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SUMMARY WITH CRITICAL APPRAISAL

Ketamine for Treatment-Resistant Depression or Post-Traumatic Stress Disorder in Various Settings: A Review of Clinical Effectiveness, Safety, and Guidelines

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Context and Policy Issues

Depression is a common mental disorder with various symptoms, including loss of interest or pleasure in regular activities, decreased energy, and poor concentration.[1] Major depressive disorder (MDD) is the most prevalent and disabling form of depression.[1] In addition to the immediate symptoms of depression, MDD may result in poor quality of life, decreased productivity, and increased mortality from suicide.[1] Anxiety, post-traumatic stress disorder (PTSD), and substance misuse are commonly co-occurring conditions that may worsen the existing depression and complicate treatment.[1]

Although depression can be a devastating illness, it often responds to treatment.[1] There are a variety of treatment options available for people with depression, including pharmacotherapy (e.g., selective serotonin reuptake inhibitors [SSRIs]), serotonin and noradrenaline reuptake inhibitors [SNRIs], and somatic therapy (e.g., electroconvulsive therapy [ECT]).[1,2] In general, SSRIs are the first choice of antidepressant drugs, followed by SNRIs. ECT is often used as a late-line therapy[2] and a gold standard for treatment-resistant depression (TRD),[3] which is most often defined as having failed to respond to two or more different antidepressants,[2,4] although there is no official consensus on its definition.[2] Nevertheless, there is still an unmet need for a novel, rapidly-acting therapy for TRD.[3]

Approved for general anesthesia,[1] ketamine has been associated with antidepressant effects in animal models of depression and with rapid antidepressant effects in human studies of depression.[4] Despite the potential of ketamine as a novel, rapid-acting therapeutic option for patients with TRD, there is a paucity of data on its effects (e.g., on neurocognitive functions) when used off-label.[5]

To inform clinical practice on the treatment of patients with TRD or PTSD, this report aimed to provide evidence on the clinical benefits and harms and evidence-based guidelines on the off-label use of ketamine in various settings.

Research Questions

1. What is the clinical effectiveness and safety of using ketamine for treatment-resistant depression or post-traumatic stress disorder in various settings?

2. What are the evidence-based guidelines associated with the use of ketamine for treatment-resistant depression or post-traumatic stress disorder in various settings?

Key Findings

Three systematic reviews, five primary studies, and two evidence-based guidelines were found on the off-label use of ketamine for treatment-resistant depression and post-traumatic stress disorder, mostly in hospital settings. Ketamine, when administered to patients with treatment-resistant depression, was effective at reducing depressive severity within minutes or hours. It was also effective at reducing post-traumatic stress disorder severity in patients with the condition. Its antidepressant effects may taper over time but last up to two weeks and be comparable or superior to other pharmacological or somatic interventions for treatment-resistant depression. Its short-term benefits were also demonstrated in improving fatigue and suicidality,

without serious adverse events or compromise in neurocognitive functioning in patients with treatment-resistant depression. Nevertheless, citing limited information on ketamine's safety and duration of effect, both guidelines recommended restricting the off-label use of ketamine to research settings.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, and Canadian and major international health technology agencies. A focused Internet search was also conducted. Methodological filters were applied to limit retrieval to health technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), randomized controlled trials (RCTs), non-randomized studies, and guidelines. The search was also limited to English language documents, published between January 1, 2012 and February 1, 2017.

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	Adults with TRD or PTSD
Intervention	Ketamine
Comparator	Q1: Antidepressants (e.g., SSRIs and SNRIs), antipsychotics, ECT, placebo, or standard of care Q2: No comparator
Outcomes	Q1: Clinical effectiveness and safety of ketamine use in various setting (e.g., offices, hospitals, and clinics) and with various monitoring (e.g., cardiac monitoring) Q2: Guidelines
Study Designs	HTAs, SRs, MAs, RCTs, non-randomized primary studies, and evidence-based guidelines

ECT = electroconvulsive therapy; HTA = health technology assessment; MA = meta-analysis; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial; SNRI = serotonin norepinephrine reuptake inhibitors; SR = systematic review; SSRI = selective serotonin reuptake inhibitor; TRD = treatment-resistant depression

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, if they were duplicate or redundant publications, or if they were published in a language other than English, prior to 2012, or not in full (e.g., conference abstracts).

Critical Appraisal of Individual Studies

The included SRs, primary studies, and evidence-based guidelines were assessed, using the Assessment of Multiple Systematic Reviews (AMSTAR) tool,[6] Downs and Black checklist,[7] and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument,[8] respectively. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were narratively described.

Summary of Evidence

Quantity of Research Available

A total of 326 citations were identified in the literature search. Following screening of titles and abstracts, 275 citations were excluded, and 51 potentially-relevant reports from the electronic search were retrieved for full-text review. Two potentially-relevant publications were retrieved from the grey literature search. Of the 53 potentially-relevant articles, 43 publications were excluded for various reasons, while 10 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest that did not meet the selection criteria are provided in Appendix 5.

Summary of Study Characteristics

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

Clinical Benefits and Harms of Ketamine for Treatment-Resistant Depression or Post-Traumatic Stress Disorder

Three SRs[2,9,10] and five primary studies[3,5,11-13] provided information on the clinical effectiveness and safety of ketamine for TRD[2,3,5,9-12] or PTSD.[13]

Study Design

The SRs[2,9,10] included three,[10] nine,[9] or 31[2] RCTs, conducted in unspecified settings[2,9] or in hospitals.[10] One SR[2] conducted network meta-analysis (NMA). Sample sizes ranged from 69 patients[10] to 5,515 patients.[2] All three SRs conducted searches up to 2014 and were published in 2016[2,9] or 2015.[10]

The primary studies[3,5,11-13] included two post hoc analyses of two RCTs,[11,12] two RCTs[5,13] and one cohort study,[3] conducted in hospitals. Sample sizes ranged from 35 patients[3] to 62 patients[5]. The primary studies[3,5,11-13] were published in 2016,[11] 2015,[3,5,12] and 2014.[13]

Two SRs[9,10] partially overlapped, including the same two RCTs in their review. Further, two primary studies[11,12] were post hoc analyses of two RCTs included in the SRs.[9,10] Nevertheless, to present all outcomes described in all relevant RCTs, all SRs[9,10] and primary studies[11,12] were included in this report.

Country of Origin

The SRs[2,9,10] were conducted in the Netherlands,[2] Australia,[9] or the United States (US).[10] The primary studies were conducted in the US[5,11-13] or Ireland.[3]

Patient Population

The SRs[2,9,10] included adult patients with treatment-resistant MDD[2,9] or bipolar depression.[9,10] The primary studies[3,5,11-13] included patients with MDD,[3,5,12] bipolar depression,[11,12] or PTSD.[13]

Interventions and Comparators

The SRs[2,9,10] compared single-dose ketamine, administered intravenously[2,10] or via any route[9] at 0.5 mg/kg[2,9] or lower[9] or unknown[10] doses, with placebo,[9,10] active placebo (i.e., midazolam),[9] or various interventions for depression, including antidepressants and ECT.[9]

The primary studies[3,5,11-13] compared single-[5,11-13] or multi-[3]dose ketamine, administered intravenously at 0.5 mg/kg, with placebo,[11,12] active placebo (i.e., midazolam),[5,13] or ECT.[3] Three RCTs[3,11,12] allowed for concomitant treatments of lithium or valproate for bipolar disorder[11,12] or other antidepressants.[3]

Midazolam, with no established antidepressant properties,[14] was used as an active placebo in one SR[9] and two primary studies[5,13] to control for non-specific treatment effects related to sedation or other acute effects of ketamine as an anesthetic.[5,13]

Outcomes

The SRs[2,9,10] described depression severity, measured with the Montgomery Åsberg depression rating scale (MADRS)[2,9,10] and Hamilton depression rating scale (HAM-D).[2,9] Two SRs[2,9] described response rates,[2,9] defined as 50% or greater reductions in the HAM-D and MADRS scores, or remission rates,[9] defined as HAM-D scores less than seven or MADRS scores less than 10. Two SRs[9,10] described suicidality, measured with HAM-D and MADRS,[9] or suicidal thoughts.[10] Two SRs[9,10] described adverse events. One SR[10] described anhedonia levels, defined as reduced abilities to experience pleasure.[15] One SR[9] described patient dropout rates.

