Review article

The acute antisuicidal effects of single-dose intravenous ketamine and intranasal esketamine in individuals with major depression and bipolar disorders: A systematic review and meta-analysis

Jiaqi Xiong [a], Orly Lipsitz [c], David Chen-Li [c], Joshua D. Rosenblat [a,b,c], Nelson B. Rodrigues [c], Isabelle Carvalho [c], Leanna M.W. Lui [c], Hartej Gill [c,d], Flora Narsi [c], Rodrigo B. Mansur [c], Yena Lee [c], Roger S. McIntyre [a,b,c,d,e,*]

[a] *Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada*
[b] *Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada*
[c] *Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, Ontario, Canada*
[d] *Institute of Medical Science, University of Toronto, Toronto, ON, Canada*
[e] *Brain and Cognition Discovery Foundation, Toronto, ON, Canada*

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ABSTRACT

The efficacy of ketamine in reducing suicidal ideation (SI) has been previously reported. We aimed to evaluate acute anti-SI effects of single-dose ketamine in different formulations/routes of administration by pooling results from randomized controlled trials (RCTs). A systematic search was conducted on Cochrane, Embase, Medline, and PubMed from inception to July 1st, 2020. Studies were selected based on pre-determined eligibility criteria. Effect sizes of different formulations/routes at various time points were computed using random-effects models. With data from nine eligible RCTs (n = 197), the pooled effect size for anti-SI effects at the 24-h time point was 1.035 (N = 6, CI: 0.793 to 1.277, p < 0.001) for intravenous (IV) racemic ketamine and 1.309 (N = 1, CI: 0.857 to 1.761, p < 0.001) for intranasal (IN) esketamine. An additional five RCTs were available for qualitative analysis. RCTs were identified for oral/sublingual ketamine for depression, however, none of these trials reported anti-SI effects preventing quantitative analysis for these routes of delivery. No RCTs for intramuscular (IM) ketamine were identified. The findings suggest that single-dose IV ketamine/IN esketamine is associated with robust reductions in suicidal thoughts at 2-h, 4-h, and 24-h post-intervention. In addition, future studies on IM/oral/sublingual ketamine and comparative studies are warranted to evaluate the anti-SI efficacy of distinct formulations and routes of administration.

1. Introduction

According to the World Health Organization (WHO; 2014), the global suicide mortality rate is over 800,000 per year while the estimated suicide attempts (SA) are around 16 million per year (WHO, 2014). Suicide has been identified as the second leading cause of death amongst individuals between the ages of 15–29, and high-income countries have the highest rates of suicide (Organization and Others, 2014, 2019). Of further relevance, the current COVID-19 pandemic has resulted in unprecedented psychological distress, unemployment rates, and financial uncertainty, which is projected to result in a substantial increase in suicide rates (McIntyre and Lee, 2020; Xiong et al., 2020).

Fast-acting anti-suicidality agents are needed for patients experiencing severe major depressive episodes or SI (Malhi et al., 2015). The National Action Alliance for Suicide Prevention has identified rapid-onset psychopharmacological agents for suicidality as a primary research vista (Claassen, 2013). The rapid-onset antidepressant effects of ketamine have been demonstrated in numerous RCTs (aan het Rot et al., 2010; Murrough et al., 2013; Zarate et al., 2006). The clinical effectiveness of ketamine in a real-world population presenting with SI has also been previously reported by our group in an open-label design (McIntyre et al., 2020b).

Although ketamine's exact mechanism of action remains to be understood, it is known to be a non-competitive N-methyl D-aspartate

(NMDA) receptor antagonist with effects at a variety of other low-affinity targets (Zanos et al., 2016). Esketamine, an enantiomer of ketamine, has recently been approved for treatment-resistant depression (TRD) by the U.S Food & Drug Administration (FDA), European Medicines Agency, and Health Canada with additional approvals occurring globally. Moreover, in the United States, the FDA has issued a supplemental indication for the treatment of adults with MDD with acute SI/suicidal behavior (Titusville, 2020). However, its clinical effectiveness in reducing SI/suicidal behavior and anti-SI mechanisms still require further research to establish. In addition, the availability of ketamine in different formulations, routes of administration, and dosage raise the possibility of differential efficacy and the design of an optimal treatment regimen.

Extant open-label trials, RCTs, and systematic reviews have demonstrated results favoring the acute anti-SI efficacy of ketamine (Bartoli et al., 2017; Reinstatler and Youssef, 2015; Wilkinson et al., 2018; Witt et al., 2020). Reinstatler and Youssef (2015) performed a systematic review examining the anti-suicidal efficacy of single-dose subanaesthetic ketamine; six clinical studies and three case reports (n = 137) were identified in which ketamine was observed to improve suicidal ideation as early as 40-min post-treatment and two studies reported a sustained improvement in SI up to 10-day post-ketamine (Reinstatler and Youssef, 2015). A meta-analysis of five open-labeled trials (n = 99) observed consistently large effect sizes of single-dose intravenous (i.v.) ketamine in reducing SI within 4-h post-intervention, with the pooled standardized mean difference (SMD) being -0.92 (95% CI = -1.40 to -0.44; p < 0.001) (Bartoli et al., 2017). Moreover, Wilkinson et al. (2018) pooled individual-participant level data from 165 subjects from 10 comparison intervention trials, in which moderate-to-large effect sizes (Cohen's d = 0.51 to 0.85) were reported at various time points after single-dose i.v. ketamine treatment. Importantly, rapid and significant reductions in SI scores were noted on both clinician-administered and self-reported scales (p < 0.001 for both) (Wilkinson et al., 2018). A recent meta-analysis by Witt et al. (2020) examining the short-term and long-term anti-SI effects of single-dose ketamine (n = 572) observed similar results that support its effectiveness. Moderate and significant reductions in SI-scores were noted at 4-h (SMD = -0.51, 95% CI = [-1.00, -0.03]), between 12 and 24-h (SMD = -0.63, 95% CI = [-0.99, -0.26]), and between 24 and 72-h (SMD = -0.57, 95% CI = [-0.99, -0.14]) post-ketamine. Nevertheless, several caveats should be noted. All included studies in Reinstatler and Youssef (2015) and Bartoli et al. (2017) were uncontrolled and non-blinded while many studies from Wilkinson et al. (2018) and Witt et al. (2020) only implemented single-item from depression inventories for SI assessment. Moreover, none of the aforementioned systematic reviews compared the effect sizes of distinct formulations/routes of administration despite potential differences in their anti-SI efficacy. Herein, we conducted a systematic review and meta-analysis in an attempt to compare the acute anti-SI effects of single-dose ketamine across different formulations/routes of administration with results from RCTs, examine potential moderator effects of the SI scales implemented, and provide insights into optimizing SI treatment with ketamine.

