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Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis

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Abstract

Background: Ketamine appears to have a therapeutic role in certain mental disorders, most notably depression. However, the comparative performance of different formulations of ketamine is less clear.

Objectives: This study aimed to assess the comparative efficacy and tolerability of racemic and esketamine for the treatment of unipolar and bipolar major depression.

Design: Systematic review and meta-analysis.

Data sources: We searched PubMed, MEDLINE, Embase, PsycINFO, the Cochrane Central Register of Controlled Clinical Trials, and the Cochrane Database of Systematic Reviews for relevant studies published since database inception and December 17, 2019.

Study eligibility criteria: We considered randomized controlled trials examining racemic or esketamine for the treatment of unipolar or bipolar major depression.

Outcomes: Primary outcomes were response and remission from depression, change in depression severity, suicidality, retention in treatment, drop-outs, and drop-outs due to adverse events.

Analysis: Evidence from randomized controlled trials was synthesized as rate ratios (RRs) for treatment response, disorder remission, adverse events, and withdrawals and as standardized mean differences (SMDs) for change in symptoms, via random-effects meta-analyses.

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Author Statement

• All authors contributed wholly and equally to the development of the manuscript, from its conceptualization to writing of the final draft. With regard to specific roles, Dr. Vazquez and Dr. Zarate undertook supervisory roles. Dr. Bahji supported all phases of the manuscript's development, including data extraction, analyses, and the initial draft of the manuscript.

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Findings: 24 trials representing 1877 participants were pooled. Racemic ketamine relative to esketamine demonstrated greater overall response (RR = 3.01 vs. RR = 1.38) and remission rates (RR = 3.70 vs. RR = 1.47), as well as lower dropouts (RR = 0.76 vs. RR = 1.37).

Conclusions: Intravenous ketamine appears to be more efficacious than intranasal esketamine for the treatment of depression.

Keywords

Esketamine; Ketamine; Depressive disorder; Major; Bipolar disorder; Depression; Randomized controlled trials; Meta-analysis

INTRODUCTION

Depression is the leading cause of disability in the world, affecting nearly 300 million individuals globally (Charlson et al., 2019; Herrman et al., 2019). Although depressive symptoms may be reduced within several weeks following the initiation of conventional antidepressants, approximately one-third of patients fail to achieve meaningful recovery (Corriger and Pickering, 2019). Consequently, there is an ongoing search for effective treatments for treatment-resistant depression (TRD) (Shah, 2016).

To that end, there is an emerging role for different formulations of ketamine in the management of TRD (Li and Vlisides, 2016). Racemic ketamine was first introduced into clinical practice in the 1960s as an invaluable anesthetic, however, its use in the management of TRD is a much more recent addition to the therapeutic armamentarium in depression (Li and Vlisides, 2016). Early ketamine studies demonstrated rapid, potent reductions in depressive symptoms following the administration of a single sub-anesthetic dose of intravenous racemic ketamine (Berman et al., 2000; Hu et al., 2016; Ionescu et al., 2015; Wilkinson et al., 2018). While these early results were promising, effective means of maintaining the acute effects were actively sought (Phillips et al., 2019). To date, the use of other glutamatergic agents to prolong the acute antidepressant effects of ketamine have been largely inconsistent, with some successful case reports and small open-label studies (Caddy et al., 2015; Ibrahim et al., 2012; Mathew et al., 2010; McCloud et al., 2015; Zarate et al., 2005). However, repeat doses of intravenous racemic ketamine have been shown to help sustain the short-term antidepressant effects (Ghasemi et al., 2014; Ionescu et al., 2019; López-Díaz et al., 2017; Murrough et al., 2013b).

In addition to antidepressant properties, racemic ketamine can rapidly reduce suicidal thoughts within one day and for up to one week in depressed patients with suicidal ideation —partially independent of its effects on mood (Grunebaum et al., 2018; López-Díaz et al., 2017; Reinstatler and Youssef, 2015; Wilkinson et al., 2018; Williams et al., 2019; Witt et al., 2020). Given the current limitations of most existing treatments for reducing suicide ideations and plans in patients suffering from moderate to severe major depression, this additional property of ketamine may be particularly helpful in the emergent management of patients in acute crisis.

Racemic ketamine has led to a lot of preclinical and biomarker findings (Zanos et al., 2016; Zanos and Gould, 2018), which are leading to new possibilities in terms of safer alternatives to mitigate dissociation and reduce the propensity for misuse or diversion of ketamine (Burger et al., 2016; Lener et al., 2017; Newport et al., 2015). To that end, the rapid antidepressant effects of ketamine seen in individuals with TRD appears to be predictive of a sustained effect (Atigari and Healy, 2013; Ionescu et al., 2014; Murrough et al., 2011, 2013b).

Fortunately, ketamine appears to ameliorate the symptoms of depression at subanesthetic doses among individuals with major depressive disorder as well as bipolar depression (Lener et al., 2017). Despite the efficacy of racemic ketamine at low doses, its dissociative effects and abuse potential persist (Zanos et al., 2018). Alongside the impracticality and high costs of intravenous ketamine administration (Cohen et al., 2018; Smith-Apeldoorn et al., 2019), clinicians and researchers have sought alternative formulations and delivery systems for ketamine (Jelen et al., 2018). Subsequently, oral (Arabzadeh et al., 2018; Domany et al., 2019; Jafarinia et al., 2016), subcutaneous (George et al., 2017; Hardy et al., 2012; Loo et al., 2016), intranasal (Canuso et al., 2018; Daly et al., 2018; Galvez et al., 2018; Lapidus et al., 2014), and intramuscular (Chilukuri et al., 2014; Loo et al., 2016) ketamine delivery routes have all been explored across the literature with promising findings in several studies. With the isolation of the enantiomeric *S*-ketamine (esketamine)—which is four-fold more potent for the NMDA receptor—there was also an option of providing much lower doses of ketamine and the opportunity to reduce the dose-dependent dissociative properties of ketamine (Correia-Melo et al., 2018). As esketamine was also available through an intranasal delivery system, it presented a substantially more practical option than intravenous racemic ketamine (Schatzberg, 2019; Tibensky et al., 2016). Ultimately, intranasal esketamine was approved by the US Food and Drug Administration on March 5th, 2019 for use in TRD (Kim et al., 2019); on December 19th, 2019, Europe followed suit with approval for esketamine for the same indication (Wei et al., 2020).

Despite its potential for benefit, there are several concerns about the efficacy and tolerability of esketamine nasal spray for TRD (Fedgchin et al., 2019; Ochs-Ross et al., 2019; Wei et al., 2020). For example, dissociative symptoms are still observed in studies using 86 mg of intranasal esketamine, which are of comparable severity to racemic intravenous ketamine (Lapidus et al., 2014; Vlerick et al., 2020). To that end, there has been an in-depth exploration into the potential mechanisms behind ketamine's antidepressant effects and adverse effects (Li and Vlisides, 2016; Sleigh et al., 2014; Zorumski et al., 2016). While the mechanisms behind ketamine's antidepressant effects have not been fully elucidated, ketamine is known to antagonize glutamatergic N-methyl-D-aspartate receptors (NMDAR) in the central nervous system (Corriger and Pickering, 2019; Newport et al., 2015). Emerging evidence suggests ketamine's mechanisms extend beyond the glutamatergic system, involving opioids, GABA, and complex second messenger pathways culminating in varied neuroplastic and neurogenic responses (Kadriu et al., 2019; Lener et al., 2017; Zanos and Gould, 2018). To date, proposed mechanisms include activation of the NMDAR and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) systems, traditional monoamines like serotonin and dopamine, brain-derived neurotrophic factor (BDNF), the mammalian target of rapamycin (mTOR), low-voltage-sensitive T-type calcium

channels, endogenous options, transforming growth factor β1, as well as the gut microbiome (Newport et al., 2015; Sleigh et al., 2014; Wei et al., 2020). In addition, accumulating evidence from preclinical studies indicate that *(R)*-ketamine (arketamine) has greater potency and longer lasting antidepressant effects than *(S)*-ketamine in animal models of depression, and that arketamine has fewer detrimental side effects than both (R,S)-ketamine or (S)-ketamine (Hashimoto, 2019; Hashimoto and Yang, 2019; Zhang and Hashimoto, 2019a).

Although clinical studies of (R)-ketamine in humans are now underway, the level of proof of efficacy remains low and more RCTs are needed to explore efficacy and safety issues of ketamine in depression (Corriger and Pickering, 2019). To date, esketamine and racemic R,S-ketamine have not been robustly compared in clinical contexts, and no extant or ongoing studies have yet investigated the comparative efficacy of racemic ketamine versus esketamine.

OBJECTIVE

We aimed to examine the available evidence for racemic ketamine and esketamine to ascertain the comparative efficacy of these two formulations ketamine on remission from and symptoms of depression—both unipolar and bipolar. We also examined the safety of ketamine for the treatment of depression, including all-cause, serious, and treatment-related adverse events and study withdrawals.

