

TITLE: Intravenous Ketamine for the Treatment of Mental Health Disorders: A Review of Clinical Effectiveness and Guidelines

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CONTEXT AND POLICY ISSUES

Mental health disorders include anxiety, mood, and personality disorders. In any given year, one in five people in Canada experiences a mental health problem or illness, with a cost to the economy of well in excess of \$50 billion.¹ For the purposes of this paper, the focus will be on major depressive disorder (MDD), post-traumatic stress disorder (PTSD) and suicidal ideation. According to a 2011-12 Statistics Canada report, MDD has affected roughly 10% of Canadians in their lifetime and nearly 4% having a depressive episode in the past 12 months.^{2,3} Nearly 10% of Canadians have had suicidal thoughts at some point in their life and just over 1% of the Canadian population is currently suffering from PTSD.^{2,3} There are many issues with current pharmacotherapies used for mental health disorders. Some of these issues include the stigma of having a psychiatric illness, the side effects, and a perceived lack of response.⁴ A prior study in MDD patients found that roughly 30% of depressed patients discontinue medications within 30 days and more than 40% discontinue within 90 days making adherence a large issue.⁴ Clinical practice guidelines recommend a 6 to 12 month trial to adequately assess efficacy but due to these issues and a delayed onset of action, current pharmacotherapies are not an ideal in treatment option for acute and chronic episodes of mental health disorder.⁴

Ketamine emerged as a novel treatment for certain mental health disorders in 2000 when Berman et al.⁵ published a seven patient RCT of intravenous (IV) ketamine compared to a saline placebo showing a reduction in the Hamilton Depression Rating Scale (Ham-D). This was the first suggestion that ketamine could be a benefit for treating mental health disorder and since previous investigations on treatment of mental health disorders have focused on the monoamines (dopamine, norepinephrine and serotonin) this approach may have great potential. Current psychiatric guidelines for treatment of MDD, PTSD, and suicidal ideation do not include statements regarding the use of ketamine however research continues to be published.

Ketamine is a rapid acting, non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that is used as a general anesthetic with analgesic properties used in human and veterinary medicine.⁶⁻⁸ The NMDA receptor mediates glutamate excitatory neurotransmission in the brain,

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and it is hypothesized that a dysfunction in this regulation may play a role in the etiology of depressive symptoms.^{6,7} Ketamine is proposed to help balance the dysfunction, however, by blocking the NMDA receptor; side effects such as vivid dreams and a dissociative effect (where the patient experiences a separation of body and mind) occur frequently.^{7,8} While these side effects are undesirable for the therapeutics, it has created an illicit market for ketamine in certain populations where it is better known as “Special K”.⁷

Ketamine can be given through several routes including intravenous push or infusions, intramuscular, intranasal, and orally.^{6,8,9} Investigations have mainly utilized IV infusions due to the precise dosing and ability to adjust if known side effects occur. Patients who receive ketamine require close monitoring of blood pressure, heart rate, respiratory rate, transcutaneous O₂ saturation as well as for emergence reactions (recovery reaction including agitation, hallucinations, dreams and depersonalization) when ketamine wears off.⁸ For this reason, current practice is for patients to receive the infusions in clinics with monitoring capabilities, which may be a significant shift in practice from current oral pharmacotherapy where patients can be monitored as outpatients.⁸⁻¹⁰

Given the lack of direction from major psychiatric associations, the utility of ketamine for certain mental health disorders is uncertain. The purpose of this report is to review the clinical effectiveness of intravenous ketamine for the treatment of depression, PTSD, and suicidal ideation, as well as the evidence-based guidelines for its use in these conditions.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of intravenous ketamine for the treatment of mental health disorders?
2. What are the evidence-based guidelines for the use of intravenous ketamine for the treatment of mental health disorders?

KEY FINDINGS

Major Depressive Disorder (MDD)

Current evidence has consistently shown that IV ketamine may improve symptoms scored by the MADRS and HAM-D scoring tools at 24 hours in patients with MDD. However, identifying which patients are most likely to respond and the duration of response remains unknown.

Post-Traumatic Stress Disorder (PTSD)

There remains a paucity of good quality evidence to fully support IV ketamine in patients experiencing PTSD as only one randomized controlled trial (RCT) was identified. This is a new area for the use of a NMDA receptor antagonist and while current evidence is optimistic, more evidence with validated outcomes is required to ascertain the clinical effectiveness of IV ketamine in PTSD.

Suicidal Ideation

Current evidence suggests that IV ketamine may be a benefit for components of depression scoring tools related to suicidal ideation, however identifying which patients would benefit is difficult. More trials of higher quality that investigate hard outcomes such as suicide attempts

and using patients at risk of imminent suicide are required to determine clinical effectiveness of IV ketamine in suicidal ideation.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 6), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and July 22, 2014.

Selection Criteria and Methods

One reviewer screened the literature search results to identify relevant publications based on publication title and abstract. Full-text articles were considered for inclusion based on the selection criteria listed in Table 1.

Table 1: Selection Criteria	
Population	Adult patients with a mental health disorder (e.g. MDD, PTSD, suicidal ideation)
Intervention	IV Ketamine (an NMDA receptor antagonist)
Comparator	Placebo or usual care
Outcomes	Clinical effectiveness (e.g. symptom reduction measured by a recognized scale, quality of life) Safety (adverse events, harms) Guidelines for use
Study Designs	Health technology assessments, systematic reviews and meta-analyses, reviews, randomized controlled trials, non-randomized studies and evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1, if they were duplicate publications, or were published prior to January 1, 2009. Reviews which included studies reported in more recent systematic reviews (SR) were excluded.

