CADTH

CADTH Health Technology Review

Ketamine for Adults With Treatment-Resistant Depression or Post-Traumatic Stress Disorder

Rapid Review

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Abbreviations

AE	adverse event
ALS-18	Affective Lability Scale short form
AGREE II	Appraisal of Guidelines for Research and Evaluation II
BDI-II	Beck Depression Inventory – II
CADSS	Clinician-Administered Dissociative State Scale
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CGI	Clinical Global Impression scale
COWAT	Controlled Oral Word Association Test
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECT	Electroconvulsive Therapy
GRADE	Grades of Recommendation Assessment, Development and Evaluation
HAM-A	Hamilton Anxiety Rating Scale
HAMD or HDRS	Hamilton Depression Rating Scale
IM	intramuscular
ITT	intention to treat
MADRS	Montgomery-Asberg Depression Rating Scale
MoCA	Montreal Cognitive Assessment
PANSS	Positive and Negative Syndrome Scale
PCL-5	PTSD Checklist for DSM-5
PHG-9	Patient Health Questionnaire-9
PTSD	post-traumatic disorder
TRD	treatment-resistant depression
RCT	randomized controlled trial
rTMS	Repetitive Transcranial Magnetic Stimulation
YMRS	Young Mania Rating Scale

Key Messages

- Two randomized controlled trials reported mixed evidence on the efficacy of repeated IV ketamine infusions for improving post-traumatic stress disorder. One randomized controlled trial with small sample size found that repeated IV ketamine infusions significantly improved post-traumatic stress disorder symptoms compared with midazolam in civilian population, while the other randomized controlled trial with larger sample size could not demonstrate a significant efficacy on post-traumatic stress disorder symptoms compared with placebo in military population. The antidepressant effects of ketamine were rapid, but the effects were not sustained after few weeks of post-treatment follow-up.

- One randomized controlled trial comparing IV ketamine with IV esketamine found both treatments had comparable acute antidepressant effects for treatment-resistant depression 24 hours following infusion.

- Two randomized controlled trials provided mixed evidence on the efficacy of single infusion of IV ketamine that was used as anesthetic agent for electroconvulsive therapy for treatment-resistant depression. One randomized controlled trial involving military population showed that patients undergoing electroconvulsive therapy for treatment-resistant depression with ketamine anesthesia had similar improvement of depression when compared with patients undergoing electroconvulsive therapy with methohexital anesthesia. However, in other randomized controlled trial comparing with propofol-based anesthesia in a civilian population, ketamine-based anesthesia provided faster improvement in depressive symptoms and fewer electroconvulsive therapy treatments to achieve disease remission.

- In a small randomized controlled trial, alternate infusions of subanesthetic dose of ketamine or midazolam with alternate electroconvulsive therapy showed no significant difference in antidepressant effects between groups.

- The efficacy of oral ketamine was demonstrated in 1 randomized controlled trial that repeated administration of oral ketamine significantly reduced depressive symptoms compared with placebo.

- A small retrospective chart review study showed that repeated administration of intramuscular ketamine had no significant differences in the improvement of depressive and anxiety symptoms compared with repeated transcranial magnetic stimulation.

- Findings suggest overall safety and tolerability of ketamine for treatment of post-traumatic stress disorder or treatment-resistant depression. Most frequent side effects associated with ketamine were dissociative symptoms and cardiovascular changes such as increased blood pressure and heart rate, but these effects were transient.

- The Danish guideline recommend against the use of IV ketamine in patients with treatment-resistant depression, due to low quality and insufficient evidence regarding the lack of long-term efficacy and the risk of abuse of ketamine. Likewise, the Canadian guideline recommends IV ketamine be considered as third-line treatment for adults with TRD, because of the short-lived efficacy of ketamine, its side effects, and the lack of strategies for relapse prevention after ketamine infusions.

Context and Policy Issues

Depression is a debilitating mental illness that affects approximately 5.4% of the Canadian population.[1] Although there are many effective first-line pharmacotherapy treatments for depression, about 21.7% of Canadians remain non-responsive to at least 2 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 drug (including alcohol) abuse, suicide, and hospitalizations.[4] A wide variety of antidepressant drug medications and 2 somatic treatments through brain stimulation, namely electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS), are available for TRD.[4]

Ketamine, an noncompetitive *N*-methyl-D-aspartate receptor antagonist, has been approved and primarily used as an IV anesthetic induction drug in doses ranging between 1.0 and 4.5 mg/kg.[5] As it also interacts with other receptors, ketamine has been explored for other indications such as depressive disorders, suicidal ideation, substance use disorders, anxiety disorders, refractory status epilepticus, bronchial asthma exacerbations, and pain management.[6] Over the past decades, numerous clinical and preclinical studies have demonstrated the rapid antidepressant effects of ketamine in subanesthetic dosages (e.g., 0.5 m/kg) in patients with major depressive disorders and TRD.[7,8] Ketamine is a racemic mixture of 2 enantiomers, S(+)-ketamine (esketamine) and R(-)-ketamine (arketamine).[9] Recently intranasal esketamine has received FDA approval for TRD in the US.[10] There are limited research on the use of other formulations of ketamine for TRD including the oral, subcutaneous, and intramuscular forms.[11]

Post-traumatic stress disorder (PTSD) is a disabling mental condition that affects about 9.2% of Canadians in their lifetime.[12] In Canadian war zone veterans, its prevalence has been estimated up to 10%.[13] Although anyone can get PTSD, the risk factors for PTSD include being female, having experienced a prior trauma, having been abused as a child, having pre-existing mental health problems, and having a family of mental illness.[12] People with PTSD commonly have associated problems including depression, panic attacks, alcohol and substance abuse, problems in relationship, and increased risk of other medical problems.[12] There are few drugs with insufficient efficacy available for treatment of PTSD.[14] A previous proof-of-concept RCT[15] provided the first evidence of rapid reduction in PTSD and depressive symptoms 24 hours after a single dose of IV ketamine infusion compared to midazolam in primarily civilian population. However, a recent RCT[16] involving patients with chronic pain with or without PTSD found no significant effects of a single infusion of ketamine in improving PTSD or pain symptoms compared with ketorolac.

This report aims to summarize the clinical effectiveness and cost-effectiveness of ketamine compared with all relevant comparators including placebo or no treatment for adults with TRD or PTSD. Additionally, this report also aims to summarize the recommendations from evidence-based guidelines regarding the use and administration of ketamine for those populations.

Research Questions

- What is the clinical effectiveness of ketamine versus placebo or no treatment for adults with TRD or PTSD?
- What is the clinical effectiveness of ketamine versus alternative interventions for adults with TRD or PTSD?
- What is the clinical effectiveness of ketamine administered via different routes for adults with TRD or PTSD?
- What is the cost-effectiveness of ketamine versus placebo or no treatment for adults with TRD or PTSD?
- What is the cost-effectiveness of ketamine versus alternative interventions for adults with TRD or PTSD?
- What is the cost-effectiveness of ketamine administered via different routes for adults with TRD or PTSD?
- What are the evidence-based guidelines regarding the use and administration of ketamine for adults with TRD or PTSD?

Methods

Literature Search Methods

This report makes use of a literature search strategy developed for a previous CADTH report.[17] 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, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised 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, controlled clinical trials, or any other type of clinical trial, health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, and economic studies. The search was limited to documents published in English between January 1, 2017, and March 7, 2022.

Selection Criteria and Methods

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

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published before 2017. Studies retrieved by the search were excluded if they were included in the previous CADTH reports.[17,18]

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: The Downs and Black checklist[19] for randomized and non-randomized studies, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[20] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 1,004 citations were identified in the literature search. Following screening of titles and abstracts, 959 citations were excluded and 45 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 37 publications were excluded for various reasons, and 10 publications met the inclusion criteria and were included in this report. These comprised 7 RCTs, 1 non-randomized study, and 2 evidence-based guidelines. Appendix 1 presents the PRISMA[21] flow chart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included primary clinical studies[22-29] (Table 2) and guidelines[30,31] (Table 3) are provided in Appendix 2.

Table 1: Selection Criteria

Criteria	Description
Population	Adults with TRD or PTSD
Intervention	Ketamine administered via any route (e.g., IV, intramuscular, subcutaneous, intranasal, oral, sublingual)
Comparator	Q1 to Q4: Placebo, no treatment
	Q2 to Q5: Pharmacotherapy (e.g., antidepressants [e.g., SSRIs, SNRIs], antipsychotic drugs), psychotherapy (e.g., cognitive behavioural therapy), electroconvulsive therapy
	Q3 to 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, and 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, and recommended patient monitoring strategies)
Study designs	Health technology assessments, systematic reviews, randomized-controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines

PTSD = post-traumatic stress disorder; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TRD = treatment-resistant depression.

Study Design

The 8 included primary clinical studies comprises 7 RCTs and 1 retrospective chart review study. The RCTs[22-28] were published between 2018 and 2022, while the retrospective chart review study[29] were published in 2021. All of the RCTs were parallel and double-blinded. Six RCTs[22-24,26-28] reported that sample size calculation for primary outcomes was performed; however, 2 RCTs[23,27] reported results from interim analysis based on smaller sample sizes than originally planned. The retrospective chart review study[29] did not perform sample size calculation. Four RCTs[23,24,26,27] analyzed the data using the intention-to-treat (ITT) approach, while 3 RCTs[22,25,28] analyzed the data as per protocol.

Both included guidelines were evidence-based, providing recommendations on 6 interventions including ketamine in 1 guideline,[30] and on the use of ketamine for treatment of TRD in the other.[31] A systematic search of the literature was conducted, and the quality of evidence and the strength of recommendations were assessed and graded using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) in 1 guideline,[30] while the Cochrane risk of bias tool was used to assess the study quality in the other.[31]

Country of Origin

The primary clinical studies were conducted by authors from US,[22,23,25,28] Brazil,[24] Israel,[26] Canada,[27] and the Netherlands.[29]

The guidelines were conducted by authors from Denmark[30] and Canada.[31]

Patient Population

One study[22] involved veterans and service members with PTSD who failed previous antidepressant treatment, 1 study[23] involved patients with chronic PTSD, who were stable with psychotropic medications for at least 3 months before randomization, and 4 studies involved patient with TRD, referring to patients who failed to respond to at least 1 antidepressant,[24] or 2 antidepressants.[25,26,28] Two studies did not provide definition for TRD.[27,29] Mean age of patients among included studies ranged between 39[25] and 49[28] years. The percent of male ranged between 17%[25] to 82%.[26] The sample sizes of the studies ranged between 12[25] to 158.[22]

In both guidelines[30,31] the target population was patients with TRD, while the intended users were health care professionals who treat patients with TRD.

Interventions and Comparators

The interventions used in the included studies were IV ketamine, oral ketamine, or intramuscular (IM) ketamine. The comparators were placebo (i.e., saline), midazolam, IV esketamine, IV propofol, IV methohexital, and rTMS. Overall, 2 studies[22,26] compared ketamine with placebo and 6 studies[23-25,27-29] compared ketamine with other treatment modalities. One study[22] compared IV ketamine with placebo, 1 study[26] compared oral ketamine with placebo, 1 study[24] compared IV ketamine with IV esketamine, 2 studies[23,25] compared IV ketamine with midazolam, 2 studies compared anesthesia-based IV ketamine with IV propofol[27] or IV methohexital[28] for ECT, and 1 study[29] compared IM ketamine with rTMS.

The Danish guideline[30] formulated its recommendations concerning 6 selected interventions comprising unilateral high frequency rTMS, IV ketamine or esketamine, bright light therapy, cognitive behavioural analysis system of psychotherapy, psychotherapy targeting rumination, and cognitive remediation for treatment of TRD. The Canadian guideline[31] provides recommendations for the use of ketamine in adults with TRD.