Two primary studies[3,13] measured depression severity, using HAM-D,[3] clinician-administered post-traumatic stress disorder scale (CAPS),[13] clinical global impression (CGI) scales,[13] impact of event scale-revised (IES-R),[13] MADRS,[13] and quick inventory of depressive symptomatology-self report (QIDS-SR).[13] One primary study[13] measured PTSD symptom severity using IES-R. One primary study[11] measured fatigue severity, using the National Institute of Health-brief fatigue inventory (NIH-BFI). One primary study[3] used HAM-D to calculate response rates, defined as 50% or greater reductions in the scores. One primary study[12] measured suicidal thoughts, using the Beck depression inventory (BDI), HAM-D, MADRS, and scale for suicidal ideation (SSI). One primary study[5] measured neurocognitive functioning, using the MATRICS consensus cognitive battery (MCCB). One primary study[13] described adverse events, using the brief psychiatric rating scale (BPRS), clinician-administered dissociative states scale (CADSS), and young mania rating scale (YMRS).

Follow-Up Duration

The SRs[2,9,10] reported one[9] or two[2,10] weeks of follow-up. The primary studies[3,5,11-13] reported three days[12] or one[3,5,13] or two[11] weeks of follow-up.

Data Analysis and Synthesis

The SRs[2,9,10] summarized the main findings by extracting data from the included studies and expressing them as mean differences or standardized mean differences. The primary studies[3,5,11-13] summarized the main findings as placebo-adjusted scores on various measures.

Quality Assessment

All three SRs[2,9,10] conducted quality assessment of the included RCTs, using the Cochrane risk of bias tool.

Evidence-Based Guidelines for the Use of Ketamine for Treatment-Resistant Depression or Post-Traumatic Stress Disorder

Two evidence-based guidelines[1,16] provided recommendations on the use of ketamine for TRD.

Country of Origin

The evidence-based guidelines[1,16] were developed by the US Department of Veteran Affairs and Department of Defense (VA/DoD)[1] and Canadian Network for Mood and Anxiety Treatments (CANMAT)[16] and published in 2016.

Patient Population

The evidence-based guidelines[1,16] were developed for adult patients with MDD.

Interventions and Comparators

The evidence-based guidelines[1,16] provided recommendations on the use of ketamine as a treatment of MDD.

Outcomes

The evidence-based guidelines[1,16] developed recommendations with panels of content experts and consideration for the efficacy and tolerability of ketamine. The evidence-based guidelines[1,16] rated the quality of evidence and strength of recommendations, using the US Preventive Services Task Force[1] or CANMAT[16] criteria and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.[1,16]

Summary of Critical Appraisal

A summary of the critical appraisal of the included literature is presented in Appendix 3.

Clinical Benefits and Harms of Ketamine for Treatment-Resistant Depression or PTSD

The SRs[2,9,10] were of mixed quality, assessed with AMSTAR.[6] All three SRs[2,9,10] conducted duplicate study selection and data extraction, provided a flow diagram for the search results, assessed the quality of the included studies, and used appropriate methods to combine the study findings. Two SRs[2,9] provided detailed search strategies. Two SRs[9,10] provided a list of the included studies and their characteristics. Two[2,10] appropriately used the quality of the included studies in formulating their conclusions. However, none of the SRs[2,9,10] provided an a priori design, listed the excluded studies, or assessed the likelihood of publication bias. Two SRs[2,10] did not conduct comprehensive searches. Two SRs[2,9] disclosed potential conflicts of interest, involving pharmaceutical companies.

The primary studies[3,5,11-13] were of mixed quality, assessed with Downs and Black.[7] All five primary studies[3,5,11-13] described the objectives, main outcomes, interventions, and main findings and used appropriate statistical tests and valid and reliable outcome measures. Four primary studies[3,5,11,13] described the characteristics of the patients and main findings. Four primary studies[5,11-13] were RCTs, recruiting the patients from the same population and randomizing them into intervention groups, and made attempts to blind the patients to the interventions they received[5,11-13] or the staff measuring the main outcomes.[11,12] However, none of the primary studies[3,5,11-13] provided evidence that their patients were representative of the entire population of interest, accounted for losses to follow-up in their analysis, or described whether they had adequate power to detect clinically-important effects. In the four RCTs,[5,11-13] it is unclear if the trial design was representative of the care setting. The cohort study[3] recruited cohorts of patients from different hospitals. Three primary studies[3,11,12] did not always report actual probabilities. Three primary studies[11-13] did not statistically compare the baseline characteristics of the patients in the different intervention groups, making it difficult to determine if adjustment for confounding was needed in the analysis.

Evidence-Based Guidelines for the Use of Ketamine for Treatment-Resistant Depression or Post-Traumatic Stress Disorder

The evidence-based guidelines[1,16] were of mixed quality, assessed with AGREE II.[8] Both guidelines[1,16] described the objectives, health questions, and target populations and users; were developed by individuals from all relevant professional groups; used systematic search methods; applied evidence selection criteria; appraised the quality of evidence; described the methods for formulating recommendations; considering benefits, harms, and quality of evidence; were reviewed externally prior to publication; provided unambiguous recommendations; and disclosed funding sources. However, neither of the guidelines[1,16] sought target population input, considered costs, described a procedure for updating, provided implementation tools or monitoring criteria, or disclosed potential conflicts of interest.

Summary of Findings

A summary of the findings of the included literature is presented in Appendix 4.

What is the clinical effectiveness and safety of using ketamine for treatment-resistant depression or post-traumatic stress disorder in various settings?

Depression Severity

Three SRs[2,9,10] reported that patients with TRD who received ketamine experienced significant and greater improvements in depression severity, measured by HAM-D[9] or MADRS,[2,9,10] compared to placebo[9,10] or other pharmacological or somatic treatments for depression.[2] One NMA[2] that compared ketamine with other pharmacological or somatic treatments for TRD ranked ketamine first. However, one primary study[3] reported that in patients with TRD, the effect of ketamine and ECT were comparable.

Reductions in depression severity were observed as early as minutes[10] or hours[9] after ketamine treatment and demonstrated for up to two weeks.[2,10] In fact, two SRs[9,10] reported that reductions were greatest 40 minutes[10] or one day[9] after ketamine treatment and attenuated afterwards.[9]

One SR[9] reported that reductions in depression severity from very-low-dose ketamine (i.e., 50 mg or 0.1-0.5 mg/kg) were smaller and shorter-lived, compared to low-dose ketamine (i.e., 0.5 mg/kg). One SR[9] reported that reductions in patients with bipolar depression were smaller, compared to those with MDD.

One primary study[13] reported that patients with PTSD who received ketamine experienced significant and greater improvements in depression severity, compared to active placebo, according to some scales (i.e., CGI and IES-R) but not others (i.e., MADRS, QIDS-SR, and CAPS).

Post-Traumatic Stress Disorder Severity

One primary study[13] reported that patients with PTSD who received ketamine experienced significant and greater improvements in PTSD severity, measured by IES-R, compared to active placebo.