Critical Appraisal of Individual Studies

Critical appraisal of a study was conducted based on a quality assessment (QA) tool appropriate for the particular study design. The AMSTAR checklist¹¹ was used for systematic reviews while the Downs and Black Checklist¹² was used for RCTs. For the critical appraisal, a numeric score was not calculated. Instead, the strength and limitations were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search identified a total of 190 citations. Of these, 178 citations were excluded during the title and abstract screening and 12 potentially relevant articles were retrieved for full-text review. Additionally, one potentially relevant clinical practice guideline was identified from the grey literature but ultimately was excluded as the population was patients with Obsessive Compulsive Disorder. Of these potentially relevant articles, two were RCTs already included in a selected SR, three were reviews superseded in the newer SR, one included only case reports, and one was a dose-response study. No evidence based-guidelines were identified for IV ketamine use in any of the mental health areas of interest. Ultimately, there was one SR included for MDD, one RCT for PTSD, and three SRs (including the one reporting on MDD) and one RCT included for suicidal ideation. A PRISMA flow chart outlining the selection process is provided in Appendix 1.

Summary of Study Characteristics

A detailed summary of included studies is provided in Appendix 2.

Major Depressive Disorder (MDD)

One high quality SR was included which originated in France.¹³ The aim of the paper was to determine the efficacy of ketamine in patients with a diagnosis of either MDD or bipolar depression regardless of prior treatment. The authors searched only for RCTs and were able to identify 13 articles for inclusion. The authors included a subgroup analysis examining IV ketamine for MDD. This subgroup contained six articles with 184 patients. One included trial used electroconvulsive therapy (ECT) as a standard of care. The efficacy of each trial was meta-analyzed using standardized mean differences (SMD) at 24 hours from the initial infusion and studies where this was unable to be calculated were excluded.

Post-traumatic Stress Disorder (PTSD)

One randomized, double-blind, active controlled (with midazolam), crossover trial was identified through the literature search specifically examining PTSD patients.¹⁴ Patients must have had a Clinician Administered PTSD Scale (CAPS) score of at least 50 without a history of alcohol use or dependence in the previous three months, active suicidal or homicidal ideation on presentation, or current use of any psychotropic medications. A total of 41 patients were identified for inclusion with the randomization deciding which infusion was first. There was a two week washout period between infusions however if any patient had a CAPS of less than 50 prior to the second infusion, they did not receive the second infusion. Patients were assessed using the Impact of Event Scale-Revised (IES-R) at 24, 48, and 72 hours then at 7 days after the initial infusion for efficacy.

Suicidal Ideation

Three SRs^{6,13,15} and one RCT¹⁶ were identified through the search originating in France, Ireland, Australia and the United States of America, respectively. The three SRs included studies with patients with a diagnosis of depression and were analyzed qualitatively for suicidal ideation based on secondary outcomes from the individual studies. In 2014, Fond¹³ published a SR of

RCTs with a meta-analysis for ketamine in depressed patients but included a subgroup of 5 RCTs that added suicidal ideation as a secondary outcome. The effects of ketamine on suicidal ideation were measured by the suicide item of the depression scales, and it is important to note that one trial excluded those at imminent risk for suicide. Naughton⁶ published a review in 2014, aiming to provide an overview of current literature regarding the rapid antidepressant effects of IV ketamine. As a subgroup, Naughton identified 7 articles that were published using ketamine in depressed patients with outcomes for suicidal ideation. These articles were of different designs including three RCTs and four open label trials, each of which had secondary outcomes assessing suicidal ideation. Previously, Katalinic¹⁵ published a review in 2013 looking specifically at subanaesthetic doses (<1mg/kg per dose) of ketamine in depressed patients. The authors identified three trials for a narrative review. Two of these articles are included in the previous systematic review by Naughton whereas the other article was an open label study including only treatment resistant MDD patients identifying the outcomes on the scale for suicidal ideation. Recently, Price¹⁶ published a randomized, double blind, active controlled (with midazolam) trial looking at the efficacy of ketamine to reduce suicidal ideation in patients who were free of psychotropic medications. The primary outcome for the trial was a difference in the suicide index composite (SI_{composite}, a combination of three different scoring tools including the Beck Scale for Suicidal Ideation (BSS), Montgomery-Asberg Depression Rating Scale Suicide Item (MADRS-SI), and the Quick Inventory of Depressive Symptoms Suicide Item (QIDS-SI)) between the two groups.

Summary of Critical Appraisal

A detailed description of individual study critical appraisal is provided in Appendix 3.

Major Depressive Disorder (MDD)

The SR by Fond¹³ reported rigorous methodology that included a comprehensive literature search of several databases with two authors working independently to ensure eligible articles were included. In addition, there was a clearly defined inclusion and exclusion criteria with a flowchart for the study selection process. The characteristics of included articles were well described in a table and the Cochrane Risk of Bias tool was used to help identify potential for bias. Of the six RCT subgroup included, two studies were identified as high risk for bias however the outcomes of these two studies did not vary from the other published literature. The blinding of ketamine is difficult given the characteristic side effect profile however some articles utilized an active placebo (a comparator that is meant to have similar side effects as the intervention) to help minimize the unblinding while others used placebo which may favor the intervention. The meta-analysis of all 6 RCTs identified an I² of 4.4% indicating the outcomes have low heterogeneity however each trial design was heterogeneous. These design differences are found in the controls, prior treatment options, use of concomitant psychiatric medications and potential for biases. The full SR included a funnel plot for publication bias which is appropriately cone shaped but does not directly assess the subgroup of studies reviewed. As well, the funding sources were stated however no conflict of interest statements were included.

