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Ketamine for Adults With Treatment-Resistant Depression or Posttraumatic Stress Disorder: A 2023 Update

Angela M. Barbara
Weiyi Xie
Quenby Mahood
Angie Hamson

Rapid Review

Key Messages

What Is the Issue?

- Many drug treatments are available for depression, but 22% of people in Canada with the condition have treatment-resistant depression (TRD). For people with TRD, standard drug treatments do not improve their symptoms or do not work for long, and their depression persists.
- Posttraumatic stress disorder (PTSD) is a disabling mental health condition that affects about 9% of people in Canada in their lifetime. Few drugs are available for treating PTSD, none of which are considered effective.
- Ketamine is a hallucinogenic drug used primarily for anesthesia. Ketamine has also been explored for other indications, such as TRD and PTSD, generating questions about whether it could be a treatment option for these conditions.

What Did We Do?

- We conducted a review of the clinical effectiveness, cost-effectiveness, and evidence-based guidelines on the use of ketamine in adults with TRD or PTSD, to help guide decisions on the use of ketamine for managing these conditions.
- An information specialist conducted a search of peer-reviewed and grey literature sources published in March 2022 or later. One reviewer screened citations and selected and critically appraised the included studies.
- CADTH engaged a patient with lived experience of TRD who shared their experiences and perspectives on ketamine-assisted psychotherapy. These perspectives helped us to contextualize the literature and appreciate nuances of the experience.

What Did We Find?

- Ketamine could lead to an immediate improvement in depressive symptoms and suicidal ideation compared to placebo or midazolam in adults with TRD. The longest follow-up was 90 days, and the longest lasting effect after a dose was 28 days. Serious side effects of ketamine — such as dissociation — were rare and short-lived, lasting hours, in adults with TRD.
- It is uncertain if ketamine is an effective and safe treatment for symptoms of PTSD, due to little to no evidence suggesting its effectiveness or safety against placebo, midazolam, or opioids.

Key Messages

- Most studies evaluated ketamine given intravenously, and we found limited evidence on intramuscular (IM), subcutaneous, and intranasal routes of administration. We found no studies on oral or sublingual administration of ketamine and no studies comparing the different ways that ketamine can be given for TRD or PTSD.
- An economic evaluation found that IV ketamine was likely to be cost-effective compared to intranasal esketamine in adults with TRD from a health care perspective in the US. However, from a patient perspective, IV ketamine was unlikely to be cost-effective compared to esketamine, due to comparable levels of clinical effectiveness and lower costs of esketamine attributable to commercial insurance coverage and manufacturer assistance programs.
- A US guideline on TRD suggests ketamine as augmentation to antidepressants. A US guideline on PTSD does not suggest the use of ketamine as therapy.
- The patient contributor CADTH engaged for this review highlighted the benefits, stigma, and barriers of ketamine therapy, including financial implications.

What Does This Mean?

- There is some clinical effectiveness and cost-effectiveness evidence and a guideline recommendation to support the short-term use of ketamine in adults with TRD.
- Clinical effectiveness evidence and a guideline recommendation do not support the use of ketamine in adults with PTSD.
- Future research is necessary to understand the effectiveness and safety of ketamine as therapy for TRD in larger populations over longer periods and for PTSD for any follow-up duration.
- Decision-makers should consider offering ketamine in an equitable manner.

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Abbreviations

DoD	US Department of Defense
ECT	electroconvulsive therapy
IM	intramuscular
MDD	major depressive disorder
PTSD	posttraumatic stress disorder
RCT	randomized controlled trial
SR	systematic review
TRD	treatment-resistant depression
VA	US Department of Veterans Affairs

Context and Policy Issues

What Is Treatment-Resistant Depression?

Depression is a debilitating mental health illness that affects approximately 5.4% of people living in Canada.[1] Although there are many effective first-line pharmacotherapy treatments for depression, about 21.7% of people in Canada remain non-responsive to 2 or more antidepressant medications from different classes. Patients with such limited responsiveness to medications are often considered to have treatment-resistant depression (TRD).[2,3] They are known to experience longer depressive episodes and are at increased risk of alcohol and drug misuse, suicide, and hospitalizations.[4] A retrospective longitudinal cohort study using Ontario administrative data found that TRD was associated with an increased economic burden to the health care system.[5]

What Is Posttraumatic Stress Disorder?

Posttraumatic stress disorder (PTSD) is a disabling mental health condition that affects about 9.2% of people in Canada in their lifetime.[6] Among veterans in Canada, its prevalence has been estimated at up to 10%.[7] Although anyone can get PTSD, the risk factors include being female, having experienced a prior trauma, having been abused as a child, having pre-existing mental health conditions, and having a family history of mental illnesses.[6] People with PTSD commonly have associated conditions, including depression, panic attacks, and alcohol and substance misuse; challenges in relationships; and an increased risk of other medical conditions.[6]

What Is the Current Treatment Practice?

Treatments for TRD and PTSD include pharmacotherapies and psychotherapies.[8-10] There are a wide variety of antidepressant drugs, including selective serotonin reuptake inhibitors,[11] monoamine oxidase inhibitors, and tricyclic antidepressants.[12] However, as mentioned previously, 2 or more trials of antidepressants will have been ineffective in persons with TRD.[2,3] There are few effective drugs available for the treatment of PTSD.[8] There are somatic treatments through brain stimulation, such as electroconvulsive therapy (ECT).[13] ECT is more effective (with a quicker onset of action) compared to conventional antidepressants.[13] However, there are many adverse events associated with ECT, including cognitive impairment, delirium, musculoskeletal pain or injury, and anesthesia-related complications.[13] Thus, there is an urgent need to identify effective, safe, and timely treatments for TRD and PTSD.

What Is Ketamine and How Might It Benefit?

Ketamine is a hallucinogenic drug that changes one's state of consciousness by affecting neurotransmitters in the brain.[14-16] Ketamine is an N-methyl D-aspartate receptor antagonist and is a mixture of 2 mirror-image molecules: R-ketamine (arketamine) and S-ketamine (esketamine).[17,18] In Canada, a number of formulations of ketamine are approved for general anesthesia.[15,19,20] Ketamine is also used as a sedative and to manage pain.[21] Over the past decades, preclinical and clinical studies have shown the pharmacotherapeutic potential of ketamine for the treatment of psychiatric illnesses, including TRD and PTSD.[22,23]

Why Is It Important to Do This Review?

A 2022 CADTH report[24] on the use of ketamine for PTSD or TRD found insufficient evidence to provide definitive conclusions about its clinical effectiveness due to mixed study findings. The report did find overall safety and tolerability of ketamine for treating PTSD or TRD. The Danish evidence-based guideline included in the 2022 CADTH report recommended against the use of IV ketamine in patients with TRD, while the Canadian guideline included in the report recommended that IV ketamine be considered as a third-line treatment for adults with TRD. The report did not identify any economic evaluations or guidelines for the use of ketamine for adults with PTSD.[24] Since the publication of the 2022 CADTH report,[24] new literature on this topic has emerged, warranting the present review.

Objective

To support decision-making about the use of ketamine for adults with TRD or PTSD, we prepared this Rapid Review report as an update to the 2022 CADTH report[24] to summarize the most recent clinical and cost-effectiveness studies and evidence-based guidelines on the use of ketamine for adults with TRD or PTSD.

Research Questions

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

Methods

Literature Search Methods

This report makes use of a literature search strategy developed for a previous CADTH report.[24] For the current report, a limited literature search was conducted by an information specialist on key resources including MEDLINE, PsycInfo, the Cochrane Database of Systematic Reviews, the international HTA database, and the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were ketamine and depression or PTSD. CADTH-developed search filters were applied to limit retrieval to guidelines; randomized controlled trials (RCTs), controlled clinical trials, or any other type of clinical trial; health technology assessments; systematic reviews (SRs); meta-analyses or network meta-analyses; and economic studies. The search was completed on November 10, 2023, and limited to English-language documents published since March 1, 2022.

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. As an update to a previous CADTH report, articles were included if they were made available since the previous search date and were not included in the 2022 CADTH report.[24] The final selection of full-text articles was based on the inclusion criteria presented in Table1.

Table 1: Selection Criteria

Criteria	Description
Population	Adults with treatment-resistant depression or PTSD
Intervention	Ketamine administered via any route (e.g., IV, intramuscular, subcutaneous, intranasal, oral, sublingual)
Comparator	Q1 and Q4: Placebo, no treatment Q2 and Q5: Pharmacotherapy (e.g., antidepressants [e.g., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors], antipsychotic drugs), psychotherapy (e.g., cognitive behavioural therapy), electroconvulsive therapy Q3 and Q6: Ketamine administered via alternative routes (e.g., IV, intramuscular, subcutaneous, intranasal, oral, sublingual) Q7: Not applicable
Outcomes	Q1 to Q3: Clinical effectiveness (e.g., symptom severity [e.g., depressive symptoms, PTSD symptoms], suicidality, hospital admission rate, length of stay, quality of life, fatigue, safety [e.g., adverse events]) Q4 to Q6: Cost-effectiveness (e.g., cost per quality-adjusted life-year gained) 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, economic evaluations, evidence-based guidelines

PTSD = posttraumatic stress disorder; Q = question.

Exclusion Criteria

The following were excluded:

- articles that did not meet the selection criteria outlined in Table 1
- duplicate publications
- articles included in the previous CADTH report[24]
- SRs in which all relevant studies were captured in other more recent or more comprehensive SRs
- SRs in which all relevant studies were included in the previous CADTH report[24]
- SRs with eligibility criteria that met our selection criteria but did not identify any primary studies from the literature search (i.e., "empty" SRs) or did not include any primary studies that met our selection criteria (i.e., SRs with no relevant primary studies)
- primary studies that were captured in 1 or more included SRs or in the previous CADTH report;[24] however, if such an SR did not provide outcome data from the relevant primary study or if we knew additional information was available (e.g., included paper "under review" was published with additional data and captured in our search), then the primary study was included
- nonrandomized studies, unless identified as relevant by the included SRs (due to the availability of randomized studies)
- guidelines with unclear methodology.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[25] for SRs, the Downs and Black checklist[26] for RCTs, the Drummond checklist[27] for economic evaluations, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[28] for guidelines. Summary scores were not calculated for the included publications; rather, each publication's strengths and limitations were described narratively.

Patient Engagement

Invitation to Participate and Consent

A recruitment invitation was disseminated by email to patient advocacy groups, on social media, and through CADTH networks. An interested individual with TRD and experience of ketamine-assisted psychotherapy was identified to participate in an interview with CADTH project team members.

Engagement Activities

One contributor shared their personal experiences through a video call during the drafting of this report. The patient's perspectives gained through the engagement processes were used to ensure the relevance of the outcomes of interest for the clinical assessment in this report and to provide insights, background, and context to help inform the Discussion section.

Patient involvement was guided by the Guidance for Reporting Involvement of Patients and the Public (Version 2) Short Form reporting checklist,[29] which is outlined in Appendix 6.

Summary of Evidence

Quantity of Research Available

This report includes 4 SRs,[30-33] 7 RCTs,[34-40] 1 economic evaluation,[41] and 2 evidence-based guidelines.[42,43] Study selection details are presented in Appendix 1. Additional references of potential interest are provided in Appendix 7.

Summary of Study Characteristics

Summaries of study characteristics are organized by research question and comparison (where appropriate). Additional details regarding the characteristics of the included publications are provided in Appendix 2. Brief descriptions of the tools used to measure effectiveness and safety outcomes are presented as footnotes in the Summary of Findings tables in Appendix 4. Of note:

- 2 SRs included 1 overlapping primary study.[30,31] To avoid duplication of reporting, outcome data from this individual study were reported once as part of 1 SR.[30] A citation matrix illustrating the degree of overlap across the 4 SRs is presented in Appendix 5
- 2 SRs[30,33] and 1 guideline[43] had broader inclusion criteria for the population than the present review, with 1 SR and the guideline[43] on major depressive disorder (MDD) and the other SR on psychiatric disorders.[33] We included findings specific to TRD[30,33,43]
- the RCT by Harvey et al.[36] was a substudy of the larger RCT by Loo et al.[38] Different outcomes were reported in each trial; therefore, we included both studies in this Rapid Review. We did not include data from a third comparison group of healthy adults in the RCT by Harvey et al[36]
- 2 RCTs[37,39] were authored by the same group of researchers. One RCT[37] was conducted in 1 veterans' hospital in Taiwan with 48 participants, and the other RCT[39] was conducted in the same veterans' hospital, as well as a general hospital in Taiwan, with 84 participants. To avoid potential duplication of reporting, data for a specific outcome were reported once from 1 RCT (e.g., depression severity and suicidal ideation were reported from 1 RCT;[37] and treatment response, remission of suicidal ideation, and adverse events were reported once from the other RCT[39]).

Included Studies for Research Question 1

We identified 2 SRs[30,31] and 2 double-blind parallel RCTs,[34,40] all of which compared ketamine with saline placebo. The RCTs were conducted in Egypt[34] and the US.[40] The SRs[30,31] did not identify the countries in which the included RCTs were conducted. One SR[30] and the 2 RCTs[34,40] included adults with TRD.[30] The other SR included adults diagnosed with both early PTSD (duration of 1 to 3 months) and chronic PTSD (duration > 3 months).[31] Most of the studies (7 out of 9) in 1 SR[30] and both studies in the other SR[31] were crossover trials. Baseline characteristics between the intervention and comparator groups in the parallel trials were not described in 1 SR;[30,31] the participants in the 2 groups were balanced in baseline demographics and clinical history in the 2 RCTs.[34,40] The interventions in the included studies were single-dose ketamine administered via IV[30,40] or intranasal routes,[30] or repeated doses of IV ketamine.[30,34] One SR did not report the route of administration.[31] In most included studies, the ketamine dose was 0.5mg/kg.[30,31,34,40] In the SR by Nikolin et al.

(2023), 3 RCTs administered lower doses, ranging from 0.1 mg/kg to 0.4 mg/kg.[30] The dose for intranasal ketamine was 50 mg.[30,31,34,40] The effectiveness outcomes were depression (e.g., change in depression severity, treatment response, remission),[30,34,40] psychological symptoms,[34] PTSD symptoms,[31] and suicidal ideation.[34] The safety outcomes were adverse events.[40]

Included Studies for Research Question 2

We identified 3 SRs[30,31,33] and 5 double-blind parallel RCTs[35-39] comparing ketamine with alternative interventions.

Ketamine Versus Midazolam

Three SRs[30,31,33] and 5 RCTs[35-39] compared ketamine with midazolam. The studies took place in Australia,[36,38] Taiwan,[37,39] and the US.[33,35] Two SRs[30,33] and 4 RCTs[36-39] included adults with treatment-resistant major depression. One SR[31] and 1 RCT[35] included adults with chronic PTSD. One study in 1 SR[30] was a crossover trial. Baseline characteristics between the intervention and comparator groups in the parallel trials were not described in the 3 SRs;[30,31,33] the participants in the 2 groups were balanced in baseline demographics in the 5 RCTs.[35-39] The interventions included single-dose IV ketamine,[30,33,35,37,39] single-dose subcutaneous ketamine,[30,36] single-dose IM ketamine, repeated doses of IV ketamine,[30,31]and repeated subcutaneous ketamine injections.[38] The dose of ketamine was 0.5mg/kg in most included studies;[30,31,33,37-39] ranged from 0.1 mg/kg to 0.5 mg/kg in 1 RCT in the SR by Nikolin et al.;[30] and was fixed at 0.5mg/kg in 1 cohort and escalated in the other cohort from 0.5 mg/kg to 0.6, 0.75, or 0.9 mg/kg based on the participant's response to treatment.[38] In all included studies, the comparator was midazolam, a short-acting benzodiazepine medication and anesthetic drug. Midazolam has pharmacokinetic properties similar to ketamine (e.g., fast onset of action and short elimination half-life).[44] The midazolam dose was 0.045 mg/kg in most studies,[30,31,33,35,37,39] 0.025 mg/kg in 1 RCT,[36] and given as a fixed subcutaneous dose of 0.25mg/kg in 1 cohort and escalated in the other cohort from 0.25 mg/kg to 0.03, 0.0375, or 0.45 mg/kg based on the participant's response to treatment.[38] The effectiveness outcomes were depression,[30,35-39] PTSD symptoms,[31,35] anxiety,[33,36] neurocognitive outcomes,[36] and suicidal ideation.[37,39] The safety outcomes were adverse events.[38,39]

ECT Versus Ketamine

One RCT included in 1 SR[32] compared ECT versus ketamine. The study was conducted in the US and included adults with TRD.[32] The intervention was ECT given 3 times per week for 3 weeks. The comparator was IV ketamine 0.5 mg/kg twice per week for 3 weeks.[32] The effectiveness outcome was depression (e.g., response, change in depression severity, acute effect, and relapse).[32] Safety outcomes were not reported.

Ketamine Versus Opioids

One cohort study reported in 1 SR by Du et al.[31] compared ketamine (0.5mg/kg) versus opioids (unknown dose). This study included adults in hospitals following accidental trauma who were experiencing early PTSD.[31] The route of administration was not reported.[31] The effectiveness outcome was PTSD symptoms.[31] Safety outcomes were not reported.