Fatigue Severity

One primary study[11] reported that patients with TRD who received ketamine experienced significant and greater improvements in fatigue severity, measured by NIH-BFI, compared to placebo. The primary study[11] reported that reductions were greatest two days after ketamine treatment and decreased until two weeks after.

Response Rate

Two SRs[2,9] reported that patients with TRD who received ketamine were more likely to respond to treatment (i.e., defined as 50% or higher reductions in HAM-D or MADRS depression severity scores), compared to placebo[2,9] or other pharmacological or somatic treatments for depression.[2] One primary study[3] reported that a majority of patients with TRD responded to ketamine two hours after treatment.

Remission Rate

One SR[9] reported that patients with TRD who received ketamine were more likely to have remission (i.e., defined as low HAM-D or MADRS depression severity scores), compared to placebo.

Dropout Rate

One SR[9] reported that patients with TRD who received ketamine were more likely to drop out of treatment, compared to placebo. However, most dropouts were reported as being due to changes in mood rather than adverse events.[9]

Suicidality or Suicidal Thoughts or Ideation

One SR[9] and one primary study[12] reported that patients with TRD who received ketamine experienced significant and greater improvements in suicidality[9] or suicidal thoughts,[12] measured by BDI,[12] HAM-D[9,12] MADRS,[9,12] or SSI,[12] compared to placebo. One SR[10] reported that ketamine reduced suicidal ideation, with no details.

One primary study[12] reported that reductions were greatest 40 minutes after ketamine treatment and decreased or plateaued until three days after.

Anhedonia Level

One SR[10] reported that ketamine reduced anhedonia, with effects lasting up to 14 days.

Neurocognitive Functioning

One primary study[5] reported that patients with TRD who received ketamine or placebo experienced significant and comparable improvements in some domains (i.e., processing speed, verbal learning, and visual learning) of neurocognitive performance but not others (i.e., working memory and reasoning), measured by MCCB.

Adverse Events

One SR[9] and one primary study[13] reported that ketamine was generally well-tolerated, with transient dissociative symptoms. The SR[9] reported the following serious adverse events associated with ketamine in the treatment of TRD: hypotension and bradycardia, a suicide attempt, tachycardia, and arterial pressure elevations. The primary study[13] reported the following adverse events as the most frequent: blurred vision, dry mouth, restlessness, fatigue, nausea or vomiting, poor coordination, and headache.

One SR[10] reported similar levels of mild-to-moderate adverse events associated between ketamine and placebo but no serious adverse events.

What are the evidence-based guidelines associated with the use of ketamine for treatment-resistant depression or post-traumatic stress disorder in various settings?

American and Canadian Recommendations and Supporting Evidence

Citing limited information on ketamine's safety and duration of effect, both the US VA/DoD[1] and CANMAT[16] recommended restricting the use of ketamine to research settings.

Limitations

There was partial overlap in the included studies across two SRs[9,10] and two primary studies.[11,12] To present all outcomes described, all SRs[9,10] and primary studies[11,12] were included in this report, and care was taken to avoid presenting redundant findings, where possible. Nevertheless, there may be redundancy in the study findings presented in this report.

Several of the included SRs[9,10] and primary studies[3,11] identified small sample sizes across trials (e.g., an average of 23 patients per trial included in one SR [9]), potentially limiting the power of those studies to detect significant differences between treatments, as a weakness in this literature. Further, data on longer follow-up[2,9,10] and repeated dosing[9,10] were also identified as needed in future studies.

Information on the exact setting was missing in two SRs.[2,9] It is unclear whether the patients recruited in one primary study[3] were all adults. Therefore, the findings presented in this report may not be entirely applicable to the specific population of interest described in Table 1.

Conclusions and Implications for Decision or Policy Making

Three SRs, five primary studies, and two evidence-based guidelines were found on the off-label use of ketamine for TRD and PTSD, mostly in hospital settings. Ketamine, when administered to patients with TRD, was effective at reducing depressive severity within minutes or hours. It was also effective at reducing PTSD severity in patients with the condition. Its antidepressant effects may taper over time but last up to two weeks and can be comparable or superior to other pharmacological or somatic interventions for TRD. Its short-term benefits were also demonstrated in improving fatigue, suicidality, and anhedonia, without serious adverse events or compromise in neurocognitive functioning in patients with TRD. Nevertheless, citing limited information on ketamine's safety and duration of effect, both guidelines recommended restricting the off-label use of ketamine to research settings. The quality of the literature included in this report was mixed. Future studies are needed with larger samples, longer follow-up, and repeated dosing.

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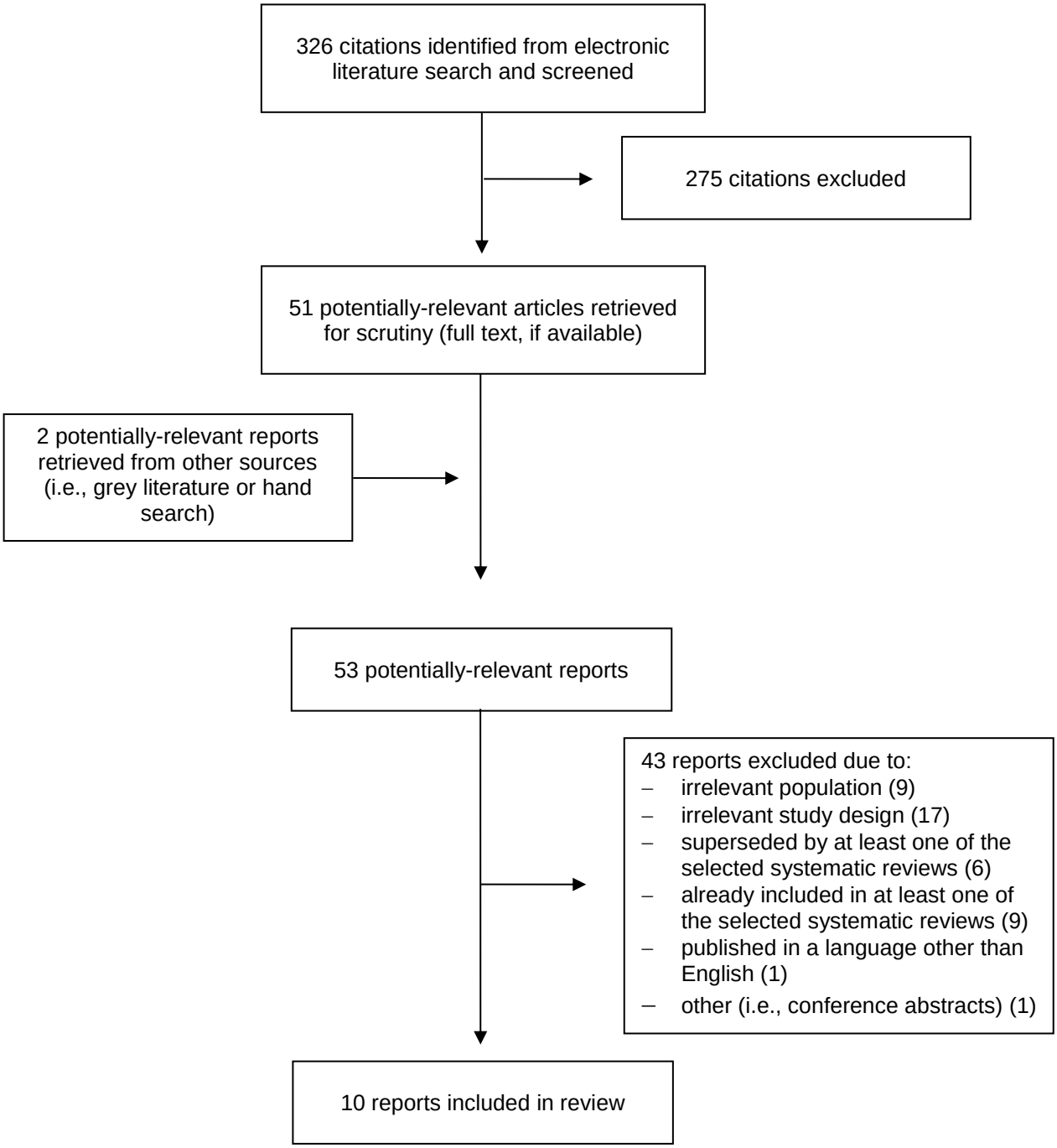
Appendix 1: Selection of Included Studies