Post-traumatic Stress Disorder (PTSD)

The randomized controlled trial by Feder¹⁴ included a well-defined *a priori* research question including an active placebo to help minimize unblinding due to the identifiable effects of ketamine. Patient flow, scoring tools, and timing of outcomes were specific however a power

calculation was not included to estimate number of participants required. As well, the study design excluded alcohol abuse patients which may limit the generalizability of the results. This was a crossover study which randomized the sequence of infusions with no description of allocation concealment. Furthermore, the second infusion may not have been indicated if the CAPS score was less than 50 for patients at 14 days from initial infusion, which from prior studies in MDD, was identified as a possible duration of effect from the initial ketamine infusion. This may cause some unblinding as well as decreasing the patient population for the subsequent infusion. Patient characteristics at baseline were not equivalent in several categories specifically; increased suicide attempts in the placebo group and more females in the intervention group, as well as a wide variety of PTSD causes. Given the attrition of 15% of the population mixed with another 15% of patients not completing the second infusion, randomization may have been compromised.

Suicidal Ideation

The three SRs^{6,13,15} included had varying primary research questions but each included a qualitative analysis of the outcomes on suicidal ideation. Each SR appeared to have comprehensive literature search strategies and included funding sources and conflict of interest statements except the review from Fond, which did not include a conflict of interest statement. The review by Fond¹³ included duplicate study extraction with study characteristics and quality assessment described for each included study. Conversely, Naughton⁶ and Katalinic¹⁵ did not have a second reviewer and the inclusion criteria were not explicit enough to permit replication. Additionally, both Naughton and Katalinic did not review included studies for methodological rigor or risk of bias.

The RCT completed by Price¹⁶ in 2014 was a subgroup of a previous study but this was not explicitly stated. The patient population and scoring tools are well defined but not validated and the use of an active placebo may minimize the risk for unblinding. However the scoring tools used were not validated. The randomization process and allocation concealment were not explicitly noted and the baseline characteristics of study groups were not equivalent with respect to a few categories including number of suicide attempts and “all suicide indices = 0”, which may favour the intervention. Furthermore, authors excluded patients at imminent risk for suicide which is questionable when trying to identify if IV ketamine can reduce suicidal ideations.

Summary of Findings

A detailed summary of individual study findings is provided in Appendix 4.

Major Depressive Disorder (MDD)

The SR¹³ included a meta-analysis for IV ketamine in MDD identifying a statistically significantly reduced SMD at 24 hours of -0.91 (95%confidence interval [CI] -1.19 to -0.64; $P < 0.01$). This is a score which is standardized across the different scales used (HAMD and MADRS) to ensure meta-analysis is appropriate. Since this outcome is for a subgroup of the entire population reviewed, the authors did not make any conclusions regarding this outcome however were able to make some general recommendations for mental health in its entirety. These recommendations include a series of baseline tests and investigations prior to ketamine administration and to be cautious in the elderly with cardiovascular disease. Furthermore, the authors were unable to determine if a dose-effect could be identified or if an anesthesiologist is necessary for infusions. However, the authors mention that the most common adverse effects

were transient and benign while the severe events (tachycardia and hypertension) occurred at doses between 0.8 mg/kg to 1.0 mg/kg.

Post-traumatic Stress Disorder (PTSD)

The included RCT¹⁴ identified that patients receiving ketamine (compared to the crossover of midazolam) had a statistically significant reduction in IES-R score by 12.7 (95% CI 2.5 to 22.8; $P=0.02$) at 24 hours from a baseline of 48.44. This is considered a rapid reduction in IES-R in a short period of time in patients with an average duration of PTSD over 10 years and an average CAPS score of 80 at baseline, signifying severe PTSD. Ketamine did not appear to effect the scoring in the MADRS or QIDS-SR scales at 24 hours but did affect the Clinical Global Impression Severity (CGI-S) and Clinical Global Impression Improvement (CGI-I) scales showing significant reductions in both compared to the patients who received midazolam. These patients all tolerated the infusion well and in several cases the reduced CAPS scores lasted more than 24 hours and in seven patients, lasted at least 14 days.

Suicidal Ideation

While each of the SRs^{6,13,15} does not explicitly make conclusions about the use of IV ketamine for suicidal ideation, each is able to suggest that there is promising potential for reducing suicidal ideation. Fond¹³ identifies that the pool of RCTs from which to make any assertions is too heterogeneous in both protocols and outcomes to formulate a conclusion. Furthermore, Fond questions whether the improvement in suicidal ideations is independent of global depression improvement. Meanwhile, Naughton⁶ suggests that the rapid antidepressant effects seen with ketamine may in part be due to the reduction in suicidal ideation and that further investigations are required. Naughton comments that the proof-of-concept has been developed given the benefits seen in reducing depression scoring as well as suicidal ideation but identifies several limitations to implementation in clinical practice. Katalinic¹⁵ specifically reviewed each of the three open label trials extracting the specific question scores from the Ham-D and MADRS on suicidal ideation. Each of the three studies was able to show a statistically significant decrease in suicidal ideation at varying times from 40 minutes to 24 hours. The sole RCT¹⁶ reviewing IV ketamine compared to midazolam on suicidal ideation identified a reduction at 24 hours in the explicit scale, $SI_{\text{composite}}$. While this is not a validated tool for identifying suicidal ideation, investigators were able to show that the differences between baseline and 24 hours for ketamine and midazolam had a large effect size as signified by the cohen d of 0.82 ($P=0.01$). Furthermore, secondary outcomes showed that 53% of ketamine treated patients scored a 0 on all three scoring tools at 24 hours compared to 24% in the midazolam group and 7% at baseline. These indicate that suicidal ideation is reduced from baseline with ketamine more so than with midazolam.