2. Methods

2.1. Search strategy and eligibility criteria

We systematically searched PubMed, Medline, Embase, and Cochrane databases from inception date to July 1st, 2020 following the PRISMA guidelines (Preferred Reporting Items for Systematic Review and Meta-Analyses) (Moher et al., 2010). Additional studies were identified from other sources. The search strings and procedures were presented as a supplementary file. Any randomized, placebo-controlled, and double-blinded clinical trials that assessed SI within 24-h after single-dose ketamine administration were eligible for inclusion. Studies were excluded if they: i) only measured SI > 24-h post-intervention. ii)

were conference abstracts/posters. iii) were observational studies, open-label trials, or trials with unpublished data. v) were not available in full text. vi) looked at a subpopulation (e.g. pediatric patients).

Titles, abstracts, and full text of the studies were screened by two reviewers (JX and DCL) independently based on eligibility criteria after duplicates were removed. Consensuses were reached via a follow-up discussion.

2.2. Data extraction

Mean differences (with SD) between baseline and endpoint mean scores or pre- and post-intervention scores (with SD) in SI measures were obtained/calculated from each study. Data from more commonly used and validated scales would be extracted if multiple SI scales were implemented in a study. Corresponding authors were contacted for data if the outcomes at the point of interest were not reported. A period of two weeks was given for response, in which three authors responded and provided relevant data. The following information were extracted: 1) Lead author; 2) Sample size; 3) Sample characteristics; 4) Study design; 5) Control/placebo (dose); 6) Ketamine (dose); 7) Route of administration; 8) Method of assessment; 9) Data for effect size calculation; 10) Primary findings. If multiple studies reported on the same dataset, the study with more exhaustive and relevant information would be included.

2.3. Statistical analysis

All statistical analyses were performed on Comprehensive Meta-Analysis 2.0 & 3.0 (CMA 2.0 & 3.0). Effect sizes (Hedge's *g*) were computed using pre- and post-intervention mean scores (with SD) at points of interest (i.e., 2-h, 230-min/4-h, and 24-h post-treatment) or their mean differences (with SD) with calculated t-values. Considering the interdependent relationship between pre- and post-intervention scores, a conventional correlation of 0.5 was taken into account when calculating the effect sizes if correlation coefficients were not reported in the study (Newby et al., 2015). A sensitivity analysis was conducted using a correlation coefficient of 0.75 and 0.25 to test the robustness of the results. For Hedge's *g* score, $g < 0.2$, $0.2 < g < 0.8$, and $g > 0.8$ indicate small, medium, and large effects respectively.

A random-effects model was used for pooling effect sizes considering a potentially high-degree of between-study heterogeneity. Effect sizes were pooled for all trials and for trials with different formulations/routes of administration to compare relative efficacy. Results of pooled effect sizes were presented in a forest plot. Meta-regression analyses were undertaken to examine any moderation effects of SI scales used (multiple-item vs. single-item scales) and the placebo administered (saline vs. midazolam).

Heterogeneity was quantified using I^2 statistics. For the I^2 statistics, 25% = small, 50% = moderate, and 75% = high heterogeneity (Higgins et al., 2003). Publication bias was examined using funnel plots. Tests for funnel plot asymmetry would be conducted as necessary following the guidelines (Page et al., 2019).

A qualitative synthesis of findings was included for RCTs that were not presented with sufficient data for inclusion in the meta-analysis.

2.4. Risk of bias assessment

Study bias assessment was conducted using the *Cochrane risk-of-bias tool for randomized trials* independently by JX and DCL (Higgins et al. n. d.). Potential biases were examined concerning six domains: risk of bias arising from randomization process, risk of bias due to deviation from intended treatment, risk of bias due to missing outcome data, risk of bias in the measurement of outcome, risk of bias in the selection of reported results, and overall risk of bias. Any conflicts were resolved through further discussion and involvement of a third reviewer (OL). The results of *the Cochrane-risk-of-bias assessment* were presented in Table 1.
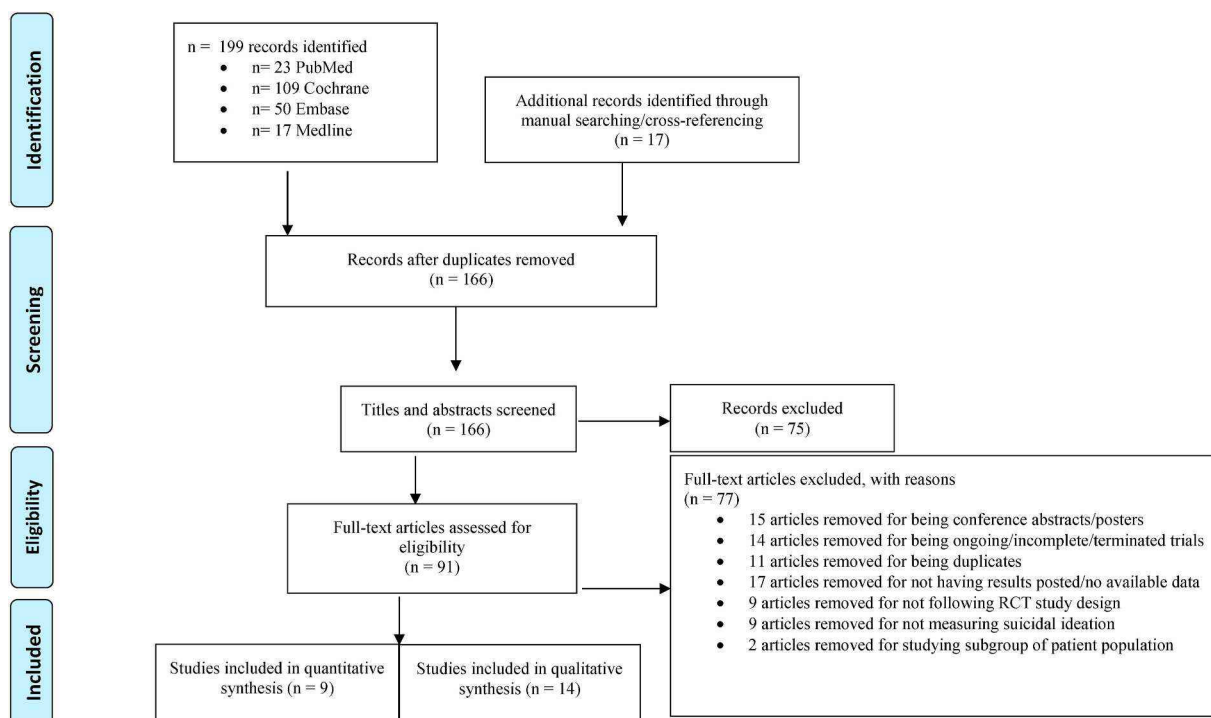
Table 1
Cochrane risk of bias assessment.