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Appendix 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Papadimitropoulou[2] 2016 The Netherlands	SR and NMA of 31 RCTs*, published between 2000 and 2014 Quality assessment using Cochrane risk of bias tool *Of the 31 placebo/sham-controlled RCTs used to build a network for the NMA, 1 RCT was on ketamine.	5,515 adult* patients with treatment-resistant MDD in unspecified settings *38-58 years of median age range across the included studies	Single-dose* ketamine** *0.5 mg/kg **Administered intravenously	ECT, MAOIs, OFCs, rTMS, SNRIs, SSRIs, TCAs, TeCAs, atypical antidepressants, antipsychotics, adjunctive use of lithium, or triiodothyronine, lamotrigine	Depression severity* and response rate** 2 weeks of follow-up *Measured by MADRS or measured by HAM-D and converted to MADRS **Defined as ≥50% reduction in MADRS
Xu[9] 2016 Australia	SR of 9 RCTs, published between 2000 and 2014 Quality assessment using Cochrane risk of bias tool	201 adult* patients with treatment-resistant MDD or bipolar depression in unspecified settings *46 years of mean age	Single-dose* ketamine** *Low doses (i.e., 0.5 mg/kg) or very low doses (i.e., 50 mg or 0.1-0.5 mg/kg) **Administered in any way, including intravenous, intranasal, intramuscular, or subcutaneous routes	Placebo* or active placebo** *Saline (0.9%) **Midazolam (0.01-0.045 mg/kg)	Depression severity*, response rate**, remission rate***, dropout rate, suicidality*, and AEs 7 days of follow-up *Measured by HAM-D or MADRS **Defined as ≥50% reduction in HAM-D or MADRS ***Defined as HAM-D<7 or MADRS<10
Parsaik[10] 2015 US	SR of 3 RCTs, published between 2010 and 2014	69 adult* patients with treatment-resistant bipolar depression in	Single-dose* ketamine**, concomitantly with	Placebo	Depression severity*, anhedonia level, suicidal thoughts, and

First Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Quality assessment using Cochrane risk of bias tool	hospitals *44.6±4.3 years of mean age	lithium or valproate *Unknown doses **Administered intravenously		AEs 14 days of follow-up *Measured MADRS

AE = adverse event; ECT = electroconvulsive therapy; HAM-D = Hamilton depression rating scale; MADRS = Montgomery Åsberg depression rating scale; MOAI = monoamine oxidase inhibitor; MDD = major depressive disorder; NMA = network meta-analysis; OFC = olanzapine and fluoxetine combination; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SNRI = serotonin norepinephrine reuptake inhibitor; SR = systematic review; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TeCA = tetracyclic antidepressant; US = United States

Table A2: Characteristics of Included Primary Studies

First Author, Publication Year, Country, Study Name (if reported)	Study Design	Patient Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Saligan[11] 2016 US	Post hoc analysis of data collected from two double-blind, crossover RCTs	36 adult* patients with treatment-resistant bipolar depression in hospitals *46.7 years of mean age	Single-dose* ketamine**, concomitantly with lithium or valproate *0.5 mg/kg **Administered intravenously	Placebo* *Saline	Fatigue severity* 14 days of follow-up *Measured by NIH-BFI
Allen[3] 2015 Ireland	Cohort study	35 patients* with treatment-resistant MDD in hospitals *49.1 years of mean age	1-3 doses* of ketamine**, concomitantly with any other antidepressant treatments *0.5 mg/kg **Administered intravenously	5-12 sessions of ECT	Depression severity* and response rate** 7 days of follow-up *Measured by HAM-D **Defined as ≥50% reduction in HAM-D
Ballard[12] 2015 US	Post hoc analysis of data collected from two double-blind,	60 adult* patients with treatment-resistant MDD or bipolar	Single-dose* ketamine**, concomitantly*** with	Placebo* *Saline	Suicidal thoughts* 3 days of follow-up

First Author, Publication Year, Country, Study Name (if reported)	Study Design	Patient Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
	crossover RCTs	depression in hospitals *41.6 years of mean age	lithium or valproate *0.5 mg/kg **Administered intravenously ***For patients with bipolar depression		*Measured by BDI, HAM-D, MADRS, and SSI
Murrough[5] 2015 US	Double-blind RCT	62 adult* patients with treatment-resistant MDD in hospitals *46.2 years of mean age	Single-dose* ketamine** *0.5 mg/kg **Administered intravenously	Active placebo* *Midazolam (0.045 mg/kg)	Neurocognitive functioning* 7 days of follow-up *Measured by MCCB
Feder[13] 2014 US	Double-blind, cross-over RCT	41 adult* patients with chronic PTSD in a hospital *36 years of mean age	Single-dose* ketamine** *0.5 mg/kg **Administered intravenously	Active placebo* *Midazolam (0.045 mg/kg)	PTSD symptom severity*, depression severity,** and AEs*** 7 days of follow-up *Measured by IES-R **Measured by CAPS, CGI-I, CGI-S, IES-R, MADRS, and QIDS-SR ***Measured by BPRS, CADSS, and YMRS

AE = adverse event; BDI = Beck depression inventory; BPRS = brief psychiatric rating scale; CADSS = clinician-administered dissociative states scale; CAPS = clinician-administered post-traumatic stress disorder scale; CGI-I = clinical global impression-improvement; CGI-S = clinical global impression-severity; ECT = electroconvulsive therapy; HAM-D = Hamilton depression rating scale; IES-R = impact of event scale-revised; MADRS = Montgomery Åsberg depression rating scale; MCCB = MATRICS consensus cognitive battery; MDD = major depressive disorder; NIH-BFI = National Institute of Health-brief fatigue inventory; PTSD = post-traumatic stress disorder; QIDS-SR = quick inventory of depressive symptomatology-self report; RCT = randomized controlled trial; SSI = scale for suicidal ideation; US = United States; YMRS = young mania rating scale

Table A3: 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[1]* 2016 US *An update to a 2009 guideline	Intended users: all health care professionals who treat MDD, especially primary care providers and general mental health care providers Target population: adult patients with MDD	Management, including diagnosis, treatment, and follow-up, of MDD	Symptoms, remission rate, relapse and recurrence rate, medication adherence and dropout, treatment retention, QoL, social and occupational functioning, comorbidities, mortality, and AEs	Systematic literature searches for SRs, MAs, and primary studies in English Syntheses based on evidence	Quality of evidence and strength of recommendations were rated, using the following USPSTF method criteria and GRADE: • Good • Fair • Poor	Recommendations were developed by a panel of content experts from psychiatry, psychology, pharmacy, nursing, social work, family medicine, internal medicine, emergency medicine, and mental and behavioural health, who considered evidence from the literature and expert opinions.	A draft guideline was subject to 14 business of peer-review.
Kennedy[16]* CANMAT 2016 Canada Funded entirely by CANMAT *An update to a 2009 guideline	Intended users: community-based psychiatrists and other mental health professionals Target population: adult patients with MDD	Pharmacological treatments for MDD	Efficacy and tolerability	Systematic literature searches for SRs and MAs in English or French* Syntheses based on evidence and clinical expert consensus *RCTs were considered when SRs and MAs	Quality of evidence was rated using the following CANMAT criteria, supplemented by modified ratings from GRADE: • Level 1: evidence from MAs with narrow CIs and/or ≥2 RCTs with adequate sample sizes (i.e., ≥30) and preferably placebo-	Recommendations were developed by a panel of content experts from psychiatry, psychology, and pharmacy who considered evidence from the literature and consensus clinical expert opinions.	A draft guideline was presented in interactive workshops at major psychiatric conferences in Canada.