Limitations

Any study that uses ketamine as the intervention will face challenges ensuring all parties stay blinded. Given the unique side effect profile (i.e. dissociative effects, hypertension and nystagmus), both patients and clinicians may be able to identify which treatment group the patient is randomized to and therefore become unblinded. While active placebos may minimize this issue, it is still an ongoing risk and one that evaluators should be aware of. Other general limitations identified include the duration of antidepressant effects. Current studies have identified ketamine's peak effects at 24 hours with duration between 1 to 2 weeks in those who respond.⁶ This time frame may be valuable to implement non-pharmacological therapy to

supplement treatment however it does not allow for reasonable chronic therapy. Current use of IV ketamine is often restricted to settings with appropriate monitoring capabilities and in certain instances, patients are admitted to hospital. Given the shorter duration of action, repeated infusions and potential for hospitalizations may dramatically reduce adherence and increase costs to healthcare plans.

Major Depressive Disorder (MDD)

Fond¹³ completed a well done SR with meta-analysis reviewing data on all depression disorders however only a subgroup was analyzed for IV ketamine use in MDD. While it included 6 articles with a total of 184 patients, two articles were at high risk for bias. Some articles included patients with treatment resistant MDD while others did not specify this as a requirement. While this SR did not specify any conclusions for this patient population, the authors include practical considerations for all patients who may receive ketamine IV. There are currently no reviews specifically for treatment resistant MDD and generalizability of current evidence should be cautiously interpreted to certain patient populations including the elderly with cardiovascular risks and those with alcohol or substance abuse issues.

Post-Traumatic Stress Disorder (PTSD)

With one RCT¹⁴ found on this topic, there is a potential risk for publication bias. Reviewing the one RCT in depth identifies other significant issues including unbalanced baseline characteristics, compromised randomization and generalizability to the PTSD community. These design and implementation issues may favor the intervention. Currently, the minimal clinically important difference has not been developed for the IES-R which questions the impact of this as a primary outcome.

Suicidal Ideation

The current SRs^{6,13,15} have not specifically reviewed suicidal ideation as a clinical question but have investigated patients who have some suicidal ideation. While these reviews have suggested a benefit, it is important to note that these are secondary outcomes and often patients imminently at risk for suicide were excluded. The RCT¹⁶ was set up specifically to help answer this question however the authors also excluded patients at imminent risk of suicide. Furthermore, the RCT still had 7% of patients at baseline score a 0 on each of the BSS, MADRS-SI and QIDS-SI which indicates not all treatment resistant MDD are at risk for suicide. Given the lack of a validated tool and the complexity in identifying patients with suicidal ideation, identifying which patients would benefit from this intervention is difficult.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Current evidence supports the use of IV ketamine to reduce depression scores (i.e. MADRS or Ham-D) in patients with MDD however there is a lack of current evidence to suggest its place in therapy. Most studies did not specify previous treatment options in patients and were compared against placebo in many cases. There were no trials identified that compared IV ketamine to current therapies (i.e. SSRIs) and in many cases, patients required overnight hospitalization for monitoring which complicates the logistics of administrations. Ultimately, with specific indicators for patient response not adequately investigated combined with previous limitations, current evidence does not support its use in all patients with MDD.

Use of IV ketamine in patients with PTSD is at its infancy with one RCT identified in the literature search. This study found a rapid reduction in IES-R in a majority of patients with

PTSD, however, given the variety of outcomes assessed and the differences found in each scoring tool, more research is currently required to identify clinical effectiveness especially against current therapies.

Suicidal ideation has been investigated as part of several RCTs however it appears that it has only been investigated as a primary outcome in one RCT. Current evidence is of relatively poor quality but supports the use of IV ketamine to reduce suicidal ideation. Given current evidence, IV ketamine requires further investigations looking at reducing validated and hard outcomes (i.e. suicide attempts) in patients who are at risk for imminent suicide attempts to determine clinical effectiveness.

IV ketamine for these mental health illnesses requires further investigations to identify which patients would benefit (treatment resistant or naïve), how to best administer (IV or IM or Intranasal), in which setting (outpatient or inpatient) as well as duration of efficacy given that relapse is common in all mental health disorders. No evidence-based guidelines were identified that comment on IV ketamine use in any of these mental health illnesses.