	Domain 1: Risk of bias arising from the randomization process	Domain 2: Risk of bias due to deviations from intended treatment	Domain 3: Risk of bias due to missing outcome data	Domain 4: Risk of bias in measurement of the outcome	Domain 5: Risk of bias in selection of the reported result	Domain 6: Overall risk of bias
Canuso et al. (2018)	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Unclear risk
Grunebaum et al. (2017)	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Grunebaum et al. (2018)	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Unclear risk
Hu et al. (2016)	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Ionescu et al. (2019)	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Murrough et al. (2015)	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Phillips et al. (2020)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Price et al. (2014)	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sinyor et al. (2018)	Unclear risk	Low risk	Low risk	Low risk	High risk	Unclear risk
Burger et al. (2016)	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Chen et al. (2019)	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Domany et al., 2019	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Fu et al. (2020)	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Unclear risk
Zarate et al. (2012)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

3. Results

3.1. Search results

The procedures of study selection are presented in a PRISMA flowchart (Fig. 1). A total of 199 publications were identified from the initial search. An additional 17 studies were identified from other sources (e.g. review paper, clinical trial report). 166 articles remained after duplicates were removed, of which 75 were excluded after titles and abstracts screening, and 91 articles were accessed for full-text evaluation. 77 publications were removed after the full-text screening for being conference abstracts/posters, being incomplete/ongoing/terminated clinical trials, being duplicates, the absence of results/data, not following RCT study design, for lacking SI assessment, for studying subpopulation (e.g. pediatric patients/the elderly population). In the remaining 14 articles, data from nine trials were obtained via extraction from the publications/results posted on clinicaltrials.gov/relevant meta-analysis (Canuso et al., 2018; Grunebaum et al., 2017; Hu et al., 2016; Ionescu

Identification

n = 199 records identified
- n= 23 PubMed
- n= 109 Cochrane
- n= 50 Embase
- n= 17 Medline

Additional records identified through manual searching/cross-referencing (n = 17)

Screening

Records after duplicates removed (n = 166)

Titles and abstracts screened (n = 166)

Records excluded (n = 75)

Eligibility

Full-text articles assessed for eligibility (n = 91)

Full-text articles excluded, with reasons (n = 77)
- 15 articles removed for being conference abstracts/posters
- 14 articles removed for being ongoing/incomplete/terminated trials
- 11 articles removed for being duplicates
- 17 articles removed for not having results posted/no available data
- 9 articles removed for not following RCT study design
- 9 articles removed for not measuring suicidal ideation
- 2 articles removed for studying subgroup of patient population

Included

Studies included in quantitative synthesis (n = 9)

Studies included in qualitative synthesis (n = 14)

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study selection flow diagram.

et al., 2019; Murrough et al., 2015; Price et al., 2014) or were sent by corresponding authors upon contact (Grunebaum et al., 2018; Phillips et al., 2020; Sinyor et al., 2018). The other five publications where data were not readily available were included only for the qualitative synthesis (Burger et al., 2016; Chen et al., 2019; Domany et al., 2020; Fu et al., 2020; Zarate et al., 2012).

3.2. Study characteristics and quality appraisal

The total pooled sample of all RCTs (k = 9) included 341 participants (n = 197 received racemic ketamine/esketamine, n = 58 received saline, n = 123 received midazolam). Seven studies implemented multiple-item SI scales (i.e., Beck Scale for Suicide Ideation- BSS/I; Scale for Suicide Ideation- SSI; The Columbia-Suicide Severity Rating Scale- C-SSRS) and two trials utilized single-item from depression inventories (i.e., The Montgomery–Åsberg Depression Rating Scale-Item 10- MADRS-SI; Quick Inventory of Depressive Symptomatology- Item 13- QIDS-SI). A majority of studies (k = 6) in the meta-analysis utilized midazolam as an active control while three used saline. Out of the thirteen studies included in the qualitative synthesis, two trials examined IN esketamine while the other eleven trials administered IV racemic ketamine. Study characteristics were summarized in Table 2.

3.3. The acute anti-SI efficacy of ketamine with distinct formulations

Included in the quantitative analysis were eight studies testing the efficacy of IV racemic ketamine (Grunebaum et al, 2017, 2018; Hu et al., 2016; Ionescu et al., 2019; Murrough et al., 2015; Phillips et al., 2020; Price et al., 2014; Sinyor et al., 2018) and one study assessing the anti-SI effects of IN esketamine (Canuso et al., 2018). While we identified several other RCTs evaluating the antidepressant effects of intranasal/sublingual/oral formulations, none of these studies reported suicidality measures so could not be included in the pooled quantitative analysis (Arabzadeh et al., 2018; Daly et al., 2018; Domany et al., 2019; Fedgchin et al., 2019; Jafarinia et al., 2016; Lapidus et al., 2014). No RCTs testing intramuscular/subcutaneous ketamine were identified.

Effect sizes were summarized in Table 3. The effect size of all formulations across all time points is 1.029 (N = 9, 95% CI: 0.748 to 1.310, p < 0.001), indicative of a significantly large effect. The effect sizes for both formulations at distinct time points are all large and significant. At 2-h post-treatment, the effect size for both formulations was 1.633 (N = 3, 95% CI: 0.802 to 2.465 p < 0.001) (Hu et al., 2016; Phillips et al., 2020; Sinyor et al., 2018). At 230-min/4-h post-intervention, the pooled effect size for IV racemic ketamine and IN esketamine was 1.096 (N = 5, 95% CI: 0.576 to 1.617, p < 0.001) (Canuso et al., 2018; Grunebaum et al, 2017, 2018; Hu et al., 2016; Ionescu et al., 2019). At 24-h post-intervention, the Hedge's *g* score for both formulations was 1.080 (N = 7, 95% CI: 0.860 to 1.300, p < 0.001) (Canuso et al., 2018; Grunebaum et al, 2017, 2018; Hu et al., 2016; Murrough et al., 2013; Phillips et al., 2020; Price et al., 2014).