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
				were not available.	controlled • Level 2: evidence from MAs with wide CIs and/or ≥1 RCTs with adequate sample sizes (i.e., ≥30) • Level 3: evidence from small-sample RCTs or non-randomized, controlled prospective studies or case series or high-quality retrospective studies • Level 4: expert opinion and/or consensus		

AE = adverse event; CANMAT = Canadian Network for Mood and Anxiety Treatments; DoD = Department of Defense; GRADE = Grading of Recommendations Assessment, Development and Evaluation; MA = meta-analysis; MDD = major depressive disorder; QoL = quality of life; RCT = randomized controlled trial; SR = systematic review; US = United States; USPSTF = United States Preventive Services Task Force; VA = Department of Veteran Affairs

Appendix 3: Critical Appraisal of Included Publications

Table A4: Strengths and Limitations of Included Systematic Reviews Using AMSTAR

Strengths	Limitations
Papadimitropoulou 2016[2]	
• There was duplicate study selection and data extraction. • A detailed search strategy and a flow diagram for the search results were provided. • The scientific quality of the included studies was assessed and documented. • The scientific quality of the included studies was used appropriately in formulating conclusions. • The methods used to combine the study findings were appropriate.	• An "a priori" design was not provided. • Although several databases were included in the literature search, no grey literature was included. • A list of the included studies and their characteristics were not provided. • A list of the excluded studies was not provided. • The likelihood of publication bias was not assessed. • All five of the authors disclosed potential conflicts of interest, either being employees of or receiving support from a pharmaceutical company. The study was conducted on behalf of the pharmaceutical company.
Xu 2016[9]	
• There was duplicate study selection and data extraction. • A comprehensive literature search, including some grey literature, was performed. A detailed search strategy and a flow diagram for the search results were provided. • A list of the included studies and their characteristics were provided. • The scientific quality of the included studies was assessed and documented. • The methods used to combine the study findings were appropriate.	• An "a priori" design was not provided. • A list of the excluded studies was not provided. • The scientific quality of the included studies was not used in formulating conclusions. • The likelihood of publication bias was not assessed. • Three of the authors disclosed potential conflicts of interest, owning a patent on the drug of interest and receiving support from pharmaceutical companies.
Parsaik 2015[10]	
• There was duplicate study selection and data extraction. • A flow diagram for the search results was provided. • A list of the included studies and their characteristics were provided. • The scientific quality of the included studies was assessed and documented. • The scientific quality of the included studies was used appropriately in formulating conclusions. • The methods used to combine the study findings were appropriate. • No conflict of interest was declared.	• An "a priori" design was not provided. • A comprehensive literature search, including grey literature, was not performed. A detailed search strategy was not provided. • A list of the excluded studies was not provided. • The likelihood of publication bias was not assessed.

AMSTAR = Assessment of Multiple Systematic Reviews

Table A5: Strengths and Limitations of Included Primary Studies Using Downs and Black

Strengths	Limitations	Irrelevant Items
Saligan 2016[11]		
Reporting • The hypothesis/aim/objective of the study was described. • The main outcomes for the study were described. • The characteristics of the patients were described. • The interventions were described. • The main findings were described. Bias • An attempt was made to blind the patients to the intervention they received. • An attempt was made to blind the staff measuring the main outcomes. • Results of any post hoc analyses were described. • The statistical tests used to assess the main outcomes were appropriate. • Compliance with the interventions was reliable. • The main outcome measures were accurate (i.e., valid and reliable). Confounding • The patients in different intervention groups were recruited from the same population over the same period of time. • The patients were randomized to intervention groups. • Intervention assignment was concealed from both patients and staff until recruitment was complete and irrevocable.	Reporting • The distributions of potential confounders in each intervention group of the patients were not described. • Estimates of the random variability in the data for the main outcomes were not always provided. • The characteristics of the patients lost to follow-up were not described. • Actual probability values were not reported. External Validity • 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 entire population of interest. • It is unclear if the trial design was representative of the care setting. Confounding • 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. • Losses of patients to follow-up were not taken into account. Power • Although the study reported significance in most of its findings, it is unclear if the study had sufficient power to detect clinically-important effects.	Reporting • This was an exploratory post hoc analysis of data collected from two double-blind crossover RCTs and did not report on specific adverse events.
Allen 2015[3]		
Reporting • The hypothesis/aim/objective of the study was described. • The main outcomes for the study were described. • The characteristics of the patients were described. • The interventions were described. • The distributions of potential confounders in each intervention group of the patients were described. • The main findings were described. External Validity	Reporting • Estimates of the random variability in the data for the main outcomes were provided in graphs, with no numerical data. • Important adverse events were not reported. • The characteristics of the patients lost to follow-up were not described. • Actual probability values were not always reported. External Validity • The patients asked to participate in	Bias • Because this was a cohort study, an attempt was not made to blind the patients to the intervention they received. • It is unclear if any post hoc analyses were conducted. Confounding • Because this was a cohort study, intervention assignment was not concealed from patients or staff.

Strengths	Limitations	Irrelevant Items
• The trial design was representative of the care setting. Bias • The statistical tests used to assess the main outcomes were appropriate. • Compliance with the interventions was reliable. • The main outcome measures were accurate (i.e., valid and reliable).	the study were not representative of the entire population of interest. • The patients included in the study were not representative of the entire population of interest. Bias • It is unclear if an attempt was made to blind the staff measuring the main outcomes. Confounding • The patients in different intervention groups were not recruited from the same population over the same period of time. • The patients were not randomized to intervention groups. • There was no adjustment for confounding in the analysis for the main findings. • Losses of patients to follow-up were not taken into account. Power • Although the study reported significance in most of its findings, it is unclear if the study had sufficient power to detect clinically-important effects.	
Ballard 2015[12]		
Reporting • The hypothesis/aim/objective of the study was described. • The main outcomes for the study were described. • The interventions were described. Bias • An attempt was made to blind the patients to the intervention they received. • An attempt was made to blind the staff measuring the main outcomes. • Results of any post hoc analyses were described. • The statistical tests used to assess the main outcomes were appropriate. • Compliance with the interventions was reliable. • The main outcome measures were accurate (i.e., valid and reliable). Confounding • The patients in different intervention groups were recruited from the same population over the same period of time. • The patients were randomized to	Reporting • The characteristics of the patients were not described in detail. • The distributions of potential confounders in each intervention group of the patients were not described. • The main findings were not described in detail. • Estimates of the random variability in the data for the main outcomes were not always provided. • The characteristics of the patients lost to follow-up were not described. • Actual probability values were not reported. External Validity • 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 entire population of interest. • It is unclear if the trial design was representative of the care setting.	Reporting • This was an exploratory post hoc analysis of data collected from two double-blind crossover RCTs and did not report on specific adverse events.

