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SUMMARY WITH CRITICAL APPRAISAL

Intravenous Ketamine for Adults with Treatment-Resistant Depression or Post-Traumatic Stress Disorder: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines

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Abbreviations

AE	adverse events
CADSS	Clinician-Administered Dissociative States Scale
CGI-I	Clinical Global Impressions – Improvement
CGI-S	Clinical Global Impressions – Severity
C-SSRS	Columbia Suicide Severity Rating Scale
ECT	electroconvulsive therapy
HAMD or HDRS	Hamilton Depression Rating Scale
HAM-D-6	6-item Hamilton Depression Rating Scale
IV	intravenous
MADRS	Montgomery Asberg Depression Rating Scale
MDD	major depressive disorder
PTSD	post-traumatic stress disorder
QIDS-SR	Quick Inventory of Depressive Symptomatology–Self Report
RCT	randomized controlled trial
SDQ	Symptoms of Depression Questionnaire
SI	suicidal ideation
TRD	treatment-resistant depression
VAS	Visual Analogue Scale

Context and Policy Issues

Treatment-resistant depression (TRD) is a condition that affects patients with depression who have not achieved an adequate response to conventional antidepressant therapies.[1] TRD is commonly defined as major depressive disorder (MDD) with at least two prior treatment failures given adequate dose and duration.[2] For patients with bipolar disorder, TRD is defined as a minimum of one prior treatment failure.[2] Compared to non-treatment resistant MDD, TRD is associated with reduced quality of life, social and occupational impairment, comorbidities, and higher likelihood of prior suicide attempts.[1] Patients with TRD are twice as likely to be hospitalized than patients with non-treatment resistant MDD; and increased hospitalization is associated with substantially increased resource utilization.[1,2] Risk factors for TRD include old age, divorced or widowed marital status, and concomitant psychiatric disorders such as anxiety and personality disorders.[2]

Post-traumatic stress disorder (PTSD) occurs as a response to a traumatic event or extreme stressor (such as military combat, sexual assault, torture, being kidnapped, severe car accidents, and natural disasters).[3] Patients experience symptoms that may include emotional impairment due to depression, anxiety, flashbacks, insomnia, feelings of guilt of having survived, and difficulty concentrating.[3] In 2008, the Canadian lifetime prevalence rate of PTSD was estimated to be 9.2%.[4]

Antidepressants including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are commonly prescribed agents for depression, while electroconvulsive therapy (ECT) is the gold standard and a late-line therapy for TRD.[5,6]

Ketamine is a N-methyl-d-aspartate (NMDA) receptor antagonist that leads to increased synaptic plasticity and may elicit a rapid antidepressant response in individuals with depression.[7]In Canada, a number of formulations of ketamine are approved for general anesthesia.[8] However, antidepressant effects of ketamine have been observed in animal models of depression and in human studies of depression, and ketamine has showed potential as a novel, rapid-acting therapeutic option for patients with TRD and PTSD.[9,10] The purpose of this report is to update the previous 2017 CADTH report[11] and to examine

the clinical effectiveness, cost-effectiveness and evidence-based guidelines on the use of intravenous ketamine for adults with TRD or PTSD.

Research Questions

1. What is the clinical effectiveness of intravenous ketamine for adults with treatment-resistant depression or post-traumatic stress disorder?
2. What is cost-effectiveness of intravenous ketamine for adults with treatment-resistant depression or post-traumatic stress disorder?
3. What are the evidence-based guidelines regarding the use and administration of intravenous ketamine for adults with treatment-resistant depression or post-traumatic stress disorder?

Key Findings

Three randomized controlled trials reported that intravenous ketamine was significantly more effective than placebo or midazolam for the treatment of adults with treatment-resistant depression. One randomized controlled trial reported no significant difference between intravenous ketamine (six repeated doses of 0.5mg/kg) and placebo. One evidence-based guideline reported a strong recommendation against treating post-traumatic stress disorder with ketamine monotherapy. No relevant evidence regarding the clinical effectiveness of intravenous ketamine for the treatment of post-traumatic stress disorder or the cost-effectiveness of intravenous ketamine for treatment-resistant depression or post-traumatic stress disorder was identified.

Methods

Literature Search Methods

This report made use of a literature search strategy developed for a previous CADTH report.[11] For the current report, a limited literature search was conducted by an information specialist on key resources including Medline and PsycINFO via OVID, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were ketamine and depression or PTSD. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, any types of clinical trials or observational studies, economic studies, and guidelines. Where possible, retrieval was limited to the human population. The search was limited to English-language documents published between January 1, 2014 and September 24, 2019 for economic studies, and documents published between January 1, 2016 and September 24, 2019 for all other study types.

Selection Criteria and Methods

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

Table 1: Selection Criteria

Population	Q1-3: Adults with treatment-resistant depression or post-traumatic stress disorder in community, primary care, hospital (inpatient and outpatient) and academic clinical practice settings
Intervention	Q1-3: Intravenous Ketamine
Comparator	Q1-2: Antidepressants (e.g., SSRIs and SNRIs), antipsychotics, electroconvulsive therapy, placebo Q3: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., symptoms [e.g., mood, suicidal ideation] admission rate, length of stay, adverse reactions, injury) Q2: Cost-effectiveness Q3: Evidence-based guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, economic evaluations, guidelines

SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Appendix 1: Selection of Included Studies, or were duplicate publications. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included randomized controlled trials (RCTs) were critically appraised using the Downs and Black Checklist,[12] and guidelines were assessed with the AGREE II instrument.[13] Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 443 citations were identified in the literature search. Following screening of titles and abstracts, 430 citations were excluded and 13 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full-text review. Of these potentially relevant articles, seven publications were excluded for various reasons, and seven publications met the inclusion criteria and were included in this report. These comprised six RCTs and one evidence-based guideline. Appendix 1 presents the PRISMA[14] flowchart of the study selection.

Summary of Study Characteristics

A summary of the characteristics of included publications is presented in Appendix 2.

Six publications[15-20] reporting on four studies provided information on the clinical effectiveness and safety of intravenous ketamine for TRD. No relevant literature was identified regarding the clinical effectiveness of intravenous ketamine for PTSD or the cost-effectiveness of intravenous ketamine for TRD or PTSD. One evidence-based guideline[21] was identified regarding the use of intravenous ketamine for PTSD.