Concerning the effect sizes of distinct formulations, IV racemic ketamine had a larger effect size than IN esketamine at 230-min/4-h and a smaller effect size at 24-h post-intervention. At 230-min/4-h post-treatment, IV racemic ketamine had a *g*-score of 1.166 (N = 4, 95% CI: 0.409 to 1.923, p = 0.003) (Grunebaum et al, 2017, 2018; Hu et al., 2016; Ionescu et al., 2019). At 24-h post-treatment, IV racemic ketamine had a Hedge's *g*-score of 1.035 (N = 6, 95% CI: 0.793 to 1.277, p < 0.001) (Grunebaum et al, 2017, 2018; Hu et al., 2016; Murrough et al., 2013; Phillips et al., 2020; Price et al., 2014). The only eligible study that tested IN esketamine had effect sizes of 1.023 (N = 1, 95% CI: 0.615 to 1.432, p < 0.001) and 1.309 (N = 1, 95% CI: 0.857 to 1.761, p < 0.001) at 230-min/4-h and 24-h post-intervention respectively (Canuso et al., 2018). The 2-h effect size of IV racemic ketamine is 1.633 (N = 3, 95% CI: 0.802 to 2.465, p < 0.001) while the IN esketamine trial did not assess SI scores at 2-h post-intervention (Hu et al., 2016; Phillips et al., 2020; Sinyor et al., 2018). Effect size measures of all studies, grouped by

routes of administration at different time points were shown in forest plots (Figs. 3 – 5).

Sensitivity analysis using a correlation coefficient of 0.75 or 0.25 supported the robustness of the results. Meta-regression analyses using random-effects models did not detect significant moderator effects of SI measurement scales used (single-item vs. multiple items) or the use of different (active) placebos (midazolam or saline).

3.4. A narrative synthesis

Notable reductions in SI-scores 2-h/230-min/4-h/24-h post-intervention were noted in all except one study in which Ionescu et al. (2019) only observed a slight and insignificant decrease in SI-scores 4 h after a single infusion of 0.5 mg/kg IV racemic ketamine.

Eleven out of thirteen included studies examined SI-treatment effects of IV racemic ketamine. Statistically significant reductions in SI-scores were noted in five out of six studies testing IV racemic ketamine at 2-h post-treatment (Chen et al., 2019; Domany et al., 2020; Hu et al., 2016; Phillips et al., 2020; Zarate et al., 2012) while the remaining study by Sinyor et al. (2018) did not report on statistical significance due to the use of exploratory analysis. Nonetheless, greater reductions in SI-scores in patients receiving ketamine were observed (Sinyor et al., 2018). Four out of seven studies examining SI reductions at 230-min/4-h post-treatment reported significantly more robust anti-SI effects of IV racemic ketamine compared to the placebo (Burger et al., 2016; Chen et al., 2019; Hu et al., 2016; Zarate et al., 2012). The two trials by Grunebaum et al. observed notable reductions in SI-scores 230-min/4-h after IV racemic ketamine administration that were nevertheless not statistically significant compared to the placebo (Grunebaum et al, 2017, 2018). Differential drug effects from IV racemic ketamine 24 h after treatment were reported in four studies (Chen et al., 2019; Hu et al., 2016; Price et al., 2014; Zarate et al., 2012). On the other hand, the IV racemic ketamine trials by Phillips et al. (2020) and Grunebaum et al. (2017, 2018) failed to detect such significant differences when compared to the placebo at the 24-h time point. Murrough et al. (2015) reported conflicting results with different SI scales, with MADRS-SI scores suggesting a significantly greater reduction 24-h post-intervention while results from BSI demonstrated significant differences at 48-h but not 24-h.

In the two trials testing IN esketamine, no statistically significant improvements in SI were reported in ketamine-treatment patients compared to the placebo at the 24-h time point (Canuso et al., 2018; Fu et al., 2020). Canuso et al. (2018) also reported SI-score changes 4-h post-intervention, at which there were differentially superior SI treatment effects of ketamine compared to the placebo when assessed by MADRS-SI.

3.5. Heterogeneity and publication bias

The heterogeneity across all studies (k = 9) was moderate-to-high and significant (p = 0.018, I^2 = 56.82%). The heterogeneity across IV racemic ketamine studies (k = 8) was moderate-to-high and significant (p = 0.013, I^2 = 60.56%). The heterogeneity of IN esketamine study could not be determined due to the small sample size (k = 1).

Funnel plot asymmetry (Fig. 2) was observed, indicating potential publication bias. Statistical tests for funnel plot asymmetry were not recommended as the number of included studies (k = 9) was smaller than ten (Page et al., 2019).

4. Discussion

This systematic review further established the acute anti-SI effects of single-dose IV racemic ketamine/IN esketamine in patients with affective disorders with the large and significant effect sizes computed from nine RCTs comprising 197 ketamine-treated patients. Despite our effort, the limited number of RCTs identified renders it improbable to compare

Table 2

Summary of study characteristics.

