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# Ketamine for Adults With Substance Use Disorders

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Rapid Review

# Key Messages

## What Is the Issue

- Accumulating research has demonstrated that subanesthetic doses of ketamine have rapid and sustained antidepressant effects. In 2019, the US FDA approved the S-enantiomer of ketamine (esketamine) for the treatment of patients with treatment-resistant depression.
- Since then, there has been interest in the development of ketamine for the treatment of a broad range of mental health conditions beyond depression, including substance use disorders (SUDs).
- Decision-makers want to know if there is any evidence to support the use of ketamine for treating SUDs in adults.

## What Did We Do?

- To inform decisions about using ketamine for treating SUDs, we sought to identify and summarize the literature comparing the clinical and cost-effectiveness of ketamine with placebo or no treatment, with alternative interventions, or among ketamine administered via different routes for SUDs. We also searched for evidence-based recommendations for the use of ketamine for SUDs.
- A research information specialist conducted a literature search of peer-reviewed and grey literature sources published between January 1, 2018, and November 28, 2023. One reviewer screened citations for inclusion based on predefined criteria, critically appraised the included studies, and narratively summarized the findings.

## What Did We Find?

- We found 2 systematic reviews (SRs) and 1 randomized controlled trial (RCT) on the use of ketamine for the treatment of patients with alcohol use disorder (AUD), cocaine use disorder (CUD), and opioid use disorder (OUD).
- Evidence from 2 SR suggests that a combination of ketamine infusion and psychotherapy treatment may be effective in promoting abstinence and reduced consumption of alcohol and cocaine use. There were mixed results regarding the effect of ketamine on withdrawal and craving.
- The effects of ketamine on OUD were inconclusive as the results were derived from a single study with a small sample size. Similarly, the effects of ketamine on health care utilization (e.g., hospital readmission, emergency department visit) in patients with severe AUD reported in a RCT were also inconclusive due to the small sample size.

# Key Messages

- Adverse events associated with ketamine treatment included the dissociative and psychotomimetic effects and nondissociative effects. The authors of the included SR reported that these events were mild and transient.
- We did not find any studies on the cost-effectiveness or evidence-based guidelines of ketamine for treating SUDs that met our criteria for this review.

## What Does It Mean?

- The conclusions on the positive effects of ketamine for AUD and CUD should be interpreted with caution due to the high risk of bias of the studies included in the SRs.
- There is a need for more robust clinical trials with larger sample sizes, blinding, and low risk of bias to provide more accurate findings on clinical efficacy, dosing strategies, and safety profile of ketamine for the treatment of AUD, CUD, and OUD.
- Additional studies on other substances of abuse (e.g., nicotine, amphetamines, and cannabis) may provide important insights into the overall efficacy of ketamine in the treatment of SUDs.

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## Abbreviations

| | |
|---|---|
| **AE** | adverse event |
| **AMSTAR 2** | A MeaSurement Tool to Assess systematic Reviews 2 |
| **AUD** | alcohol use disorder |
| **CUD** | cocaine use disorder |
| **IM** | intramuscular |
| **IQR** | interquartile range |
| **MD** | mean difference |
| **OUD** | opioid use disorder |
| **RCT** | randomized controlled trial |
| **SR** | systematic review |
| **SUD** | substance use disorder |

# Context and Policy Issues

## SUDs in Canada

SUDs are mental health conditions that affect the brain and behaviour of a person, leading to the inability to control their use of substances such as alcohol, nicotine, cannabis, prescription drugs, or illicit drugs.[1] People with SUDs may also have other co-occurring mental health disorders, such as depression, anxiety disorders, bipolar disorders, personality disorders, and schizophrenia.[1]

Statistics Canada data from 2022 estimated that more than 5 million people living in Canada aged 15 and older met the diagnostic criteria for a mood disorder, anxiety, or SUD in the previous 12 months.[2] Alcohol is the most commonly used substance in Canada.[3] An estimated 15% of people who drink alcohol consume more than the levels recommended by Canada's Low Risk Alcohol Drinking Guidelines.[3] Nicotine, tobacco, and cannabis, are other examples of commonly used substances.[3] About 3% of people living in Canada have used 1 of 5 illicit drugs (i.e., cocaine, ecstasy, methamphetamines, hallucinogens, and heroin).[3] The cost of substance use in Canada, including the cost of health care, criminal justice, and loss of productivity, was estimated to be over $46 billion in 2017, and more than one-third of the cost was related to alcohol use.[3] About 47,000 deaths in Canada are linked to SUDs each year.[3]

## What Is the Current Practice?

People with SUDs often receive a combined treatment approach involving behavioural therapy and medications.[1] Effective behavioural therapies for adults with SUDs and co-occurring mental health disorders include cognitive behavioural therapy, dialectical behavioural therapy, assertive community treatment, therapeutic communities, and contingency management.[1] Health Canada has approved naltrexone, acamprosate, and disulfiram for treating AUD.[4] For individuals with OUD, recommended medications include methadone, buprenorphine, and naltrexone.[5] Promising medications for the treatment of CUD include dopamine agonists such as long-acting amphetamine and modafinil, gamma-aminobutyric acidergic and glutamatergic medications such as topiramate, and a combination of topiramate and long-acting amphetamine.[6] Bupropion and varenicline are effective medications for the treatment of nicotine addiction.[1] There are currently no Health Canada-approved medications for CUD.[7]

## Why Is it Important to Do This Review?

Ketamine is an *N*-methyl-D-aspartate receptor antagonist that was first approved for use as anesthetic drug.[8] In addition to its well-characterized anesthetic effect, ketamine also exhibits analgesic, anti-inflammatory, and antidepressant properties.[9] In recent years, evidence has demonstrated the potential antidepressant effects of ketamine, particularly in patients with depression resistant to conventional treatments.[10] In 2019, the US FDA approved the S-enantiomer of ketamine (esketamine) as augmentation therapy for treatment-resistant depression.[11] The effects of ketamine may be partly mediated through its ability to normalize cortical glutamate homeostasis and induce neural plasticity (e.g., neurogenesis, synaptogenesis), facilitating the learning of new coping mechanisms and behaviours.[12] Consequently, there has been growing interest in understanding the potential effects of ketamine for the treatment of various chronic mental health

conditions, including SUDs, which are thought to be associated with diminished plasticity and decreased glutamatergic synaptic transmission.[12]

By conducting this review, we can explore the available evidence to determine whether ketamine is an effective option for the treatment of SUDs.

### Objective

The aim of this report is to summarize the evidence regarding the clinical and cost-effectiveness of ketamine for treating SUDs in adults. This report also aims to review the evidence-based guidelines regarding the use and administration of ketamine for adults with SUDs.

## Research Questions

1. What is the clinical effectiveness of ketamine versus placebo or no treatment for adults with substance use disorders?
2. What is the clinical effectiveness of ketamine versus alternative interventions for adults with substance use disorders?
3. What is the clinical effectiveness of ketamine administered via different routes for adults with substance use disorders?
4. What is the cost-effectiveness of ketamine versus placebo or no treatment for adults with substance use disorders?
5. What is the cost-effectiveness of ketamine versus alternative interventions for adults with substance use disorders?
6. What is the cost-effectiveness of ketamine administered via different routes for adults with substance use disorders?
7. What are the evidence-based guidelines regarding the use and administration of ketamine for adults with substance use disorders?

## Methods

### Literature Search Methods

An information specialist conducted a literature search on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were ketamine and substance use disorders.

Comments, newspaper articles, editorials, and letters were excluded, and retrieval was limited to the human population. The search was completed on November 28, 2023, and limited to English-language documents published since January 1, 2018.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

### Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 or were published before 2018. SRs in which all relevant studies were captured in other more recent or more comprehensive SRs were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included SRs. Studies were excluded if they involved ketamine-assisted or ketamine-facilitated psychotherapy for the treatment of SUDs.

### Critical Appraisal of Individual Studies

One reviewer critically appraised the included publications using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[13] for SRs and the Downs and Black checklist[14] for RCTs. Summary scores were not calculated for the included studies; rather, each publication's strengths and limitations were described narratively.

## Summary of Evidence

### Quantity of Research Available

We identified a total of 493 citations from the literature search. Following screening of titles and abstracts, we excluded 470 citations and retrieved 23 potentially relevant reports from the electronic search for full-text review. We found 2 potentially relevant publications from the grey literature search. Of the 25 potentially relevant articles, we excluded 22 publications for various reasons and included 3 that met the inclusion criteria. These comprised 2 SRs and 1 RCT. Appendix 1 presents the PRISMA[15] flow chart of the study selection.

### Summary of Study Characteristics

Appendix 2 provides details regarding the characteristics of 2 included SRs[16,17] (Table 2), and 1 primary study[18] (Table 3).

#### Study Design

The SR by Kelson et al. (2023)[16] included 11 studies (5 RCTs, 4 cohort studies, 2 case series; published between 2019 and 2022) with a total of 854 adult patients with AUD, ranging from 5 to 211 patients in each

## Table 1: Selection Criteria

| Criteria | Description |
|---|---|
| **Population** | Adults with substance use disorders |
| **Intervention** | Ketamine administered via any route (e.g., IV, intramuscular, subcutaneous, intranasal, oral, sublingual), used alone or in combination with other interventions. |
| **Comparator** | Q1 and Q4: Placebo, no treatment<br>Q2 and Q5: Pharmacotherapy (e.g., acamprosate, opioid agonists) or non-pharmacological interventions (e.g., psychotherapy, counselling, inpatient treatment)<br>Q3 and Q6: Ketamine administered via alternative routes (e.g., IV, intramuscular, subcutaneous, intranasal, oral, sublingual)<br>Q7: Not applicable |
| **Outcomes** | Q1 to Q3: Clinical benefits (e.g., symptom severity, abstinence, hospitalizations, quality of life, functional status) and harms (e.g., adverse events)<br>Q4 to Q6: Cost-effectiveness (e.g., cost per quality-adjusted life-year gained)<br>Q7: Recommendations regarding best practices (e.g., appropriate patient populations or clinical settings, treatment protocols, contraindications, recommended patient monitoring strategies) |
| **Study designs** | Health technology assessments, systematic reviews, randomized controlled trials, nonrandomized studies, economic evaluations, and evidence-based guidelines. |

primary study. Ten of the 11 studies were relevant to our report, while 1 study was not relevant as it involved ketamine-enhanced psychotherapy. The authors of the SR[16] searched multiple databases since inception to July 2022, with restriction to manuscripts written in English or Spanish language. The authors of the SR[16] narratively summarized the results of each of the included studies without pooling.