Study Design

Four relevant primary studies, in six publications, were identified regarding the clinical effectiveness of intravenous ketamine for TRD; two were double-blinded placebo controlled RCTs,[17,18] one was a double-blind crossover RCT,[19] and three publications reported on a single double-blinded placebo controlled RCT.[15,16,20] Sample sizes ranged from 26 patients[18] to 99 patients.[17] The primary studies[15-20] were published in 2017,[20] 2018,[15,17] and 2019.[16,18,19]

The evidence-based guideline was developed by the United States (US) Department of Veterans Affairs and the Department of Defense (VA/DoD) and was published in 2017.[21] The guideline was informed by a systematic review done by the guideline authors; the systematic review search timeframe was from 2009 to 2017 and systematic reviews, RCTs and non-randomized studies were eligible for inclusion.[21] The quality of evidence (rated as very low, low, moderate, or high) and strength of recommendations (rated as weak or strong) were determined by a modified Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach and US Preventive Services Task Force (USPSTF) methodology.[21] The recommendations were based on consensus of the panel.[18,22]

Country of Origin

The primary studies were conducted in Taiwan,[15,16,20] US,[17,18] or Canada.[19] The evidence-based guideline[21] was developed by the US VA/DoD.

Patient Population

The primary studies[15-20] included patients with TRD in hospital settings. The evidence-based guideline[21] was developed for the target population of adult patients with PTSD and acute stress disorder and with the intended guideline users being all health care professionals who treat PTSD and acute stress disorder.

Interventions and Comparators

In the RCTs,[15-20] the intervention was single[15-17,20] or multiple[18,19] dose of ketamine administered intravenously (at doses of 0.1, 0.2, 0.5, or 1.0 mg/kg)[15-20] compared with placebo (saline; four studies)[15,16,18,20] or active placebo midazolam (two studies).[17,19]Two RCTs allowed for concomitant treatments with other antidepressants.[17,18]

The evidence-based guideline[21] provided recommendations on the use of ketamine as a treatment of PTSD. The guideline considered management, including diagnosis, treatment (such as SNRI, SSRI, and ketamine), and follow-up measures of PTSD.[21]

Outcomes

The clinical outcomes in the three publications that reported on a single RCT were depression severity as measured with the Hamilton Depression Rating Scale (HAMD or HRDS) and Montgomery Asberg Depression Rating Scale (MADRS), cognitive function measured by working memory and responses in the go/no-go tasks, depressive symptoms, response rate, blood pressure, and adverse events (AEs).[15,16,20] The outcomes in another RCT were antidepressant efficacy measured by HDRS score, anti-suicidal efficacy measured by the Columbia Suicide Severity Rating Scale – suicidal ideation (C-SSRS SI), and dissociative symptom adverse events measured by the Clinician-Administered Dissociative States Scale (CADSS).[18] The outcomes in another RCT were depression

severity measured with the MADRS and the Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR), adverse events, and dissociative symptoms measured by CADSS.[19]

The outcomes of interest in the evidence-based guideline were the efficacy and tolerability of ketamine.[21]

Summary of Critical Appraisal

The primary studies were of moderate quality, assessed with Downs and Black.[15-20] All six primary studies described the objectives, interventions, main outcomes, the characteristics of the patients, main findings and used appropriate statistical tests and valid and reliable outcome measures.[15-20] All primary studies were RCTs, with patients in different study groups within the studies recruited from the same population , and randomized into intervention groups.[15-20]The patients were blinded to the interventions they received; the staff measuring the main outcomes were also blinded.[15-20] However, none of the primary studies described whether they had adequate power to detect clinically-important effects.[15-20]In three RCTs, it is unclear if the trial center settings were representative of the care setting of interest.[15-18,20]

The evidence-based guideline[21] was of moderate to high quality, assessed with AGREE II.[13] The guideline had the following strengths: clearly described objectives, health questions, and target populations and users; it used systematic search methods to identify relevant evidence; applied evidence selection criteria; appraised the quality of evidence; described the methods for formulating recommendations; considered benefits, harms, and quality of evidence; was reviewed externally prior to publication; and provided unambiguous recommendations. [6] However, the guideline development group did not seek target population input, consider costs, describe a procedure for updating the guideline, provide implementation tools or monitoring criteria, or disclose potential conflicts of interest despite having reported processes in place to disclose the conflicts of interest.[21] It was not clear that the guideline was developed by individuals from all relevant professional groups.[21]

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical Effectiveness of Intravenous Ketamine for TRD

Efficacy

In the included RCT that was reported on by three publications, the anti-suicidal effect (measured by HAMD Item 3 [suicide] and MADRS item 10 [suicidal thoughts]) was significantly greater in both the 0.5 mg/kg and 0.2 mg/kg intravenous ketamine groups (single dose) compared with placebo groups.[16] In the same study, there was no significant difference in cognitive function (measured by working memory and go/no-go tasks) between ketamine (single dose) and placebo groups.[15] Depression severity (measured by HAMD total score) was significantly lower and the response rate was significantly higher in the 0.5 mg/kg intravenous ketamine group versus the placebo group, however depression severity and response rate were not significantly different between the 0.2 mg/kg intravenous ketamine and placebo groups.[20]

The second RCT reported that six repeated, non-escalating intravenous doses of 0.5 mg/kg ketamine was not significantly different than placebo in patients for antidepressant efficacy (measured by HDRS total score) or for antisuicidal efficacy (measured by C-SSRS SI score and C-SSRS SI intensity).[18]

The crossover RCT reported that the decrease in depression severity (measured by MADRS total score)was statistically significantly greater in the ketamine group than the midazolam group.[19] At 24-hours post-infusion the anti-depressant response rate was found to be 27% in the ketamine group and 0% in the midazolam group; the remission rate was reported to be 5% in the ketamine group versus 0% in the midazolam group (not compared statistically). It was also reported that repeated once-weekly ketamine infusions had sustained antidepressant response and remission rate and maintained the reductions in depressive symptoms measured by MADRS score.[19]

In the fourth RCT, depression severity (measured by HAM-D-6) was significantly lower in the 0.5 mg/kg and 1.0 mg/kg IV ketamine groups compared to the placebo group.[17] Using different measures, depression severity was also significantly lower in the 0.5 mg/kg intravenous ketamine group versus placebo on day 1 (measured by SDQ, PAS, MADRS, CGI-S) and day 3 (measured by MADRS) postinfusion.[17] For the lower ketamine doses (0.1 mg/kg and 0.2 mg/kg), there was no significant difference between the ketamine groups and the placebo group in depression severity (measured by HAM-D-6). [17]

