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ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ieds20

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To cite this article: Anees Bahji, Carlos A. Zarate & Gustavo H. Vazquez (2022) Efficacy and safety of racemic ketamine and esketamine for depression: a systematic review and meta-analysis, Expert Opinion on Drug Safety, 21:6, 853-866, DOI: 10.1080/14740338.2022.2047928

To link to this article: https://doi.org/10.1080/14740338.2022.2047928

EXPERT OPINION ON DRUG SAFETY
2022, VOL. 21, NO. 6, 853–866
https://doi.org/10.1080/14740338.2022.2047928

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SYSTEMATIC REVIEW AND META-ANALYSIS

Efficacy and safety of racemic ketamine and esketamine for depression: a systematic review and meta-analysis

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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.

ARTICLE HISTORY
Received 12 December 2021
Accepted 25 February 2022

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

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.

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Supplemental data for this article can be accessed publisher's website.

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 I^2 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; I^2 = 65%), remission (RR = 1.64; 95% CI, 1.33–2.02; I^2 = 39%), and depression severity (d = −0.63; 95% CI, −0.80 to −0.45; I^2 = 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; I^2 < 1%), dropouts due to adverse events (RR = 1.56; 95% CI, 1.00–2.45; I^2 < 1%), or the overall number of adverse events reported per participant (OR = 2.14; 95% CI, 0.82–5.60; I^2 = 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; I^2 < 1%; k = 25 comparisons)
- Hypertension (OR = 2.53; 95% CI, 1.56–4.11; I^2 < 1%; k = 9 comparisons)
- Nausea (OR = 3.09; 95% CI, 2.23–4.27; I^2 = 15%; k = 20 comparisons)
- Vomiting (OR = 3.18; 95% CI, 1.80–5.60; I^2 = 17%; k = 13 comparisons)
- Vertigo (OR = 5.98; 95% CI, 3.36–10.66; I^2 = 27%; k = 11 comparisons)
- Somnolence (OR = 3.06; 95% CI, 1.90–4.95; I^2 = 34%; k = 14 comparisons)
- Hypoesthesia (OR = 8.57; 95% CI, 4.23–17.37; I^2 < 1%; k = 7 comparisons)
- Paresthesia (OR = 4.80; 95% CI, 2.89–7.96; I^2 < 1%; k = 13 comparisons)
- Dissociation (OR = 8.19; 95% CI, 5.62–11.95; I^2 < 1%; k = 18 comparisons)
- Anxiety (OR = 1.67; 95% CI, 1.00–2.77; I^2 < 1%; k = 10 comparisons)
- Dysgeusia (OR = 1.88; 95% CI, 1.28–2.76; I^2 = 39%; k = 10 comparisons)
- Headache (OR = 1.38; 95% CI, 1.05–1.82; I^2 = 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