The SR by Walsh et al. (2021)[17] included 83 studies, 10 of which were relevant to our report. Of the 10 relevant studies, 6 studies on AUD were included in the SR by Kelson et al. (2023),[16] and therefore they were not included during the description of this SR. Table 13 of Appendix 5 presents the overlap of relevant primary studies between SRs. Thus, the remaining 4 studies consisted of 3 studies (described in 4 publications) on CUD (published between 2014 and 2019), and 1 study on OUD (published in 2006). The 3 studies on CUD had 8, 20, and 55 patients, while the study on OUD had 50 patients. The authors of the SR[17] searched 2 databases since inception to 21 October 2020, with restriction to manuscripts written in the English language. The authors narratively summarized the results of each of the included studies, without pooling.

The primary study by Terasaki et al. (2022)[18] was a 3-arm open-label RCT involving 44 adult patients with severe AUD, who had been hospitalized in the previous year. The authors did not calculate sample size to detect a hypothesized treatment difference between groups. The results were analyzed using the intention-to-treat approach. The study was published in 2022.

### Country of Origin

Authors from the US conducted the SR by Kelson et al. (2023)16. The relevant primary studies included in this SR were conducted by authors from the US (6 studies), the UK (2 studies), and Russia (2 studies).

Authors from the UK conducted the SR by Walsh et al. (2021).[17] The relevant primary studies included in this SR were conducted by authors from the US (3 studies) and Lithuania (1 study).

The included primary study by Terasaki et al. (2022)[18] was conducted by authors from the US.

### Patient Population

Patients in the relevant studies included in the SR by Kelson et al. (2023)[16] were adults with AUD (6 studies), heavy drinkers at moderate to high risk of developing AUD (1 study), and those with alcohol withdrawal (3 studies). Nine studies had a mean age ranging from 27.5 to 53 years, while 1 study had a median age of 50 years (interquartile range [IQR] = 47 to 54). The proportions of male and female participants ranged from 61% to 100% and 0% to 39%, respectively. Patients' comorbidities were not reported.

Patients in the relevant studies included in the SR by Walsh et al. (2021)[17] were adult patients with cocaine dependence (4 studies) or opiate withdrawal syndrome (1 study). Population characteristics were not clearly reported.

Patients in the included primary study by Terasaki et al. (2022)[18] were adults with severe AUD, who had been hospitalized in the previous year. The mean age was 45.1 years. The proportions of male and female participants were 79.5% and 20.5%, respectively. The mean number of daily drinks at baseline was 12.0, the mean number of previous-year emergency department visits was 10.9, and the mean number of previous-year hospital admissions was 3.2.

### Interventions and Comparators

In the SR by Kelson et al. (2023),[16] 9 studies evaluated the efficacy of ketamine for the treatment of patients with AUD, while 1 study involved heavy drinkers at moderate to high risk of developing AUD. The interventions and comparators in each study were as follows:

Treatment of AUD:

- Intramuscular (IM) ketamine (2.5 mg/kg or 3 mg/kg) plus IM aethimizol plus IV bemegride plus psychotherapy versus conventional AUD treatment (2 studies).
- IV ketamine (0.5 mg/kg) plus injectable naltrexone (380 mg) versus baseline (1 study).
- IV ketamine (plasma concentration of 350 ng/dL) after alcohol use versus IV ketamine (plasma concentration of 350 ng/dL) plus no alcohol versus IV saline after alcohol use (1 study).
- IV ketamine (0.71 mg/kg) plus motivational enhancement therapy versus IV midazolam plus motivational enhancement therapy (2 studies).
- IV ketamine (0.8 mg/kg) plus psychotherapy versus IV saline plus psychotherapy versus IV ketamine plus alcohol education versus IV saline plus alcohol education (1 study).
- IV ketamine (mean initial dose 0.21 mg/kg/h; median infusion dose 0.20 mg/kg/h, IQR 0.12 to 0.23; with or without loading dose 0.3 mg/kg) plus conventional withdrawal treatment versus baseline (1 study).

- IV ketamine (0.15 to 0.3 mg/kg/h) with or without ketamine bolus plus conventional withdrawal treatment versus conventional withdrawal treatment (1 study).
- IV ketamine (median initial dose 0.75 mg/kg/h, IQR 0.5 to 1.0; mean max daily infusion 1.6 mg/kg/h) plus conventional withdrawal treatment versus baseline (1 study).

In the SR by Walsh et al. (2021),[17] 3 studies (described in 4 publications) evaluated the effects of ketamine on CUD, and 1 study evaluated the effect of ketamine in assisting withdrawal from opiates. The interventions and comparators in each study were as follows:

Treatment of CUD:

- IV ketamine (0.41 mg/kg first dose; 0.71 mg/kg second dose; 48 hours between doses; 52-minute infusions) versus lorazepam (2 mg; 52-minute infusions) (1 study, described in 2 publications).
- IV ketamine (0.11mg/kg 2-minute bolus followed by 0.60 mg/kg) versus 2-minute saline bolus followed by active control midazolam (0.025 mg/kg) (1 study).
- IV ketamine (0.5 mg/kg, slow drip 40 minutes infusion) plus mindfulness-based relapse prevention therapy versus active control midazolam (0.025 mg/kg) plus mindfulness-based relapse prevention therapy (1 study).

For Treatment of Opiates Withdrawal from Patients with OUD:

- IV ketamine (0.5 mg/kg) versus placebo (i.e., saline solution) (1 study).

The included primary study by Terasaki et al. (2022)[18] compared IV ketamine (0.5 mg/kg over 40 minute) versus IM naltrexone (380 mg once) versus linkage alone (i.e., no pharmacological intervention, but patients still received outpatient addiction clinic linkage and the research stipends).

### Outcomes

The main outcomes reported in the SRs[16,17] included abstinence, withdrawal, craving, and consumption. In the SR by Kelson et al. (2023),[16] treatment durations of the included studies for AUD varied from 1 week to 3 months, and the follow-up periods varied from 1 hour postperfusion to 3 years posttreatment. In the SR by Walsh et al. (2021),[17] follow-up periods for the treatment of CUD were 24 hours and 2 weeks, and follow-up period for OUD was 4 months.

- Abstinence from alcohol use was assessed by self-reported, Timeline Followback (confirmed by glucuronide test or telephone interview 6 months after treatment), and Secure Continuous Remote Alcohol Monitor (an ankle bracelet that continuously monitors and measures alcohol consumption 24 hours a day, 7 days per week). Abstinence from cocaine use was assessed with a self-reported questionnaire and urine toxicology.
- Withdrawal from alcohol use was assessed with benzodiazepine dose requirements based on Withdrawal Assessment Scale greater than 10 (score: 1 to 20 = mild withdrawal; 21 to 40 = moderate withdrawal; 41 to 60 = severe withdrawal; 61 to 80 = very severe withdrawal), Clinical Institute Withdrawal Assessment for Alcohol (score less than 8 = minimal withdrawal; 8 to 15 = moderate withdrawal; 15 or more = severe withdrawal), Motor Activity Assessment Scale (a 9-item scale to assess areas of motor function; items are assessed using a 7-point scale [0 to 6]; a score of 6

indicates optimal motor behaviour). Withdrawal from opioid use was assessed with the Objective Opioid Withdrawal Scale (a 13-item clinical rating tool for assessing and monitoring opiate withdrawal symptoms).

- Craving for alcohol was assessed with various self-reported measures, including the Obsessive Compulsive Drinking Scale (a 14-item questionnaire that measures alcohol use and attempts to control drinking; with 2 subscales [items 1 to 6 for obsessive subscale, and items 7 to 14 for compulsive subscale]; each item is scored from 0 to 4; total scores range from 0 to 56), the Alcohol Craving Questionnaire (one should indicate how much 1 agree or disagree with each of the 47 statements), a visual analogue scale (not described), and a Likert Scale (not described). Craving for cocaine was assessed with a visual analogue scale (not described), motivation to quit cocaine was assessed with University of Rhode Island Change Assessment Scale (a 32-item self-report measure that includes 4 subscales measuring the stages of change: Precontemplation, Contemplation, Action, and Maintenance; responses are given on a 5-point Likert Scale, ranging from 1 = strong disagreement to 5 = strong agreement), and the choice of cocaine use was assessed with self-reported questionnaire.
- Consumption of alcohol was assessed with self-reported questionnaire, and Timeline Followback. Consumption of cocaine was assessed with self-reported questionnaire and urine toxicology.

The outcomes reported in the included primary study by Terasaki et al. (2022)[18] were alcohol-related clinical outcomes including all-cause 30-day hospital readmission, all-cause 30-day emergency department visit, and 14-day clinic attendance. These outcomes were obtained from medical records. The study also reported other outcomes such as acceptability and perceived effectiveness of intervention, which were assessed with 10-point Likert Scales. The outcomes were followed from post-intervention up to 30 days.

The SR by Walsh et al. (2021)[17] and the included primary study by Terasaki et al. (2022)[18] reported ketamine-related adverse events (AEs) during treatment of CUD, OUD and AUD.

## Summary of Critical Appraisal

Appendix 3 details the strengths and limitations of the included SRs[16,17] (Table 4) and primary study[18] (Table 5).