Included Studies for Research Question 3

No clinical effectiveness studies of ketamine administered via different routes for adults with TRD or PTSD were identified; therefore, no summary can be provided.

Included Studies for Research Question 4

No cost-effectiveness studies of ketamine versus placebo or no treatment for adults with TRD or PTSD were identified; therefore, no summary can be provided.

Included Studies for Research Question 5

One economic evaluation[41] conducted a cost-utility analysis of esketamine nasal spray compared to IV ketamine in patients with TRD in the US, using a Markov model with a 1-month cycle length. The analysis was conducted from US health care and patient perspectives over a 3-year time horizon. The clinical trial efficacy data were from 4 phase III clinical trials included in an FDA Advisory Committee briefing document for esketamine and a meta-analysis for ketamine.[41] The real-world effectiveness data were from psychiatric clinic electronic health records and medical chart reviews. Utility values were taken from a prospective cohort study that used the EQ-5D to assess quality of life among outpatients treated for MDD with pharmacotherapy.[41] Costs under the health care perspective included medication, physician visits at each presentation of dosing, and observation by a medical assistant after each dose administration. Under the patient perspective, costs included patient time and medication copayments. The time horizon varied from 1 year to 5 years in the sensitivity analysis, with future costs and quality-adjusted life-years (QALYs) discounted at 3% annually.[41]

Included Studies for Research Question 6

No cost-effectiveness studies of ketamine administered via different routes for adults with TRD or PTSD were identified; therefore, no summary can be provided.

Included Studies for Research Question 7

Two evidence-based guidelines[42,43] were included in this review. Both guidelines were developed by the US Department of Veterans Affairs (VA) and the US Department of Defense (DoD) to update previously published guidelines. Both guidelines[42,43] conducted systematic searches of SRs and meta-analyses and RCTs. Recommendations for both guidelines were developed by a guideline development work group in discussion with clinical experts and reviewed by external experts. Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, work group members rated evidence quality, and clinical experts assessed recommendation strength. The 2023 VA/DoD guideline[42] focused on adults with PTSD or acute stress disorder, and the intended users were providers and others involved in the care of active-duty service members and veterans with PTSD. The target population of the 2022 VA/DoD guideline[43] was adults with MDD, including MDD that is severe or has partial or limited response to initial treatment, with all health care providers caring for patients with MDD as intended users.

Summary of Critical Appraisal

Critical appraisal summaries are organized by study design. Additional details regarding the strengths and limitations of the included publications are provided in Appendix 3.

Systematic Reviews

The 4 SRs[30-33] had clearly defined research questions and study eligibility criteria that included components of population, intervention, comparator, and outcomes. All 4 SRs[30-33] registered their protocol a priori on PROSPERO, thus reducing the risk of reporting bias. The authors of the 4 SRs[30-33] performed literature searches in 2 or more electronic databases,[30-33] described the search strategies in detail,[30,32,33] or provided the search terms.[31] These methodological strengths increase the transparency and reproducibility of the literature searches and article selection process. Three SRs[30-33] presented a flow chart illustrating the study selection process. Study selection was performed in duplicate in all SRs,[30-33] thus reducing the likelihood that relevant studies were missed.[30,31] Data extraction was performed in duplicate in 2 SRs,[30,33] thus limiting the possibility of errors in data extraction in those 2 SRs. The 4 SRs[30-33] used the Cochrane tool to assess the risk of bias of the included RCTs.

There were several limitations that were common to the included SRs.[30-33] None incorporated searches of the grey literature or reported funding sources for the included primary studies. Three SRs[31-33] did not provide a list of excluded studies. Two SRs[30,31] did not indicate if risk of bias was accounted for in their findings.

Randomized Controlled Trials

The 7 RCTs[34-40] clearly defined the objective, outcomes, inclusion and exclusion criteria, interventions used, and demographics of included participants. Six RCTs[34-39] indicated that the trial protocol had been registered before conducting the trial. Each RCT used appropriate statistical tests for analysis, and outcomes of interest were assessed using validated scales.[34-40]

In 4 RCTs,[34,36,38,39] the methods of randomization and allocation concealment were described and appropriate, reducing the risk of selection bias. The patients, personnel administering the interventions, and personnel assessing the outcomes were blinded to the interventions in all RCTs,[34-40] reducing the risk of performance and detection bias. Because ketamine was administered by study personnel, it was assumed that adherence to the intervention was reliable for each RCT. Each RCT provided information related to any funding received for the trial. Four RCTs[34,36,37,39] reported no conflicts of interest, and 3 RCTs[35,38,40] declared potential conflicts of interests.

There were several limitations across the included RCTs.[34-40] Five RCTs[35-37,39] had very small study populations (ranging from 21 to 84 participants) that might not represent the entire population from which they were recruited. Four RCTs[34-37] did not report adverse events. Three RCTs[36,37,39] did not report a sample size calculation. In 4 RCTs,[35,37,39,40] the recruitment methods were not described.

Economic Evaluation

The economic evaluation by Brendle et al.[41] clearly described the study design, including the research question and its economic importance, health care and patient perspectives, the selected alternative

intervention, time horizon, and the form of economic evaluation used. The study[41] also reported data collection methods, including the details of clinical trial efficacy data and real-world effectiveness data, sources of cost data, and sources of utility values. In addition, authors described the Markov model, key model parameters, and discount rate used.[41] However, the study[41] did not justify the choices of the model and discount rate and lacked details on price adjustments for inflation. For the analysis and interpretation of results, authors used deterministic (1-way) and probabilistic sensitivity analyses to determine the impact of model parameter uncertainty without providing reasons for the choice of analysis variables or the ranges over which they were varied.[41] Authors presented major outcomes in disaggregated and aggregated forms.[41] However, authors did not report confidence intervals of main outcome data; therefore, the uncertainty of outcome estimates was unknown.[41]

Evidence-Based Guidelines

Both included guidelines[42,43] clearly outlined their scope and purpose, including objectives, health questions, and the target population. They both reported stakeholder involvement details, including the target users, development groups, and patient groups whose preferences and views were sought.[42,43] In addition, both guidelines[42,43] demonstrated strength in clearly presenting specific, unambiguous, and easily identifiable recommendations as well as different options for management of the conditions. The 2 guidelines[42,43] reported systematic evidence search methods, evidence selection criteria, strengths and limitations of the body of evidence, and methods for formulating the recommendations. They also considered health benefits, side effects, and risks in formulating the recommendations and demonstrated the link between the recommendations and the supporting evidence.[42,43] Both guidelines[42,43] were externally reviewed by experts before their publication, but neither provided a procedure for updating the guidelines.

Regarding applicability, both guidelines[42,43] provided tools for implementing recommendations, but only the 2022 VA/DoD guideline[43] described facilitators and barriers to the application. Moreover, both guidelines[42,43] considered potential resource implications of applying the recommendations, but neither presented monitoring or auditing criteria. For editorial independence, the 2022 VA/DoD guideline[43] reported no competing interests of guideline development group members, while the 2023 VA/DoD guideline[42] described the disclosure process but did not present the results. Neither guideline[42,43] stated whether the funding body influenced the content of the guideline.

Summary of Findings

The main findings from the included publications are summarized in the following sections and in Appendix 4.

Clinical Effectiveness of Ketamine Versus Placebo or no Treatment for Adults With TRD or PTSD

Ketamine Versus Placebo

Depression

Nine RCTs included in an SR[30] and another RCT[40] assessed the effects of single-dose ketamine compared to placebo on depression within **24 hours** following treatment in patients with **TRD** and reported:

- **depression severity**: statistically significantly greater reductions from baseline with IV ketamine (0.5 mg/kg) or intranasal ketamine compared to placebo in some studies (6 RCTs in 1 SR[30] and 1 RCT[40]), but no statistically significant differences between the 2 groups in others (3 RCTs in 1 SR[30])
  - one RCT in the SR[30] found subgroup effects: a statistically significantly greater reduction from baseline in depression severity **4 hours** following a single high dose (≥ 0.5mg/kg) of IV ketamine compared to placebo, but not at a single low dose (< 0.5mg/kg), in patients with TRD
- **treatment response** (50% or higher reduction in depressive symptoms from baseline): no statistically significant differences between the 2 groups in some studies (6 RCTs in 1 SR[30]) but statistically significantly greater treatment response rates with ketamine compared to placebo in others (2 RCTs in 1 SR[30] and 1 RCT[40]), with some reporting wide confidence intervals (2 RCTs in 1 SR[30])
- **remission**: no statistically significant differences between the 2 groups in some studies (5 RCTs in 1 SR[30]) but statistically significantly greater remission rates with ketamine compared to placebo in another (1 RCT[40]).

Eight RCTs included in an SR[30] and 2 RCTs[34,40] assessed depression from **3 to 28 days** following single-dose or repeated ketamine treatment compared to placebo in adults with **TRD** and reported:

- **depression severity**:
  - statistically significantly greater reductions from baseline at **3 days** following treatment with single-dose IV ketamine compared to placebo in some studies (4 RCTs in 1 SR[30]) but no statistically significant differences between the 2 groups in others (4 RCTs in 1 SR[30])
  - statistically significantly greater reductions from baseline at **1 week** following treatment with a single dose or repeated treatment of ketamine compared to placebo (1 RCT in 1 SR[30] and 1 RCT[34])
  - statistically significantly greater reductions from baseline at **28 days** following treatment with single-dose ketamine or repeated-dose ketamine plus automated self-association training (automated training designed to shift implicit self-associations in a positive direction) compared to placebo (1 RCT in 1 SR[30] and 1 RCT[40])
- **treatment response**: no statistically significant differences in response rates at **3 days** following treatment with single-dose ketamine versus placebo in some studies (5 RCTs in 1 SR[30]) but statistically significantly greater treatment response rates with ketamine compared to placebo in others (3 RCTs in 1 SR[30])
- **remission**: no statistically significant differences in remission rates at **3 days** following treatment with single-dose ketamine and placebo (4 RCTs in 1 SR[30]).

Psychological Symptoms

In patients with **TRD**, the RCT by Ahmed et al.[34] found:

- higher frequency of "abnormal" (as reported by study authors) responses in obsessive-compulsive, interpersonal sensibility, and paranoid ideation measures with ketamine compared to placebo at **1 week** following treatment, and the differences between the 2 groups were statistically significant[34]
- higher frequency of "abnormal" (as reported by study authors) responses in somatization, anxiety, anger-hostility, phobic anxiety, and psychosis measures with ketamine compared to placebo at **1 week** following treatment, but the differences between the 2 groups were not statistically significant.[34]

PTSD

Two RCTs in the SR by Du et al.[31] studied the effect of ketamine versus placebo on PTSD symptoms in patients with **PTSD** and found no statistically significant difference between the 2 groups at **24 hours** after treatment.[31] However, baseline scores were not reported for the 2 groups in the 2 trials.[31]

Suicidal Ideation

The RCT by Ahmed et al.[34] found a statistically significant reduction in suicidal ideation from baseline to **1 week** following treatment for **TRD** in the ketamine group and no change in the placebo group, but between-group differences were not reported.[34]

Adverse Events

In patients with **TRD**, the following mild to moderate adverse events were reported more frequently at **24 hours** after ketamine treatment compared to placebo (statistical significance not reported) in 1 RCT:[40] dissociation, dizziness, dry mouth, and decreased energy. Most adverse events were no longer reported at 30 days after treatment.[40]

Clinical Effectiveness of Ketamine Versus Alternative Interventions for Adults With TRD or PTSD

Ketamine Versus Midazolam

Depression

In patients with **TRD**, the following were reported on the effects of **single-dose** ketamine versus midazolam:

- **depression severity:**
  - statistically significantly greater reduction at **24 hours** after single-dose IV or subcutaneous ketamine (0.5 mg/kg) compared to midazolam (1 RCT in 1 SR[30] and 1 RCT[36])
  - statistically significantly greater reductions in depression scores with low-dose **subcutaneous or IM** ketamine (0.2 mg/kg or 4 mg/kg) compared to midazolam at **24 hours** after treatment, but no statistically significant differences between low-dose **IV** ketamine and midazolam (1 RCT in 1 SR[30])
  - statistically significantly greater reductions in depression **3 days** after single-dose ketamine compared to midazolam (1 RCT[37])

- **treatment response:**
  - no statistically significant differences in response rates between low-dose subcutaneous, IM, or IV ketamine and midazolam at **24 hours** following treatment (1 RCT in 1 SR[30] and 1 RCT[36])
  - statistically significantly greater response rates **3 days** following single ketamine infusion compared to midazolam in 1 study (1 RCT[39]), but no statistically significant differences between the 2 groups in another study (1 RCT in 1 SR[30])
- **remission:** no statistically significant differences in remission rates between low-dose subcutaneous, IM, or IV ketamine and midazolam at **24 hours** following treatment (1 RCT in 1 SR[30] and 1 RCT[36]).

The RCT by Loo et al.[38] found that the effects of a 4-week course of **repeated** subcutaneous ketamine injections for adults with **TRD** depended on dosing:

- With **fixed-dose** ketamine (0.5 mg/kg) compared to fixed-dose midazolam (0.25 mg/kg), there were no statistically significant differences in change in depression scores, response rates, or remission rates after treatment.[38] There were also no statistically significant differences between the 2 groups in response or remission rates at the 4-week follow-up. There were no statistically significant between-group differences in mental health scores after treatment, but there were statistically significant differences at 4 weeks favouring midazolam.[38]
- With **flexible-dose** ketamine (0.5 to 0.9 mg/kg) compared to flexible-dose midazolam (0.025 to 0.045 mg/kg), where dosing was increased depending on response, there were statistically significant differences in posttreatment depression scores and remission rates in favour of flexible-dose ketamine.[38] At the 4-week follow-up, there was a statistically significant difference in depression scores favouring flexible-dose ketamine but no statistically significant difference in remission rates.[38] There were statistically significantly greater changes in mental health scores in the ketamine group after treatment but no statistically significant between-group differences at 4 weeks.[38]

In patients with **PTSD**, 1 RCT[35] reported no statistically significant difference in depression scores with single-dose ketamine versus midazolam at the **end of treatment** and at the **90-day** follow-up.[35]

Anxiety

In patients with **TRD**, 1 RCT in the SR by Marchi et al.[33] found no statistically significant between-group differences in anxiety 1 day after single-dose treatment.[33] The RCT by Harvey et al.[36] found statistically significant time effects on anxiety 1 day after treatment but did not attribute the significance to the single-dose ketamine or midazolam given to patients with TRD.[36]

PTSD

One RCT in the SR by Du et al.[31] found no statistically significant difference in **PTSD** symptoms with ketamine compared to midazolam between 1 day and 1 week following treatment for chronic PTSD.[31] The RCT by Duek et al.[35] recorded PTSD symptoms in patients with PTSD before treatment, at the end of a single infusion of ketamine or midazolam, at 1 week, and at 90 days. Although PTSD symptoms improved over time, there were no statistically significant between-group differences in the rate of improvement or PTSD score at any time points.[35]

Neurocognitive Outcomes

The RCT by Harvey et al.[36] assessed neurocognitive changes following single-dose ketamine or midazolam treatment in patients with **TRD** and reported:

- statistically significant time effects and statistically significant group effects for verbal fluency, showing better overall performance in the midazolam group
- a statistically significant time by group interaction was found for negative affective bias; post hoc testing revealed that participants in the ketamine group performed significantly better on the Scramble Sentence test after treatment
- no statistically significant interactions for response time to affective stimuli, concentration and selective attention (total speed), and affective bias.[36]

Suicidal Ideation

One RCT[37] found statistically significantly greater reductions in suicidal ideation 3 days after single-dose ketamine versus midazolam in patients with **TRD**. Another RCT[39] found statistically significant remission rates up to 5 days after treatment in favour of single-dose ketamine versus midazolam in patients with TRD. In the same trial,[39] there were no statistically significant differences between the 2 groups at 1 week and 2 weeks following treatment.

Adverse Events

Two RCTs[38,39] reported adverse events with ketamine compared to midazolam in patients with **TRD**. In the RCT by Su et al.,[39] derealization, dizziness, and crying were reported more often during treatment with ketamine compared to midazolam, and the differences were statistically significant. The RCT by Loo et al.[38] found that the following adverse events were reported statistically significantly more often 1 hour following treatment with ketamine compared to midazolam: lightheadedness, reduced concentration, dissociation, and anxiety. Loo et al.[38] reported 2 severe adverse effects in the ketamine group that were related to the drug: major dissociative episode and auditory hallucination. Both acute events resolved within 2 hours. No participants required medical attention. No severe events related to the study drug were reported in the midazolam group.[38]

ECT Versus Ketamine

Depression

One RCT in the SR by Shafiee et al.[32] found statistically significant improvements in depression scores and response rates in favour of repeated-dose ketamine over ECT following treatment in patients with **TRD**. There were no statistically significant differences in depression scores or relapse rates between ketamine and ECT at the 30-day follow-up.[32]

Ketamine Versus Opioids

PTSD

One cohort study in the SR by Du et al.[31] reported a statistically significant increase in PTSD symptoms within 3 days of treatment with ketamine versus opioids in patients with **PTSD**.