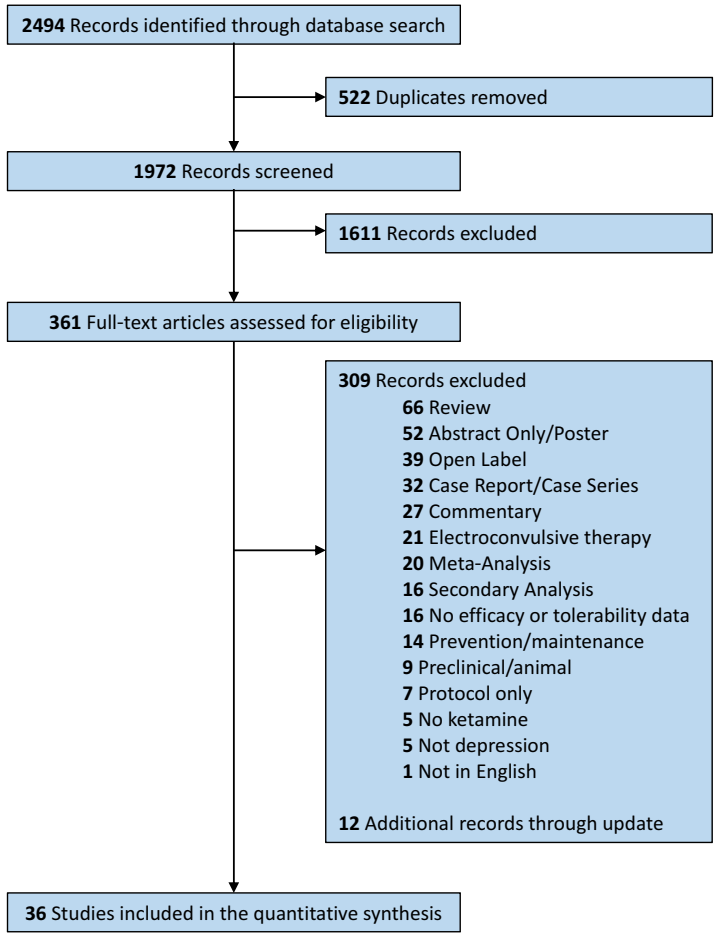

Figure 1. PRISMA flow diagram outlining the updated systematic review process.

technique, the revised effect sizes for response (RR = 1.48; 95% CI, 1.19–1.83; k = 20 added studies; I^2 = 63%) and remission (RR = 1.40; 95% CI, 1.12–1.76; k = 13 added studies; I^2 = 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

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
Gálvez 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
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.*