### Systematic Reviews

Both SRs[16,17] were explicit in their objectives, inclusion criteria for the review, and selection of the study designs for inclusion. The literature search strategy was comprehensive and clearly described in both SRs,[16,17] using multiple combinations of keywords. The authors of both SRs[16,17] also handsearched the reference lists of the included studies. Providing details of the literature search strategy increases the reproducibility of the reviews. Both SRs[16,17] reported that a protocol had been published before the conduct of the review; thus, reducing bias in modifying the methods after the review had been conducted. There were no changes between the approach outlined in the protocol and the methods conducted in the review. Study selection, data extraction and quality assessment of the included studies were independently performed with 2 reviewers in the SR by Kelson et al. (2023),[16] or with 4 reviewers in the SR by Walsh et al. (2021).[17] This

exercise reduced the risk of inconsistencies in these processes. Both SRs[16,17] described the characteristics of the included studies in adequate details, with respect to study design, intervention, control, treatment duration, follow-up time, and outcomes. However, patient characteristics (e.g., age, gender, comorbidities) of the included studies in both SRs[16,17] were not adequately described. In both SRs,[16,17] the methodological quality of the included studies was assessed using appropriate tools (i.e., the Cochrane Risk of Bias tool for RCTs, the Risk Of Bias In Nonrandomized Studies of Interventions tool for nonrandomized studies, and AMSTAR 2 for SRs). In both SRs,[16,17] the authors judged that most included RCTs were either having high risk of bias or some concerns in at least 1 domain, while most of the nonrandomized studies were also judged to be at high risk of bias. The SR by Walsh et al. (2021)[17] provided a list of excluded studies and the reasons for exclusion, while the SR by Kelson et al. (2023)[16] did not. No justification for the excluded studies could bias the results of the review. None of the SRs[16,17] reported the sources of funding for the included studies. This is potentially a concern because funding received from industry can introduce bias in favour of the intervention.[19] The review authors of both SRs[16,17] discussed the heterogeneity among study design, inclusion criteria, dosing regimen, use of concomitant medication, outcome variables, treatment duration, and follow-up period, which was the main reason for not conducting a meta-analysis. The SR by Walsh et al. (2021)[17] reported the source of funding for the work, while the SR by Kelson et al. (2023)[16] did not. The review authors of both SRs[16,17] declared that they had no conflicts of interest related to their work. Overall, both SRs[16,17] that narratively summarized the findings from the included studies used appropriate methodological approaches regarding the literature search strategy, data collection process, quality assessment of the included studies, and reporting. The limitations of the primary studies included in both SRs[16,17] may increase the uncertainty of the findings.

### Primary Study

For reporting, the included RCT[18] clearly described the study's objective, the intervention of interest, the main outcomes, and the study's main findings. However, the characteristics of the participants included in the study were not clearly described. It was unclear if there were any group differences (i.e., potential confounders) in the demographics of the randomized participants. The authors reported the AEs of the intervention and actual P values for the main outcomes. For external validity, the study was conducted in an outpatient hospital setting, which was representative of the treatment the majority of the patients receive. However, patients were recruited from a single centre, and the sample size was small (N = 44); therefore, it was unlikely that the patients who participated were representative of the entire population from which they were recruited. For internal validity related to bias, there were potential risks of selection, performance, and detection biases, as the study was an open-label trial. All patients were followed up for the same period, which was 30 days. Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. For internal validity related to confounding, patients in both intervention groups appeared to be recruited from the same population over the same period. The authors of the study did not perform a sample size calculation. Thus, it was unclear if the nonsignificant differences in outcome measures observed between interventions groups were the result of the lack of power to detect a hypothesized treatment effect. The methods of randomization and allocation concealment were not described. Although the results were analyzed using the intention-to-treat approach, 15.9% of the total sample had inpatient protocol deviations,

such as not receiving the assigned pharmacological intervention, receiving an intervention in an incorrect manner, or full clinic intake not performed before discharge. Overall, this study had several limitations related to reporting, external validity due to the small sample size, internal validity relating to bias, and internal validity relating to confounding that may reduce the certainty of the findings.

## Summary of Findings

Appendix 4 presents the main study findings, which were summarized by outcome (i.e., abstinence is presented in Table 6, withdrawal in Table 7, craving in Table 8, consumption in Table 9, alcohol-related clinical outcomes in Table 10, acceptability and effectiveness of intervention in Table 11, and AEs in Table 12).

### Clinical Effectiveness of Ketamine versus Placebo or No Treatment for Adults with SUDs

#### *Abstinence*

##### Alcohol Use Disorder

In the SR by Kelson et al. (2023),[16] a double-blind, placebo-controlled phase II clinical trial studied the effects of ketamine therapy in the treatment of AUD with relapse prevention-based psychological therapy. The 96 patients were randomly assigned to 1 of 4 groups: 3 weekly ketamine infusions (0.8 mg/kg) and psychotherapy, 3 weekly saline infusions and psychotherapy, 3 weekly ketamine infusions and alcohol education, or 3 weekly saline infusions and alcohol education. At 6-month follow-up, there was statistically significantly greater number of days of abstinence in the pooled ketamine group compared to placebo (mean difference [MD] = 10.1; 95% CI, 1.1 to 19). Compared with saline plus alcohol education group at 3-month follow-up, ketamine plus psychotherapy group had statistically significantly greater number of days of abstinence (MD = 15.9; 95% CI, 3.8 to 28.1).

#### *Withdrawal*

##### Alcohol Use Disorder

The SR by Kelson et al. (2023)[16] included 2 noncontrol studies evaluating the efficacy of ketamine for treatment of alcohol withdrawal.

- A single-group, retrospective cohort study examined the effectiveness of adjunctive ketamine therapy with a conventional withdrawal treatment protocol (benzodiazepine ± dexmedetomidine ± phenobarbital ± propofol ± antipsychotics ± clonidine ± intubation) in patients with alcohol withdrawing symptoms. The mean initial dose of ketamine was 0.21 mg/kg/h. Compared with baseline, there was no change in Withdrawal Assessment Scale scores (defined as a benzodiazepine-equivalent requirement of 40 mg/h of diazepam for alcohol withdrawal management) in patients within 6 hours of ketamine initiation. Ketamine treatment correlated with no statistically significant change in median benzodiazepine requirements of −40.0 mg (IQR = −106.7 to 21.7; P = 0.11) and −13.3 mg (IQR = −86.7 to 50.0, P = 0.33) at 12- and 24-hours post-infusion, respectively.
- A retrospective cohort study investigated the use of adjunctive ketamine therapy for the reduction of lorazepam infusion requirements and symptom control in patients with benzodiazepine-resistant alcohol withdrawal. The median initial infusion dose of ketamine was 0.75 mg/kg/h. The results showed that 100% of patients achieved initial symptom control at 1 hour after ketamine infusion

compared to baseline. One day after ketamine infusion, lorazepam's infusion requirements decreased by approximately 4 mg/h ($P < 0.05$). In the 48 hours following ketamine therapy, 48% of patients completely weaned off all lorazepam infusions.

#### Opioid Use Disorder

The SR by Walsh et al. (2021)[17] included a randomized placebo-controlled double-blind trial, which examined the effect of ketamine infusion (0.5 mg/kg) in assisting withdrawal from opiates. The results showed that the ketamine group was associated with less additional medication compared to the control group (i.e., carbamazepine [473 ± 335 mg versus 957 ± 423 mg; $P < 0.001$] and clonazepam [5.0 ± 2.7 mg versus 8.6 ± 3.7 mg; $P < 0.001$]) required to manage acute opiate withdrawal at 48 hours. However, there was no statistically significant difference in opiate use between the ketamine and control groups at 4 months.

### *Craving*

#### Alcohol Use Disorder

The SR by Kelson et al. (2023)[16] included 1 case series and 2 RCTs evaluating the efficacy of ketamine for alcohol craving.

- In a case series of patients with depression and AUD, a combination of naltrexone and IV ketamine (0.5 mg/kg) was associated with 80% (4/5) of patients reported improvement in alcohol cravings.
- A single-blind, placebo-controlled RCT assigned patients with AUD into either the intervention (IV ketamine targeting a plasma concentration of 350 ng/dL after alcohol use) or placebo groups (IV ketamine with no alcohol consumption or IV saline after alcohol use). Compared to day 1, 10-day posttreatment resulted in significant reductions in the intervention group in the urge to drink a beer placed in front ($P < 0.001$) and in the urge to drink more beer after drinking ($P < 0.001$), with no significant reduction in the control groups.
- A double-blind, placebo-controlled phase II clinical trial that studied the effects of ketamine therapy in the treatment of AUD with relapse prevention-based psychological therapy found no statistically significant difference across groups (i.e., 3 weekly ketamine infusions and psychotherapy, 3 weekly saline infusions and psychotherapy, 3 weekly ketamine infusions and alcohol education, and 3 weekly saline infusions and alcohol education) in craving for alcohol use.

### *Consumption*

#### Alcohol Use Disorder

The SR by Kelson et al. (2023)[16] included a single-blind, placebo-controlled RCT examining the effects of ketamine on alcohol consumption. The study assigned patients to either the intervention (IV ketamine targeting a plasma concentration of 350 ng/dL after alcohol use) or placebo groups (IV ketamine with no alcohol consumption or IV saline after alcohol use). After 10 days of intervention, there was statistically significant reduction in drinking (days/week; binges/week) occurred in the ketamine group ($P < 0.001$), but not in the control group. From day 10 to 9 months of follow-up, mean weekly alcohol consumption in the ketamine group decreased from approximately 672 g to 328 g.

### Opioid Use Disorder

The SR by Walsh et al. (2021)[17] included a placebo-controlled double-blind trial, which examined the effect of ketamine infusion (0.5 mg/kg) in assisting withdrawal from opiates. The results showed that, at 4 months of follow-up, there was no statistically significant difference in opiate use between the ketamine and placebo groups (mean opiate-free weeks were 9.4 versus 8, respectively).