METHODS

Protocol and registration

We registered this study with the Open Science Framework (https://osf.io/ksvnb/). We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Liberati et al., 2009).

Eligibility criteria

We included randomized controlled trials examining the use of ketamine in adults (aged 18 years or older) to treat primary unipolar or bipolar depression. We considered studies examining any intravenous ketamine or intranasal esketamine as a standalone treatment or in combination with psychotropic medications or psychotherapies. As per existing systematic reviews examining the efficacy of ketamine for depressive disorders, we limited eligibility to randomized controlled trials (Abdallah et al., 2015; Fond et al., 2014; Han et al., 2016; Kennedy et al., 2016; Lee et al., 2015; McGirr et al., 2015; Reinstatler and Youssef, 2015; Wilkinson et al., 2018; Witt et al., 2020). We excluded observational designs (i.e., cross-sectional studies, cohort studies, case-control studies), reviews of mechanisms of ketamine, commentary articles, and clinical overviews that did not assess and synthesize individual studies. We also excluded studies pairing ketamine with a neurostimulation-based treatment. We only included studies reporting at least one primary outcome—either remission or change in depression symptomology.

Information sources and search

We searched MEDLINE, Embase, PsycINFO, the Cochrane Central Register of Controlled Clinical Trials (CENTRAL), and the Cochrane Database of Systematic Reviews via Ovid for studies published from inception to December 13, 2019 (Appendix 1). To identify ongoing or unpublished studies, we also searched ClinicalTrials.gov, the EU Clinical Trials Register, and the Australian and New Zealand Clinical Trials Registry using the keywords “ketamine” and “depression.” We also hand-searched reference lists of included studies and topical reviews for potentially relevant articles.

Study selection

Two reviewers (AB, GV) independently examined titles and abstracts by use of the web-based systematic review programme Covidence (Veritas Health Innovation, 2019). Relevant articles were obtained in full and assessed for inclusion independently by the two reviewers. The disagreement between reviewers was resolved via discussion to reach consensus.

Data collection process and data items

Two reviewers extracted data via a pre-piloted, standardized data extraction tool in Microsoft Excel 2016. We extracted data on details of the populations, interventions, comparisons, outcomes of significance to the mental disorder, study methods, ketamine dose and route of administration, study withdrawals, and study withdrawals due to adverse events. Where there was missing data, we contacted the authors for additional information. When authors reported multiple analyses (e.g., intention-to-treat or per-protocol), we extracted the more conservative analysis with a preference for intention-to-treat analyses. We used Review Manager (RevMan), version 5.3, for generating the risk of bias plots (The Cochrane Collaboration, 2014).

Outcomes

We used the following seven outcome measures:

1. Improvement in depression score, defined as the change in depression severity from baseline to study endpoint using a validated depression rating scale.
2. Response to treatment, defined as the proportion of participants who achieved a minimum reduction of 50% in their baseline depression score.
3. Remission from depression, defined as the proportion of participants who had a depression rating of less than or equal to 12 on the Montgomery-Åsberg Depression Rating Scale or seven on the Hamilton Depression Rating Scale.
4. Improvement in suicidality, defined as the change in suicidal ideation severity from baseline to study endpoint using a validated suicidality rating scale.
5. Completion of treatment, defined as the proportion of participants who remained in the study until its primary endpoint.
6. Drop-outs, defined as the proportion of participants who prematurely discontinued their participation in the study for any cause.

7. Drop-outs due to adverse events, defined as the proportion who dropped out of the study prematurely due to adverse events.

Assessment of heterogeneity

We assessed between-study heterogeneity using the I^2 statistic: values of 0–39% were low, 40–74% as moderate, and 75–100% as high (Cochrane Collaboration, 2014).

Risk of bias in individual studies

We assessed the risk of bias within individual trials using the Cochrane risk of bias tool for randomized controlled trials. Specifically, the risk of bias tool assesses indicators of selection bias, performance bias, detection bias, attrition bias, and reporting bias (Higgins et al., 2011). The risk of bias assessments were completed independently by two reviewers (AB or GV). Inter-reviewer disagreements were resolved via discussion to reach consensus.

Summary measures

Continuous outcomes (outcomes 1 and 4) were pooled as standardized mean differences (SMDs) and dichotomous outcomes (outcomes 2, 3, 5, 6, and 7) as rate ratios (RRs), with random-effects, generic inverse variance meta-analyses.

Analytic methods

As we anticipated high heterogeneity, we undertook a random effects meta-analytic strategy, rather than using a fixed-effects model. For pairwise meta-analyses, we applied a Mantel-Haenszel approach and a DerSimonian-Laird estimator for heterogeneity using the *meta* package within R studio version 3.5.3 (Schwarzer, 2007). A continuity correction of 0.5 was applied to studies with zero events. We also considered the comparative performance of intravenous ketamine and intranasal esketamine across several time points: overall, at 24 hours, 48 hours, 72 hours, one week, two weeks, three weeks, four weeks, six weeks, and eight weeks post-treatment. Where raw depression scores were provided without corresponding response rates, a validated method of imputation was applied as per previous meta-analyses (Samara et al., 2013). For crossover studies, the reported results refer to the first period before crossover.

Risk of bias across studies

To assess publication bias, we applied a weighted linear regression of the treatment effect on the inverse of the total sample size using the variance of the average event rate as weights (Peters et al., 2006). The test statistic follows a t distribution with the number of studies minus two degrees of freedom (df = k-2); this test is available for meta-analyses comparing two binary outcomes or combining single proportions.

Role of the funding source

This study was not funded; thus, funders had no role in study design, data collection, data analysis, data interpretation, the writing of the report, or the decision to submit the paper for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Study selection

The search strategy identified a total of 2494 records (Figure 1). After duplicates were removed, a total of 1972 unique records were screened by title and abstract for potential relevance in the systematic review and meta-analysis. After title and abstract screening, 1611 irrelevant records were excluded, leaving 361 documents for full-text review. After full-text review, 24 randomized controlled trials met the final inclusion criteria for the systematic review and meta-analysis (Berman et al., 2000; Canuso et al., 2018; Correia-Melo et al., 2020; Daly et al., 2018; Diazgranados et al., 2010; Fava et al., 2018; Fedgchin et al., 2019; Grunebaum et al., 2017, 2018; Hu et al., 2016; Ionescu et al., 2019; Kudoh et al., 2002; Lapidus et al., 2014; Li et al., 2016; Murrough et al., 2013b; Ochs-Ross et al., 2019; Phillips et al., 2019; Popova et al., 2019; Singh et al., 2016a, 2016b; Sos et al., 2013; Su et al., 2017; Zarate et al., 2006, 2012).

Characteristics of studies, participants, and interventions

Table 1 provides an overview of study characteristics. Seven trials (Berman et al., 2000; Diazgranados et al., 2010; Lapidus et al., 2014; Phillips et al., 2019; Sos et al., 2013; Zarate et al., 2006, 2012) were crossover, while the remainder were parallel arm trials. By country, the majority of studies were from the United States (71%) or Taiwan (13%). Across trials, the total number of participants with depression was 1877. The majority (n=1836; 97.8%) were diagnosed with unipolar major depression; the remaining 41 were diagnosed with a bipolar spectrum depression (n=41; 2.2%). Diagnoses were confirmed by standardized means of assessments, with the most frequently used instruments being the Structured Clinical Interview for the DSM (First, 2015; Spitzer et al., 1994) or the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). There was considerable variation in sample sizes between the studies, as the total number of participants with depression ranged from nine participants (Berman et al., 2000) to 342 participants (Fedgchin et al., 2019). Three studies had a sample size of more than 100 participants (Fedgchin et al., 2019; Ochs-Ross et al., 2019; Popova et al., 2019). The mean age ranged from 35.9 to 70.0 years. All studies included both male and female participants, with an overall proportion of females of 60.7% (n=1139/1877). Three trials (Berman et al., 2000; Murrough et al., 2013a; Zarate et al., 2006) tested ketamine as a monotherapy (i.e., participants were required to discontinue any concomitant psychotropic medications before ketamine initiation). In contrast, the remainder tested ketamine as an adjunctive treatment (i.e., in augmentation of concomitant psychotropic medications). The majority of trials involved participants with TRD, defined as having an inadequate response to a minimum of one (21%), two (62%), or three (15%) previous antidepressant trials; only six trials involved non-TRD (Berman et al., 2000; Canuso et al., 2018; Grunebaum et al., 2018, 2017; Kudoh et al., 2002; Sos et al., 2013).

Exclusion criteria across studies

In most studies, individuals with other significant medical or psychiatric conditions were not eligible for participation. Psychotic disorders (such as schizophrenia or schizoaffective disorder), acute medical complications, and severe substance use disorders (involving ketamine or other substances) were exclusion criteria for the majority of trials. Participants

with acute suicidality were excluded from most studies unless the trial was explicitly intended for the treatment of acute suicidality with ketamine. Finally, pregnant and breastfeeding women were not permitted to participate in any of the trials.