Strengths	Limitations	Irrelevant Items
intervention groups. • Intervention assignment was concealed from both patients and staff until recruitment was complete and irrevocable.	Confounding • Because the distributions of potential confounders in each intervention group of the patients were not described, it is unclear if adjustment for confounding was needed in the analysis for the main findings. • Losses of patients to follow-up were not taken into account. Power • Although the study reported significance in most of its findings, it is unclear if the study had sufficient power to detect clinically-important effects.	
Murrough 2015[5]		
Reporting • The hypothesis/aim/objective of the study was described. • The main outcomes for the study were described. • The characteristics of the patients were described. • The interventions were described. • The distributions of potential confounders in each intervention group of the patients were described. • The main findings were described. • Estimates of the random variability in the data for the main outcomes were provided. • Important adverse events were reported. • The characteristics of the patients lost to follow-up were described. • Actual probability values were reported. Bias • An attempt was made to blind the patients to the intervention they received. • The statistical tests used to assess the main outcomes were appropriate. • Compliance with the interventions was reliable. • The main outcome measures were accurate (i.e., valid and reliable). Confounding • The patients in different intervention groups were recruited from the same population over the same period of time. • The patients were randomized to intervention groups.	Reporting • The characteristics of the patients lost to follow-up were not described. External Validity • The patients asked to participate in the study were not representative of the entire population of interest. • The patients included in the study were not representative of the entire population of interest. • It is unclear if the trial design was representative of the care setting. Bias • It is unclear if an attempt was made to blind the staff measuring the main outcomes. Confounding • Losses of patients to follow-up were not taken into account. Power • Although the study reported significance in most of its findings, it is unclear if the study had sufficient power to detect clinically-important effects.	Bias • It is unclear if any post hoc analyses were conducted.

Strengths	Limitations	Irrelevant Items
• Intervention assignment was concealed from both patients and staff until recruitment was complete and irrevocable. • Based on the distributions of potential confounders in each intervention group of the patients, no adjustment was needed for confounding in the analysis for the main findings.		
Feder 2014[13]		
Reporting • The hypothesis/aim/objective of the study was described. • The main outcomes for the study were described. • The characteristics of the patients were described. • The interventions were described. • The main findings were described. • Estimates of the random variability in the data for the main outcomes were provided. • Important adverse events were reported. • Actual probability values were reported. Bias • An attempt was made to blind the patients to the intervention they received. • The statistical tests used to assess the main outcomes were appropriate. • Compliance with the interventions was reliable. • The main outcome measures were accurate (i.e., valid and reliable). Confounding • The patients in different intervention groups were recruited from the same population over the same period of time. • The patients were randomized to intervention groups. • Intervention assignment was concealed from both patients and staff until recruitment was complete and irrevocable.	Reporting • The distributions of potential confounders in each intervention group of the patients were not described. • The characteristics of the patients lost to follow-up were not described. External Validity • The patients asked to participate in the study were not representative of the entire population of interest. • The patients included in the study were not representative of the entire population of interest. • It is unclear if the trial design was representative of the care setting. Bias • It is unclear if an attempt was made to blind the staff measuring the main outcomes. Confounding • Because the distributions of potential confounders in each intervention group of the patients were not described, it is unclear if adjustment for confounding was needed in the analysis for the main findings. • Losses of patients to follow-up were not taken into account. Power • Although the study reported significance in most of its findings, it is unclear if the study had sufficient power to detect clinically-important effects.	Bias • It is unclear if any post hoc analyses were conducted.

Table A6: Strengths and Limitations of Included Guidelines Using AGREE II

Strengths	Limitations
VA/DoD 2016[1]	
Scope and Purpose • Objectives were described. • Health questions were described. • Target populations were described. Stakeholder Involvement • The guideline was developed by individuals from all relevant professional groups. • Targets users were described. Rigour of Development • Systematic search methods were used. • Evidence selection criteria were described. • Appraisals on the quality of included evidence were provided. • Methods for formulating recommendations were described. • Recommendations considered benefits, harms, and quality of evidence, and their links to supporting evidence tables were explicit. • The guideline was externally reviewed by experts prior to its publication. Clarity of Presentation • Recommendations were unambiguous, specific for different types of conditions or issues, and easily identifiable. Editorial Independence • Funding sources were disclosed.	Stakeholder Involvement • Target population input was not sought. Rigour of Development • Recommendations did not consider costs. • A procedure for updating the guideline was not described. Applicability • Facilitators and barriers to implementing the guideline were not described. • The guideline did not provide links to tools and resources. • The guideline did not consider resource implications. • The guideline did not provide monitoring and/or auditing criteria. Editorial Independence • Potential conflicts of interest were reported but not disclosed in the report.
Kennedy 2016[16]	
Scope and Purpose • Objectives were described. • Health questions were described. • Target populations were described. Stakeholder Involvement • The guideline was developed by individuals from all relevant professional groups. • Targets users were described. Rigour of Development • Systematic search methods were used. • Evidence selection criteria were described. • Appraisals on the quality of included evidence were provided. • Methods for formulating recommendations were described. • Recommendations considered benefits, harms, and quality of evidence. • The guideline was externally reviewed through interactive workshops at major national conferences prior to its publication. Clarity of Presentation • Recommendations were unambiguous, specific for different types of conditions or issues, and easily identifiable. Editorial Independence • Funding sources were disclosed.	Stakeholder Involvement • Target population input was not sought. Rigour of Development • Recommendations did not consider costs, and their links to supporting evidence tables were not always explicit. • A procedure for updating the guideline was not described. Applicability • Facilitators and barriers to implementing the guideline were not described. • The guideline did not provide links to tools and resources. • The guideline did not consider resource implications. • The guideline did not provide monitoring and/or auditing criteria. Editorial Independence • Potential conflicts of interest were reported.

AGREE = Appraisal of Guidelines for Research and Evaluation; DoD = Department of Defense; VA = Department of Veteran Affairs

Appendix 4: Main Study Findings and Author's Conclusions

Table A7: Summary of Findings of Included Systematic Reviews

Main Study Findings	Author's Conclusion
Papadimitropoulou 2016[2]	
Depression Severity • In patients receiving ketamine, there was a significant reduction in placebo/sham-adjusted MADRS depression severity scores (MD = -14.0, 95% CI = -19.9 to -8.0). The effect size of ketamine was higher than that of any other comparator. • When ranked based on outcomes summarizing the median rank, ketamine was first, followed by risperidone augmentation and quetiapine augmentation. Response Rate • Compared to placebo/sham, the percentage of responders was 14-fold higher for ketamine. Ketamine showed a five-fold higher percentage of responders, compared to aripiprazole augmentation or rTMS. Study Quality • The overall quality of the included studies was rated as good, assessed by the Cochrane risk of bias tool, despite the majority of pharmacological and somatic interventions studies not adequately reporting the randomization and allocation concealment schemes.	• Ketamine demonstrated superior efficacy, with a faster reduction in depression severity and a higher response rate than any other pharmacological or somatic interventions for TRD at two weeks.
Xu 2016[9]	
Depression Severity • In patients receiving either low-dose or very-low-dose ketamine, there was a significant and largest reduction in placebo-adjusted HAM-D or MADRS depression severity scores after one day, which was attenuated after three and seven days. ○ Low and very-low doses combined (6 studies): ▪ 1 day: SMD = -1.1, 95% CI = -1.7 to -0.6, I^2 = 43.5% ▪ 3 days: SMD = -0.8, 95% CI = -1.4 to -0.3, I^2 = 41.6% ▪ 7 days: SMD = -0.5, 95% CI = -1.0 to 0.1, I^2 = 47.5% • Compared to patients receiving low-dose ketamine, patients receiving very-lose-dose ketamine experienced smaller and shorter-lived reductions in placebo-adjusted HAM-D or MADRS depression severity scores (p = 0.02 for the three-day comparison). ○ Low dose (4 studies): ▪ 1 day: SMD = -1.4, 95% CI = -2.0 to -0.9, I^2 = 0.0% ▪ 3 days: SMD = -1.2, 95% CI = -1.7 to -0.7, I^2 = 0.0% ▪ 7 days: SMD = -0.7, 95% CI = -1.3 to -0.1, I^2 = 35.9% ○ Very-low dose (2 studies): ▪ 1 day: SMD = -0.5, 95% CI = -1.5 to 0.5, I^2 = 54.0% ▪ 3 days: SMD = -0.1, 95% CI = -0.8 to 0.6, I^2 = 0.0% ▪ 7 days: SMD = -0.1, 95% CI = -1.2 to 1.1, I^2 = 65.7% • A large reduction in depression severity was evident within four hours in most trials. Treatment effects were largest after one day. • Treatment effects were smaller in patients with bipolar depression, compared to those with MDD, which was evident after 24 hours. Response Rate • Patients receiving low-dose ketamine were significantly more likely to be responders, compared to those receiving placebo. While patients receiving very-low-dose ketamine were not significantly more or less likely to be responders, compared to those receiving placebo, no	• A large, rapid benefit was observed in response and remission following a single dose of ketamine in patients with TRD. There was also a reduction in suicidality. There were no major medical events. Ketamine appears promising for the acute treatment of TRD. • Low-dose ketamine appeared more effective than very-low-dose ketamine.

