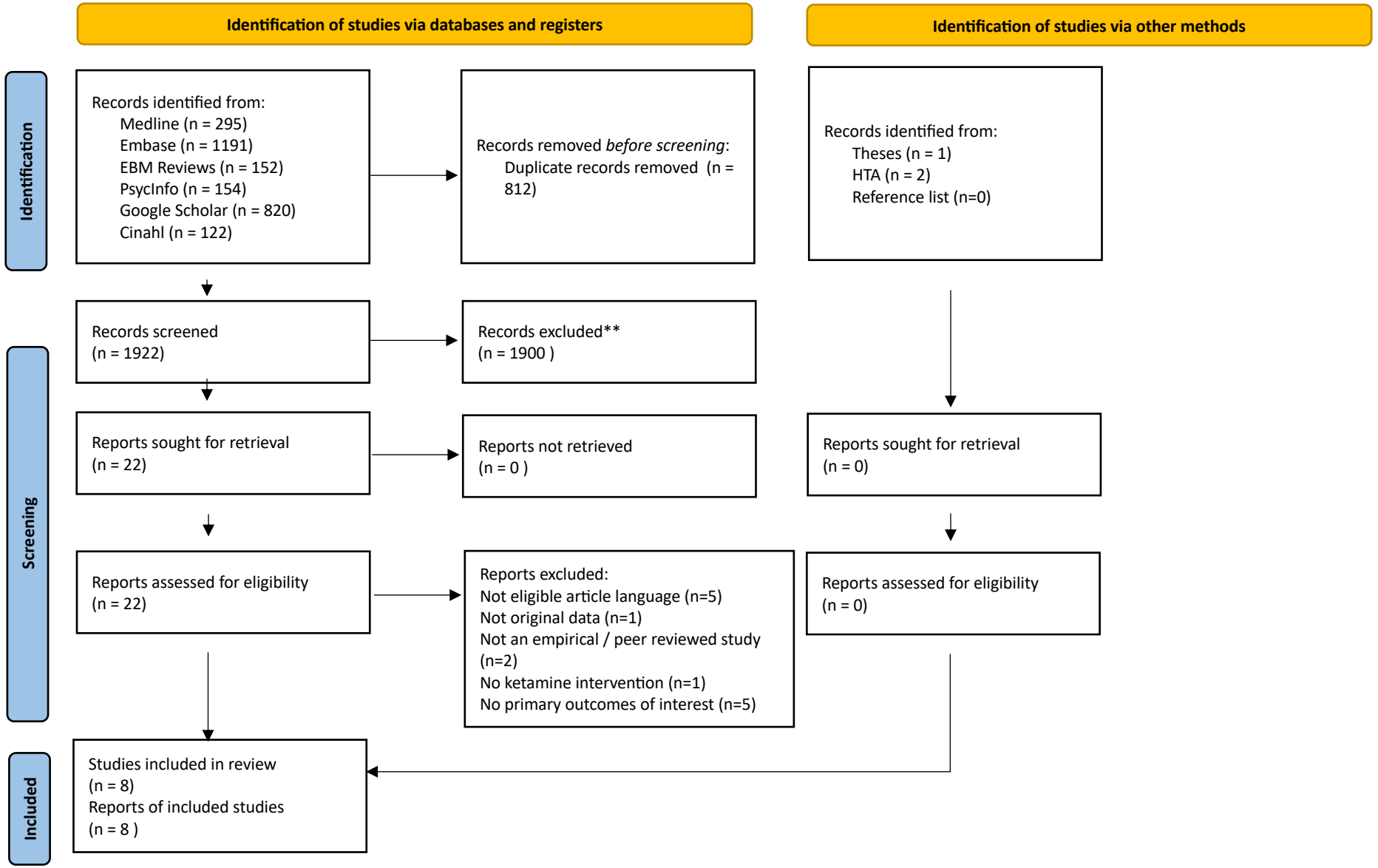


Figure 2. Summary of risk of bias assessments of individual RCT outcomes according to study characteristics using the ROB-2 tool

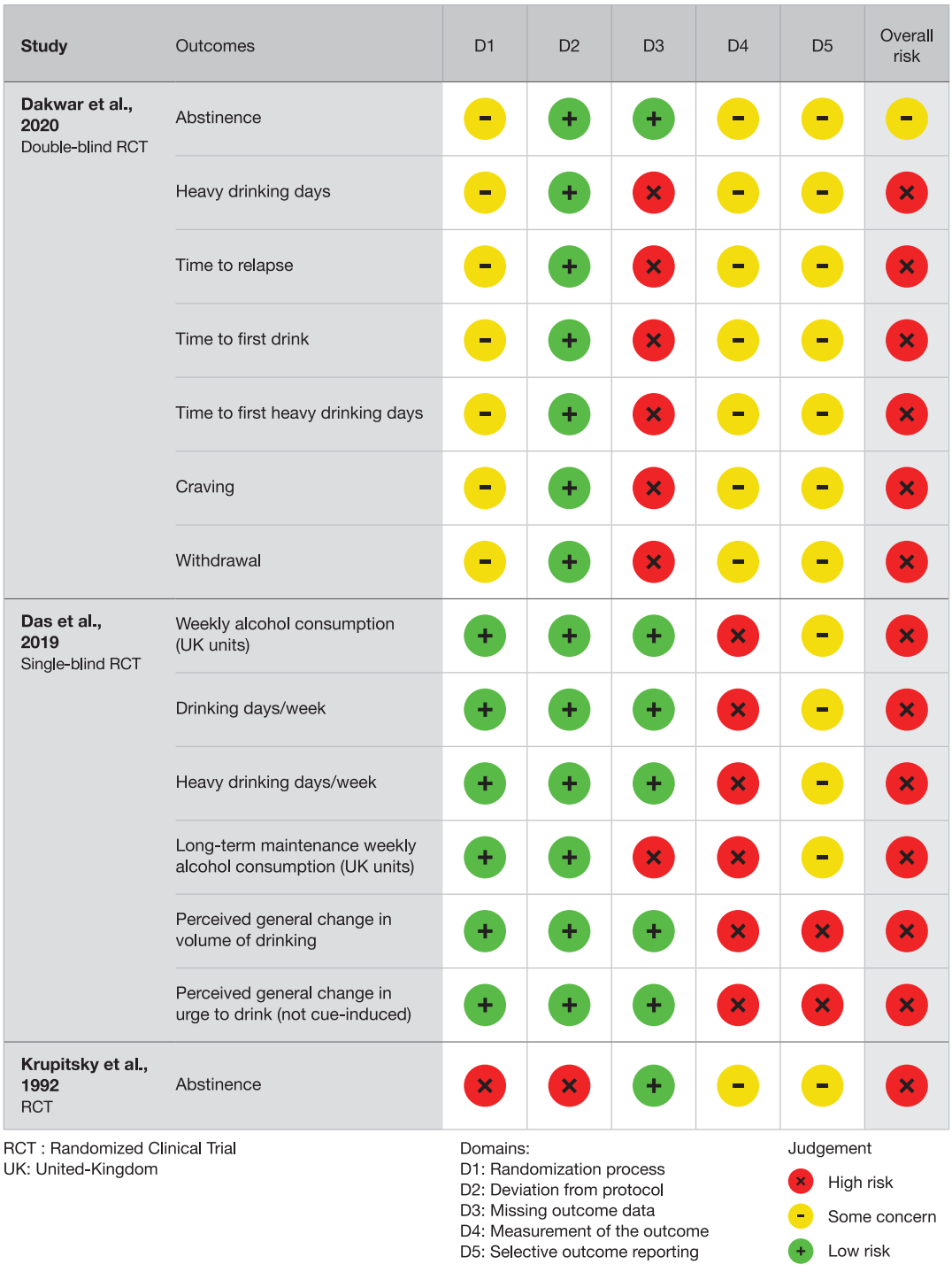
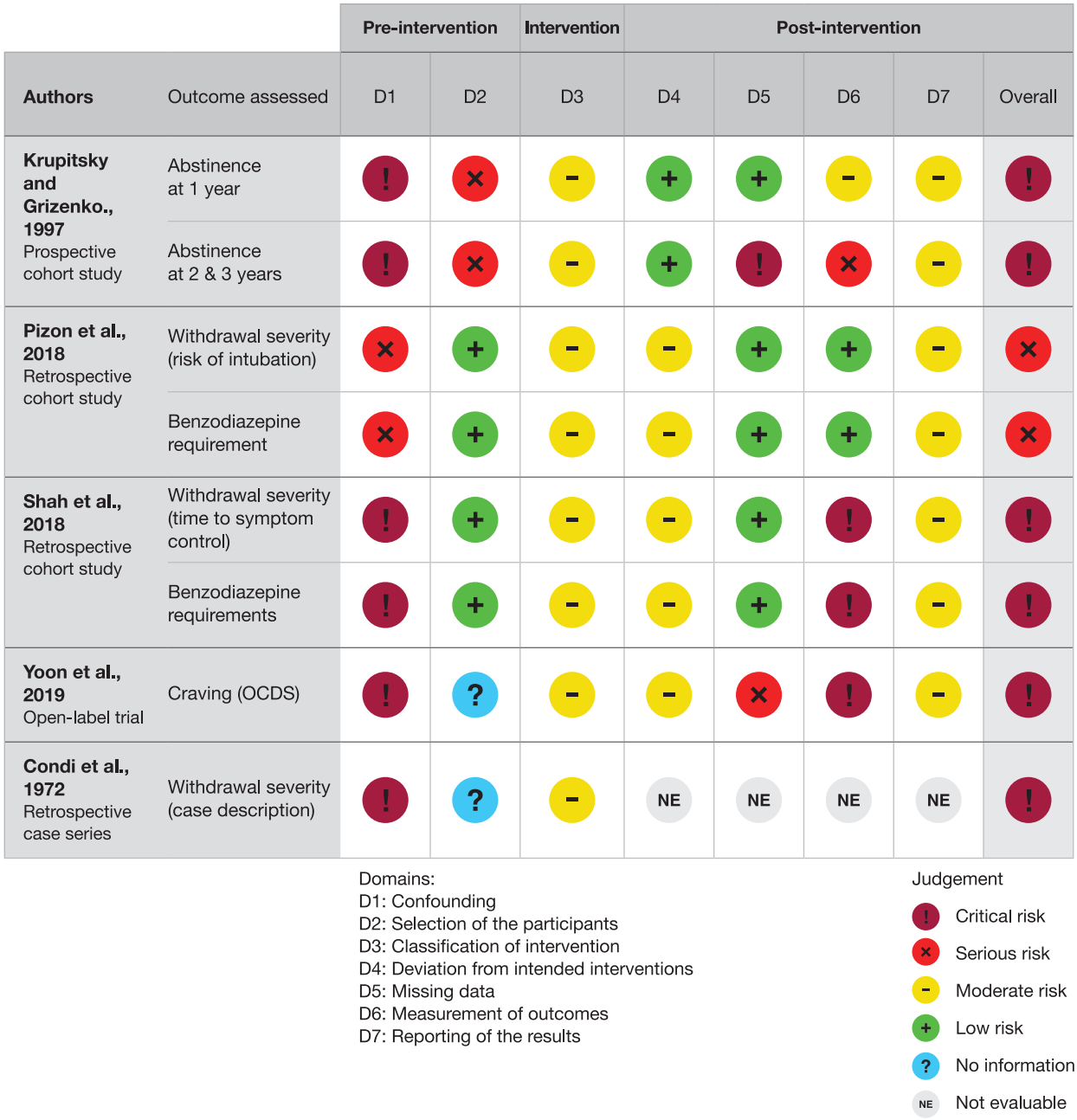