Overview of results of pairwise meta-analyses

All trials reported depression rating scores and rates of response, the proportion of participants who completed the trial, the proportion who experienced adverse events, and the proportion who dropped out due to adverse events. Rates of remission were available for 19 trials (Arabzadeh et al., 2018; Berman et al., 2000; Canuso et al., 2018; Correia-Melo et al., 2020; Daly et al., 2018; Diazgranados et al., 2010; Domany et al., 2019; Fedgchin et al., 2019; George et al., 2017; Grunebaum et al., 2018, 2017; Hu et al., 2016; Ionescu et al., 2019; Jafarinia et al., 2016; Loo et al., 2016; Murrough et al., 2013a; Ochs-Ross et al., 2019; Phillips et al., 2019; Popova et al., 2019; Singh et al., 2016a, 2016b; Sos et al., 2013; Su et al., 2017; Zarate et al., 2006, 2012), while suicidality was reported by 11 trials (Canuso et al., 2018; Grunebaum et al., 2018, 2017; Hu et al., 2016; Ionescu et al., 2019; Kudoh et al., 2002; Murrough et al., 2013a; Phillips et al., 2019; Sos et al., 2013; Su et al., 2017; Zarate et al., 2012).

Table 2 provides a summary of the pooled meta-analysis outcomes—both crude and corrected for publication bias. Overall, ketamine demonstrated a significant improvement in response (RR = 2.0382, 95% CI: 1.5748; 2.6380, Figure 2) and remission rates (RR = 2.0029 [1.5005; 2.6735], Figure 3) relative to control conditions, alongside a significant reduction in depression severity (SMD = −1.1430 [−1.4613; −0.8247], Figure 4) and suicidality scores (SMD = −0.3867 [−0.7082; −0.0653]).

Study completion and drop-out rates were proxies for ketamine tolerability. Of the 1011 participants who were to receive ketamine, 147 (14.5%) dropped out, compared to 141/980 (14.4%) who were to receive control interventions (RR 0.97, 95% CI 0.72—1.29, z = −0.23, p = 0.82). Across studies, adverse events resulting in study discontinuation were only observed in 11 of the 31 trials (Canuso et al., 2018; Daly et al., 2018; Diazgranados et al., 2010; Fedgchin et al., 2019; Ionescu et al., 2016; Li and Vlisides, 2016; Murrough et al., 2013b; Ochs-Ross et al., 2019; Popova et al., 2019; Singh et al., 2016a, 2016b). Across studies, 52 such adverse events resulting in study discontinuation were observed, with 37 in experimental arms and 15 in control arms. One study reported cardiovascular side-effects in 2 of 47 patients (n = 1 refractory hypertension, n = 1 hypotension and bradycardia) who received ketamine and no such side-effects among control patients (Murrough et al., 2013a). The only recorded induction of mania/hypomania occurred in a patient with BD who was receiving saline placebo infusion (Diazgranados et al., 2010). No severe psychotic symptoms occurred in any patient.

Performance of ketamine over time

Table 3 provides an overview of the efficacy and tolerability of ketamine and esketamine over time points ranging from 24 hours to four weeks following the receipt of treatment. The pooled response and remission rates, as well as the change in depression rating scores, were statistically significant across all timepoints. However, reductions in suicidality were not

statistically significant at the two- or four-week timepoints. While there was no clear pattern in the effect sizes observed for the response or remission rates, the effect on suicidality appeared to decrease over time.

Moderator analyses

Table 4 provides an overview of the results of the subgroup analyses for racemic ketamine vs. esketamine; TRD vs. non-TRD; unipolar vs. bipolar depression; crossover vs. parallel trial; monotherapy vs. adjunctive ketamine; and placebo vs. active control. Relative to intranasal esketamine, intravenous ketamine demonstrated more significant overall response and remission rates, as well as lower drop-outs due to adverse events. As well, more substantial response and remission rates were observed in crossover trials, while more significant improvements in depression rating scores were observed in parallel trials. There was no significant association between treatment resistance, depression type, treatment strategy, or comparator type on any of the seven outcome measures. There was no significant association between mean age (in years) or the study-level proportion of female participants (%) on any of the seven outcomes.

Publication bias

The results of publication bias assessments are illustrated in Figure 5. In summary, there were significant publication bias in response, remission, and depression rating scores. However, there was lower evidence for publication bias in the other four outcomes. Given this finding, the overall results in Table 2 were corrected for publication bias using the trim and fill method. Consequently, there were substantial reductions in the effect sizes for response rates (RR = 1.4209 [1.0950; 1.8438]), remission rates (RR = 1.5521 [1.1472; 2.1000]), and depression rating scores (SMD = −0.4832 [−0.8453; −0.1212]). There was a small increase in the effect size for suicidality reduction following correction for publication bias (SMD = −0.5034 [−0.8180; −0.1888]); however, the remaining three outcomes were not significantly changed following correction for publication bias.

Study quality and risk of bias

The overall quality of the 24 trials included in the meta-analysis was very high, with only a handful of studies having any “high risk” domains (Figure 6).

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis that has compared the performance of intravenous ketamine to intranasal esketamine for the treatment of unipolar and bipolar depression. Relative to intranasal esketamine, intravenous racemic ketamine demonstrated more significant overall response and remission rates, as well as lower drop-outs due to adverse events. In contrast, we did not find any significant differences between the effect of racemic ketamine or esketamine in TRD vs. non-TRD or between MDD vs. BD populations. Thus, while intravenous racemic ketamine tended to outperform intranasal ketamine, the specific differences at the subgroup level were nonsignificant. Furthermore, this points to a need for additional head-to-head studies in order to determine the specific reasons for this finding.

Several previous reviews have demonstrated the merits of intravenous racemic ketamine for the treatment of depression, either as a standalone treatment or in combination with electroconvulsive therapy (Caddy et al., 2015; Corriger and Pickering, 2019; Fond et al., 2014; Lee et al., 2015; McCloud et al., 2015; McGirr et al., 2015; Xu et al., 2016). While the present data suggest that intravenous racemic ketamine is superior to intranasal esketamine, the latter is FDA-approved and has more long-term data and larger sample sizes. The evidence base to date would suggest the recommendation of intravenous ketamine over intranasal esketamine for treatment-resistant major depressive disorders, as there are no published studies on the efficacy of the latter for the treatment of bipolar depression. In contrast, several prior studies indicate that there is a role for intravenous ketamine in the treatment of bipolar depression (Alberich et al., 2017; Bobo et al., 2016; Gałuszko-Węgielnik et al., 2019; Ionescu et al., 2015; Kraus et al., 2017; López-Díaz et al., 2017). In the present meta-analysis, there was no significant difference in clinical response between patients with unipolar major depression and bipolar depression to intravenous ketamine. Thus, it remains somewhat unclear if the clinical responsiveness to ketamine differs between patients with major depression or bipolar depression. For very short-term use, the available data demonstrates a clear and consistent antidepressive effect of ketamine vs esketamine treatment, relative to a variety of control conditions, beginning within hours of administration, and lasting up to 7 days after a single dose.

There is a real necessity in our therapeutic armamentarium for discovering and adding more effective and safer treatments for patients who have an unsatisfactory response or intolerable side effects to the current conventional antidepressive treatments (Gao et al., 2016). All studies of ketamine and esketamine for major depression enrolled patients that were resistant to one or more conventional antidepressants, second-generation antipsychotics or mood-stabilizing medications. However, the specific definitions of TRD varied, with the minimum number of unsuccessful trials required for trial participation ranging from one to three, indicating ketamine's role as a 'last resort' treatment. Thus, it remains unclear how ketamine may perform in individuals with non-TRD depression (Aan Het Rot et al., 2012).

Part of the challenge in elucidating the comparative performance of different formulations of ketamine may lie in the lack of a clear consensus on the mechanisms underlying ketamine's therapeutic effects (Strasburger et al., 2017; Zanos and Gould, 2018). While intravenous racemic ketamine has more side effects than intranasal esketamine, a recent open-label trial with the former seemed to have lower dissociative side effects. Ketamine blockade of glutamatergic neurotransmission via antagonism of the NMDA pathway promotes AMPA receptor activation (Aleksandrova et al., 2017; Zorumski et al., 2016). AMPA activation triggers second messenger pathways required for several neuroplastic changes, ultimately conferring the rapid and sustained antidepressant effects of ketamine (Evans et al., 2018; Maeng and Zarate, 2007).

While the antagonism of the NMDA pathway represents the primary antidepressant mechanism of ketamine, some studies have implied a role for opioid neurotransmission, as ketamine also appears to activate the mu, kappa, and delta-opioid receptors (Finck and Ngai, 1982; Freye et al., 1994, p.; Jonkman et al., 2018; Sarton et al., 2001). While the precise implications of these properties are currently under investigation, available studies indicate

that the endogenous opioid system plays a role in mediating the antidepressant properties of ketamine (Mathew and Rivas-Grajales, 2019; Williams et al., 2019, 2018). To that end, the antidepressant effects of ketamine appear to require the activation of the opioid system, as the administration of the opioid antagonist naloxone abolishes the antidepressant properties of ketamine (Williams et al., 2018); however, another study contested these findings, claiming a lack of opioid system involvement in the antidepressant effects of ketamine (Zhang and Hashimoto, 2019b). Still, the role of the opioid system to ketamine's antidepressant effects remains unclear and must consider the risk of abuse.