Lead author	Sample size (n)	Sample characteristics	Study design	Control (dose)	Ketamine (dose)	Routes	SI-scale	Statistics for effect-size calculation	Hedge's g score	Study Findings
Canuso et al. (2018)	C = 31 E = 34	Aged 19–64 years old; MDD diagnosis based on DSM-IV; MADRS ≥22; Imminent risk for suicide	Parallel RCT	Saline + standard-of-care treatment	84 mg esketamine + standard-of-care treatment	IN	Self-report BSS	4-h mean difference (mean ± SD): Esketamine = 10.2 (9.74) 24-h mean difference (mean ± SD): Esketamine = 12.9 (9.63)	4-h = 1.023 24-h = 1.309	Levels of improvement in SI differed with different SI-scales being implemented. With MADRS-SI, significantly greater improvement in SI was observed 4-h post-ketamine but not at 24-h or day 25. With the clinician global judgment of suicide risk, no statistically significant differences were observed when comparing ketamine and the placebo.
Grunebaum et al. (2017)	C = 9 K = 7	Aged 18–65 years old; BD diagnosis based on DSM-IV; HDRS-17 ≥ 16; SSI ≥4	Parallel RCT	0.02 mg/kg midazolam	0.5 mg/kg racemic ketamine hydrochloride	IV	Clinician-rated SSI	Baseline (mean ± SD): Ketamine = 16.7 (8.4) 230-min (mean ± SD): Ketamine = 5.71 (6.10) 24-h (mean ± SD): Ketamine = 4.29 (5.74)	230-min = 1.271 24-h = 1.451	Reductions in SI were noted 230-min and 24-h post-ketamine. Differences were not statistically significant between two treatment groups despite the large effect size observed with ketamine treatment.
Grunebaum et al. (2018)	C = 40 K = 40	Aged 18–65 years old; MDD diagnosis based on DSM-IV; HAMD ≥16; SSI ≥4	Parallel RCT	0.02 mg/kg midazolam	0.5 mg/kg racemic ketamine hydrochloride	IV	Clinician-rated SSI	230-min mean difference (mean ± SD): Ketamine = 9.28 (6.99) 24-h mean difference (mean ± SD): Ketamine = 8.23 (6.99)	230-min = 1.155 24-h = 1.300	Clinically meaningful improvements in SI were observed 230-min and 24-h in ketamine receiving group.
Ionescu et al. (2019)	C = 13 K = 13	Aged 18–65 years old; MDD diagnosis based on DSM-IV; HDRS-28 ≥ 20; C-SSRS ≥1	Parallel RCT	Saline	0.5 mg/kg racemic ketamine hydrochloride	IV	C-SSRS	Baseline (mean ± SD): Ketamine = 14.4 (5.2) 4-h (mean ± SD): Ketamine = 13.1 (5.5)	4-h = 0.227	No obvious and significant improvement in SI in ketamine-treatment patients 4 h after single-fusion when compared to placebo-treated patients.
Hu et al. (2016)	C = 14 K = 13	Aged 18–60 years old; MDD diagnosis based on DSM-IV; HAMD ≥24	Parallel RCT	Saline + 10 mg/kg escitalopram	0.5 mg/kg racemic ketamine hydrochloride + 10 mg/kg escitalopram	IV	Self-report QIDS-SI	Baseline (mean ± SD): Ketamine = 1.9 (0.7) 2-h (mean ± SD): Ketamine = 0.3 (0.4) 4-h (mean ± SD): Ketamine = 0.3 (0.5) 24-h (mean ± SD): Ketamine = 0.7 (0.7)	2-h = 2.462 4-h = 2.399 24-h = 1.605	Adjunctive ketamine treatment with escitalopram is significantly more rapid and effective than the placebo with escitalopram in alleviating SI (from 2-h to 72-h post-intervention).
Murrough et al. (2015)	C = 12 K = 12	Aged 18–80 years old; Presence of mood disorders; MADRS-SI ≥4	Parallel RCT	0.045 mg/kg midazolam + standard-of-care treatment	0.5 mg/kg racemic ketamine hydrochloride	IV	Self-report BSI	Baseline (mean ± SD): Ketamine= 17.5 (7.2) 24-h (mean ±	24-h = 0.786	Significantly more reductions in SI in the ketamine-treated group when compared to the

Table 2 (*continued*)

Lead author	Sample size (n)	Sample characteristics	Study design	Control (dose)	Ketamine (dose)	Routes	SI-scale	Statistics for effect-size calculation	Hedge's g score	Study Findings
					+ standard-of-care treatment			SD): Ketamine= 10.8 (8.5)		midazolam-treated group at 48-h post-treatment but not at 24 h, as indicated by BSI-score. MADRS-SI in the ketamine-treated group had more significant reductions at 24-h post-treatment as compared to the placebo.
Phillips et al. (2020)	37 (cross-over)	Aged 18–65 years old; MDD diagnosis based on the DSM-IV-TR; MADRS ≥25; TRD; MADRS-SI ≥2	Cross-over RCT	0.03 mg/kg midazolam	0.5 mg/kg racemic ketamine hydrochloride	IV	Clinician-rated MADRS-SI	2-h mean difference (mean ± SD): Ketamine = 1.51 (1.69) 24-h MADRS-SI score (mean ± SD): Ketamine = 1.65 (1.42)	2-h = 1.138 24-h = 0.870	When compared to the placebo-treated group, there were greater reductions in SI in the ketamine group as indicated by MADRS-SI scores 2-h and 7-day after treatment. No differential anti-SI effects were observed 24-h post-intervention as compared to placebo.
Price et al. (2014)	C = 21 K = 36	Aged 21–80 years old; MDD diagnosis based on DSM-IV; TRD; IDS-C ≥32	Parallel RCT	0.045 mg/kg midazolam	0.5 mg/kg racemic ketamine hydrochloride	IV	Self-report BSS	Baseline (mean ± SD): Ketamine = 6.11 (6.76) 24-h (mean ± SD: Ketamine = 1.13 (2.65)	24-h = 0.826	There were significant reductions in explicit suicide cognition 24-h post-treatment in the ketamine group when compared to the placebo group.
Sinyor et al. (2018)	C = 4 K = 5	Aged 18–65 years old; MDD diagnosis; SSI/CSSRS>0	Parallel RCT	0.045 mg/kg midazolam	0.5 mg/kg racemic ketamine hydrochloride	IV	Clinician-rated SSI	2-h change in mean SSI-score (mean ± SD): Ketamine = 11.6 (5.68)	2-h = 1.634	Greater reductions in SI were noted in ketamine treated patients 2-h post-intervention when compared to placebo.
Burger et al. (2016)	C = 7 K = 3	Aged 18–65; Acute depression and suicidality; BSS≥4	Parallel RCT	Saline	0.2 mg/kg racemic ketamine hydrochloride	IV	Self-report BSS	N/A	N/A	Patients receiving ketamine reported significant improvement in SI 4-h posttreatment.
Chen et al. (2019)	C = 24 K = 23 (0.2 mg/kg) K = 24 (0.5 mg/kg)	Aged 21–64 years old; MDD diagnosis based on DSM-IV;	Parallel RCT	Saline	0.2 or 0.5 mg/kg racemic ketamine hydrochloride	IV	HAMD-item 3; MADRS-SI	N/A	N/A	Subanaesthetic doses of ketamine had significantly more anti-SI effects when compared to placebo. The effects of which may last up to 2 weeks. BDNF Val55Met polymorphism modulates ketamine's anti-SI effects.
Domany et al., 2019	C = 9 K = 9	Aged 18–65 years old; MDD diagnosis based on DSM-IV; Baseline suicidal ideation (BSS-5>3; C-SSRS>3)	Parallel RCT	Saline	0.2 mg/kg racemic ketamine hydrochloride	IV	Self-report BSS; Clinician-rated MADRS-SI	N/A	N/A	Single infusion of 0.2 mg/kg ketamine over 5 min was more effective in alleviating SI at 90-to-180-min post-intervention as compared to placebo as assessed by BSS. According to MADRS-SI, greater alleviation in SI was observed 120-min post-intervention.
Fu et al. (2020)	C = 112 E = 111	Aged 18–64 years old; MDD	Parallel RCT	Nasal spray placebo +	84 mg esketamine +	IN		N/A	N/A	Intranasal esketamine +

Table 2 (*continued*)

Lead author	Sample size (n)	Sample characteristics	Study design	Control (dose)	Ketamine (dose)	Routes	SI-scale	Statistics for effect-size calculation	Hedge's g score	Study Findings
		diagnosis based on DSM-5; MADRS >28		standard-of-care treatment	standard-of-care treatment		Clinician-rated CGI–SS–r			standard-of-care treatment provided greater improvement in SI in patients with active SI at 24-h post-treatment. Differences in anti-SI effects were not statistically significant when compared to placebo.
Zarate et al. (2012)	15 (cross-over)	Aged 18–65 years old; BPD-I/II diagnosis based on DSM-IV; MADRS ≥20	Cross-over RCT	Saline	0.5 mg/kg racemic ketamine hydrochloride	IV	Clinician-rated MADRS-SI, HDRS-SI; Self-report BDI.	N/A	N/A	Significant SI improvement was observed in ketamine-treated patients at 40-min to 3-day post-treatment when compared to the placebo group.