Figure 3. Summary of risk of bias assessments of individual non-RCT outcomes according to study characteristics using the ROBIN-1 tool



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What about benzodiazepine withdrawal?

We have demonstrated, by systematically reviewing the literature, that there is preliminary evidence that adjuvant ketamine may be effective in controlling withdrawal symptoms of patients whose alcohol withdrawal symptoms are refractory to benzodiazepines. Animal studies have shown that NDMA receptors were increased in several cerebrocortical regions in rats undergoing diazepam withdrawal [1], and that administration of NDMA receptor antagonists such as dizocilpine or ifenprodil can attenuate the onset of benzodiazepine withdrawal signs [2]. Animal studies have also shown that ketamine at the doses of 2.5 and 5.0 mg/kg were able to reduce the number of mice developing diazepam withdrawal tonic convulsions and mortality rates [3].

Though ketamine has never been studied in benzodiazepine-withdrawal, several trials have demonstrated that benzodiazepines reduce ketamine's antidepressant effect. At the Douglas Mental Health University Institute Ketamine Clinic, a protocol of treatment has thus been established to gradually discontinue benzodiazepines during the initiation of ketamine therapy for severe depression, in the aim of optimizing the antidepressant effects of ketamine. This management has proven to be highly successful in multiple depressed patients for whom attempts at benzodiazepine discontinuation had been unsuccessful in the past. This led us to further investigate the clinical trajectory of these patients.

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Manuscript 2: Intravenous ketamine for benzodiazepine deprescription and withdrawal management in treatment-resistant depression: a preliminary report

1. Introduction

Approximately 30-50% of patients with depression are prescribed benzodiazepines and/or z-drugs (also known as Benzodiazepines and Related Drugs (BZDRs)) at some point during their illness [1]. Although international depression guidelines generally recommend only short-term BZDR use [2], chronic use eventually arises in 10-15% of patients with depression – particularly those with treatment resistant depression (TRD) [3,4]. Long-term BZDR use has been linked to increased risks of falls and motor-vehicle accidents, cognitive impairment, suicide, and drug overdose mortality [5-9]. Deprescribing BZDRs may therefore yield benefits, in appropriate patients, but is often clinically challenging due to common and distressing withdrawal symptoms like rebound anxiety, insomnia, and depressive symptoms including increased suicidality [6,7,10,11]. Anticipation of distressing withdrawal symptoms is often cited by patients and physicians as a reason to not pursue BZDR discontinuation in patients who may benefit [12].

Psychological and physical BZDR withdrawal symptoms are thought to arise from reduced GABAergic receptor responsiveness and increased expression of excitatory glutamatergic receptors [13-15]. Following BZDR cessation, withdrawal symptoms typically begin after 1-3 days, peak after 1-2 weeks, and resolve after about one month [5,11], though they may potentially persist for months or years [16,17]. Indeed, the term Post-Acute Withdrawal Syndrome has been conceptualized as such persistent symptoms occurring alongside significant psychological decline during or after benzodiazepine tapers [16,18].

Few interventions have proven efficacy for facilitating BZDR discontinuation, particularly in patients with psychiatric illnesses like anxiety and depression that may increase vulnerability to withdrawal symptoms and their consequences [5,6,10,19]. Clinical wisdom suggests that BZDR deprescription should generally only be considered in depressed patients who have achieved remission or at least stability [6]. To date, only one study has attempted BZDR deprescription in patients with active symptoms of depression [10,20]. In that 10-week intervention, depressed chronic users of BZDRs were randomized to receive paroxetine or a placebo and switched to diazepam which was gradually tapered. The authors concluded that the addition of SSRI treatment to the valium-taper was of limited value [20,21]. To our knowledge, no study has tested a behavioral and/or pharmacological intervention for BZDR deprescription in patients suffering from TRD.

In this study, we evaluated whether low-dose intravenous (IV) ketamine may facilitate long-term BZDR discontinuation in patients with active and severe TRD. Ketamine is a non-competitive inhibitor of glutamatergic NMDA receptors with GABA agonistic activities and evidence for rapid (<24 hour) benefits against TRD [22]. Our ketamine-TRD service routinely attempts to discontinue all BZDRs given preliminary (albeit conflicting [23]) evidence that they may blunt ketamine's antidepressant effects [22] and increase the rate of serious adverse events (according to post-marketing study of esketamine) [24], in addition to the potential long-term harms of BZDRs. For willing patients, we thus taper BZDRs such that last doses coincide within one or two days of the first ketamine treatment, based on the hypothesis that ketamine may reduce glutamatergic hypersensitivity – as suggested by preclinical and emerging clinical evidence for ketamine against alcohol withdrawal/addiction [15,25] – and may mitigate common/severe

BZDR acute withdrawal symptoms [15]. I.e., the rapid benefits of low-dose ketamine infusions against symptoms of depression [22], anxiety [26,27], insomnia [28,29], and suicidality may offset acute deteriorations caused by BZDR discontinuation [27,28]. To explore these hypotheses, we examined group- and patient-level changes in these latter symptoms across six infusions of ketamine administered over one month, as well as subsequent BZDRs abstinence on follow-up, for patients in our service attempting BZDRs discontinuation.

2. Methods

2.1 Setting

This ambi-directional (i.e., containing both retrospective and prospective phases) single group cohort study occurred at the Ketamine Service of the Douglas Mental Health University Institute in Montreal, Quebec, Canada. Patients were referred from psychiatrists across the province of Quebec to this tertiary care service to receive ketamine for highly treatment-refractory unipolar and bipolar depression. The study was approved in November 2021 by the institutional review board of the Douglas Mental Health University Institute (#IUSMD-21-29) and individual written consent was obtained. Data collection was performed until August 2022. EQUATOR reporting guidelines were followed.

2.2 Participants

Participants were recruited on an ongoing basis from the Douglas Ketamine service between November 2021 and May 2022. As is common in Montreal, participants were either primary French or English speaking. Inclusion criteria for the study were: 1) age > 18, < 75 years old; 2) received at least one ketamine infusion at the ketamine service for an episode of unipolar or

bipolar depression diagnosed by a trained psychiatrist (according to DSM-5), which had not responded to at least two adequate trials of psychotropic drugs with level 1 evidence against bipolar and/or unipolar depression; 3) at least one long-term (>6 month) active BZDR prescription at the time of the first ketamine psychiatric evaluation; 4) no medication changes 2-weeks before and during treatment (except for BZDR reduction); and 5) provision of written informed consent. Otherwise, no exclusion criteria were utilised for this study, though all eligible patients had been accepted for ketamine treatments and thus met our service's criteria, provided in the Appendix 1 information. Two noteworthy exclusion criteria are: current or recent history (i.e., in the past 12 months) of alcohol or cannabis abuse or dependence, and current or lifetime history of substance abuse or dependence (including all substances except for caffeine or nicotine), as defined by DSM-5 criteria [30].