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

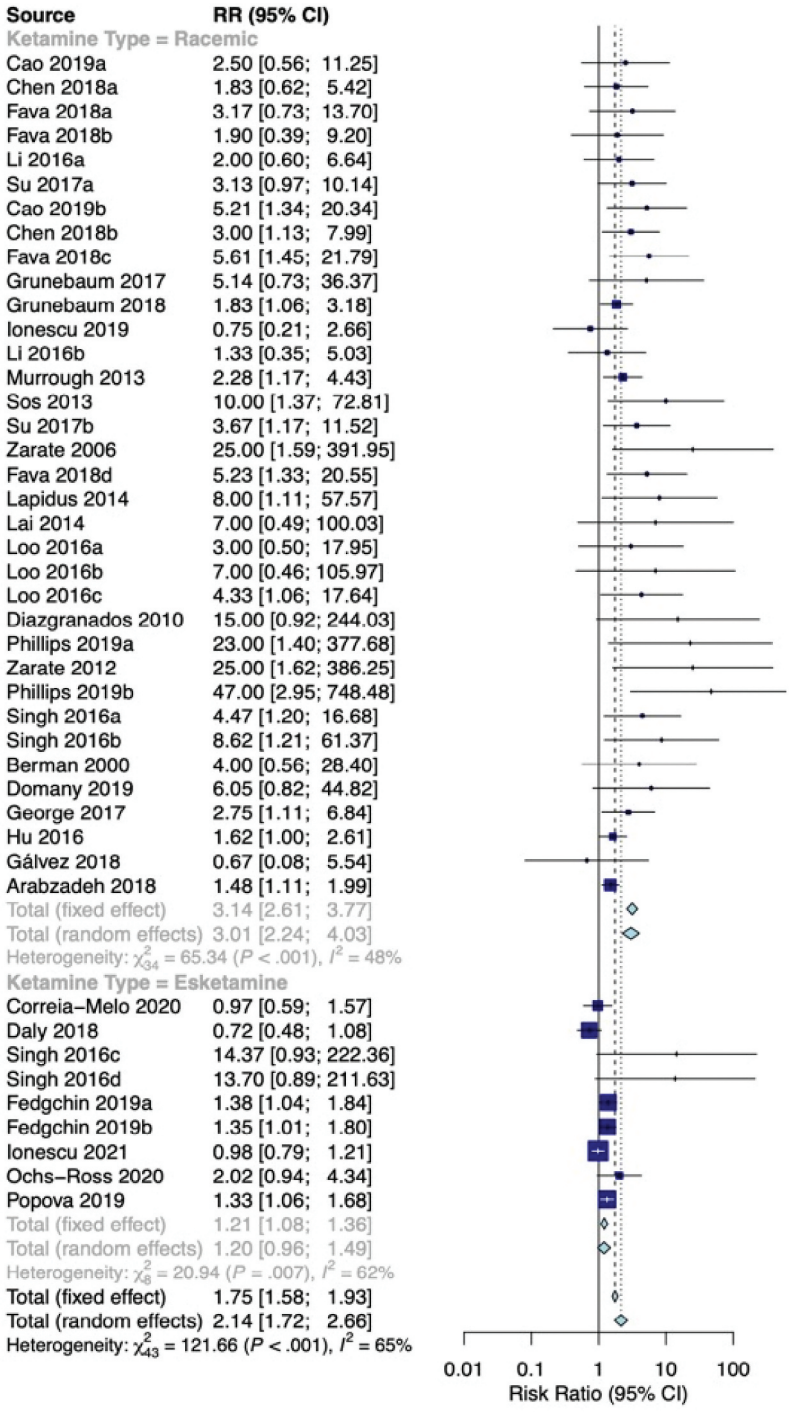

Figure 2. Forest plot showing random-effects subgroup meta-analysis for comparative response rates from randomized controlled trials involving ketamine versus esketamine.

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.

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.

Reviewer disclosures

A peer reviewer on this manuscript has disclosed that they have a patent awarded for development of a controlled release ketamine tablet for TRD. All other peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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APPENDIX A. Search Strategy

Medline search strategy for depression (17 December 2019 to 23 November 2021).

1	Ketamine.mp or exp Ketamine/	19,329
2	drug therapy.mp. or exp Drug Therapy/	2,899,818
3	random*.ti,ab.	1,093,759
4	(crossover* or 'cross over' or cross-over*).ti,ab.	84,283
5	placebo*.ti,ab.	210,148
6	double blind.tw.	136,906
7	single blind.tw.	13,239
8	randomized controlled trial.mp. or exp Randomized controlled Trial/	522,666
9	assign*.ti,ab.	305,491
10	allocat*.ti,ab.	114,182
11	evaluation study.mp. or exp Evaluation Studies/	250,653
12	intervention.mp.	586,290
13	treatment effectiveness evaluation.mp.	12
14	prospective study.mp. or exp Prospective Studies/	563,939
15	Comparative study/	1,848,346
16	'comparative study.'ti,ab.	76,030
17	N-of-1.mp.	72,041
18	Clinical trials.mp.	403,731
19	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	4,433,706
20	depression.mp. or exp Depression/ or exp Depression, Postpartum/ or exp Long-Term/	387,330
21	exp Depressive disorder/ or exp Depressive disorder, Major/ or major depression.mp.	114,254
22	20 or 21	417,220
23	1 and 19 and 22	665
24	limit 23 to yr = '1980 -Current'	650

PsycINFO search strategy for depression (17 December 2019 to 23 November 2021).

1	Ketamine.mp or exp Ketamine/	3489
2	drug therapy.mp. or exp Drug Therapy/	144,767
3	random*.ti,ab.	193,615
4	(crossover* or 'cross over' or cross-over*).ti,ab.	7325
5	placebo*.ti,ab.	39,397
6	double blind.tw.	22,534
7	single blind.tw.	1935
8	randomized controlled trial.mp. or exp Randomized controlled Trial/	17,388
9	assign*.ti,ab.	94,095
10	allocat*.ti,ab.	29,496
11	evaluation study.mp. or exp Evaluation Studies/	1432
12	intervention.mp.	262,214
13	treatment effectiveness evaluation.mp.	23,720
14	prospective study.mp. or exp Prospective Studies/	11,575
15	Comparative study/	0
16	'comparative study.'ti,ab.	11,966
17	N-of-1.mp.	10,234
18	Clinical trials.mp.	27,575
19	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	660,114
20	depression.mp. or exp Depression/ or exp Depression, Postpartum/ or exp Long-Term/	319,029
21	exp Depressive disorder/ or exp Depressive disorder, Major/ or major depression.mp.	125,325
22	20 or 21	319,029
23	1 and 19 and 22	579
24	limit 23 to yr = '1980 -Current'	576

Medline search strategy for bipolar disorder (17 December 2019 to 23 November 2021).