Safety

In the RCT that was reported in three publications, cognitive function was not significantly different between patients with TRD treated with a single intravenous dose of ketamine (0.5 mg/kg or 0.2 mg/kg) or placebo.[15] The adverse events reported across all groups (ketamine or placebo) in this study were nausea in 8.5% of the patients and transient behavioural effect in 1 patient.[20] Another study reported significantly higher rates of adverse events (including headache, nausea, vomiting, depression, and suicide ideation) in the ketamine group than the midazolam control group.[17]

The safety outcome “dissociative symptoms” (measured by CADSS) was reported by two RCTs.[17,18] In one RCT, the CADSS score was significantly different between the ketamine and placebo groups; the 0.5mg/kg ketamine group had significantly higher rates of dissociative symptoms than the placebo group.[18] In the other RCT, the CADSS score was significantly greater in the ketamine 0.5 mg/kg and 1 mg/kg groups than midazolam group, but was not significantly different between 0.1 mg/kg or 0.2 mg/kg ketamine groups and the midazolam group.[17]

Clinical Effectiveness of Intravenous Ketamine for PTSD

No relevant evidence regarding the clinical effectiveness intravenous ketamine for PTSD was identified; therefore, no summary can be provided.

Cost-Effectiveness of Intravenous Ketamine for TRD or PTSD

No relevant evidence regarding the cost-effectiveness intravenous ketamine for TRD or PTSD was identified; therefore, no summary can be provided.

Evidence-Based Guideline of Intravenous Ketamine for TRD or PTSD

The US VA/DoD guideline strongly recommends against the use of intravenous ketamine as monotherapy for PTSD.[21] The quality of evidence for this recommendation was reported as very low.[21]

No relevant evidence-based guideline regarding ketamine for TRD was identified; therefore, no summary can be provided.

Limitations

Sample sizes ranged from 26 to 99 patients across trials, and the sample may not be representative of patients with TRD in the real world.[15-20] The RCTs had follow up periods of 14 days to 3 months.[15-20] Two out of the four RCTs investigated single-dose infusion instead of a repeated intravenous infusions regimen.[15-17,20] Further efficacy and safety data on longer follow-up (for example, 1 year follow-up) and repeated maintenance dosing are needed in future studies, due to the treatment-resistant nature of the disease. Additionally, of the four primary studies, one was conducted in Taiwan with a Chinese patient population[15,16,20] and two were conducted in US hospitals with less heterogenous population ethnicity than in Canada.[17,18] The guideline was developed for US health care professionals caring for patients with PTSD, and the generalizability to the Canadian health care context is unknown.[21]

Conclusions and Implications for Decision or Policy Making

Three randomized controlled trials reported that intravenous ketamine was significantly more effective than placebo and midazolam for the treatment of adults with treatment-resistant depression.[15-17,19,20] One randomized controlled trial reported no significant difference between intravenous ketamine (six repeated doses of 0.5 mg/kg) and placebo.[18] One evidence-based guideline reported a strong recommendation based on low quality evidence against treating PTSD with ketamine monotherapy.[21] No relevant evidence regarding the clinical effectiveness of intravenous ketamine for PTSD or the cost-effectiveness of intravenous ketamine for TRD or PTSD was identified.

The 2017 CADTH report on this topic identified three systematic reviews, five primary studies, and two evidence-based guidelines.[11] Overall, ketamine was reported to be effective at reducing depression severity within minutes or hours for patients with TRD, and effective at reducing PTSD severity in patients with PTSD.[11] Both guidelines included in the 2017 report recommended restricting the off-label use of ketamine for TRD to research settings.[11] The current report builds on these previous findings with newer evidence on repeated dosing of ketamine 0.5mg/kg, while the previous report included mostly studies with single-dose infusion of ketamine.[11,18] The included guideline in this report recommended against the use of ketamine in patients with PTSD.[21] Additional safety evidence was provided in this current report that aligns with the common and severe adverse events reported in the 2017 report.[11,15,17,18,20]

Further primary clinical studies, research guidelines and recommendations on intravenous ketamine for adults with TRD or PTSD, may help to reduce uncertainty in this area. The majority of the publications considered in this CADTH review were not conducted in Canada.[15-18,20,21] The health care resource requirements, training requirements and budgetary implications may differ between countries. Therefore, the applicability of these findings to the Canadian healthcare setting may be limited.