Clinical Effectiveness of Ketamine Administered via Different Routes for Adults With TRD or PTSD

No clinical effectiveness studies of ketamine administered via different routes for adults with TRD or PTSD were identified; therefore, no summary can be provided.

Cost-Effectiveness of Ketamine Versus Placebo or no Treatment for Adults With TRD or PTSD

No cost-effectiveness studies of ketamine versus placebo or no treatment for adults with TRD or PTSD were identified; therefore, no summary can be provided.

Cost-Effectiveness of Ketamine Versus Alternative Interventions for Adults With TRD or PTSD

The economic evaluation[41] assessed the cost-utility of esketamine nasal spray versus IV ketamine in patients with **TRD** in the US.

From the health care perspective, IV ketamine was likely to be cost-effective compared to esketamine:

- In the base-case analysis, IV ketamine was dominant, regardless of the source of effectiveness data (i.e., clinical trial or real-world data).
- In the sensitivity analysis, there were no scenarios in which esketamine was cost-effective compared to IV ketamine.[41]

From a patient perspective, Brendle et al.[41] found that IV ketamine was unlikely to be cost-effective compared to esketamine due to similar levels of clinical effectiveness and lower costs of esketamine attributable to insurance coverage and manufacturer assistance programs:

- In the base-case analysis, the incremental cost-effectiveness ratio of ketamine compared to esketamine was $867,606 per QALY with clinical trial estimates and $7,037,560 per QALY with real-world effectiveness data. Both incremental cost-effectiveness ratios exceeded the willingness-to-pay threshold of $150,000 per QALY, with medication costs driving the total costs.
- In the sensitivity analysis, at a threshold of $150,000 per QALY, the probability that esketamine was superior compared to ketamine was 0.0055 using clinical trial efficacy estimates and 0.35 using real-world evidence.

Cost-Effectiveness of Ketamine Administered via Different Routes for Adults With TRD or PTSD

No cost-effectiveness studies of ketamine administered via different routes for adults with TRD or PTSD were identified; therefore, no summary can be provided.

Evidence-Based Guidelines on the Use and Administration of Ketamine for Adults With TRD or PTSD

The 2022 VA/DoD guideline[43] suggests ketamine or esketamine as an option for augmentation for patients with MDD who have not responded to several “adequate” (from original source and undefined) pharmacologic trials (weak recommendation based on low-quality evidence). The guideline noted that while most patients were willing to accept the risk of adverse events associated with ketamine, they may have varying preferences about the route of administration. In addition, the guideline identified resource and feasibility challenges related to administrating ketamine.

The 2023 VA/DoD guideline[42] does not suggest ketamine for the treatment of PTSD (weak recommendation based on very low-quality evidence). The guideline stated that the benefits of using ketamine as monotherapy were outweighed by the potential harm.

Limitations

Evidence Gaps

No evidence was found for the following; therefore, no conclusions can be formed on the respective research questions:

- the clinical effectiveness of ketamine administered via different routes for adults with TRD or PTSD
- the cost-effectiveness of ketamine versus placebo or no treatment for adults with TRD or PTSD
- the cost-effectiveness of ketamine administered via different routes for adults with TRD or PTSD.

We identified 1 crossover RCT reported in 1 SR[30] that compared IV, subcutaneous, and IM routes of administering ketamine in 15 adults with TRD. The SR authors compared ketamine administered via different routes with midazolam for this RCT (e.g., IV ketamine versus midazolam, subcutaneous ketamine versus midazolam, and IM ketamine versus midazolam). However, they did not report head-to-head comparisons (e.g., IV ketamine versus subcutaneous ketamine versus IM ketamine).[30]

All included studies investigated the short-term effects of ketamine, with follow-up periods ranging from 3 days[37] to 3 months.[35] Therefore, longer term effects of ketamine are unknown.

There was limited evidence for some comparisons, with 1 RCT in 1 SR[32] comparing ketamine to ECT and 1 RCT in another SR[31] comparing ketamine to opioids, potentially limiting the reliability of these findings.

None of the studies included oral or sublingual ketamine; therefore, no conclusions can be formed on the impact of these routes of administration.

None of the studies reported hospital admission or quality of life as outcomes; therefore, no conclusions can be formed on the impact of ketamine on these outcomes.

Certainty of the Evidence

Risk of Bias of Included Studies in Systematic Reviews

Of the included studies in the 4 SRs, as assessed by the review authors, 2 studies from 2 of the SRs[31,32] were at low risk of bias, while the other studies from 3 of the SRs[30,31,33] had either some concerns or high risk of bias related to random sequence generation, allocation concealment, blinding of outcome assessors, and selective reporting.

Quality of Evidence in Included Guidelines

Both evidence-based guidelines[42,43] provided weak recommendations based on low-quality or very low-quality evidence.

Generalizability

None of the clinical effectiveness studies[31-39] were conducted in Canada, which may limit the generalizability of the findings of this Rapid Review to the Canadian health care context. Two SRs[30,31] did not identify the countries in which the studies were conducted; therefore, the generalizability of their findings is unknown.

Most of the evidence in adults with TRD was specific to MDD, except for 2 crossover RCTs included in 1 SR[30] with very small samples (n = 15 and n = 18) of adults with treatment-resistant bipolar depression. Therefore, the overall findings may not be applicable in adults with treatment-resistant bipolar depression.

There was limited clinical effectiveness evidence for veteran populations, with 2 RCTs[37,39] conducted by the same group of researchers in a veterans' hospital in Taiwan, and another RCT[35] whose study population included 29% with combat trauma. The SRs[30-33] did not report whether the populations were veterans or civilians; therefore, the generalizability of the findings to these specific populations is unknown.

Both evidence-based guidelines[42,43] focused on adults eligible for care in the VA or DoD health care delivery systems in the US. Due to potential differences in health care systems and resource availability between the US and Canada, the generalizability of the recommendations to veterans in Canada is unknown.

The cost-effectiveness study[41] was based in the US and assumed that all patients had commercial health insurance covering treatment costs and manufacturer assistance programs, raising uncertainty about the relevance of findings under a patient perspective to the Canadian context. Moreover, authors acknowledged potential differences between real-world postrelapse treatment patterns and their assumption that patients would follow a similar and consistent pattern of treatment after relapse.[41] Consequently, the generalizability of findings is unclear.

Heterogeneity

The definition of TRD varied among studies.[30] The mean number of unsuccessful trials of antidepressants also varied. The criteria for an "adequate" (from original source and undefined) trial were not specified in the included studies, and patients' history with nonpharmacological therapy was inconsistently reported across studies.

Three SRs[30,32,33] did not specify whether the unsuccessful trials of antidepressants were in the current episode or over the lifetime for each of their included studies.

Among the included RCTs, inclusion and exclusion criteria were not homogeneous. For example, suicidal ideation or suicidal behaviour were part of the inclusion criteria in 2 RCTs[34,39] but were excluded in another RCT.[37] Substance use was reported in 1 RCT[35] but excluded in other RCTs.[37,39]

Most studies used ketamine as add-on therapy and allowed patients to continue using concomitant medication or psychotherapy during treatment, and the concomitant therapies across studies were heterogeneous. However, 2 RCTs included in 1 SR[30] assessed ketamine as monotherapy and required discontinuation of other psychotropic medications.

Imprecision

With the exception of 1 RCT reported in the SR by Shafiee et al.,[32] all included studies had small sample sizes. Therefore, the total number of events on dichotomous outcomes (e.g., depression-based response and remission) were very low. Effect estimates for several outcomes had wide confidence intervals.[30,31,38] The economic evaluation[41] obtained clinical efficacy data from trials with small sample sizes. Therefore, the results presented in this Rapid Review are generally imprecise.

Conclusions and Implications for Decision- or Policy-Making

This report comprises 4 SRs[30-33] and 7 RCTs[34-40] on the clinical effectiveness of ketamine, 1 economic evaluation[41] on the cost-effectiveness of ketamine, and 2 evidence-based guidelines[42,43] on the use of ketamine in adults with TRD or PTSD.

Ketamine Compared to Placebo

Patients With TRD

In adults with TRD, single-dose ketamine compared to placebo may have a favourable effect on depression severity within 24 hours and 3 days following treatment, but this finding is uncertain due to high heterogeneity and potential publication bias.[30,40] The 24-hour effects on depression treatment response and remission were mixed across the included studies and therefore uncertain.[30,40] Ketamine had a neutral effect (e.g., no statistically significant between-group difference) compared to placebo on depression response and remission 3 days following single-dose ketamine.[30] In adults with TRD, repeated doses of ketamine may improve depression severity,[30,34,40] response,[34] and suicidal ideation compared to placebo,[34] but these findings are uncertain due to imprecision and potential indirectness. There were no severe adverse events reported with ketamine in patients with TRD.[34]

Patients With PTSD

In adults with PTSD, ketamine may not have an effect on PTSD symptoms 24 hours after treatment compared to placebo, but this finding is uncertain due to imprecision.[31] Also, our confidence in the results of this SR[31] is low (based on our assessment using AMSTAR 2).

Ketamine Compared to Alternative Therapies

Ketamine Compared to Midazolam

Patients With TRD

In adults with TRD, single-dose ketamine may have a favourable effect on depression severity and response within 24 hours and 3 days following treatment compared to midazolam, but these findings are uncertain due to imprecision.[30,36,37,39] The 24-hour effect on anxiety was mixed across included studies and therefore uncertain.[33,36] Single-dose ketamine may have a favourable effect on suicidal ideation within 3 days following treatment compared to midazolam, but this result is uncertain due to imprecision and indirectness.[37,39] Compared to midazolam, single-dose ketamine treatment may also improve negative affective bias but have

no effect on other neurocognitive outcomes, but these results are uncertain due to imprecision.[36] Repeated doses of ketamine may have a favourable effect on depression when administered with a flexible dosing schedule compared to midazolam, but this finding is uncertain due to imprecision.[38] Serious adverse events related to ketamine were rare and resolved within 2 hours.[37]

Patients With PTSD

In adults with PTSD, ketamine may not have an effect on PTSD symptoms compared to midazolam, but these findings are uncertain due to imprecision and potential indirectness.[35]

Ketamine Compared to ECT

Patients With TRD

In patients with TRD, repeated doses of ketamine had a favourable effect on depression and response rates at end of treatment compared to ECT.[32] There may be no effect of ketamine on depression scores or relapse rates at 30-day follow-up compared to ECT, but these findings are uncertain due to imprecision.[32]

Ketamine Compared to Opioids

Patients With PTSD

In hospital patients with early PTSD due to accidental trauma, ketamine may aggravate PTSD symptoms within 3 days of treatment compared to opioids, but this finding is uncertain due to imprecision and low confidence in the results of the SR.[31]

Ketamine Compared to Esketamine

Patients With TRD

From the health care perspective, IV ketamine was likely to be cost-effective compared to esketamine for the treatment of TRD in the US. However, from the patient perspective, IV ketamine was unlikely to be cost-effective compared to esketamine due to similar levels of effectiveness and lower costs of esketamine attributable to insurance coverage and manufacturer assistance programs.[41]

Recommendations Regarding Ketamine

Patients With TRD

The VA/DoD guideline suggests using ketamine to augment treatment for TRD.[43]

Patients With PTSD

The VA/DoD guideline does not suggest using ketamine for the treatment of PTSD.[42]

Findings From Previous CADTH Reports

CADTH previously published 3 Rapid Response reports on this topic.[24,45,46]

The 2017 CADTH report[46] identified 3 SRs, 5 primary studies, and 2 evidence-based guidelines. Overall, IV ketamine was reported to be effective at reducing depression severity within minutes or hours for patients

with TRD, and effective at reducing PTSD severity in patients with PTSD. Both guidelines included in the 2017 CADTH report recommended restricting the off-label use of ketamine for TRD to research settings.[46]

The 2019 CADTH report identified 6 primary clinical studies and 1 evidence-based guideline.[45] Three RCTs reported that IV ketamine was significantly more effective than placebo and midazolam for the treatment of adults with TRD. One RCT reported no significant difference between IV ketamine (6 repeated doses of 0.5 mg/kg) and placebo. The 2017 VA/DoD guideline reported a strong recommendation against treating PTSD with ketamine monotherapy, based on very low-quality evidence.[45] In this Rapid Review, we included the most recent VA/DoD guideline on PTSD, which maintained the weak recommendation on ketamine, reflecting the findings of recently published RCTs.[42]

The 2022 CADTH report[24] identified 7 RCTs, 1 retrospective chart review study, and 2 guidelines. In the report, there were varied findings across individual RCTs regarding the treatment effect of ketamine for patients with TRD, namely:

- significantly greater reduction in depressive symptoms with repeated administration of oral ketamine compared with placebo
- faster improvement in depressive symptoms and fewer ECT treatments for disease remission with IV ketamine-based anesthesia versus propofol-based anesthesia
- improvement of depression in patients with TRD using IV ketamine as an anesthetic drug or methohexital anesthesia for ECT
- comparable acute antidepressant effects 24 hours after infusion for IV ketamine and IV esketamine
- no significant differences in depression and anxiety improvement between repeated administration of IM ketamine and repeated transcranial magnetic stimulation.[24]

The 2022 CADTH report[24] also suggested that repeated IV ketamine infusions showed rapid but potentially unsustainable antidepressant effects in patients with PTSD, although the 2 studies reported mixed evidence on the effectiveness of ketamine for improving PTSD.[24] The Danish guideline included in the report provided weak recommendations against the use of IV ketamine as an add-on to usual antidepressant treatment in patients with TRD. The Canadian guideline included in the report recommended IV ketamine be considered as a third-line treatment for adults with TRD.[24]

This Rapid Review builds on these clinical effectiveness findings, provides guidance from recent guidelines, and includes evidence on cost-effectiveness.

Considerations for Future Research

Further effectiveness and safety data on longer follow-up and maintenance treatment in larger populations are needed in future studies of TRD. Due to the uncertainty of existing evidence on PTSD and anxiety, more robust trials are warranted. There is a need to investigate head-to-head randomized comparisons of different routes of ketamine administration. The evidence in this report focused on ketamine administered via IV in a standard dose of 0.5 mg/kg. Future research should assess whether less invasive routes of administration are more acceptable to patients. Investigators of future trials may want to consider using outcome measures

identified as important by the patient contributor engaged for this review that were not included in the evidence of this Rapid Review (e.g., quality of life, potential for misuse).

To help address health equity concerns in future studies, researchers should consider collecting equity-relevant population characteristics (e.g., gender, education, socioeconomic status, place of residence) to assess potential health inequities related to ketamine treatment for TRD and PTSD. The burden of psychiatric disorders disproportionately affects people at lower levels of socioeconomic status,[47,48] and as such, researchers should consider that certain equity-deserving groups may face barriers to accessing treatment. This was reinforced by the patient contributor engaged for this review, who highlighted the significant financial implications of ketamine-assisted therapy in private clinics. The patient contributor also identified the stigma surrounding ketamine use, including being dissuaded by clinicians. Both cost and stigma may lead to greater inequities in access.

Implications for Clinical Practice

The findings of this report suggest a potential benefit of ketamine use in TRD without negative neurocognitive outcomes or severe adverse events. The patient contributor engaged for this review confirmed the immediate benefits (and no adverse events) of repeated ketamine for TRD. In contrast, ketamine may aggravate symptoms of PTSD, and its use is not recommended for veterans with PTSD in the US.[42]

Health care providers should consider ketamine as part of an overall TRD treatment approach. They should also closely monitor patients receiving ketamine therapy. Although the short-term side effects of ketamine were well tolerated, the safety of extended use is unknown. As the evidence base on ketamine for TRD and PTSD is continually expanding, decision-makers should stay abreast of recent findings and best practices.

