HHS Public Access

Author manuscript

Expert Opin Drug Saf. Author manuscript; available in PMC 2023 June 01.

Published in final edited form as:

Expert Opin Drug Saf. 2022 June ; 21(6): 853–866. doi:10.1080/14740338.2022.2047928.

EFFICACY AND SAFETY OF RACEMIC KETAMINE AND ESKETAMINE FOR DEPRESSION: A SYSTEMATIC REVIEW AND META-ANALYSIS

Anees Bahji[a,b], **Carlos A. Zarate**[c], **Gustavo H. Vazquez**[d]

[a.]Department of Psychiatry, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada;

[b.]British Columbia Centre on Substance Use, Vancouver, British Columbia, Canada;

[c.]Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada;

[d.]Department of Psychiatry, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

Abstract

Background—Racemic ketamine and esketamine have demonstrated rapid antidepressant effects. We aimed to review the efficacy and safety of racemic and esketamine for depression.

Research design and methods—We conducted a PRISMA-guided review for relevant randomized controlled trials of racemic or esketamine for unipolar or bipolar major depression from database inception through 2021. We conducted random-effects meta-analyses using pooled rate ratios (RRs) and Cohen's standardized mean differences (d) with their 95% confidence intervals (CI).

Results—We found 36 studies (2903 participants, 57% female, 45.1 +/− 7.0 years). Nine trials used esketamine, while the rest used racemic ketamine. The overall study quality was high. Treatment with any form of ketamine was associated with improved response (RR=2.14; 95% CI, 1.72–2.66; I2=65%), remission (RR=1.64; 95% CI, 1.33–2.02; I2=39%), and depression severity (d=−0.63; 95% CI, −0.80 to −0.45; I2=78%) against placebo. Overall, there was no association between treatment with any form of ketamine and retention in treatment (RR=1.00; 95% CI, 0.99–1.01; I2<1%), dropouts due to adverse events (RR=1.56; 95% CI, 1.00–2.45; I2<1%), or the overall number of adverse events reported per participant (OR=2.14; 95% CI, 0.82–5.60; I2=62%) against placebo.

Conclusions—Ketamine and esketamine are effective, safe, and acceptable treatments for individuals living with depression.

Keywords

esketamine; ketamine; depressive disorder; major; bipolar disorder; depression; randomized controlled trials; meta-analysis

Correspondence: Gustavo H. Vazquez, g.vazquez@queensu.ca.

1. INTRODUCTION

Depression is a leading cause of global disability, impacting 300 million persons [1,2]. The impact of depression on the global burden of disease has been intensified by the increasing recognition of treatment-resistant depression (TRD). TRD, while variably defined, occurs when a person with major depression fails to respond adequately to one or two conventional antidepressants, like selective serotonin reuptake inhibitors (SSRIs) [3–5]. Available data suggest that TRD affects approximately one-third of persons with depression. Consequently, there is a need for new, evidence-based treatments with potent, rapid antidepressant properties for persons with TRD [6,7].

The dissociative anesthetic and N-methyl-D-aspartate antagonist (NMDA) ketamine has been studied as a novel treatment for TRD [8,9]. Early clinical studies identified rapid, potent antidepressant properties with a single sub-anesthetic dose of intravenous racemic ketamine [10]. Meta-analyses have demonstrated racemic ketamine<apos;>s efficacy for unipolar depression [11–15], suicidal ideation [16–18], bipolar depression [13,19–26], and as a therapeutic adjunct for electroconvulsive therapy [27–47]. However, maintaining ketamine<apos;>s acute antidepressant properties has become another research priority. Adjunctive administration of other glutamatergic agents has shown inconsistent evidence for prolonging the acute effects of ketamine [48–55]. In addition, while repeated doses of intravenous racemic ketamine can maintain the short-term antidepressant effects, there remains a need to identify the optimal maintenance dosing schedules to prevent depression relapse [8].

More recently, researchers have focused on identifying effective means of optimizing the effectiveness of ketamine and reducing its potential for adverse effects. Another area of interest has been elucidating the therapeutic profiles of differing enantiomeric formulations of ketamine, particularly the [S] and [R] enantiomers of racemic ketamine – termed esketamine and arketamine, respectively [56–62]. For example, esketamine gained FDA approval for the treatment of TRD, with some studies identifying its benefits in depression [63–65]. There is also some preliminary evidence of arketamine in depression [60,66–69]. In this area, there has also been increasing interest in identifying preclinical and biomarker findings [60,70] and safer alternatives to mitigate dissociation and misuse of ketamine 71–73].

Consequently, understanding the comparative efficacy, safety, and acceptability of varying ketamine regimens is a research priority.

1.1. Objective

We aimed to provide an updated evidence synthesis on the efficacy, safety, and acceptability of racemic and esketamine for treating depression.

2. METHODS

2.1. Overview

The present article represents an updated review of a previous meta-analysis on the comparative efficacy and safety of racemic ketamine and esketamine [74]. Earlier articles were registered with the Open Science Framework (https://osf.io/ksvnb/) and PROSPERO. In addition, we followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [75].

2.2. Eligibility criteria

We restricted review eligibility to English-language randomized controlled trials (RCTs) comparing racemic or esketamine to a comparator condition for adults with unipolar or bipolar depression reporting at least one of the following outcomes:

1. Response, defined as the number of participants achieving a reduction of at least 50% in the baseline depression score (as measured on the Montgomery-Åsberg Depression Rating Scale [MADRS] or Hamilton Depression Rating Scale [HDRS]).
2. Remission, defined as the number of participants showing a clinically significant improvement in depression (e.g. MADRS<10).
3. Depression severity, defined as the difference between the experimental and control group endpoint depression scores.
4. Retention in treatment, defined as the number of participants who remained in the study until its primary endpoint.
5. Dropouts due to adverse events, defined as the number of participants who dropped out of the study prematurely due to treatment-emergent adverse events.
6. Adverse events, defined as the number of participants experiencing at least one treatment-emergent adverse event. Specific adverse events included nausea, vomiting, abdominal pain, dissociation, tremor, anxiety, dysgeusia, headache, vertigo, somnolence, dizziness, hypertension, hypoesthesia, and paresthesia.

2.3. Information sources and search

We updated our previous search strategy [74,76] of PubMed, MEDLINE, Embase, PsycINFO, and the Cochrane Registries from 2019 through 23 November 2021 (Appendix A).

2.4. Study selection

Using Cochrane<apos;>s Covidence [77], a web-based systematic review manager, two co-authors (AB, GV) independently screened records by title/abstract and then in full against the pre-specified eligibility criteria; we resolved discrepancies by consensus.

2.5. Data collection process and data items

Two reviewers (AB, GV) 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. In addition, we cross-referenced our data against prior ketamine reviews and commentaries [51,52,78–82].

2.6. Assessment of heterogeneity

We assessed between-study heterogeneity using the I2 statistic, with 50% or higher values indicating significant heterogeneity [83].

2.7. Risk of bias in individual studies

We assessed the risk of bias using the Cochrane risk of bias tool (ROBT2) for randomized controlled trials, assessing the quality of trial randomization, treatment allocation concealment, blinding, selective reporting, and attrition bias [84]. Two authors (AB or GV) independently assessed each study using the ROBT2; disagreements were resolved via consensus (Appendix B).

2.8. Summary measures

For binary outcomes, we used rate ratios (RRs) to synthesize outcomes 1,2,4 and 5, while we odds ratios (ORs) for outcome 6, given the lower study yield for the latter. We used Cohen<apos;>s standardized mean differences (d) to pool continuous data (outcome 3). We reported the accompanying 95% confidence intervals (CIs) for all effect sizes.

2.9. Analytic methods

We adhered to the meta-analytic methods described in our previous review articles [74,85–87]. As we anticipated high heterogeneity, we undertook random effects meta-analytic strategy rather than a fixed-effect model. We applied a Mantel-Haenszel approach and a DerSimonian-Laird estimator for heterogeneity using the meta-package within R studio version 3.5.3 [88]. The reported results refer to the first period before crossover for crossover studies.

2.10. Risk of bias across studies

We graphed funnel plots and assessed their symmetry using Egger<apos;>s test to assess publication bias. We adjusted the pooled effect size using the trim-and-fill technique when there was a significant risk for publication bias. We also considered components of the GRADE framework, such as heterogeneity, imprecision (determined using the relative width of 95% CIs), and ranking on the ROBT2, to appraise the overall strength of evidence.