## Clinical Effectiveness of Ketamine Versus Alternative Interventions for Adults With SUD

### *Abstinence*

### Alcohol Use Disorder

The SR by Kelson et al. (2023)[16] included 3 studies that appraised the effectiveness of ketamine compared with alternative interventions for the treatment of AUD.

- An RCT examined the effectiveness of "affective contra-attribution" method of alcohol dependent treatment, which consisted of introductory psychotherapy, ketamine psychedelic treatment (3 mg/kg IM) in combination with aethimizol and bemegride, and group therapy. The aim of this method was to change patients' attitudes toward alcohol consumption by creating a negative association with alcohol. The comparator group received conventional AUD treatment (aversive emetic therapy, pharmacologic treatment for cravings, and psychotherapy). The treatment duration was 3 months. At 1-year follow-up, 69.8% (60/86) of patients in the ketamine group reported sobriety compared to 24% (24/100) in the control group. The statistical significance of this finding was not reported.
- The same authors conducted a subsequent cohort study to analyze the effectiveness of ketamine psychedelic therapy (aethimizol, bemegride, ketamine [2.5 mg/kg IM], and psychotherapy) versus conventional AUD treatment. The ketamine psychedelic therapy focused more on existential and transpersonal psychology. The treatment duration was 3 months. At 1-year follow-up, 65.8% (73/111) of patients in the ketamine group reported complete sobriety compared to 24% (24/100) in the control group. The statistical significance of this finding was not reported.
- A randomized, midazolam-controlled pilot trial was conducted to study the effects of a single ketamine infusion (0.71 mg/kg) combined with motivational enhanced therapy (6 sessions) for the treatment of AUD. During 21 days after infusion, the proportion of patients with abstinence in the ketamine group remained stable, while it decreased substantially in the midazolam group. At 6 months, 75% (6/8) of patients in the ketamine group and 27% (3/11) in the control remained abstinent. The statistical significance of this finding was not reported.

### Cocaine Use Disorder

The SR by Walsh et al. (2021)[17] included an RCT comparing a single dose of IV ketamine (0.5 mg/kg) with active control midazolam. Both groups received mindfulness-based relapse prevention therapy. At the end of the 2-week study period, 48.2% (13/27) patients in the ketamine group remained abstinent compared to 10.7% (3/28) of patients in the midazolam group (P = 0.02).

### *Withdrawal*

#### Alcohol Use Disorder

The SR by Kelson et al. (2023)[16] included 2 studies (1 retrospective cohort study, 1 RCT) examining the efficacy of ketamine infusion in improving outcomes in patients with severe alcohol withdrawal.

- In a retrospective cohort study, patients were either treated with IV ketamine (0.15 to 0.3 mg/kg/h) plus conventional withdrawal treatment or conventional withdrawal treatment alone. The results showed that ketamine therapy was associated with a statistically significant reduction in the mean of benzodiazepine dose compared to control (1,508.5 mg versus 2,525.1 mg; P = 0.02). Patients treated with ketamine had shorter duration of stay in intensive care unit (MD = −2.83 days; 95% CI, −5.58 to −0.089; P = 0.043) and were less likely to be intubated (odds ratio = 0.14; 95% CI, 0.04 to 0.49; P < 0.01) compared to control.
- An RCT comparing a single ketamine infusion (0.71 mg/kg) plus motivational enhanced therapy with midazolam infusion plus motivational enhanced therapy found no statistically significant difference between groups in the alleviation of withdrawal symptoms.

### *Craving*

#### Alcohol Use Disorder

The SR by Kelson et al. (2023)[16] included an RCT examining the effects of a single ketamine infusion (0.71 mg/kg) combined with motivational enhanced therapy compared with midazolam infusion plus motivational enhanced therapy in patients with AUD. The results showed no statistically significant difference between groups in craving for alcohol use.

#### Cocaine Use Disorder

The SR by Walsh et al. (2021)[17] included 3 RCTs assessing the effects of a single dose of ketamine infusion with active control lorazepam or midazolam on craving for cocaine use.

- One RCT compared ketamine infusions (51 minutes infusions; 0.41 mg/kg first dose; 0.71 mg/kg second dose; 48 hour between doses) with lorazepam. A single dose of ketamine infusion (0.41 mg/kg) statistically significantly increased motivation to quit cocaine use (median 3.6 points versus 0.15 points; P = 0.012), and reduced craving (median change −126 points vs 65 points; P = 0.012) compared to lorazepam. Subsequent injection of ketamine (0.71 mg/kg) resulted in further reductions in craving compared to lorazepam (median −18 points vs 53 points; P = 0.046) but did not have a statistically significant impact on motivation to quit cocaine use (P = 0.11). A subsequent publication from the same research group reported that ketamine-induced mystical experiences mediated the effects, but not its dissociative effects.
- One RCT compared ketamine infusions (0.11 mg/kg for 2-minute bolus followed by 0.60 mg/kg) with a 2-minute saline bolus followed by active control midazolam. The results showed that ketamine significantly reduced craving at 24-hour post-infusion compared to midazolam, but not throughout the monitoring period (i.e., 6 days).

- One RCT assigned patients to either ketamine infusion (0.5 mg/kg) or midazolam combined with mindfulness-based relapse prevention therapy. At the end of the 14-day study period, craving scores assessed with visual analogue scale were 58.1% lower in the ketamine group compared to the midazolam group (P = 0.01).

### *Consumption*

#### Alcohol Use Disorder

The SR by Kelson et al. (2023)[16] included a randomized, midazolam-controlled trial examining the effects of a single ketamine infusion (0.71 mg/kg) combined with motivational enhanced therapy for the treatment of AUD. At 3-week follow-up after infusion, 47.1% (8/17) in the ketamine group and 59.1% (13/22) in the midazolam group used alcohol products. The statistical significance of this finding was not reported. There was statistically significant reduction with time in heavy drinking days in the ketamine group compared with midazolam group (P < 0.001).

#### Cocaine Use Disorder

The SR by Walsh et al. (2021)[17] included 2 RCTs assessing the effects of a single dose of ketamine infusion with active control midazolam on cocaine use.

- One RCT compared ketamine infusions (0.11 mg/kg for 2 minutes bolus followed by 0.60 mg/kg) with 2-minute saline bolus followed by active control midazolam. Compared to midazolam, ketamine significantly reduced cocaine choices 28 hour after administration (1.61 choices versus 4.33 choices; P < 0.0001), representing a 67% reduction in cocaine choices with ketamine compared to baseline. Furthermore, ketamine group reported statistically significant reduction in cocaine use initially compared to midazolam (P < 0.05), but the effect lasted only for several days, and disappeared after 2 weeks.
- One RCT assigned patients to either ketamine infusion (0.5 mg/kg) or midazolam combined with mindfulness-based relapse prevention therapy. The results showed that 55.5% (15/27) of patients in the ketamine group continued to use cocaine compared to 92.9% (26/28) in the midazolam group (P = 0.01). The odds of cocaine use in the control group were 7.8 times the odds in the ketamine group. There was no change in drug use over a 5-week follow-up period in either group, suggesting that the early improvement by ketamine was maintained throughout the trial.

### *Alcohol-Related Clinical Outcomes*

The included primary study by Terasaki et al. (2022)[18] was a 3-arm, open-label RCT, assigning patients with AUD to IV ketamine (0.5 mg/kg), naltrexone, or linkage alone. After discharge, follow-up outcomes included a 30-day all-cause hospital readmission rate, a 30-day all-cause emergency department visit, and 14-day clinic attendance. The study found no statistically significant differences among groups in any of those outcomes.

### *Acceptability and Perceived Effectiveness*

The included primary study by Terasaki et al. (2022)[18] used a 10-point Likert Scale to assess the acceptability and anticipated effectiveness of the intervention immediately post-administration. The study found no statistically significant differences between ketamine and naltrexone groups for either outcome.

*Adverse Events*

Ketamine-related AEs reported in the SR by Walsh et al. (2021)[17] included increased blood pressure, tachycardia and bradycardia at higher doses of ketamine, severe cardiac effects, including intermittent atrial fibrillation and single salve of ventricular extrasystoles, dissociative and psychotomimetic effects (e.g., unusual thought content, visual hallucinations, and conceptual disorganization), dysphoria and treatment-emergent suicidal ideation, mania and hypomania, and nondissociative effects (e.g., mild sedation, agitation, nausea and vomiting, headache, dizziness, blurred vision, dry or numb mouth, delirium, irritability, sensory changes, urination problems, vertigo and drowsiness). The authors reported that most of those AEs were mild and transient.

Ketamine-related AEs reported in the included primary study by Terasaki et al. (2022)[18] were shortness of breath, anxiety, poor concentration, fatigue, restlessness, rise in blood pressure, and dissociative symptoms. The authors did not observe any serious AEs.

**Clinical Effectiveness of Ketamine Administered via Different Routes for Adults With SUD**

We did not identify any relevant evidence regarding the clinical effectiveness of ketamine administered via different routes for adults with SUDs; therefore, no summary can be provided.

**Cost-Effectiveness of Ketamine Versus Placebo or No Treatment for Adults With SUDs**

We did not identify any relevant evidence regarding the cost-effectiveness of ketamine versus placebo or no treatment for adults with SUDs; therefore, no summary can be provided.

**Cost-Effectiveness of Ketamine Versus Alternative Interventions for Adults With SUDs**

We did not identify any relevant evidence regarding the cost-effectiveness of ketamine versus alternative interventions for adults with SUDs; therefore, no summary can be provided.

**Cost-Effectiveness of Ketamine Administered via Different Routes for Adults With SUDs**

We did not identify any relevant evidence regarding the cost-effectiveness of ketamine administered via different routes for adults with SUDs; therefore, no summary can be provided.