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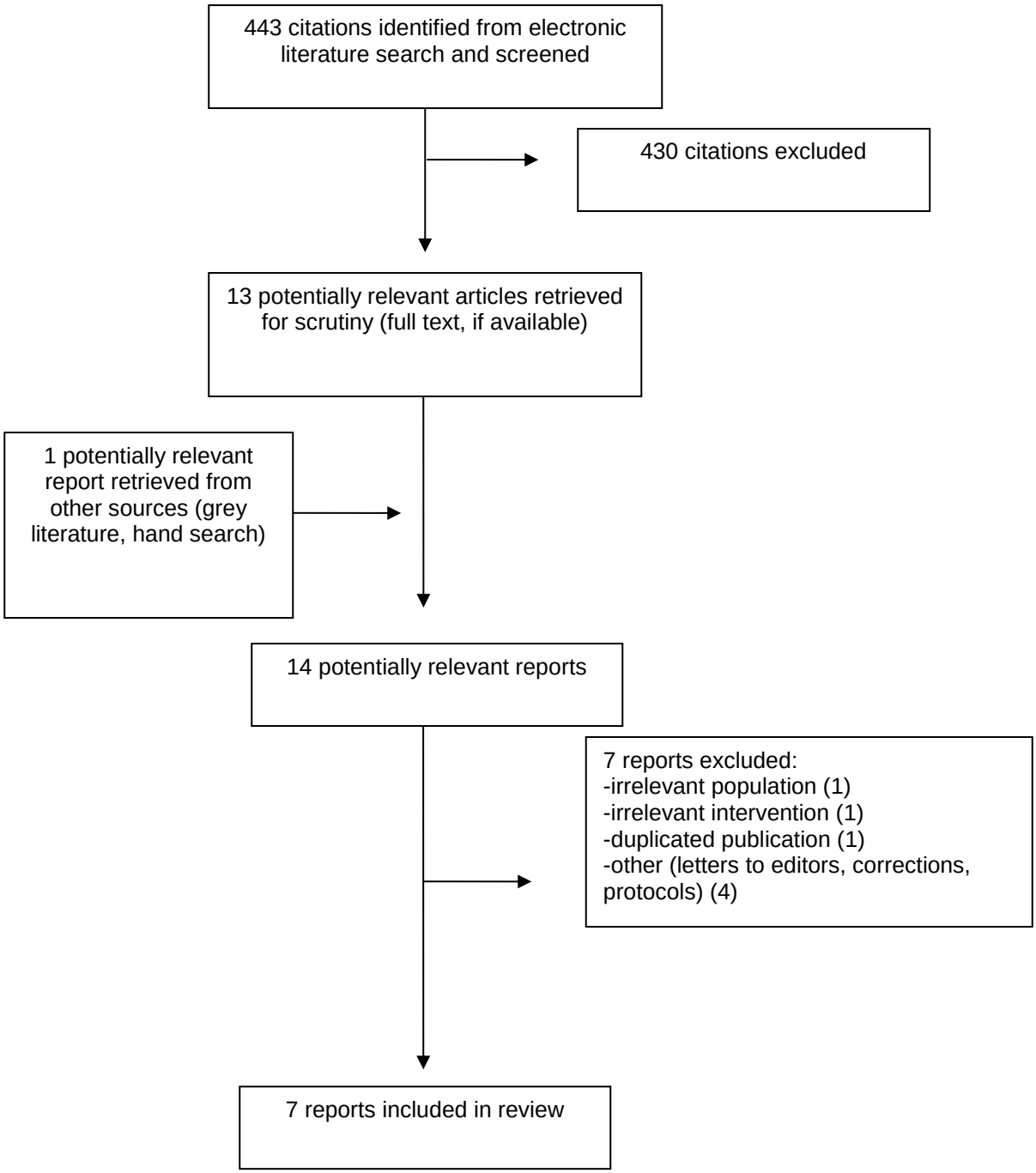
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Randomized Controlled Trials

First Author, Publication Year, Region	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Chen, 2019[16,a] **Taiwan**	Double-blind, placebo-controlled RCT	71 adults age 21-64 years old with TRD • ketamine 0.5 mg/kg: n= 24 • ketamine 0.2 mg/kg: n = 23 • placebo: normal saline: n = 24 Mean age (years ± SD): • ketamine 0.5 mg/kg (48.46 ± 11.01) • ketamine 0.2 mg/kg (44.96 ± 12.31) • placebo: normal saline (48.63 ± 8.12)	A single IV dose of: • ketamine 0.5 mg/kg • ketamine 0.2 mg/kg • placebo: normal saline	Item 3 (suicide) of the HAMD, item 10 (suicidal thoughts) of the MADRS 14-day follow-up
Chen, 2018[15,a] **Taiwan**				Cognitive function measured by working memory and responses in the go/no-go tasks, HDRS, depressive symptoms 14-day follow-up
Su, 2017[20,a] **Taiwan**				Dose-related efficacy measured by HAMD, response rate, BDNF blood pressure, AE 14-day follow-up
Ionescu, 2019[18] **United States**	Double-blind, placebo-controlled RCT	26 adults age 18-65 years old with TRD • ketamine 0.5 mg/kg: n = 13 • saline placebo: n = 13 Mean age (years ± SD): • total sample (45.4 ± 12.4) • ketamine (45.5 ± 13.6) • placebo (45.4 ± 11.7)	6 IV doses over 3 weeks (2 infusions per week) • ketamine 0.5 mg/kg • saline placebo Concomitant with stable antidepressant therapy	Antidepressant efficacy measured by HDRS score, anti-suicidal efficacy measured by C-SSRS SI, CADSS 3-month follow-up
Phillips, 2019[19] **Canada**	Double-blind crossover comparison RCT	43 adults age 18-65 years old with TRD • Phase 1: n= 43 • Phase 2: n = 41 • Phase 3: n = 23 Mean age (years ± SD): 41.7 ± 12.3	Ketamine IV 0.5 mg/kg, diluted in 0.9% saline, infused over 40 minutes Midazolam 30 mg/kg, to obtain an approximate dose of 2 mg, diluted in saline Phase 1: patients randomized to single dose of ketamine or midazolam, then crossover to receive midazolam/ketamine after ≥7 days	Efficacy measured by MADRS, QIDS-SR; safety measured by AE, CADSS Length of follow up: Phase 1: at least 7 days Phase 2 and 3: 3 days after final infusion

Table 2: Characteristics of Included Randomized Controlled Trials

First Author, Publication Year, Region	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
			after participants return to 80% of baseline MADRS score (relapse) Phase 2 (after participants return to 80% of baseline MADRS score): All participants receive 6 open-label doses of ketamine, 3 times weekly over 2 weeks Phase 3 (for participants that had an antidepressant response after Phase 2): ketamine once per week for 4 weeks	
Fava, 2018[17] **United States**	Double-blind, placebo-controlled RCT	99 adults age 18–70 years old with a diagnosis of MDD with TRD • 0.1 mg/kg ketamine: n = 18 • 0.2 mg/kg ketamine: n = 20 • 0.5 mg/kg ketamine: n = 22 • 1.0 mg/kg ketamine: n= 20 • 0.045 mg/kg midazolam: n = 19 Mean age (years ± SD): • 0.1 mg/kg ketamine (43.1 ± 11.9) • 0.2 mg/kg ketamine (45.5 ± 14.6) • 0.5 mg/kg ketamine (48.6 ± 12.9) • 1.0 mg/kg ketamine(47.4 ± 10.1) • Midazolam (45.6 ± 13.8)	Single-dose IV infusion of: • 0.1 mg/kg ketamine • 0.2 mg/kg ketamine • 0.5 mg/kg ketamine • 1.0 mg/kg ketamine • 0.045 mg/kg midazolam n = 4 mistakenly received lower doses than planned due to calculation errors – analyzed in originally randomized group Concomitant with stable antidepressant therapy	Efficacy measured by HAM-D-, MADRS, self-rated SDQ, self-rated PAS, self-rated SHAPS, CGI-S, CGI-I, VAS, C-SSRS, CADSS Safety measured by vital signs including blood pressure and heart rate, AE 30-day follow-up

CADSS = Clinician-Administered Dissociative States Scale; CGI-I = Clinical Global Impressions – Improvement; CGI-S = Clinical Global Impressions – Severity; C-SSRS = Columbia Suicide Severity Rating Scale; HAMD or HDRS = Hamilton Depression Rating Scale; HAM-D-6 = 6-item Hamilton Depression Rating Scale; IV = intravenous; MADRS = Montgomery Asberg Depression Rating Scale; MDD = major depressive disorder; QIDS-SR = Quick Inventory of Depressive Symptomatology–Self Report; RCT = randomized controlled trial; SDQ = Symptoms of Depression Questionnaire; SI = suicidal ideation; VAS = Visual Analogue Scale.