2.11. Additional analyses

After conducting the primary analyses (where treatment with either racemic or esketamine was pooled to assess ‘ketamine’ treatment). We ran subgroup and sensitivity analyses for each primary outcome overall and then for racemic and esketamine separately. We

conducted stratified (i.e. subgroup) analyses for categorical variables, which were significant if the test for subgroup differences had a p-value of 0.05 or less. To ensure sufficient statistical power for additional analyses, we required a minimum of five studies per subgroup. We considered the following variables in subgroup analyses: ketamine type (racemic vs. esketamine for overall analyses only); dose (<0.5 mg/kg, 0.5 mg/kg, >0.5 mg/kg); dosing category (single vs. repeated); route of ketamine administration (IV vs. IN); treatment-resistance (TRD vs. non-TRD); trial design (crossover vs. parallel RCT); regimen (adjunct vs. monotherapy); depression severity instrument used (MADRS vs. HDRS); eligibility criteria for RCT inclusion (minimum depression severity required vs. not); ketamine dose titration (yes vs. no); and timepoint for measurement of efficacy (24 hours vs. >24 hours but ≤1 week vs. >1 week). For sensitivity analyses, we excluded studies with bipolar depression (n = 3) and studies with active comparators (e.g. Correia-Melo et al. 2020, which compared racemic to esketamine).

3. RESULTS

3.1. Study selection

After title/abstract screening and full-text review, we identified 36 eligible RCTs [89–124] (Figure 1).

3.2. Characteristics of studies, participants, and interventions

We broke down eight studies by dose arm for analytic purposes [91,92,95,100,102,103,107,108], leading to 48 separate treatment comparisons (Table 1, Appendix C). For example, the Fava et al. RCT was one study with four treatment arms for each of the four dosing regimens of racemic ketamine [107]. In total, there were 2,914 participants across treatment comparisons (56% female, 45.2 ± 7.0 years). Overall, the 36 studies spanned 2000 through 2021, with the majority coming from the United States (n = 20). There were ten crossover trials, while the rest were parallel RCTs.
All studies used DSM criteria, and major depressive disorder (MDD) was the focus of most studies (n = 33), while three studies exclusively looked at participants with bipolar depression. Most studies looked at treatment-resistant depression (n = 28), while eight did not [93,98,111,112,114,116,120,124]. Across studies, nine RCTs [97–101,108,109,114,119] involved esketamine, while the rest involved racemic ketamine. One RCT was a head-to-head comparison of esketamine to racemic ketamine [101]. Two RCTs used subcutaneous racemic ketamine [94,95], one used intramuscular racemic ketamine [95], two involved oral racemic ketamine [93,125], and two used intranasal racemic ketamine [96,110].
Most esketamine trials used intranasal esketamine; however, two esketamine RCTs used intravenous esketamine [100,101]. Across trials, six involved ketamine dose titration [94,95,99,100,115,119], while the rest had fixed-dosing regimens.

3.3. Synthesis of results across trials

3.3.1 Overall efficacy—Overall, ketamine (pooled for racemic and esketamine) was associated with improved end-of-treatment response (RR = 2.14; 95% CI, 1.72–2.66; I2 = 65%), remission (RR = 1.64; 95% CI, 1.33–2.02; I2 = 39%), and depression severity (d = −0.63; 95% CI, −0.80 to −0.45; I2 = 78%) against placebo.

3.3.2 Overall safety—Overall, there was no association between treatment with any form of ketamine and retention in treatment (RR = 1.00; 95% CI, 0.99–1.01; I2 < 1%), dropouts due to adverse events (RR = 1.56; 95% CI, 1.00–2.45; I2 < 1%), or the overall number of adverse events reported per participant (OR = 2.14; 95% CI, 0.82–5.60; I2 = 62%) against placebo.

3.3.3 Specific adverse events—While there was no significant association with abdominal pain or tremor, ketamine (pooled for racemic and esketamine) was associated with a statistically significantly greater likelihood of the following treatment-emergent adverse events:

- Dizziness (OR = 3.85; 95% CI, 2.98–4.98; I2 < 1%; k = 25 comparisons)
- Hypertension (OR = 2.53; 95% CI, 1.56–4.11; I2 < 1%; k = 9 comparisons)
- Nausea (OR = 3.09; 95% CI, 2.23–4.27; I2 = 15%; k = 20 comparisons)
- Vomiting (OR = 3.18; 95% CI, 1.80–5.60; I2 = 17%; k = 13 comparisons)
- Vertigo (OR = 5.98; 95% CI, 3.36–10.66; I2 = 27%; k = 11 comparisons)
- Somnolence (OR = 3.06; 95% CI, 1.90–4.95; I2 = 34%; k = 14 comparisons)
- Hypoesthesia (OR = 8.57; 95% CI, 4.23–17.37; I2 < 1%; k = 7 comparisons)
- Paresthesia (OR = 4.80; 95% CI, 2.89–7.96; I2 < 1%; k = 13 comparisons)
- Dissociation (OR = 8.19; 95% CI, 5.62–11.95; I2 < 1%; k = 18 comparisons)
- Anxiety (OR = 1.67; 95% CI, 1.00–2.77; I2 < 1%; k = 10 comparisons)
- Dysgeusia (OR = 1.88; 95% CI, 1.28–2.76; I2 = 39%; k = 10 comparisons)
- Headache (OR = 1.38; 95% CI, 1.05–1.82; I2 = 16%; k = 20 comparisons)

3.4. Risk of bias within and across studies

The overall risk of bias in the individual study domains was low (Appendix B). Across outcomes, response and remission, but not depression severity scores, demonstrated publication bias ($p < 0.01$). After correction with the trim-and-fill technique, the revised effect sizes for response (RR = 1.48; 95% CI, 1.19–1.83; k = 20 added studies; I2 = 63%) and remission (RR = 1.40; 95% CI, 1.12–1.76; k = 13 added studies; I2 = 43%).

3.5. Additional analyses

Random-effects models showed a substantial numerical advantage in response rates for racemic ketamine (RR = 3.01; 95% CI, 2.24–4.03) than esketamine (RR = 1.20; 95% CI, 0.96–1.49; Figure 2). Subgroup analyses also indicated that crossover RCTs had a larger effect size than parallel RCTs for racemic ketamine (RR = 5.93 vs. 2.19; $p < 0.01$). However, all other subgroup analyses (i.e. dose, dosing category, route, treatment-resistance, dosing regimen, depression severity instrument, minimum depression severity for trail inclusion, titration, and timepoint) did not reach statistical significance or could not be run due to a lack of a sufficient number of studies per subgroup. Similarly, random-effects models indicated an advantage in remission rates for racemic ketamine (RR = 3.78; 95% CI, 2.44–

5.78) than esketamine (RR = 1.28; 95% CI, 1.11–1.47; p < 0.01). For depression severity scores post-treatment, these again numerically favored racemic over esketamine (d = −0.75 vs. −0.38; p = 0.03). However, none of the subgroup analyses for remission or depression scores were significant for either esketamine or racemic ketamine. To avoid duplication of data across studies, we excluded data from the Su et al. 2017 study [121], as the majority of these patients (n = 48/74) had already been reported in Li et al. 2017 [126]. After excluding Su et al. 2017 data from the meta-analysis, we did not detect significant changes in the above estimates. Another post-hoc sensitivity analysis excluded Correia-Melo et al. 2020, as this was the only head-to-head comparison between racemic and esketamine. Again, we did not detect significant changes in the above estimates.

4. DISCUSSION

4.1. Summary of findings

The present meta-analysis identified 36 RCTs of racemic and esketamine for treating adults with unipolar (n = 33) or bipolar depression (n = 3). Overall, evidence indicates that racemic and esketamine are effective and safe treatments for depression. While there were no differences in adverse event profiles across racemic and esketamine overall, individual studies reported adverse events inconsistently, making it difficult to fully assess their comparative safety profiles. While most subgroup analyses, particularly those involving ketamine dose, dose frequency (repeated vs. single), and route of administration did not reach statistical significance, the overall analyses indicated a numerical advantage favoring racemic ketamine over esketamine. We discuss specific findings from our meta-analysis and contextualize our findings below.

4.2. Implications of findings

Ketamine blocks glutamatergic neurotransmission by antagonizing the NMDA pathway and promoting AMPA receptor activation [127,128]. In turn, AMPA activation triggers key second messenger cascades that initiate neuroplastic changes, conferring both rapid and sustained antidepressant effects [10,129]. However, there is growing interest in furthering our understanding of the application of ketamine to the treatment of depression. Some of the key questions facing the field concerns formulation (racemic, esketamine, arketamine), dosing frequency (single, repeated, maintenance), and optimal dose.

To that end, ongoing research aims to understand differential mechanisms underlying racemic and esketamine<apos;>s therapeutic effects [60,130]. For example, a recent study suggested that racemic ketamine<apos;>s abuse liability may be caused by the pharmacological effects of its (S)-enantiomer rather than the (R)-enantiomer [131]. While racemic ketamine and esketamine are both evidence-based treatments for depression [8,11,13,15,36,51,52,64,65,74], only esketamine has FDA-approval, due to more long-term data with larger sample sizes. To date, however, there are no approved ketamine formulations for the treatment of bipolar depression.