Outcomes

Seven RCTs[22-28] reported both efficacy and safety outcomes, while the retrospective chart review study[29] reported only efficacy outcomes. The efficacy outcomes comprised PTSD symptoms, depression, and anxiety. PTSD symptoms were measured using the PTSD Checklist for DSM-5 (PCL-5) or the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). Depression was measured using the Montgomery-Asberg Depression Rating Scale (MADRS), the Hamilton Depression Rating Scale (HDRS or HAMD), the Beck Depression Inventory – II (BDI-II), the Patient Health Questionnaire-9 (PHQ-9), or the Clinical Global Impression scale (CGI). Anxiety was measured using the Hamilton Anxiety Rating Scale (HAM-A).

The safety outcomes assessed in the included studies included dissociation, presence and severity of positive and negative symptoms, anxiety, cognitive changes, verbal fluency, and sudden mood changes over the past week. Changes in those outcomes were measured, respectively, using the Clinician-Administered Dissociative State Scale (CADSS), the Positive and Negative Syndrome Scale (PANSS), the Young Mania Rating Scale (YMRS), the Montreal Cognitive Assessment (MoCA), the Controlled Oral Word Association Test (COWAT), and the short form of the Affective Lability Scale (ALS-18). Other adverse events (AEs) related to ketamine treatment were also reported.

Brief descriptions of the scorings of the tools used to measure the efficacy and safety outcomes are presented as footnotes of Table 2 in Appendix 2.

Three studies[23,26,29] assessed the outcomes at the end of treatment, while 5 studies measured the outcomes after last treatment at 4 weeks,[22] 7 days,[24] 3 weeks,[25] 3 days[28] and 30 days.[27]

Both guidelines[30,31] considered all efficacy, tolerability, and safety outcomes that were clinically relevant for making recommendations.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included primary clinical studies (Table 4) and guidelines (Table 5) are provided in Appendix 3.

With respect to reporting, all primary studies including 7 RCTs[22-28] and 1 retrospective chart review study[29] clearly described the objective of the study, the interventions of interest, the main outcomes, and the main findings of the study. The baseline characteristics of the patients included in the study were clearly described in all studies, except in 1 study.[25] Without a clear description of patient baseline characteristics, it was not possible to assess if there were potential confounders that could potentially affect the interpretation of the results. One RCT[24] had no patients lost to follow-up. Two RCTs[23,26] reported the reasons why patients were lost to follow-up, and 4 RCTs[22,25,27,28] did not. None of the studies that lost patients to follow-up described the characteristics of those patients. In 1 RCT,[22] missing data were treated as treatment failure (i.e., nonresponder). Three RCTs[23,26,27] used the ITT approach in the data analyses to account for patients lost to follow-up. Not accounting for patients lost to follow-up in the analyses may increase potential risk of attrition bias. Actual P values (i.e., P values) and the random variability in the data for the main outcomes (e.g., confidence interval, standard deviation, or interquartile range) were reported in all included studies.[22-29] In a non-inferiority study,[24] the pre-specified margin was set at 20%, meaning a difference in remission rates between groups that was less than 20% would be considered non-inferiority. As the difference in remission rates between groups was only 5.3%, the margin was totally valid. Regarding external validity, all studies, except 1,[22] had relatively small sample size

(i.e., 15 to 52 patients in total), whose participants may not be representative of the entire population from which they were recruited.[23-29] For internal validity, all RCTs were double-blinded to the investigators and patients; thus, the risk of biases for selection, performance, and detection were low. Two RCTs[22,24] reported the methods of randomization and allocation concealment, while 4 RCTs[23,25-27] did not report either, and 1 RCT[28] only reported the method of randomization. Not performing allocation concealment may result in risk of selection bias. The retrospective chart review study[29] may be prone to high risk of bias for selection, performance, and detection due to the nature of the observational study design. Additionally, confounding variables that may have significant impact to the findings were not identified and adjusted for in the analyses in this study.[29]

Appropriate statistical tests were used to assess the main outcomes, and reliable and validated outcome measures were used in all studies.[22-29] Patients in different intervention groups appeared to be recruited from the same population and over the same period of time in all studies.[22-29] Six studies[22-24,26-28] reported sample size calculation, while 2 studies[25,29] did not. Of those reported sample size calculation, 2 RCTs[23,27] reported results from the interim analysis based on a much smaller sample sizes than that pre-determined by the calculation. It was unclear if using data from a smaller sample size than originally planned may have reduced the studies' power to detect significant differences in certain outcomes. Patient compliance was not assessed in all studies.[22-29] Overall, 5 included studies[22-24,26,28] were of moderate methodological quality, and 3 studies[25,27,29] were of low methodological quality.

Both guidelines[30,31] were explicit in terms of scope and purpose (i.e., objectives, health questions, and populations), and had clear presentation (i.e., specific, and unambiguous recommendations, different options for management of the condition or health issue, and easy to find key recommendations). In terms of stakeholder involvement, both guidelines[30,31] clearly defined target users and the development groups. However, it was unclear if the views and preferences of the patients were sought in the Canadian guideline.[31] For rigour of development, both guidelines[30,31] reported systematic methods used to search for evidence, criteria for selecting evidence, explicit link between recommendations and the supporting evidence, and methods of formulating the recommendations. Both guidelines[30,31] considered health benefits, side effects, and risks in formulating the recommendations, and were externally peer-reviewed before publication. One guideline[30] used GRADE methodology to assess and grade its recommendations, while the other[31] used the Cochrane risk of bias tool to assess the study quality, based on which the line-of-treatment recommendations were determined by expert consensus after assessing the efficacy, tolerability, safety, and feasibility of the intervention. For clarity, the recommendations in both guidelines[30,31] are specific and unambiguous, provide different options for management of the condition, and are easily identifiable. For applicability, both guidelines[30,31] were not explicit in terms of facilitators and barriers to application, advice and/or tools on how the recommendations can be put into practice, resource implications (e.g., considering costs in recommendations), and monitoring or auditing criteria. For editorial independence, both guidelines[30,31] reported competing interests of guideline development group members, and that the views of the funding body did not have influence on the content of the guidelines. Overall, both included guidelines[30,31] were of good methodological quality.

Summary of Findings

Appendix 4 presents the main study findings of the primary clinical studies[22-29] (Table 6 to Table 9) and the summary of guideline recommendations[30,31] (Table 10). The findings are

presented by outcome, which are PTSD (Table 6), depression (Table 7), anxiety (Table 8), and safety (Table 9).

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

Two RCTs compared IV ketamine[22] or oral ketamine[26] with placebo (i.e., saline) were identified.

PTSD

The RCT by Abdallah et al. (2022)[22] tested whether IV ketamine at standard dose (0.5 mg/kg) and low dose (0.2 mg/kg) could reduce PTSD symptoms compared with placebo in veterans. Eight 40-minute IV infusions of ketamine or saline were administered twice weekly for 4 weeks, followed by 4 weeks follow-up. Analyses on the PCL-5 scores revealed that the scores improved over time in all treatment groups, and there was no significant difference in PCL-5 scores between standard dose and placebo after first infusion (i.e., 24 hour), at end of treatment (i.e., 4 weeks), and at 4 weeks of follow-up. Similarly, the PCL-5 scores between low dose and placebo were not significantly different after first infusion and at the end of treatment. There were no significant differences in PCL-5 scores between standard and low dose of ketamine. Similar results were obtained for the effect of ketamine on CAPS-5 scores. There were no significant differences in response rates among the 3 groups. Response was defined as a 25% or more improvement in PCL-5 scores from baseline.

Depression

The RCT by Abdallah et al. (2022)[22] found that standard dose, but not the low dose, of ketamine significantly lowered MADRS scores compared with placebo at 24 hours post-infusion (P = 0.05), and at end of treatment (P = 0.01) However, the difference in MADRS scores between standard dose and placebo were not significant at 4 weeks of follow-up. There were no significant differences in MADRS scores between standard and low dose of ketamine.

The RCT by Domany et al. (2019)[26] compared oral ketamine (1 mg/kg thrice weekly for 21 days) with placebo in patients with TRD and found that ketamine significantly reduced MADRS scores at end of treatment (P < 0.001). The response was defined as achieving a 50% or more reduction of MADRS scores from baseline. At 21 days, the response rate was significantly higher in the ketamine group (31.8%) than the placebo group (5.6%); P < 0.05. Similar results were obtained for the effect of ketamine on remission, defined as MADRS fewer than 10 points. After 21 days of treatment, 27.3% patients in the ketamine group achieved remission compared to none in the placebo group (P < 0.05).

Safety

The RCT by Abdallah et al. (2022)[22] used CADSS to examine the dissociative effects of ketamine. Ketamine dose-dependently induced increase in the CADSS scores at 30 minutes from the start of infusion, and both the standard and low doses of ketamine had significantly higher CADSS scores than those of placebo (P < 0.05). However, the dissociative symptoms induced by ketamine returned to the placebo levels after the treatment was completed at 120 minutes. At post-treatment follow-up, there were no significant differences between treatment groups (P > 0.05). Additionally, the authors used the PANSS to examine the psychotomimetic effects of ketamine and found that there were no significant differences in PANSS scores between ketamine (both standard and low dose) and placebo during treatment. At post-treatment follow-up, both ketamine doses had significantly lower in PANSS scores compared to placebo (P < 0.05). The incidences of treatment-related AEs in the standard dose, low dose,

and placebo were 39.5%, 39.5% and 21%, respectively. The AEs most likely associated with both ketamine doses and not present in the placebo were agitation (5.7%), anxiety (3.8%), irritability (7.6%), constipation (2.9%), and sweating (2.9%).

The RCT by Domany et al. (2019)[26] found that 40% in the ketamine group compared to 18.2% in the placebo group had transient elevation of systolic blood pressure more than 20 mm Hg at first administration. Common AEs associated with ketamine included euphoria, dizziness, and drowsiness. The authors stated that those AEs and blood pressure increase were resolved within 1 hour and were milder at later administration of ketamine.

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

Two RCTs[23,25] compared IV ketamine with midazolam, 1 RCT[24] compared IV ketamine with IV esketamine, 2 RCTs[27,28] compared anesthesia-based IV ketamine with anesthesia-based IV propofol or IV methohexital, and 1 retrospective chart review[29] compared IM ketamine with rTMS.

PTSD

The RCT by Feder et al. (2021)[23] randomized patients with chronic PTSD, who were stable on psychotropic medications for at least 3 months before randomization to receive 6 infusions of ketamine (0.5 mg/kg per day) or midazolam (0.045 mg/kg per day) 3 days per weeks over 2 consecutive weeks. PTSD severity assessment using the CAPS-5 showed that improvement in the total scores over the course of treatment were significantly lower in the ketamine group compared with the midazolam group at week 1 ($P = 0.030$) and at week 2 ($P = 0.004$). Response rate, defined as a 30% or more reduction in CAPS-5 scores from baseline, was significantly higher in the ketamine group (67%) compared with the midazolam group (20%); $P = 0.03$. However, the effects of ketamine on CAPS-5 scores were gradually lost over time. The median time to loss of response (defined as < 30% improvement from baseline) among responders was 27.5 days (IQR: 23 days to 32 days).

Depression

The RCT by Feder et al. (2021)[23] found that depressive symptoms in PTSD patients measured by MADRS scores was significantly improved in the ketamine group compared with the midazolam groups at week 1 and week 2 ($P < 0.05$).

The RCT by Altinay et al. (2019)[25] compared ketamine (0.5 mg/kg) with midazolam (0.045 mg/kg) infused on alternate days with ECT days for 1 week in patients with TRD. Depressive symptoms measured using MADRS scores showed no significant difference between ketamine and midazolam groups. Similar results were also observed with the HAMD scores. The response rates and remission rates were also not statistically significantly different between the treatment groups.

The non-inferiority clinical trial by Correia-Melo et al. (2020)[24] assessed the efficacy of esketamine compared to ketamine in patients with TRD. There were no significant differences in mean MADRS scores between the 2 treatments at 24 hours, 72 hours, and 7 days after a single infusion of ketamine 0.5 mg/kg or esketamine 0.25 mg/kg. There were also no significant differences between treatment groups in the response rates or the remission rates at all follow-up time points. Similar results were observed with the CGI scores, with both ketamine and esketamine groups showing improvement in depressive symptoms without significant differences between groups at any time point.