[a] Reported results from the same RCT.

Table 3: Characteristics of Included Guidelines

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users/ Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence collection, Selection and Synthesis	Evidence Quality and Strength	Recommendations Development and Evaluation	Guideline Validation
VA/DoD, 2017[21]* US *An update to a 2010 guideline	Intended users: all health care professionals who treat PTSD and ASD Target population: adult patients with PTSD and ASD	Management, including diagnosis, treatment (including pharmacological agents, trauma-focused psychotherapies, non-pharmacologic biological treatments, and complementary and integrative treatments), and follow-up, of PTSD and ASD	Global PTSD severity, AEs, retention/dropout rate, loss of diagnosis/remission, self-reported PTSD, symptoms, comorbid symptoms. QoL, functional status, patient satisfaction	Systematic literature searches for SRs, MAs, and primary studies in English Syntheses based on evidence	Rated using a modified GRADE and USPSTF methodology Quality of evidence: • Very low • Low • Moderate • No data Strength of recommendations: • Weak • Strong	Recommendations were developed by a panel of multidisciplinary experts, who considered evidence from the literature and expert opinions.	A draft guideline was posted on a wiki website and subject to 14 business days of peer-review.

ASD = acute stress disorder; PTSD = posttraumatic stress disorder; QoL = quality of life; VA/DOD = Department of Veterans Affairs and the Department of Defense.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Clinical Studies using Downs and Black [12]

Strengths	Limitations
Chen, 2019[16,a] Chen, 2018[15,a] Su, 2017[20,a]	
• The objective of the study, the characteristics of the patients included, the interventions of interest, main outcomes to be measured, and the main findings of the study were described clearly • Actual probability values were reported. • Patients were blinded to the intervention they received. The staff measuring the main outcomes were blinded. • The statistical tests used to assess the main outcomes were appropriate. • Adherence with the interventions was reliable with single-dose IV infusion. • The main outcome measures were accurate (i.e., valid and reliable). • The patients in different intervention groups were recruited from the same population over the same period. • The patients were randomized to intervention groups. • Intervention assignment was concealed from both patients and staff until recruitment was complete and irrevocable.	• It is unclear if the patients asked to participate in the study were recruited representative of the entire population of interest. • It is unclear if the patients included in the study were representative of the real world population of interest. • Losses of patients to follow-up were not considered. • Although the study reported statistical significance for most findings, it was unclear if the between-group differences were clinically significant.
Ionescu, 2019[18]	
• The objective of the study, the characteristics of the patients included, the interventions of interest, potential confounders, main outcomes to be measured, and the main findings of the study were described clearly • Estimates of the random variability in the data for the main outcomes were provided. • Actual probability values were reported. • An attempt was made to blind the patients to the intervention they received and to blind the staff measuring the main outcomes. • The statistical tests used to assess the main outcomes were appropriate. • Adherence with the interventions was reliable with single-dose IV infusion • The main outcome measures were accurate (i.e., valid and reliable). • The patients in different intervention groups were recruited from the same population over the same period. • The patients were randomized to intervention groups. • Intervention assignment was concealed from both patients and staff until recruitment was complete and irrevocable.	• The characteristics of the patients lost to follow-up were not described. • It is unclear if the patients asked to participate in the study were recruited representative of the real world population of interest. • It is unclear if the patients included in the study were representative of the entire population of interest. • Because the distributions of potential confounders in each intervention group of the patients were not described, it is unclear if there was adequate adjustment for confounding in the analysis for the main findings. • Although the study reported statistical significance for most findings, it was unclear if the between-group differences were clinically significant.

Table 4: Strengths and Limitations of Clinical Studies using Downs and Black [12]

Strengths	Limitations
Phillips, 2019[19]	
• The objective of the study, the characteristics of the patients included, the interventions of interest, potential confounders, main outcomes to be measured, and the main findings of the study were described clearly • Estimates of the random variability in the data for the main outcomes were provided. • Actual probability values were reported. • An attempt was made to blind the patients to the intervention they received and to blind the staff measuring the main outcomes. • The statistical tests used to assess the main outcomes were appropriate. • The main outcome measures were accurate (i.e., valid and reliable). • The patients in different intervention groups were recruited from the same population over the same period. • The patients were randomized to intervention groups. • Intervention assignment was concealed from both patients and staff until recruitment was complete and irrevocable.	• It is unclear if the patients asked to participate in the study were recruited representative of the entire population of interest. • It is unclear if the patients included in the study were representative of the real world population of interest. • Because the distributions of potential confounders in each intervention group of the patients were not described, it is unclear if there was adequate adjustment for confounding in the analysis for the main findings. • Although the study reported statistical significance for most findings, it was unclear if the between-group differences were clinically significant.
Fava, 2018[17]	
• The objective of the study, the characteristics of the patients included, the interventions of interest, main outcomes to be measured, and the main findings of the study were described clearly • Estimates of the random variability in the data for the main outcomes were provided. • Actual probability values were reported. • An attempt was made to blind the patients to the intervention they received and to blind the staff measuring the main outcomes. • The statistical tests used to assess the main outcomes were appropriate. • Adherence with the interventions was reliable with single-dose IV infusion • The main outcome measures were accurate (i.e., valid and reliable). • The patients in different intervention groups were recruited from the same population over the same period. • The patients were randomized to intervention groups. • Intervention assignment was concealed from both patients and staff until recruitment was complete and irrevocable.	• The characteristics of the patients lost to follow-up were not described. • It is unclear if the patients asked to participate in the study were recruited representative of the entire population of interest. • It is unclear if the patients included in the study were representative of the real world population of interest. • Because the distributions of potential confounders in each intervention group of the patients were not described, it is unclear if there was adequate adjustment for confounding in the analysis for the main findings. • Although the study reported statistical significance for most findings, it was unclear if the between-group differences were clinically significant.