In this meta-analysis, subgroup analyses found substantial differences in efficacy outcomes favoring racemic ketamine. While these differences are large numerically and might show

that esketamine is an inferior treatment for TRD than racemic ketamine, there are alternative explanations. First, there are biological differences between racemic and esketamine, and the observed differences in efficacy might be an epiphenomenon of lower dosing used in esketamine trials or lower bioavailability from intranasal (versus intravenous) drug administration. To that end, doses are based on body weight for racemic infusions. In contrast, for nasal esketamine, the doses are fixed (28–84 mg) regardless of the body weight. However, in one head-to-head study comparing intravenous esketamine to racemic ketamine, when esketamine was dosed as a weight-based agent, it was found to be non-inferior to racemic ketamine [101]. Furthermore, the eligibility criteria in the nasal esketamine studies are different from many ketamine infusions studies.

While prior studies have established some evidence for racemic ketamine<apos;>s efficacy in bipolar depression [19,20,76,132–135], there are no published studies involving esketamine for bipolar depression. Although some individual studies have sought to clarify dose-response relationships or the ideal dosing frequency to maintain depression response or remission, these differences were not significant across the body of evidence in the meta-analysis. Ultimately, we did not find significant differences in efficacy by treatment-resistance, dose, dosing regimen, or dosing frequency across studies, so there are still many unanswered questions involving ketamine<apos;>s optimal treatment settings.

4.3. Limitations

Although this review has strengths, there are some limitations. The primary limitation of this review stems from the high heterogeneity encountered by pooling the data across the 36 RCTs, which differed by clinical samples, treatment details, outcomes, and study designs. To maximize statistical power and to include all available evidence on racemic and esketamine for depression, we pooled studies regardless of their ketamine formulation, dose, frequency, route of administration, or duration of treatment. For example, there were two intravenous esketamine studies, while six of the racemic ketamine studies used non-intravenous routes (two intranasal, two oral, and two subcutaneous). As a result, there are probably important nuances that our review could not address. However, as there is no standardized ketamine RCT protocol, this heterogeneity was unavoidable to some extent and not a specific limitation of this review. While we accounted for these sources of heterogeneity using subgroup analyses, there remains significant unmeasurable residual heterogeneity in our review. While there was low level of bias in individual studies, there was a significant publication bias in some outcomes. Thus, negative studies – particularly for response and remission rates – may not have been identified by our search protocol, which may inflate the effect sizes. In addition, beyond the acute treatment window, there remains minimal information on the longer-term efficacy and safety of ketamine, with the longest RCT having just eight weeks of acute treatment. Finally, participants in the trials were mostly unrepresentative of the real-world population with depression and usually excluded participants who had other psychiatric conditions or medical comorbidity.

4.4. Conclusions

While the present data suggest that intravenous racemic ketamine may be superior to intranasal esketamine, the latter is FDA-approved and has more long-term safety 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.

Ultimately, this work aimed to review and compare the evidence both for racemic ketamine and esketamine on the safety and efficacy of this therapeutic agents for the management of depressive disorders, rather than recommend one formulation over the other. Many other factors, such as treatment cost, insurance coverage, local and international health agencies approval, access to intravenous pumps and oether equipment, and patient preference, are also important in selecting the specific ketamine formulation and method of delivery for an individual patient.

Ketamine and esketamine are efficacious, safe, and acceptable treatments for individuals living with depression, including TRD. For some efficacy outcomes, indirect comparisons suggest racemic ketamine has a slight advantage over esketamine. However, there is a need for further research.

5. EXPERT OPINION

To develop agents with improved safety profiles that are as potent and rapidly acting as ketamine and esketamine, several studies examined how antidepressant effects are mediated by ketamine and its molecular derivative. Ketamine is a racemic mixture of the (S)- and (R)-ketamine enantiomers. Intravenous racemic ketamine and esketamine as well as intranasal esketamine administrations have been shown to exert rapid and sustained antidepressant effects in patients suffering with depression. Comparative studies of racemic ketamine and esketamine IV infusions as well as its intranasal administration demonstrate that esketamine elicits significant and robust antidepressant effects akin to that of racemic ketamine; however, it still can lead to adverse psychomimetic effect. Reviewed published evidence indicates that racemic ketamine and esketamine are safe and effective innovative treatments for depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

Funding for this work was provided in part by the Intramural Research Program at the National Institute of Mental Health and the National Institutes of Health (IRP-NIMH-NIH; ZIAMH002857).

Declaration of interests

CA Zarate Jr. is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation. In addition, they are listed as co-inventor on a patent for the use of (2R,6R)- hydroxynorketamine, (S)-dehydronorketamine, and other stereoisomeric dehydro and hydroxylated metabolites of (R, S)-ketamine metabolites in the treatment of depression and neuropathic pain; and as co-inventor on a patent application for the use of (2R,6R)-hydroxynorketamine and (2S,6S)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and posttraumatic stress disorders. He has assigned his patent rights to the US government but will share a percentage of any government<apos;>s royalties. The NIH had no further role in study design, data collection, data analysis, data interpretation, the writing of the report, or the decision to submit the

paper for publication. A Bahji reports research grants from the National Institutes of Health/National Institute on Drug Abuse (NIDA) [R25-DA037756, R25DA033211] through the International Collaborative Addiction Medicine Research Fellowship and the Research in Addiction Medicine Scholars Program through Boston University School of Medicine. In addition, they are a recipient of the 2020 Friends of Matt Newell Endowment from the University of Calgary Cumming School of Medicine. They also received financial support from a 2020 Research Grant on the Impact of COVID-19 on Psychiatry by the American Psychiatric Association and the American Psychiatric Association Foundation. G Vazquez has received consulting and speaking honoraria from AbbVie, Allergan, CANMAT,

Elea/Phoenix, Eurofarma, Gador, Janssen, Lundbeck, NeonMind Biosciences, Tecnofarma, Raffo, Otsuka, Psicofarma, and Sunovion, and research grants from CAN-BIND, CIHR, PCH and Queen<apos;>s University. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

REFERENCES

1. Herrman H, Kieling C, McGorry P, et al. , Reducing the global burden of depression: a lancet–world psychiatric association commission. Lancet. 393(10189): e42–e43. 2019. 10.1016/S0140-6736(18)32408-5. [PubMed: 30482607]
2. Charlson F, van OM, Flaxman A, et al. New WHO prevalence estimates of mental disorders in conflict settings: a systematic review and meta-analysis. Lancet. 2019;394(10194):240–248. DOI:10.1016/S0140-6736(19)30934-1. [PubMed: 31200992]
3. Diagnosis Fava M. and definition of treatment-resistant depression. Biol Psychiatry. 2003;53(8):649–659. [PubMed: 12706951]
4. Gaynes BN, Lux L, Gartlehner G, et al. , Defining treatment-resistant depression. Depress Anxiety. 37(2): 134–145. 2020. 10.1002/da.22968. [PubMed: 31638723]
5. Trevino K, McClintock SM, McDonald Fischer N, et al. Defining treatment-resistant depression: a comprehensive review of the literature. Ann Clin Psychiatry Off J Am Acad Clin Psychiatr. 2014;26:222–232.
6. Shah AA. Novel approaches for managing treatment-resistant depression. Psychiatr Ann. 2016;46(4):220–222.
7. Thomas L, Kessler D, Campbell J, et al. Prevalence of treatment-resistant depression in primary care: cross-sectional data. Br J Gen Pract J R Coll Gen Pract. 2013;63(617):e852–858. DOI:10.3399/bjgp13X675430.
8. Corriger A, Pickering G. Ketamine and depression: a narrative review. Drug Des Devel Ther. 2019;13:3051–3067.
9. Li L, Vlisides PE. Ketamine: 50 years of modulating the mind. Front Hum Neurosci. Internet] 2016 [cited 2019 Dec 10];10. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5126726/
10. Maeng S, Zarate CA. The role of glutamate in mood disorders: results from the ketamine in major depression study and the presumed cellular mechanism underlying its antidepressant effects. Curr Psychiatry Rep. 2007;9(6):467–474. [PubMed: 18221626]
11. Fond G, Loundou A, Rabu C, et al. Ketamine administration in depressive disorders: a systematic review and meta-analysis. Psychopharmacology (Berl). 2014;231(18):3663–3676. DOI:10.1007/s00213-014-3664-5. [PubMed: 25038867]
12. Han Y, Chen J, Zou D, et al. Efficacy of ketamine in the rapid treatment of major depressive disorder: a meta-analysis of randomized, double-blind, placebo-controlled studies. Neuropsychiatr Dis Treat. 2016;12:2859–2867. [PubMed: 27843321]
13. Lee EE, Della Selva MP, Liu A, et al. Ketamine as a novel treatment for major depressive disorder and bipolar depression: a systematic review and quantitative meta-analysis. Gen Hosp Psychiatry. 2015;37(2):178–184. DOI:10.1016/j.genhosppsych.2015.01.003. [PubMed: 25698228]
14. McGirr A, Berlim MT, Bond DJ, et al. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. Psychol Med. 2015;45(4):693–704. DOI:10.1017/S0033291714001603. [PubMed: 25010396]