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* BDI: Beck's Depression Inventory.
* BSI/BSS: Beck Scale for Suicidal Ideation.
* C-SSRS: Columbia-Suicide Severity Rating Scale.
* C= Control; E=Esketamine; K= Ketamine.
* CGI-SS-r: The Clinical Global Impression - Severity of Suicidality - Revised.
* DSM-IV: Diagnostic and Statistical Manual of Mental Disorder.
* HAM-D: Hamilton Depression Rating Scale.
* IDS-C: Inventory for Depressive Symptomatology-Clinician.
* IN= Intranasal; IV= Intravenous.
* MADRS-SI: Montgomery-Asberg Depression Rating Scale- Suicide Item.
* MDD: Major Depressive Disorder; BD: Bipolar Disorder.
* QIDS-SI: The Quick Inventory of Depressive Symptomatology- Self-Report.
* RCT: Randomized Controlled Trial.
* SI: Suicidal Ideation.
* SSI: The Scale for Suicidal Ideation.
* TRD: Treatment Resistant Depression.

Table 3
The effect sizes (Hedge's g score) of IV racemic ketamine vs. IN esketamine.

	IV racemic ketamine	IN esketamine	All routes	Pooled sample size [IV]	Pooled sample size [IN]
2-h	1.633 (n = 3)	N/A	1.633 (n = 3)	55	N/A
230-mins/4-h	1.166 (n = 4)	1.023 (n = 1)	1.096 (n = 5)	73	34
24-h	1.035 (n = 6)	1.309 (n = 1)	1.080 (n = 7)	145	34
Pooled Within Category	1.015 (n = 8)	1.166 (n = 1)	1.029 (n = 9)	163	34
				197	

the anti-SI efficacy of ketamine across disparate formulations and/or routes. The failure to identify RCTs for IM/oral/sublingual formulations that reported suicidality measures also suggested a lack of sufficiently high-quality studies with these formulations.

The inclusion of RCTs that mostly (7/9) utilized multiple-item SI scales (i.e., BSS, SSI, C-SSRS) in our meta-analysis adds to the growing body of evidence implicating the rapid anti-SI effects of ketamine. Multiple-item SI scales assess suicidality concerning various aspects, such as ideation, planning, SI frequency and duration, and active/passive SI, etc. The validity and inter-rater consistency of these scales were also suggested by previous studies (Beck et al, 1988, 1997; Posner et al., 2011). Additionally, SSI- and BSS- scores were also found to be correlated with suicidality, suggesting some degree of clinical predictive

utility (Brown et al., 2000; Burger et al., 2016). C-SSRS, on the other hand, assesses SI more comprehensively as categories such as histories of suicide attempts/self-harm were also evaluated (Sinyor et al., 2018). In contrast, the use of single-item scales from a depression inventory (i.e., notably MADRS-SI) in most studies failed to acknowledge the distinct components of SI, which may result in lower sensitivity in evaluating SI severity.

Heterogeneity at various levels should be examined when evaluating the findings. The overall statistical and methodological heterogeneity across the nine studies were moderate as indicated by the I^2 index and results of risk of bias assessment. Clinical heterogeneity exists in various aspects. Although patient populations were similar across studies, with all participants being diagnosed with mood disorders (k = 7 for MDD; k = 1 for any mood disorders; k = 1 for bipolar disorders) and mostly aged around 18–65 years old. There was notable heterogeneity in terms of SI measurement scales implemented, presence of standard-of-care treatment/inpatient hospitalization, the baseline level of SI, and the use of different controls (midazolam vs. saline), all of which may impact the observed effect sizes.

4.1. Acute anti-suicidal effects and clinical implications

The overall evidence supporting ketamine's acute and clinically meaningful anti-SI efficacy is strong despite a lack of statistical significance in some studies, which could be attributed to several factors. Firstly, the small sample size in some studies led to limited power for statistical analyses (Grunebaum et al, 2017, 2018; Ionescu et al., 2019; Sinyor et al., 2018) Secondly, the severe treatment resistance and chronicity of SI in some may have rendered a 0.5 mg/kg racemic
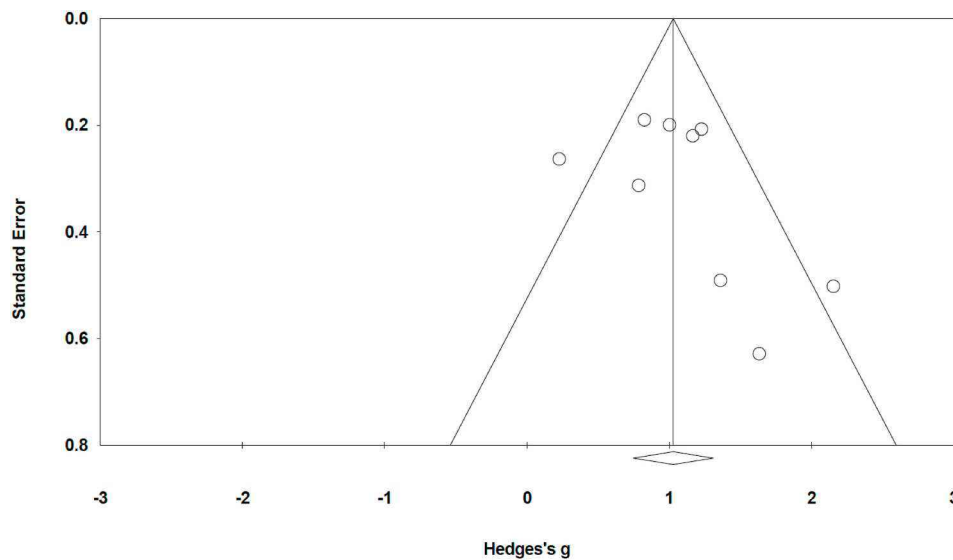
Fig. 2. Funnel plot of standard error by Hedge's *g*. Asymmetry of funnel plot is observed, indicating potential publication bias. Statistical analysis of funnel plot was not recommended due to small sample size (k=9).
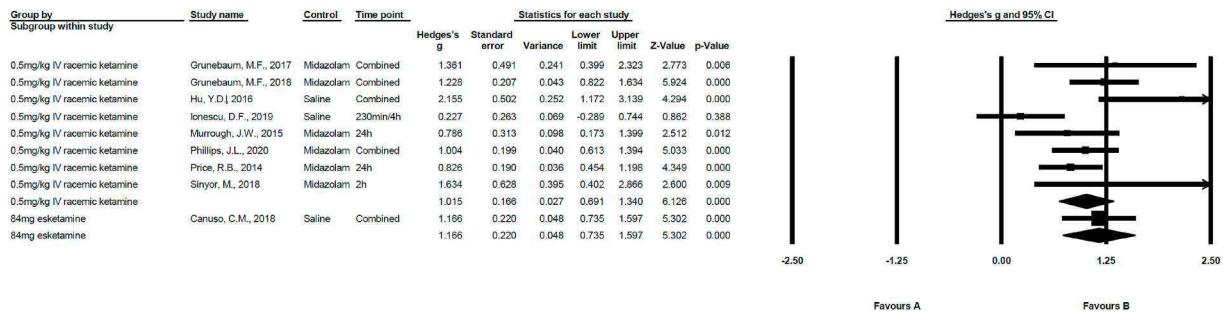