a. Reported results from the same RCT

Table 5: Strengths and Limitations of Guidelines using AGREE II[13]

Item	Guideline
	VA/DoD, 2017[21]
Domain 1: Scope and Purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes
Domain 2: Stakeholder Involvement	
4. The guideline development group includes individuals from all relevant professional groups.	Not reported
5. The views and preferences of the target population (patients, public, etc.) have been sought.	No
6. The target users of the guideline are clearly defined.	Yes
Domain 3: Rigour of Development	
7. Systematic methods were used to search for evidence.	Yes
8. The criteria for selecting the evidence are clearly described.	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes
10. The methods for formulating the recommendations are clearly described.	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Yes
14. A procedure for updating the guideline is provided.	No
Domain 4: Clarity of Presentation	
15. The recommendations are specific and unambiguous.	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes
17. Key recommendations are easily identifiable.	Yes
Domain 5: Applicability	
18. The guideline describes facilitators and barriers to its application.	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	No
20. The potential resource implications of applying the recommendations have been considered.	No
21. The guideline presents monitoring and/or auditing criteria.	No

Table 5: Strengths and Limitations of Guidelines using AGREE II[13]

Item	Guideline
	VA/DoD, 2017[21]
Domain 6: Editorial Independence	
22. The views of the funding body have not influenced the content of the guideline.	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Disclosure process described but not disclosed in the report

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings of Included Primary Clinical Studies

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Chen, 2019[16,a]</td></tr>
<tr><td>
Antisuicidal Effect:

HAMD Item 3 (suicide):
0.5 mg/kg ketamine group showed significantly lower score than the 0.2 mg/kg ketamine and placebo group[b]
0.2 mg/kg ketamine group lower than placebo group at all post-infusion time points[b]
Group effect: P = 0.007
Time effect: P = 0.004
Group*Time effect: P = 0.509

MADRS item 10 (suicidal thoughts):
0.5 mg/kg ketamine group showed lower score than the 0.2 mg/kg ketamine group at most follow-up time points, except at Day 3 post infusion, the 0.5 mg/kg ketamine group appeared to have similar value as the 0.2 mg/kg ketamine group[b]
0.2 mg/kg ketamine group lower than placebo group at all time points[b]
Group effect: P = 0.002
Time effect: P = 0.063
Group*Time effect: P = 0.020

Subgroup analysis:
Patients with lower baseline suicidal symptom scores (HAMD item 3 ≥ 1 [n=67] or MADRS item 10 ≥ 2 [n=58]):
0.5 mg/kg ketamine group showed lower scores than the 0.2 mg/kg ketamine and placebo group[b]
0.2 mg/kg ketamine group had lower scores than the placebo group at all time points[b]
<table>
<tr><td></td><td>HAMD item 3</td><td>MADRS item 10</td></tr>
<tr><td>Group effect</td><td>P = 0.005</td><td>P < 0.001</td></tr>
<tr><td>Time effect</td><td>P = 0.025</td><td>P = 0.227</td></tr>
<tr><td>Group*Time effect</td><td>P = 0.026</td><td>P < 0.001</td></tr>
</table>
Patients with higher baseline suicidal symptom scores (HAMD item 3 ≥ 2 [n=47] or MADRS item 10 ≥ 4 [n=24]):
0.5 mg/kg ketamine group showed lower HAMD item 3 and MADRS item 10 scores than the 0.2 mg/kg ketamine group at most follow-up time points, except at Day 7 post infusion the 0.5 mg/kg ketamine group appeared to have similar HAMD item 3 value as the 0.2 mg/kg ketamine group[b]
<table>
<tr><td></td><td>HAMD item 3</td><td>MADRS item 10</td></tr>
<tr><td>Group effect</td><td>P = 0.005</td><td>P < 0.001</td></tr>
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<tr><td>Group*Time effect</td><td>P = 0.026</td><td>P < 0.001</td></tr>
</table>
</td><td>
"The study findings supported our study hypotheses that low-dose (0.5 and 0.2 mg/kg) ketamine infusion exhibited a superior antisuicidal effect compared with the placebo" (p.165)

"In conclusion, low-dose ketamine infusion reduced the suicidal ideation significantly among Taiwanese patients with TRD. For patients who had higher levels suicidal ideation or carried Met/Met of BDNF, 0.5 mg/kg ketamine is the optimal dose, but for those with any Val allele, 0.2 mg/kg ketamine can also be considered. In contrast to only 7 days of antisuicidal effect of a single dose of ketamine infusion in Caucasian patients, the duration of antisuicidal effect of ketamine may persist for up to 14 days." (p. 167)
</td></tr>
<tr><td colspan="2">Chen, 2018[15,a]</td></tr>
<tr><td>
Cognitive function with GEE model analysis:
No significant group effect, time effect, or no group × time interaction effect for cognitive function at baseline, Day 3, and Day 14 among the 0.2 mg/kg, 0.5 kg/mg ketamine and placebo groups
</td><td>
"In conclusion, our study results indicated that a single subanesthetic dose of ketamine infusion did not impair the cognitive function of patients with TRD." (p. 5)
</td></tr>
</table>

Table 6: Summary of Findings of Included Primary Clinical Studies

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td>

Working memory:

	Correction	Error	Omission	Reaction time
Group effect	*P* = 0.409	*P* = 0.768	*P* = 0.409	*P* = 0.456
Time effect	*P* = 0.275	*P* = 0.505	*P* = 0.275	*P* = 0.589
Group*Time effect	*P* = 0.287	*P* = 0.762	*P* = 0.287	*P* = 0.387

Go/no-go task:

	Correction	Error	Omission	Reaction time
Group effect	*P* = 0.259	*P* = 0.461	*P* = 0.258	*P* = 0.490
Time effect	*P* = 0.062	*P* = 0.014	*P* = 0.062	*P* = 0.367
Group*Time effect	*P* = 0.416	*P* = 0.075	*P* = 0.416	*P* = 0.746

</td><td></td></tr>
<tr><td colspan="2">Su, 2017[20,a]</td></tr>
<tr><td>

Depression severity
Overall Estimated least square means for HAMD total scores (Tukey's-adjusted p value):

- 0.5 mg/kg ketamine group statistically significantly lower than placebo (*P* = 0.008);
- 0.2mg/kg ketamine group not statistically significantly different than placebo (*P* = 0.20);
- 0.5mg /kg ketamine group not statistically significantly different from the 0.2 mg/kg ketamine group (*P* = 0.37)