15. Xu Y, Hackett M, Carter G, et al. Effects of low-dose and very low-dose ketamine among patients with major depression: a systematic review and meta-analysis. Int J Neuropsychopharmacol. 2016;19(4):pyv124. DOI:10.1093/ijnp/pyv124. [PubMed: 26578082]

16. Wilkinson ST, Ballard ED, Bloch MH, et al. , The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. Am J Psychiatry. 175(2): 150–158. 2018. 10.1176/appi.ajp.2017.17040472. [PubMed: 28969441] • of interest on the potential antisuicide effects of ketamine

17. Witt K, Potts J, Hubers A, et al. Ketamine for suicidal ideation in adults with psychiatric disorders: a systematic review and meta-analysis of treatment trials. Aust N Z J Psychiatry. 2020;54(1):29–45. DOI:10.1177/0004867419883341. [PubMed: 31729893]

18. Xiong J, Lipsitz O, Chen-Li D, et al. 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. J Psychiatr Res. 2021;134:57–68. [PubMed: 33360864]

19. Alberich S, Martínez-Cengotitabengoa M, López P, et al. Efficacy and safety of ketamine in bipolar depression: a systematic review. Rev Psiquiatr Salud Ment. 2017;10:104–112. [PubMed: 27387226]

20. Bobo WV, Vande Voort JL, Croarkin PE, et al. Ketamine for treatment-resistant unipolar and bipolar major depression: critical review and implications for clinical practice. Depress Anxiety. 2016;33(8):698–710. DOI:10.1002/da.22505. [PubMed: 27062450]

21. Ortiz R, Niciu MJ, Lukkahati N, et al. Shank3 as a potential biomarker of antidepressant response to ketamine and its neural correlates in bipolar depression. J Affect Disord. 2015;172:307–311. [PubMed: 25451430]

22. Romeo B, Choucha W, Fossati P, et al. Meta-analysis of short- and mid-term efficacy of ketamine in unipolar and bipolar depression. Psychiatry Res. 2015;230(2):682–688. DOI:10.1016/j.psychres.2015.10.032. [PubMed: 26548981]

23. Rong C, Park C, and Rosenblat JD, et al. Predictors of response to ketamine in treatment resistant major depressive disorder and bipolar disorder. Int J Environ Res Public Health. 2018;15(4):1–10.

24. Sienaert P, Lambrichts L, Dols A, et al. Evidence-based treatment strategies for treatment-resistant bipolar depression: a systematic review. Bipolar Disord. 2013;15(1):61–69. DOI:10.1111/bdi.12026. [PubMed: 23190379]

25. Villaseñor A, Ramamoorthy A, Dos SMS, et al. A pilot study of plasma metabolomic patterns from patients treated with ketamine for bipolar depression: evidence for a response-related difference in mitochondrial networks. Br J Pharmacol. 2014;171(8):2230–2242. DOI:10.1111/bph.12494. [PubMed: 24684390]

26. Zhao X, Venkata SLV, Moaddel R, et al. Simultaneous population pharmacokinetic modelling of ketamine and three major metabolites in patients with treatment-resistant bipolar depression. Br J Clin Pharmacol. 2012;74(2):304–314. DOI:10.1111/j.1365-2125.2012.04198.x. [PubMed: 22295895]

27. Fernie G, Currie J, Perrin JS, et al. Ketamine as the anaesthetic for electroconvulsive therapy: the KANECT randomised controlled trial. Br J Psychiatry. 2017;210(6):422–428. DOI:10.1192/bjp.bp.116.189134. [PubMed: 28254962]

28. Abdallah CG, Fasula M, Kelmendi B, et al. Rapid antidepressant effect of ketamine in the electroconvulsive therapy setting. J ECT. 2012;28(3):157–161. DOI:10.1097/YCT.0b013e31824f8296. [PubMed: 22847373]

29. Ainsworth NJ, Sepehry AA, Vila-Rodriguez F. Effects of ketamine anesthesia on efficacy, tolerability, seizure response, and neurocognitive outcomes in electroconvulsive therapy: a comprehensive meta-analysis of double-blind randomized controlled trials. J ECT. 2020;36(2):94–105. [PubMed: 31725054]

30. Anderson IM, Blamire A, Branton T, et al. Ketamine augmentation of electroconvulsive therapy to improve neuropsychological and clinical outcomes in depression (ketamine-ECT): a multicentre, double-blind, randomised, parallel-group, superiority trial. Lancet Psychiatry. 2017;4(5):365–377. DOI:10.1016/S2215-0366(17)30077-9. [PubMed: 28359862]

31. Chen Q, Min S, Hao X, et al. Effect of low dose of ketamine on learning memory function in patients undergoing electroconvulsive therapy-A randomized, double-blind, controlled clinical study. J ECT. 2017;33(2):89–95. DOI:10.1097/YCT.0000000000000365. [PubMed: 27828927]
32. Dong J, Min S, Qiu H, et al. Intermittent administration of low dose ketamine can shorten the course of electroconvulsive therapy for depression and reduce complications: a randomized controlled trial. Psychiatry Res. 2019;281:112573. [PubMed: 31586838]
33. Gamble JJ, Bi H, Bowen R, et al. Ketamine-based anesthesia improves electroconvulsive therapy outcomes: a randomized-controlled study. Can J Anesth Can Anesth. 2018;65(6):636–646. DOI:10.1007/s12630-018-1088-0.
34. Ghasemi M, Kazemi MH, Yoosefi A, et al. Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy in hospitalized patients with major depressive disorder. Psychiatry Res. 2014;215(2):355–361. DOI:10.1016/j.psychres.2013.12.008. [PubMed: 24374115]
35. Järventausta K, Chrapek W, Kampman O, et al. Effects of S-ketamine as an anesthetic adjuvant to propofol on treatment response to electroconvulsive therapy in treatment-resistant depression: a randomized pilot study. J Ect. 2013;29(3):158–161. DOI:10.1097/YCT.0b013e318283b7e9. [PubMed: 23475029]
36. McGirr A, Berlim MT, Bond DJ, et al. A systematic review and meta-analysis of randomized controlled trials of adjunctive ketamine in electroconvulsive therapy: efficacy and tolerability. J Psychiatr Res. 2015;62:23–30. [PubMed: 25684151]
37. McGirr A, Berlim MT, Bond DJ, et al. Adjunctive ketamine in electroconvulsive therapy: updated systematic review and meta-analysis. Br J Psychiatry J Ment Sci. 2017;210(6):403–407. DOI:10.1192/bjp.bp.116.195826.
38. Rasmussen KG, Kung S, Lapid MI, et al. A randomized comparison of ketamine versus methohexital anesthesia in electroconvulsive therapy. Psychiatry Res. 2014;215(2):362–365. DOI:10.1016/j.psychres.2013.12.027. [PubMed: 24388729]
39. Ray-Griffith SL, Eads LA, Han X, et al. A randomized pilot study comparing ketamine and methohexital anesthesia for electroconvulsive therapy in patients with depression. J ECT. 2017;33(4):268–271. DOI:10.1097/YCT.0000000000000413. [PubMed: 28422805]
40. Salehi B, Mohammadbeigi A, Kamali AR, et al. Impact comparison of ketamine and sodium thiopental on anesthesia during electroconvulsive therapy in major depression patients with drug-resistant; a double-blind randomized clinical trial. Ann Card Anaesth. 2015;18(4):486. DOI:10.4103/0971-9784.166444. [PubMed: 26440233]
41. Wang X, Chen Y, Zhou X, et al. Effects of propofol and ketamine as combined anesthesia for electroconvulsive therapy in patients with depressive disorder. J ECT. 2012;28(2):128–132. DOI:10.1097/YCT.0b013e31824d1d02. [PubMed: 22622291]
42. Wojdacz R, Swiecicki L, Antosik-Wojcinska A. Comparison of the effect of intravenous anesthetics used for anesthesia during electroconvulsive therapy on the hemodynamic safety and the course of ECT [review]. Psychiatr Pol. 2017;51(6):1039–1058. [PubMed: 29432502]
43. Yoosefi A, Sepehri AS, Kargar M, et al. Comparing effects of ketamine and thiopental administration during electroconvulsive therapy in patients with major depressive disorder: a randomized, double-blind study. J ECT. 2014;30(1):15–21. DOI:10.1097/YCT.0b013e3182a4b4c6. [PubMed: 24091902]
44. Zhang M, Rosenheck R, Lin X, et al. A randomized clinical trial of adjunctive ketamine anesthesia in electro-convulsive therapy for depression. J Affect Disord. 2018;1:372–378.
45. Zheng W, X-h L, Zhu X-M, et al. Adjunctive ketamine and electroconvulsive therapy for major depressive disorder: a meta-analysis of randomized controlled trials. J Affect Disord. 2019;250:123–131. [PubMed: 30852364]
46. Zhong X, He H, Zhang C, et al. Mood and neuropsychological effects of different doses of ketamine in electroconvulsive therapy for treatment-resistant depression. J Affect Disord. 2016;201:124–130. [PubMed: 27208499]
47. Shams Alizadeh N, Maroufi A, Nasseri K, et al. Antidepressant effect of combined ketamine and electroconvulsive therapy on patients with major depressive disorder: a randomized trial. Iran J Psychiatry Behav Sci. 2015;9(3):e1578. DOI:10.17795/ijpbs-1578. [PubMed: 26576166]

48. Ibrahim L, Diazgranados N, Franco-Chaves J, et al. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2012;37(6):1526–1533. DOI:10.1038/npp.2011.338.