1	Ketamine.mp or exp Ketamine/	19,329
2	drug therapy.mp. or exp Drug Therapy/	2,899,818
3	random*.ti,ab.	1,093,759
4	(crossover* or 'cross over' or cross-over*).ti,ab.	84,283
5	placebo*.ti,ab.	210,148
6	double blind.tw.	136,906
7	single blind.tw.	13,239
8	randomized controlled trial.mp. or exp Randomized controlled Trial/	522,666
9	assign*.ti,ab.	305,491
10	llocate*.ti,ab.	114,182
11	evaluation study.mp. or exp Evaluation Studies/	250,653
12	intervention.mp.	586,290
13	treatment effectiveness evaluation.mp.	12
14	prospective study.mp. or exp Prospective Studies/	563,939
15	Comparative study/	1,848,346
16	'comparative study.'ti,ab.	76,030
17	N-of-1.mp.	72,041
18	Clinical trials.mp.	403,731
19	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	4,433,706
20	bipolar disorder.mp. or exp Bipolar Disorder/	48,214
21	bipolar.mp.	77,112
22	bipolar depression.mp. or exp Bipolar Disorder/	40,079
23	manic depressive illness.mp.	907
24	mania.mp.	10,325
25	20 or 21 or 22 or 23 or 24	79,345
26	1 and 19 and 25	93
27	limit 26 to yr = '1980 -Current'	93

PsycINFO search strategy for bipolar disorder (17 December 2019 to 23 November 2021).

1	Ketamine.mp or exp Ketamine/	3489
2	drug therapy.mp. or exp Drug Therapy/	144,767
3	random*.ti,ab.	193,615
4	(crossover* or 'cross over' or cross-over*).ti,ab.	7325
5	placebo*.ti,ab.	39,397
6	double blind.tw.	22,534
7	single blind.tw.	1935
8	randomized controlled trial.mp. or exp Randomized controlled Trial/	17,388
9	assign*.ti,ab.	94,095
10	allocat*.ti,ab.	29,496
11	evaluation study.mp. or exp Evaluation Studies/	1432
12	intervention.mp.	262,214
13	treatment effectiveness evaluation.mp.	23,720
14	prospective study.mp. or exp Prospective Studies/	11,575
15	Comparative study/	0
16	'comparative study.'ti,ab.	11,966
17	N-of-1.mp.	10,234
18	Clinical trials.mp.	27,575
19	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	660,114
20	bipolar disorder.mp. or exp Bipolar Disorder/	41,110
21	bipolar.mp.	41,587
22	bipolar depression.mp. or exp Bipolar Disorder/	30,258
23	manic depressive illness.mp.	910
24	mania.mp.	15,389
25	20 or 21 or 22 or 23 or 24	51,673
26	1 and 19 and 25	151
27	limit 26 to yr = '1980 -Current'	151

EMBASE search strategy for depression (17 December 2019 to 23 November 2021).

1	Ketamine.mp or exp Ketamine/	42,034
2	drug therapy.mp. or exp Drug Therapy/	5,492,882
3	random*.ti,ab.	1,494,826
4	(crossover* or 'cross over' or cross-over*).ti,ab.	104,898
5	placebo*.ti,ab.	305,836
6	double blind.tw.	194,498
7	single blind.tw.	17,870
8	randomized controlled trial.mp. or exp Randomized controlled Trial/	768,310
9	assign*.ti,ab.	384,751
10	allocat*.ti,ab.	147,688
11	evaluation study.mp. or exp Evaluation Studies/	68,228
12	intervention.mp.	927,648
13	treatment effectiveness evaluation.mp.	29
14	prospective study.mp. or exp Prospective Studies/	632,820
15	Comparative study/	867,857
16	'comparative study.'ti,ab.	102,187
17	N-of-1.mp.	113,816
18	Clinical trials.mp.	344,763
19	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	8,731,937
20	depression.mp. or exp Depression/ or exp Depression, Postpartum/ or exp Long-Term/	715,063
21	exp Depressive disorder/ or exp Depressive disorder, Major/ or major depression.mp.	469,823
22	20 or 21	715,063
23	1 and 19 and 22	4439
24	limit 23 to yr = '1980 -Current'	4383
25	limit 24 to (human and english language)	3562
26	Limit 25 to exclude medline journals	462