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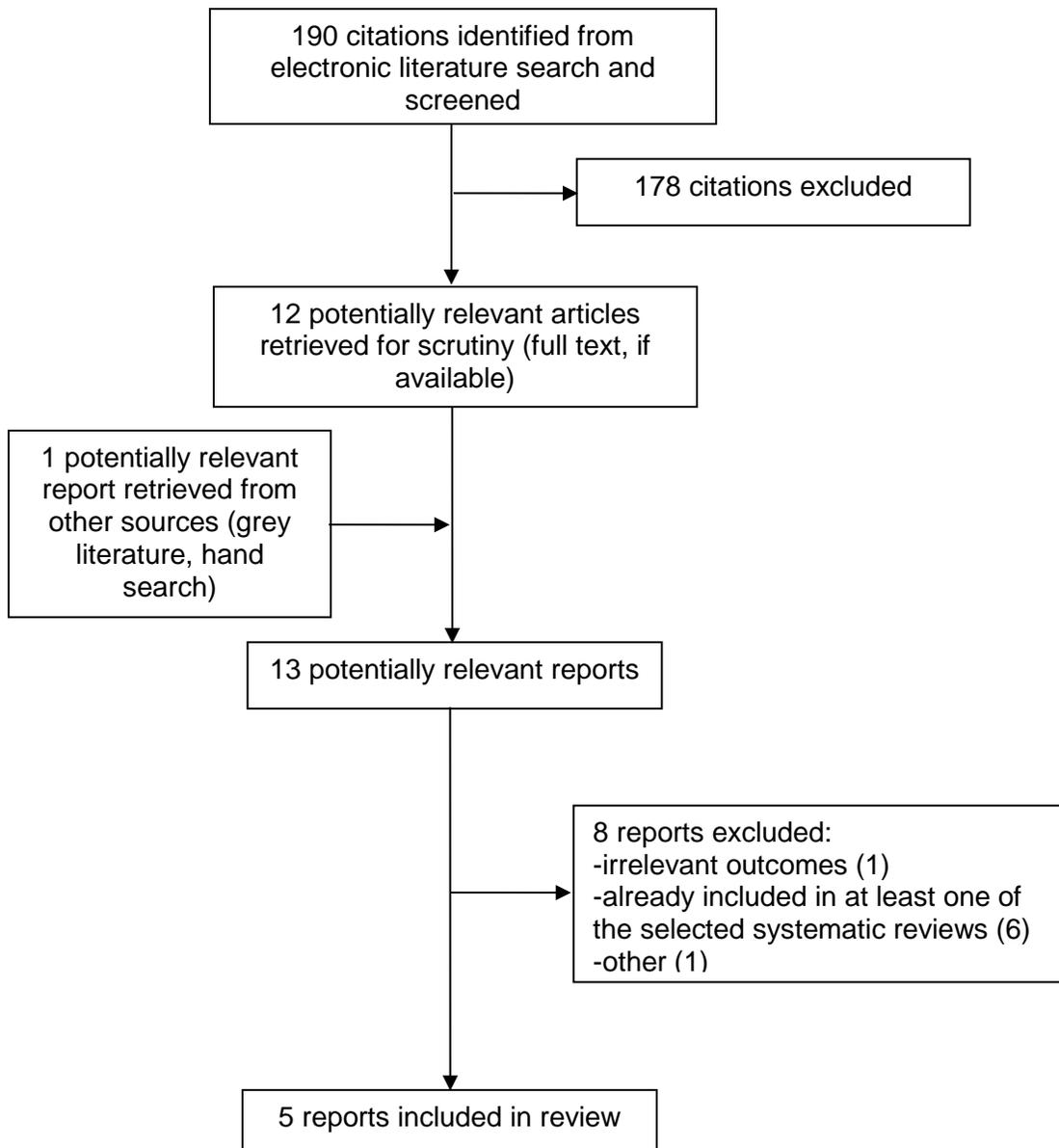
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APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Studies

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size (n)	Intervention	Comparators	Outcomes Measured
Systematic reviews (SR)					
<i>Major Depressive Disorder (MDD)</i>					
Fond, 2014, France ¹³	SR-MA (subgroup analysis with 6 RCTs for ketamine IV in MDD only) Inclusion RCTs, ketamine, participants with diagnosis of MDD or BD, validated scale for depression severity Exclusion absence of comparison, if a SMD could not be calculated	MDD (defined by DSM-IV, MADRS ≥ 20 , and/or MMSE ≥ 27), n = 184 (Some patients were their own controls)	1. Ketamine IV 2. Ketamine IV + thiopental 3. Ketamine IV + fentanyl + propofol	1. Placebo or midazolam 2. ECT + thiopental 3. Propofol + fentanyl	Primary SMD @ 24 hours of MADRS or Ham-D, Secondary Efficacy on suicidal ideation, dose effect, ADRs, duration of efficacy
<i>Suicidal Ideation</i>					
Fond, 2014, France ¹³	SR (presented as a qualitative review of 5 RCT's found measuring suicidal ideation) Inclusion RCTs, ketamine, participants with diagnosis of MDD or BD,	MDD (defined by DSM-IV, MADRS ≥ 20 , and/or MMSE ≥ 27), n = 150 (Some patients were their own controls) *one study excluded patients at serious or imminent	1. Ketamine IV 2. Ketamine IV + thiopental 3. Ketamine IV + fentanyl + propofol	1. Placebo or midazolam 2. ECT + thiopental 3. Propofol + fentanyl	Secondary Efficacy on suicidal ideation

	<p>validated scale for depression severity</p> <p>Exclusion absence of comparison, if a SMD could not be calculated</p>	suicidal risk"			
Naughton, 2014, Ireland ⁶	<p>SR</p> <p>Inclusion Relevant clinical reports involving the assessment of ketamine's antidepressant potential were considered</p> <p>Exclusion No focus on ketamine as antidepressants, abstract form, non-English trials</p>	Berman et al., 2000; Zarate et al., 2006; Price et al., 2009; DiazGranados et al., 2010b; Zarate et al., 2012	N/A	N/A	N/A
Katalinic, 2013, Australia ¹⁵	<p>SR</p> <p>Inclusion depressed patients receiving ketamine, ketamine dose <1mg/kg, assessing mood outcomes, publication in a peer-reviewed journal</p>	Price et al., 2009; Larkin et al., 2011; Thakurta et al., 2012	N/A	N/A	N/A