A chronological, retrospective chart review of all patients of the ketamine-TRD service identified eligible patients who were initially contacted by telephone (by a research assistant) to introduce the study and to seek informed consent. Consenting patients were enrolled into the study's prospective long-term follow-up phase and BZDR use-patterns were evaluated at multiple timepoints as detailed below.

2.3 Intervention

Phase 1: Initial evaluation at the ketamine service and benzodiazepine gradual taper:

All patients referred to the ketamine-TRD service underwent a 60-120 minute psychiatric/medical evaluation, including laboratory investigations and an electrocardiogram, to

determine their suitability for treatment by IV ketamine. After evaluation, accepted patients received one or two 30–60-minute additional visits with the service's clinicians before beginning ketamine for the purposes of psychological support, psychoeducation, and establishing rapport. Our service further ensures that all patients accepted for ketamine treatments receive one hour per week of psychological support or psychotherapy (e.g., with a psychologist, social worker, occupational therapist, counsellor, etc.) during the acute ketamine treatment phase, typically with external clinicians, given evidence that ketamine can be psychologically destabilizing and that psychological treatments of TRD are often underutilized [31,32]. The broad aim of these additional supports is to optimize the chances for acute and sustained antidepressant effects of ketamine.

BZDR discontinuation was discussed with all patients accepted for ketamine treatment based on evidence for harms as described above. Patients interested in stopping BZDRs were then offered to gradually decrease their dose by 10-25% per week before beginning their course of ketamine, aiming to take the last dose (i.e., 25% of the initial dose) within one or two days of the first treatment. All participants were taking intermediate-duration BZDRs, and thus withdrawal symptoms were expected to begin within 1 to 3 days of cessation, peak after 1 to 2 weeks, and resolve within one month [11], coinciding with the ketamine treatment phase. All patients were provided with the telephone number of the clinic's nurse in case of issues arising before beginning ketamine treatments, including but not limited to BZDR withdrawal symptoms.

Phase 2: Ketamine infusions

The ketamine treatment consisted of six IV infusions (0.5mg/kg of bodyweight) given over four weeks; twice weekly for two weeks then weekly for two weeks. Prior to every infusion, baseline vital signs were measured and a urinary drug screen plus a urine pregnancy test (if relevant) were administered. The urine drug screen was performed with PROFILE®-V drug testing cassette devices and a MEDTOXScan reader from MEDTOX Diagnostic Inc., a solid-phase immunoassay device, conforming with ISO 13485, capable of detecting 13 drugs including benzodiazepines. Pre-infusion questionnaires (including measures of mood, anxiety, suicidality, and sleep) were completed, and patients were also routinely asked if they had experienced any specific side-effects or adverse events from previous infusions. Any such events were recorded.

The patients received their infusions in a quiet room, laying on a bed. A vein was cannulated, and ketamine hydrochloride was diluted in 250mL of normal saline by the treating team's nurse, according to the patient's weight and with verification by one other member of the treating team. In patients with a body mass index (BMI) greater than 30, ketamine doses were calculated based on a normalized BMI of 30, given that greater hemodynamic changes with a BMI above 30 have been observed [32]. Ketamine infusions were given in the presence of the nurse and a physician with ongoing assessments of patients' physiological and mental status during the infusion, including respiratory status and cardiovascular functioning. Some patients were provided with music during their treatment sessions. Prior to discharge, patients were required to remain on premises for at least 1 hour of observation after the infusion's end. For emergent agitation or anxiety, midazolam (maximum dose 2.5mg PO or IM) or another short-acting benzodiazepine were available (but not administered to any patients in the study sample).

Following the course of six infusions, the patients of our ketamine-TRD service are discharged to the care of their referring psychiatrists. Any decisions to restart BZDRs following the ketamine treatment course were made by patients and their healthcare providers, independent of our service.

2.4 Outcomes and measures

Before initiating the study, we hypothesized that ketamine infusions in combination with a gradual taper would facilitate the deprescription of BZDRs in TRD patients by mitigating patient's psychological deterioration and reducing common rebound anxiodepressive symptoms and insomnia [6,17]. We set *a priori* continuation rules as described in the statistical analysis section.

2.4.1 Sample characteristics

Sociodemographic and clinical characteristics (e.g., age, sex, psychiatric diagnosis, medical comorbidities) and prescribed medications were retrospectively compiled from the ketamine-service charts of all participants.

2.4.2 Benzodiazepine and z-drug prescription information

BZDR prescription patterns (type, dosage, frequency, length of use) were collected using multiple sources of information at the initial evaluation, prior to every infusion, and at the end of the 4-week ketamine intervention. Sources included patient self-reports, referral documents, urine toxicology results, and the current prescriptions detailed in the *Dossier Santé Quebec* (DSQ). The DSQ is a secure provincial communication platform that facilitates timely sharing of

health information between authorized organizations, physicians, and stakeholders, that collects and stores diverse health information on Quebec patients including active and past prescriptions. The DSQ is thus a reliable way to verify current and past prescriptions of a given patient.

Post-treatment BZDR use was obtained by contacting participants by telephone every 3-6 months post-treatment using a timeline follow-back approach (TLFB) [33], and by the provincial prescription database. The TLFB approach is a calendar–based form in which people provide retrospective estimates of their daily drug/medication consumption over a specified period of time [33]. Memory aids are used to enhance recall. The TLFB method has been extensively evaluated with a wide range of clinical populations and was chosen by the American Psychiatric Association as meeting criteria for inclusion in their Handbook of Psychiatric Measures [34]. Although less objective than urinary toxicology, the combination of self-report TLFB and provincial registry data would only theoretically miss illicit BZDR use, which was judged as unlikely for this population given that they had no significant histories of substance use disorders and were actively followed by prescribers who had previously prescribed them BZDRs. The study entry date of participants, determined by their ketamine treatment dates, dictated the length of follow-up and the number of post-treatment assessments. We used the following dose equivalencies for benzodiazepines, based on the most recent scientific evidence [35] : 15 mg of oxazepam equivalent to 5 mg of diazepam, 1 mg of lorazepam, 0.5 mg of clonazepam, and 0.5 mg of alprazolam. Z-drugs doses were not converted to benzodiazepine equivalence because of the inconsistencies in the literature, and thus were not used in the calculation of mean diazepam doses.

2.4.3 Definition of abstinence

A variety of BZDR abstinence/discontinuation outcomes have been used in past research, including in depressed populations [20,21]. We chose the percentage of complete abstinence (*no* active BZDRs use) at the end of the ketamine intervention and on follow-up as our pre-specified primary outcome, as detailed in the study protocol submitted to the Douglas Mental Health Ethical Review Board in June 2021 prior to data collection. This stringent definition reflects the service's aim of total BZDR discontinuation, when possible, in order to optimize ketamine response [22]. There is no evidence, to our knowledge, indicating a dose-response interaction of BZDRs on the antidepressant response of ketamine.

2.4.4 Psychological withdrawal outcomes

The secondary outcomes of this study were the clinical trajectories of common withdrawal symptoms observed in BZDRs discontinuation – depression, anxiety, sleep, and suicidality [6,11,17] – which we hypothesized would not significantly worsen despite the ketamine treatment process overlapping with the acute phase of BZDRs withdrawal.

For depressive symptoms, we utilized the Beck Depressive Inventory II (BDI-II) [36], a 21-item self-report scale with higher scores indicating more severe depressive symptomatology. Each item is scored on a 4-point Likert scale (total score range: 0-63) [36]. The BDI-II shows high internal consistency and test-retest reliability, reflects a broad range of depressive symptoms, and has been extensively utilized in clinical and research settings [37].

Current anxiety symptoms were measured by the State Trait Anxiety Inventory (STAI-A) [39], state sub-scale, which has 20 items rated on a 4-point scale (total score range: 20-80) with higher scores indicating greater anxiety [39]. Considerable evidence attests to the construct and concurrent validity of the scale, and its high test-retest reliability [40].

Sleep was assessed by the Leeds Sleep Evaluation Questionnaire (LSEQ), a scale initially designed to assess changes in sleep quality over the course of a psychopharmacological interventions [42,43]. It contains 10 self-rated 100-mm-line analogue questions (score ranges from 0-100) concerning versus aspects of sleep: getting to sleep, quality of sleep, awakening from sleep, and behaviors following wakefulness. Lower scores indicate more sleep difficulties and impairment. The LSEQ is one of the most commonly use sleep evaluation questionnaires in clinical settings, has high validity, and is sensitive to change [43,44]. As the LSEQ assesses treatment-related changes in sleep quality, it was not administered at the first treatment, and thus the second ketamine treatment was utilized as the baseline value in all analyses.