**Evidence-Based Guidelines Regarding the Use and Administration of Ketamine for Adults With SUDs**

We did not identify any evidence-based guidelines regarding the use and administration of ketamine for adults with;SUDs therefore, no summary can be provided.

# Limitations

## Evidence Gaps

There were no cost-effectiveness studies or evidence-based guidelines that could be identified in this review. Studies comparing different routes of administration of ketamine were not identified. None of the included studies described the effects of ketamine on patient-reported outcomes such as quality of life. Additional

clinical studies with long-term follow-up are needed to better understand the safety of ketamine for the treatment of SUDs. Studies on specific populations such as veterans were not identified. None of the primary studies included in the SRs were conducted in Canada.

### Certainty of the Evidence

The included SRs[16,17] had several limitations. First, many of the included studies in the SRs[16,17] had small sample size. Nine of 11 studies on AUD included in the SR by Kelson et al. (2023)[16] had number of patients less than 100, including 2 case series. The SR by Walsh et al. (2021) included 3 studies on CUD with sample sizes of 8, 20 and 55 patients, and 1 study on OUD with 50 patients. Second, a meta-analysis could not be conducted in both SRs[16,17] due to substantial heterogeneity among the study design, inclusion criteria, dosing regimen, use of concomitant medications, outcome variables, treatment duration, and follow-up period. Third, blinding in some RCTs included in the SRs[16,17] may have been compromised due to the dissociative and psychogenic properties of ketamine. Fourth, most studies included in the SRs[16,17] were graded by the authors as associated with a moderate to high risk of bias due to methodological limitations, thus reducing the certainty of the overall findings. Fifth, the efficacy of ketamine for participants in the studies included in the SRs[16,17] may not be generalizable to all patients with AUD, CUD, or OUD due to strict eligibility criteria. The included RCT by Terasaki et al. (2022)[18] was a pilot trial underpowered to detect statistically significant differences between groups. The study could not be blinded due to the unique psychoactive effects of ketamine.

## Conclusions and Implications for Decision- or Policy-Making

This review included 2 SRs[16,17] and 1 RCT[18] regarding the clinical effectiveness of ketamine for treating patients with AUD,[16,18] and CUD and OUD.[17]

Findings from the 2 included SRs[16,17] suggested that a combination of ketamine and psychotherapy treatment may be effective in promoting abstinence and reducing alcohol and cocaine use. The results were mixed concerning withdrawal and craving. Findings from a single study included in the SR by Walsh et al. (2022)[17] on the effect of ketamine for the treatment of OUD for consumption and withdrawal were inconclusive. The effect of ketamine on health care utilization in patients with severe AUD reported in the included RCT was also inconclusive due to small sample size. At subanesthetic dosing, ketamine treatment was associated with dissociative and psychotomimetic effects, and nondissociative effects. While these effects were mild and transient, the dissociative or psychomimetic characteristics and abuse potential of ketamine remains a concern in long-term treatments.[20]

Further high-quality clinical trials with larger sample sizes, blinding, and low risk of bias would help to provide more accurate findings on clinical efficacy, dosing strategies, and safety profile of ketamine for the treatment of AUD, CUD and OUD. Studies on other substances of abuse (e.g., nicotine, amphetamines, and cannabis) may provide important insights to the overall efficacy of ketamine in the treatment of SUDs. Research on optimal dose, route and frequency of administration, and combination of psychotherapy will also be paramount to determine the optimal treatment protocol of ketamine for treating of each specific SUDs.

Economic studies are also warranted to determine the cost-effectiveness of ketamine for treating SUDs. Evidence-based guidelines are needed to provide recommendations on the optimal protocols for maximizing the clinical effectiveness of ketamine for treatment of SUDs and minimizing the risks for ketamine-related adverse effects.

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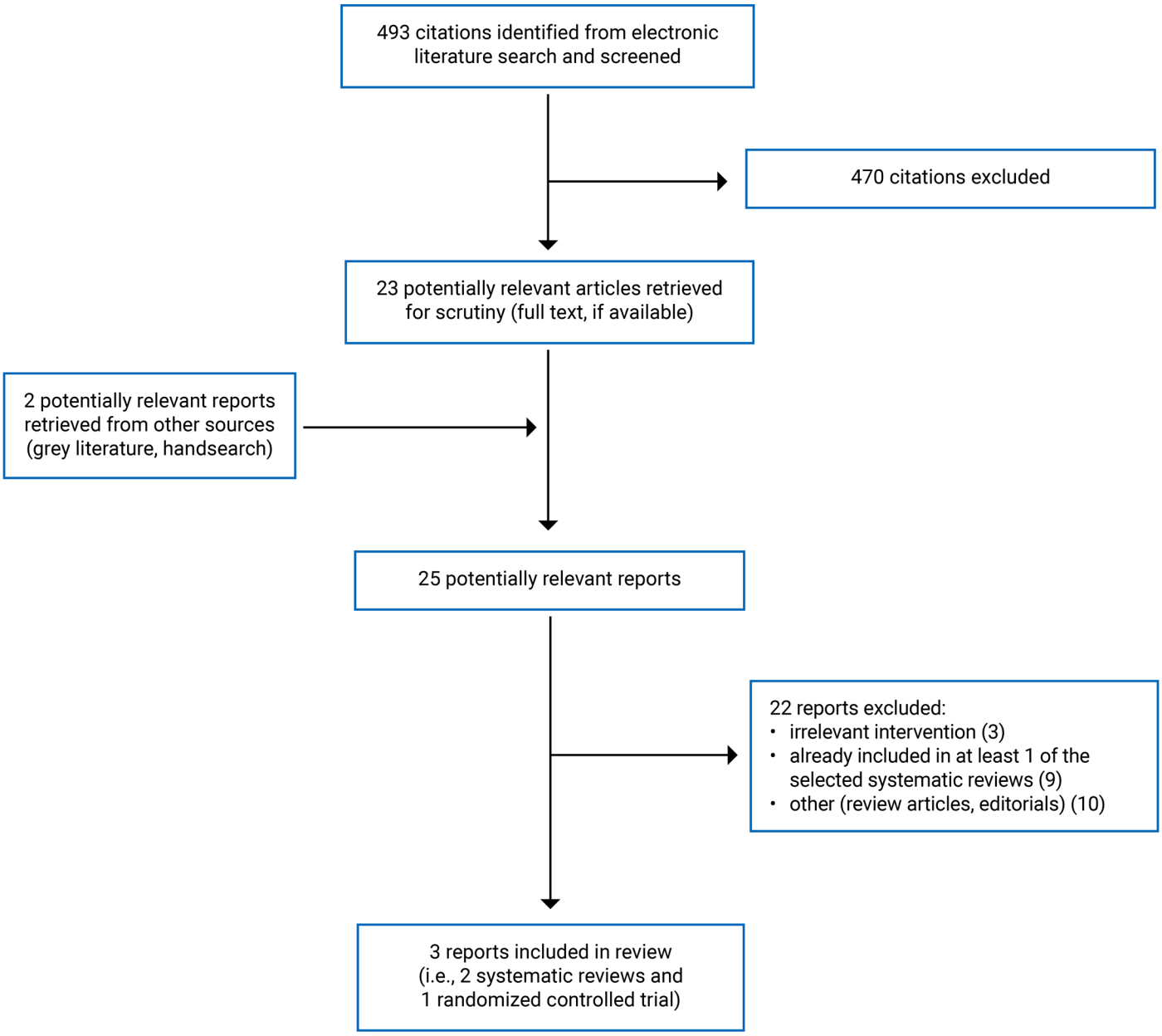
# Appendix 1: Selection of Included Studies

## Figure 1: Selection of Included Studies



# Appendix 2: Characteristics of Included Publications

## Table 2: Characteristics of Included Systematic Reviews

| Study citation, country, funding source | Study designs and numbers of primary studies included | Population characteristics | Intervention and comparator(s) | Clinical outcomes, length of follow-up |
|---|---|---|---|---|
| Kelson et al. (2023)[16]<br>**Country:** US<br>**Funding source:** NR | SR<br>Total 11 studies (5 RCTs, 4 cohort studies, 2 case series)<br>Relevant studies to our report: 10 (excluded 1 study on ketamine-enhanced psychotherapy)<br>**Sample size**: Total 854 adult patients (ranging from 5 to 211 patients in each primary study)<br>**Countries of the primary studies**: US (7), UK (2), Russia (2)<br>**Publication year of primary studies**: 1992 to 2022 | Patients with AUD (7 studies)<br>Heavy drinkers and at moderate to high risk of developing AUD (1 study)<br>Patients with alcohol withdrawal (3 studies)<br>Age:<br>• Range of mean age, years: 27.5 to 53 (9 studies)<br>• Median age: 50 (IQR = 47 to 54) (1 study)<br>Sex, % (in 10 relevant studies):<br>• Male: 100 to 61<br>• Female: 0 to 39 | **Intervention vs. Comparator:**<br>• IM ketamine (2.5 mg/kg or 3 mg/kg) + IM aethimizol + IV bemegride + psychotherapy vs. conventional AUD treatment[a] (2 studies)<br>• IV ketamine (mean initial dose 0.21 mg/kg/h; median infusion dose 0.20 mg/kg/h, IQR 0.12 to 0.23; ± loading dose 0.3 mg/kg) + conventional withdrawal treatment[b] vs. baseline (1 study)<br>• IV ketamine (0.15 to 0.3 mg/kg/h) ± ketamine bolus + conventional withdrawal treatment vs. conventional withdrawal treatment (1 study)<br>• IV ketamine (median initial dose 0.75 mg/kg/h, IQR 0.5 to 1.0; mean max daily infusion 1.6 mg/kg/h) + conventional withdrawal treatment vs. baseline (1 study)<br>• IV ketamine (0.5 mg/kg) + injectable naltrexone (380 mg) vs. baseline (1 study)<br>• IV ketamine (350 ng/dL) after alcohol use vs. IV ketamine (350 ng/dL) + no alcohol vs. IV saline after alcohol use (1 study)<br>• IV ketamine (0.71 mg/kg) + MET vs. IV midazolam + MET (2 studies)<br>• IV ketamine (0.8 mg/kg) + psychotherapy vs. IV saline + psychotherapy vs. IV | **Outcomes:**<br>• Abstinence<br>• Withdrawal<br>• Craving<br>• Consumption<br>Treatment duration: 1 week to 3 months<br>**Follow-up**: 1 hour postperfusion to 3 years posttreatment |