Outside of depressive contexts, ketamine is an adjuvant to opioid-based pharmacotherapy of pain (Bell et al., 2003). Ketamine appears to counter opioid-induced respiratory depression (Jonkman et al., 2018), which suggests that there may be a farther-reaching interplay between the ketamine and opioid neurotransmitter systems outside of only depression. Furthermore, ketamine and esketamine have shown great potential as potent and rapid anti-suicidal agents (Grunebaum et al., 2018; López-Díaz et al., 2017; Reinstatler and Youssef, 2015; Wilkinson et al., 2018; Williams et al., 2019; Witt et al., 2020). Given the current limitations of most existing treatments for reducing suicide ideations and plans in patients suffering from moderate to severe major depression, this additional property of ketamine may be helpful in the emergent management of patients in acute crisis.

Limitations

Although this review has several strengths, a few fundamental limitations deserve some expansion here.

While the risk of bias assessments indicated that there was a low level of bias in individual studies, there was significant publication bias at the review-level. Thus, negative studies—particularly regarding response and remission rates—may not have been identified by our search protocol, which may inflate the effect sizes.

Our review attempted to cover as much follow-up time as possible following the administration of ketamine treatment, there remains minimal information regarding longer-term follow-up. The longest trials considered by this review only offered a follow-up to the four to the eight-week mark. Hence, the results of our study are also limited to this treatment window; extrapolation beyond this point is beyond the scope of the presented analyses.

Participants in the trials were mostly unrepresentative of the real-world population with depression. While some of the trials captured individuals with treatment-resistant depression, most trials excluded participants who had significant psychiatric or medical comorbidity, which is an unlikely scenario in most clinical settings. Thus, the results of the trials may not represent the real-world efficacy of ketamine.

One of the paper's main aims was to evaluate the acceptability of racemic ketamine and esketamine. However, we only reported on dropout rates and general adverse event rates). Unfortunately, we could not report on specific side effects given inconsistent reporting across studies for dissociation, headaches, nausea, or other adverse effects.

In our review, we observed greater efficacy ratings for intravenous racemic ketamine in terms of response and remission. However, this superiority in performance appeared to drop after the fourth week after administration, when only the reduction of depression scale scores was observed. Thus, when appraising the relative efficacy of racemic ketamine to intranasal esketamine, one must also consider the timepoint.

The high heterogeneity within the selected studies could have impacted our results. Specifically, there were differences between unipolar and bipolar depressive patients, and patients with TRD vs. non-TRD. As well, some studies explored single doses while others involved repeated administration of ketamine (for example, Singh et al. 2016 and Ionescu et al. 2019 used repeated ketamine administration). Finally, some RCTs administered ketamine as a monotherapy, while others used it in augmentation with other psychotropics. We accounted for these sources of heterogeneity using subgroup analyses and meta-regression, however, statistical strategies can only account for measurable contributions. Hence, it is likely that there is unmeasurable, residual heterogeneity in our review.

Conclusions

This review finds that relative to intranasal esketamine, intravenous ketamine demonstrated more significant overall response and remission rates, as well as lower drop-outs due to adverse events. It is essential to underscore that, in contrast to esketamine, there is no current FDA approval of racemic ketamine for the treatment of major bipolar or unipolar depression (Commissioner, 2019; Kim et al., 2019). Therefore, the prescription of racemic ketamine for the treatment of depression remains an off-label intervention. While racemic ketamine has demonstrated significant short-term benefits in several clinical studies, the long-term benefits remain insufficiently explored, and this may be a contributor to the current lack of FDA approval for racemic ketamine. At present, the level of proof of efficacy remains low and more randomized controlled trials are needed to explore efficacy and safety issues for the administration of all forms of ketamine in the treatment of depression. Moreover, although ketamine represents an innovative, rapidly acting, experimental treatment for bipolar and unipolar depression, the route of administration presents a practical limitation that has been solved to some extent with the intranasal formulation of esketamine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix 1.: Search Strategy

MEDLINE: inception to December 19, 2019

Step	Search Criteria	Citations
1.	ketamine.mp. or exp Ketamine/	20289
2.	depression.mp. or exp Depression/	407001
3.	1 and 2	2444
4.	limit 3 to humans	1126

Step	Search Criteria	Citations
5.	limit 4 to randomized controlled trial	189

PsycINFO: inception to December 13, 2019

Step	Search Criteria	Citations
1.	exp Ketamine/ or ketamine.mp.	3745
2.	exp Major Depression/ or exp Treatment Resistant Depression/ or depression.mp.	332697
3.	1 and 2	1256
4.	limit 3 to (human and “0300 clinical trial”)	99

EMBASE: inception to December 13, 2019

Step	Search Criteria	Citations
1.	ketamine.mp. or exp ketamine/	42871
2.	exp depression/ or depression.mp.	720295
3.	1 and 2	6555
4.	limit 3 to human	5033
5.	limit 4 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)	1040

Cochrane Library: inception to December 13, 2019

Step	Search Criteria	Citations
1.	Ketamine	5025
2.	Depression	76586
3.	1 and 2	896

ClinicalTrials.gov: inception to December 13, 2019

Step	Search Criteria	Citations
1.	“Ketamine” and “depression”	190

The EU Clinical Trials Register: inception to December 13, 2019

Step	Search Criteria	Citations
1.	“Ketamine” and “depression”	37

The Australian and New Zealand Clinical Trials Registry: inception to December 13, 2019

Step	Search Criteria	Citations
1.	“Ketamine” and “depression”	43

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Highlights

- We reviewed the peer-reviewed academic literature to synthesize evidence for the comparative efficacy and acceptability of racemic ketamine and esketamine.
- 24 randomized controlled trials were identified and data across studies were pooled by way of systematic review and meta-analysis.
- 24 trials representing 1877 participants were pooled. Racemic ketamine relative to esketamine demonstrated greater overall response (RR = 3.01 vs. RR = 1.38) and remission rates (RR = 3.70 vs. RR = 1.47), as well as lower dropouts (RR = 0.76 vs. RR = 1.37).
- Racemic ketamine appears to be more efficacious than esketamine for the treatment of depression. Head to head comparisons are needed to confirm the present findings.