Two RCTs, 1 by Carspecken et al. (2018)[28] and 1 by Gamble et al. (2018)[27] evaluated the ketamine's antidepressant effects in ECT as a primary anesthetic . In the RCT by Carspecken et al. (2018),[28] veterans with TRD were infused with IV ketamine (1 mg/kg to 2 mg/kg) or IV methohexital (1 mg/kg to 2 mg/kg) for induction of general anesthesia for each ECT session, and ECT course was scheduled with consecutive sessions 3 times a week with length determined by clinical response per the treating psychiatrist. Patients in both groups had depressive symptom improvement (i.e., decreased of HAMD or PHQ-9 scores) after completing the ECT index course compared with baseline.[28] However, there was no significant difference in HAMD scores or PHQ-9 scores between ketamine and methohexital groups at final ECT session or at 72 hours follow-up.[28]

The RCT by Gamble et al. (2018)[27] also compared the antidepressive effects between IV ketamine-based anesthesia (0.75 mg/kg) and IV propofol-based anesthesia (1 mg/kg) in TRD patients referred to ECT. Compared to the propofol group, the ketamine group had higher response rates (100% versus 83%) and remission rates (100% versus 58%) assessed using MADRS scores. Multivariate survival analysis adjusted for age and sex showed that patients in the ketamine group were more than twice as likely to achieve response and remission compared with the propofol group. Patients allocated in the ketamine groups significantly required fewer number of ECT treatments to achieve a 50% reduction in MADRS scores compared with those in the propofol group (P = 0.01). There were no significant differences in the relapse rates (MADRS > 20) between groups at 30-day follow-up.

The retrospective chart review study by Mikellides et al. (2021)[29] compared the antidepressant efficacy of both ketamine therapy and rTMS therapy in patients with TRD. Intramuscular ketamine was administered twice weekly for 8 sessions at an initial dose of 0.25 mg/kg, then the dosage was titrated upwards to a maximum of 1 mg/kg by session 4. There were significant decreases in HAMD and BDI-II scores in the post-treatment compared to pre-treatment in both groups. However, there was no significant differences in the response rates or remissions rates between groups.

Anxiety

In the retrospective chart review study by Mikellides et al. (2021),[29] the HAM-A scores were significantly reduced in the post-treatment compared to pre-treatment in both IM ketamine and rTMS group, but there were no significant differences in the response rates or remissions rates between groups.

Safety

The RCT by Feder et al. (2021)[23] found that the dissociative symptoms observed during ketamine infusions were transient, resolving by 2 hours after the start of infusion. No significant psychotic or manic symptoms were observed after ketamine infusions. There were no suicidal behaviours present during the assessment period. Most frequent AEs of ketamine compared with midazolam after the start of infusions included blurred visions (54% versus 0%), dizziness (33% versus 13%), headache (27% versus 13%), and nausea, or vomiting (20% versus 7%). Statistical comparisons were not reported.

The RCT by Altinay et al. (2019)[25] found no significant difference between ketamine and midazolam groups in cognitive testing (by MoCA or COWAT scores), or in manic symptoms (by YMRS scores).

The RCT by Correia-Melo et al. (2020)[24] found that no significant difference in dissociative symptoms between ketamine and esketamine groups. The authors reported that most

common treatment emergent AEs associated with ketamine or esketamine were increased blood pressure, heart rate, nausea, and dissociation. However, proportions and statistical comparisons between groups were not described. Three patients (1 ketamine and 2 esketamine) had to pause the infusion due to increased blood pressure above 30% of the baseline values. The authors reported that no life-threatening or other serious adverse events were observed.

The RCT by Carspecken et al. (2018),[28] found no significant difference in cognitive impairment between IV ketamine-based anesthesia and IV methohexital-based anesthesia administered before and after ECT. There were also no significant differences between groups in blood pressure, heart rate, mean number of seizures in index course per patient, mean seizure length, or mean length of post-anesthesia care unit stay. Two patients in the ketamine group experienced transient memorable dissociative symptoms during treatment, but no recurrences were reported during follow-up visits.

The RCT by Gamble et al. (2018)[27] found no significant difference in dissociative symptoms between IV ketamine-based anesthesia and IV propofol-based anesthesia groups across ECT sessions. For both groups, there was a decrease in CADSS scores with an increased number of ECT treatments. The ALS-18 scores for measuring sudden mood change over the past week significantly decreased at 30-day follow-up, but the change did not significantly differ between groups. The rates of AEs such as blood pressure increase or decrease, nausea or vomiting, and headache were not significantly different between groups.

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

No studies comparing 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

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

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.

Guidelines

The Danish guideline by Moeller et al. (2021)[30] provides weak recommendation against the use of IV ketamine as add-on to usual antidepressant treatment in patients with TRD. The rationale for the recommendation was that the benefits was short-lived, while the evidence on long-term efficacy and side effects, including the risk of abuse, was unclear.

The Canadian guideline by Swainson et al. (2021)[31] acknowledges the short-term efficacy of IV ketamine (relapse within 10 days for most patients), the lack of strategies for relapse prevention, and limited evidence on the efficacy of repeated ketamine treatment either by IV infusions of IV or different routes of administration, including oral, intranasal, and sublingual formulations. Therefore, the guideline recommends IV ketamine be considered as third line of treatment for adults with TRD.

Limitations

A general limitation of the included primary clinical studies was that 7 of 8 studies had small sample sizes that limit the generalizability of the findings. In double-blind RCTs, the high rate of transient dissociative symptoms in the ketamine group potentially affects the blinding that may lead to negative outcome expectations from the comparators, thus exaggerating differences between groups. Definition of TRD varied among studies, and 1 study[23] examining the effect of ketamine in PTSD did not require history of nonresponse to antidepressant. As all studies used ketamine as add-on therapy that allow patients to continue using stable dosages of other psychotropic medications (e.g., antidepressants, antpsychotic drugs, or mood stabilizers) during treatment, the concomitant antidepressant treatments across studies were not standardized. The retrospective chart review study[29] was limited by its retrospective design, without the advantages of randomization to minimize bias. The study[29] was prone to selection and attrition biases as it selected only patients who completed the total number of rTMS or ketamine sessions required, and patients with complete clinical evaluations before and after treatment, without collecting information of patients who terminated the treatment prematurely or those with incomplete assessment.

The recommendations from both included guidelines[30,31] were mostly based on low-quality evidence. No guidelines regarding the use of ketamine for treatment of PTSD were identified.

Conclusions and Implications for Decision- or Policy-Making

This report identified 7 RCTs,[22-28] 1 retrospective chart review study,[29] and 2 guidelines.[30,31] The identified primary clinical studies provided evidence for the efficacy and safety of ketamine compared with placebo or alternative interventions for treatment of TRD or PTSD in adults. Evidence comparing the clinical effectiveness of ketamine administered via different routes were not identified. Also, no evidence was identified regarding the cost-effectiveness of ketamine compared with placebo or alternative interventions; or of 1 ketamine formulation versus others for adults with TRD or PTSD.

The effects of ketamine on PTSD symptoms were reported in 2 RCTs[22,23] with mixed findings. A small sample size RCT[23] (15 patients per group) found that repeated IV ketamine infusions significantly improved PTSD symptoms compared with midazolam in civilian population of mostly females. A larger RCT[22] (around 50 patients per groups) could not demonstrate a significant efficacy on PTSD symptoms compared with placebo in military population of mostly males. It is unclear if the population and sex differences may have played a role in differing outcomes. However, the standard dose of IV ketamine (0.5 mg/kg) in both studies was superior to placebo[22] or midazolam[23] to reduce depressive symptoms. The antidepressant effects of ketamine were rapid, but the effects were not sustained during 4

weeks of post-treatment follow-up.[22] An RCT[24] comparing IV ketamine with IV esketamine found both treatments had comparable acute antidepressant effects for TRD 24 hours following infusion. When a single infusion of IV ketamine was used as anesthetic agent for ECT, patients undergoing ECT for TRD with ketamine anesthesia had similar improvement of depression when compared with patients undergoing ECT with methohexital anesthesia.[28] However, in another study[27] comparing with propofol-based anesthesia, ketamine-based anesthesia provided faster improvement in depressive symptoms and required fewer ECT treatments to achieve disease remission. It is unclear if the differences in outcomes between studies[27,28] may be due difference in comparators. In a small RCT,[25] alternate infusions of ketamine or midazolam with alternate ECT showed no significant difference in antidepressant effects between groups. The efficacy of oral ketamine was demonstrated in 1 RCT[26] in which repeated administration of oral ketamine significantly reduced depressive symptoms compared to placebo. A small retrospective chart review study[29] showed that the reduction in depressive and anxiety symptoms with repeated administration of IM ketamine was not significantly different compared with rTMS. Findings from included RCTs suggest overall safety and tolerability of ketamine for treatment of PTSD or TRD.[22-28] Most frequent AEs associated with ketamine were dissociative symptoms and cardiovascular changes such as increased blood pressure and heart rate, but these effects were transient. The Danish guideline[30] recommend against the use of IV ketamine in patients with TRD, due to low-quality and insufficient evidence regarding the lack of long-term efficacy and the risk of abuse of ketamine. Likewise, the Canadian guideline[31] recommends that IV ketamine be considered as third-line treatment for adults with TRD, because of the short-lived efficacy of ketamine, its side effects, and the lack of strategies for relapse prevention after ketamine infusions.

CADTH previously published 2 Rapid Response reports[17,18] on this topic. The 2017 CADTH report[18] identified 3 systematic reviews, 5 primary studies, and 2 evidence-based guidelines. The 2019 CADTH report[17] identified 6 primary clinical studies and 1 evidence-based guideline. Overall, the included studies showed that the IV ketamine had rapid antidepressant effects for treatment of TRD and single-dose infusion of ketamine was effective at reducing PTSD severity. However, an RCT involving repeated infusions found no difference in depression severity or suicidal ideation between ketamine and placebo. All 3 guidelines included in the 2 previous CADTH reports[17,18] recommended against the use of ketamine for patients with TRD or PTSD. The current report extends the scope of the 2 previous CADTH reports to include all ketamine formulations and all comparators of interest.