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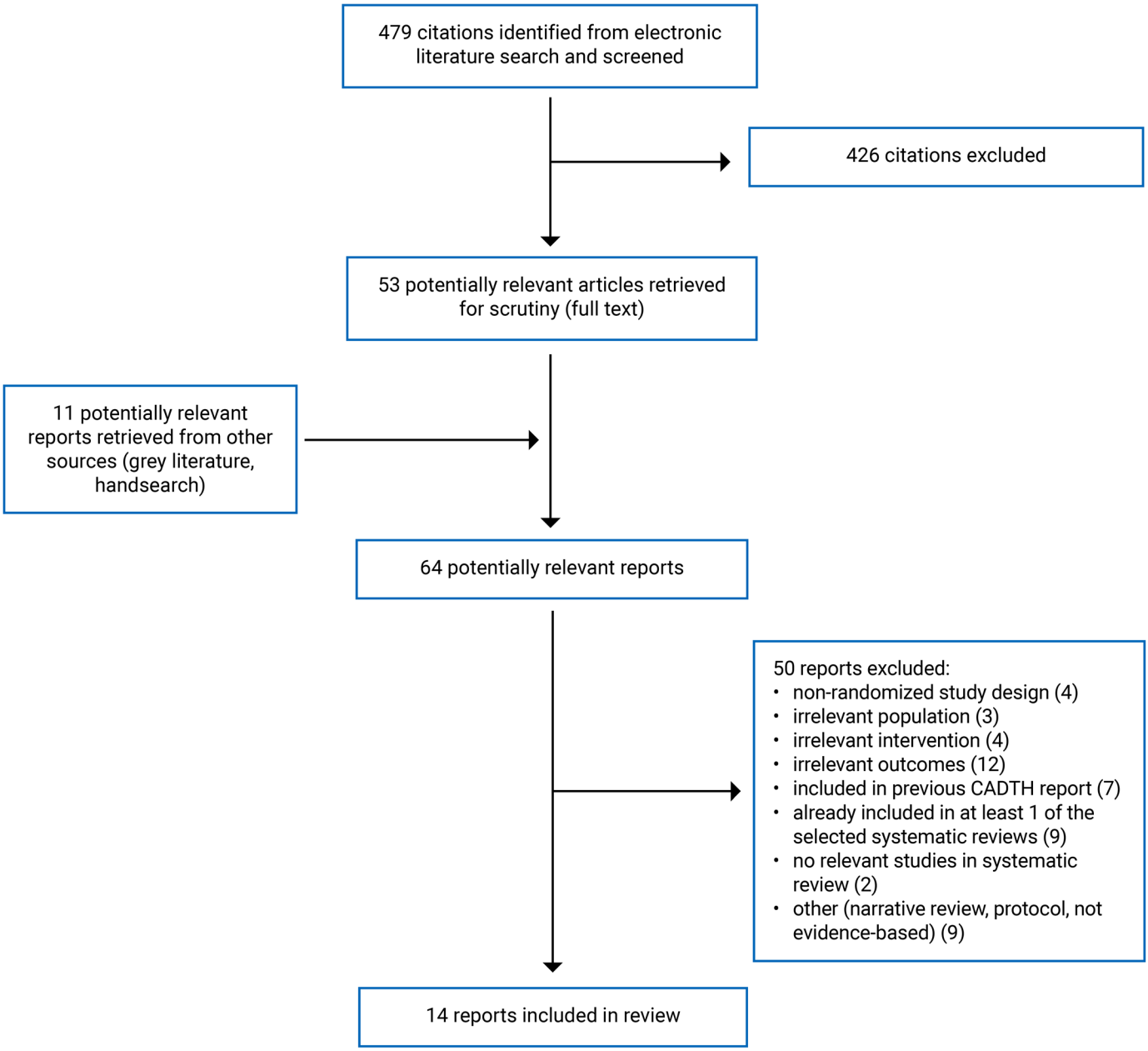
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Systematic Reviews

Study citation, country, funding source	Study design, outcomes	Intervention and comparators	Included studies	Population characteristics
Nikolin et al. (2023)[30] Australia **Funding**: None	SR of RCTs Literature searched until April 2023. **Relevant outcomes:** Depression (measured by standardized depression scales [e.g., MADRS or HDRS]).	**Relevant interventions:** Ketamine **Relevant comparators:** • Saline placebo • Midazolam	49 RCTs included in the SR. 12 RCTs relevant to this report. Relevant studies published between 2008 and 2023.	**Relevant population:** Adults diagnosed with MDD in accordance with DSM criteria and failed ≥ 1 to ≥ 5 antidepressants.
Shafiee et al. (2023)[32] Iran **Funding**: None	SR of RCTs Date of literature search: NR **Relevant outcomes:** Depression (measured by MADRS, QIDS-SR-16)	**Relevant intervention:** ECT **Relevant comparator:** IV ketamine	7 RCTs included in the SR. 1 RCT relevant to this report. Relevant study published in 2023.	**Relevant population:** Patients with TRD; ECT candidates.
Du et al. (2022)[31] China **Funding source**: National Natural Science Foundation of China	SR of RCTs, case-control, and cohort studies Literature searched until May 2021. **Relevant outcomes:** PTSD symptoms (measured by CAPS, PCL-C, IES-R, ASDS).	**Relevant intervention:** Ketamine **Relevant comparators:** • Saline placebo • Midazolam • Opioids.	10 studies included in the SR. 3 RCTs and 1 cohort study relevant to this report. Relevant studies published between 2008 and 2019.	**Relevant population:** Adults diagnosed with early or chronic PTSD.
Marchi et al. (2022)[33] Italy **Funding source**: NR	SR of RCTs Literature searched until April 2022. **Relevant outcomes:** Anxiety (measured by STAI-S).	**Relevant intervention:** IV ketamine **Relevant comparators:** Midazolam.	22 RCTs included in the SR. 2 RCTs relevant to this report. Relevant studies published between 2012 and 2014.	**Relevant population:** Adults with a diagnosis of TRD.

ASDS = Acute Stress Disorder Scale; CAPS-5 = Clinician-Administered PTSD Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; ECT = electroconvulsive therapy; HDRS = Hamilton Depression Rating Scale; ICD = International Classification of Diseases; IES-R = Impact of Event Scale-Revised; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; NR = not reported; PCL-C = PTSD Checklist — Civilian Version; PTSD = posttraumatic stress disorder; QIDS-SR-16 = Quick Inventory of Depressive Symptomatology-Self-Report; RCT = randomized controlled trial; SR = systematic review; STAI-S = State-Trait Anxiety Inventory — State; TRD = treatment-resistant depression.

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Ahmed et al. (2023)[34] Egypt **Funding source:** No funding	Single-centre, double-blind, parallel RCT Conducted in 1 neurology and psychiatry hospital inpatient department	Patients aged 16 to 65 years with treatment-resistant MDD as defined by EMA (not responding to > 2 "adequate" [from original source and undefined] trials with antidepressant agents for > 4 weeks each); and current suicidal risk, based on psychiatric interview (N = 36) Sex, %: • Ketamine: female 44.4, male 55.6 • Placebo: female 38.9, male 61.1 Age (years), mean (SD): • Ketamine: 36.11 (13.83) • Placebo: 36.61 (13.65) History of trauma or abuse, %: • Ketamine: 66.6 • Placebo: 44.4	**Intervention:** Ketamine 0.5 mg/kg, single infusion per week for 2 weeks (n = 18) **Comparator**: Saline placebo, single infusion per week for 2 weeks (n = 18) Concomitant therapies allowed: Other psychotropic drugs at stable dosages ≥ 3 months before randomization.	**Outcomes** Depression: HDRS Psychological symptoms: SCL-90 Suicidal ideation: SPS **Follow-up**: 1 week
Duek et al. (2023)[35] US **Funding source:** Brain and Behaviour Research Foundation; American Brain Society; Clinical Neurosciences Division of the National Center for PTSD; and National Center for Advancing Translational Science.	Single-centre, double-blind, parallel RCT Conducted in 1 hospital	Adults meeting the diagnostic criteria for chronic PTSD for > 1 year (N = 27) Sex, %: • Ketamine: female 71.4, male 28.6 • Midazolam: female 53.8, male 46.2 Age (years), mean (SD): • Ketamine: 40.7 (10.7) • Midazolam: 35.1 (10.34) Experienced combat trauma, %: • Ketamine: 28.6 • Midazolam: 0	**Intervention:** Ketamine 0.5 mg/kg, single infusion for 40 minutes (n = 14) **Comparator**: Midazolam 0.045 mg/kg, single infusion (n = 13) Concurrent therapy in both groups: • Psychoeducation (before study infusion) • Exposure psychotherapy (1 to 4 days following study infusion)	**Outcomes** PTSD: PCL-5 Depression: BDI-II **Follow-up**: 90 days

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Harvey et al. (2023)[36] Australia **Funding source:** National Health and Medical Research Council	Single-centre, double-blind, parallel RCT Conducted in a single site in the KADS Trial[37] in Australia.	Adults with MDD of at least 3 months' duration based on DSM-5 criteria; insufficient response to ≥ 2 "adequate" (from original source and undefined) trials of antidepressant medications; any concurrent antidepressant medication at stable dosage ≥ 4 weeks before and during the RCT; and MADRS score ≥ 20 (N = 21) Sex, %: • Ketamine: female 20, male, 80 • Midazolam: female 18, male 82 Age (years), mean (SD): • Ketamine: 44.7 (10.3) • Midazolam: 49.1 (14.1) Antidepressants, %: • Ketamine: 100 • Midazolam: 80	**Intervention:** SC ketamine hydrochloride 0.5 mg/kg, single injection (n = 10) **Comparators**: Midazolam hydrochloride 0.025 mg/kg, single injection (n = 11)	**Outcomes** Depression: DASS-21 Neurocognitive outcomes: • SST • EST • AGNG • Ruff 2 and 7 • COWAT **Follow-up**: Immediately after treatment
Li et al. (2023)[37] Taiwan **Funding source:** Taipei Veterans General Hospital; Yen Tjing Ling Medical Foundation; Ministry of Science and Technology, Taiwan; Taipei, Taichung, Kaohsiung Veterans General Hospital, Tri-Service General Hospital, Academia Sinica Joint Research Program; and Veterans General Hospitals and University System of Taiwan Joint Research Program	Double-blind, parallel RCT. Did not report setting.	Adult patients aged between 20 and 64 years diagnosed with unipolar TRD, and with prominent suicidal ideation (N = 48) Sex (female), %: • Ketamine: 62.5 • Midazolam: 75.0 Age (years), mean (SD): • Ketamine: 30.58 (11.03) • Midazolam: 34.13 (11.05) PTSD comorbidity, %: • Ketamine: 33.3 • Midazolam: 25.0	**Intervention:** Ketamine 0.5 mg/kg, single infusion (n = 24) **Comparator**: Midazolam 0.045 mg/kg, single infusion (n = 24) Concurrent antidepressants in both groups.	**Outcomes** Depression: • HDRS • MADRS Suicidal ideation: CSSRS-ISS **Follow-up**: 3 days

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Loo et al. (2023)[38] Australia **Funding source:** Australian National Health and Medical Research Council	Multicentre, double-blind, parallel RCT Conducted in 7 specialist mood disorders centres (6 in Australia and 1 in New Zealand)	Adults with MDD of at least 3 months' duration; insufficient response to ≥ 2 "adequate" (from original source and undefined) trials of antidepressant medications; any concurrent antidepressant medication at stable dosage ≥ 4 weeks before and during the RCT; and MADRS score ≥ 20 (N = 184). Sex (female), %: • Ketamine fixed: 27.3 • Ketamine flexible: 37.7 • Midazolam fixed: 22.9 • Midazolam flexible: 39.6 Age (years), mean (SD): • Ketamine fixed: 45.9 (13.6) • Ketamine flexible: 44.5 (13.6) • Midazolam fixed: 48.2 (13.6) • Midazolam flexible: 46.2 (15.3) Concurrent psychotropic medications, %: • Ketamine fixed: 80 • Ketamine flexible: 90.9 • Midazolam fixed: 86.8 • Midazolam flexible: 90.6	**Interventions:** SC racemic ketamine hydrochloride for 4 weeks • Fixed dose: 0.5 mg/kg (n = 38) • Flexible dose: start at 0.5 mg/kg and escalate to 0.6 mg/kg, 0.75 mg/kg, and 0.9 mg/kg based on MADRS score (n = 54) **Comparators**: SC midazolam hydrochloride for 4 weeks • Fixed dose: 0.025 mg/kg (n = 35) • Flexible dose: start at 0.025 mg/kg and escalate to 0.03 mg/kg, 0.0375 mg/kg, and 0.045 mg/kg based on MADRS score (n = 54)	**Outcomes** Depression: • MADRS • CGI-S • CGI-I Adverse events **Follow-up**: 4 weeks
Su et al. (2023)[39] Taiwan **Funding sources:** Taipei Veterans General Hospital; Yen Tjing Ling Medical Foundation; Ministry of Science and Technology Taiwan; Taipei, Taichung, Kaohsiung Veterans	Single-centre, double-blind, parallel RCT Conducted at 1 veterans' hospital.	Outpatients 20 to 64 years of age with MDD based on the DSM-5 criteria; with "inadequate" (from original source and undefined) response to ≥ 2 different antidepressants with "adequate" (from original source and undefined) dosage and treatment duration; and prominent suicidal ideation (≥ 4 on MADRS item 10) (N = 84)	**Intervention:** Ketamine 0.5 mg/kg, single infusion (n = 42) **Comparators**: Midazolam 0.045 mg/kg, single infusion (n = 42)	**Outcomes** Depression: MADRS Suicidal ideation: CSSRS-ISS Adverse events **Follow-up**: 2 weeks

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
General Hospital, Tri-Service General Hospital; Academia Sinica Joint Research Program; and Veterans General Hospitals and University System of Taiwan Joint Research Program		Sex (female), %: • Ketamine: 66.7 • Midazolam 73.8 Age (years), mean (SD): • Ketamine: 34.26 (13.34) • Midazolam: 36.88 (12.21) PTSD comorbidity, %: • Ketamine: 26.2 • Midazolam 26.2		
Price et al. (2022)[40] US **Funding sources:** National Institute of Mental Health and University of Pittsburgh	Single-centre, double-blind, parallel RCT Did not report setting.	Patients aged 18 to 60 years with MDD of at least 3 months' duration based on DSM-5 criteria; ≥ 1 unsuccessful "adequate" (from original source and undefined) trial of an approved antidepressant medication based on ATRQ; MADRS score ≥ 25; score > 1 SD above normative mean on CTI "self" subscale or < 1 SD below normative mean on RSES; and any existing depression treatment regimens were stably maintained ≥ 4 weeks before screening (N = 154) Sex (assigned female at birth), %: • Ketamine + ASAT: 60.4 • Ketamine: 64.0 • ASAT: 64.7 Gender, %: • Ketamine + ASAT: cisgender male 39.6, cisgender female 54.7, transgender: female-to-male 1.9, transgender: male-to-female 0, nonbinary or gender fluid 1.9, gender undisclosed or unknown 1.9 • Ketamine: cisgender male 34, cisgender female 56, transgender: female-to-male 0,	**Interventions:** Ketamine 0.5 mg/kg for 8 sessions • Ketamine plus active ASAT (n = 53) • Ketamine plus sham ASAT (n = 50) **Comparator:** Saline 50 mL plus active ASAT for 8 sessions (n = 51)	**Outcomes** Depression: MADRS Adverse events **Follow-up:** 30 days

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		transgender: male-to-female 0, nonbinary or gender fluid 2.0, gender undisclosed or unknown 8.0 • ASAT: cisgender male 33.3, cisgender female 64.7, transgender: female-to-male 0, transgender: male-to-female 2.0, nonbinary or gender fluid 0, gender undisclosed or unknown 0 Age (years), mean (SD): • Ketamine + ASAT: 34.7 (10.1) • Ketamine: 34.6 (11.6) • ASAT: 33.5 (9.9)		

AGNG = Affective Go/No Go; ASAT = automated self-association training; BDI = Beck Depression Inventory; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CGI = Clinical Global Impression; CGI-I = CGI-improvement; CGI-S = CGI-severity; COWAT: Controlled Word Association Test; CSSRS-ISS = Columbia-Suicide Severity Rating Scale — Ideation Severity Subscale; CTI = Cognitive Triad Inventory; DASS-21 = Depression Anxiety Stress Scale; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECT = electroconvulsive therapy; EMA = European Medicines Agency; EST = Emotional Stroop Test; GSE = Global Self-Evaluation of Memory; HDRS = Hamilton Depression Rating Scale; IN = Intranasal; KADS = Ketamine for Adult Depression Study; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; PGI-I = Patient Global Impression — Improvement; PCL-5 = PTSD Checklist for DSM-5; QIDS-SR-16 = Quick Inventory of Depressive Symptomatology-Self-Report; RCT = randomized controlled trial; SC = subcutaneous; SD = standard deviation; SPS = Suicide Probability Scale; SST = Scrambled Sentence Test; TRD = treatment-resistant depression.

Note: Sex and/or gender categories were reported differently in the studies included in this table; the original source wording from each study has been retained here.

Table 4: Characteristics of Included Economic Evaluation

Study citation country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator(s)	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
Brendle et al. (2022)[41] US **Funding source:** No funding	**Analysis**: Cost-utility analysis **Time horizon**: 3 years (1 to 5 years in sensitivity analysis) **Perspective**: US health care sector and patient	Simulated population with age of 40 (± 13.2) years with 64.2% female, based on an analysis of insurance claims for patients with TRD	**Intervention:** Esketamine, twice weekly at a starting dose of 56 mg, with subsequent doses of 56 mg or 84 mg thereafter. **Comparator**: Ketamine, given twice weekly at a starting dose of 0.5 mg/kg, with subsequent doses of 0.5 mg/kg or 1.0 mg/kg thereafter.	A cost-effectiveness framework using a Markov model with a 1-month cycle length.	Clinical trial data were based on 4 clinical trials included in an FDA Advisory Committee briefing document for esketamine and meta-analysis on IV administration of ketamine in patients with TRD. Real-world effectiveness data were taken from psychiatric clinic EHR and medical chart review. Utility values were taken from a prospective cohort study that used EQ-5D to assess quality of life among outpatients treated for MDD with pharmacotherapy. Costs included medication, physician visits at each presentation of dosing, and observation by medical assistant after each dose administration.	Patient were assumed to have commercial health insurance. Equal relapse rates were assumed for ketamine and esketamine. Patients were assumed to follow a similar and consistent pattern of treatment following relapse. IM ketamine efficacy estimates were assumed to be similar to IV ketamine efficacy.