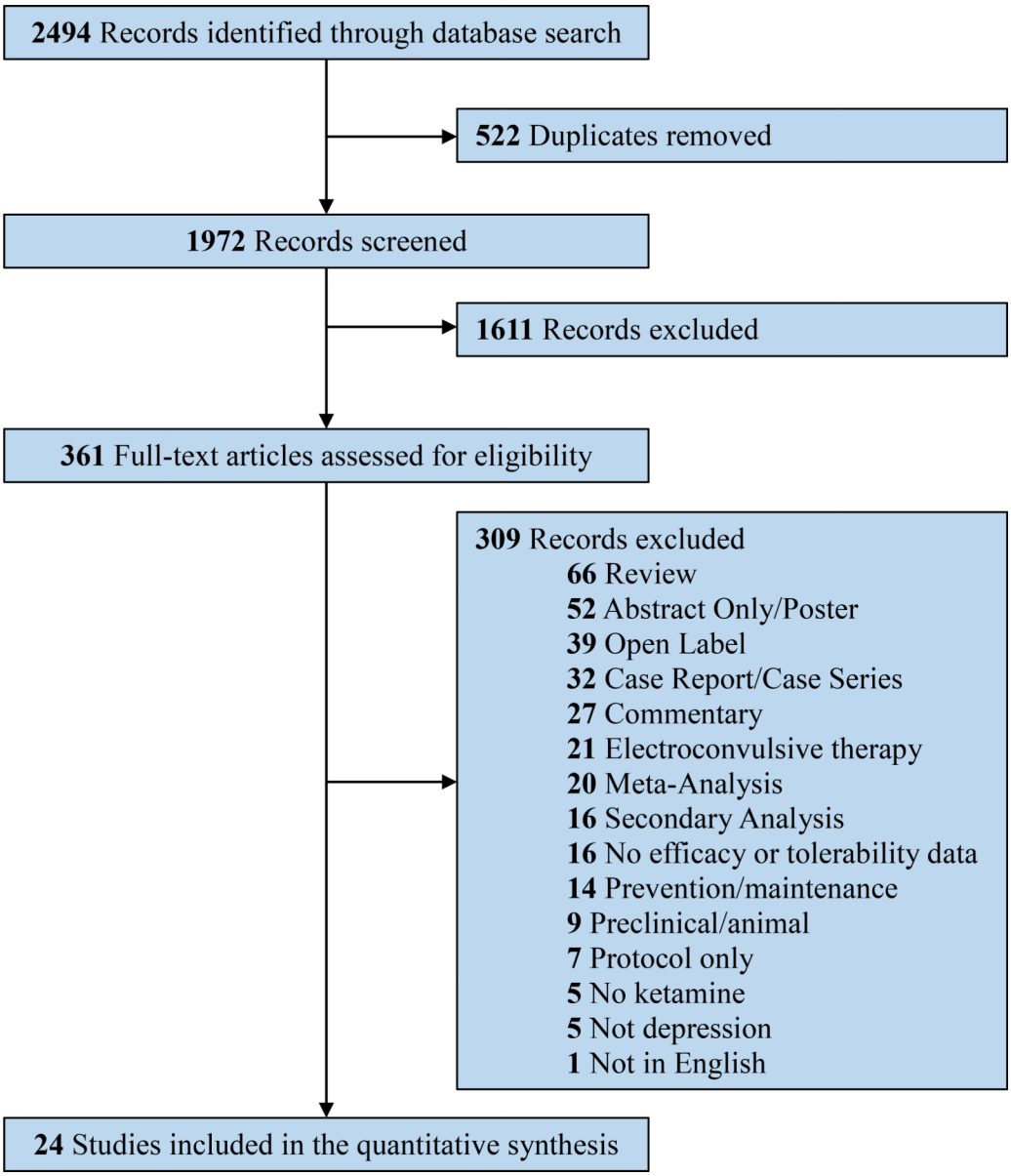

Figure 1.
PRISMA flow diagram outlining the systematic review process.

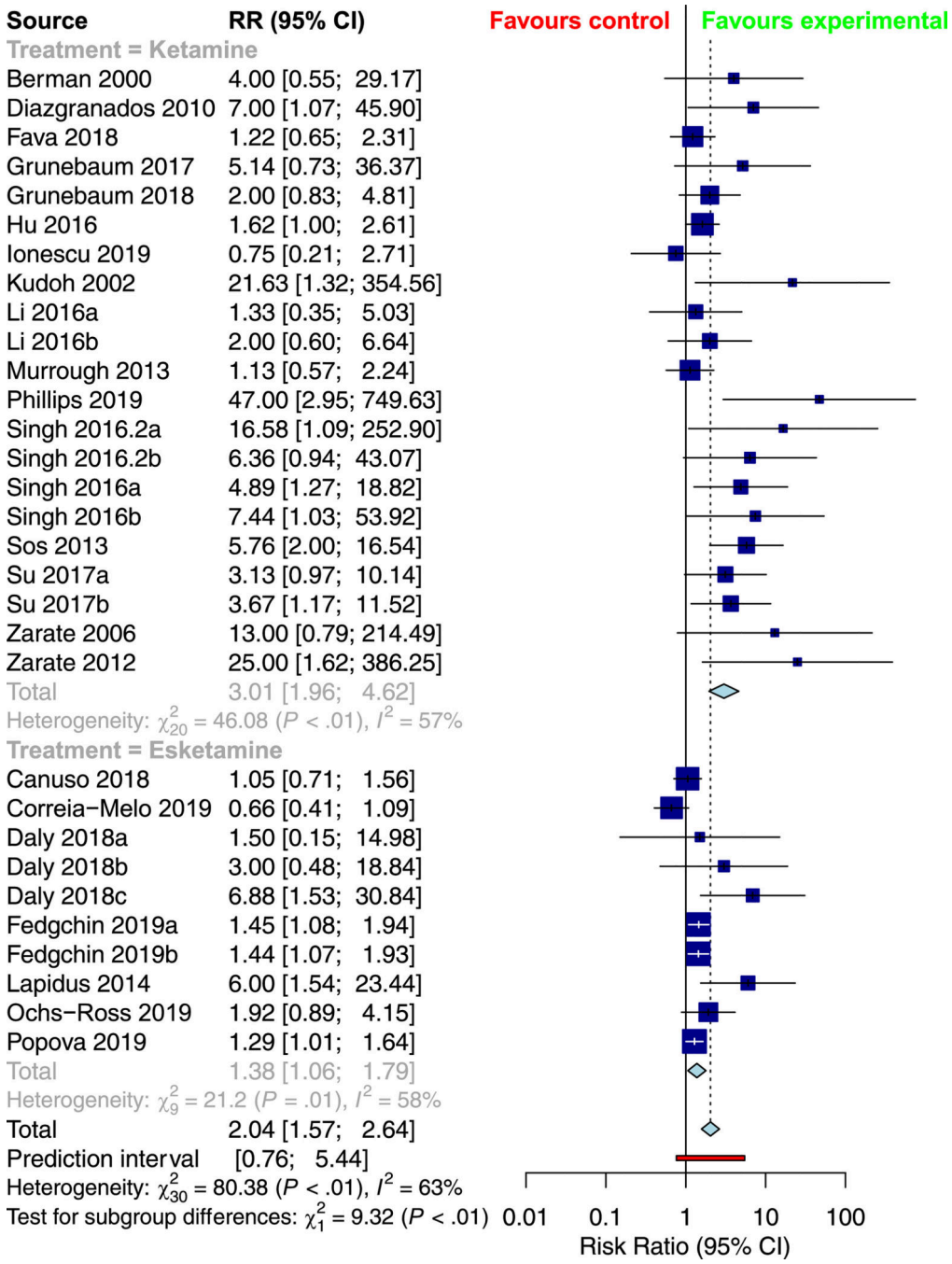

Figure 2.

Subgroup meta-analysis of response rates in the treatment of depression with racemic ketamine versus esketamine

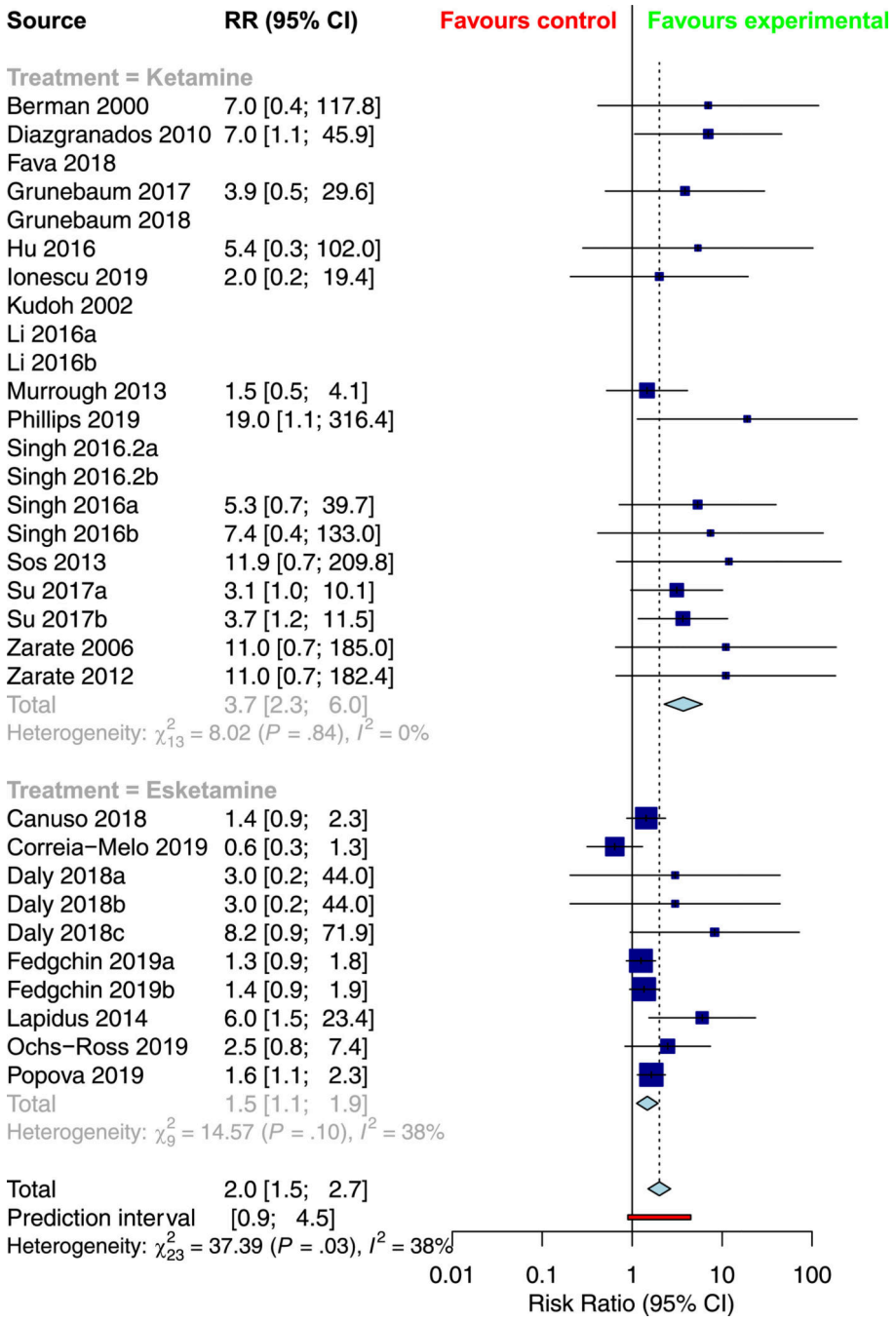

Figure 3.