49. Mathew SJ, Murrough JW, aan het Rot M, et al. Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placebo-controlled continuation trial. Int J Neuropsychopharmacol. 2010;13(1):71–82. DOI:10.1017/S1461145709000169. [PubMed: 19288975]

50. Zarate CA Jr, Quiroz JA, Singh JB, et al. An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. Biol Psychiatry. 2005;57(4):430–432. De Sarro Benoit B Berman, Frizzo First, Lacomblez Hebert, Montgomery Maj, Tonen Paul, Wang Wagner, Zarate Young, Zarate Zarate, editor. DOI:10.1016/j.biopsych.2004.11.023. [PubMed: 15705360]

51. Caddy C, Amit BH, McCloud TL, et al. Ketamine and other glutamate receptor modulators for depression in adults. Cochrane Database Syst Rev [Internet]. 2015 [cited 2019 Dec 1]; Available from: http://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011612.pub2/full.

52. McCloud TL, Caddy C, Jochim J, et al. Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults. Cochrane Database Syst Rev. 2015;CD011611. DOI:10.1002/14651858.CD011611.pub2. [PubMed: 26415966]

53. Chen M-H, Cheng C-M, Gueorguieva R, et al. Maintenance of antidepressant and antisuicidal effects by D-cycloserine among patients with treatment-resistant depression who responded to low-dose ketamine infusion: a double-blind randomized placebo-control study. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2019;44(12):2112–2118. DOI:10.1038/s41386-019-0480-y.

54. Pickering G, Pereira B, Morel V, et al. Rationale and design of a multicenter randomized clinical trial with memantine and dextromethorphan in ketamine-responder patients. Contemp Clin Trials. 2014;38(2):314–320. DOI:10.1016/j.cct.2014.06.004. [PubMed: 24948402]

55. Sanacora G, Smith MA, Pathak S, et al. Lanicemine: a low-trapping NMDA channel blocker produces sustained antidepressant efficacy with minimal psychotomimetic adverse effects. Mol Psychiatry. 2014;19(9):978–985. DOI:10.1038/mp.2013.130. [PubMed: 24126931]

56. Hashimoto K Rapid-acting antidepressant ketamine, its metabolites and other candidates: a historical overview and future perspective. Psychiatry Clin Neurosci. 2019;73(10):613–627. [PubMed: 31215725]

57. Hashimoto K Molecular mechanisms of the rapid-acting and long-lasting antidepressant actions of (R)-ketamine. Biochem Pharmacol. 2020;177:113935. [PubMed: 32224141]

58. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther. 2013;19(6):370–380. [PubMed: 23575437]

59. Wei Y, Chang L, Hashimoto K. A historical review of antidepressant effects of ketamine and its enantiomers. Pharmacol Biochem Behav. 2020;190:172870. [PubMed: 32035078]

60. Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. Mol Psychiatry. 2018;23(4):801–811. [PubMed: 29532791]

61. Zhang K, Hashimoto K. An update on ketamine and its two enantiomers as rapid-acting antidepressants. Expert Rev Neurother. 2019;19(1):83–92. [PubMed: 30513009]

62. Jelen LA, Young AH, Stone JM. Ketamine: a tale of two enantiomers. J Psychopharmacol Oxf Engl. 2021;35(2):109–123.

63. Dold M, Bartova L, Kasper S. Treatment response of add-on esketamine nasal spray in resistant major depression in relation to add-on second-generation antipsychotic treatment. Int J Neuropsychopharmacol. 2020;23(7):440–445. [PubMed: 32570275]

64. Zheng W, Cai D-B, Xiang Y-Q, et al. Adjunctive intranasal esketamine for major depressive disorder: a systematic review of randomized double-blind controlled-placebo studies. J Affect Disord. 2020;265:63–70. [PubMed: 31957693]

65. Papakostas GI, Salloum NC, Hock RS, et al. , Efficacy of esketamine augmentation in major depressive disorder: a meta-analysis. J Clin Psychiatry. 81(19): r12889. 2020. 10.4088/

JCP.19r12889.• of considerable interest for a systematic meta anlitical reviewed on IN esketamine for TRD

66. Leal GC, Bandeira ID, Correia-Melo FS, et al. Intravenous arketamine for treatment-resistant depression: open-label pilot study. Eur Arch Psychiatry Clin Neurosci. 2021;271(3):577–582. DOI:10.1007/s00406-020-01110-5. [PubMed: 32078034]
67. Zanos P, Highland JN, Liu X, et al. (R)-ketamine exerts antidepressant actions partly via conversion to (2R,6R)-hydroxynorketamine, while causing adverse effects at sub-anaesthetic doses. Br J Pharmacol. 2019;176(14):2573–2592. DOI:10.1111/bph.14683. [PubMed: 30941749]
68. Zanos P, Thompson SM, Duman RS, et al. Convergent mechanisms underlying rapid antidepressant action. CNS Drugs. 2018;32(3):197–227. DOI:10.1007/s40263-018-0492-x. [PubMed: 29516301]
69. Zanos P, Moaddel R, Morris PJ, et al. Ketamine and ketamine metabolite pharmacology: insights into therapeutic mechanisms. Pharmacol Rev. 2018;70(3):621–660. DOI:10.1124/pr.117.015198. [PubMed: 29945898]
70. Zanos P, Moaddel R, Morris PJ, et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature. 2016;533(7604):481–486. DOI:10.1038/nature17998. [PubMed: 27144355]
71. Newport DJ, Carpenter LL, McDonald WM, et al. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. Am J Psychiatry. 2015;172(10):950–966. DOI:10.1176/appi.ajp.2015.15040465. [PubMed: 26423481]
72. Burger J, Capobianco M, Lovern R, et al. A double-blinded, randomized, placebo-controlled sub-dissociative dose ketamine pilot study in the treatment of acute depression and suicidality in a military emergency department setting. Mil Med. 2016;181(10):1195–1199. DOI:10.7205/MILMED-D-15-00431. [PubMed: 27753551]
73. Lener MS, Kadriu B, Zarate CA. Ketamine and beyond: investigations into the potential of glutamatergic agents to treat depression. Drugs. 2017;77(4):381–401. [PubMed: 28194724]
74. Bahji A, Vazquez GH, and Zarate CA. Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. J Affect Disord. 2021;278:542–555. [PubMed: 33022440]
75. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLOS Med. 2009;6(7):e1000100. DOI:10.1371/journal.pmed.1000100. [PubMed: 19621070]
76. Bahji A, Zarate CA, Vazquez GH. Ketamine for bipolar depression: a systematic review. Int J Neuropsychopharmacol. 2021;24(7):535–541. *. of interest for a systematic meta analysis review on ketamine for BD. DOI:10.1093/ijnp/pyab023. [PubMed: 33929489]
77. Veritas Health Innovation. Covidence systematic review software. Melbourne, Australia; 2019.
78. Bahji A, Vazquez GH, Zarate CA. Response to commentary on the comparative efficacy of esketamine vs. ketamine meta-analysis: putting the cart before the horse? J Affect Disord. 2021;282:258–260. [PubMed: 33418376]
79. Bahji A, Vazquez GH, Zarate CA. Erratum to “comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis”. [journal of affective disorders 278C (2021) 542–555] J Affect Disord. 2021;281(281):1001. [PubMed: 33229028]
80. Drevets WC, Popova V, Daly EJ, et al. Comments to Drs. Bahji, Vazquez, and Zarate. J Affect Disord. 2021;283:262–264. [PubMed: 33571795]
81. Ekstrand J Letter to the editor: comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. J Affect Disord. 2021;289:88–89. [PubMed: 33957360]
82. Souza-Marques B, Mello RP, Jesus-Nunes AP, et al. Letter to the editor - comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. J Affect Disord. 2021;283:265–266. [PubMed: 33571796]
83. Collaboration Cochrane. Cochrane handbook: general methods for cochrane reviews. [Internet]. Heterogeneity. 2014 [cited 2019 Jul 17]. Available from: https://handbook-5-1.cochrane.org/chapter_9/9_5_heterogeneity.htm.