EHR = electronic health record; IM = intramuscular; MDD = major depressive disorder; TRD = treatment-resistant depression.

Table 5: Characteristics of Included Guidelines

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, synthesis, and quality assessment	Recommendations development and evaluation	Guideline validation
VA/DoD (2023)[42,a]					
Intended users: Providers and others involved in the care of active-duty service members and veterans with PTSD **Target population:** Adults with PTSD or ASD caused by any type of trauma who are eligible for care in VA or DoD health care delivery systems.	Treatment (including pharmacotherapies) of PTSD.	**Critical outcomes:** Improvement in global PTSD severity. **Important outcomes:** Serious adverse events, retention/ dropout rate, loss of diagnosis/remission, self-reported PTSD, comorbid symptoms (e.g., depression, anxiety, sleep, aggression), QoL (including functional status).	Systematic literature search was conducted to update 2017 guideline. GRADE system used to assess quality of evidence (high, moderate, low, and very low) and strength of recommendations (strong for or against, weak for or against, and neither for nor against).	The guideline development work group included 37 professionals in internal medicine, neurology, nursing, pharmacy, psychiatry, psychology, social work, and surgery. The guideline development process followed the CPG Policy Guidance for VA/DoD Clinical Practice Guidelines. A systematic review of evidence was distributed to the work group before a virtual meeting. During the meeting, the work group interpreted the systematic review's findings, reviewed recommendations from previous guidelines, and developed new recommendations in discussions with clinical experts. Using the GRADE approach, work group members rated evidence quality, and clinical experts assessed recommendation strength. The strength and direction of each recommendation were determined by assessing the	Once the work group completed a near-final draft, they identified experts from the VA and DoD health care systems and outside organizations generally viewed as experts in the respective field to review that draft. The work group considered all feedback from the peer reviewers and modified the CPG where justified, in accordance with the evidence.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, synthesis, and quality assessment	Recommendations development and evaluation	Guideline validation
				quality of the overall evidence base, the associated benefits and harms, patient values and preferences, and other implications (e.g., resource use, equity, acceptability, feasibility, and subgroup considerations).	
VA/DoD (2022)[43,b]					
Intended users: All health care providers caring for patients with MDD. **Target population**: Adults with DSM-5, ICD-9, or ICD-10 diagnosis of MDD who are eligible for care in the VA or DoD health care delivery systems.	Treatment (including pharmacotherapies) of MDD, including MDD that is severe or has partial or limited response to initial treatment.	**Critical outcomes**: Improvement of depression symptoms, remission rate, adverse events. **Important outcomes**: Improvement in QoL, functional status measures, relapse/ recurrence rate, suicidal behaviour, mortality.	Systematic literature search was conducted to update 2016 guideline. GRADE system used to assess quality of evidence (high, moderate, low, and very low) and strength of recommendations (strong for or against, weak for or against, and neither for nor against).	The guideline development work group included 41 professionals in psychology, psychiatry, neuropsychiatry, pharmacy, sleep medicine, internal medicine, social work, and nursing. The guideline development process followed the CPG Policy Guidance for VA/DoD Clinical Practice Guidelines. A systematic review of evidence was distributed to the work group before a virtual meeting. During the meeting, the work group interpreted the systematic review's findings, reviewed recommendations from previous guidelines, and developed new recommendations in discussions with clinical experts. Using the GRADE approach, work group members rated evidence	Once the work group completed a near-final draft, they identified experts from the VA and DoD health care systems and outside organizations generally viewed as experts in the respective field to review that draft. The work group considered all feedback from the peer reviewers and modified the CPG where justified, in accordance with the evidence.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, synthesis, and quality assessment	Recommendations development and evaluation	Guideline validation
				quality, and clinical experts assessed recommendation strength. The strength and direction of each recommendation were determined by assessing the quality of the overall evidence base, the associated benefits and harms, patient values and preferences, and other implications (e.g., resource use, equity, acceptability, feasibility, and subgroup considerations).	

ASD = acute stress disorder; CPG = clinical practice guideline; DSM-5 = Statistical Manual of Mental Disorders, Fifth Edition; DoD = US Department of Defense; DTD = difficult-to-treat depression; GRADE = Grades of Recommendation Assessment, Development and Evaluation; ICD = International Classification of Diseases; MAGICapp = Making GRADE the Irresistible Choice; MDD = major depressive disorder; PTSD = posttraumatic stress disorder; QoL = quality of life; VA = US Department of Veterans Affairs.

[a]Update to 2017 guideline.

[b]Update to 2016 guideline.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 6: Strengths and Limitations of SRs Using AMSTAR 2[25]

Strengths	Limitations
Nikolin et al. (2023)[30]	
• The population, intervention, comparators, and outcomes of interest were clearly stated. • A protocol was registered a priori in PROSPERO. • The search was conducted in 4 databases, plus handsearching of reference lists, and clinical trial registries. • The search strategies were provided. No language restrictions were applied. • Two reviewers selected studies, extracted data, and assessed risk of bias in duplicate. • An appropriate tool (Cochrane ROB tool for RCTs) was used to assess the risk of bias of the included studies. • For the included studies, the population, intervention, comparators, and outcomes were adequately described. • The authors provided a list of excluded studies with the reasons for their exclusion. • The authors reported their declarations of interest and that there was no funding for the SR.	• The authors did not provide a justification for only including RCTs. • The authors did not search the grey literature. • While the authors assessed studies as high risk of bias on the item "other bias" of the Cochrane tool due to funding being provided by a pharmaceutical company, they did not report the sources of funding for each study. • The authors assessed the risk of bias for each study but did not discuss the potential impact of risk of bias on the results. • While the authors reported heterogeneity for the meta-analyses (i.e., I^2), they did not discuss the sources of heterogeneity in the results. • There was some evidence of publication or small study bias observed following a visual inspection of funnel plots.
Shafiee et al. (2023)[32]	
• The population, intervention, comparators, and outcomes of interest were clearly stated. • A protocol was registered a priori in PROSPERO. • The reviewers searched 2 databases and clinical trial registry. • The search strategies for each online database were provided. • Two authors screened studies based on titles, abstracts, and full texts in duplicate. • An appropriate tool (Cochrane ROB 2 tool for RCTs) was used to assess the risk of bias of the included studies. • For the included studies, the interventions and outcomes were adequately described. • The authors assessed the potential impact of risk of bias on the results. • The authors reported no conflicts of interest and that there was no funding for the SR.	• The authors did not provide an explanation for including only RCTs. • The authors did not search the reference lists of included studies or the grey literature. • It is unclear whether data abstraction and risk of bias assessment were performed in duplicate. • The authors did not report the sources of funding for each study. • The authors did not provide a list of excluded studies.

Strengths	Limitations
Du et al. (2022)[31]	
• The population, intervention, comparators, and outcomes of interest were clearly stated. • A protocol was registered a priori in PROSPERO. • The search was conducted in 4 databases as well as clinical trial registries. • The key search terms were provided. • Two reviewers selected studies based on the inclusion and exclusion criteria in duplicate. Two reviewers assessed the risk of bias of included studies in duplicate. • An appropriate tool (Cochrane ROB tool for RCTs) was used to assess the risk of bias of the included RCTs. • For the included studies, the outcomes were adequately described.	• The authors included cohort studies and case-control studies in addition to RCTs but did not provide an explanation for inclusion of the study designs. • The authors did not search the grey literature. They did not manually review reference lists of relevant articles. • It was unclear if language restrictions were applied to the literature search. • It was unclear if data extraction was performed in duplicate. • A tool that was intended to assess risk of bias in RCTs was also used for cohort and case-control studies. • While the population, intervention, and comparators were reported, relevant details were not described (e.g., population demographics, route of administration of treatment). • The authors did not report the sources of funding for each study. • While the authors provided the number of excluded studies and reasons for their exclusion, they did not provide references for the excluded studies. • The authors assess the risk of bias for each study but did not discuss the potential impact of risk of bias on the results. • The authors did not report if there were any potential conflicts of interest. • The authors did not report the role or involvement of the funding sponsor.
Marchi et al. (2022)[33]	
• The population, intervention, comparators, and outcomes of interest were clearly stated. • A protocol was registered a priori in PROSPERO. • The search was conducted in 3 databases. • The search strings for each database were provided. • Three reviewers screened the titles and abstracts for inclusion in triplicate. Two groups of reviewers screened full texts for inclusion in duplicate. • For each eligible trial, 2 groups of reviewers independently extracted the relevant data. Extraction sheets were cross-checked for consistency and any disagreement was resolved by discussion within the research group. • Three reviewers assessed risk of bias in triplicate. • An appropriate tool (Cochrane ROB tool for RCTs) was used to assess the risk of bias of the included studies. • For the included studies, the population, interventions, comparators, and outcomes were adequately described. • The authors assessed the potential impact of risk of bias on the results.	• The authors did not provide a justification for only including RCTs. • The authors did not search the reference lists of included studies, trial registries, or the grey literature. • The authors did not report the sources of funding for each study. • While the authors provided the number of excluded studies and reasons for their exclusion, they did not provide references for the excluded studies.

Strengths	Limitations
• The authors reported no conflicts of interest and that there was no funding for the SR.	

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; RCT = randomized controlled trial; ROB = risk of bias; SR = systematic review.

Table 7: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist[26]

Strengths	Limitations
Ahmed et al. (2023)[34]	
Reporting: • The aim of the study, the outcomes to be measured, the characteristics of the patients included in the study, the interventions of interest, and the main findings were clearly described. • No significant differences were found between groups for any baseline demographic factors, clinical history, and ECT history. • The authors did not report any patients lost to follow-up. • Actual P values were reported. **External validity:** • The study was conducted at a hospital inpatient department, where the staff, setting, and facilities, were representative of the treatment that most patients receive. **Internal validity — bias:** • The Sequentially Numbered, Opaque, Sealed Envelope technique was used for randomization and blinding. • The treatment assignment was blinded except to the research pharmacist who was responsible for group allocation. • The time between the intervention and outcome was the same for the intervention and comparator groups. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. • Patient adherence was reliable. • All patients were included in the analyses. **Internal validity — confounding:** • Patients in different interventions groups were recruited from the same population and over the same period and randomized. **Power:** • The researchers performed sample size calculation, which determined that 17 samples were required for each arm.	**Reporting:** • Adverse events were not reported. **External validity:** • The study population was small (N = 36) due to challenges in recruitment. • It is uncertain if the patients asked to participate in the study were representative of the entire population from which they were recruited.
Duek et al. (2023)[35]	
Reporting: • The aim of the study, the outcomes to be measured, the characteristics of the patients included in the study, the interventions of interest, and the main findings were clearly	**Reporting:** • Methods of recruitment were not reported. • Actual P values were not reported for the main outcomes except for probability < 0.001.

Strengths	Limitations
described. • There were no group differences in demographics of the randomized participants. **External validity:** • The staff, place, and facility where the patients were treated, were representative of the treatment most of the patients receive. **Internal validity — bias:** • An independent pharmacy managed the randomization using counterbalanced blocks stratified by gender. • The participants and study team were blinded to treatment assignment. • The time between the intervention and outcome was the same for the intervention and comparator groups. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. • All but 1 of 28 participants completed the study and were included in the analyses.	• Adverse events were not reported. **External validity:** • The small population (N = 27) was from a single centre and may not represent the entire population from which they were recruited. **Internal validity — confounding:** • Methods of allocation concealment were not reported. **Power:** • The researchers performed sample size calculation, which determined that a sample size of 40 (n = 20 in each group) was required. However, due to COVID-19 restrictions, data collection was halted earlier, and the sample size was not reached.
Harvey et al. (2023)[36]	
Reporting: • The objective of the study, the primary and secondary outcomes to be measured, the characteristics of the patients included in the study, the interventions of interest, and the main findings were clearly described. • No significant differences were found between groups for any baseline demographic factors. • The study provided estimates of the random variability in the data for the main outcomes. • The authors did not report any patients lost to follow-up. • Actual P values were reported. **External validity:** • The study was conducted at a treatment centre, where the staff, setting, and facilities, were representative of the treatment that most patients receive. **Internal validity — bias:** • A trial statistician computer-generated a permuted-block randomization sequence. • Participants, mood raters, and cognitive test administrators were blinded to treatment allocation. • The time between the intervention and outcome was the same for the intervention and comparator groups. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. • Patient adherence was reliable. **Internal validity — confounding:**	**Reporting:** • Adverse events of the intervention were not reported. **External validity:** • The small population (N = 21) was from a single centre and may not represent the entire population from which they were recruited. **Power:** • sample size calculation was performed.

Strengths	Limitations
• Patients in different groups were recruited from the same population and over the same period and randomized.	
Li et al. (2023)[37]	
Reporting: • The objective of the study, the outcomes to be measured, the characteristics of the patients included in the study, the intervention and comparator, and the main findings were clearly described. • No significant differences were found between groups for any baseline demographic characteristics. • The study provided estimates of the random variability in the data for the main outcomes. • Actual P values were reported. **External validity:** • The staff, places, and facilities where the patients were treated, were representative of the treatment most of the patients receive. **Internal validity — bias:** • Permuted-block randomization was performed. • The trial was double-blinded. • Statistical tests were used appropriately, and the outcome measures were accurate and reliable. • Patient adherence was reliable. • All patients were followed up for 3 days.	**Reporting:** • Methods of recruitment were not reported. • Adverse events were not reported. • Effect estimates were not reported for outcomes of interest. **External validity:** • The small population (N = 48) may not represent the entire population from which they were recruited. **Internal validity - confounding:** • Methods of allocation concealment were not reported. **Power:** • Sample size calculation was not reported.
Loo et al. (2023)[38]	
Reporting: • The objective of the study, the primary and secondary outcomes to be measured, the characteristics of the patients included in the study, the interventions of interest, and the main findings were clearly described. • Actual P values and estimates of the random variability in the data were reported for the main outcomes. • Adverse events were reported. **External validity:** • The study was conducted at 7 treatment centres, where the staff, setting, and facilities, were representative of the treatment that most patients receive. **Internal validity — bias:** • All study personnel were blinded, except for the trial statistician generating the randomization sequence, trial pharmacist and the DSMB members. • The time between the intervention and outcome was the same for the intervention and comparator groups. • The statistical analysis plan was published before data analysis, and the main outcome measures were accurate and reliable.	**Reporting:** • The characteristics of patients lost to follow-up were not described. • Although there appeared to be no group differences in demographics of the randomized participants, statistical comparisons were not reported. **External validity:** • Study recruitment was affected by the COVID-19 pandemic, being halted in April 2020 and with significant challenges in restarting. **Power:** • Neither study group achieve the originally planned sample size.

Strengths	Limitations
• Patient adherence was reliable. **Internal validity — confounding:** • Patients in different interventions groups were recruited from the same population and over the same period and randomized. • The analyses were performed using a modified ITT approach.	
Su et al. (2023)[39]	
Reporting: • The objective of the study, the main outcomes to be measured, the characteristics of the patients included in the study, the interventions of interest, and the main findings were clearly described. • There were no group differences in demographics of the randomized participants. • Adverse events of the intervention were reported. **External validity:** • The staff, place, and facility where the patients were treated, were representative of the treatment most of the patients receive. **Internal validity — bias:** • All patients were followed up for 3 days. • Patient adherence was reliable. • The main outcome measures were valid and reliable.	**Reporting:** • Methods of recruitment were not reported. • Effect estimates were not reported for outcomes of interest. **External validity:** • It is uncertain if the study sample represented the entire population from which they were recruited. **Internal validity — bias:** • Although this was reported as a double-blind RCT in the title, no details were provided. **Internal validity — confounding:** • Methods of randomization and allocation concealment were not reported. **Power:** • No sample size calculation was reported.
Price et al. (2022)[40]	
Reporting: • The objective of the study, the main outcomes to be measured, the characteristics of the patients included in the study, the interventions of interest, and the main findings were clearly described. • Actual P values and estimates of the random variability in the data were reported for the main outcomes. • Adverse events were reported. **Internal validity — bias:** • Participants and study personnel were blinded. • The time between the intervention and outcome was the same for the intervention and comparator groups. • The authors reported the number of withdrawals (2.6% overall) and reasons per study group. • Patient adherence was reliable. **Power:** • The authors reported the sample size calculation and recruited the target sample sizes in each group for sufficient power.	**Reporting:** • Methods of recruitment were not reported. • Although there appeared to be no group differences in demographics of the randomized participants, statistical comparisons were not reported. **External validity:** • The staff, place, and facility where the patients were treated were not described. • It is uncertain if the study sample represented the entire population from which they were recruited. **Internal validity — confounding:** • Methods of randomization and allocation concealment were not reported.