	Exclusion Non-English articles				
Randomized Controlled Trials					
<i>Post-Traumatic Stress Disorder (PTSD)</i>					
Feder, 2014, USA ¹⁴	R, DB, AC, XO trial Inclusion Chronic PTSD (defined by DSM-IV-TR and CAPS ≥ 50) Exclusion History of psychotic or bipolar disorder, alcohol abuse, suicidal / homicidal ideation, or use of any psychotropic medications	18-55 y/o, n = 41 (pt's were own control with 2 week washout period, would receive next infusion if CAPS ≥ 50)	Ketamine IV 0.5mg/kg over 40 minutes	Midazolam IV 0.045mg/kg over 40 minutes	Primary Outcome IES-R @ 24 hours Secondary Outcome IES-R @ 48, 72 hours, 7 days MADRS, QIDS-SR, CGI-S, CGI-I @ 24,48,72 hours and 7 days Safety ADRs
<i>Suicidal Ideation</i>					
Price, 2014, USA ¹⁶	R, DB, AC trial (2:1 ratio) Inclusion outpatients with CRIDS ≥ 32 , free of psychotropic medication- for ≥ 1 week prior to infusion (or 4 weeks if on fluoxetine) Exclusion If patient	> 18 y/o With treatment resistant MDD not at imminent risk for suicide, n = 57	Ketamine IV 0.5mg/kg over 40 minutes once	Midazolam IV 0.045mg/kg over 40 minutes once	Primary Outcome explicit SI composite score at 24 hr

	deemed unsafe by psychiatrists				
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SR – systematic review, MDD – Major depressive disorder, MA – Meta-analysis, IV – Intravenous, RCT – Randomized controlled trial, BD – Bipolar disorder, SMD – Standardized mean difference, DSM-IV - Diagnostic and Statistical Manual of Mental Disorders 4th edition, MADRS - Montgomery–Asberg Depression Rating Scale, MMSE – Mini-mental state exam, n – Number of patients, ECT – Electroconvulsive therapy, Ham-D – Hamilton depression rating scale, ADR – Adverse drug reaction, PTSD – Post-traumatic stress disorder, N/A – Not applicable, R – Randomized, DB – Double blind, AC – Active control, XO – Crossover, CAPS – Clinician administered post-traumatic stress disorder scale, IES-R – Impact of event scale revised, QIDS-SR – Quick inventory of depressive symptomatology self-reported, CGI-S – Clinical global impression severity scale, CGI-I – Clinical global impression improvement scale, CRIDS – Clinician rated inventory of depressive symptomatology score, SI – suicidal ideation

APPENDIX 3: Summary of Study Strengths and Limitations

First Author, Publication Year, Country	Strengths	Limitations
Systematic reviews (SR) and meta-analyses (MA)		
<i>Major Depressive Disorder (MDD)</i>		
Fond, 2014, France ¹³	<ul style="list-style-type: none"> • The objective was clearly stated • The inclusion and exclusion criteria were stated • Comprehensive literature search • Study selection described and flow chart presented • List of included studies provided • Article selection and data extraction were done in duplicate • Characteristics of the individual studies were provided • Quality assessments of studies were conducted • Methods used to combine the findings of studies were appropriate • Publication bias was assessed • Funding source stated 	<ul style="list-style-type: none"> • Grey literature was not included • List of excluded studies was not provided • Subgroup analysis used for Ketamine IV in MDD • No conflict of interest statement
<i>Suicidal Ideation</i>		
Fond, 2014, France ¹³	<ul style="list-style-type: none"> • The objective was stated • The inclusion and exclusion criteria were stated • Comprehensive literature search • Study selection described and flow chart presented • List of included studies provided • Article selection and data extraction were done in duplicate • Characteristics of the individual studies were provided • Quality assessments of studies were conducted • Methods used to combine the findings of studies were appropriate • Publication bias was assessed • Funding source stated 	<ul style="list-style-type: none"> • Grey literature was not included • List of excluded studies was not provided • Qualitative review only • No conflict of interest statement
Naughton, 2014, Ireland ⁶	<ul style="list-style-type: none"> • The objective was stated • Comprehensive literature search including the bibliographies of papers identified 	<ul style="list-style-type: none"> • List of excluded studies was not provided • Does not appear to search grey literature

	<ul style="list-style-type: none"> List of included studies provided Funding source and conflict of interest stated 	<ul style="list-style-type: none"> Search strategy and article identification completed by one person Study selection not well defined Inclusion criteria vaguely stated as “relevant clinical reports involving the assessment of ketamine’s antidepressant potential” Patient characteristics not provided in detail No assessment for methodological rigor or risk of bias in included studies
Katalinic, 2013, Australia ¹⁵	<ul style="list-style-type: none"> The objective was stated The inclusion and exclusion criteria were stated Comprehensive literature search including all types of published literature List of included studies provided Characteristics of the individual studies were provided in detail Funding source and conflict of interest stated 	<ul style="list-style-type: none"> Grey literature was not included List of excluded studies was not provided Search strategy and article identification completed by one person Study selection not well defined No assessment for methodological rigor or risk of bias in included studies
Randomized Controlled Trials		
<i>Post-Traumatic Stress Disorder (PTSD)</i>		
Feder, 2014, USA ¹⁴	<ul style="list-style-type: none"> Well described background and a specific hypothesis Well defined scoring tools and timing of measurements for primary and secondary outcomes Patient characteristics clearly defined Patient flow well described Active placebo (internal validity) Adverse reactions described Randomized infusion schedule 	<ul style="list-style-type: none"> More females in treatment arm and causes of PTSD variable Trial design excludes CAPS score <50 for 2nd infusion Excluded patients with alcohol abuse or dependence in 3 months (likely NOT representative of entire population) No allocation concealment described Blinding an issue given distinct adverse effects of ketamine (internal validity) Large attrition bias (15%) with another 15% not completing the 2nd infusion due to design Power calculation done but not achieved
<i>Suicidal Ideation</i>		
Price, 2014,	<ul style="list-style-type: none"> Well described background and 	<ul style="list-style-type: none"> Study is a part of another study