Fig. 3. The forest plot for all studies included, grouped by administration. Squares plot effect size of individual studies, diamonds plots summary measures of each formulation and overall findings. **Favours A (Placebo); Favours B (Es/ketamine).**
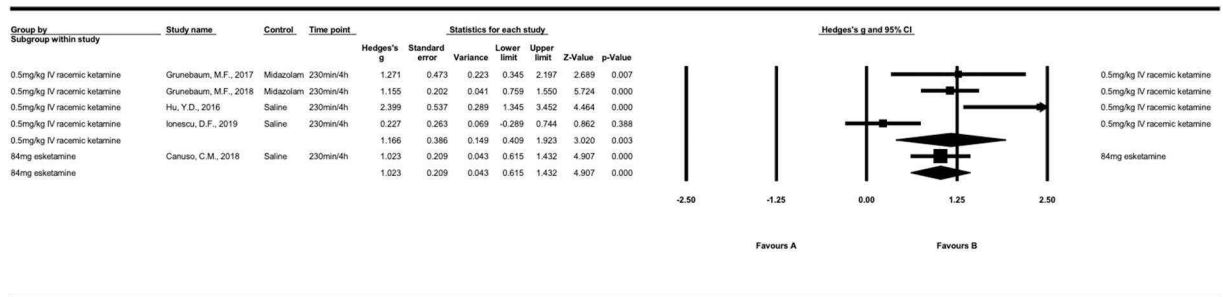

Fig. 4. The forest plot for studies with suicidal ideation measures at 230min/4h post-ketamine, grouped by administration. Squares plot effect size of individual studies, diamonds plots summary measures of each formulation and overall findings. **Favours A (Placebo); Favours B (Es/ketamine).**

ketamine insufficient (Grunebaum et al, 2017, 2018; Ionescu et al., 2019; Sinyor et al., 2018). A larger dose of ketamine may be required for suicidal ideation in severely treatment-resistant and chronically depressed patients (Cusin et al., 2017; Ionescu et al., 2016). Additionally, the implementation of varying intensities of psychiatric treatment (e.g., hospitalization) may have also contributed to decreased suicidality reducing the assay sensitivity of direct effects ascribed to ketamine (Fu et al., 2020).

We focused on the acute efficacy of ketamine in that acute anti-SI effects are of clinical significance, especially in an emergency. Currently, the only pharmacological agents that have unequivocally been shown to lower suicidality are clozapine and lithium (Cipriani et al, 2006, 2013; Griffiths et al., 2014; Meltzer et al., 2003; Memon et al., 2020). Traditional antidepressants were known to have some degree of anti-SI effects, but the lack of rapid onset (about 4–6 weeks) limits its use for acute suicidal crises (Montgomery et al., 1995; Nakajima et al., 2010). On the contrary, ketamine has been demonstrated to produce rapid and clinically meaningful anti-SI effects that can be observed as early as 40-mins post-treatment (Zarate et al., 2012). Importantly, the dynamic nature of SI and impulsivity-driven suicide indicate the necessity of a rapid-acting and efficacious anti-suicidal agent for an emergency (Hadzic et al., 2019; Hallensleben et al., 2018; Lee et al.,
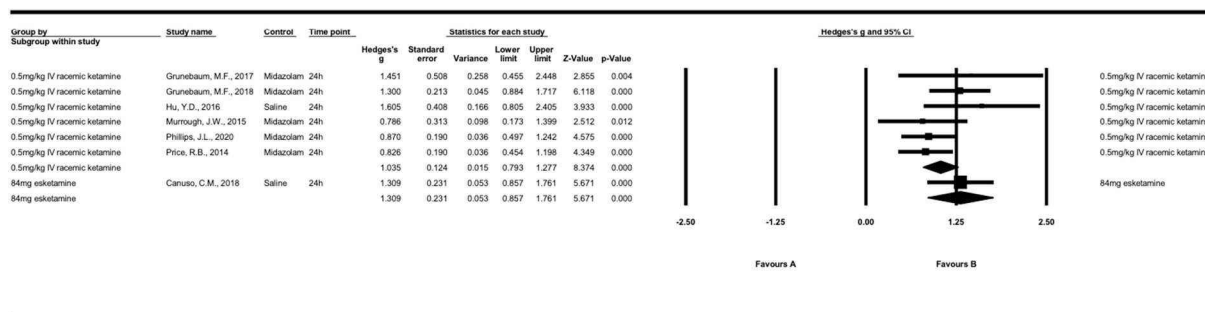
Fig. 5. The forest plot for studies with suicidal ideation measures at 24h post-ketamine, grouped by administration. Squares plot effect size of individual studies, diamonds plots summary measures of each formulation and overall findings. **Favours A (Placebo); Favours B (Es/ketamine).**

2016). In addition, acute and intense SI can be a common reason for the utilization of healthcare services including, but not limited to, emergency rooms (Griffin et al., 2019; Perera et al., 2018). Treatments that are capable of offering acute SI relief may also reduce service utilization which would increase the cost-effectiveness of the intervention.

4.2. Distinct formulations, routes, and dosage of ketamine and clinical implications

We were unable to arrive at conclusions on the superiority of different formulations/routes in their anti-SI efficacy owing to the insufficient number of existing RCTs. However, it is still critical to examine and compare their relative efficacy, advantages, and shortcomings, which may provide insights into ketamine's anti-suicidal mechanisms and the optimization of treatment for SI.