Subgroup meta-analysis of remission rates in the treatment of depression with ketamine versus esketamine

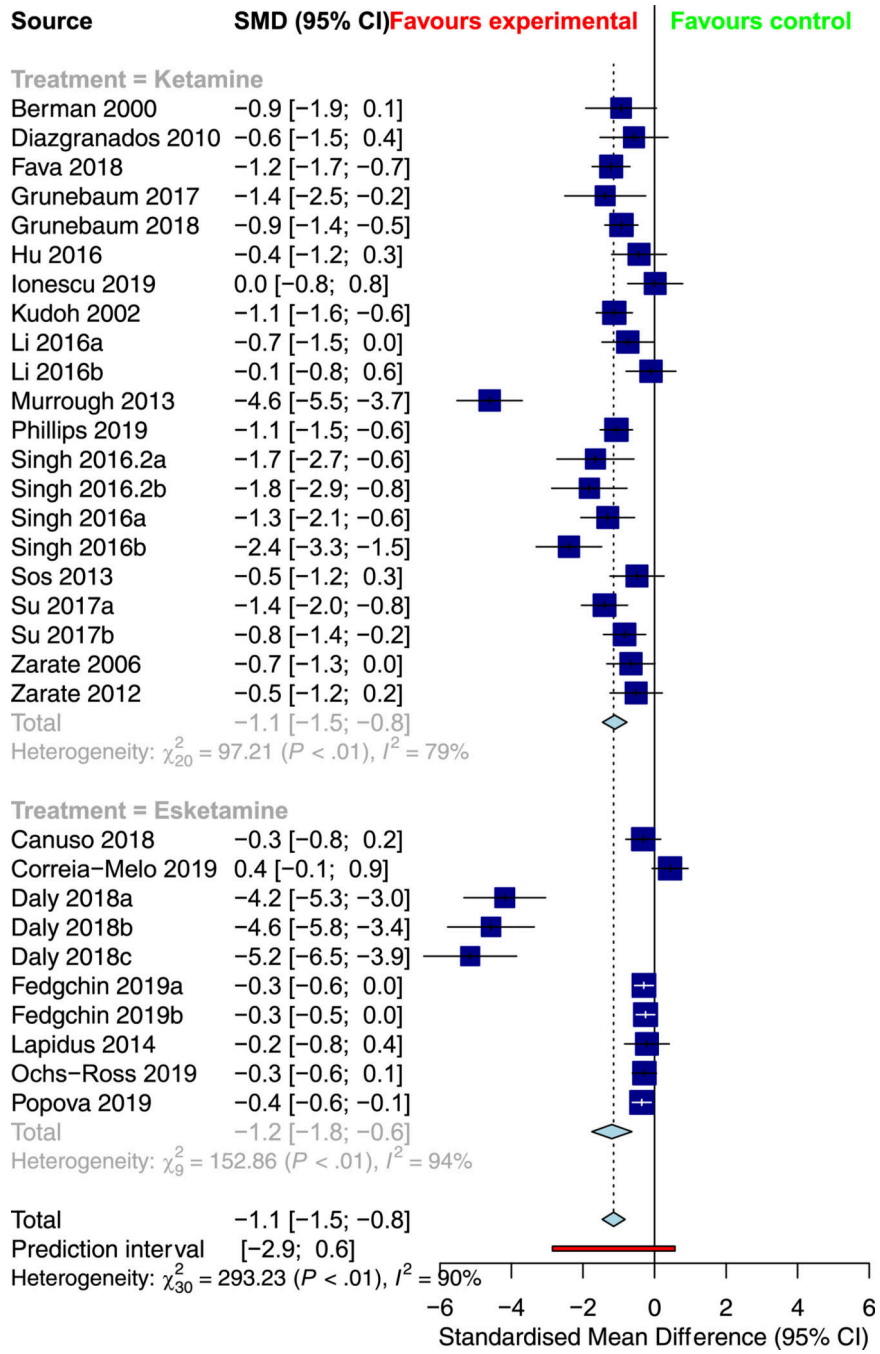

Figure 4.

Subgroup meta-analysis of depression rating scores in the treatment of depression with ketamine versus esketamine

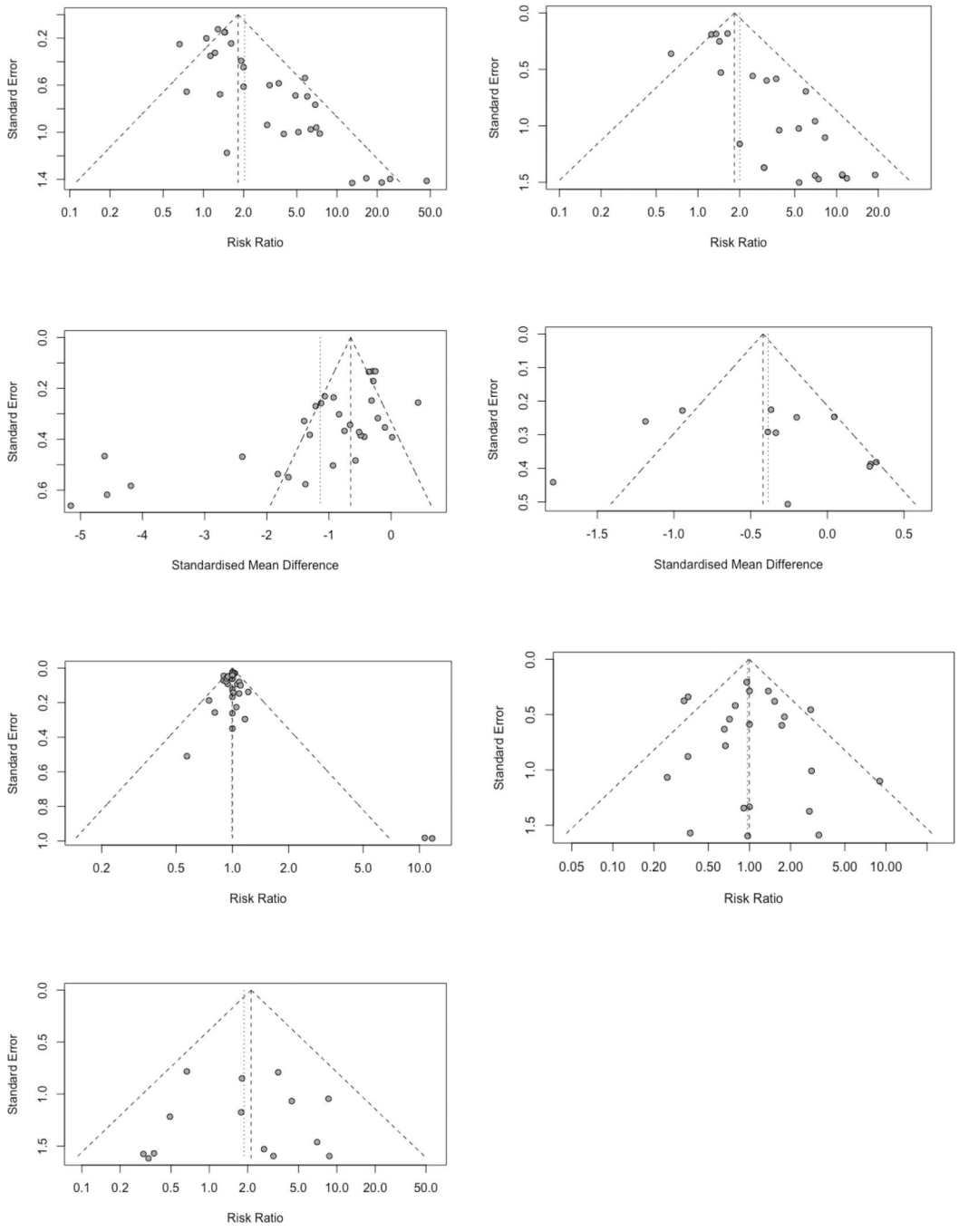

Figure 5.