<p>USA¹⁶</p>	<p>a specific hypothesis</p> <ul style="list-style-type: none"> • Well defined scoring tools and timing of measurements for primary and secondary outcomes • Patient population and treating facility are generalizable to expected settings • Active placebo (internal validity) • Results well described with intention to treat analysis • Loss to follow up not an issue 	<p>and does not describe randomization or allocation concealment</p> <ul style="list-style-type: none"> • Patient characteristics defined but randomization may have been compromised due to subgroup selection • Patient baseline characteristics similar except more suicide attempts in midazolam and more “all suicide indices = 0”, older patients and longer duration of illness in ketamine group • Excluded patients at imminent risk for suicide • Adverse events reported in prior trial may not be indicative of these patients • Blinding an issue given distinct adverse effects of ketamine (internal validity) • Conflict of interest states financial benefits if FDA approves indication
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SR – systematic review, MA – Meta-analysis, MDD – Major depressive disorder, IV – Intravenous, PTSD – Post-traumatic stress disorder, CAPS – Clinician administered post-traumatic stress disorder scale, FDA – United States Food and Drug Administration

APPENDIX 4: Main Study Findings and Authors' Conclusions

Author, Publication Year, Country	Main Findings and Authors' Conclusion	
Systematic reviews (SR) and meta-analyses (MA)		
<i>Major Depressive Disorder (MDD)</i>		
Ford, 2014, France ¹³	Main findings:	
	Subgroup of Ketamine IV in MDD only	
	Primary Outcome	Findings
	SMD of depression scores at 24 hours	-0.91; 95%CI -1.19, -0.64; P<0.01; I ² =4.4%
	Secondary Outcome	Findings
	Efficacy on suicidal ideation	See chart under Suicidal Ideation
	Dose effect	No comment for specific subgroup
	Adverse events	Dissociative symptoms (i.e., feeling outside of one's body or perceiving that time is moving more slowly or more quickly than normal), emotional blunting, euphoria, dizziness, headache, blurred vision, dry mouth, poor concentration, increased blood pressure, nausea, vomiting, increased libido, poor coordination, restlessness
Duration of efficacy	No comment on specific subgroup	
Author's Conclusions:		
There are no comments or conclusions from the authors regarding the ketamine IV in MDD subgroup population.		
The authors have several notes about the use of ketamine in mental health:		
<ul style="list-style-type: none"> • “patients with alcohol dependence and substance abuse were excluded ... as well as those with a history of psychotic episode” (page 12) • “results cannot be extrapolated to date to ... mood disorders in the elderly for whom the cardiovascular risk of ketamine administration may outweigh the benefit.” (page 12) • “the calculation of a dose effect was not possible” (page 9) 		
And several recommendations:		
<ul style="list-style-type: none"> • “All patients should have a physical examination, routine hematologic and biochemical tests, urine toxicology measurements, and an electrocardiogram to detect unstable medical illness or substance use before ketamine administration.” (page 12) • “it does not seem possible to determine if the presence of an anesthesiologist is necessary during ketamine administration in a psychiatric ward.” (page 12) 		
Overall Conclusions		

	<ul style="list-style-type: none"> • “The present meta-analysis confirmed ketamine’s efficacy in depressive disorders.” (page 13) • “The use of ketamine should remain cautious for patients with cardiovascular history.” (page 13) • “Middle- and long-term efficacy and side effects are still not known to date.” (page 13) 						
<i>Suicidal Ideation</i>							
<p>Fond, 2014, USA¹³</p>	<p>Results: “The effect of ketamine administration on suicidal thoughts was mostly measured by the suicide item of the depression scales in the non-ECT studies” (page 9)</p> <ul style="list-style-type: none"> • patients at serious and imminent suicidal risk were excluded, but those only presenting suicidal ideations were not <p>“... patients who received ketamine had lower suicidal ideation scores from the 40th minute to day 2 and at day 10” (page 9)</p> <p>Author’s Conclusion</p> <ul style="list-style-type: none"> • “Promising results ... should be confirmed in future studies because of the high degree of heterogeneity of current protocols and assessments of suicidal ideations.” (page 12) • “...not possible to conclude to a specific effect of ketamine on suicidal ideations” (page 12) 						
<p>Naughton, 2014, Ireland⁶</p>	<p>Results: “[Studies] demonstrated that ketamine was associated with robust and rapid antisuicidal effects” (page 3) “...early antisuicidal effects (within one day) were found with ketamine and these effects remained significant for several weeks” (page 3) “Repeated ketamine infusions can also reduce suicidality ratings (MADRS-SI) but only as long as the duration of the 12-day repeated infusion trial” (page 3)</p> <p>Author’s Conclusions:</p> <ul style="list-style-type: none"> • “... provided us with clinical proof-of-concept that ketamine ... have rapid antidepressant effects in affective disorders and appear to reduce suicidal ideation” (page 3) • “... ketamine’s effect peaks at 24 hours post infusion and, in general, last 1–2 weeks” (page 3) • “If these rapid-acting antidepressants could be safely integrated into treatment, one might shorten or mitigate hospitalization, prevent lost work or school days, reduce suicide and reduce healthcare costs” (page 9) 						
<p>Katalinic, 2013, Australia¹⁵</p>	<p>Results: Three open-label studies have suggested that ketamine may be an appropriate treatment to rapidly reduce acute suicide risk in depressed patients</p> <table border="1" data-bbox="418 1829 1386 1896"> <thead> <tr> <th>Study</th> <th>Time</th> <th>Ham-D-SI</th> </tr> </thead> <tbody> <tr> <td>Thakurta et al.,</td> <td>Baseline</td> <td>1.37 (1.3)</td> </tr> </tbody> </table>	Study	Time	Ham-D-SI	Thakurta et al.,	Baseline	1.37 (1.3)
Study	Time	Ham-D-SI					
Thakurta et al.,	Baseline	1.37 (1.3)					