Suicidality was assessed by the current-moment Beck Scale for Suicide Ideation (SSI), a widely used instrument to assess suicidality [45]. The SSI contains 19 items measuring severity of actual suicidal wishes and plans, with higher scores indicating a higher level of suicidal ideation (scores range from 0 to 38) [45]. The most sensitive cut-off for high versus low risk of suicide is > 2, according to multiple studies [46].

For Francophone participants, we used the validated French versions of the BDI-II [38], STAI [41], LSEQ [44], and SSI [47].

2.4.5 Subjective impressions of the intervention

Many patients in this study had made previous, unsuccessful attempts to discontinue BZDRs. As such, their feedback was elicited regarding the potential utility of ketamine using a brief questionnaire administered at follow-up ~~including a single Likert question~~ as follows: “Please indicate, on a scale of 0-4, to what extend you agree with the following statement: “The ketamine intervention was helpful in stopping my prescription of <drug name>”.” Responses were given on a 5-point Likert scale (strongly disagree = 0, disagree = 1, neutral = 2, agree = 3, strongly agree = 4). Patients were also asked in an open-ended fashion to describe why the ketamine treatment was helpful or not helpful for discontinuing BZDRs, the results of which were thematically classified by the study team.

2.4.6 Tolerability and drop-out

Adverse events and proportion of patients discontinuing the ketamine treatment for benzodiazepine withdrawal tolerability related reasons were recorded.

2.5 Statistical analyses

We ran a pilot multi-method longitudinal investigation including both group- and person-level analysis methods. To determine if a clinical trial formally evaluating ketamine as an intervention for BZDRs deprescription is warranted, we set *a priori* continuation rules based on the only previous study on benzodiazepine discontinuation in depressed patients [20,21]. For abstinence outcomes: 1) >65% of participants will be categorized as successful discontinuers (BZDR-abstinent as evidenced by self-report and urinary evaluation) by the end of the ketamine

treatment; and 2) during follow-up, >30% of participants will be categorized as successful discontinuers (BZDRs-abstinent as evidenced by self-report). For withdrawal symptoms: 1) < 40% of participants will show reliable clinical deteriorations in depression, anxiety, suicidality, and/or sleep; and 2) BZDR discontinuation will not lead to serious negative consequences (unexpected, clearly trial- or treatment-related serious adverse reaction) and/or significant treatment drop-out.

2.5.1 Benzodiazepine abstinence

Patients who successfully discontinued all BZDRs and remained abstinent throughout follow-up were categorized as "abstinent". Patients who never successfully discontinued all BZDRs by the end of the 4-week ketamine treatment protocol were categorized as "never abstinent", and the remainder who successfully discontinued all BZDRs by the end of the 4-week ketamine treatment, but who restarted their BZDRs medication during follow-up were categorized as "restarted". Descriptive statistics of clinical characteristics were calculated according to these abstinence outcomes. Additionally, we conducted a Kaplan-Meier survival analysis using the 'survival' package in R-4.2.3 to examine the rate, timing, and prediction of restarting BZDRs.

2.5.2 Psychological withdrawal symptoms

For psychological withdrawal symptoms during the ketamine treatment course, we first examined intra-individual changes in withdrawal symptoms with latent growth curve (LGM) models using restricted maximum likelihood estimation of mixed-effects models. This approach performs well with small sample sizes to address bias in standard error estimates and inflated operating type I error rates [48]. Latent mixed-effects modelling was conducted with lmer()

function from the lme4 package [49], in combination with lmerTest package [50], as implemented in R-4.2.3. We created latent growth curve models for each symptom using a stepped approach consistent with Bollen and Curran [51]. In a first step, we calculated an intercept-only model including the random effects of participants to provide a baseline comparison (model 0 – intercept only). Subsequently, we ran a fixed effects model with time during treatment (in weeks) entered as a fixed predictor of symptoms (model 1 – intercept model with level-1 predictor) and a random slope model with time as a random slope (model 2 – intercept model with level-1 predictor and random slope). We used the function r.squaredGLMM() of the MuMIn package in R [1] to estimate the variance explained by both fixed and random factors as a measure of effect size. This allowed examination of the average linear rate of changes, in a given symptom dimension, across the treatment period, and whether patient-specific trajectories deviated from the baseline model.

Additionally, we conducted complementary percent correct classification (PCC) analyses, also known as person-centered effect sizes [52], as there is increasing recognition that statistical inferences drawn from groups of individuals may not accurately describe the individuals themselves [52].. Using the PCC approach, we examined how many patients matched the hypothesized benefits of ketamine in the management of BZDRs withdrawal – i.e., no reliable deteriorations in depression, anxiety, sleep, and suicidal ideation at subsequent treatment sessions (session 2, 3, 4, 5, or 6 vs. session 1).

Reliable change (RC) indices were calculated for each patient to determine whether they experienced changes in any of the four symptom dimensions that were statistically reliable and

clinically significant, using the Leeds RC indicator tool [53]. Calculation of RC requires means and standard deviations (SDs) of clinical and comparison norms, in addition to scale reliability estimates. We used the following coefficient alphas for each scale: 0.92 (BDI-II) [54], 0.94 (STAI) [40], 0.84 (SSI) [45], and 0.84 (LSEQ) [55]. Following the statistical approach of Jacobson and Truax [56], individuals experiencing any reliable deterioration at a subsequent ketamine treatment (sessions 2, 3, 4, 5, or 6), relative to their baseline at the initial ketamine treatment (session 1), were classified as "deteriorated" in that symptom dimension regardless of whether they also experienced reliable improvements at any other point. Patients experiencing no reliable deteriorations were then classified as either overall "improved" (i.e., a reliable improvement at the session 6 relative to session 1), or "no change" (no reliable deterioration or improvement as defined above). In other words, patients experiencing any reliable deterioration were classified as deteriorated, whereas only those experiencing a reliable improvement at session 6 and no prior deteriorations were classified as improved.

3. Results

3.1 Clinical characteristics and demographics

Of the 50 TRD patients treated by our ketamine service between July 2019 and February 2022, 44% (22/50) were chronic (>6 month) BZDR users on evaluation. All 22 chronic BZDRs users satisfied other inclusion/exclusion criteria and were approached for enrollment, with 100% (22/22) consenting to participate (Fig 1). 64% were female; mean [range] age, 49 [23-69] years; 95% were Caucasian. All patients had severe TRD, unipolar or bipolar, with a mean baseline BDI-II score of 36.6 (SD=12.6). Significant suicidality at baseline was present in 82% of the sample (SSI $\geq$ 2) with an average SSI score of 10.5 (SD=9.5). Fifty-nine percent of patients were

diagnosed with a comorbid anxiety disorder (n=13) and 45% with a personality disorder (n=10). Thirty-six percent were suffering from obstructive sleep apnea (n=5). Regarding BZDR prescriptions, 64% (n=14) were treated with only benzodiazepines, 18% with only z-drugs (n=4), and 18% with both (n=4). Benzodiazepines were reported to have been prescribed for comorbid anxiety disorders and/or for anxious distress associated with TRD, whereas Z-drugs were reportedly prescribed for insomnia. Baseline mean (SD) diazepam dose-equivalents (excluding z-drugs) and exposure duration were 15.6 (12.9) mg/day and 3.9 (4.8) years. Most patients (55%; n=12) reported one or more past unsuccessful attempts at discontinuing chronic BZDRs, due to uncomplicated withdrawal symptoms and/or the unmasking of original targeted symptoms. No patients reported past discontinuation attempts with complicated or severe adverse events such as seizures or hospitalizations. Clinical characteristics and demographics are detailed in Table 1.

3.2 Primary outcome: BZDR discontinuation

All patients with BZDR prescriptions on evaluation agreed to receive six infusions of ketamine and attempt BZDR discontinuation. Twenty-one patients (95%) completed the ketamine intervention per protocol. Only one client did not complete all ketamine sessions and discontinued after four infusions. At the end of the 4-week intervention, 20 patients (91%) had successfully stopped all BZDRs as confirmed by urine testing, self-report, and the centralized provincial prescription databank. During the subsequent follow-up period of mean [range] 12 months [3-24], 14 patients (64%) remained BZDR-free. The other six discontinuers reinitiated BZDRs and were thus classified as “restarted”, albeit with a mean [range] 53% [0-85] decrease in daily dose. Several primary reasons were reported by these six patients for restarting BZDRs: four patients reported an exacerbation of insomnia/anxiety symptoms (with stable mood

symptoms), one reported a depressive episode relapse, and one reported restarting BZDRs to mitigate the side effects of initiating a new antidepressant medication.

Figure 2 presents the survival curve for the full cohort. The mean survival time was 72 weeks, with the probability of abstinence decreasing gradually post-treatment until levelling off at six months, yielding a cumulative survival rate of 68% (95% CI: 0.51-0.91).