Funnel plots and publication bias assessment for response rates (top left), remission rates (top right), depression rating scores (upper middle left), suicidality (upper middle right), completion (lower middle left), drop-outs (lower middle right), and drop-outs due to adverse events (bottom left)

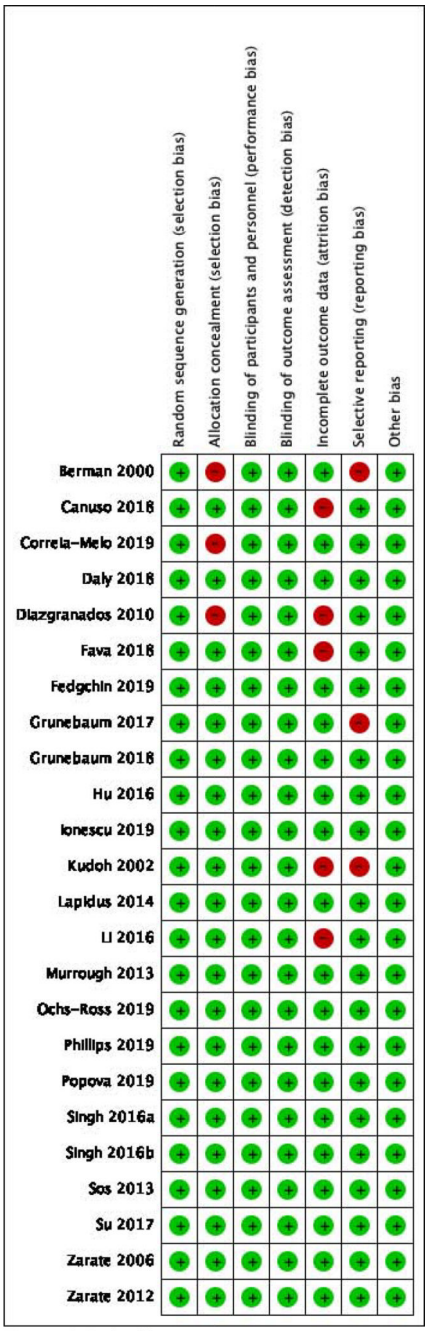

Figure 6. Risk of bias summary

Figure 6.
Risk of bias summary

Table 1.

Study characteristics

Study	Design	Population	N	Female (%)	Mean age	Formulation	Dose	Scale	Comparator
Berman 2000 (Berman et al., 2000)	Crossover	Non-TRD MDD	9	55.6	37.0	Racemic, monotherapy	0.5 mg/kg IV, multiple	HDRS	Placebo
Kudoh 2002 (Kudoh et al., 2002)	Parallel	Non-TRD	70	N/R	47.6	Racemic, adjunctive	1 mg/kg IV, single	HDRS	Placebo
Zarate 2006 (Zarate et al., 2006)	Crossover	TRD MDD	18	66.7	46.7	Racemic, monotherapy	0.5 mg/kg IV, multiple	HDRS	Placebo
Diazgranados 2010 (Diazgranados et al., 2010)	Crossover	TRD BD	9	66.7	47.9	Racemic, adjunctive	0.5 mg/kg IV, multiple	MADRS	Placebo
Zarate 2012 (Zarate et al., 2012)	Crossover	TRD BD	15	53.3	46.7	Racemic, adjunctive	0.5 mg/kg IV, multiple	MADRS	Placebo
Sos 2013 (Sos et al., 2013)	Crossover	Non-TRD	30	50.0	43.4	Racemic, adjunctive	0.5 mg/kg IV, single	MADRS	Placebo
Murrough 2013 (Murrough et al., 2013a)	Parallel	TRD MDD	72	51.4	44.8	Racemic, monotherapy	0.5 mg/kg IV, single	MADRS	Midazolam
Lapidus 2014 (Lapidus et al., 2014)	Crossover	TRD MDD	20	25.0	48.0	Esketamine, adjunctive	50 mg/day IN	MADRS	Placebo
Hu 2016 (Hu et al., 2016)	Parallel	TRD MDD	27	63.0	38.9	Racemic, adjunctive	0.5 mg/kg IV, multiple	MADRS	Placebo
Singh 2016a (Singh et al., 2016b)	Parallel	TRD MDD	67	70.6	43.0	Racemic, adjunctive	0.5 mg/kg IV, multiple	MADRS	Placebo
Singh 2016b (Singh et al., 2016a)	Parallel	TRD MDD	40	57.9	43.7	Esketamine, adjunctive	0.2–0.4 mg/kg IV, single	MADRS	Placebo
Li 2016 (Li et al., 2016)	Parallel	TRD MDD	64	75.0	46.6	Racemic, adjunctive	0.2–0.5 mg/kg IV	HDRS	Placebo
Grunebaum 2017 (Grunebaum et al., 2017)	Parallel	Non-TRD BD	16	62.5	41.0	Racemic, adjunctive	0.5 mg/kg IV, single	HDRS	Midazolam
Su 2017 (Su et al., 2017)	Parallel	TRD MDD	95	71.0	47.3	Racemic, adjunctive	0.2–0.5 mg/kg IV, single	HDRS	Placebo
Canuso 2018 (Canuso et al., 2018)	Parallel	Non-TRD	66	65.2	35.9	Esketamine, adjunctive	84 mg twice/week IN	MADRS	Placebo
Grunebaum 2018 (Grunebaum et al., 2018)	Parallel	TRD MDD	80	60.0	39.6	Racemic, adjunctive	0.5 mg/kg IV, single	HDRS	Midazolam
Daly 2018 (Daly et al., 2018)	Parallel	Non-TRD	133	57.0	45.4	Esketamine, adjunctive	28–84 mg twice/week IN	MADRS	Placebo
Fava 2018 (Fava et al., 2018)	Parallel	TRD MDD	99	57.6	46.5	Racemic, adjunctive	0.1–1 mg/kg IV, single	HDRS	Midazolam

Study	Design	Population	N	Female (%)	Mean age	Formulation	Dose	Scale	Comparator
Phillips 2019 (Phillips et al., 2019)	Crossover	TRD MDD	43	55.8	41.7	Racemic, adjunctive	0.5 mg/kg IV, single	MADRS	Midazolam
Ionescu 2019 (Ionescu et al., 2019)	Parallel	TRD MDD	26	38.5	45.4	Racemic, adjunctive	0.5 mg/kg IV, multiple	HDRS	Placebo
Popova 2019 (Popova et al., 2019)	Parallel	TRD MDD	223	61.9	45.7	Esketamine, adjunctive	56–84 mg twice/week IN	MADRS	Placebo
Fedgchin 2019 (Fedgchin et al., 2019)	Parallel	TRD MDD	455	71.1	46.6	Esketamine, adjunctive	56–84 mg twice/week IN	MADRS	Placebo
Correia-Melo 2019 (Correia-Melo et al., 2020)	Parallel	TRD MDD	63	60.3	47.1	Esketamine, adjunctive	0.25 mg/kg IN, single	MADRS	Racemic ketamine (0.5 mg/kg IV)
Ochs-Ross 2020 (Ochs-Ross et al., 2020)	Parallel	TRD MDD	137	62.0	70.0	Esketamine, adjunctive	28– 84 mg twice/week IN	MADRS	Placebo

IV = intravenous; IN = intranasal; TRD = Treatment-Resistant Depression; MADRS = Montgomery-Åsberg Depression Rating Scale; HDRS = Hamilton Depression Rating Scale

Table 2

Summary of meta-analysis results (overall).

Outcome	Random effects model	Corrected for publication bias	*z*	*p-value*	I^2	*k*
Response	RR = 2.0382 [1.5748; 2.6380]	RR = 1.4209 [1.0950; 1.8438]	5.41	< 0.0001	62.7%	31
Remission	RR = 2.0029 [1.5005; 2.6735]	RR = 1.5521 [1.1472; 2.1000]	4.71	< 0.0001	38.5%	24
Score	SMD = −1.1430 [−1.4613; −0.8247]	SMD = −0.4832 [−0.8453; −0.1212]	−7.04	< 0.0001	89.8%	31
Suicidality	SMD = −0.3867 [−0.7082; −0.0653]	SMD = −0.5034 [−0.8180; −0.1888]	−2.36	0.0184	71.3	12
Completion	RR = 0.9929 [0.9681; 1.0182]	RR = 0.9876 [0.9576; 1.0185]	−0.56	0.5773	14.0	31
Dropouts	RR = 0.9664 [0.7234; 1.2911]	RR = 0.9229 [0.6864; 1.2410]	−0.23	0.8173	40.5	24
Adverse events	RR = 1.8703 [1.0271; 3.4076]	RR = 2.0087 [1.1150; 3.6188]	2.05	0.0406	0.0	14

RR = rate ratio; SMD = standardized mean difference; *z* = *z*-score (on normal distribution); I^2 = measure of heterogeneity (closer to 100.0 indicates higher heterogeneity); *k* = number of trials involved in the sub analysis.

Table 3.