DSMB = Data Safety Monitoring Board; ECT = electroconvulsive therapy; ITT = intention to treat; RCT = randomized controlled trial.

Table 8: Strengths and Limitations of Economic Evaluation Using the Drummond Checklist[27]

Strengths	Limitations
Brendle et al. (2022)[41]	
Study design: • The research question and its economic importance were clearly stated. • The rationale for choosing alternative interventions compared was stated, and the alternatives being compared were clearly described. • The viewpoint and form of economic analysis were clearly stated and justified. **Data collection:** • The source(s) of effectiveness estimates were stated. • Details of the methods of meta-analysis for the clinical trial efficacy data were given. • Details of the real-world effectiveness data were given. • The primary outcome measures for the economic evaluation were clearly stated. • Methods to value health states, utilities, and other benefits were stated. • Quantities of resource use were reported separately from costs. • Methods for the estimation of quantities and unit costs were described. • Details of the Markov model were given. • Key parameters of the model were clearly stated. **Analysis and interpretation of results:** • Time horizon of costs and benefits, as well as discount rate, were stated. • The approach to sensitivity analyses was reported. • Incremental analysis was reported. • Major outcomes were presented in disaggregated as well as aggregated form. • The research question was answered with appropriate conclusions and caveats described.	**Data collection:** • Details of currency price adjustments for inflation were not given. • The choice of model used was not justified. **Analysis and interpretation of results:** • The choice of discount rate was not justified. • Confidence intervals were not provided for main outcome data. • The choice of variables for sensitivity analysis and the ranges over which they were varied were not justified.

Table 9: Strengths and Limitations of Guidelines Using AGREE II[28]

Item	VA/DoD (2023)[42]	VA/DoD (2022)[43]
Domain 1: scope and purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes
Domain 2: stakeholder involvement		
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes	Yes
6. The target users of the guideline are clearly defined.	Yes	Yes
Domain 3: rigour of development		
7. Systematic methods were used to search for evidence.	Yes	Yes
8. The criteria for selecting the evidence are clearly described.	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes
10. The methods for formulating the recommendations are clearly described.	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes
13. The guideline has been externally reviewed by experts before its publication.	Yes	Yes
14. A procedure for updating the guideline is provided.	No	No
Domain 4: clarity of presentation		
15. The recommendations are specific and unambiguous.	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes
Domain 5: applicability		
18. The guideline describes facilitators and barriers to its application.	No	Yes
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	Yes
20. The potential resource implications of applying the recommendations have been considered.	Yes	Yes

Item	VA/DoD (2023)[42]	VA/DoD (2022)[43]
21. The guideline presents monitoring and/or auditing criteria.	No	No
Domain 6: editorial independence		
22. The views of the funding body have not influenced the content of the guideline.	NR	NR
23. Competing interests of guideline development group members have been recorded and addressed.	Disclosure process described but not disclosed in the report	Yes

AGREE II = Appraisal of Guidelines for Research and Evaluation II; NR = not reported; VA/DoD = US Department of Veterans Affairs and Department of Defense.

Appendix 4: Main Study Findings

Table 10: Summary of Findings by Comparison — Ketamine Versus Placebo

Citation, PTSD or TRD population	Study design	Outcome	Primary study or subgroup	Outcome result or sample size		Effect estimate or test statistic (95% CI)	P value
				Ketamine	Placebo		
Depression: at 24 hours after single/first dose							
Nikolin et al. (2023)[30] TRD	SR (9 RCTs)	Change in depression severity from baseline (using standardized depression scales, e.g., MADRS[a] or HDRS[b])	Nugent 2019	N = 35	N = 35	SMD −0.90 (−1.39 to −0.41)	NR
			Cao 2018	N = 37	N = 18	SMD −0.36 (−0.93 to 0.21)	NR
			Li 2016[c] (high dose)[d]	N = 16	N = 16	SMD −0.73 (−1.45 to −0.02)	NR
			Li 2016[c] (low dose)[e]	N = 16	N = 16	SMD −0.08 (−0.78 to 0.61)	NR
			Lai 2014	N = 4	N = 4	SMD −1.28 (−2.91 to 0.35)	NR
			Lapidus 2014 (IN)	N = 18	N = 18	SMD −0.87 (−1.55 to −0.18)	NR
			Sos 2013	N = 9	N = 19	SMD −1.08 (−1.93 to −0.23)	NR
			Zarate 2012	N = 7	N = 8	SMD −1.29 (−2.43 to −0.14)	NR
			Diazgranados 2010	N = 8	N = 9	SMD −0.72 (−1.71 to 0.27)	NR

Citation, PTSD or TRD population	Study design	Outcome	Primary study or subgroup	Outcome result or sample size		Effect estimate or test statistic (95% CI)	P value
				Ketamine	Placebo		
			Zarate 2006	N = 9	N = 9	SMD −2.35 (−3.61 to −1.09)	NR
	SR (7 RCTs)	Treatment response (≥ 50% reduction in depressive symptoms from baseline), n of N	Nugent 2019	12 of 35	0 of 35	OR 3.63 (0.76 to 6.51)	NR
			Li 2016[b]	4 of 16	3 of 16	OR 0.37 (−1.32 to 2.06)	NR
			Li 2016[b]	6 of 16	3 of 16	OR 0.96 (−0.66 to 2.57)	NR
			Lapidus 2014 (IN)	8 of 18	1 of 18	OR 2.61 (0.39 to 4.85)	NR
			Sos 2013	4 of 11	0 of 19	OR 1.91 (−0.50 to 4.32)	NR
			Zarate 2012	3 of 7	0 of 8	OR 2.58 (−0.59 to 5.76)	NR
			Diazgranados 2010	3 of 8	0 of 9	OR 2.49 (−0.65 to 5.64)	NR
			Zarate 2006	7 of 9	0 of 9	OR 4.04 (0.86 to 7.23)	NR
	SR (5 RCTs)	Remission, n of N	Lai 2014	1 of 4	0 of 4	OR 1.35 (−2.14 to 4.84)	NR
			Sos 2013	3 of 11	1 of 18	OR 1.91 (−0.50 to 4.32)	NR
			Zarate 2012	2 of 7	0 of 8	OR 2.04 (−1.18 to 5.26)	NR

Citation, PTSD or TRD population	Study design	Outcome	Primary study or subgroup	Outcome result or sample size		Effect estimate or test statistic (95% CI)	P value
				Ketamine	Placebo		
			Diazgranados 2010	1 of 8	0 of 9	OR 1.21 (−2.12 to 4.54)	NR
			Zarate 2006	2 of 9	0 of 9	OR 1.85 (−1.34 to 5.03)	NR
Price et al. (2023)[40] TRD	RCT	MADRS-based treatment response (≥ 50% decrease in score from baseline), %	NA	52	25	NNT 3.7	NR
		Remission (MADRS score ≤ 9), %	NA	28	4	NNT 4.2	NR
		MADRS scores	NA	N = 103	N = 51	Group × time: t(150) 4.29	< 0.0001
Depression: at 3 days after single or first dose							
Nikolin et al. (2023)[30] TRD	SR (8 RCTs)	Change in depression severity from baseline	Nugent 2019	N = 35	N = 35	SMD −0.78 (−1.27 to −0.29)	NR
			Cao 2018	N = 37	N = 18	SMD −0.20 (−0.77 to 0.36)	NR
			Lai 2014	N = 4	N = 3	SMD −1.33 (−2.98 to 0.31)	NR
			Lapidus 2014 (IN)	N = 18	N = 18	SMD −0.26 (−0.92 to 0.39)	NR
			Sos 2013	N = 9	N = 19	SMD −1.20 (−2.06 to −0.34)	NR
			Zarate 2012	N = 7	N = 8	SMD −1,17 (−2.30 to −0.05)	NR

Citation, PTSD or TRD population	Study design	Outcome	Primary study or subgroup	Outcome result or sample size		Effect estimate or test statistic (95% CI)	P value
				Ketamine	Placebo		
			Diazgranados 2010	N = 8	N = 9	SMD −0.62 (−1.64 to 0.40)	NR
			Zarate 2006	N = 9	N = 9	SMD −1.22 (−2.5 to −0.19)	NR
Nikolin et al. (2023)[30] TRD	SR (4 RCTs)	Treatment response (≥ 50% reduction in depressive symptoms from baseline), n of N	Cao 2018	5 of 37	0 of 18	OR 1.83 (−1.12 to 4.79)	NR
			Lai 2014	0 of 4	0 of 4	OR 0 (−4.13 to 4.13)	NR
			Lapidus 2014 (IN)	6 of 18	2 of 18	OR 1.39 (−0.38 to 3.15)	NR
			Zarate 2006	5 of 7	1 of 8	OR 2.30 (−0.16 to 4.76)	NR
	SR (5 RCTs)	Remission, n of N	Lai 2014	0 of 4	0 of 4	OR 0.0 (−4.13 to 4.13)	NR
			Sos 2013	3 of 11	1 of 19	OR 1.91 (−0.50 to 4.32)	NR
			Zarate 2012	1 of 7	0 of 8	OR 1.37 (−1.99 to 4.73)	NR
			Diazgranados 2010	1 of 9	0 of 9	OR 1.21 (−2.12 to 4.54)	NR
			Zarate 2006	3 of 9	0 of 9	OR 2.33 (−0.80 to 5.45)	NR

Citation, PTSD or TRD population	Study design	Outcome	Primary study or subgroup	Outcome result or sample size		Effect estimate or test statistic (95% CI)	P value
				Ketamine	Placebo		
Depression: at 1 week after repeated doses							
Nikolin et al. (2023)[30] TRD	SR (1 RCT)	Change in depression severity from baseline	Singh 2016a (3 times per week)	N = 16	N = 17	SMD −1.70 (−2.52 to −0.89)	NR
			Singh 2016a (2 times per week)	N = 18	N = 16	SMD −1.25 (−1.99 to −0.50)	NR
Ahmed et al. (2023)[34] TRD	RCT	HDRS-based full response to treatment (> 50% reduction from baseline), n of N	NA	2 of 18	0 of 18	Chi-square 18.0	0.001
		HDRS-based partial response to treatment (25% to 50% reduction from baseline), n of N		10 of 18	0 of 18		
		HDRS-based nonresponse to treatment (< 20% reduction), n of N		6 of 18	18 of 18		
		HDRS score, mean (SD)		Pre: 28.28 (4.45) Post: 20.22 (4.26)	Pre: 31.22 (5.26) Post: 30.5 (5.33)	F(1,34) 81.242	< 0.0001
Depression: at 28 to 30 days after treatment							
Nikolin et al. (2023)[30] TRD	SR (1 RCT)	Change in depression severity at 4 weeks from baseline	Singh 2016a (3 times per week)	N = 16	N = 17	SMD −1.84 (−2.67 to −1.01)	NR
			Singh 2016a (2 times per week)	N = 18	N = 16	SMD −1.49 (−2.26 to −0.72)	

Citation, PTSD or TRD population	Study design	Outcome	Primary study or subgroup	Outcome result or sample size		Effect estimate or test statistic (95% CI)	P value
				Ketamine	Placebo		
Price et al. (2023)[40] TRD	RCT	MADRS scores at 30 days	Ketamine + ASAT	N = 53	N = 51	Group: t(148) −3.62	0.0004
						Group × time: t(568) 1.39	0.164
			Ketamine + sham ASAT	N = 50	N = 51	Group × time: t(568) 2.35	0.019
Psychological symptoms: at 1 week after treatment							
Ahmed et al. (2023[34]) TRD	RCT	"Abnormal" (as reported by study authors) on SCL-90[f] somatization subscale, n of N (%)	NA	17 of 18 (94.4)	12 of 18 (66.7)	Chi-square 4.43	0.08
		"Abnormal" (as reported by study authors) on SCL-90[f] obsessive-compulsive subscale, n of N (%)		16 of 18 (88.9)	9 of 18 (50)	Chi-square 6.41	0.027
		"Abnormal" (as reported by study authors) on SCL-90[f] interpersonal sensibility subscale, n of N (%)		17 of 18 (94.4)	11 of 18 (61.1)	Chi-square 5.78	0.004
		"Abnormal" (as reported by study authors) on SCL-90[f] anger-hostility subscale, n of N (%)		7 of 18 (38.9)	2 of 18 (11.1)	Chi-square 3.7	0.12

Citation, PTSD or TRD population	Study design	Outcome	Primary study or subgroup	Outcome result or sample size		Effect estimate or test statistic (95% CI)	P value
				Ketamine	Placebo		
		"Abnormal" (as reported by study authors) on SCL-90[f] anxiety subscale, n of N (%)		17 of 18 (94.4)	12 of 18 (66.7)	Chi-square 4.43	0.08
		"Abnormal" (as reported by study authors) on SCL-90[f] phobic anxiety subscale, n of N (%)		15 of 18 (83.3)	10 of 18 (55.6)	Chi-square 3.27	0.14
		"Abnormal" (as reported by study authors) on SCL-90[f] paranoid ideation subscale, n of N (%)		12 of 18 (66.7)	3 of 18 (16.7)	Chi-square 9.25	0.006
		"Abnormal" (as reported by study authors) on SCL-90[f] psychosis subscale, n of N (%)		8 of 18 (44.4)	4 of 18 (22.2)	Chi-square 2.0	0.28
PTSD symptoms: at 24 hours after treatment							
Du et al. (2022)[31] PTSD	1 SR (2 RCTs)	PCL-C[g] score on day 1, mean (SD)	Pradhan 2017	25.6 (3.78), N = 5	25.6 (7.63), N = 4	MD −1.0 (−9.18 to 7.18)	NR
		CAPS[h] score on day 1, mean (SD)	Pradhan 2018	25.8 (8.15), N = 10	26.3 (6.82), N = 10	MD −0.50 (−7.09 to 6.09)	NR
			Pradhan 2017	17.8 (5.21), N = 5	23.4 (8.99), N = 4	MD −5.60 (−15.52 to 4.32)	NR

Citation, PTSD or TRD population	Study design	Outcome	Primary study or subgroup	Outcome result or sample size		Effect estimate or test statistic (95% CI)	P value
				Ketamine	Placebo		
Suicidal ideation: at 1 week after treatment							
Ahmed et al. (2023)[34] TRD	RCT	SPS[i] score, mean (SD)	NA	Pre: 93.11 (19.07) Post: 75.76 (20.58)	Pre: 81.83 (13.07) Post: 80.67 (13.15)	Treatment × time: F(1.76, 59.86) 44.709	< 0.0001
Adverse events: at 24 hours after treatment							
Price et al. (2023)[40] TRD	RCT	Dissociative effects, n (%)	NA	100 (97.1)	11 (21.6)	NR	NR
		Dizziness, n (%)		70 (68%)	10 (19.6)	NR	NR
		Dry mouth, n (%)		40 (38.8)	5 (9.8)	NR	NR
		Decreased energy, n (%)		16 (15.5)	3 (5.9)	NR	NR
		Elevated blood pressure, n (%)		7 (6.8)	2 (3.9)	NR	NR
Adverse events: at 30 days after treatment							
Price et al. (2023)[40] TRD	RCT	Dissociative effects, n (%)	NA	0	0	NR	NR
		Dizziness, n (%)		4 (3.9)	0	NR	NR
		Dry mouth, n (%)		2 (1.9)	0	NR	NR
		Decreased energy, n (%)		6 (5.8)	5 (9.8)	NR	NR
		Elevated blood pressure, n (%)		0	0	NR	NR

ASAT = automated self-association training; BDI = Beck Depression Inventory; CAPS = Clinician-Administered PTSD Scale; CI = confidence interval; HDRS = Hamilton Depression Rating Scale; IN = intranasal; MADRS = Montgomery-Asberg Depression Rating Scale; MD = mean difference; MDD = major depressive disorder; NA = not applicable; NR = not reported; OR = odds ratio; PCL-C = PTSD Checklist — Civilian Version; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SCL = Symptom Checklist; SD = standard deviation; SMD = standardized mean difference; SPS = Suicide Probability Scale; SR = systematic review, TRD = treatment-resistant depression.

Note that this appendix has not been copy-edited.

[a]MADRS has 10 items and is used by clinicians to assess the severity of depression in patients with a diagnosis of depression. Higher scores indicate more severe depression.[49]

[b]HDRS is used to measure the severity of symptoms of depression based on 17-item scales. The sum of all items makes up the total score: 0 to 7 = no depression; 8 to 13 = mild depression; 14 to 18 = moderate depression; 19 to 22 = severe depression; and ≥ 23 = very severe depression.[50]

[c]Assessed 4 hours following treatment.

[d]IV high dose = ≥ 0.5 mg/kg.

[e]IV low dose = < 0.5 mg/kg.