	(2012)		
		40 minutes	0.41
		230 minutes	1.37
			Suicidal Ideation item on MADRS
	Larkin and Beautrais (2011)	Baseline	3.9 (SEM 0.4)
		40 minutes	0.6 (SEM 0.2)
		80 minutes	0.6 (SEM 0.2)
		120 minutes	0.7 (SEM 0.2)
		240 minutes	0.6 (SEM 0.1)
	Price et al., (2009)	Baseline	2.85 (1.64)
	24 hours	0.77 Response defined as > 50% decrease	
Author's Conclusion:			
<ul style="list-style-type: none"> No conclusions from authors about suicidal ideation "While almost all studies have found significant antidepressant effects with ketamine administration, it is clear that not all patients respond ... research should begin to focus on identifying predictors of response" (page 16) "Of the studies that followed participants until relapse, about one-third reported relapse within 3 days, one-third reported relapse in about a week, and one-third reported relapse between 20 and 40 days" (page 16) 			
Randomized Controlled Trials			
<i>Post-Traumatic Stress Disorder (PTSD)</i>			
Feder, 2014, USA ¹⁴	Main Findings:		
	Primary Outcome	Change in scores (95%CI)	
	IES-R @ 24 hours, compared to crossover	12.7 (2.5, 22.8; p=0.02)	
	Secondary Outcome	Findings	
	MADRS change @ 24 hrs, compared to crossover	3.7 (-7.5, 14.9; p=0.51)	
	QIDS-SR change @ 24 hrs, compared to crossover	0.2 (-3.9, 4.3; p=0.93)	
	CGI-S change @ 24 hrs, compared to crossover	1.0 (0.1, 1.9; p=0.03)	
	CGI-I change @ 24 hrs, compared to crossover	1.2 (0.5, 1.9; p=0.003)	
	Safety Outcomes	Findings	
	Adverse Effects	Common: Blurred vision, dry mouth, restlessness, fatigue, nausea/vomit, poor coordination Serious: 3 patients required acute beta-	

	<p style="text-align: right;">blocker use due to hypertensive urgency</p> <p>Author Identified Limitations "... several patients did not receive a second infusion" (page 7) "...ketamine was associated with transient but higher rates of dissociative symptoms than midazolam, likely affecting the blind" (page 7)</p> <p>Author's Conclusions:</p> <ul style="list-style-type: none"> • "A single dose of ketamine was associated with rapid reduction of core PTSD symptoms ... in patients with chronic PTSD" (page 7) • "We also demonstrated that a single dose of IV ketamine is a safe and generally well-tolerated intervention for patients with chronic PTSD" (page 7) 																																				
<i>Suicidal Ideation</i>																																					
Price, 2014, USA ¹⁶	<p>Results:</p> <table border="1" data-bbox="418 787 1323 1171"> <thead> <tr> <th>Primary Outcome</th> <th>Time</th> <th>Ketamine</th> <th>Midazolam</th> </tr> </thead> <tbody> <tr> <td rowspan="2">SI_{composite}</td> <td>Baseline</td> <td>0.15 (2.66)</td> <td>-0.21 (2.12)</td> </tr> <tr> <td>24 hours</td> <td>-2.23 (1.63)</td> <td>-0.91 (2.52)</td> </tr> <tr> <td colspan="4" style="text-align: center;">Cohen d = 0.82 (p=0.01)</td> </tr> <tr> <td rowspan="2">BSS</td> <td>Baseline</td> <td>6.11 (6.76)</td> <td>6.19 (6.68)</td> </tr> <tr> <td>24 hours</td> <td>1.13 (2.65)</td> <td>3.95 (6.46)</td> </tr> <tr> <td rowspan="2">MADRS-SI</td> <td>Baseline</td> <td>1.61 (1.37)</td> <td>1.48 (1.03)</td> </tr> <tr> <td>24 hours</td> <td>0.72 (1.05)</td> <td>1.24 (1.26)</td> </tr> <tr> <td rowspan="2">QIDS-SI</td> <td>Baseline</td> <td>0.97 (0.84)</td> <td>0.76 (0.76)</td> </tr> <tr> <td>24 hours</td> <td>0.22 (0.54)</td> <td>0.62 (0.74)</td> </tr> </tbody> </table> <ul style="list-style-type: none"> • "53% of ketamine-treated patients scored 0 on all three explicit suicide measures at 24 hours, compared with 24% of the midazolam group at 24 hours ($P = 0.03$) and 7% of all patients at baseline" (page 4) • 86.1% of ketamine-treated patients scored below a BSS score of 4 (sometimes considered a clinically meaningful cut-off) at 24 hours compared to 61.9% of the midazolam group at 24 hours ($p = 0.04$) and 47.4% of all patients at baseline" (page 4) <p>Author's Conclusion:</p> <ul style="list-style-type: none"> • "... ketamine-treated patients exhibited large, rapid reductions in explicit suicidal cognition, which were significantly greater than reductions observed in midazolam-treated patients" (page 6) • "...results are consistent with the contention that ketamine's rapid antidepressant actions could have life-saving potential" (page 7) • "... ketamine may work most efficaciously in individuals at the highest risk of suicide" (page 7) 	Primary Outcome	Time	Ketamine	Midazolam	SI _{composite}	Baseline	0.15 (2.66)	-0.21 (2.12)	24 hours	-2.23 (1.63)	-0.91 (2.52)	Cohen d = 0.82 (p=0.01)				BSS	Baseline	6.11 (6.76)	6.19 (6.68)	24 hours	1.13 (2.65)	3.95 (6.46)	MADRS-SI	Baseline	1.61 (1.37)	1.48 (1.03)	24 hours	0.72 (1.05)	1.24 (1.26)	QIDS-SI	Baseline	0.97 (0.84)	0.76 (0.76)	24 hours	0.22 (0.54)	0.62 (0.74)
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