Time-course analysis of outcomes

Outcome	Random effects model	*z*	*p-value*	I^2	*k*
4–12 hours					
Suicidality	SMD = −0.7045 [−1.2148; −0.1942]	−2.71	0.0068	82.9	9
24 hours					
Response	RR = 2.6011 [1.8599; 3.6378]	5.59	< 0.0001	61.0	28
Remission	RR = 3.2823 [2.0966; 5.1385]	5.20	< 0.0001	8.7	14
Score	SMD = −1.0636 [−1.3926; −0.7346]	−6.34	< 0.0001	89.3	28
Suicidality	SMD = −0.6876 [−1.1461; −0.2291]	−2.94	0.0033	81.2	9
48 hours					
Response	RR = 1.4124 [1.0217; 1.9524]	2.09	0.0366	57.2	12
Score	SMD = −1.0474 [−1.5189; −0.5759]	−4.36	< 0.0001	79.5	12
72 hours					
Response	RR = 2.1836 [1.4397; 3.3120]	3.67	0.0002	68.5	18
Remission	RR = 2.3576 [1.1980; 4.6396]	2.48	0.0130	51.0	8
Score	SMD = −0.8763 [−1.2076; −0.5450]	−5.18	< 0.0001	75.4	18
Suicidality	SMD = −0.9243 [−1.5804; −0.2683]	−2.76	0.0058	79.9	5
One week					
Response	RR = 1.8660 [1.3805; 2.5220]	4.06	< 0.0001	56.5	25
Remission	RR = 2.5868 [1.2728; 5.2574]	2.63	0.0086	50.2	11
Score	SMD = −1.0179 [−1.3615; −0.6743]	−5.81	< 0.0001	89.6	24
Suicidality	SMD = −0.4287 [−0.8202; −0.0373]	−2.15	0.0318	67.6	8
Two weeks					
Response	RR = 1.5796 [1.1926; 2.0921]	3.19	< 0.0001	50.2	15
Remission	RR = 7.5979 [2.8489; 20.2632]	4.05	< 0.0001	0.0	5
Score	SMD = −0.6418 [−0.9020; −0.3817]	−4.84	< 0.0001	75.8	15
Suicidality	SMD = −0.2506 [−0.5182; 0.0170]	−1.84	0.0665	0.0	5
Three weeks					
Response	RR = 5.4566 [2.7713; 10.7437]	4.91	< 0.0001	70.2	7
Remission	RR = 4.9525 [1.0471; 23.4241]	2.02	0.0436	10.2	2
Score	SMD = −0.2618 [−0.3908; −0.1328]	−3.96	< 0.0001	0.0	7
Four weeks					
Response	RR = 1.3891 [1.1655; 1.6557]	3.67	0.0002	27.8	7
Remission	RR = 1.5309 [1.2056; 1.9438]	3.49	0.0005	25.2	7
Score	SMD = −0.3037 [−0.4346; −0.1728]	−4.55	< 0.0001	0.0	6

Outcome	Random effects model	*z*	*p-value*	I^2	*k*
Suicidality	SMD = −0.1602 [−0.4472; 0.1268]	−1.09	0.2741	0.0	4

RR = rate ratio; SMD = standardized mean difference; z = z-score (on normal distribution); I^2 = measure of heterogeneity (closer to 100.0 indicates higher heterogeneity); k = number of trials involved in the sub analysis

Table 4

Summary of subgroup meta-analyses.

Outcome Treatment	**Ketamine**	**Esketamine**	**Subgroup test (*p*-value)**
Response	RR = 3.0096 [1.9599; 4.6220]	RR = 1.3779 [1.0623; 1.7874]	0.0023
Remission	RR = 3.6999 [2.2772; 6.0112]	RR = 1.4724 [1.1197; 1.9361]	0.0012
Score	SMD = −1.1140 [−1.4551; −0.7729]	SMD = −1.1932 [−1.7539; −0.6326]	0.8129
Suicidality	SMD = −0.4323 [−0.7729; −0.0917]	SMD = 0.0450 [−0.4385; 0.5284]	0.1137
Completion	RR = 1.0088 [0.9553; 1.0652]	RR = 0.9759 [0.9313; 1.0227]	0.3662
Dropouts	RR = 0.7557 [0.5245; 1.0889]	RR = 1.3616 [0.9129; 2.0307]	0.0331
Adverse events	RR = 1.0601 [0.4307; 25601]	RR = 3.0168 [1.3412; 6.7856]	0.0860
Treatment-resistance	**Non-TRD**	**TRD**	**Subgroup test (p-value)**
Response	RR = 3.0967 [1.2143; 7.8973]	RR = 1.9265 [1.4637; 2.5358]	0.3404
Remission	RR = 2.5747 [0.9236; 7.1776]	RR = 2.0454 [1.4754; 2.8356]	0.6751
Score	SMD = −0.8008 [−1.1184; −0.4831]	SMD = −1.2343 [−1.6159; −0.8526]	0.0871
Suicidality	SMD = −0.3173 [−0.8435; 0.2090]	SMD = −0.4347 [−0.8777; 0.0083]	0.7379
Completion	RR = 1.0048 [0.9555; 1.0566]	RR = 0.9887 [0.9578; 1.0205]	0.5950
Dropouts	RR = 0.9245 [0.5309; 1.6099]	RR = 0.9754 [0.6922; 1.3744]	0.8722
Adverse events	RR = 4.4286 [0.5467; 35.8730]	RR = 1.7319 [0.9262; 3.2386]	0.3994
Depression type	**MDD only**	**BD only**	**Subgroup test (p-value)**
Response	RR = 1.8658 [1.4505; 2.4000]	RR = 7.9859 [2.3698; 26.9114]	0.0564
Remission	RR = 1.8233 [1.3733; 2.4208]	RR = 6.1295 [1.7744; 21.1733]	0.1176
Score	SMD = −1.1906 [−1.5378; −0.8434]	SMD = −0.7111 [−1.2257; −0.1964]	0.3116
Suicidality	SMD = −0.2988 [−0.6110; 0.0134]	SMD = −1.0438 [−2.5431; 0.4556]	0.3404
Completion	RR = 0.9921 [0.9652; 1.0197]	RR = 0.9908 [0.7574; 1.2960]	0.9988
Dropouts	RR = 0.9507 [0.6843; 1.3207]	RR = 1.2615 [0.7435; 2.1402]	0.6725
Adverse events	RR = 2.2547 [1.1751; 4.3260]	RR = 0.6667 [0.1440; 3.0855]	0.1515
Trial type	**Crossover trial**	**Parallel trial**	**Subgroup test (p-value)**
Response	RR = 7.2920 [3.8053; 13.9737]	RR = 1.5838 [1.2761; 1.9657]	< 0.0001
Remission	RR = 8.1568 [3.5519; 18.7320]	RR = 1.5500 [1.2431; 1.9327]	0.0002
Score	SMD = −0.6863 [−0.9428; −0.4339]	SMD = −1.3112 [−1.7015; −0.9208]	0.0088
Suicidality	SMD = −0.7928 [−1.8251; 0.2395]	SMD = −0.2752 [−0.5706; 0.0203]	0.3447
Completion	RR = 1.0521 [0.8948; 1.2371]	RR = 0.9906 [0.9637; 1.0183]	0.4723
Dropouts	RR = 1.0468 [0.8013; 1.3675]	RR = 0.9766 [0.6191; 1.5404]	0.7966
Adverse events	RR = 0.5848 [0.1472; 2.3238]	RR = 2.4527 [1.2603; 4.7731]	0.0666
Treatment strategy	**Monotherapy**	**Adjunctive**	**Subgroup test (p-value)**
Response	RR = 2.5714 [0.5883; 11.2394]	RR = 2.0586 [1.5727; 2.6946]	0.7712
Remission	RR = 2.8075 [0.7458; 10.5678]	RR = 1.9845 [1.4670; 2.6845]	0.6170
Score	SMD = −2.0618 [−4.5233; 0.3997]	SMD = −1.0288 [−1.3281; −0.7294]	0.4142
Suicidality	SMD = −0.1999 [−0.6863; 0.2864]	SMD = −0.4051 [−0.7604; −0.0499]	0.5043
Completion	RR = 1.1001 [0.9705; 1.2470]	RR = 0.9891 [0.9643; 1.0145]	0.1031
Dropouts	RR = 0.3923 [0.1199; 1.2830]	RR = 1.0158 [0.7516; 1.3730]	0.1272
Adverse events	RR = 2.6842 [0.1339; 53.8059]	RR = 1.8429 [0.9993; 3.3985]	0.8096

Outcome Treatment	**Ketamine**	**Esketamine**	**Subgroup test (*p*-value)**
Comparator	**Placebo**	**Active**	**Subgroup test (p-value)**
Response	RR = 2.2107 [1.6780; 2.9125]	RR = 1.6145 [0.7625; 3.4184]	0.4408
Remission	RR = 2.0228 [1.5364; 2.6633]	RR = 1.8103 [0.5393; 6.0762]	0.8609
Score	SMD = −1.0634 [−1.3862; −0.7406]	SMD = −1.4133 [−2.4375; −0.3892]	0.5230
Suicidality	SMD = −0.3431 [−0.8222; 0.1360]	SMD = −0.4828 [−0.8570; −0.1087]	0.6524
Completion	RR = 0.9901 [0.9603; 1.0209]	RR = 0.9998 [0.9510; 1.0510]	0.7457
Dropouts	RR = 0.9989 [0.6997; 1.4259]	RR = 0.9178 [0.6388; 1.3185]	0.7439
Adverse events	RR = 1.9688 [1.0552; 3.6735]	RR = 1.0035 [0.1135; 8.8691]	0.5600

RR = rate ratio; SMD = standardized mean difference: TRD = treatment-resistant depression; MDD = major depressive disorder (i.e., unipolar depression); BD = bipolar depression.