Patients with low baseline depression severity (baseline HAMD scores 1 SD above the mean baseline HAMD score of 18):
Estimated least square means for HAMD total scores (Tukey's-adjusted *P* value):

- no significant difference between 3 groups (*P* > 0.15)

Patients with "average" baseline depression severity (baseline HAMD scores 1 SD above the mean baseline HAMD score of 23):
Estimated least square means for HAMD total scores (Tukey's-adjusted p value):

- Significantly lower in 0.5 mg/kg ketamine group compared with placebo group (*P* = 0.01)
- 0.2 mg/kg ketamine group comparison not reported, *P* value not reported

Patients with high baseline depression severity (baseline HAMD scores 1 SD above the mean baseline HAMD score of 28):
Estimated least square means for HAMD total scores (Tukey's-adjusted p value):

- Significantly lower in the 0.5 mg/kg ketamine group versus in the 0.2 mg/kg ketamine group (*P* = 0.05).
- 0.2 mg/kg ketamine group not statistically significantly different from placebo group (*P* > 0.15)

Response Rate
Responders, n (%):

</td><td>"In conclusion, the current study provides the first evidence that ketamine has dose-related antidepressant effects that are moderated by baseline depression severity. It also supports the antidepressant efficacy of this drug in a Chinese population." (p. 2491)</td></tr>
</table>

Table 6: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
• 0.5 mg/kg ketamine group 11(45.8%); • 0.2 mg/kg ketamine group 9 (39.1%); • placebo group 3 (12.5%) Response rates significantly different across the 3 groups (Fisher's exact test p-value =0.03) and significant linear trend test for the dose effect (*P* = 0.01). Responder rate (post hoc test p value) • Greater in the 0.5 mg/kg ketamine group than placebo group (p =0.01) • Greater in the 0.2 mg/kg ketamine group than placebo group (*P* = 0.05) No statistically significant difference between 2 ketamine groups (p= 0.77) **Hemodynamic Effects** Systolic blood pressure: increased significantly with increasing doses of ketamine (*P* = 0.004) Diastolic blood pressure (DBP): increased significantly with increasing doses of ketamine (*P* = 0.01) Heart rate: increased in a dose-related manner (*P* = 0.005**)** **Adverse Events, n (%)** • Nausea: 6 (8.5%) • Ketamine infusion stopped due to transient behavioral effects that dissipated without intervention**:** 1 (1.4%) • No significant dose-related psychosis	
Ionescu, 2019[18]	
Efficacy: **Antidepressant efficacy:** HDRS total scores: no statistically significant differences between the ketamine group and placebo group across the 6 infusions (group x time interaction) *P* = 0.47 After 6 infusions: **Mean HDRS Score (score ± SD):** • **Ketamine group**: (**20.2** ± 11.1) • Placebo: (20 **± 10.7)** Antidepressant response, n (%): • Ketamine group: **3** (25%) • Placebo: **4 (33%)** Remissions, n (%): • Ketamine group: 2 (17%) • Placebo: 1 (8%) • Difference between ketamine group and placebo group p > 0.05 At 3-month follow-up after final infusion: Antidepressant response, n (%): • Ketamine group: 2 (22%) • Placebo 3 (27%) Remissions, n (%): • Ketamine group: 2 (22%) • Placebo: 2 (18%) • Difference between ketamine group and placebo group *P* > 0.05	"Repeated, non-escalating doses of ketamine did not outperform placebo in this double-blind, placebo-controlled study of patients with severe TRD and current, chronic suicidal ideation. This result may support our previously published open-label data that, in this severely and chronically ill outpatient population, the commonly used dose of 0.5 mg/kg is not sufficient." (p. 516)

Table 6: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Antisuicidal efficacy: **C-SSRS SI score:** no significant group x time interaction between ketamine group and placebo groups (p=0.32) **C-SSRS SI intensity**: no significant group x time interaction between ketamine group and placebo groups (p=0.23) Absence of SI (C-SSRS SI score=0) after 6 infusions: • Ketamine group: 2 (17%) • Placebo: 1 (8%) • Difference between ketamine group and placebo group p > 0.05 Absence of SI (C-SSRS SI score=0) at 3 months after final infusion, n / total N: • Ketamine group: 1 / 9 • Placebo: 2 / 10 **Safety** • Mean CADSS total scores; significant difference between ketamine group[b] • Dissociative symptoms: ketamine group had higher rates than placebo (*P* < 0.001) .	
Phillips, 2019[19]	
Phase 1 - single ketamine/ midazolam infusion MADRS total scores: • Ketamine group: score mean decrease 10.9 points (SD = 8.9) • Midazolam group: score mean decrease 2.8 points (SD = 3.6) • Ketamine group had significantly lower score than midazolam group at 2 hours, 24 hours and 7 days post-infusion[b] **24 hours post infusion:** Antidepressant response, n (%): • Ketamine group: 11 (27%) • Midazolam group: 0 (0%) Remissions, n (%): • Ketamine group: 2 (5%) • Midazolam group: 0 (0%) Self-reported depression severity: • QIDS-SR total scores: ketamine group significantly lower than midazolam group at 24 hours and 4 days post-infusion **Phase 2 - repeated ketamine infusions** **MADRS scores** Overall mean decrease: 21.6 points (SD = 5.8) Non-responders mean decrease: 3.1 points (SD = 5.7) Antidepressant response, n (%): 23 (59%) • 77% of responders received 3 or more infusions before response **Remissions,** n (%): 9 (23%)	"Repeated ketamine infusions have cumulative and sustained antidepressant effects. Reductions in depressive symptoms were maintained among responders through once-weekly infusions. These findings provide novel data on efficacious administration strategies for ketamine in patients with treatment-resistant depression." (p. 401)