Given the aforementioned limitations of the included studies in this report, there is insufficient evidence to provide definitive conclusions about the clinical effectiveness of ketamine for treatment of TRD or PTSD. Future research is needed to address questions such as optimal dose regimens, patient selection, and treatment duration with longer follow-up period to determine whether ketamine should be used for treatment of TRD or PTSD.
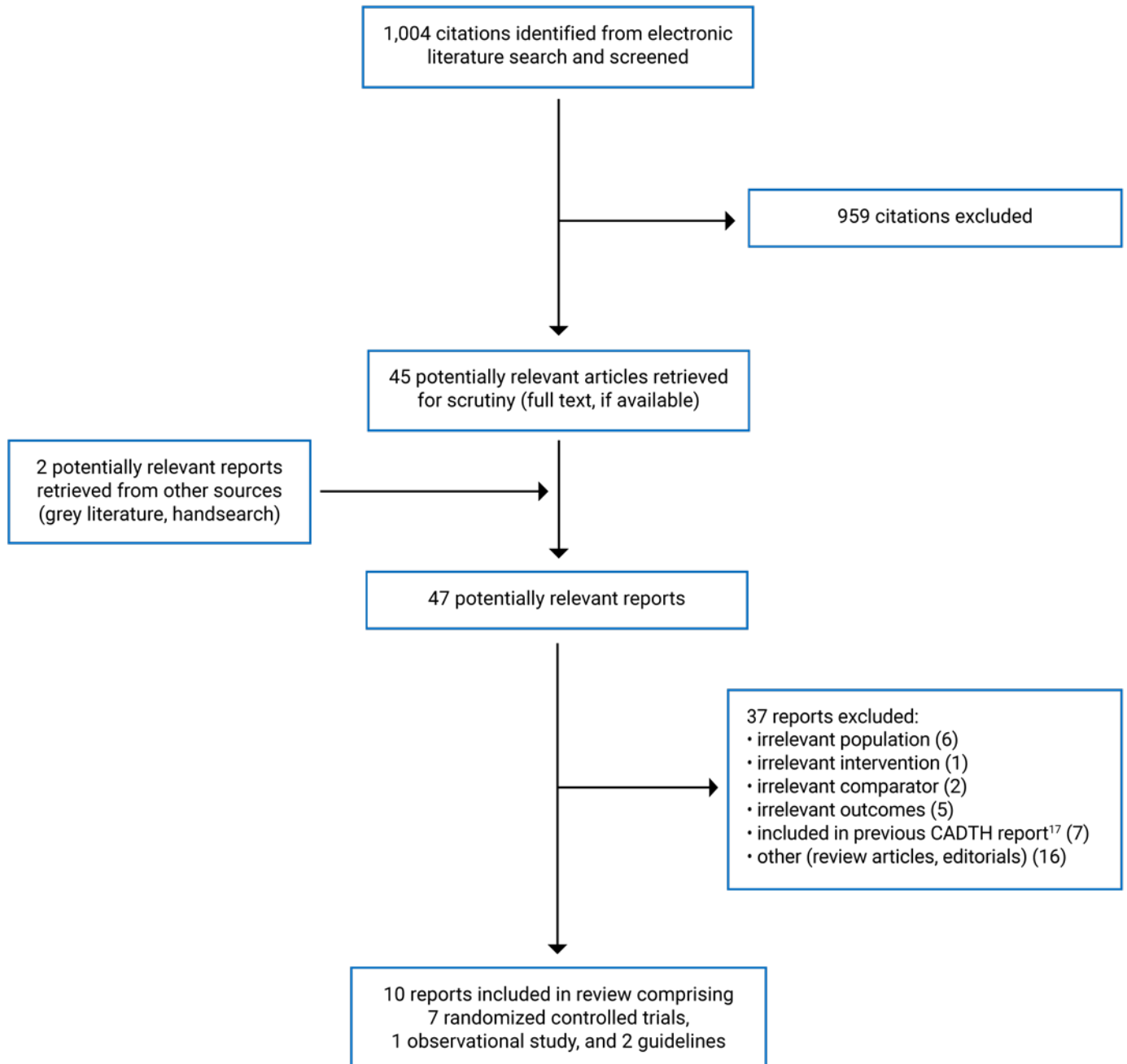
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Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies

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┌─────────────────────────────────────────┐
│ 1,004 citations identified from electronic│
│ literature search and screened            │
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                    │
                    │──────────────────────►  ┌──────────────────────────┐
                    │                          │ 959 citations excluded   │
                    │                          └──────────────────────────┘
                    ▼
┌─────────────────────────────────────────┐
│ 45 potentially relevant articles retrieved│
│ for scrutiny (full text, if available)    │
└─────────────────────────────────────────┘
┌──────────────────────────┐
│ 2 potentially relevant    │────────►
│ reports retrieved from    │
│ other sources (grey       │
│ literature, handsearch)   │
└──────────────────────────┘
                    ▼
┌─────────────────────────────────────────┐
│ 47 potentially relevant reports           │
└─────────────────────────────────────────┘
                    │
                    │──────────────►  ┌───────────────────────────────────────┐
                    │                 │ 37 reports excluded:                   │
                    │                 │ • irrelevant population (6)            │
                    │                 │ • irrelevant intervention (1)          │
                    │                 │ • irrelevant comparator (2)            │
                    │                 │ • irrelevant outcomes (5)              │
                    │                 │ • included in previous CADTH report[17] (7)│
                    │                 │ • other (review articles, editorials) (16)│
                    │                 └───────────────────────────────────────┘
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┌─────────────────────────────────────────┐
│ 10 reports included in review comprising  │
│ 7 randomized controlled trials,           │
│ 1 observational study, and 2 guidelines   │
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Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: 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
RCT				
Abdallah et al. (2022)[22] US Source of funding: US Department of Defense and US Department of Veteran Affairs	Multicenter, double-blind, parallel 1:1:1, placebo-controlled RCT Sample size calculation: Yes ITT analysis: No	Veterans and service members with PTSD (N = 158) who failed previous antidepressant treatment. % Male: • Standard dose: 74.5 • Low dose: 81.1 • Placebo: 74.1; P = 0.63 Mean age (SD), years: • Standard dose: 43.2 (12.7) • Low dose: 45.2 (11.2) • Placebo: 42.0 (10.8); P = 0.37 Mean years of military services (SD): • Standard dose: 11.2 (7.5) • Low dose: 12.0 (8.6) • Placebo: 10.9 (8.3); P = 0.77 Mean PCL-5[a] (SD): • Standard dose: 47.5 (14.5) • Low dose: 46.6 (17.7) • Placebo: 48.6 (12.8); P = 0.80 Mean CAPS-5[b] (SD): • Standard dose: 25.1 (13.6) • Low dose: 25.8 (17.7) • Placebo: 29.7 (14.6); P = 0.38 Mean MADRS[c] (SD): • Standard: 27.8 (9.3) • Low: 27.8 (10.3) • Placebo: 28.2 (8.4); P = 0.97	IV ketamine: • Standard dose (n = 51): 0.5 mg/kg • Low dose (n = 53): 0.2 mg/kg Placebo (n = 54): Saline Eight 40-minute IV infusions of ketamine or placebo (saline) were administered twice weekly	Outcomes: Primary: • PTSD (PCL-5[a]) • Response (≥ 25% improvement in PCL-5) Secondary: • PTSD (CAPS-5[b]) • Depression (MADRS[c]) AEs • Dissociation effects (CADSS[d]) • Psychotomimetic effects (PANSS[e]) Follow-up: 4 weeks post-treatment

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Feder et al. (2021)[23] US Source of funding: Private funding	Single centre, double-blind, parallel 1:1, placebo-controlled RCT Sample size calculation: Yes; but enrolled only 30 patients instead of 40 as planned. ITT analysis: Yes	Patients with chronic PTSD, who were stable with psychotropic medications for at least 3 months before randomization (N = 30) % Male: • Ketamine: 13.3 • Midazolam: 33.3 Mean age (SD), years: • Ketamine: 39.3 (13.8) • Midazolam: 38.5 (13.0) Mean duration of PTSD (SD), years: • Ketamine: 15.1 (17.8) • Midazolam: 14.6 (7.8) Mean CAPS-5[b] (SD): • Ketamine: 41.9 (6.1) • Midazolam: 40.1 (5.9) Mean MADRS[c] (SD): • Ketamine: 27.6 (8.2) • Midazolam: 26.4 (7.2)	IV ketamine (n = 15): 0.5 mg/kg Midazolam (n = 15): 0.045 mg/kg Three infusions per week for 2 weeks, with a total of 6 infusions Patients were assessed on each infusion day, 24 hours, and 2 weeks after the first infusion	Outcomes: • PTSD (CAPS-5[b]) • Depression (MADRS[c]) • Loss of response • Safety (dissociation [CADSS[d]], other AEs) Follow-up: 2 weeks (end of treatment) after the first infusion; 100 days for loss of response
Correia-Melo et al. (2020)[24] Brazil Source of funding: Public funding	Bicentre, non-inferiority, double-blind, parallel-controlled, 1:1, RCT Sample size calculation: Yes ITT analysis: Yes Non-inferiority would be demonstrated if the difference in remission rates between ketamine and esketamine was less than the pre-specified margin of 20%.	Patients with TRD (N = 63) who failed to respond to at least 1 antidepressant. % Male: • Ketamine: 29.7 • Esketamine: 44.2 Mean age (SD), years: • Ketamine: 48.7 (15.1) • Esketamine: 45.5 (14.5) Mean MADRS[c] (SD): • Ketamine: 33.1 (9.3) • Esketamine: 26.4 (7.2)	IV ketamine (n = 29): 0.5 mg/kg IV esketamine (n = 34): 0.25 mg/kg 40-minute single infusion	Outcomes: • Depression (MADRS[c], CGI[k]) • Safety (dissociation [CADSS[d]], other AEs) Follow-up: 7 days CGI-S performed at baseline CGI-I performed at 24 hours, 72 hours and 7 days after infusion

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Altinay et al. (2019)[25] US **Source of funding:** Cleveland Clinic Foundation Research Project Committee	Single centre, double-blind, parallel 1:1, placebo-controlled RCT Sample size calculation: No ITT analysis: Unclear	Patients with TRD (N = 12) who failed to respond to at least 2 antidepressants, and who were referred for ECT. % Male: • ECT + ketamine: 14 • ECT + midazolam: 20 Mean age (SD), years: • ECT + ketamine: 39 (11) • ECT + midazolam: 38 (15) HAMD (SD): • ECT + ketamine: 23 (3) • ECT + midazolam: 24 (5) MoCA (SD): • ECT + ketamine: 26 (2) • ECT + midazolam: 26 (2)	ECT + IV ketamine (n = 7) ECT + midazolam (n = 5) Ketamine: 0.5 mg/kg over 40-minute infusion Midazolam (as placebo): 0.045 mg/kg over 40-minute infusion ECT: Mondays, Wednesdays, and Fridays Infusions: Tuesdays and Thursdays	Outcomes: • Depression (HAMD[f], MADRS[c]) • Safety (manic symptoms [YMRS[g]], cognitive impairment [MoCA[h]], verbal learning and memory [HVLT-R[i]], verbal fluency [COWAT[j]]) Follow-up: 3 weeks
Domany et al. (2019)[26] Israel **Source of funding:** Private funding	Single centre, double-blind, parallel 1:1, placebo-controlled RCT Sample size calculation: Yes ITT analysis: Yes	Patients with TRD (N = 41) who had inadequate response to at least 2 antidepressants and were stable with current treatment. They were randomly assigned to ketamine or placebo on top of usual care. % Male: • Ketamine: 77.3 • Placebo: 82.1; P = 0.03 Mean age (SD), years: • Ketamine: 38.7 (13.3) • Placebo: 37.9 (13.4); P = 0.86 Mean MADRS (SD): • Ketamine: 33.4 (5.5) • Placebo: 29.99 (7.4); P = 0.16	Oral ketamine (n = 22): 1 mg/kg thrice weekly for 21 days Placebo (n = 19): Saline thrice weekly for 21 days	Outcomes: • Depression (MADRS[c]) • AEs Follow-up: 21 days (end of treatment)

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Carspecken et al. (2018)[28] US Source of funding: US Department of Veterans Affairs	Single centre, double-blind (patients and outcome assessors, parallel 1:1, RCT Sample size calculation: Yes ITT analysis: No	Veterans and service members with TRD (N = 52) who failed to respond to at least 2 antidepressants and were referred for ECT. % Male: • Ketamine: 74 • Methohexital: 89 Mean age (SD), years: • Ketamine: 50 (12) • Methohexital: 47 (12) Mean number of psychiatric medication (SD): • Ketamine: 2.7 (1.2) • Methohexital: 2.8 (1.3) Baseline PHQ-9: NR Baseline HAMD: NR	IV ketamine-based anesthesia (n = 27): 1 to 2 mg/kg IV methohexital-based anesthesia (n = 25): 1 to 2 mg/kg ECT course was scheduled with consecutive sessions 3 times a week with length determined by clinical response per the treating psychiatrist.	Outcomes: • Depression (PHQ-9°, HAMD[f]) • Safety (MoCA[h], AEs) Follow-up: 3 days after final ECT treatment for PHQ-9 and HAMD; 2 to 4 weeks after ECT completion for MoCA.
Gamble et al. (2018)[27] Canada Source of funding: Schulman Research Award (University of Saskatchewan) and the Royal University Hospital foundation (Saskatoon, Saskatchewan)	Single centre, double-blind, parallel 1:1, RCT Sample size calculation: Yes ITT analysis: Yes (modified)	Patients with TRD (N = 24) who were referred for ECT. Definition for TRD was not provided. % Male: • Ketamine: 50 • Propofol: 50 Mean age (SD), years: • Ketamine: 42 (16) • Propofol: 46 (16) Mean MADRS[c] (SD): • Ketamine: 30.0 (5.0) • Propofol: 29.0 (5.2) Mean ALS-18[l] (SD): • Ketamine: 36.9 (11.9) • Propofol: 40.6 (12.1) Previously had ECT: • Ketamine: 17% • Propofol: 42%	IV ketamine-based anesthesia (n = 12): 0.75 mg/kg IV propofol-based anesthesia (n = 12): 1 mg/kg Both arms received IV remifentanil 1 mcg/kg and succinylcholine 0.75 mg/kg All patients received 8 ECT sessions scheduled at 2 or 3 sessions/week.	Outcomes: • MADRS[c] • Safety (CADSS[d], ALS-18[l], AEs) Follow-up: 30 days after the final ECT session