[f]SCL-90 is a self-report instrument that includes 90 items and 9 subscales to assess a wide range of psychological issues and psychopathology symptoms.[51] Scores on the depression subscale were not reported in the RCT by Ahmed et al.[34]

[g]PCL is a standardized self-report rating scale for PTSD comprising 17 Likert-type items that correspond to the key symptoms of PTSD. Two versions of the PCL exist: PCL-M is specific to PTSD caused by military experiences and PCL-C is applied generally to any traumatic event. Higher scores indicate more severe PTSD.[52]

[h]CAPS is a structured interview for PTSD diagnostic status and symptom severity. Hight scores indicate more severe PTSD.[53]

[i]SPS is a self-report 36-item Likert-type scale to assess suicide risk. Suicide probability is calculated by total scores. In males, 0 to 36 = no clinical depression; 37 to 44 = mild; 45 to 51 = moderate; and > 52 = severe. In females, a total score of 0 to 33 = no clinical depression; 34 to 38 = mild; 39 to 43 = moderate; and > 44 = severe.[34]

Table 11: Summary of Findings by Comparison — Ketamine Versus Midazolam

Citation, PTSD or TRD population	Study design	Outcome	Primary study or subgroup	Outcome result or sample size		Effect estimate (95% CI)	P value
				Ketamine	Midazolam		
Depression: various durations after single dose							
Nikolin et al. (2023)[30] TRD	SR (2 RCTs)	Change in depression severity on MADRS[a] at day 1 from baseline	Loo 2016 (SC)	N = 6	N = 6	SMD −1.32 (−2.62 to −0.02)	NR
			Loo 2016 (IM)	N = 5	N = 5	SMD −2.10 (−3.92 to −0.27)	NR
			Loo 2016 (IV)	N = 4	N = 3	SMD −0.42 (−1.95 to 1.11)	NR
			Murrough 2013	N = 47	N = 25	SMD −0.93 (−1.44 to −0.42)	NR
		Change in depression severity on MADRS at day 3 from baseline	Loo 2016 (SC)	N = 5	N = 6	SMD −0.30 (−1.50 to 0.89)	NR
			Loo 2016 (IM)	N = 3	N = 5	SMD −2.13 (−4.14 to −0.11)	NR
			Loo 2016 (IV)	N = 3	N = 3	SMD 0.02 (−1.58 to 1.62)	NR
		Treatment response (≥ 50% reduction in depressive symptoms from baseline) on day 1, n of N	Loo 2016 (SC)	4 of 6	0 of 6	OR 3.15 (−0.11 to 6.42)	NR
			Loo 2016 (IM)	2 of 4	0 of 5	OR 2.40 (−0.99 to 5.78)	NR
			Loo 2016 (IV)	1 of 4	1 of 3	OR −0.41 (−3.70 to 2.89)	NR

Citation, PTSD or TRD population	Study design	Outcome	Primary study or subgroup	Outcome result or sample size		Effect estimate (95% CI)	P value
				Ketamine	Midazolam		
			Murrough 2013	30 of 47	7 of 25	OR 1.51 (0.46 to 2.57)	NR
		Response on day 3, n of N	Loo 2016 (SC)	1 of 5	1 of 6	OR 0.22 (−2.84 to 3.29)	NR
			Loo 2016 (IM)	3 of 3	0 of 5	OR 4.34 (0.20 to 8.49)	NR
			Loo 2016 (IV)	1 of 3	1 of 2	OR 0 (−3.39 to 3.39)	NR
			Murrough 2013	28 of 47	5 of 25	OR 1.77 (0.63 to 2.91)	NR
		Remission on day 1, n of N	Loo 2016 (SC)	2 of 6	0 of 6	OR 1.98 (−1.29 to 5.24)	NR
			Loo 2016 (IM)	2 of 4	0 of 5	OR 2.40 (−0.99 to 5.78)	NR
			Loo 2016 (IV)	1 of 4	0 of 3	OR 1.10 (−2.43 to 4.63)	NR
Duek et al. (2023)[35] PTSD	RCT	BDI-II[b] scores at end of treatment (unknown duration), mean (SD)	NA	16.5 (12.9), N = 14	17.1 (10.7), N = 13	t(25) = −0.12	nss
Harvey et al. (2023)[36] TRD	RCT	DASS-21[c] Depression scores at day 1, mean (SD)	NA	Pre 34.4 (6.0), N = 10 Post 30.2 (6.4), N = 10	Pre 36.6 (6.7), N = 10 Post 25.0 (8.9), N = 10	Time: F(1,18) = 19.47	< 0.001
Li et al. (2023)[37] TRD	RCT	MADRS score at 3 days, mean (SD)	NA	24.46 (10.94), N = 24	33.21 (9.26), N = 24	NR	0.004

Citation, PTSD or TRD population	Study design	Outcome	Primary study or subgroup	Outcome result or sample size		Effect estimate (95% CI)	P value
				Ketamine	Midazolam		
		HDRS[d] score at 3 days, mean (SD)		14.50 (66.4), N = 24	18.63 (6.02), N = 24	NR	0.029
Su et al. (2023)[39] TRD	RCT	MADRS-based response to treatment at 3 days (≥ 50% decrease in score from baseline), n of N (%)	NA	15 of 42 (35.7)	5 of 42 (11.9)	NR	0.020
Depression: at trial end after repeated doses over 4 weeks							
Loo et al. (2023)[38] TRD	RCT	Remission (MADRS score ≤ 10), n (%)	Fixed dose[e]	3 (8.8)	2 (6.3)	OR 1.34 (0.22 to 8.21)	0.76
			Flexible dose[f]	1 (2.0)	10 (19.6)	OR 12.11 (2.12 to 69.17)	0.005
						NNT 6.01 (3.34 to 30.58)	NR
		MADRS-based treatment response (≥ 50% decrease in score from baseline), n (%)	Fixed dose	3 (8.8)	3 (9.4)	OR 2.20 (0.36 to 13.33)	0.39
			Flexible dose	2 (4.1)	15 (29.4)	OR 12.25 (2.71 to 55.44)	0.001
		CGI-S[g] score — change from baseline, mean (SD)	Fixed dose	0.44 (0.89)	0.28 (0.81)	Difference −0.16 (−0.60 to 0.28)	0.48
			Flexible dose	0.48 (0.35)	0.88 (1.29)	Difference 0.60 (0.19 to 1.02)	0.005
		CGI-I[g] score — change from baseline, mean (SD)	Fixed dose	3.47 (0.96)	3.31 (1.12)	Difference −0.12 (−0.60 to 0.36)	0.62
			Flexible dose	3.73 (0.76)	2.84 (1.17)	Difference −0.92 (−1.32 to 0.52)	< 0.0001

Citation, PTSD or TRD population	Study design	Outcome	Primary study or subgroup	Outcome result or sample size		Effect estimate (95% CI)	P value
				Ketamine	Midazolam		
Depression: at 3 days to 1 week							
Li et al. (2023)[37] TRD	RCT	MADRS score at 3 days, mean (SD)	NA	24.46 (10.94), N = 24	33.21 (9.26), N = 24	NR	0.004
		HDRS score at 3 days, mean (SD)		14.50 (66.4), N = 24	18.63 (6.02), N = 24	NR	0.029
Su et al. (2023)[39] TRD	RCT	MADRS-based treatment response at 3 days (≥ 50% decrease in score from baseline), n of N (%)	NA	15 of 42 (35.7)	5 of 42 (11.9)	NR	0.020
Depression: at follow-up							
Duek et al. (2023)[35] PTSD	RCT	BDI-II scores at 90 days, mean (SD)	NA	20.9 (12.2), N = 14	14.5 (11.1), N = 13	t(22) = 1.4	nss
Loo et al. (2023)[38] TRD	RCT	Remission (MADRS score ≤ 10) at 4 weeks, n (%)	Fixed dose	2 (6.9)	0	aOR 0.47 (0.04 to 5.49)	0.55
			Flexible dose	1 (2.1)	4 (8.0)	aOR 2.02 (0.04 to 10.28)	0.40
		MADRS-based treatment response (≥ 50% decrease in score from baseline) at 4 weeks, n (%)	Fixed dose	2 (6.9)	0	aOR 0.44 (0.04 to 5.58)	0.53
			Flexible dose	1 (2.1)	5 (10.0)	aOR 3.02 (0.60 to 15.15)	0.18
		CGI-S score — change from baseline at 4 weeks, mean (SD)	Fixed dose	0.29 (0.90)	−0.15 (0.53)	Difference −0.41 (−0.82 to −0.001)	0.049
			Flexible dose	0.32 (0.66)	0.50 (1.13)	Difference 0.21 (−0.16 to 0.58)	0.26

Citation, PTSD or TRD population	Study design	Outcome	Primary study or subgroup	Outcome result or sample size		Effect estimate (95% CI)	P value
				Ketamine	Midazolam		
		CGI-I score — change from baseline at 4 weeks, mean (SD)	Fixed dose	3.61 (1.07)	4.26 (0.81)	Difference 0.65 (0.15 to 1.16)	0.01
			Flexible dose	3.79 (0.86)	3.42 (1.26)	Difference −0.40 (−0.85 to 0.05)	0.084
Anxiety: 1 day after single dose							
Marchi et al. (2022)[33] TRD	SR (1 RCT)	STAI-S[h] score 1 day after treatment, mean (SD)	Price 2014	42.31 (16.31), N = 36	44.10 (16.33), N = 21	SMD −0.11 (−0.65 to 0.43)	NR
Harvey et al. (2023)[36] TRD	RCT	DASS-21 Anxiety scores at day 1, mean (SD)	NA	Pre: 7.4 (1.10), N = 10 Post: 6.2 (8.1), N = 10	Pre: 9.4 (11.0), N = 10 Post: 4.0 (5.8), N = 10	Time: F(1,18) = 6.69	0.019
PTSD symptoms: 1 to 90 days after single dose							
Du et al. (2022)[31] PTSD	SR (1 RCT)	PTSD[i] score at day 1 mean (SD)	Feder 2014	12 (7.9), N = 22	10.1 (9.7), N = 19	MD 2.50 (−2.97 to 7.97)	NR
		CAPS-5[j] score at 1 week, mean (SD)		54.0 (23.63), N = 19	65.69 (16.36), N = 15	MD −11.69 (−25.16 to 1.78)	NR
		IES-R[k] score at 1 week, mean (SD)		25.76 (19.4), N = 19	36.32 (13.73), N = 15	MD −10.56 (−21.71 to 0.59)	NR
Duek et al. (2023)[35] PTSD	RCT	PCL-5[l] scores at end of treatment, mean (SD)	NA	29.5 (20.7), N = 14	35.1 (16.8), N = 13	t(25) −0.76	nss
		PCL-5 scores at 90 days, mean (SD)		32.7 (14.95), N = 14	28.1 (18.1), N = 13	t(25) 0.66	nss
Neurocognitive outcomes: 1 day after single dose							
Harvey et al. (2023)[36] TRD	RCT	SST[m] scores, mean (SD)	NA	Pre: 50.1 (31.8) Post: 30.1 (26.9)	Pre: 36.8 (19.4) Post: 41.8 (20.9)	Time: NR	0.17

Citation, PTSD or TRD population	Study design	Outcome	Primary study or subgroup	Outcome result or sample size		Effect estimate (95% CI)	P value
				Ketamine	Midazolam		
						Group: NR	0.93
						Time × Group: F(1:19) = 5.73	0.027
						Cohen d 0.67	< 0.001
		ESTⁿ NEB response time (minutes), mean (SD)		Pre: 41.9 (131.9) Post: 41.3 (100.5)	Pre: −51.3 (202.8) Post: 39.7 (174.6)	Time: NR	0.46
						Group: NR	0.20
						Time × Group: NR	0.45
		ESTⁿ PEB response time (minutes), mean (SD)		Pre: −0.69 (78.0) Post: 10.6 (77.5)	Pre: −43.0 (165.8) Post: 33.6 (52.6)	Time: NR	0.74
						Group: NR	0.22
						Time × Group: NR	0.97
		AGNGº Negative (minutes), mean (SD)		Pre: 500.4 (79.9) Post: 507.7 (105.3)	Pre: 542.9 (65.4) Post: 536.1 (63.4)	Time: NR	0.99
						Group: NR	0.28
						Time × Group: NR	0.62
		AGNGº Positive (minutes), mean (SD)		Pre: 483.1 (67.5) Post: 495.0 (76.7)	Pre: 534.5 (56.6) Post: 545.6 (58.8)	Time: NR	0.23
						Group: NR	0.07
						Time × Group: NR	0.96
		Ruff 2 and 7ᵖ total speed T scores, mean (SD)		Pre: 49.6 (4.9) Post: 51.2 (5.5)	Pre: 44.00 (5.1) Post: 47.8 (6.4)	Time: F(1,17) = 8.367	0.01

Citation, PTSD or TRD population	Study design	Outcome	Primary study or subgroup	Outcome result or sample size		Effect estimate (95% CI)	P value
				Ketamine	Midazolam		
						Group: NR	0.08
						Time × Group: NR	0.28
		COWAT[q] total correct scores, mean (SD)		Pre: 35.5 (6.6) Post: 36.9 (9.0)	Pre: 43.5 (9.6) Post: 48.3 (11.5)	Time: F (1,18) = 4.675	0.044
						Group: F (1,18) = 6.136	0.023
						Time × Group: NR	0.25
Suicidal ideation							
Li et al. (2023)[37] TRD	RCT	MADRS item 10 score at 3 days, mean (SD)	NA	2.21 (1.47)	3.21 (1.38)	NR	0.01
		CSSRS- ISS[r] score at 3 days, mean (SD)		1.58 (1.50)	2.38 (1.25)	NR	0.05
Su et al. (2023)[39] TRD	RCT	Remission (total CCSRS-ISS scores = 0) at 240 minutes after treatment, n of N (%)	NA	14 of 42 (33.3)	3 of 42 (7.1)	NR	0.005
		Remission at day 2, n of N (%)		14 of 42 (33.3)	4 of 42 (9.5)	NR	0.015
		Remission at day 3, n of N (%)		14 of 42 (33.3)	3 of 42 (7.1)	NR	0.005
		Remission at day 5, n of N (%)		11 of 42 (26.2)	3 of 42 (7.1)	NR	0.038
		Remission at day 7, n of N (%)		8 of 42 (19.0)	5 of 42 (11.9)	NR	0.548
		Remission at day 14, n of N (%)		7 of 42 (16.7)	7 of 42 (16.7)	NR	> 0.999

Citation, PTSD or TRD population	Study design	Outcome	Primary study or subgroup	Outcome result or sample size		Effect estimate (95% CI)	P value
				Ketamine	Midazolam		
Adverse events							
Loo et al. (2023)[38] TRD	RCT	Death, n of N	Fixed dose	0 of 33	0 of 35	NR	NR
			Flexible dose	0 of 53	0 of 53	NR	NR
		Serious adverse events related to study drug	Fixed dose	0 of 33	0 of 35	NR	NR
			Flexible dose	2 of 53 (major dissociative episode, hallucination)	0 of 53	NR	NR
		Sedation within 1 hour after treatment, n/N (%)	Fixed dose	29 of 33 (87.9)	29 of 35 (82.9)	NR	0.74
			Flexible dose	45 of 53 (84.9)	50 of 53 (94.3)	NR	0.20
		Light-headedness within 1 hour after treatment, n of N (%)	Fixed dose	20 of 33 (60.6)	10 of 35 (28.6)	NR	0.01
			Flexible dose	42 of 53 (79.2)	14 of 53 (26.4)	NR	< 0.001
		Reduced concentration within 1 hour after treatment, n of N (%)	Fixed dose	18 of 33 (54.5)	9 of 35 (25.7)	NR	0.03
			Flexible dose	39 of 53 (73.6)	18 of 53 (34.0)	NR	< 0.001
		Dissociation within 1 hour after treatment, n of N (%)	Fixed dose	16 of 33 (48.5)	4 of 35 (11.4)	NR	0.001
			Flexible dose	41 of 53 (77.4)	13 of 53 (24.5)	NR	< 0.001
		Weakness/fatigue within 1 hour after treatment, n of N (%)	Fixed dose	17 of 33 (51.5)	8 of 35 (22.9)	NR	0.02

Citation, PTSD or TRD population	Study design	Outcome	Primary study or subgroup	Outcome result or sample size		Effect estimate (95% CI)	P value
				Ketamine	Midazolam		
			Flexible dose	27 of 53 (50.9)	9 of 53 (17.0)	NR	< 0.001
		Headache/pressure in head within 1 hour after treatment, n of N (%)	Fixed dose	8 of 33 (24.2)	7 of 35 (20)	NR	0.77
			Flexible dose	14 of 53 (26.4)	8 of 53 (15.1)	NR	0.23
		Anxiety within 1 hour after treatment, n of N (%)	Fixed dose	10 of 33 (30.3)	1 of 35 (2.9)	NR	0.003
			Flexible dose	16 of 53 (30.2)	7 of 53 (13.2)	NR	0.06
		Nausea within 1-hour post-treatment, n of N (%)	Fixed dose	6 of 33 (18.2)	2 of 35 (5.7)	NR	0.14
			Flexible dose	10 of 53 (18.9)	3 of 53 (5.7)	NR	0.07
Su et al. (2023)[39] TRD	RCT	Derealization during treatment, n of N (%)	NA	29 of 42 (69)	7 of 42 (16.7)	NR	< 0.001
		Dizziness during treatment, n of N (%)		24 of 42 (57.1)	5 of 42 (11.9)	NR	< 0.001
		Nausea during treatment, n of N (%)		2 of 42 (4.8)	4 of 42 (9.5)	NR	0.676
		Crying during treatment, n of N (%)		6 of 42 (14.3)	0 of 42	NR	0.026
		Somnolence during treatment, n of N (%)		1 of 42 (2.4)	0 of 42	NR	> 0.999

AGNG Neg = Affective Go/No Go Task Negative Shift; AGNG Pos = Affective Go/No Go Positive Shift; aOR = adjusted odds ratio; BDI-II = Beck Depression Inventory, version 2; CAPS = Clinician-Administered PTSD Scale; CCSRS-ISS = Columbia-Suicide Severity Rating Scale — Ideation Severity Subscale; CGI = Clinical Global Impression; CGI-I = CGI — improvement; CGI-S = CGI — severity; CI = confidence interval; COWAT = Controlled Word Association Test; DASS-21 = Depression Anxiety Stress Scale; EST Emotional Stroop Task; Impact of Event Scale-Revised; MADRS = Montgomery-Asberg Depression Rating Scale; NA = not applicable; NEB = Negative Expressions Bias; NR = not reported; nss = not statistically significant; PCL = PTSD Checklist; OR = odds ratio; PEB = Positive Expressions Bias; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; Ruff 2 and 7 = Ruff 2 and 7 Selective Attention Test; SC = subcutaneous; SD = standard deviation; SST = Scrambled Sentence test; STAI-S = State-Trait Anxiety Inventory — State; TRD = treatment-resistant depression.