| Study citation, country, funding source | Study designs and numbers of primary studies included | Population characteristics | Intervention and comparator(s) | Clinical outcomes, length of follow-up |
|---|---|---|---|---|
| | | | ketamine + alcohol education vs. IV saline + alcohol education (1 study) | |
| Walsh et al. (2021)[17]<br>**County:** UK<br>**Funding source:** Medical Research Council | SR<br>Total 83 studies on unipolar depression and major depressive disorder, bipolar disorder, suicidal ideation, generalized and social anxiety disorders, posttraumatic stress disorder, eating disorders, and SUD.<br>Relevant studies to our report: 5 studies (4 studies on CUD and 1 study on OUD)<br>The 6 studies on AUDs were also included in the SR by Kelson et al. (2023)[16]<br>**Countries of the primary studies:**<br>• CUD: US (4)<br>• OUD: Lithuania (1)<br>**Publication year of primary studies:**<br>• CUD: 2014 to 2019<br>• OUD: 2006 | Relevant populations to our report were patients with CUD and those with OUD.<br>Population characteristics were not reported. | **Intervention vs. Comparator:**<br>Cocaine use disorder:<br>• Ketamine (0.41 mg/kg first dose; 0.71 mg/kg second dose; 48 hour between doses; 52 minute infusions) vs. lorazepam (2 mg; 52 minute infusions) (1 study, described in 2 publications)<br>• Ketamine (0.11 mg/kg 2 minute bolus followed by 0.60 mg/kg) vs. 2-minute saline bolus followed by active control Midazolam (0.025 mg/kg) (1 study)<br>• Ketamine (0.5 mg/kg, slow drip 40 minutes infusion. Single dose.) + MRPT vs. active control midazolam (0.025 mg/kg) + MRPT (1 study)<br>Opioid use disorder:<br>• Ketamine (0.5 mg/kg) vs. placebo (saline solution) (1 study) | **Outcomes:**<br>• Consumption<br>• Craving<br>• Withdrawal<br>• AEs<br>**Follow-up:**<br>• Cocaine use disorders: 24 hours, 2 weeks<br>• Opioid use disorders: From posttreatment to up to 4 months |

AE = adverse effect; AUD = alcohol use disorder; CUD = cocaine use disorder; IM = intramuscular; IQR = interquartile range; MET = motivational enhancement therapy; min = minute; MRPT = mindfulness-based relapse prevention therapy; NR = not reported; OUD = opioid use disorder; RCT = randomized controlled trial; SR = systematic review.

[a]Conventional AUD treatment included aversive emetic therapy, pharmacologic treatment of cravings, psychotherapy.

[b]Conventional withdrawal treatment included benzodiazepine ± dexmedetomidine ± phenobarbital ± propofol ± antipsychotics ± clonidine ± intubation.

Note: This table has not been copy-edited.

## Table 3: Characteristics of Included Primary Clinical Study

| Study citation, country, funding source | Study design | Population characteristics | Intervention and comparator(s) | Clinical outcomes, length of follow-up |
|---|---|---|---|---|
| Terasaki et al. (2022)[18]<br>**Country:** US<br>**Funding source:** Grant within the institution | 3-arm, open-label RCT<br>Total 44 patients<br>Sample size calculation: No<br>ITT analysis: Yes | Adult patients with severe AUD<br>Mean age, years (SD): 45.11 (10.90)<br>Gender, %:<br>• Male: 79.5<br>• Female: 20.5<br>Mean number of daily drinks (SD): 12.0 (9.69)<br>Mean number of ED visits in the previous year (SD): 10.91 (8.29)<br>Mean number of hospital admission in the previous year (SD): 3.23 (3.88) | **Intervention:**<br>• IV ketamine (0.5 mg/kg over 40 minute) (n = 13)<br>**Comparator:**<br>• IM naltrexone (380 mg once) (n = 14)<br>• Linkage alone[a] (n = 17) | **Outcomes:**<br>• 30-day hospital readmission<br>• 30-day ED visit<br>• 14-day clinic attendance<br>• Acceptability[b]<br>• Effectiveness of intervention[b] (in terms of reducing alcohol intake)<br>• Safety (AEs at post-intervention and at follow-up visit)<br>**Follow-up:** From post-intervention to 30 days |

AE = adverse event; AUD = alcohol use disorder; ED = emergency department; IM = intramuscular; ITT = intention to treat; RCT = randomized controlled trial; SD = standard deviation.

[a]Linkage alone: No pharmacological intervention, but patients still received outpatient addiction clinic linkage and the research stipends.

[b]Acceptability and effectiveness of intervention were measured using a 10-point Likert Scale (1 to 10), with 1 represents the least positive experience and 10 represents the most positive experience.

# Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

## Table 4: Strengths and Limitations of SR Using AMSTAR 2[13]

| Strengths | Limitations |
|---|---|
| **Kelson et al. (2023)[16]** | |
| • The research question or objective and the inclusion criteria for the review clearly include the components of PICO.<br>• A study protocol was published before conducting the review.<br>• The review authors explained their selection of eligible study designs, which were RCTs and nonrandomized studies.<br>• The literature search strategy was comprehensive and clearly described, using multiple combinations of keywords. The authors also hand searched the reference lists of the included studies.<br>• The review authors performed study selection, data extraction, and quality assessment of the included studies in duplicate. This reduced the risk of inconsistencies in these processes.<br>• The characteristics of the included studies were described in adequate details, including study design, intervention, control, treatment duration, follow-up time, and outcomes.<br>• The methodological quality of the included studies was assessed using the Cochrane Risk of Bias tool for RCTs, and ROBINS-I for nonrandomized studies.<br>• The review authors provided a discussion of the heterogeneity observed in the results, which was the main reason for not conducting a meta-analysis.<br>• The review authors declared that they had no conflicts of interest related to this work. | • Patient characteristics were not adequately described.<br>• A list of excluded studies and the reasons for exclusion were not provided. Therefore, it was not possible to assess whether any relevant articles were excluded and if so, for what reasons.<br>• The review authors assessed several of the included primary studies to be at high risk of bias due to methodological limitations.<br>• The review authors did not report the sources of funding for the included studies. This is potentially a concern because funding received from industry can introduce bias in favour of the intervention.<br>• The review authors did not report the source of funding of the study. |
| **Walsh et al. (2021)[17]** | |
| • The research question or objective and the inclusion criteria for the review clearly include the components of PICO.<br>• A study protocol was published before conducting the review.<br>• The review authors explained their selection of study designs, which included all study designs except case studies.<br>• The literature search strategy was comprehensive and clearly described, using multiple combinations of keywords. The authors also hand searched the reference lists of the included studies.<br>• The review authors performed study selection, data extraction and quality assessment of the included studies with 4 reviewers. This reduced the risk of inconsistencies in these processes.<br>• The characteristics of the included studies were described in adequate details, including study design, intervention, control, treatment duration, follow-up time, and outcomes. | • Patient characteristics were not adequately described.<br>• The review authors assessed several of the included primary studies to be at high risk of bias due to methodological limitations.<br>• The review authors did not report the sources of funding for the included studies. |

| Strengths | Limitations |
|---|---|
| • The methodological quality of the included studies was assessed using the Cochrane Risk of Bias tool for RCTs, ROBINS-I for nonrandomized studies, and AMSTAR 2 for SR.<br>• A list of excluded studies and the reasons for exclusion were provided.<br>• The review authors provided a discussion of the heterogeneity observed in the results, which was the main reason for not conducting a meta-analysis.<br>• The review authors reported the source of funding and declared that they had no conflicts of interest related to this work. | |

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; PICO = population, intervention, comparator, and outcome; RCT = randomized controlled trial; ROBINS-I = Risk of Bias in Nonrandomized Studies of Interventions; SR = systematic review.

## Table 5: Strengths and Limitations of Clinical Study Using the Downs and Black Checklist[14]

| Strengths | Limitations |
|---|---|
| **Terasaki et al. (2022)[18]** | |
| **Reporting:**<br>• The objective of the study, the characteristics of participants, the main outcomes to be measured, the interventions of interest, and the main findings were clearly described.<br>• There were no patients lost to follow-up, but there were 7 significant inpatient protocol deviations (15.6% of total sample), which was clearly reported.<br>• Adverse events of the intervention were reported.<br>• Actual P values were reported for the main outcomes.<br>**External validity:**<br>• The staff, places, and facilities where the patients were treated were representative of the treatment the majority of the patients receive. The study was conducted in an outpatient hospital setting.<br>**Internal validity – bias:**<br>• All patients were followed up for the same period of time, which was up to 30 days.<br>• Statistical tests were used appropriately, and the main outcome measures were accurate and reliable.<br>• The primary outcomes were accurately measured.<br>**Internal validity – confounding:**<br>• Patients in both intervention groups appeared to be recruited from the same population and over the same period.<br>• All participants were included in the intent-to-treat analysis. | **Reporting:**<br>• Due to small sample size, it was unclear if there were any group differences (i.e., potential confounders) in demographics of the randomized participants.<br>**External validity:**<br>• Patients were recruited from a single centre. Sample size was small (N = 44); therefore, it was unlikely that the patients who participated were representative of the entire population from which they were recruited.<br>**Internal validity – bias:**<br>• This was an open-label RCT, which may have high risk of bias.<br>**Internal validity – confounding:**<br>• Methods of randomization and allocation concealment were not described.<br>• Sample size calculation was not performed.<br>• It was unclear if there were any confounders among groups. |

# Appendix 4: Main Study Findings

Note that this appendix has not been copy-edited.