3.3 Secondary outcomes: withdrawal symptoms

Overall, significant pre-post improvements in depression, anxiety, suicidality, but not sleep quality were observed with group-level LGM analyses. On average, participants reported significant decreases in BDI-II (β = -2.57, SE = 0.36, t(107) = -7.19, $p < .001$), STAI-A (β = -1.81, SE = 0.36, t(107) = -5.09, $p < .001$), and SSI (β = -1.16, SE = 0.26, t(104) = -4.39, $p < .001$) scores with each ketamine treatment, but not LSEQ scores (β = 0.71, SE = 0.61, t(86) = 1.15, p = .251c) (see supplement for more information on LGM results and model fit). This corresponds to meaningful overall decreases in depressive symptoms (baseline mean BDI-II score 36.6 (SD=12.6), posttreatment mean BDI-II score 23.1 (SD = 12.7)), anxiety (baseline mean STAI-A score 58.5 (SD=11.8), posttreatment mean STAI-A score 46.9 (SD = 12.7)), and suicidality (baseline mean SSI score 10.5 (SD=9.5), posttreatment mean SSI 4.0 (SD = 5.9)), without significant changes in subjective sleep quality (baseline mean LSEQ score 40.9 (SD=10.4), posttreatment LSEQ score 42.7 (SD=12.4).

PCC analyses revealed that the large majority of participants did not experience any significant deterioration at any treatment visit, relative to baseline, in depression (86%) (Fig. 3A), anxiety

(86%) (Fig 3B), sleep (77%) (Fig 3C), or suicidality (96%) (Fig 3D) (see Table 1 for more information on PCC analyses). PCC analyses largely converged with LGM group trajectories. At the end of treatment, more than half of patients had reliable improvements in depression (55%; n=12) and anxiety (59%; n=13), versus approximately a quarter for sleep (18%, n=4), and suicidality (27%, n=6). Of those experiencing any reliable deterioration at any treatment timepoint, most had returned to baseline or had reliably improved at the final infusion, in terms of depression (2/3), anxiety (2/3), and sleep (4/5), but not suicidality (0/1) (see Table S2 in supplement for raw scores).

3.4 Subjective appreciation

On average, our sample of 22 long-term BZDR users patients reported two prior unsuccessful attempts at discontinuing BZDRs, suggesting some pre-existing motivation to decrease or stop BZDRs prior to the ketamine treatment process. After the intervention, 12 out of 22 clients (54.5%) rated their agreement with the statement that ketamine had been helpful for BZDRs discontinuation as 4 of a maximum 4 (“strongly agree”). Only one client reported 0 of 4 (“strongly disagree”) (Table 2).

Patients gave convergent reasons for why the ketamine treatment process had been helpful for discontinuing BZDRs: 1) decreased depressive symptomatology; 2) decreased anxiety levels; 3) reduced withdrawal symptoms (including sleep impairment); 4) motivation to potentially increase the antidepressive effects of ketamine; and 5) benefits from support received throughout the treatment process. These reports may reflect some desirability bias.

3.5 Tolerability

Only one patient did not complete the study protocol due to poor tolerability of ketamine's psychoactive effects resulting in discontinuation of treatment after four infusions. This patient was one of the two patients who did not discontinue BZDRs. Outside of the psychological symptoms analyzed in this study, three patients complained of physical withdrawal symptoms during the first week of the treatment: muscle spasms, tinnitus, and muscle pain/ stiffness. All were mild and transient. Additionally, four participants reported significant desires to use their prescribed BZDR medications during the first two weeks of the study, while receiving bi-weekly ketamine infusions, due to transient increases in anxiety or insomnia.

4. Discussion

In this cohort study, we report treatment outcomes and follow-up data of 22 severe TRD participants attempting chronic-BZDR discontinuation with a course of six ketamine infusions. Twenty-one participants completed all six treatments of the 4-week ketamine protocol and, using the stringent criteria of total abstinence, 91% (20/22) successfully discontinued all BZDRs by its end, as confirmed by several means including urine toxicology. Sixty-four percent (14/22) of patients remained abstinent after an average naturalistic follow-up of one year, as per self-report and the provincial prescription database, with the risk of restarting BZDRs stabilizing after six months.

Only a minority ($\leq 25\%$) of participants experienced clinically significant deterioration in depression, anxiety, sleep, or suicidality at any timepoint during the treatment process by PCC analysis. Indeed, group-level analyses revealed overall improvements (all $p < 0.001$), except for

sleep quality. These results contrast with typical rates of BZDR withdrawal symptoms occurring in 40-100% of discontinuers, even with gradual tapering, most commonly in the days-weeks following the last quarter of the original dose [17,20,57].

Chronic BZDR deprescription is a complex endeavor for both clinicians and patients, and is even more challenging in patients actively suffering from psychiatric illness like depression [16,20,21]. To our knowledge, this is the first report of a successful intervention to deprescribe BZDRs in chronic users during an acute episode of TRD. Only one other study of patients with active depression has been conducted, to our knowledge, finding 6-month and 24-month abstinence rates of 32% and 14% following a 10-week intervention combining paroxetine and diazepam [20].

There is evidence to suggest that rational deprescription of BZDRs may be of particular value in TRD populations despite inherent challenges. In our real-world sample of severe unipolar and bipolar TRD patients, nearly 50% received long-term BZDR, with an elevated average daily dose of 15.6mg (diazepam equivalent). Indeed, similarly elevated rates of benzodiazepine prescription have been found in other studies of ketamine [4,58], congruent with the two to threefold increased risk of sedative use disorder in TRD [59]. Preliminary evidence further suggests a potential correlation between BZDRs and more severe/chronic illness courses in depression (although the causality of this link has yet to be established) [60]. TRD populations are also at higher risk than general and non-resistant depressed populations for polypharmacy and medical comorbidities like OSA [61], which may increase the potential harms of BZDRs [62]. Indeed, 36% of our study sample had a diagnosis of OSA and patients, on average, received 2.7

psychotropic medications (excluding BZDRs and ketamine). Lastly, TRD is associated with greater levels of cognitive impairment than non-resistant depression, especially executive functioning, which has been linked to social and occupational dysfunction [63]. The potential for long-term cognitive harms of BZDRs further suggests therapeutic value in rational deprescription interventions [64].

As our results suggest, a course of sub-anesthetic ketamine treatments for mood disorders may provide a unique window of opportunity for making challenging medication changes, especially discontinuing BZDRs, due to several complementary mechanisms. Ketamine's benefits may generally mitigate associated clinical deteriorations by rapidly alleviating common and dangerous depressive symptoms, including suicidality [22]. Pre-clinical evidence also suggests that ketamine may have direct benefits against the withdrawal states of GABAergic psychotropics (including common emotional withdrawal symptoms) [65], which have been associated with elevated NDMA receptor density in several cerebrocortical regions [13,66]. Indeed, preliminary clinical evidence has found benefits of ketamine in severe alcohol withdrawal and refractory seizures [25], as well as in acute and severe benzodiazepine withdrawal (in one recent benzodiazepine use disorder case reports) [67], putatively due to neurotrophic and modulatory effects of ketamine on neuroexcitatory NMDA stimulation. Those findings suggest that our results in TRD may also hold relevance for patients with benzodiazepine use disorder, though the higher medical risks for such populations would likely necessitate closer monitoring such as is available in inpatient settings. Finally, the novelty and public interest in ketamine as an antidepressant may translate into enhanced motivation for patients to undertake the often-challenging process of discontinuing long-term medications, in

order to increase their chance of responding to a treatment often seen as “last-line”. Indeed, at our ketamine-TRD service, 100% of patients agreed to attempt BZDR discontinuation.

The interpretation of this preliminary report is limited by its small sample size, lack of a control group, varying length of follow-up, inability to examine the impact of sex on outcomes of interest, and, most importantly, the lack of standardized scales of BZDRs withdrawal. Despite those limitations, we present the first quantitative and qualitative evidence that ketamine may facilitate discontinuation of chronic BZDRs in a particularly challenging real-world population of severe TRD patients with substantial comorbidity and suicidality.

Conclusion:

Our preliminary results of high rates of successful BZDRs discontinuation and low rates of significant psychological withdrawal symptoms may reflect ketamine’s benefits in in BZDRs withdrawal states. Future research, including controlled trials that rigorously assess physiological as well as psychological withdrawal symptoms, for this potential application of ketamine, is warranted.

Tables and figures Manuscript 2.

Table 1. Patient demographic and clinical characteristics at baseline, categorized by follow-up outcomes.