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
NRSs				
Mikellides et al. (2021)[29] The Netherlands Source of funding: NR	Retrospective chart review from a single centre Sample size calculation: No Adjustment for confounders: No	Patients with TRD (N = 24). Definition for TRD was not provided. % Male: • Ketamine: 41.7 • rTMS: 50; P = 0.15 Mean age (SD), years: • Ketamine: 44.1 (13.2) • rTMS: 51.7 (11.4); P = 0.68 Mean number of failed antidepressants (SD): • Ketamine: 2.67 (0.78) • rTMS: 2.50 (0.80); P = 0.61 Mean HDRS (SD): • Ketamine: 33.3 (6.0) • rTMS: 30.3 (3.1); P = 0.30 Mean HAM-A (SD): • Ketamine: 34.8 (5.8) • rTMS: 34.2 (5.8); P = 0.78 Mean BDI-II (SD): • Ketamine: 45.3 (11.0) • rTMS: 38.7 (13.7); P = 0.21	IM ketamine (n = 12): twice weekly for 8 sessions; 0.25 mg/kg first, then the dosage was titrated upwards to a maximum of 1 mg/kg by session 4. rTMS (n = 12): 5 iTBS sessions were administered per week for 6 weeks, over the left of dorsal lateral prefrontal cortex.	Outcomes: • HDRS[f] • HAM-A[m] • BDI-II[n] Follow-up: Only pre- and post-treatment assessment (4 weeks for IM ketamine; 6 weeks for rTMS)

AEs = adverse events; ALS-18 = the short form of the Affective Lability Scale (also known as ALS-SF); BDI-II = Beck Depression Inventory – II; CADSS = Clinician-Administered Dissociative State Scale; ALS-18 = the short form of the Affective Lability Scale; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CGI = Clinical Global Impression; CGI-I = CGI-improvement; CGI-S = CGI-severity; COWAT = Controlled Oral Word Association Test; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition); ECT = electroconvulsive therapy; HAM-A = Hamilton Anxiety Rating Scale; HAMD = Hamilton Depression Scale; HDRS = Hamilton Depression Rating Scale; HVLT-R = Hopkins Verbal Learning Test – Revised; IM = intramuscular; iTBS = intermittent theta-burst stimulation; ITT = intention-to-treat; MADRS = Montgomery-Asberg Depression Rating Scale; MoCA = Montreal Cognitive Assessment; NR = not reported; NRS = non-randomized study; PANSS = Positive and Negative Syndrome Scale; PCL-5 = PTSD Checklist for DSM-5; PHQ-9 = Patient Health Questionnaire-9; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; TRD = treatment-resistant depression; YMRS = Young Mania Rating Scale.

[a]The PCL-5 is a 20-item self-report 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 (range - 0 to 80) 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.[32]

[b]The CAPS-5, a 30-item structured interview, is the gold standard in PTSD assessment. The frequency and intensity information were converted into a single 5-point (0 to 4) symptom severity score. The anchor points for this severity scale are 0 = absent, 1 = mild/subthreshold, 2 = moderate/threshold, 3 = severe/markedly elevated, and 4 = extreme/incapacitating.[33]

[c]The MADRS has 10 items and used by clinicians to assess the severity of depression in patients with a diagnosis of depression. Each item has a severity scale from 0 to 6, with higher scores reflecting more severe symptoms. Ratings can be added to form an overall score (from 0 to 60). The proposed cut-offs: scores of 0 to 6 indicate an absence of symptoms; 7 to 19 represent mild depression; 20 to 34 moderate; 35 to 60 indicate severe depression.[34]

[d]The CADSS is a scale used to measure dissociative states, consisting of 23 clinician-administered items, each scored from 0 (not at all) to 4 (extreme).[35]

[e]The PANSS is a standardized, clinical interview that rates the presence and severity of positive and negative symptoms, as well as general psychopathology for people with schizophrenia. It consists of 30 items, 7 are positive symptoms, 7 are negative symptoms, and 16 are general psychopathology symptoms. Symptom severity for each item is rated in the 7-point scale (1 = absent; 7 = extreme).[36]

[f]The HAMD, also termed HDRS, is used to measure the severity of symptoms of depression based on 17-item scales rated on either a 3- or 5-point scale, with the sum of all items making up the total score. The scores of 0 to 7 are considered as being normal, 8 to 16 suggest mild depression, 17 to 23 moderate depression and scores over 24 are indicative of severe depression; the maximum score being 52.[37]

[g]The YMRS is an 11-item rating scale used to assess manic symptoms. Four items are rated on a 0 to 8 scale, while the remaining 7 items are rated on a 0 to 4 scale. The optimal YMRS severity threshold of 25 (positive predictive value [PPV] = 83.0%; negative predictive value [NPV] = 66.0%) was determined to be classified as severely ill. The

YMRS minimal clinically significant difference was 6.6 points.[38]

[h]The MoCA is a 30-point screening test for detecting cognitive impairment. MoCA scores range between 0 and 30. A score of ≥ 26 is considered to be normal. People with mild cognitive impairment had an average score of 22.1. People with Alzheimer disease scored an average of 16.2.[39]

[i]The HVLT-R provides a brief assessment of verbal learning and memory (delayed recall and recognition) for individuals aged 16 years and older. The test is a 12-item 3 learning trial verbal learning test with delayed recall and recognition memory test. Raw scores are derived from Total Recall, Delayed Recall, Retention (% retained), and a Recognition Discrimination Index.[40]

[j]The 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.[41]

[k]The CGI is a standardized assessment scale for determining the effect of mental health treatment among psychiatric patients. 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 taken after treatment and compared with baseline. It rates the improvement on a 1 to 7 scale, with 1 representing 'very much improved,' 7 for 'very much worse' due to treatment, and 4 for no change from treatment.[42]

[l]The ALS-18 is an 18-item scale that retrospectively measures sudden mood change over the past week. Each item is rated on a 4-point (0 to 3) scale, ranging from 0 = "Very uncharacteristic of me" to 3 = "Very characteristic of me." The ALS-18 also includes a total score and scores of three subscales: Anxiety/ Depression, depression/ Elation, and Anger.[43]

[m]The HAM-A that assesses anxiety severity, consists of 14 items measuring different symptoms. Each item is rated on a 5-point (0 to 4) scale, ranging from 0 = Not present to 4 = Very severe. Total score ranges from 0 to 56, where scores < 17 indicate mild severity, scores between 18 and 24 indicate mild to moderate severity, and scores between 25 to 30 indicate moderate to severe anxiety.[44]

[n]The BDI-II that assesses depression severity, consists of 21 items. Each item is rated on a 4-point (0 to 3) scale, with a total score ranging from 0 to 63. Scores of 0 to 10 indicate absent or minimal depression, 14 to 19 for mild depression, 20 to 28 for moderate depression, and 29 to 63 for severe depression.[45]

[o]The PHQ-9 is a 9-item depression scale. Each item is rated on 4-point (0 [not at all] to 3 [nearly every day]) scale, with a total score ranging from 0 to 27. Scores of 0 to 4 indicates none or minimal depression, 5 to 9 mild depression, 10 to 14 moderate depression, 15 to 19 moderately severe depression, and 19 to 27 severe depression.[46]

Table 3: Characteristics of Included Guidelines

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations, development, and evaluation	Guideline validation
DHA, Moeller et al. (2021)[30]						
Intended users: All health care professionals who treat patients with difficult-to-treat depression Target population: Patients with difficult-to-treat depression (defined as without remission despite at least 2 antidepressants; chronic depression [i.e., lasting for 2 or more years regardless of treatment], or treatment-resistant using an assessment scale)	Six selected interventions: unilateral high frequency, IV ketamine or esketamine, bright light therapy, cognitive behavioural analysis system of psychotherapy, psychotherapy targeting rumination, and cognitive remediation.	All efficacy, tolerability, and safety outcomes that were clinically relevant.	The evidence from literature was systematically identified. Data extraction was conducted independently by 2 reviewers. Data were synthesized using meta-analysis wherever appropriate.	Quality of evidence and strength of recommendations were graded using GRADE. The program MAGICapp was used to formulate the recommendations,[a] taking into considerations of 1) the quality of evidence, 2) the efficacy and tolerability of the intervention, 3) the patient preference concerning the intervention, and 4) practical issues (e.g., a demand for special training or equipment)	Recommendations were developed by a guideline working group comprising professionals in psychiatry, clinical psychology, nursing, general practice, academic experts in psychiatry and psychology, and a patient representative. The program Making GRADE the Irresistible Choice (MAGICapp) was used to formulate the recommendations. Options for recommendations: strong recommendation for/or against the intervention, weak recommendation for/or against the intervention or a good clinical practice (in the absence of relevant evidence).	The guideline was reviewed by various organizations before publishing in a peer-reviewed journal.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations, development, and evaluation	Guideline validation
CANMAT, Swainson et al. (2021)[31]						
Intended Users: Clinicians who treat patients with TRD Target population: Patients with TRD	Racemic ketamine	All efficacy, tolerability, feasibility, and safety outcomes that were relevant to developer-specified research questions.	The evidence from literature was systematically identified. Recent consensus statement and guidelines were also reviewed.	The Cochrane risk of bias tool was used to assess the quality of evidence. Clinical recommendations were graded by line of treatment[b] with level of evidence[c] supporting each recommendation.	A task force developed 14 clinical questions. The recommendations were given in a question-answer format.	Published in peer-reviewed journal.

CANMAT = The Canadian Network for Mood and Anxiety Treatments; DHA = Danish Health Authority; GRAGE = Grades of Recommendation, Assessment, Development, and Evaluation; TRD = treatment-resistant depression.

[a]Options for recommendations were as follows: strong recommendation for/against the intervention, weak recommendation for/against the intervention or good clinical practice (in the absence of sufficiently relevant evidence).

[b]**Line of treatment[31]:**

First: Level 1 or level 2 evidence for efficacy plus clinical support for safety/tolerability/feasibility.

Second: Level 3 or higher evidence for efficacy plus clinical support for safety/tolerability/feasibility.

Third: Level 4 evidence of higher for efficacy plus clinical support for safety/tolerability/feasibility.

Not recommended: Level 1 evidence for lack of efficacy or level 2 evidence for lack of efficacy plus expert consensus.

Level of evidence[31]:

Level 1: Meta-analysis with narrow confidence interval or replicated double-blind (DB), randomized controlled trial (RCT) that includes a placebo or active comparison condition (n ≥ 30 in each active treatment arm).

Level 2: Meta-analysis with wide confidence interval or 1 DB RCT with placebo or active comparison condition (n ≥ 30 in each active treatment arm).

Level 3: At least 1 DB RCT with placebo or active comparison condition (n = 10 to 29 in each active treatment arm).

Level 4: Pilot study (RCT with n < 10 participants in each active treatment arm), uncontrolled trial, anecdotal reports, or expert opinion.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 4: Strengths and Limitations of Clinical Studies Using the Downs and Black checklist[19]

Strengths	Limitations
Abdallah et al. (2022)[22]	
RCTs	
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. • Adverse events of the intervention were reported. • There were no group differences in demographics of the randomized participants. • Actual probability and standard deviation values were reported for the main outcomes. External validity: • Participants were recruited from 3 centres of the US Veterans Affairs and Army Medical Center. It was likely that the participants represent the entire population from which they were recruited. • The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of the patients receive. Internal validity — bias: • This was a double-blind RCT, where the investigators and patients were blinded. This may have been associated with low risk of performance and selection bias. • All patients were followed up for 4 weeks. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. Internal validity — confounding: • Patients in different interventions groups appeared to be recruited from the same population and over the same period of time. • Patients were randomly allocated using a method described in a previous publication. This minimizes selection bias. • Patients lost to follow-up were treated as treatment failure and considered as nonresponder. Thus, lost to follow-up data were accounted in the analyses. • A sample size calculation was performed.	Reporting: • The characteristics of patients lost to follow-up were not described. 18% of patients did not complete any follow-up. There were no differences in proportions of patients lost to follow-up among groups. However, missing data were treated as treatment failure (i.e., nonresponder). Internal validity – bias: • Patient compliance was not assessed.