## Table 6: Summary of Findings by Outcome — Abstinence

| Study citation, study design, condition | Method of measurement | Intervention vs. comparator | Results |
|---|---|---|---|
| Kelson et al. (2023)[16]<br>SR<br>AUD | Assessed with monthly self-reported alcohol consumption | IM ketamine (3 mg/kg) + IM aethimizol + IV bemegride + psychotherapy vs. conventional AUD treatment (1 study) | 69.8% (60/86) of patients in the ketamine group reported sobriety at 1 year follow-up compared to 24% (24/100) in the control group. The statistical significance of this finding was not reported. |
| | | IM ketamine (2.5 mg/kg) + IM aethimizol + IV bemegride + psychotherapy vs. conventional AUD treatment (1 study) | • 65.8% (73/111) of patients in the ketamine group reported complete sobriety at 1-year follow-up compared to 24% (24/100) in the control group. The statistical significance of this finding was not reported.<br>• 40.7% (33/81) of patients in the ketamine group maintained sobriety after 2-year follow-up. The statistical significance of this finding was not reported.<br>• 33.3% (14/42) of patients in the ketamine group maintained sobriety after 3-year follow-up. The statistical significance of this finding was not reported. |
| | Assessed with TLFB; confirmed by glucuronide test; telephone interview 6 months after treatment | IV ketamine (0.71 mg/kg) + MET vs. IV midazolam + MET (1 study) | • During 21 days after infusion, the proportion of patients with abstinence in the ketamine group remained stable, while it decreased substantially in the midazolam group.<br>• At 6 months, 75% (6/8) of patients in the ketamine group and 27% (3/11) in the control remained abstinence. The statistical significance of this finding was not reported. |
| | Assessed with TLFB and SCRAM | IV ketamine (0.8 mg/kg) + psychotherapy vs. IV saline + psychotherapy vs. IV ketamine + alcohol education vs. IV saline + alcohol education (1 study) | • At 6-month follow-up, there was significantly greater number of days abstinent in the ketamine group compared to placebo (MD = 10.1; 95% CI, 1.1 to 19)<br>• At 3-month follow-up, ketamine + therapy group had significantly |

| Study citation, study design, condition | Method of measurement | Intervention vs. comparator | Results |
|---|---|---|---|
| | | | greater number of days abstinent compared to saline + education (MD = 15.9; 95% CI, 3.8 to 28.1). |
| Walsh et al. (2021)[17]<br>SR<br>CUD | Assessed with self-reported questionnaire and urine toxicology | Ketamine (0.5 mg/kg, slow drip 40 minutes infusion. Single dose.) + MRPT vs. active control midazolam (0.025 mg/kg) + MRPT (1 study) | 48.2% (13/27) patients in the ketamine group remained abstinence over the last 2 weeks of trial compared to 10.7% (3/28) of patients in the midazolam group (P = 0.02). |

AUD = alcohol use disorder; CI = confidence interval; CUD = cocaine use disorder; IM = intramuscular; MD = mean difference; MET = motivational enhancement therapy; MRPT = mindfulness-based relapse prevention therapy; SCRAM = Secure Continuous Remote Alcohol Monitor; SR = systematic review; TLFB = Timeline Follow back; URICA = University of Rhode Island Change Assessment.

## Table 7: Summary of Findings by Outcome — Withdrawal

| Study citation, study design, condition | Method of measurement | Intervention vs. comparator | Results |
|---|---|---|---|
| Kelson et al. (2023)[16]<br>SR<br>AUD | Assessed with benzodiazepine dose requirements; WAS | IV ketamine (mean initial dose 0.21 mg/kg/h; median infusion dose 0.20 mg/kg/h, IQR 0.12 to 0.23; ± loading dose 0.3 mg/kg) + conventional withdrawal treatment[a] vs. baseline (1 study) | • No change in WAS scores in patients within 6 hours of ketamine initiation.<br>• Statistically nonsignificant change in median benzodiazepine requirements of −40.0 mg (IQR = −106.7 to 21.7; P = 0.11) and −13.3 mg (IQR = −86.7 to 50.0, P = 0.33) at 12- and 24-hours post-infusion, respectively. |
| | Assessed with benzodiazepine dose requirements based on WAS > 10; ICU days; intubations | IV ketamine (0.15 to 0.3 mg/kg/h) ± ketamine bolus + conventional withdrawal treatment vs. conventional withdrawal treatment (1 study) | • Significant reduction in mean benzodiazepine dose in the ketamine group compared to control (1,508.5 mg vs. 2,525.1 mg; P = 0.02).<br>• Patients treated with ketamine had decrease ICU stay by 2.83 days (95% CI = −5.58 to −0.089; P = 0.043).<br>• Patients treated with ketamine were less likely to be intubated (OR = 0.14; 95% CI, 0.04 to 0.49); P < 0.01). |
| | Assessed with benzodiazepine dose requirements; CIWA-Ar; MAAS | IV ketamine (median initial dose 0.75 mg/kg/h, IQR 0.5 to 1.0; mean max daily infusion 1.6 mg/kg/h) + conventional withdrawal treatment vs. baseline (1 study) | • At 1 hour after ketamine infusion, 100% of patients achieved initial symptom control (defined as CIWA-Ar < 20 or if intubated, a MASS score < 4).<br>• 43% (13/30) of patients weaned off all infusions within 48 hour of ketamine initiation. |

| Study citation, study design, condition | Method of measurement | Intervention vs. comparator | Results |
|---|---|---|---|
| | | | • 1 day after ketamine infusion, there was statistically significant reduction in lorazepam requirement (~4 mg/h; P < 0.05). |
| | Assessed with CIWA | IV ketamine (0.71 mg/kg) + MET vs. IV midazolam + MET (1 study) | Statistically nonsignificant difference between groups. |
| Walsh et al. (2021)[17]<br>SR<br>OUD | Assessed with OOWS for withdrawal severity during anesthesia | Ketamine (0.5 mg/kg) vs. placebo (saline solution) (1 study) | • Ketamine was associated with less additional medication (i.e., carbamazepine [473 ± 335 mg vs. 957 ± 423 mg; P < 0.001] and clonazepam [5.0 ± 2.7 mg vs. 8.6 ± 3.7 mg; P < 0.001]) required to manage acute opiate withdrawal at 48 hour.<br>• At 4 months, there was no significant difference in opiate use between the ketamine and control groups. |

AUD = alcohol use disorder; CI = confidence interval; CIWA = Clinical Institute Withdrawal Assessment for Alcohol; CIWA-AR = Clinical Institute Withdrawal Assessment for Alcohol, revised; h = hour; ICU = intensive care unit; IQR = interquartile range; MASS = Motor Activity Assessment Scale; MET = motivational enhancement therapy; OOWS = Objective Opioid Withdrawal Scale; OR = odds ratio; OUD = opioid use disorder; SR = systematic review; WAS = Withdrawal Assessment Scale.

[a]Conventional withdrawal treatment includes benzodiazepine ± dexmedetomidine ± phenobarbital ± propofol ± antipsychotics ± clonidine ± intubation.

## Table 8: Summary of Findings by Outcome — Craving

| Study citation, study design, condition | Method of measurement | Intervention vs. comparator | Results |
|---|---|---|---|
| Kelson et al. (2023)[16]<br>SR<br>AUD | Assessed with OCDS | IV ketamine (0.5 mg/kg) + injectable naltrexone (380 mg) vs. baseline (1 study) | 80% (4/5) of patients reported improvement in alcohol cravings. |
| | Assessed with Likert Scale | IV ketamine (plasma concentration of 350 ng/dL) after alcohol use vs. IV ketamine (350 ng/dL) + no alcohol vs. IV saline after alcohol use (1 study) | Significant reduction in the ketamine group for urges to drink before consumption (P < 0.001) and after consumption (P < 0.001). |
| | Assessed with VAS | IV ketamine (0.71 mg/kg) + MET vs. IV midazolam + MET (1 study) | Statistically nonsignificant difference between groups. |
| | Assessed with ACQ-NOW | IV ketamine (0.8 mg/kg) + psychotherapy vs. IV saline + psychotherapy vs. IV ketamine + alcohol education vs. IV saline + alcohol education (1 study) | Statistically nonsignificant difference across groups. |

| Study citation, study design, condition | Method of measurement | Intervention vs. comparator | Results |
|---|---|---|---|
| Walsh et al. (2021)[17]<br>SR<br>CUD | Assessed with URICA for motivation to quit cocaine; VAS for craving | Ketamine (0.41 mg/kg first dose; 0.71 mg/kg second dose; 48 hour between doses; 52 minute infusions) vs. lorazepam (2 mg; 52 minute infusions) (1 study) | • The first ketamine dose (0.41 mg/kg) significantly increased motivation to quit cocaine use (median 3.6 points vs. 0.15 points; P = 0.012), and reduced craving (median change −126, vs 65; P = 0.012) compared to lorazepam.<br>• Subsequent injection of ketamine (0.71 mg/kg) resulted in further reductions in craving compared to lorazepam (median −18 vs 53; P = 0.046), but did not change motivation to quit cocaine use (P = 0.11).<br>• The effects were mediated by ketamine-induced mystical experiences. |
| | Assessed with VAS for craving | Ketamine (0.11mg/kg 2 minute bolus followed by 0.60 mg/kg) vs. 2-minute saline bolus followed by active control midazolam (0.025 mg/kg) (1 study) | Ketamine significantly reduced craving at 24 hour post-infusion compared to midazolam, but not throughout the monitoring period (i.e., 6 days). |
| | Assessed with VAS | Ketamine (0.5 mg/kg, slow drip 40 minutes infusion. Single dose.) + MRPT vs. active control midazolam (0.025 mg/kg) + MRPT (1 study) | At the end of 14-day study period, craving scores were 58.1% lower in the ketamine group compared to the midazolam group (P = 0.01). |

ACQ-NOW = Alcohol Craving Questionnaire; AUD = alcohol use disorder; CUD = cocaine use disorder; h = hour; MET = motivational enhancement therapy; MRPT = mindfulness-based relapse prevention therapy; OCDS = Obsessive Compulsive Drinking Scale; SR = systematic review; URICA = University of Rhode Island Craving Assessment; VAS = visual analogue scale.