84. Higgins JPT, Altman DG, Gøtzsche PC, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. [PubMed: 22008217]
85. Bahji A, Ermacora D, Stephenson C, et al. Comparative efficacy and tolerability of pharmacological treatments for the treatment of acute bipolar depression: a systematic review and network meta-analysis. J Affect Disord. 2020;269:154–184. [PubMed: 32339131]
86. Bahji A, Ermacora D, Stephenson C, et al. Comparative efficacy and tolerability of adjunctive pharmacotherapies for acute bipolar depression: a systematic review and network meta-analysis. Can J Psychiatry Rev Can Psychiatr. 2021;66(3):274–288. DOI:10.1177/0706743720970857.
87. Vázquez GH, Bahji A, Undurraga J, et al. Efficacy and tolerability of combination treatments for major depression: antidepressants plus second-generation antipsychotics vs. esketamine vs. Lithium J Psychopharmacol Oxf Engl. 2021;35:890–900. DOI:10.1177/02698811211013579• of interest for efficacy and safety of adjunctive options for MDD
88. Schwarzer G meta: an R package for meta-analysis [Internet]. USA: R; 2007 [cited 2019 Nov 3]. Available from: https://cran.r-project.org/web/packages/meta/meta.pdf.
89. Ionescu DF, Bentley KH, Eikermann M, et al. Repeat-dose ketamine augmentation for treatment-resistant depression with chronic suicidal ideation: a randomized, double blind, placebo controlled trial. J Affect Disord. 2019;243:516–524. [PubMed: 30286416]
90. Phillips JL, Norris S, Talbot J, et al. Single, repeated, and maintenance ketamine infusions for treatment-resistant depression: a randomized controlled trial. Am J Psychiatry. 2019;176(5):401–409. DOI:10.1176/appi.ajp.2018.18070834. [PubMed: 30922101]
91. Singh JB, Fedgchin M, Daly EJ, et al. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. Am J Psychiatry. 2016;173(8):816–826. DOI:10.1176/appi.ajp.2016.16010037. [PubMed: 27056608]
92. C-T L, Chen M-H, Lin W-C, et al. The effects of low-dose ketamine on the prefrontal cortex and amygdala in treatment-resistant depression: a randomized controlled study. Hum Brain Mapp. 2016;37:1080–1090. [PubMed: 26821769]
93. Arabzadeh S, Hakkikazazi E, Shahmansouri N, et al. Does oral administration of ketamine accelerate response to treatment in major depressive disorder? Results of a double-blind controlled trial. J Affect Disord. 2018;235:236–241. [PubMed: 29660637]
94. George D, Gálvez V, Martin D, et al. Pilot randomized controlled trial of titrated subcutaneous ketamine in older patients with treatment-resistant depression. Am J Geriatr Psychiatry. 2017;25(11):1199–1209. DOI:10.1016/j.jagp.2017.06.007. [PubMed: 28739263]
95. Loo CK, Gálvez V, O'Keefe E, et al. Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression. Acta Psychiatr Scand. 2016;134(1):48–56. DOI:10.1111/acps.12572. [PubMed: 27028832]
96. Lapidus KAB, Levitch CF, Perez AM, et al. A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol Psychiatry. 2014;76(12):970–976. DOI:10.1016/j.biopsych.2014.03.026. [PubMed: 24821196]
97. Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry. 2018;75(2):139–148. DOI:10.1001/jamapsychiatry.2017.3739. [PubMed: 29282469]
98. Canuso CM, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. Am J Psychiatry. 2018;175(7):620–630. DOI:10.1176/appi.ajp.2018.17060720. [PubMed: 29656663]
99. Popova V, Daly EJ, Trivedi M, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. Am J Psychiatry. 2019;176(6):428–438. DOI:10.1176/appi.ajp.2019.19020172. [PubMed: 31109201]
100. Singh JB, Fedgchin M, Daly E, et al. Intravenous esketamine in adult treatment-resistant depression: a double-blind, double-randomization, placebo-controlled study. Biol Psychiatry. 2016;80(6):424–431. DOI:10.1016/j.biopsych.2015.10.018. [PubMed: 26707087]

101. Correia-Melo FS, Leal GC, Vieira F, et al. Efficacy and safety of adjunctive therapy using esketamine or racemic ketamine for adult treatment-resistant depression: a randomized, double-blind, non-inferiority study. J Affect Disord. 2020;264:527–534. [PubMed: 31786030]
102. Cao Z, Lin C-T, Ding W, et al. Identifying ketamine responses in treatment-resistant depression using a wearable forehead EEG. IEEE Trans Biomed Eng. 2019;66(6):1668–1679. DOI:10.1109/TBME.2018.2877651. [PubMed: 30369433]
103. Chen M-H, C-T L, Lin W-C, et al. Cognitive function of patients with treatment-resistant depression after a single low dose of ketamine infusion. J Affect Disord. 2018;241:1–7. [PubMed: 30081380]
104. Diazgranados N, Ibrahim L, Brutsche NE, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch Gen Psychiatry. 2010;67(8):793–802. DOI:10.1001/archgenpsychiatry.2010.90.. [PubMed: 20679587] • of interest due to be the first trial on ketamine for BD
105. Domany Y, Shelton RC, McCullumsmith CB. Ketamine for acute suicidal ideation. An emergency department intervention: a randomized, double-blind, placebo-controlled, proof-of-concept trial. Depress Anxiety [Internet]. 2019 [cited 2020 Jan 2];n/a. Available from: http://onlinelibrary.wiley.com/doi/abs/10.1002/da.22975.
106. Downey D, Dutta A, McKie S, et al. Comparing the actions of lanicemine and ketamine in depression: key role of the anterior cingulate. Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol. 2016;26(6):994–1003. DOI:10.1016/j.euroneuro.2016.03.006.
107. Fava M, Freeman MP, Flynn M, et al. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). Mol Psychiatry. 2018;25(7):1592–1603. DOI:10.1038/s41380-018-0256-5. [PubMed: 30283029]
108. Fedgchin M, Trivedi M, Daly EJ, et al. Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: results of a randomized, double-blind, active-controlled study (TRANSFORM-1). Int J Neuropsychopharmacol. 2019;22(10):616–630. DOI:10.1093/ijnp/pyz039. [PubMed: 31290965]
109. Fu D-J, Ionescu DF, Li X, et al. Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients who have active suicidal ideation with intent: double-blind, randomized study (ASPIRE I). J Clin Psychiatry. Internet] 2020 [cited 2020 Dec 29];81. Available from.;(3). https://www.psychiatrist.com/JCP/article/Pages/2020/v81/19m13191.aspx
110. Gálvez V, Li A, Huggins C, et al. Repeated intranasal ketamine for treatment-resistant depression – the way to go? Results from a pilot randomised controlled trial. J Psychopharmacol (Oxf). 2018;32(4):397–407. DOI:10.1177/0269881118760660.
111. Grunebaum MF, Ellis SP, Keilp JG, et al. Ketamine versus midazolam in bipolar depression with suicidal thoughts: a pilot midazolam-controlled randomized clinical trial. Bipolar Disord. 2017;19(3):176–183. DOI:10.1111/bdi.12487. [PubMed: 28452409]
112. Grunebaum MF, Galfalvy HC, Choo T-H, et al. Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. Am J Psychiatry. 2018;175(4):327–335. DOI:10.1176/appi.ajp.2017.17060647. [PubMed: 29202655]
113. Y-d H, Xiang Y-T, Fang J-X, et al. Single i.v. ketamine augmentation of newly initiated escitalopram for major depression: results from a randomized, placebo-controlled 4-week study. Psychol Med. 2016;46:623–635. [PubMed: 26478208]
114. Ionescu DF, D-J F, Qiu X, et al. Esketamine nasal spray for rapid reduction of depressive symptoms in patients with major depressive disorder who have active suicide ideation with intent: results of a phase 3, double-blind, randomized study (ASPIRE II). Int J Neuropsychopharmacol. 2021;24(1):22–31. *. of interest on the safety and efficacy of IN Esketamine for severe MDD with active suicidal risks. DOI:10.1093/ijnp/pyaa068. [PubMed: 32861217]
115. Lai R, Katalinic N, Glue P, et al. Pilot dose–response trial of i.v. ketamine in treatment-resistant depression. World J Biol Psychiatry. 2014;15(7):579–584. DOI:10.3109/15622975.2014.922697. [PubMed: 24910102]
116. Murrough JW, Soleimani L, DeWilde KE, et al. Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. Psychol Med. 2015;45(16):3571–3580. DOI:10.1017/S0033291715001506. [PubMed: 26266877]