Main Study Findings	Author's Conclusion
significant differences were identified between the two doses (p = 0.09 for the three-day comparison). ○ Low and very-low doses combined (8 studies): ▪ 1 day: RR = 2.6, 95% CI = 1.6 to 4.4, p = 0.0003 ▪ 3 days: RR = 2.4, 95% CI = 1.4 to 4.1, p = 0.002 ▪ 7 days: RR = 3.4, 95% CI = 1.6 to 7.1, p = 0.001 ○ Low dose (5 studies): ▪ 1 day: RR = 2.9, 95% CI = 1.6 to 5.2, p = 0.0004 ▪ 3 days: RR = 3.1, 95% CI = 1.7 to 5.9, p = 0.0004 ▪ 7 days: RR = 3.4, 95% CI = 1.6 to 7.3, p = 0.002 ○ Very-low dose (3 studies): ▪ 1 day: RR = 1.8, 95% CI = 0.6 to 5.7, p = 0.3 ▪ 3 days: RR = 1.1, 95% CI = 0.4 to 3.1, p = 0.9 ▪ 7 days: RR = 3.5, 95% CI = 0.2 to 62.3, p = 0.4 <u>Remission Rate</u> • Patients receiving low-dose ketamine were significantly more likely to have remission, compared to those receiving placebo. While patients receiving very-low-dose ketamine were not significantly more or less likely to have remission, compared to those receiving placebo, no significant differences were identified between the two doses (p = 0.12 for the three-day comparison). ○ Low and very-low doses combined (8 studies): ▪ 1 day: RR = 5.2, 95% CI = 2.1 to 12.9, p = 0.0003 ▪ 3 days: RR = 2.5, 95% CI = 1.2 to 5.0, p = 0.01 ▪ 7 days: RR = 2.6, 95% CI = 1.2 to 5.7, p = 0.02 ○ Low dose (5 studies): ▪ 1 day: RR = 5.1, 95% CI = 2.0 to 13.1, p = 0.0008 ▪ 3 days: RR = 3.4, 95% CI = 1.5 to 7.5, p = 0.003 ▪ 7 days: RR = 2.6, 95% CI = 1.2 to 6.0, p = 0.02 ○ Very-low dose (3 studies): ▪ 1 day: RR = 7.0, 95% CI = 0.4 to 120.2, p = 0.2 ▪ 3 days: RR = 0.9, 95% CI = 0.2 to 3.8, p = 0.9 ▪ 7 days: RR = 2.1, 95% CI = 0.1 to 44.4, p = 0.6 <u>Dropout Rate</u> • According to five studies, 26.1% of patients (i.e., 12/46) who received ketamine, compared to 9.1% of patients (i.e., 5/55) who received placebo, dropped out after treatment. However, most dropouts were reported as being due to changes in mood rather than adverse events. <u>Suicidality</u> • According to four studies, reported suicidality scores were generally low at baseline, with an average of 1.6 out of six on the MADRS suicidality item score. Nevertheless, in patients receiving either low-dose or very-low-dose ketamine, there was a significant reduction in placebo-adjusted HAM-D or MADRS suicide item scores after one and three days. ○ Low and very-low doses combined (7 studies): ▪ 1 day: SMD = -0.4, 95% CI = -0.7 to -0.2, I^2 = 0.0% ▪ 3 days: SMD = -0.4, 95% CI = -0.7 to -0.1, I^2 = 2.0% ▪ 7 days: SMD = -0.1, 95% CI = -0.4 to 0.1, I^2 = 0.0% <u>Adverse Events</u> • According to eight studies, low-dose ketamine was generally well-tolerated, with transient, mild-to-moderate dissociative symptoms and increases in blood pressure or heart rate in a minority of patients. Eleven events were reported in the ketamine group as serious AEs and included hypotension and bradycardia, a suicide attempt, tachycardia, and arterial pressure elevations.	

Main Study Findings	Author's Conclusion
Study Quality • The overall quality of the included studies was mixed, assessed by the Cochrane risk of bias tool.	
Parsaik 2015[10]	
Depression Severity • According to three studies, in patients receiving ketamine, there was a significant reduction in placebo-adjusted MADRS depression severity scores (SMD = -1.01, 95% CI = -1.37 to -0.66, $p < 0.0001$, $I^2 = 0\%$). • Treatment effects reached maximum after 40 minutes and lasted up to 14 days. Anhedonia Level • Ketamine reduced anhedonia, with effects lasting up to 14 days (no numerical data reported). Suicidal Thoughts • Ketamine reduced suicidal ideation (no numerical data reported). Adverse Events • According to two studies, no serious AEs were reported in any study. Mild-to-moderate AEs reported were similar between the ketamine and placebo groups and included feeling woozy or drowsy, cognitive impairment, fear, anxiety, nausea, dizziness, blurred vision, and headache. Study Quality • All three studies were of good quality, assessed using the Cochrane risk of bias tool, with low risk of bias across the criteria.	• Ketamine causes rapid and robust antidepressant response in patients with bipolar depression that may last up to 14 days. • Ketamine may also reduce anhedonia and suicidal ideation. • The safety and tolerability of ketamine was excellent, with none of the patients showing serious AEs.