## Table 9: Summary of Findings by Outcome — Consumption

| Study citation, study design, condition | Method of measurement | Intervention vs. comparator | Results |
|---|---|---|---|
| Kelson et al. (2023)[16]<br>SR<br>AUD | Quantitative drinking days/week, binges/week, and total alcohol use assessed with TLFB | IV ketamine (350 ng/dL) after alcohol use vs. IV ketamine (350 ng/dL) + no alcohol vs. IV saline after alcohol use (1 study) | • After 10 days of intervention, a significant reduction in drinking (days/week; binges/week) occurred in the ketamine group (P < 0.001), but not in the control group.<br>• From day 10 to 9 months of follow-up, mean weekly consumption in the ketamine group decreased from ~672 g to ~328 g. The statistical |

| Study citation, study design, condition | Method of measurement | Intervention vs. comparator | Results |
|---|---|---|---|
| | | | significance of this finding was not reported. |
| | Heavy drinking days – assessed with TLFB | IV ketamine (0.71 mg/kg) + MET vs. IV midazolam + MET (1 study) | • At 3-week follow-up, 47.1% (8/17) in the ketamine group and 59.1% (13/22) in the midazolam group used alcohol products. The statistical significance of this finding was not reported.<br>• There was significant reduction with time in heavy drinking days in the ketamine group compared with midazolam group (P < 0.001). |
| Walsh et al. (2021)[17]<br>SR<br>CUD | Assessed by self-administration and self-reported for choice of cocaine use | Ketamine (0.11mg/kg 2 minute bolus followed by 0.60 mg/kg) vs. 2-minute saline bolus followed by active control midazolam (0.025 mg/kg) (1 study) | • Compared to midazolam, ketamine significantly reduced cocaine choices 28 hour after administration (1.61 choices vs. 4.33 choices; P < 0.0001), representing a 67% reduction in cocaine choices with ketamine compared to baseline.<br>• Ketamine led to significant reduction in cocaine use initially compared to midazolam, but lasted only for several days. |
| | Assessed with self-reported and urine toxicology | Ketamine (0.5 mg/kg, slow drip 40 minutes infusion. Single dose.) + MRPT vs. active control midazolam (0.025 mg/kg) + MRPT (1 study) | In the ketamine group, 55.5% (15/27) continued to use cocaine compared to 92.9% (26/28) in the midazolam group (P = 0.01). There was no change in drug use over time in either group. |
| Walsh et al. (2021)[17]<br>SR<br>OUD | Assessed with self-reported | Ketamine (0.5 mg/kg) vs. placebo (saline solution) (1 study) | At 4-month follow-up, there was no significant difference in opiate use between the ketamine and placebo groups (mean opiate free weeks 9.4 vs 8). |

AUD = alcohol use disorder; CUD = cocaine use disorder; MET = motivational enhancement therapy; MRPT = mindfulness-based relapse prevention therapy; OUD = opioid use disorder; SR = systematic review; TLFB = Timeline Follow back.

## Table 10: Summary of Findings by Outcome — Alcohol-Related Clinical Outcomes

| Study citation, study design, condition | Method of measurement | Intervention vs. comparator | Results |
|---|---|---|---|
| Terasaki et al. (2022)[18]<br>RCT<br>AUD | Assessed with electronic health record | IV ketamine (0.5 mg/kg over 40 minute) vs. IM naltrexone (380 mg once) vs.<br>Linkage alone | • 30-day hospital readmission: 15.4% (2/13) vs. 21.4% (3/14) vs. 41.2% (7/17); NS among groups<br>• 30-day ED visit: 53.9% (7/13) vs. 57.1% (8/14) vs. 70.6% (12/17); NS among groups<br>• 14-day clinic attendance: 61.5% (8/13) vs. 50.0% (7/14) vs. 41.2% (7/17); NS among groups |

ED = emergency department; IM = intramuscular; NS = no statistically significant difference; RCT = randomized controlled trial.

## Table 11: Summary of Findings by Outcome — Acceptability and Perceived Effectiveness of Intervention

| Study citation, study design, condition | Method of measurement | Intervention vs. comparator | Results |
|---|---|---|---|
| Terasaki et al. (2022)[18]<br>RCT<br>AUD | Assessed with Likert Scale (ranging from 1 to 10) | IV ketamine (0.5 mg/kg over 40 minute) vs. IM naltrexone (380 mg once) | • Acceptability: 9.50 vs. 9.17; NS between groups<br>• Perceived effectiveness: 8.75 vs. 7.75; NS between groups |

AUD = alcohol use disorder; IM = intramuscular; NS = no statistically significant difference; RCT = randomized controlled trial.

## Table 12: Summary of Findings by Outcome — Adverse Events

| Study citation, study design, condition | Method of measurement | Intervention | Results |
|---|---|---|---|
| Walsh et al. (2021)[17]<br>SR<br>CUD; OUD | Self-reported or clinician assessed | IV ketamine | The authors of the SR described that most AEs reported in the included primary studies were mild and transient.<br>• Increase in blood pressure.<br>• Tachycardia and bradycardia at higher doses of ketamine.<br>• More severe cardiac effects, including intermittent atrial fibrillation and single salve of ventricular extrasystoles.<br>• Dissociative and psychotomimetic effects: unusual thought content, visual hallucinations, and conceptual disorganization.<br>• Dysphoria and treatment-emergent suicidal ideation.<br>• Mania and hypomania. |

| Study citation, study design, condition | Method of measurement | Intervention | Results |
|---|---|---|---|
| | | | • Nondissociative effects: mild sedation, agitation, nausea and vomiting, headache, dizziness, blurred vision, dry or numb mouth, delirium, irritability, sensory changes, urination problems, vertigo, and drowsiness. |
| Terasaki et al. (2022)[18]<br>RCT<br>AUD | Self-reported or clinical assessed | IV ketamine | • Shortness of breath, anxiety, poor concentration, fatigue, restlessness.<br>• Rise in blood pressure (both systolic and diastolic).<br>• Dissociative symptoms.<br>• No serious AEs reported. |

AE = adverse event; AUD = alcohol use disorder; CUD = cocaine use disorder; NS = no statistically significant difference; OUD = opioid use disorder; RCT = randomized controlled trial; SR = systematic review.

# Appendix 5: Overlap Between Included SR

Note that this appendix has not been copy-edited.

## Table 13: Overlap in Relevant Primary Studies Between Included SRs

| Primary study citation | Kelson et al. (2023)[16] | Walsh et al. (2021)[17] |
|---|---|---|
| **AUD** | | |
| Krupitsky EM, Grineko AY, Berkaliev TN, Paley AI, Tetrov UN, Mushkov KA, Borodikin YS. Alcohol Treat Q. 1992, 9:99 to 105. | Yes | Yes |
| Krupitsky EM, Grinenko AY: Ketamine psychedelic therapy (KPT). J Psychoactive Drugs. 1997, 29:165 to 83. | Yes | Yes |
| Wong A, Benedict NJ, Armahizer MJ, Kane-Gill SL. Ann Pharmacother. 2015, 49:14 to 9. | Yes | Yes |
| Pizon AF, Lynch MJ, Benedict NJ, et al. Crit Care Med. 2018, 46:e768 to 71. | Yes | Yes |
| Shah P, McDowell M, Ebisu R, Hanif T, Toerne T. J Med Toxicol. 2018, 14:229 to 36. | Yes | Yes |
| Yoon G, Petrakis IL, Krystal JH. JAMA Psychiatry. 2019, 76:337 to 8. | Yes | — |
| Das RK, Gale G, Walsh K, et al. Nat Commun. 2019, 10:5187. | Yes | — |
| Dakwar E, Levin F, Hart CL, Basaraba C, Choi J, Pavlicova M, Nunes EV. Am J Psychiatry. 2020, 177:125 to 33. | Yes | Yes |
| Rothberg RL, Azhari N, Haug NA, Dakwar E. J Psychopharmacol. 2021, 35:150 to 8. | Yes | — |
| Grabski M, McAndrew A, Lawn W, et al. Am J Psychiatry. 2022, 179:152 to 62. | Yes | — |
| **CUD** | | |
| Dakwar E, Levin F, Foltin RW, Nunes EV, Hart CL. Biol Psychiatry 2014; 76(1): 40 to 6. | — | Yes |
| Dakwar E, Anerella C, Hart CL, Levin FR, Mathew SJ, Nunes EV. Drug Alcohol Depend 2014; 136: 153 to 7. | — | Yes |
| Dakwar E, Hart CL, Levin FR, Nunes EV, Foltin RW. Mol Psychiatry 2017; 22(1): 76 to 81. | — | Yes |
| Dakwar E, Nunes EV, Hart CL, Foltin RW, Mathew SJ, Carpenter KM, et al. Am J Psychiatry 2019; 176(11): 923 to 30. | — | Yes |
| **OUD** | | |
| Jovaiša T, Laurinėnas G, Vosylius S, Šipylaitė J, Badaras R, Ivaškevičius J. Medicina (Kaunas) 2006; 42(8): 625 to 34. | — | Yes |

AUD = alcohol use disorder; CUD = cocaine use disorder; OUD = opioid use disorder.

The SR by Walsh et al. (2021)[17] had 6 primary studies on alcohol use disorder that were completely overlapped with those in the SR by Kelson et al. (2023).[16] To avoid double-counting data, the characteristics of these primary studies and their findings were only extracted from the SR by Kelson et al. (2023).[16]

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