Strengths	Limitations
**Feder et al. (2021)[23]**	
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. • Adverse events of the intervention were reported. • There were no apparent group differences in demographics of the randomized participants. • One patient withdrew from the intervention due to safety concern, and the analyses were conducted using the ITT approach. • Actual probability and standard deviation values were reported for the main outcomes. External validity: • The study was conducted at a treatment centre, where the staff, setting, and facilities, were representative of the treatment majority of patients receive. Internal validity — bias: • The study was a double-blind RCT, where the investigators and patients were blinded. Thus, the potential risk for performance bias may have been low. • All patients were followed up for 2 weeks after the first infusion, and 100 days for loss of response. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. Internal validity — confounding: • Patients in different interventions groups appeared to be recruited from the same population and over the same period of time.	Reporting: • The characteristics of patients lost to follow-up were not described. Internal validity — bias: • Patient compliance was not assessed. External validity: • Small population (N = 30) of participants was recruited from a single centre that may not represent the entire population from which they were recruited. Internal validity — confounding: • Methods of randomization and allocation concealment were not reported. • Although sample size calculation was performed, the interim analyses of the study was conducted with only 30 patients instead of the planned 40 patients. The sample size was relatively small, thus, limiting the generalizability of the findings.

Strengths	Limitations
Correia-Melo et al. (2020)[24]	
Reporting:	External validity:
• 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.	• Patients were recruited from 2 centres with a total sample size of 63 that may not represent the entire population from which they were recruited. Internal validity – bias:
• Adverse events of the interventions were reported.	• Patient compliance was not assessed.
• There were no apparent group differences in demographics of the randomized participants, although statistical comparisons were not reported.	Internal validity — confounding:
• No patient lost to follow-up.	• Although sample size calculation was performed having a planned sample size of 96 patients, the interim analyses in this study was conducted with only 63 patients. The sample size was relatively small, thus, limiting the generalizability of the findings.
• Actual probability and 95% CI were reported for the main outcomes.	
• The non-inferiority margin was set at 20%. A difference in remission rates between groups less than 20% would be considered as non-inferiority. As the difference in remission rates between groups was only 5.3%, the interpretation of the findings was valid.	
External validity:	
• The study was performed at 2 hospitals. The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of the patients receive.	
Internal validity — bias:	
• This was a double-blind RCT, in which the participants and outcome assessors were blinded. Only a single investigator and a nurse were aware of the drug being infused.	
• All patients were followed up for 7 days.	
• Statistical tests were used appropriately, and the main outcome measures were accurate and reliable.	
Internal validity — confounding:	
• Patients in different interventions groups appeared to be recruited from the same population and over the same period of time.	
• Methods of randomization and allocation concealment were reported.	
• The analyses were conducted using the ITT approach.	

Strengths	Limitations
Altinay et al. (2019)[25]	
Reporting: • The objective of the study, the main outcomes to be measured, the interventions of interest, and the main findings were clearly described. • Adverse events of the interventions were reported. • Actual P values were reported. External validity: • The study was conducted at an outpatient clinic. The staff, places, and facilities where the patients were treated, might be representative of the treatment the majority of the patients receive. Internal validity — bias: • This was a double-blinded RCT. • All patients were followed up for 3 weeks. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. Internal validity — confounding: • Patients in different interventions groups appeared to be recruited from the same population and over the same period of time.	Reporting: • The characteristics of the patients included in the study were not clearly described. • Statistical comparisons of patient demographics between groups were not reported. • Three patients (20%) lost to follow-up, and only 12 of 15 were included in the analyses. External validity: • Small population (N = 15) of participants was recruited from a single centre that may not represent the entire population from which they were recruited. Internal validity — bias: • Patient compliance was not assessed. Internal validity — confounding: • Methods of randomization and allocation concealment were not reported. • It was unclear if there were any confounding variables present. • Patients lost to follow-up were not accounted in the analyses. • The study included small sample size (N = 15) and none of the outcomes were found statistically significant between groups. It is unclear if statistical power was done.

Strengths	Limitations
Domany et al. (2019)[26]	
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. • Adverse events of the intervention were reported. • There were no group differences in most demographics of the randomized participants. However, female was predominant in the placebo group (P = 0.03). • Actual probability and standard deviation values were reported for the main outcomes. • The characteristics of patients lost to follow-up were described. External validity: • The staff, places, and facilities where the patients were treated, might be representative of the treatment the majority of the patients receive. Internal validity – bias: • This was a double-blinded RCT. • All patients were followed up for 21 days. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. Internal validity — confounding: • Patients in different interventions groups appeared to be recruited from the same population and over the same period of time. • The analyses were conducted using the ITT approach. • A sample size calculation was performed.	External validity: • Patients were recruited from one centre with a total sample size of 41. Patients might not be representative of the population they were recruited. Internal validity —bias: • Patient compliance was not assessed. Internal validity — confounding: • Methods of randomization and allocation concealment were not reported.

Strengths	Limitations
Gamble et al. (2018)[27]	
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. • Adverse events of the intervention were reported. • There were no apparent group differences in demographics of the randomized participants, although statistical comparisons were not reported. • Actual probability and standard deviation values were reported for the main outcomes. External validity: • The study was conducted at an electroconvulsive therapy clinic. The staff, places, and facilities where the patients were treated, might be representative of the treatment the majority of the patients receive. Internal validity — bias: • This was a double-blinded RCT. • All patients were followed up for 30 days. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. Internal validity — confounding: • Patients in different interventions groups appeared to be recruited from the same population and over the same period of time. • The analyses were conducted using the modified ITT approach.	Reporting: • The characteristics of patients lost to follow-up were not described. External validity: • Small population (N = 27) of participants was recruited from a single centre that may not represent the entire population from which they were recruited. Internal validity — bias: • Patient compliance was not assessed. Internal validity — confounding: • Methods of randomization and allocation concealment were not reported. • Although sample size calculation was performed having a planned sample size of 56 patients, the interim analyses in this study was conducted with only 27 patients. The sample size was relatively small, limited the generalizability of the findings.

Strengths	Limitations
Carspecken et al. (2018)[28]	
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. • Adverse events of the intervention were reported. • There were no apparent group differences in demographics of the randomized participants, although statistical comparisons were not reported. • Actual probability and standard deviation values were reported for the main outcomes. External validity: • The study was conducted at an electroconvulsive therapy clinic. The staff, places, and facilities where the patients were treated, might be representative of the treatment the majority of the patients receive. Internal validity — bias: • This was a double-blinded RCT. • All patients were followed up for 3 days. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. Internal validity — confounding: • Patients in different interventions groups appeared to be recruited from the same population and over the same period of time. • Method of randomization was reported. • A sample size calculation was performed.	Reporting: • The characteristics of patients lost to follow-up were not described. External validity: • Patients were recruited from one centre with a total sample size of 52. Patients might not be representative of the population they were recruited. Internal validity — bias: • Patient compliance was not assessed. Internal validity — confounding: • Method of allocation concealment was not reported. • The analyses did not take patients lost to follow-up into account.

Strengths	Limitations
NRS	
Mikellides et al. (2021)[29]	
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 apparent group differences in reported demographics of the included participants. • Actual probability and standard deviation values were reported for the main outcomes. External validity: • The clinical records were collected from a mental health clinic. The staff, places, and facilities where the patients were treated, might be representative of the treatment the majority of the patients receive. Internal validity — bias: • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable.	Reporting: • Adverse events of the intervention were not reported. External validity: • As the study population was relatively small (N = 24), it was unclear if the study participants represented the entire population from which they were recruited. Internal validity — bias: • Patient compliance was not assessed. • This was a non-randomized study, which was prone to high risk of bias for selection, performance, and detection. • There was no follow-up. Only pre- and post-treatment assessment was performed. Internal validity — confounding: • It was unclear if patients in different interventions groups were recruited from the same population and over the same period of time. • Confounding variables were not identified and adjusted for in the analyses. This may have significant impact to the findings. • The authors of the study did not provide a sample size calculation.

CI = confidence interval; ITT = intention-to-treat; NRS = non-randomized study; RCT = randomized controlled trial.

Table 5: Strengths and Limitations of Guidelines Using AGREE II[20]

Item	DHA, Moeller et al. (2021)[30]	CANMAT, Swainson et al. (2021)[31]
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	Unclear
6. The target users of the guideline are clearly defined.	Yes	Yes

Item	DHA, Moeller et al. (2021)[30]	CANMAT, Swainson et al. (2021)[31]
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.	Unclear	Unclear
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.	Unclear	Unclear
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Unclear	Unclear
20. The potential resource implications of applying the recommendations have been considered.	Unclear	Unclear
21. The guideline presents monitoring and/or auditing criteria.	Unclear	Unclear
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	No	No
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes

AGREE II = Appraisal of Guidelines for Research and Evaluation II; CANMAT = The Canadian Network for Mood and Anxiety Treatments; DHA = Danish Health Authority; NR = not reported; NA = not applicable.

Appendix 4: Main Study Findings

Note that this appendix has not been copy-edited.

Table 6: Summary of Findings by Outcome – PTSD symptoms

Study citation, study design, and patient model	Study findings
PCL-5 scores	
Standard dose IV Ketamine 0.5 mg/kg (n = 51) vs. Low dose IV ketamine 0.2 mg/kg (n = 53) vs. Placebo (n = 54)	
Abdallah et al. (2022)[22] RCT Veterans and service members with PTSD (N = 158) who failed previous antidepressant treatment	After 24 hour – MD ± SEM • Standard dose vs. placebo: 6.6 ± 3.1; adj. P = 0.11 • Low dose vs. placebo: 3.3 ± 3.1; adj. P = 0.57 • Standard dose vs. low dose: adj. P > 0.5 End of treatment (i.e., 4 weeks) – MD ± SEM • Standard dose vs. placebo: 5.0 ± 3.4; adj. P = 0.28 • Low dose vs. placebo: 6.4 ± 3.3; adj. P = 0.16 • Standard dose vs. low dose: adj. P > 0.5 At 4 weeks of follow-up – MD ± SEM • Standard dose vs. placebo: adj. P = 0.34 • Low dose vs. placebo: 15.3 ± 5.8; adj. P = 0.03 • Standard dose vs. low dose: 9.8 ± 4.8; adj. P = 0.09 Response (≥ 25% improvement in PCL-5) after 24 hours: • Standard dose vs. low dose vs. placebo: 47% vs. 47% vs. 33%; P = 0.08 • Standard dose vs. placebo: OR (95% CI) = 1.88 (0.84 to 4.22) • Low dose vs. placebo: OR (95% CI) = 1.82 (0.82 to 4.05)
CAPS-5 scores	
Standard dose IV Ketamine 0.5 mg/kg (n = 51) vs. Low dose IV ketamine 0.2 mg/kg (n = 53) vs. Placebo (n = 54)	
Abdallah et al. (2022)[22] RCT Veterans and service members with PTSD (N = 158) who failed previous antidepressant treatment	After 24 hour – MD ± SEM • Standard dose vs. placebo: 4.7 ± 2.8; adj. P = 0.09 • Low dose vs. placebo: 6.0 ± 2.7; adj. P = 0.57 • Standard dose vs. low dose: adj. P = 0.65 At 4 weeks of follow-up – MD ± SEM • Standard dose vs. placebo: 5.7 ± 3.7; adj. P = 0.25 • Low dose vs. placebo: 8.4 ± 3.7; adj. P = 0.09 • Standard dose vs. low dose: 2.7 ± 3.4; adj. P = 0.43

Study citation, study design, and patient model	Study findings
IV Ketamine 0.5 mg/kg (n = 15) vs. IV Midazolam 0.045 mg/kg (n = 15)	
Feder et al. (2021)[23] RCT Patients with chronic PTSD, who were stable with psychotropic medications for at least 3 months before randomization (N = 30)	Total CAPS-5 scores were significantly lower in the ketamine group compared with the midazolam group: • At week 1: MD = 8.8; SEM = 3.93; P = 0.030 • At week 2: MD = 11.88; SEM = 3.96; P = 0.004 Response (≥ 30% reduction from baseline): • At week 2: 67% in the ketamine group vs. 20% in the midazolam group attained response; P = 0.03. Loss of response (< 30% improvement from baseline): • Among responders to ketamine, the median time to loss of response was 27.5 days (IQR: 23 days to 32 days).