Ketamine is available in several forms, including (R)-ketamine, (S)-ketamine/esketamine, and racemic ketamine (Hashimoto, 2019). Esketamine has been shown to exhibit a higher affinity for NMDA receptors and differential potency as compared to (R)-ketamine (Hashimoto, 2019). The role of NMDA receptors has been implicated as relevant to suicidal behaviour in some patients (Nowak et al., 1995; Sowa-Kućma et al., 2013). Thus, therapeutic differences may exist between various formulations in their anti-SI efficacy which is speculatively due to differential effects across the NMDA receptor and/or effects of ketamine at other molecular targets (Hashimoto, 2019). Further comparative studies on distinct formulations controlling for the routes may be needed to investigate any differential effects.

Concerning the appropriate route of administration, both clinical practicality and differential anti-SI efficacy should be considered. IM/slow IV infusions under hospital settings may not be feasible in all cases. Intranasal/oral/sublingual routes, on the other hand, are more practical, less invasive, and easier to administer as it requires less infrastructure (i. e., equipment) and personnel. No conclusion can be made regarding the differential anti-SI effects of different routes owing to the lack of high-quality studies. Extant literature on the anti-SI effects of IM/oral/sublingual ketamine is mostly limited to case reports, from which mixed results of its efficacy were reported (Dadiomov and Lee, 2019; De Gioannis and De Leo, 2014). The nature of case reports (i.e., lack of generalizability, retrospective designs, etc.) also renders it difficult to properly interpret the findings. Further studies with RCT design may be needed to establish the anti-SI efficacy of routes other than IV/IN. Speculatively speaking, the IV route preserves nearly 100% bioavailability of ketamine and may have superior anti-SI effects compared to IN/IM/oral/sublingual routes, however, such postulation must be evaluated through further research that compares relative anti-SI efficacy of distinct routes.

The dosage of ketamine needs to be optimized for its anti-suicidal effects. In the presence of clinically meaningful SI reductions, a lower dosage of ketamine is preferred to prevent dose-related psychoactive side-effects and a prolonged infusion. Most of the included studies

utilized 0.5 mg/kg IV racemic ketamine that required a slow 40-min infusion. However, preliminary evidence indicated the promising anti-SI efficacy of a lower dosage. It has been demonstrated that a rapid infusion of 0.2 mg/kg racemic ketamine exerted rapid and significant anti-SI effects when compared to the placebo (Burger et al., 2016; Domany et al., 2020). Additionally, Chen et al. (2020) demonstrated a potential association between ketamine dosage and its anti-SI effects using a placebo, 0.2 mg/kg, and 0.5 mg/kg of IV racemic ketamine. They have also identified the modulatory effects of BDNF Val66Met polymorphism on the duration and extent of ketamine's anti-SI efficacy, suggesting its potential for personalized medicine (Chen et al., 2019). A lower dose of ketamine may be sufficient to achieve clinically meaningful SI improvements compared to its antidepressant dosage. Fava et al. (2020) found that a lower dose (0.1 mg/kg) ketamine was not effective in individuals with TRD. Previous research also indicated the partial independence of ketamine's anti-SI effects from its antidepressant effects, together with observed differential treatment dosage, suggesting potentially different pharmacodynamics/pharmacokinetics in the anti-SI and antidepressant effects (Phillips et al., 2020; Wilkinson et al., 2018). Also, a recent meta-analysis investigating the anti-suicidal efficacy of lithium in drinking water observed that the therapeutic/blood level of lithium (0.6–1.0 mmol/L) in mood disorders appears to be higher than the dose required for anti-suicidal effects of lithium, indicating possible distinctions in anti-SI and mood-stabilising mechanisms (Memon et al., 2020).

Taken together, various clinical parameters concerning SI treatment with ketamine should be considered for individual cases to maximize its anti-SI benefits.

4.3. Limitations and future directions

Several limitations of our systematic review/meta-analysis should be noted. First of all, the small study sample size (k = 9) with a limited amount of information restrained us from making any meaningful conclusions concerning the efficacy of distinct routes/formulations. Secondly, ketamine's ability to alleviate SI cannot be interpreted as synonymous with its ability to lower suicidal behavior and/or completion despite previous research suggesting that SI may be predictive of future suicide (Brown et al., 2000; Oquendo et al., 2004). Importantly, they are separate constructs with distinct predictive/associated factors (Klonsky et al., 2016). Thirdly, tests for funnel plot asymmetry were not conducted owing to the small sample size (k = 9), indicating potential publication bias. The last aspect of limitation pertains to the generalizability of study results to patients without major mood disorders (i.e., bipolar/unipolar depression), such as those with chronic diseases, cancer, and personality disorders.

Notwithstanding the evidence on the acute anti-suicidal effects of ketamine among individuals with mood disorders, larger-scale RCTs of ketamine are warranted in the future with the aim to examine and compare the efficacy of different dosage, formulations, or routes of

administration. Despite the preliminary evidence of ketamine's anti-SI effects on individuals with bipolar disorders (Grunebaum et al., 2017), additional RCTs are needed to establish this observation considering its substantial potential in bipolar patients who have one of the highest suicide completion rates among patients with mood disorders. Current pharmacological treatments (i.e. notably lithium) are limited to their efficacy and side-effects (Rhee et al., 2020). Ketamine, on the contrary, may provide clinically desired anti-SI benefits to bipolar patients who often present symptoms of anxiety, agitation, and irritability that render them more likely to have suicidal behaviors (McIntyre et al., 2020a). Effects of ketamine on suicidal behavior and completion may be explored in the future though it may be difficult to demonstrate reductions in suicide completion owing to low assay sensitivity. Additionally, the fact that ketamine may affect SI independent of depressive symptoms suggests that it may be exacting an effect on brain systems subserving characteristics of suicide (e.g., impulsivity) (Lee et al., 2016), suggesting its potential use in suicidal patients without mood disorders, which could also be examined in future RCTs.

5. Conclusion

To summarize, our systematic review/meta-analysis serves as an updated piece of evidence supporting the anti-suicidal effects of single-dose ketamine/esketamine 2-h, 4-h, and potentially 24-h post-treatment. We also provided insights into planning for optimization treatments with ketamine. Further research to compare the relative effects of different formulations/routes of administration/dosage are warranted considering their clinical significance.

Author statement

All authors have approved the final manuscript and note that this is our original work. The article is not under review with any other journal or publication.

Authorship contribution statement

JX contributed to the overall design, article selection, review, study quality appraisal, and manuscript preparation. OL contributed to manuscript preparation and review. DCL contributed to article selection and study quality appraisal. All authors contributed to review, editing, and submission.

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Declaration of competing interest

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