Table 6: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Self-reported depression severity: • QIDS-SR total score: significant fixed effect of time (p,0.001) **Phase 3 - maintenance infusions** MADRS score: no further change in MADRS score; no main effect of time on change in MADRS total score (*P* = 0.49) Antidepressant response, n (%): 21 (91%) Self-reported depression severity: • QIDS-SR total score**:** no effect for time (***P*** = 0.30) **Safety Outcome** No serious AE reported during the trial Most common side effects in ketamine group: cardiorespiratory effects, numbness or tingling, dissociation, dizziness, and visual disturbances Elevation of blood pressure during ketamine infusion**,** maximum mean change: • Systolic, 25.3 mmHg; • Diastolic, 15.7 mmHg Heart rate, maximum mean change: 10.2 bpm Average time before blood pressure and heart rate return to pre-infusion levels: 24 minutes (range 5–40 minutes). Dissociative effects (change in CADSS score) in Phase 1: • Significantly higher CADSS scores in ketamine group than in midazolam group (*P* < 0.001) • Time to return to baseline level in ketamine group: 2 hours post-infusion (*P* = 0.10) • **D**issociative effects during the ketamine infusion were significantly correlated with antidepressant response at 24 hours post-infusion (change in MADRS total score, Pearson's r = –0.46, *P* =0.03) Dissociative effects (change in CADSS score) in Phase 2: CADSS scores after 1st ketamine infusion: mean=18.0, SD=14.3 CADSS scores after final ketamine infusion: 7th infusion overall; mean=4.6, SD=7.3 Decrease in dissociative side effects with repeated infusions (*P* = 0.001)	
Fava, 2018[17]	
Depression Severity measured by HAM-D-6 K**etamine combined vs.** midazolam 2-group analysis: statistically significant day by group interaction effect (*P* = 0.0278) Ketamine 0.1 mg/kg, 0.2 mg/kg, 0.5 mg/kg, 1.0 mg/kg and 0.045 mg/kg midazolam 5-group analysis: • statistically significant (*P* = 0.0391) day by group interaction effect • After adjusting for multiple comparisons, 0.5 mg/kg and 1.0 mg/kg ketamine dose remained statistically superior to midazolam at Day 1 **Depression severity measured by SDQ, PAS, MADRS, CGI-S** **On day 1:**	"When the four ketamine groups were collapsed into one group and compared to active placebo (midazolam), there were no significant differences in rates of any of AEs. However, there were numerically higher rates of headache, nausea, vomiting, and depression among ketamine-treated patients." (p. 11) "Our results suggest that there is evidence for the efficacy of the 0.5 mg/Kg and 1.0 mg/Kg subanesthetic doses of IV ketamine and no clear or consistent

Table 6: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
With adjustment for multiple comparisons, 0.5 mg/kg ketamine group was superior to placebo on: • SDQ (adjusted *P* = 0.02) • PAS (adjusted *P* = 0.0347) • CGI-S (adjusted *P* = 0.01) • CGI-I (adjusted *P* = 0.03) 1.0 mg/kg ketamine group was superior to placebo on the CGI-S (adjusted *P* = 0.05) **On day 3:** 0.5 mg/kg ketamine group was superior to placebo on MADRS (adjusted *P* = 0.02) **Dissociative Symptoms by CADSS** At 40 minutes post-infusion: • 0.5 mg/kg and 1 mg/kg doses significantly greater than midazolam, indicating more dissociative symptoms • 0.1 mg/kg and 0.2 mg/kg were not significantly different from midazolam **AE** No significant differences in any of AE rates of 4 ketamine groups combined vs. midazolam group Rates of specific AEs in ketamine group compared to midazolam group (%): • Headache (11.3% vs 0%) • Nausea (10% vs 0%) • Vomiting (5% vs 0%) • Depression (3.8% vs 0%) • spontaneously-reported SI was reported by 2 patients in ketamine group, but none in midazolam group Serious AE: 1 patient in the received ketamine 0.2 mg/kg group attempted suicide by overdosing on Day 11 and was sent to the ER **C-SSRS** **Ketamine vs. midazolam:** non-significantly lower rates of active SI without intent to act, non-specific active suicidal thoughts, and wishing to be dead **Blood Pressure** Dose-response relationship: **I**ncreasingly higher systolic and diastolic blood pressure values occurring in groups with increasingly higher ketamine dosages	evidence for clinically meaningful efficacy of lower doses of IV ketamine." (p. 15)

CADSS = Clinician-Administered Dissociative States Scale; CGI-I = Clinical Global Impressions – Improvement; CGI-S = Clinical Global Impressions – Severity; C-SSRS = Columbia Suicide Severity Rating Scale; GEE = generalized estimating equation; HAMD or HDRS = Hamilton Depression Rating Scale; HAM-D-6 = 6-item Hamilton Depression Rating Scale; IV = intravenous; MADRS = Montgomery Asberg Depression Rating Scale; MDD = major depressive disorder; QIDS-SR = Quick Inventory of Depressive Symptomatology–Self Report; RCT = randomized controlled trial; SDQ = Symptoms of Depression Questionnaire; SD = standard deviation; SI = suicidal ideation; VAS = Visual Analogue Scale.

a. Reported results from the same RCT.

b. Results only shown in a figure; therefore no numerical values to report.

Table 7: Summary of Recommendations in Included Guidelines

Supporting Evidence	Recommendations	Strength of Evidence and Recommendations
VA/DoD, 2017[21]		
"Major depression frequently co-occurs with PTSD. Feder et al. evaluated the efficacy of a single intravenous (IV) sub-anesthetic dose of ketamine in patients with PTSD since preliminary evidence suggests that sub-anesthetic doses of IV ketamine has rapid antidepressant effects in treatment-resistant depression. The study compared ketamine versus midazolam in 41 patients with PTSD in a two-week crossover, low quality RCT.[165] Ketamine administration significantly reduced self-rated PTSD symptoms at 24 hours, but not seven days after the infusion. Furthermore, clinician-rated PTSD symptom severity was also not significantly different between subjects given ketamine or midazolam one week after administration. Additionally, there was no significant difference between ketamine and midazolam with respect to the severity of depressive symptoms. Individuals who received ketamine had greater rates of blurred vision, dry mouth, restlessness, nausea and vomiting, headache, and poor coordination compared to midazolam. In the context of limited information on the efficacy of ketamine in PTSD combined with its significant side effects and potential for abuse, we recommend against the use of ketamine for the primary treatment of PTSD in a clinical setting. Future, well-designed studies could help shed light on the efficacy of ketamine on clinician-rated PTSD and depressive symptoms." (p. 57)	**"**We recommend against treating PTSD with divalproex, tiagabine, guanfacine, risperidone, benzodiazepines, ketamine, hydrocortisone, or D-cycloserine, as monotherapy due to the lack of strong evidence for their efficacy and/or known adverse effect profiles and associated risks.**"** (p. 56)	Quality of Evidence: Very low Recommendation: Strong Against

PTSD = posttraumatic stress disorder.