Adj. = adjusted; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CI = confidence interval; IQR = interquartile range; MD = mean difference; OR = odds ratio; PCL-5 = PTSD checklist for DSM-5; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; SEM = standard error of the mean; vs. = versus.

Table 7: Summary of Findings by Outcome – Depression

Study citation, study design, and patient model	Study findings
MADRS scores	
Standard dose IV Ketamine 0.5 mg/kg (n = 51) vs. Low dose IV ketamine 0.2 mg/kg (n = 53) vs. Placebo (n = 54)	
Abdallah et al. (2022)[22] RCT Veterans and service members with PTSD (N = 158) who failed previous antidepressant treatment	After 24 hour – MD ± SEM • Standard dose vs. placebo: 4.6 ± 1.9; adj. P = 0.05 • Low dose vs. placebo: adj. P = 0.2 • Standard dose vs. low dose: 3.9 ± 1.9; adj. P = 0.08; however, the finding did not survive correction for multiple comparisons. End of treatment (i.e., 4 weeks) – MD ± SEM • Standard dose vs. placebo: 6.4 ± 2.2; adj. P = 0.01 • Low dose vs. placebo: adj. P = 0.27 • Standard dose vs. low dose: adj. 3.3 ± 2.2; adj. P = 0.27 At 4 weeks of follow-up – MD ± SEM • Standard dose vs. placebo: adj. P = 0.48 • Low dose vs. placebo: 7.9 ± 3.5; adj. P = 0.08 • Standard dose vs. low dose: adj. P = 0.48
IV Ketamine 0.5 mg/kg (n = 15) vs. IV Midazolam 0.045 mg/kg (n = 15)	
Feder et al. (2021)[23] RCT Patients with chronic PTSD, who were stable with psychotropic medications for at least 3 months before randomization (N = 30)	Depression was significantly improved in the ketamine group compared with the midazolam groups at week 1 and week 2 (P < 0.05). Data were presented graphically without numerical values.

Study citation, study design, and patient model	Study findings
IV ketamine 0.5 mg/kg (n = 29) vs. IV esketamine 0.25 mg/kg (n = 34)	
Correia-Melo et al. (2020)[24] RCT Patients with TRD (N = 63) who failed to respond to at least 1 antidepressant	Mean MADRS scores at: • 24 hours: 16.2 vs. 17.5; MD = 1.3 (95% CI = −4.6 to 6.1); P = 0.67 • 72 hours: 14.9 vs. 17.4; MD = 2.6 (95% CI = −4.0 to 9.1); P = 0.44 • 7 days: 14.3 vs. 20.6; MD = 6.3 (95% CI = −0.9 to 13.5); P = 0.08 Remission rate (%) at: • 24 hours: 24.1 vs. 29; MD = 5.27 (95% CI_{LB} = −13.6) • 72 hours: 39.3 vs. 35.5; MD = −3.8 (95% CI_{LB} = −24.6) • 7 days: 41.4 vs. 28.1; MD = −13.2 (95% CI_{LB} = −33.2) Response rate (%; ≥ 50% reduction from baseline) at: • 24 hours: 51.7 vs. 50; MD = −1.72 (95% CI_{LB} = −22.5) • 72 hours: 57.1 vs. 48.2; MD = −8.76 (95% CI_{LB} = −30.1) • 7 days: 62.1 vs. 43.7; MD = −18.3 (95% CI_{LB} = −39.0)
ECT + IV ketamine 0.5 mg/kg (n = 7) vs. ECT + midazolam 0.045 mg/kg (n = 5)	
Altinay et al. (2019)[25] RCT Patients with TRD (N = 12) who failed to respond to at least 2 antidepressants, and who were referred for ECT	There was no significant difference between ketamine and midazolam groups. • b = 1.22; SE = 3.28; P = 0.72
Oral ketamine 1 mg/kg thrice weekly for 21 days (n = 22) vs. Placebo (n = 19)	
Domany et al. (2019)[26] RCT Patients with TRD (N = 41) who had inadequate response to at least 2 antidepressants and were stable with current treatment.	Mean change of MADRS scores at day 21 from baseline: • Ketamine: 12.75 (from 33.4 [SEM = 2.18] to 20.65 [SEM = 2.28]) • Placebo: 2.49 (from 29.99 [SEM = 2.44] to 27.5 [SEM = 2.61]) • P < 0.001 compared between ketamine and placebo Response (≥ 50% reduction from baseline) at day 21: • 31.8% vs. 5.6%; P < 0.05 Remission (MADRS ≤ 10) at day 21: • 27.3% vs. 0; P < 0.05

Study citation, study design, and patient model	Study findings
IV ketamine-based anesthesia 0.75 mg/kg (n = 12) vs. IV propofol-based anesthesia 1 mg/kg (n = 12)	
Gamble et al. (2018)[27] RCT Patients with TRD (N = 24) who were referred for ECT. Definition for TRD was not provided.	Response (≥ 50% reduction from baseline): • 100% vs. 83%; P value not reported. • Multivariate survival analysis adjusted for age and sex showed that patients in the ketamine group were more than twice as likely to achieve response (HR [95% CI] = 3.20 [2.00 to 5.13]) compared with the propofol group. Remission (MADRS ≤ 10): • 100% vs. 58%; P value not reported. • Multivariate survival analysis adjusted for age and sex showed that patients in the ketamine group were more than twice as likely to achieve a remission (HR [95% CI] = 3.67 [2.13 to 6.32]) compared with the propofol group. Relapse (MADRS > 20) at 30-day follow-up: • 1/12 (8.3%) vs. 1/12 (8.3%); P = 0.77 Median (IQR) of ECT treatments to a 50% reduction in MADRS scores: • 2 (1 to 4) vs. 4 (2 to 7); P = 0.01
HAMD or HDRS scores	
ECT + IV ketamine 0.5 mg/kg (n = 7) vs. ECT + midazolam 0.045 mg/kg (n = 5)	
Altinay et al. (2019)[25] RCT Patients with TRD (N = 12) who failed to respond to at least 2 antidepressants, and who were referred for ECT	There was no significant difference between ketamine and midazolam groups. • b = 1.22; SE = 3.28; P = 0.72 Response (≥ 50% decrease in scores): • 3 of 7 (42%) in the ECT + ketamine group showed early response compared with 1 of 5 (20%) in the ECT + midazolam. Remission (HAMD < 8) • 3 of 7 (42%) in the ECT + ketamine group showed remission compared with 0 of 5 (0%) in the ECT + midazolam.
IV ketamine-based anesthesia 1 to 2 mg/kg (n = 27) vs. IV methohexital-based anesthesia 1 to 2 mg/kg (n = 25)	
Carspecken et al. (2018)[28] RCT Veterans and service members with TRD (N = 52) who failed to respond to at least 2 antidepressants, and who were referred for ECT.	Patients in both groups had depression score improvement (decreased) after completing the ECT index course. • At baseline: 27.6 ± 8.7 vs. 28.8 ± 5.2; P = 0.54 • At final ECT session: 12.3 ± 7.6 vs. 15 ± 6.9; P = 0.22
IM ketamine 0.25 mg/kg first, then 1 mg/kg (n = 12) vs. rTMS (n = 12)	
Mikellides et al. (2021)[29] Retrospective chart review study Patients with TRD (N = 24). Definition for TRD was not provided.	• Responder (≥ 50% decrease from baseline): 33.3% (4/12) vs. 25% (3/12); P > 0.05 • Remitters (HAMD ≤ 7): 66.7% (8/12) vs. 66.7% (8/12); P > 0.05

Study citation, study design, and patient model	Study findings
BDI-II	
IM ketamine 0.25 mg/kg first, then 1 mg/kg (n = 12) vs. rTMS (n = 12)	
Mikellides et al. (2021)[29] Retrospective chart review study Patients with TRD (N = 24). Definition for TRD was not provided.	• Responder (≥ 50% decrease from baseline): 25% (3/12) vs. 8.3% (1/12); P > 0.05 • Remitters (BDI-II ≤ 13): 58.3% (7/12) vs. 75% (9/12); P > 0.05
PHQ-9 scores	
IV ketamine-based anesthesia 1 to 2 mg/kg (n = 27) vs. IV methohexital-based anesthesia 1 to 2 mg/kg (n = 25)	
Carspecken et al. (2018)[28] RCT Veterans and service members with TRD (N = 52) who failed to respond to at least 2 antidepressants, and who were referred for ECT.	Patients in both groups had depression score improvement (decreased) after completing the ECT index course. • At baseline: 21.1 ± 3.9 vs. 21.5 ± 3.6; P = 0.74 • At final ECT session: 7.2 ± 4.4 vs. 8.7 ± 5.3; P = 0.31 • At 72 hours after ECT: 8.6 ± 6.7 vs. 9.4 ± 6.4; P = 0.70
CGI scores	
IV ketamine 0.5 mg/kg (n = 29) vs. IV esketamine 0.25 mg/kg (n = 34)	
Correia-Melo et al. (2020)[24] RCT Patients with TRD (N = 63) who failed to respond to at least 1 antidepressant	Median (IQR) of GCI-Improvement scores at: • 24 hours: 3 (1 to 3) vs. 3 (2 to 3); P = 0.95 • 72 hours: 2 (1 to 4) vs. 2 (1 to 3); P = 0.46 • 7 days: 2 (1 to 4) vs. 2.5 (1 to 4); P = 0.32

adj. = adjusted; BDI-II = Beck Depression Inventory − II; CGI = Clinical Global Impression; CI = confidence interval; CGI = Clinical Global Impression; ECT = electroconvulsive therapy; HAMD = Hamilton depression scale; HDRS = Hamilton Depression Rating Scale; HR = hazard ratio; IQR = interquartile range; IV = IV; LB = lower bound; MADRS = Montgomery-Asberg Depression Rating Scale; LM = lower bound; MD = mean difference; PHQ-9 = Patient Health Questionnaire-9; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SEM = standard error of the mean; SE = standard error; TRD = treatment-resistant depression; vs. = versus.

Table 8: Summary of Findings by Outcome — Anxiety

Study citation, study design, and patient model	Study findings
HAM-A scores	
IM ketamine 0.25 mg/kg first, then 1 mg/kg (n = 12) vs. rTMS (n = 12)	
Mikellides et al. (2021)[29] Retrospective chart review study Patients with TRD (N = 24). Definition for TRD was not provided.	• Responder (≥ 50% decrease from baseline): 25% (3/12) vs. 25% (3/12); P > 0.05 • Remitters (HAM-A ≤ 7): 75% (9/12) vs. 75% (9/12); P > 0.05

HAM-A = Hamilton Anxiety Rating Scale; TRD = treatment-resistant depression; rTMS = repetitive transcranial magnetic stimulation.