			BZDR outcomes categories during follow-up		
		Total sample n=22	**Abstinent n=14**	**Restarted n=6**	**Never abstinent n=2**
Gender	Female No. (%)	14 (64)	8 (57)	4 (67)	2 (100)
	Male No. (%)	8 (36)	6 (43)	2 (33)	0
Age (years)	M (SD)	49 (13)	47.6 (14.7)	50.0 (9.9)	58 (1.4)
Ethnicity (Caucasian)	No. (%)	21 (95)	13 (93)	6 (100)	2 (100)
Education (college)	No. (%)	16 (73)	11 (79)	4 (67)	1 (50)
Duration of BZDR perscription (years)	M (SD)	3.9 (4.8)	4.3 (5.7)	2.3 (1.5)	6.0 (5.6)
	Range	0.5 - 23.0	0.5 - 23.0	1.0 - 5.0	2.0-10.0
Dosage in diazepam equivalence (mg/day)	M (SD)	15.6 (12.9)	17.3 (12.9)	12.0 (5.7)	40.0 (NA)
Days of use (per week)	M (SD)	6.7 (0.9)	6.6 (1.1)	7.0 (0)	7.0 (0)
BZDR category	Clonazepam No. (%)	13 (59)	10 (71)	2 (33)	1 (50)
	Lorazepam No. (%)	5 (36)	3 (21)	2 (33)	0
	Alprazolam No. (%)	1 (5)	0	1 (17)	0
	Z-drugs No. (%)	8 (57)	4 (29)	1 (17)	1 (50)
Combination of two sedative/hypnotics	No. (%)	6 (27)	4 (29)	0	0
Length of gradual taper pre-ketamine (weeks)	M (SD)	6.2 (3.8)	6.1 (3.4)	5.1 (4.0)	0
	Range	0 - 12	2 - 8	4 - 12	0
Length of follow-up post-treatment (weeks)	M (SD)	52 (32.4)	51.2 (33.2)	66.6 (24.6)	25.5 (19.1)
	Range	12 - 110	12 - 110	24 - 98	12 - 39
Past failed attempts at BZDR discontinuation	M (SD)	1.7 (4.3)	2.2 (4.0)	0.8 (4.0)	0.5 (NA)
Type of mood disorder	MDD No. (%)	17 (77)	4 (29)	5 (83)	2 (100)
	BD No. (%)	5 (36)	10 (71)	1 (17)	0
Psychiatric comorbidities	Anxiety* No. (%)	13 (59)	8 (57)	5 (83)	0
	PTSD No. (%)	6 (27)	4 (29)	2 (33)	0

	ADHD No. (%)	4 (18)	2 (14)	2 (33)	0
	PD No. (%)	10 (45)	6 (42.9)	2 (33)	2 (100)
	Other No. (%)	13 (59)	8 (57)	2 (33)	2 (100)
Non-BZDR Psychotropes	M (SD)	2.7 (1.5)	2.7 (1.7)	3.0 (0.3)	2.0 (1.4)
Antidepressant	No. (%)	19 (86)	13 (93)	6 (100)	1 (50)
Antipsychotic	No. (%)	11 (50)	6 (43)	3 (50)	2 (100)
Mood stabilizer	No. (%)	8 (57)	6 (43)	1 (17)	1 (50)
Psychostimulant	No. (%)	6 (27)	3 (21)	3 (50)	0
Chronic physical conditions	No. (%)	17 (77)	11 (79)	5 (83)	1 (50)
OSA	No. (%)	5 (36)	4 (29)	0	1 (50)
Baseline scale scores					
BDI-II	M (SD)	36.6 (12.6)	36.6 (14.3)	35.3 (9.4)	40.5 (14.8)
STAI-A	M (SD)	58.5 (11.7)	55.8 (12.3)	59.3 (7.3)	75.0 (4.2)
SSI	M (SD)	10.5 (9.5)	11.9 (10.6)	7.1 (8.2)	9.5 (9.2)
LSEQ	M (SD)	40.9 (10.4)	44.0 (10.4)	36.4 (11.2)	39.4 (10.8)

*Anxiety disorders includes Social Anxiety Disorder, Generalized Anxiety Disorder, Panic Disorder and Agoraphobia. Abbreviations: ADHD: Attention deficit/hyperactivity disorder; BDI-II: Beck Depressive Inventory II; BZDR: benzodiazepine and/or z-drugs; LSEQ: Leeds Sleep Evaluation Questionnaire; OSA: Obstructive sleep apnea; PD: Personality disorder; PTSD: Post-traumatic stress disorder; SSI: Scale for Suicide Ideation (current); STAI-A: State-Trait-Anxiety-Inventory (state)

Table 2. Subjective appreciation outcomes of ketamine therapeutic impact on benzodiazepine discontinuation based on response to statement: "The ketamine intervention was helpful in stopping my prescription of <drug name>".

Likert scale results	**Total Sample No. (%)**
0/4 – "strongly disagree"	**1 (5)**
1/4 – "disagree"	**0**
2/4 – "neither agree nor disagree"	**2 (9)**
3/4 – "agree"	**7 (32)**
4/4 – "strongly agree"	**12 (55)**

Table 3. Psychological withdrawal symptom trajectories according to discontinuation results on long-term follow-up

	Abstinent **N (%)**			**Restarted / Never abstinent** **N (%)**		
	Deteriorated	**Improved**	**No change**	**Deteriorated**	**Improved**	**No change**
BDI-II	2 (9.1)	8 (36.4)	4 (18.2)	1 (4.5)	4 (18.2)	3 (13.6)
STAI-A	2 (9.1)	10 (45.5)	2 (9.1)	1 (4.5)	3 (13.6)	1 (4.5)
LSEQ	3 (13.6)	3 (13.6)	8 (36.4)	2 (9.1)	1 (4.5)	5 (22.7)
SSI	0 (0)	6 (27.3)	8 (36.4)	1 (4.5)	0 (0)	7 (31.8)

Abbreviation : BDI-II: Beck depression Inventory-II; STAI-A: State-Trait-Anxiety-Inventory (State); LSEQ: LEEDs Sleep Evaluation Questionnaire; SSI: Scale for suicide ideation

Table 4. Raw scores and reliable change of patients with deteriorations during treatment											
	BDI-II Total						**Reliable Change**				
Participants	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**	**S2 vs. S1**	**S3 vs. S1**	**S4 vs. S1**	**S5 vs. S1**	**S6 vs. S1**
1	30	33	52	44	47	41	Nochange	Deteriorate	Deteriorate	Deteriorate	Deteriorate
2	9	6	9	5	20	12	Nochange	Nochange	Nochange	Deteriorate	Nochange
3	39	40	40	34	50	18	Nochange	Nochange	Nochange	Deteriorate	Improve
	STAI-A Total						**Reliable Change**				
	S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S2 vs. S1**	**S3 vs. S1**	**S4 vs. S1**	**S5 vs. S1**	**S6 vs. S1**
2	35	29	56	37	51	44	Nochange	Deteriorate	Nochange	Deteriorate	Deteriorate
4	61	70	64	64	66	66	Deteriorate	Nochange	Nochange	Nochange	Nochange
5	35	31	46	41	39	26	Nochange	Deteriorate	Nochange	Nochange	Improve
	LSEQ Total						**Reliable Change**				
	S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S3 vs. S2**	**S4 vs. S2**	**S5 vs. S2**	**S6 vs. S2**	
1	NA	31.79	11.89	16.84	26.63	28.21	Deteriorate	Deteriorate	Nochange	Nochange	
3	NA	58.42	11.79	20.11	10.32	42.11	Deteriorate	Deteriorate	Deteriorate	Deteriorate	
4	NA	42.15	27.59	31.52	33.67	32.41	Deteriorate	Nochange	Nochange	Nochange	
6	NA	56.67	56.67	36.36	47.66	45.64	Nochange	Deteriorate	Nochange	Nochange	

7	NA	42.53	27.22	41.9	44.68	42.53	Deteriorate	Nochange	Nochange	Nochange	
	SSI Total						**Reliable Change**				
ID	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**	**S2 vs. S1**	**S3 vs. S1**	**S4 vs. S1**	**S5 vs. S1**	**S6 vs. S1**
1	3	0	17	12	12	11	Nochange	Deteriorate	Nochange	Nochange	Nochange

Abbreviation: BDI-II: Beck depression Inventory-II; STAI-A: State-Trait-Anxiety-Inventory (State); LSEQ: Leeds Sleep Evaluation Questionnaire; SSI: Scale for suicide ideation; S = session number; NA = not available