117. Murrough JW, Iosifescu DV, Chang LC, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry. 2013;170(10):1134–1142. DOI:10.1176/appi.ajp.2013.13030392. [PubMed: 23982301]
118. Nugent AC, Ballard E, Gould TD, et al. Ketamine has distinct electrophysiological and behavioral effects in depressed and healthy subjects. Mol Psychiatry. 2019;24(7):1040–1052. DOI:10.1038/s41380-018-0028-2. [PubMed: 29487402]
119. Ochs-Ross R, Daly EJ, Zhang Y, et al. Efficacy and safety of esketamine nasal spray plus an oral antidepressant in elderly patients with treatment-resistant depression—TRANSFORM-3. Am J Geriatr Psychiatry. 2020;28(2):121–141. DOI:10.1016/j.jagp.2019.10.008. [PubMed: 31734084]
120. Šóš P, Klírová M, Novak T, et al. Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression. Neuro Endocrinol Lett. 2013;34(4):287–293. [PubMed: 23803871]
121. T-P S, Chen M-H, C-T L, et al. Dose-related effects of adjunctive ketamine in Taiwanese patients with treatment-resistant depression. Neuropsychopharmacology. 2017;42(13):2482–2492. DOI:10.1038/npp.2017.94. [PubMed: 28492279]
122. Zarate CA, Brutsche NE, Ibrahim L, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. Biol Psychiatry. 2012;71:939–946. [PubMed: 22297150]
123. Zarate CA, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006;63(8):856–864. DOI:10.1001/archpsyc.63.8.856. [PubMed: 16894061]
124. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000;47(4):351–354. DOI:10.1016/S0006-3223(99)00230-9. [PubMed: 10686270]
125. Domany Y, Bleich-Cohen M, Tarrasch R, et al. Repeated oral ketamine for out-patient treatment of resistant depression randomised, double-blind, placebo-controlled, proof-of-concept study. Br J Psychiatry. 2019;214(1):20–26. DOI:10.1192/bjp.2018.196. [PubMed: 30246667]
126. Li M, Demenescu LR, Colic L, et al. Temporal dynamics of antidepressant ketamine effects on glutamine cycling follow regional fingerprints of AMPA and NMDA receptor densities. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2017;42(6):1201–1209. DOI:10.1038/npp.2016.184.
127. Aleksandrova LR, Phillips AG, Wang YT. Antidepressant effects of ketamine and the roles of AMPA glutamate receptors and other mechanisms beyond NMDA receptor antagonism. J Psychiatry Neurosci JPN. 2017;42:222–229. [PubMed: 28234212]
128. Zorumski CF, Izumi Y, Mennerick SK. NMDA receptors and beyond. J Neurosci. 2016;36:11158–11164. [PubMed: 27807158]
129. Evans JW, Szczepanik J, Brutsche N, et al. Default mode connectivity in major depressive disorder measured up to 10 days after ketamine administration. Biol Psychiatry. 2018;84(8):582–590. DOI:10.1016/j.biopsych.2018.01.027. [PubMed: 29580569]
130. Strasburger SE, Bhimani PM, Kaabe JH, et al. What is the mechanism of ketamine's rapid-onset antidepressant effect? A concise overview of the surprisingly large number of possibilities. J Clin Pharm Ther. 2017;42:147–154. [PubMed: 28111761]
131. Bonaventura J, Lam S, Carlton M, et al. Pharmacological and behavioral divergence of ketamine enantiomers: implications for abuse liability. Mol Psychiatry. 2021;26(11):6704–6722. DOI:10.1038/s41380-021-01093-2. [PubMed: 33859356]
132. López-Díaz Á, Fernández-González JL, Luján-Jiménez JE, et al. Use of repeated intravenous ketamine therapy in treatment-resistant bipolar depression with suicidal behaviour: a case report from Spain. Ther Adv Psychopharmacol. 2017;7(4):137–140. DOI:10.1177/2045125316675578. [PubMed: 28540033]
133. Gałuszko-Węgielnik M, Wiglusz MS, Słupski J, et al. Efficacy of ketamine in bipolar depression: focus on anhedonia. Psychiatria Danubina. 2019;31(Suppl 3):554–560. [PubMed: 31488790]
134. Ionescu DF, Luckenbaugh DA, Niciu MJ, et al. A single infusion of ketamine improves depression scores in patients with anxious bipolar depression. Bipolar Disord. 2015;17(4):438–443. DOI:10.1111/bdi.12277. [PubMed: 25400146]

135. Kraus C, Rabl U, Vanicek T, et al. Administration of ketamine for unipolar and bipolar depression. Int J Psychiatry Clin Pract. 2017;21(1):2–12. DOI:10.1080/13651501.2016.1254802. [PubMed: 28097909]

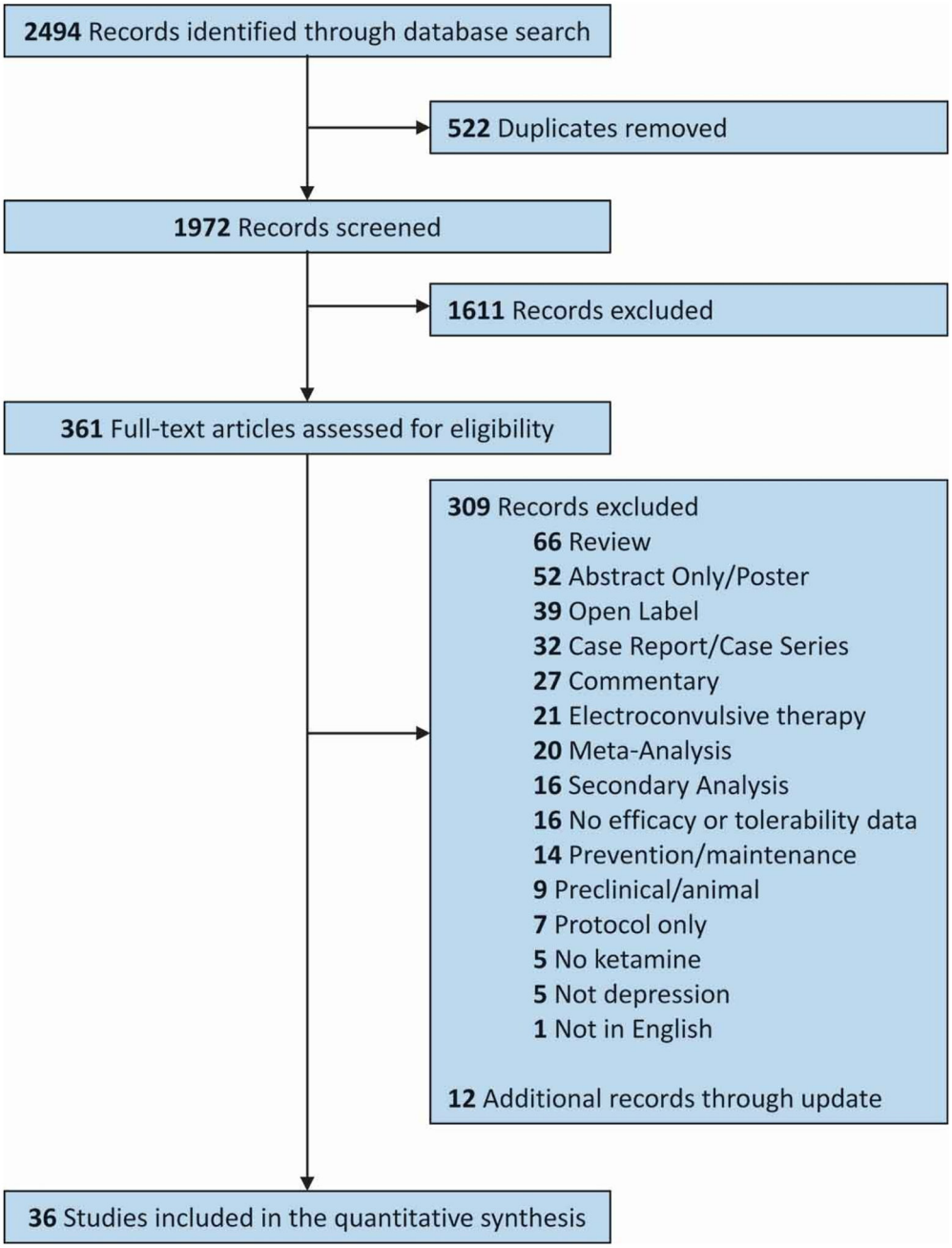

Figure 1.
PRISMA flow diagram outlining the updated systematic review process.