[a]MADRS has 10 items and is used by clinicians to assess the severity of depression in patients with a diagnosis of depression. Higher scores indicate more severe depression.[49]

[b]BDI-II assesses depression severity and consists of 21 Likert-type items. Higher scores indicate more severe depression.[54]

[c]DASS-21 is a self-rating scale which assesses depressive, anxiety, and stress symptoms. Higher scores indicate elevated depression, anxiety, or stress.[55]

[d]HDRS is used to measure the severity of symptoms of depression based on 17-item scales. The sum of all items makes up the total score: 0 to 7 = no depression; 8 to 13 = mild depression; 14 to 18 = moderate depression; 19 to 22 = severe depression; and ≥ 23 = very severe depression.[50]

[e]Fixed dose = 0.025 mg/kg.

[f]Flexible dose = started at 0.025 mg/kg and escalated to 0.03 mg/kg, 0.0375 mg/kg, and 0.045 mg/kg based on MADRS score.

[g]CGI is a standardized assessment scale for determining the effect of mental health treatment among patients with psychiatric conditions. It has 2 separate global subscales: Severity Illness (CGI-S) and Global Improvement (CGI-I). The CGI-S rates the severity on a 1 to 7 scale, with 1 representing normal symptoms (patient is not ill), 4 representing moderately ill, and 7 representing most severely ill. The CGI-I is taken after treatment and compared with baseline. It rates the improvement on a 1 to 7 scale, with 1 representing very much improved, 4 for no change from treatment, 7 for very much worse due to treatment.[56]

[h]STAI is the definitive instrument for measuring anxiety in adults. The STAI clearly differentiates between the temporary condition of "state anxiety" and the more general and long-standing quality of "trait anxiety." The qualities evaluated by the STAI-S Anxiety scale are feelings of apprehension, tension, nervousness, and worry. Higher scores indicate greater anxiety.[57]

[i]PTSD scale was NR.

[j]CAPS was adapted as the Diagnostic and Statistical Manual of Mental Disorders (DSM) moved from DSM-IV (CAPS-IV) to DSM-5 (CAPS-5). CAPS-5, a 30-item structured interview, is the gold standard in PTSD assessment. Higher scores indicate more frequent and intense PTSD symptoms.[58]

[k]IES-R is a self-report measure of current subjective distress in response to a specific traumatic event). The 22-item scale comprises 3 subscales: intrusion, avoidance, and hyperarousal. Higher scores indicate a greater degree of distress.[59]

[l]PCL-5 is a 20-item self-report Likert-type measure that assesses the 20 DSM-5 symptoms of PTSD. Each item was rated on a 5-point Likert (0 = "not at all" to 4 = "extremely"). A total symptom severity score (0 to 80 range) can be obtained by summing the scores for each of the 20 items. A 5-to-10-point change represents reliable change (i.e., change not due to chance) and a 10-to-20-point change represents clinically significant change.[60]

[m]SST assesses hostility (negative cognitive bias, referring to tendency to react more strongly to negative stimuli). Participants unscramble as many sentences as possible from 20 trials of scrambled words into grammatically correct sentences within 4 minutes. The total score is the number of hostile (negative) sentences assembled.[36,61]

[n]EST assesses response inhibition in the context of affective stimuli. 25 words were presented in random order and colour in each of 5 categories (positive, negative, aggressive, neutral, and colour). The primary outcomes were mean response time (minutes) for positive and negative words subtracted from the mean response time for neutral words.[36]

[o]AGNG assesses affective bias. The tasks consisted of 10 blocks (of 18 words each) with rapidly presented positive (intrinsically attractive) and negative (intrinsically aversive) valence words. The outcomes were the response latencies (minutes) in blocks where the target valence had shifted from negative to positive or positive to negative.[36]

[p]Ruff 2 and 7 assesses concentration and selective attention. Participants were required to cross out 2s and 7s as quickly as possible without making mistakes. The task has 20 blocks, each containing 3 lines. Each line had 10 targets and 40 distractors. The outcome was total speed t score, which reflects the total accurate identifications, adjusted based on age and education.[36]

[q]COWAT is a verbal fluency test that measures spontaneous production of words with the given letter (C, F, or L). Individuals are also instructed to exclude proper nouns, numbers, and the same word with a different suffix.[62]

[r]CCSRS-ISS assesses suicide symptoms using 5 yes or no questions, including question 1: wish to be dead; question 2: nonspecific suicidal thoughts; and questions 3 to 5: more specific suicidal thoughts and intent to act. Higher scores indicate more severe symptoms.[39,63]

Table 12: Summary of Findings by Comparison — ECT Versus IV Ketamine

Citation, PTSD or TRD population	Study design	Outcome	Primary study	Outcome result		Effect size (95% CI)
				ECT	IV ketamine	
Depression						
Shafiee et al. (2023)[32] TRD	SR (1 RCT)	QIDS-SR-16[a]-based response (≥ 50% decrease in score from baseline) after treatment (unknown duration), n of N	Anand 2023	70 of 170	108 of 195	RR 0.74 (0.60 to 0.93)
		Change in MADRS[b] score after treatment (unknown duration)		NR	NR	SMD 0.23 (0.03 to 0.44)

Citation, PTSD or TRD population	Study design	Outcome	Primary study	Outcome result		Effect size (95% CI)
				ECT	IV ketamine	
		Acute effect in depression score after treatment (unknown duration)		NR	NR	SMD 0.29 (0.09 to 0.50)
		Depression score at 30 days		NR	NR	SMD 0.22 (−0.14 to 0.57)
		Relapse rate at 30 days, n of N		21 of 48	30 of 85	RR 1.24 (0.81 to 1.91)

CI = confidence interval; ECT = electroconvulsive therapy; MADRS = Montgomery-Asberg Depression Rating Scale; NR = not reported; PTSD = posttraumatic stress disorder; QIDS-SR-16 = Quick Inventory of Depressive Symptomatology-Self-Report; RCT = randomized controlled trial; RR = risk ratio; SMD = standardized mean difference; TRD = treatment-resistant depression.

[a]QIDS-SR-16 is a 16-item self-report rating scale of depressive symptom severity within the past 7 days. The measure assesses all of the clinical domains used in making a diagnosis of major depressive disorder.[64]

[b]MADRS has 10 items and is used by clinicians to assess the severity of depression in patients with a diagnosis of depression. Higher scores indicate more severe depression.[49]

Table 13: Summary of Findings by Comparison — Ketamine Versus Opioids

Citation	PTSD or TRD population	Study design	Outcome	Primary study	Sample size		MD (95% CI)
					Ketamine	Opioids	
PTDS symptoms							
Du et al. (2022)[31]	PTSD	SR (1 cohort study)	ASDS[a] scores at < 3 days	Schönenberg 2008	N = 13	N = 24	2.68 (1.53 to 3.83)

ASDS = Acute Stress Disorder Scale; CI = confidence interval; MD = mean difference; PTSD = posttraumatic stress disorder; SR = systematic review; TRD = treatment-resistant depression.

[a]ASDS is a self-report 19-item inventory that assesses acute stress disorder and predicts PTSD on the following subscales: avoidance, dissociation, hyperarousal, and reexperiencing. Higher scores indicate greater acute stress.[65]

Table 14: Summary of Findings of Included Economic Evaluation

Main study findings	Authors' conclusion
Brendle et al. (2022)[41]	

Cost-utility analysis of esketamine nasal spray relative to IV ketamine in patients with TRD over a 3-year time horizon.
Base-case results
With clinical trial efficacy data:
• QALYs of esketamine vs. IV ketamine: 1.98 vs. 2.03
• Under the health care perspective
  ○ Total costs (USD) of esketamine vs. IV ketamine: 195,478 vs. 19,157
  ○ ICER (USD per QALY): NR, esketamine was dominated by IV ketamine
• Under the patient perspective
  ○ Total costs (USD) of esketamine vs. IV ketamine: 23,143 vs. 65,675
  ○ ICER (USD per QALY) of IV ketamine vs. esketamine: 867,606
With RWE data
• QALYs of esketamine vs. IV ketamine: 1.98 vs. 1.99
• Under the health care perspective
  ○ Total costs (USD) of esketamine vs. IV ketamine: 193,465 vs. 20,547
  ○ ICER (USD per QALY): NR, esketamine was dominated by IV ketamine
• Under the patient perspective
  ○ Total costs (USD) of esketamine vs. IV ketamine: 22,891 vs. 70,497
  ○ ICER (USD per QALY) of IV ketamine vs. esketamine: 7,037,560
One-way sensitivity analysis results
With clinical trial efficacy data:
• Under the health care perspective, the ICER did not become positive with variation in any single individual parameter.
• Under the patient perspective, the lowest ICER attained was $464,389 per QALY when applying the lower limit of esketamine co-payment.
With RWE data:
• Under the health care perspective, the ICER did not become positive with variation in any single individual parameter.
• Under the patient perspective, the lowest ICER attained with any parameter variation was $712,747 per QALY when applying the upper limit of the probability of response to ketamine.
Probabilistic sensitivity analysis results, at a threshold of $150,000 per QALY
Under the health care perspective:
• Over a 3-year time horizon, there were no scenarios where esketamine was cost- effective compared to ketamine.
• When varying the time horizon from 1 to 5 years, esketamine was dominated by ketamine.
Under the patient perspective:
• Over a 3-year time horizon, probability that esketamine is superior compared to ketamine was 0.0055 with clinical trial efficacy estimates and 0.35 with RWE estimates.
• When varying the time horizon from 1 to 5 years, the base-case ICERs
	"Esketamine is unlikely to be cost-effective compared to ketamine under a healthcare sector perspective. Under a patient perspective, esketamine has similar effectiveness and becomes substantially less costly compared to ketamine due to insurance coverage and manufacturer assistance programs that make esketamine treatment accessible to patients with TRD." (p. 395)[41]

Main study findings	Authors' conclusion
projected with a 1-year or 5-year time horizon did not fall below $150,000 per QALY.	

ICER = incremental cost-effectiveness ratio; NR = not reported; QALY = quality-adjusted life-year; RWE = real-world effectiveness; TRD = treatment-resistant depression; USD = US dollars; vs = versus.

Table 15: Summary of Recommendations in Included Guidelines

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
VA/DoD (2023)[42]	
"We suggest against divalproex, guanfacine, ketamine, prazosin, risperidone, tiagabine, or vortioxetine for the treatment of PTSD." (p. 62) Supporting evidence: 4 SRs and 1 RCT.	Quality of evidence: Very low Strength of recommendation: Weak against
VA/DoD (2022)[43]	
"For patients with MDD who have not responded to several adequate pharmacologic trials, we suggest ketamine or esketamine as an option for augmentation." (p. 50) Supporting evidence: 2 SRs and meta-analyses of the effect of ketamine vs. placebo or midazolam on depressive symptoms.	Quality of evidence: Low Strength of recommendation: Weak for

MDD = major depressive disorder; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SR = systematic review; VA/DoD = US Department of Veterans Affairs and Department of Defense.

Appendix 5: Overlap Between Included Systematic Reviews

Note that this appendix has not been copy-edited.

Table 16: Overlap in Relevant Primary Studies Between Included Systematic Reviews

Primary study citation	Nikolin et al. (2023)[30]	Shafiee et al. (2023)[32]	Du et al. (2022)[31]	Marchi et al. (2022)[33]
Anand A, et al. N Engl J Med. 2023; 38(25): 2315 to 25.	—	Yes	—	—
Nugent AC, et al. Mol Psychiatry. 2019; 24(7): 1040 to 52.	Yes	—	—	—
Cao Z, et al. IEE Trans Biomed Engl. 2018; 66(6): 1668 to 79.	Yes	—	—	—
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Appendix 6: Patient Involvement

Note that this appendix has not been copy-edited.

Table 17: Summary of Patient Involvement Using the Guidance for Reporting Involvement of Patients and the Public (Version 2) Short Form Reporting Checklist[29]

Section and topic	Item	Report section
Aim	A patient with TRD was invited to share their thoughts, perspectives, and priorities about ketamine-assisted therapy, contextualizing the information found in the literature.	Key Messages
Methods	A recruitment email was disseminated to patient advocacy groups, on social media, and through CADTH networks. An interested individual with relevant experience was identified to participate. The patient signed an informed consent form and was invited to participate in an interview with a Patient Engagement Officer and the Clinical Research Officer authoring the report. The 1-hour call occurred virtually, over Zoom, to facilitate engagement from individuals located across Canada. The patient contributor shared their experiences, perspectives, and priorities about ketamine-assisted psychotherapy. A short summary of the key points was drafted, approved by the patient, and shared with the Clinical Research Officer. A choice of honorarium or gift card was offered to the patient as a gesture of thanks for their time and expertise, and they elected to remain anonymous in the report's acknowledgements section.	Methods
Results of engagement	The patient contributor lives with TRD and has tried numerous different antidepressants since adolescence. After an increase in symptoms, they elected for a short-term course of ketamine-assisted psychotherapy in an attempt to minimize their symptoms. They had a course of 6 sessions of ketamine-assisted psychotherapy and 1 psychotherapy session afterward, without ketamine. The patient contributor highlighted several key benefits to ketamine-assisted therapy for TRD. They reported that their daily panic attacks had ceased completely and noted that their regular migraines became less frequent. Their anxiety has decreased, they have noticed an improvement in sleep quality, and they feel calmer. They are hopeful that these effects will last but mentioned that some individuals return for maintenance visits if necessary. The patient contributor also detailed the challenges and barriers they experienced. They described the stigma they encountered, including that their clinicians did not all support the patient contributor's interest in pursuing the therapy. The patient contributor identified a local private clinic and did not require a referral, so they found the access to be unaffected by their physician's reluctance. However, the financial burden of the	Conclusions and Implications for Decision- or Policy-Making

Section and topic	Item	Report section
	course of treatment was prohibitive, which would bar access to individuals without benefits or with lower incomes.	
Discussion and conclusions	The patient contributor noted several benefits to ketamine-assisted therapy and no adverse events or harms. They spoke highly of the treatment and hope that the effects will last. They appreciated that there was a local private clinic in their city, but noted that others living in more remote areas may have difficulties finding a location. The clinic was accessed via self-referral, so that enabled the patient to access services despite their physician's reluctance to refer them. There are also significant financial implications, creating further inequities in access. Many individuals would not want to invest thousands of dollars without guarantees of treatment success.	
Reflections and critical perspective	The patient contributor was highly engaged in their participation with CADTH. They were supported in their engagement by a Patient Engagement Officer, and the interview was attended by a Clinical Research Officer. The introductory and engagement calls were scheduled at the patient's convenience, and the patient was sent the questions in advance so that they could prepare. The patient was offered the opportunity to be thanked by name in the acknowledgements section of the report but preferred to remain anonymous. A choice of honorarium or gift card was offered as a gesture of thanks for their time and expertise. One limitation was our methodology. While our virtual approach enabled participation from individuals across Canada, the need for patients to have reliable technology and internet access to participate in a Zoom or telephone call potentially excluded some voices.	Conclusions and Implications for Decision- or Policy-Making

TRD = treatment-resistant depression.

Appendix 7: References of Potential Interest

Note that this appendix has not been copy-edited.

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Authors: Angela M. Barbara, Weiyi Xie, Quenby Mahood, Angie Hamson

Contributor: Joanne Kim

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Questions or requests for information about this report can be directed to Requests@CADTH.ca