Figure 1. Consort Diagram

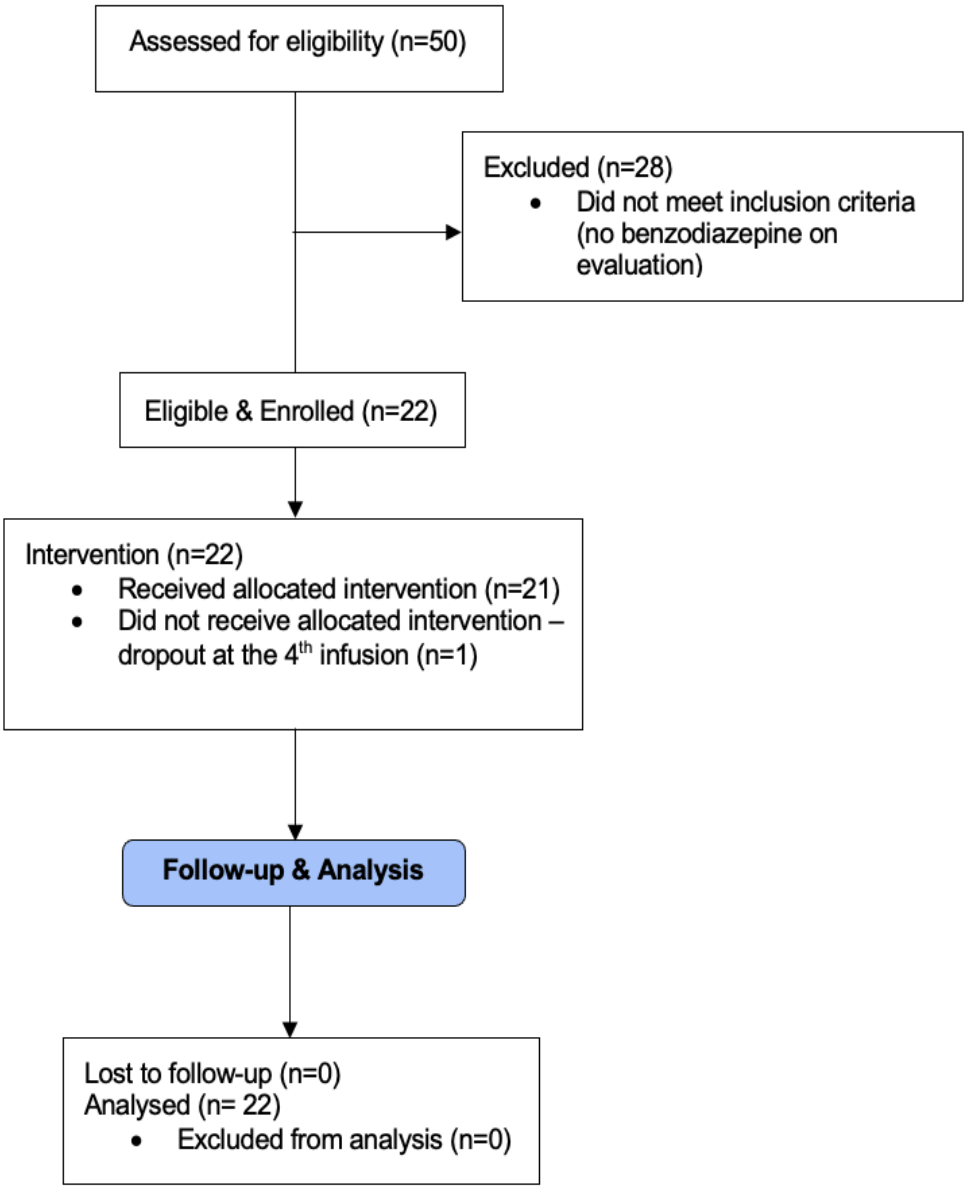

Figure 2. Unadjusted Kaplan-Meier estimates of BZDR restarting for successful discontinuers after the ketamine intervention.

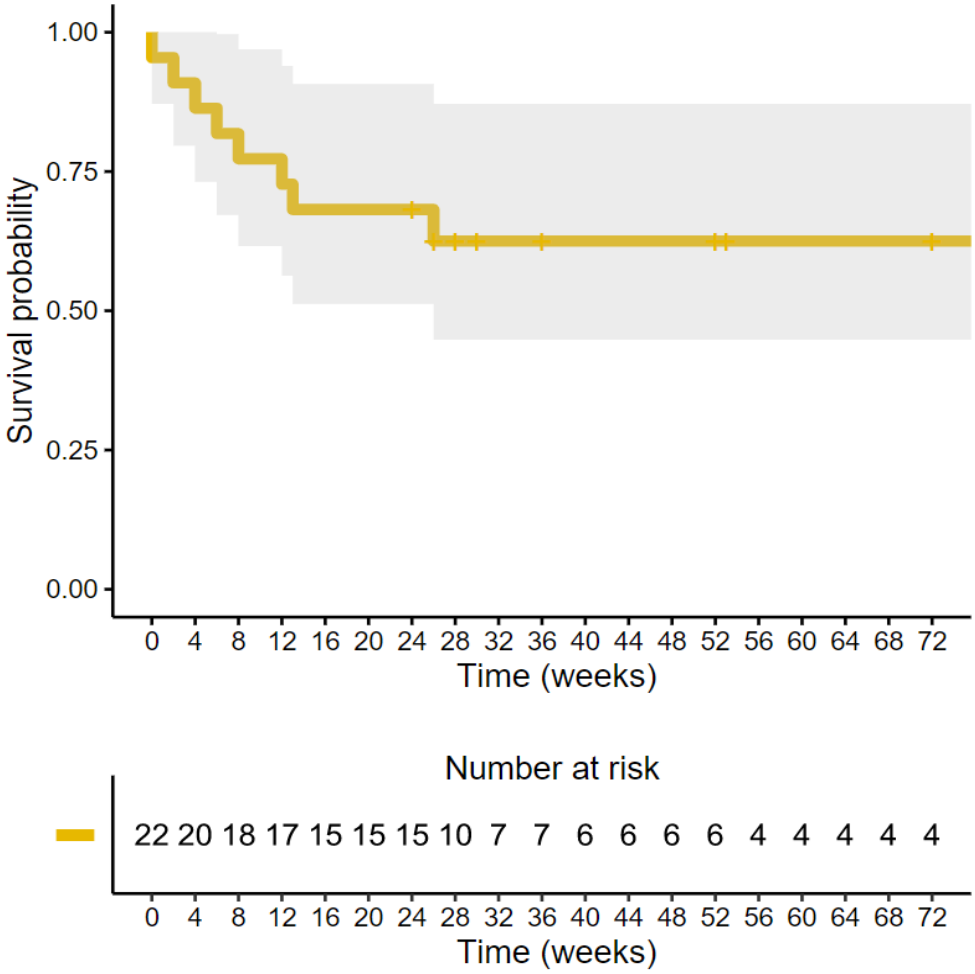

Figure 2 legend:

Kaplan–Meier survival curve showing time to restarting BZDRs, in weeks, with an estimated cumulative survival rate of 68% (95% CI: 0.51-0.91)
The numbers below the Kaplan–Meier curves represent the numbers of patients followed up and the numbers censored at each timepoint.

Figure 3. Symptom trajectories during treatment and acute withdrawal for (a) depression (BDI-II), (b) anxiety (STAI-A), (c) sleep (LSEQ), and (d) suicidality (SSI).

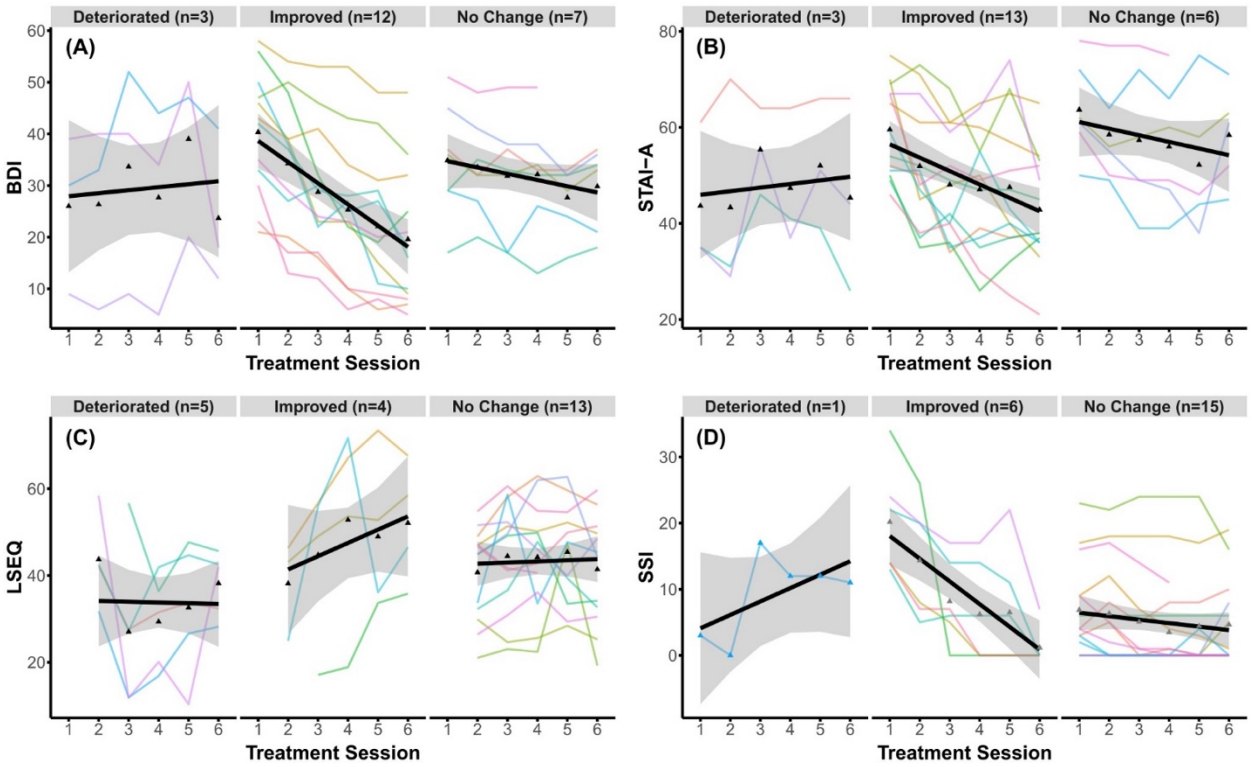

Figure 3 legend:

Note: Illustration of raw clinical scores (Y axis) over each ketamine treatment session (X axis) for each subgroup of treatment responses. The black line represents estimated changes in symptoms over time for each subgroup with the mean at each treatment session (triangular dot) and standard error of the mean (grey). Each subject's raw clinical trajectory is displayed as colored lines. Individual patients grouped as deteriorated (any significant deterioration), improved (significant improvement without any significant deterioration), or no change (no significant deterioration or improvement). BDI-II: Beck depression Inventory; STAI-A: State-Trait-Anxiety-Inventory (State); LSEQ: Leeds Sleep Evaluation Questionnaire; SSI: Scale for suicide ideation (current)

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Concluding paragraph

In this thesis, we presented two manuscripts: 1) a systematic review of ketamine for alcohol use disorders and withdrawal in humans beings and 2) an ambi-directional cohort study on the potential benefits of ketamine on BZDR discontinuation for patients suffering from TRD. We found that ketamine infusions may facilitate both the treatment of alcohol use disorders and BZDR physiologic dependence. The potential mechanisms for these shared benefits may be mediated by potentiating GABAA receptor function, by normalizing aberrant glutaminergic neurotransmission, by increasing neuroplasticity (creating a window of enhanced learning capacity), by producing antidepressive effects (which may decrease the drive towards self-medication for anxiodepressive symptoms), and/or potentially psychedelic mechanisms that lead to enhanced insight and motivation that increase capacities to alter maladaptive behaviors. These benefits are of great clinical importance as both conditions are prevalent and difficult to treat, exerting important consequences for individuals and for society at large. Further controlled trials are warranted into these potential novel applications of ketamine in addictions.

Appendix 1

Exclusion criteria of the Douglas Mental Health University Institute Ketamine Clinic

1) Previous non-response to ketamine in the current major depressive episode;
2) Known intellectual deficiency
3) Prior or current substance abuse or dependence (except for caffeine or nicotine dependence) and/or recent history (last 12 months) of alcohol or cannabis abuse or dependence, as defined by DSM-5 criteria;
4) Acute psychotic symptoms, as judged by the initial clinical interview or reported by referring clinicians; 5) Known risk factors for intracranial hemorrhage, including previous significant trauma, known aneurysm, or previous neurosurgery;
6) Pregnant, lactating, or of childbearing potential unwilling to use highly effective contraception;
7) A clinical medical finding that is unstable or that, in the opinion of the treating clinician(s), would be negatively affected by, or would affect, ketamine (e.g., liver function tests three times the upper normal limit at screening, uncontrolled hypertension, etc.).

Appendix 2: Standardized Scales

Beck Depression Inventory

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today.** Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 15 (Cheanges in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. **Sadness**
0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. **Pessimism**
0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. **Past Failure**
0 I do not feel like a failure.
1 I have failed more than I should.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. **Loss of Pleasure**
0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. **Guilty Feelings**
0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. **Punishment Feelings**
0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. **Self-Dislike**
0 I feel I have the same about myself as ever.

1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. **Self-Criticalness**
0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. **Suicidal Thoughts or Wishes**
0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had that chance.

10. **Crying**
0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

11. **Agitation**
0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12. **Loss of Interest**
0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have most of my interest in other people or things.
3 It's hard to get interested in anything.

13. **Indecisiveness**
0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14. **Worthlessness**
0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. **Loss of Energy**
0 I have as much energy as ever.
1 I have les energy than I used to have.
2 I don't have enough energy to do very much.

3 I don't have enough energy to do anything.

16. **Changes in Sleeping Pattern**
0 I have not experienced any change in my sleeping pattern.
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1-2 hours early and can't get back to sleep

17. **Irritability**
0 I am no more irritable than usual.
1 I am no more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. **Changes in Appetite**
0 I have not experienced any change in my appetite.
1a My appetite is somewhat less than usual.
1b My appetite is somewhat more than usual.
2a My appetite is much less than before.
2b My appetite is much greater than usual.
3a I have no appetite at all.
3b I crave food all the time.

19. **Concentration Difficulty**
0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. **Tiredness or Fatigue**
0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. **Loss of Interest in Sex**
0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

Scale of Suicidal Ideation – Current

Instructions: Please answer the following questions based on your current situation.

1. Evaluate your wish to live in this moment:
0 – Moderate to strong
1 – Weak
2 – None

2. Evaluate your wish to die in this moment:
0 – None
1 – Weak
2 – Moderate to strong

3. Considering your reasons to live or to die, evaluate if:
0 – Your reasons to live outweigh those to die
1 – Your reasons to live are equal to your reasons to die
2 – Your reasons to die outweigh those to live

4. Evaluate your current will to perform an act to commit suicide:
0 – None
1 – Weak
2 – Moderate to strong

5. Do you currently:
0 – Take the precautions to save your life
1 – Leave life or death to chance
2 – Avoid the necessary steps to save or maintain your life

If your answer was « 0 » to all of the above questions, please move on to the next questionnaire. If not, continue.

6. Presently, does it happen that you think about ending your life?
0 – Does not apply
0 – Rarely, occasionally
1 – Intermittently
2 – Persistently or continuously

7. Are these moments:
0– Does not apply
0 – Brief, fleeting periods
1 – Longer periods
2- Continuous (chronic) or almost continuous

8. Currently, what is your attitude towards the idea of ending your life?
0 – Rejecting the idea
1 – Ambivalent or indifferent
2 – Accepting the idea

9. Presently, do you have control of your wish to end your life?
0 – Does not apply
0 – I have a sense of control
1 – I am unsure of controlling it
2 – I have no sense of control

10. Presently, do you have particular reasons that prevents you from committing suicide (family, religion, irreversibility of the act?
0 – There is not attempt because of a deterrent
1 – There is some concern about the deterrents
2 – There is minimal or no concern about the deterrents

11. Currently, what are the reasons that make you want to perform an act that would end your life?
0 – No contemplated attempt
0 – To manipulate the environment, get attention or revenge
1 – To escape, solve my problems and to get attention/ seek revenge
2 – To escape, surcease, solve my problems

12. Have you planned the means that you would use to commit suicide?
0 – No contemplated attempt
0 – Not considered
1 – Considered, but details not worked out
2 – Details worked out/well formulated

13. Currently, are the conditions favorable for you to commit suicide?
0 – No contemplated attempt
0 – Method not available, no opportunity
1 – Method would take time/effort, opportunity not readily available
2 – Method and opportunity available, or will be in a near future

14. Do you feel capable of doing some gesture to commit suicide?
0-Does not apply
0 – Too afraid of doing the gesture to commit suicide
1 – Unsure of committing the gesture
2– Surely capable of doing the gesture to commit suicide

15. Currently, do you plan on performing an act to commit suicide?
0 – No
1 – Uncertain, not sure
2 – Yes

16. Is you plan sufficiently ready to be implemented?
0 – No contemplated attempt
0 – No
1 – Partial
2 – Complete

17. Have you written a goodbye letter?
0 – Does not apply
0 – No

1– Started but not completed, only thought about it
2 – Completed

18. Have you prepared documents such as your will?
0-Does not apply
0 – No
1– Thought about or made some arrangements
2 – Made definite plans or completed arrangements

19. Have you told someone about your wish to die?
0 – No contemplated attempt
0 – Revealed ideas openly
1 – Held back on revealing
2 – Attempted to deceive, conceal, or lie about it

State-Trait-Anxiety-Inventory (State)

STAI-Y A

Instructions: A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel right now, that is, at this moment. There are no right and wrong answers. Do not spend too much time to any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately so	Very much so
1. I feel calm …….....	1	2	3	4
2. I feel secure……....	1	2	3	4
3. I am tense…….....	1	2	3	4
4. I feel strained …….....	1	2	3	4
5. I feel at ease …….....	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes ……	1	2	3	4
8. I feel satisfied	1	2	3	4
9. I feel frightened	1	2	3	4
10. I feel comfortable	1	2	3	4
11. I feel self-confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I am jittery	1	2	3	4
14. I feel indecisive	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel confused	1	2	3	4
19. I feel steady	1	2	3	4
20. I feel pleasant	1	2	3	4

Leeds Sleep Evaluation Questionnaire

LSEQ

Instructions: Please place a vertical mark on the line to indicate your present self-evaluation.

Getting to sleep

How would you describe the way you currently fall asleep in comparison to usual?

1.	More difficult than usual	_____	Easier than usual
2.	Slower than usual	_____	More quickly than usual
3.	I feel less sleepy than usual	_____	More sleepy than usual

Quality of sleep

How would you describe the quality of your sleep compared to normal sleep?

4.	More restless than usual	_____	Calmer than usual
5.	With more wakeful periods than usual	_____	With less wakeful periods than usual

Awake following sleep

How would you describe your awakening in comparison to usual?

6.	More difficult than usual	_____	Easier than usual
7.	Requires a period of time longer than usual		Shorter than usual

Behavior following wakening

How do you feel when you wake up?

8. Tired _____ Alert

How do you feel now?

9. Tired _____ Alert

How would you describe your balance and co-ordination upon awakening?

10. More disrupted than usual _____ Less disrupted than usual