AE = adverse event; CI = confidence interval; HAM-D = Hamilton depression rating scale; MADRS = Montgomery Åsberg depression rating scale; MD = mean difference; MDD = major depressive disorder; RR = relative risk; rTMS = repetitive transcranial magnetic stimulation; SMD = standardized mean difference; TRD = treatment-resistant depression

Table A8: Summary of Findings of Included Primary Studies

Main Study Findings	Author's Conclusion
Saligan 2016[11]	
Fatigue Severity • In patients receiving ketamine, there were significant reductions in placebo/sham-adjusted NIH-BFI fatigue severity scores over the course of 14 days, except for the 7th day. The effect size of the ketamine-placebo difference increased until, and was greatest on, the 2nd day (Cohen's d = 0.59, $p < 0.001$). It then decreased over time until the 14th day, reaching the lowest on the 7th day (Cohen's d = 0.14, $p > 0.05$).	• Ketamine rapidly improved fatigue relative to placebo in a group of individuals with treatment-resistant bipolar depression.
Allen 2015[3]	
Depression Severity • Ketamine and ECT were both associated with significant reductions in depressive symptoms, measured by HAM-D scores that decreased from about 20 pre-treatment to about 10 post-treatment (data presented as bar graphs; $p = 0.001$). Response Rates • A majority of patients receiving ketamine indicated a ≥50% reduction in HAM-D scores two hours after treatment.	• The efficacy of ECT and ketamine in TRD are comparable.
Ballard 2015[12]	
Suicidal Thoughts • In patients receiving ketamine, there were reductions in placebo/sham-adjusted BDI, HAM-D, MADRS, and SSI suicidal thought scores over the course of three days. The	• Repeated suicidal assessments over minutes to days appeared to detect improvements in suicidal

Main Study Findings	Author's Conclusion
effect size of the ketamine-placebo difference was greatest 40 minutes after treatment ($p < 0.05$). It then decreased or plateaued until the 3rd day.	thoughts after ketamine treatment, compared to placebo.
Murrough 2015[5]	
Neurocognitive Functioning • In patients receiving ketamine or active placebo, there were significant improvements in some domains (i.e., processing speed, verbal learning, and visual learning) of neurocognitive performance but not others (i.e., working memory and reasoning), measured by MCCB, between baseline and seven days after treatment. The effect of ketamine and that of active placebo were comparable.	• A single sub-anesthetic dose of ketamine had no deleterious effect on neurocognitive performance seven days after treatment, compared to midazolam.
Feder 2014[13]	

PTSD Severity
• In patients receiving ketamine, there were reductions in active placebo-adjusted IES-R scores 24 hours after treatment (MD = 12.7, 95% CI = 2.5 to 22.8, $p = 0.02$).
Depression Severity
• In patients receiving ketamine, there were significant reductions in active placebo-adjusted CGI-I, CGI-S, and some of the IES-R subscale scores but not in MADRS or QIDS-SR scores 24 hours after treatment. There were no significant reductions in active placebo-adjusted CAPS scores seven days after treatment.
  • CGI-I: MD = 1.2, 95% CI = 0.5 to 1.9, $p = 0.003$
  • CGI-S: MD = 1.0, 95% CI = 0.1 to 1.9, $p = 0.03$
  • IES-R intrusion subscale: MD = 4.0, 95% CI = -0.3 to 8.3, $p = 0.07$
  • IES-R avoidance subscale: MD = 4.8, 95% CI = 0.2 to 9.3, $p = 0.04$
  • IES-R hyperarousal subscale: MD = 3.9, 95% CI = 0.6 to 7.2, $p = 0.02$
  • MADRS: MD = 3.7, 95% CI = -7.5 to 14.9, $p = 0.51$
  • QIDS-SR: MD = 0.2, 95% CI = -3.9 to 4.3, $p = 0.93$
  • CAPS: MD = 8.7, 95% CI = -4.8 to 22.2, $p = 0.20$
Adverse Events
• Dissociative symptoms after treatment with ketamine, measured by BPRS, CADSS, and YMRS scores, were short-lived, peaking at 40 minutes, and had resolved by 120 minutes. No emergence of significant psychotic or manic symptoms was observed.
• The most frequently reported general AEs of ketamine versus active placebo in the first 24 hours following infusion included the following:
  • Blurred vision (36% versus 19%)
  • Dry mouth (21% versus 16%)
  • Restlessness (23% versus 10%)
  • Fatigue (21% versus 23%)
  • Nausea or vomiting (21% versus 3%)
  • Poor coordination (15% versus 3%)
  • Headache (13% versus 13%)
	• A single dose of ketamine was associated with rapid reductions in PTSD symptoms and comorbid depressive symptoms in patients with chronic PTSD.
	• Ketamine was generally well-tolerated without clinically-significant, persistent dissociative symptoms.

AE = adverse event; BDI = Beck depression inventory; BPRS = brief psychiatric rating scale; CADSS = clinician-administered dissociative states scale; CAPS = clinician-administered post-traumatic stress disorder scale; CGI-I = clinical global impression-improvement; CGI-S = clinical global impression-severity; CI = confidence interval; ECT = electroconvulsive therapy; HAM-D = Hamilton depression rating scale; IES-R = impact of event scale-revised; MADRS = Montgomery Åsberg depression rating scale; MCCB = MATRICS consensus cognitive battery; MD = mean difference; NIH-BFI = National Institute of Health-brief fatigue inventory; PTSD = post-traumatic stress disorder; QIDS-SR = quick inventory of depressive symptomatology-self report; SSI = scale for suicidal ideation; TRD = treatment-resistant depression; YMRS = young mania rating scale

Table A9: Summary of Findings of Included Guidelines

Recommendations and Supporting Evidence
VA/DoD 2016[1]
• Recommendation: Given the limited information on ketamine's safety and duration of effect, we recommend against the use of ketamine to treat severe, chronic, or recurrent MDD outside of a research setting (recommendation strength: strong). ○ Supporting evidence: Ketamine has demonstrated a rapid response in persons with MDD following a single infusion. A systematic review and meta-analysis assessed nine, non-electroconvulsive therapy studies that compared ketamine to placebo or midazolam in patients with treatment-resistant depression (n=192). Compared to controls, patients who received ketamine had significantly greater improvement on global depression scores within 24 hours of administration. Suicidal ideation was reduced in the two studies in which it was assessed. Ketamine's efficacy was maintained in patients on or off antidepressants in all subgroups and sensitivity analyses. Common side effects included dry mouth, tachycardia, increased blood pressure and the feeling of disassociation. Despite these preliminary positive findings in a limited number of studies, many questions remain unanswered. The studies to date have given a single dose of ketamine leaving the number and frequency of doses needed to treat an episode of MDD undetermined. The most common dose has been 0.5 mg/kg of body weight. Higher doses may be more likely to result in cardiovascular adverse effects and no dose ranging studies have been conducted. Ketamine has also not been studied in persons with co-occurring conditions. Thus, the identification of patients who would most benefit from ketamine and the best approach to dosing has not been established. Ketamine has shown promise as a treatment for patients with treatment-resistant MDD. Until the practical questions and long-term safety and efficacy concerns are addressed, ketamine should be reserved for investigational clinical trials. The panel encourages such clinical trials within and supported by the VA and DoD.
Kennedy 2016[16]
• Recommendation: CANMAT considers ketamine an experimental treatment and recommends its use be limited to academic depression treatment centres. ○ Supporting evidence: Several meta-analyses have shown that single doses of intravenous ketamine at 0.5 mg/kg have rapid antidepressant effects in treatment-resistant depression. However, ketamine is associated with psychotomimetic adverse effects, carries potential for abuse, and still has very limited data on safety and efficacy with longer-term use.

CANMAT = Canadian Network for Mood and Anxiety Treatments; DoD = Department of Defense; MDD = major depressive disorder; VA = Department of Veteran Affairs

Appendix 5: Additional References of Potential Interest

Guidelines under development:

- National Institute for Health and Care Excellence [Internet]. London: National Institute for Health and Care Excellence. Depression in adults: recognition and management; [in progress] [cited 2017 Feb 28]. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0725/documents

- National Institute for Health and Care Excellence [Internet]. London: National Institute for Health and Care Excellence. Post-traumatic stress disorder (update); [in progress] [cited 2017 Feb 28]. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ng10013/documents

Non-evidence-based guidelines:

- Ketamine: drug information. In: UpToDate [Internet]. Waltham (MA): UpToDate; 2017 [cited 2017 Feb 28]. Available from: www.uptodate.com Subscription required.