Table 9: Summary of Findings by Outcome — Safety

Study citation, study design, and patient model	Study findings
CADSS scores	
Standard dose IV Ketamine 0.5 mg/kg (n = 51) vs. Low dose IV ketamin 0.2 mg/kg (n = 53) vs. Placebo (n = 54)	
Abdallah et al. (2022)[22] RCT Veterans and service members with PTSD (N = 158) who failed previous antidepressant treatment	• Ketamine dose-dependently induced dissociation (P < 0.0001) during treatment dissipating 80 minutes after 40 minutes infusion. • There were time effects of ketamine on CADSS (P < 0.0001), with a reduction of dissociative symptoms observed over the 8-infusion treatment period. • At post-treatment, there were no significant differences between treatment groups (P > 0.05).
IV Ketamine 0.5 mg/kg (n = 15) vs. IV Midazolam 0.045 mg/kg (n = 15)	
Feder et al. (2021)[23] RCT Patients with chronic PTSD, who were stable with psychotropic medications for at least 3 months before randomization (N = 30)	The authors reported that "*Dissociative symptoms that emerged during ketamine infusions were transient, with highest levels reported at the infusion-end assessment (40 minutes), and had resolved by the next assessment,120 minutes after start of infusion.*"
IV ketamine 0.5 mg/kg (n = 29) vs. IV esketamine 0.25 mg/kg (n = 34)	
Correia-Melo et al. (2020)[24] RCT Patients with TRD (N = 63) who failed to respond to at least 1 antidepressant	No significant difference in mean CADSS scores between groups: • 18.2 (SD = 16.1) vs. 14.9 (SD = 16.2) • MD (95% CI) = 3.1 (−11.4 to 5.1); P = 0.45
IV ketamine-based anesthesia 0.75 mg/kg (n = 12) vs. IV propofol-based anesthesia 1 mg/kg (n = 12)	
Gamble et al. (2018)[27] RCT Patients with TRD (N = 24) who were referred for ECT. Definition for TRD was not provided.	• No significant difference in mean CADSS scores between groups across ECT sessions • For both groups, there was a decrease in CADSS scores with an increased number of ECT treatments (B = −0.57, SE = 0.74)
PANSS scores	
Standard dose IV Ketamine 0.5 mg/kg (n = 51) vs. Low dose IV ketamine 0.2 mg/kg (n = 53) vs. Placebo (n = 54)	
Abdallah et al. (2022)[22] RCT Veterans and service members with PTSD (N = 158) who failed previous antidepressant treatment	• During treatment, there were no significant differences in psychomimetic effects between ketamine (both standard and low dose) and placebo. • At post-treatment, both ketamine doses had significantly lower in PANSS scores compared to placebo (P < 0.05).
YMRS scores	
ECT + IV ketamine 0.5 mg/kg (n = 7) vs. ECT + midazolam 0.045 mg/kg (n = 5)	
Altinay et al. (2019)[25] RCT Patients with TRD (N = 12) who failed to respond to at least 2 antidepressants, and who were referred for ECT	There was no significant difference between ketamine and midazolam groups. • b = 1.22; SE = 3.28; P = 0.72

Study citation, study design, and patient model	Study findings
MoCA scores	
ECT + IV ketamine 0.5 mg/kg (n = 7) vs. ECT + midazolam 0.045 mg/kg (n = 5)	
Altinay et al. (2019)[25] RCT Patients with TRD (N = 12) who failed to respond to at least 2 antidepressants, and who were referred for ECT	There was no significant difference between ketamine and midazolam groups. • b = 0.98; SE = 1.12; P = 0.40
IV ketamine-based anesthesia 1 to 2 mg/kg (n = 27) vs. IV methohexital-based anesthesia 1 to 2 mg/kg (n = 25)	
Carspecken et al. (2018)[28] RCT Veterans and service members with TRD (N = 52) who failed to respond to at least 2 antidepressants, and who were referred for ECT.	Patients in both groups had no cognitive impairment after completing the ECT index course. • At baseline: 27.4 ± 2.0 vs. 26.7 ± 3.9; P = 0.25 • At final ECT session: 25.6 ± 3.8 vs. 24.4 ± 4.1; P = 0.42
COWAT scores	
ECT + IV ketamine 0.5 mg/kg (n = 7) vs. ECT + midazolam 0.045 mg/kg (n = 5)	
Altinay et al. (2019)[25] RCT Patients with TRD (N = 12) who failed to respond to at least 2 antidepressants, and who were referred for ECT	There was no significant difference between ketamine and midazolam groups. • b = 3.72; SE = 3.71; P = 0.34
ALS-18 scores	
IV ketamine-based anesthesia 0.75 mg/kg (n = 12) vs. IV propofol-based anesthesia 1 mg/kg (n = 12)	
Gamble et al. (2018)[27] RCT Patients with TRD (N = 24) who were referred for ECT. Definition for TRD was not provided.	At 30-day follow-up: • B = −8.03; SE = 3.23; P = 0.55
Other AEs	
Standard dose IV Ketamine 0.5 mg/kg (n = 51) vs. Low dose IV ketamine 0.2 mg/kg (n = 53) vs. Placebo (n = 54)	
Abdallah et al. (2022)[22] RCT Veterans and service members with PTSD (N = 158) who failed previous antidepressant treatment	• Related AEs during treatment: standard dose (39.5%); low dose (39.5%); placebo (21%) • AEs most likely associated with both ketamine doses and not present in the placebo: agitation (5.7%), anxiety (3.8%), irritability (7.6%), constipation (2.9%), sweating (2.9%).

Study citation, study design, and patient model	Study findings
IV Ketamine 0.5 mg/kg (n = 15) vs. IV Midazolam 0.045 mg/kg (n = 15)	

Feder et al. (2021)[23]
 	
RCT
 	
Patients with chronic PTSD, who were stable with psychotropic medications for at least 3 months before randomization (N = 30)
	• No significant psychotic or manic symptoms were observed after ketamine infusions.
	• No suicidal behaviour present during the assessment period.
	• Most frequent AEs after the start of infusions (ketamine vs. midazolam)
	  ○ Blurred vision: 53% vs. 0%
	  ○ Dizziness: 33% vs. 13%
	  ○ Fatigue: 33% vs. 87%
	  ○ Headache: 27% vs. 13%
	  ○ Nausea and vomiting: 20% vs. 7%
	  ○ Poor concentration: 13% vs. 0%

IV ketamine 0.5 mg/kg (n = 29) vs. IV esketamine 0.25 mg/kg (n = 34)	
Correia-Melo et al. (2020)[24] RCT Patients with TRD (N = 63) who failed to respond to at least 1 antidepressant	• The authors reported that most common TEAEs associated with ketamine or esketamine were increased blood pressure, heart rate, nausea, and dissociation. However, proportions and statistical comparison between groups were not described. • Three participants (1 ketamine and 2 esketamine) had to pause the infusion due to increased blood pressure above 30% of the baseline values. • No life-threatening or other serious adverse events.
Oral ketamine 1 mg/kg thrice weekly for 21 days (n = 22) vs. Placebo (n = 19)	

Domany et al. (2019)[26]
 	
RCT
 	
Patients with TRD (N = 41) who had inadequate response to at least 2 antidepressants and were stable with current treatment.
	• 40% in the ketamine group vs. 18.2% in the placebo group had transient elevation of systolic blood pressure more than 20 mm Hg at first administration. This AE was resolved within 1 hour.
	• Common AEs (They were resolved within 1 hour, and were milder in the later administration):
	  ○ Euphoria: 18.2% vs. 0; P = 0.96
	  ○ Dissociative symptoms: 4.5% vs. 0%; P = 0.36
	  ○ Dizziness: 18.2% vs. 5.6%; P = 0.23
	  ○ Drowsiness: 9.1% vs. 5.6%; P = 0.67
	  ○ Nausea: 4.5% vs. 11.1%; P = 0.43
	  ○ Blurred vision: 4.5% vs. 0%; P = 0.36
	  ○ Headache: 0% vs. 5.6%; P = 0.26

Study citation, study design, and patient model	Study findings
• IV ketamine-based anesthesia 0.75 mg/kg (n = 12) vs. IV propofol-based anesthesia 1 mg/kg (n = 12)	
Gamble et al. (2018)[27] RCT Patients with TRD (N = 24) who were referred for ECT. Definition for TRD was not provided.	No significant differences in rates of other AEs: • Mild blood pressure increase (20 to 50 mm Hg): 17% vs. 13%; P = 0.66 • Significant blood pressure increase (> 50 mm Hg): 22% vs. 24%; P = 0.58 • Mild blood pressure decrease (20 to 50 mm Hg): 10% vs. 18%; P = 0.18 • Nausea and vomiting: 25% vs. 16%; P = 0.18 • Headache: 33% vs. 35%; P = 0.87
IV ketamine-based anesthesia 1 to 2 mg/kg (n = 27) vs. IV methohexital-based anesthesia 1 to 2 mg/kg (n = 25)	
Carspecken et al. (2018)[28] RCT Veterans and service members with TRD (N = 52) who failed to respond to at least 2 antidepressants, and who were referred for ECT.	Effect of anesthesia on periprocedural clinical outcomes: • Mean (SD) number of seizures in index course per patient: 5.5 (2.7) vs. 5.8 (1.6); P = 0.61 • Mean (SD) seizure length, second: 71 (21) vs. 72 (22); P = 0.84 • Mean (SD) length of PACU stay, day: 66 (12.5) vs. 59 (13); P = 0.06 • Mean (SD) PACU agitation events post-ECT:12 (9) vs. 29 (18); P = 0.02 • Mean (SD) doses of propofol received post-ECT: 5 (4) vs. 30 (19); P < 0.0001 • Heart rate: No difference between groups (data shown in graph) • Blood pressure: No difference between groups (data shown in graph) • Two patients in the ketamine group experienced transient memorable dissociative symptoms.

AE = adverse event; ALS-18 = the short form of the Affective Lability Scale; CADSS = Clinician-Administered Dissociative State Scale; COWAT = Controlled Oral Word Association Test; ECT = electroconvulsive therapy; MoCA = Montreal Cognitive Assessment; PACU = post-anesthesia care unit; PANSS = Positive and Negative Syndrome Scale; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; TEAE = treatment emergent adverse events; TRD = treatment-resistant depression; YMRS = Young Mania Rating Scale.

Table 10: Summary of Recommendations in Included Guidelines

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
DHA, Moeller et al. (2021)[30]	
"Do not use intravenous ketamine/esketamine in patients with DTD, as benefits are uncertain and short-lived. The adverse effects are considerable, and the long-term effects, including the risk of abuse, unknown."[30] (p. 6) Evidence supporting this recommendation came from 4 RCTs published from 2016 to 2019.	Weak recommendation against IV ketamine/esketamine

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
CANMAT, Swainson et al. (2021)[31]	
"Efficacy • IV (IV) ketamine is efficacious in single infusion studies (level 1), but relapse occurs within 10 days for most patients. There is still limited evidence for efficacy for a course of 6 to 8 repeated infusions (level 3). • There is still insufficient evidence about strategies for relapse prevention following single-dose IV ketamine or a course of repeated infusions. Some protocols suggest tapering the frequency of infusion sessions for maintenance treatment (level 4). • There is only level 3 evidence for efficacy of oral ketamine and level 4 evidence for intranasal and sublingual formulations of racemic ketamine. Non-IV formulations should only be used by specialists with ketamine-prescribing expertise and affiliations with tertiary or specialized centers (level 4)."[31] (p. 116) Evidence for recommendation on the efficacy of IV ketamine in acute treatment of DTD came from 7 meta-analyses, 6 RCTs, and 4 open-label studies. Evidence for recommendation on the efficacy of other formulations of ketamine came from 1 systematic review, 7 RCTs and 1 retrospective case series.	
"Patient selection • IV ketamine is considered a third-line recommendation for adults with TRD. Treatment resistance should exceed minimum criteria for TRD, for example, failed trials of 2 or more first-line antidepressants from different classes and 1 or more adjunctive agents (level 4). • There is insufficient evidence to recommend IV ketamine for pediatric and geriatric populations (level 3). • Patients should be informed about the benefits and risks of ketamine as well as the limited evidence for relapse prevention following an acute course of treatment (level 3). • Relative contraindications for ketamine include patients with psychotic symptoms, poorly controlled hypertension, unstable medical conditions (e.g., cardiovascular or respiratory disease), substance use/dependence, and pregnancy/breastfeeding (level 3)."[31] (p. 116) Evidence for recommendation on who should receive ketamine came from previous CANMAT guidelines.	

CANMAT = The Canadian Network for Mood and Anxiety Treatments; DHA = Danish Health Authority; DTD = difficult-to-treat depression.

Appendix 5: References of Potential Interest

Studies Included in the Previous CADTH Report[17]

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