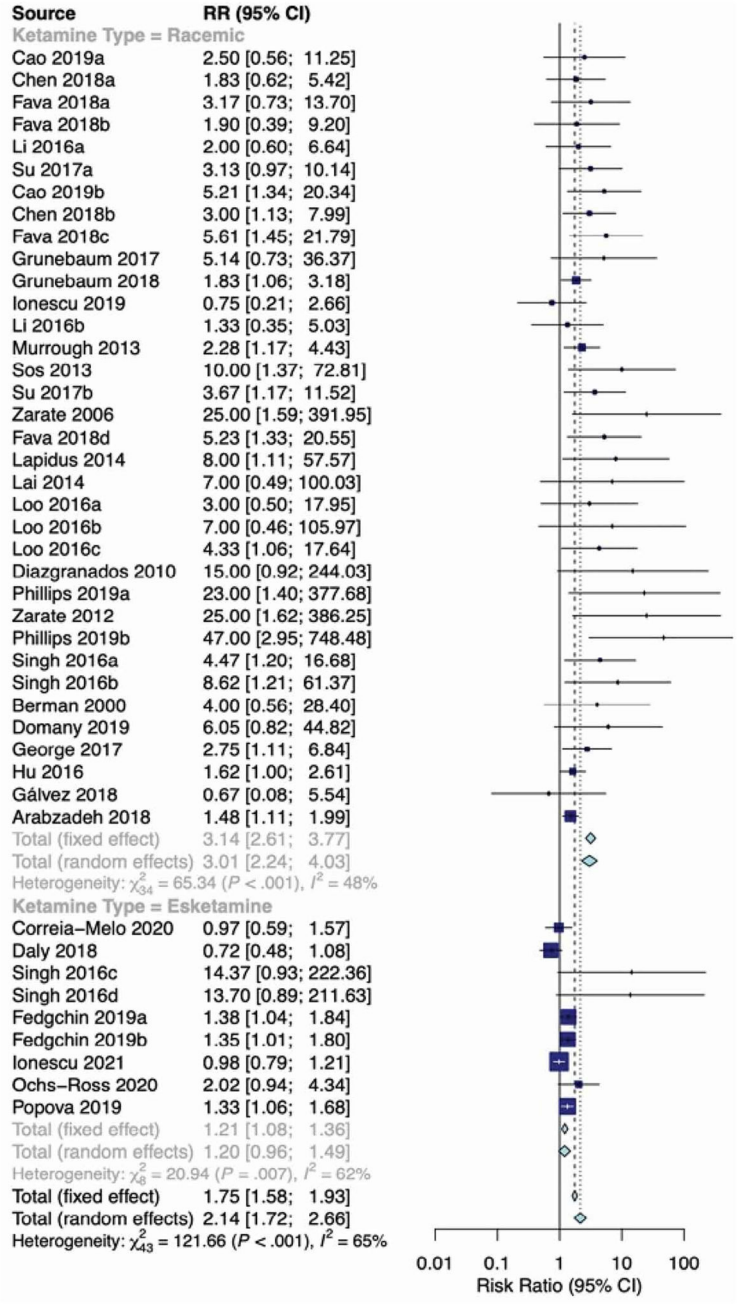

Figure 2.

Forest plot showing random-effects subgroup meta-analysis for comparative response rates from randomized controlled trials involving ketamine versus esketamine.

Table 1.

Study characteristics.

Study	Ketamine	Dose	Route	Category	Comparator	Endpoint	TRD	Depression
Arabzadeh 2018	Racemic	50 mg	O	Repeated	Placebo	6 weeks	No	MDD
Berman 2000	Racemic	0.5 mg/kg	IV	Single	Placebo	1 week	No	MDD
Canuso 2018	Esketamine	84 mg	IN	Repeated	Placebo	4 weeks	No	MDD
Cao 2019a	Racemic	0.2 mg/kg	IV	Single	Placebo	1 week	Yes	MDD
Cao 2019b	Racemic	0.5 mg/kg	IV	Single	Placebo	1 week	Yes	MDD
Chen 2018a	Racemic	0.2 mg/kg	IV	Single	Placebo	1 day	Yes	MDD
Chen 2018b	Racemic	0.5 mg/kg	IV	Single	Placebo	1 day	Yes	MDD
Correia-Melo 2020	Esketamine	0.25 mg/kg	IV	Single	Ketamine	1 week	Yes	MDD
Daly 2018	Esketamine	28–84 mg	IN	Single	Placebo	1 week	Yes	MDD
Diazgranados 2010	Racemic	0.5 mg/kg	IV	Single	Placebo	1 week	Yes	BD
Domany 2019	Racemic	1 mg/kg	O	Repeated	Placebo	3 weeks	Yes	MDD
Downey 2016	Racemic	0.5 mg/kg	IV	Single	Placebo	1 week	No	MDD
Fava 2018a	Racemic	0.1 mg/kg	IV	Single	Midazolam	3 days	Yes	MDD
Fava 2018b	Racemic	0.2 mg/kg	IV	Single	Midazolam	3 days	Yes	MDD
Fava 2018c	Racemic	0.5 mg/kg	IV	Single	Midazolam	3 days	Yes	MDD
Fava 2018d	Racemic	1 mg/kg	IV	Single	Midazolam	3 days	Yes	MDD
Fedgchin 2019a	Esketamine	56 mg	IN	Repeated	Placebo	4 weeks	Yes	MDD
Fedgchin 2019b	Esketamine	84 mg	IN	Repeated	Placebo	4 weeks	Yes	MDD
Fu 2020	Esketamine	84 mg	IN	Repeated	Placebo	4 weeks	No	MDD
Galvez 2018	Racemic	100 mg	IN	Repeated	Midazolam	4 weeks	Yes	MDD
George 2017	Racemic	0.1–0.5 mg/kg	SC	Single	Midazolam	1 week	Yes	MDD
Grunebaum 2017	Racemic	0.5 mg/kg	IV	Single	Midazolam	1 day	No	BD
Grunebaum 2018	Racemic	0.5 mg/kg	IV	Single	Midazolam	1 day	No	MDD
Hu 2016	Racemic	0.5 mg/kg	IV	Single	Placebo	1 week	Yes	MDD
Ionescu 2019	Racemic	0.5 mg/kg	IV	Repeated	Placebo	3 weeks	Yes	MDD
Ionescu 2021	Esketamine	84 mg	IN	Repeated	Placebo	4 weeks	No	MDD
Lai 2014	Racemic	0.33 mg/kg	IV	Single	Placebo	1 week	Yes	MDD
Lapidus 2014	Racemic	50 mg	IN	Single	Placebo	1 week	Yes	MDD
Li 2016a	Racemic	0.2 mg/kg	IV	Single	Placebo	4 hours	Yes	MDD
Li 2016b	Racemic	0.5 mg/kg	IV	Single	Placebo	4 hours	Yes	MDD
Loo 2016a	Racemic	0.1–0.5 mg/kg	IV	Single	Midazolam	1 week	Yes	MDD
Loo 2016b	Racemic	0.1–0.5 mg/kg	IM	Single	Midazolam	1 week	Yes	MDD
Loo 2016c	Racemic	0.1–0.5 mg/kg	SC	Single	Midazolam	1 week	Yes	MDD
Murrough 2013	Racemic	0.5 mg/kg	IV	Single	Midazolam	1 week	Yes	MDD
Murrough 2015	Racemic	0.5 mg/kg	IV	Single	Midazolam	1 week	Yes	MDD
Nugent 2019	Racemic	0.5 mg/kg	IV	Single	Placebo	1 week *	Yes	MDD
Ochs-Ross 2020	Esketamine	84 mg	IN	Repeated	Placebo	4 weeks	Yes	MDD
Phillips 2019	Racemic	0.5 mg/kg	IV	Single	Midazolam	1 week	Yes	MDD
Popova 2019	Esketamine	84 mg	IN	Repeated	Placebo	4 weeks	Yes	MDD

Study	Ketamine	Dose	Route	Category	Comparator	Endpoint	TRD	Depression
Singh 2016a	Racemic	0.5 mg/kg	IV	Repeated	Placebo	4 weeks	Yes	MDD
Singh 2016b	Racemic	0.5 mg/kg	IV	Repeated	Placebo	4 weeks	Yes	MDD
Singh 2016c	Esketamine	0.2 mg/kg	IV	Single	Placebo	3 days	Yes	MDD
Singh 2016d	Esketamine	0.4 mg/kg	IV	Single	Placebo	3 days	Yes	MDD
Sos 2013	Racemic	0.27 mg/kg	IV	Single	Placebo	1 week	No	MDD
Su 2017a	Racemic	0.2 mg/kg	IV	Single	Placebo	1 week	Yes	MDD
Su 2017b	Racemic	0.5 mg/kg	IV	Single	Placebo	1 week	Yes	MDD
Zarate 2006	Racemic	0.5 mg/kg	IV	Single	Placebo	1 week	Yes	MDD
Zarate 2012	Racemic	0.5 mg/kg	IV	Single	Placebo	1 week	Yes	BD

IV = intravenous; IN = intranasal; O = Oral; SC = Subcutaneous; TRD = Treatment-Resistant Depression; MADRS = Montgomery-Åsberg Depression Rating Scale; HDRS = Hamilton Depression Rating Scale; MDD = Major Depressive Disorder (Unipolar Depression); BD = Bipolar Depression.

* Study went out to 11 days.