EMBASE search strategy for bipolar disorder (17 December 2019 to 23 November 2021).

1	Ketamine.mp or exp Ketamine/	42,034
2	drug therapy.mp. or exp Drug Therapy/	5,492,882
3	random*.ti,ab.	1,494,826
4	(crossover* or 'cross over' or cross-over*).ti,ab.	104,898
5	placebo*.ti,ab.	305,836
6	double blind.tw.	194,498
7	single blind.tw.	17,870
8	randomized controlled trial.mp. or exp Randomized controlled Trial/	768,310
9	assign*.ti,ab.	384,751
10	allocat*.ti,ab.	147,688
11	evaluation study.mp. or exp Evaluation Studies/	68,228
12	intervention.mp.	927,648
13	treatment effectiveness evaluation.mp.	29
14	prospective study.mp. or exp Prospective Studies/	632,820
15	Comparative study/	867,857
16	'comparative study.'ti,ab.	102,187
17	N-of-1.mp.	113,816
18	Clinical trials.mp.	344,763
19	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	8,731,937
20	bipolar disorder.mp. or exp Bipolar Disorder/	70,162
21	bipolar.mp.	113,010
22	bipolar depression.mp. or exp Bipolar Disorder/	64,127
23	manic depressive illness.mp.	1243
24	mania.mp.	26,164
25	exp rapid cycling bipolar disorder/ or exp bipolar disorder/ or exp bipolar depression/ or exp bipolar II disorder/ or bipolar.mp. or exp bipolar I disorder/ or exp bipolar mania/	113,428
26	20 or 21 or 22 or 23 or 24 or 25	124,031
27	1 and 19 and 26	651
28	limit 27 to yr = '1980 -Current'	649
29	limit 28 to (human and english language)	577
30	Limit 29 to exclude medline journals	76

COCHRANE search strategy for depression (17 December 2019 to 23 November 2021).

1	MeSH descriptor: [Ketamine] explode all trees	1938
2	Ketamine.mp	4733
3	1 or 2	4733
4	MeSH descriptor: [Depression] explode all trees	10,719
5	Depression.mp	71,984
6	Postpartum depression.mp	1821
7	Depressive disorder.mp	18,293
8	Major depression.mp	26,860
9	Long-term depression.mp	6037
10	4 or 5 or 6 or 7 or 8 or 9, limit to 1980–2019	806

Cochrane search strategy for bipolar disorder (17 December 2019 to 23 November 2021).

1	MeSH descriptor: [Ketamine] explode all trees	1938
2	Ketamine.mp	4733
3	1 or 2	4733
4	MeSH descriptor: [Bipolar Disorder] explode all trees	2440
5	MeSH descriptor: [Bipolar and Related Disorders] explode all trees	2441
6	Bipolar.mp	8648
7	Mania.mp	2601
8	Hypomania.mp	430
9	Manic depressive illness.mp	348
10	Bipolar affective disorder.mp	1228
11	#4 or #5 or #6 or #7 or #8 or #9 or #10	9374
12	#3 and #11	119
11	Limit 9 to yr = '1980 -Current'	119

Appendix B. Risk of bias across studies

Study	Randomization	Allocation	Blinding	Attrition	Reporting	Other
Arabzadeh 2018	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Berman 2000	Low risk	Low risk	Low risk	High risk	High risk	Low risk
Canuso 2018	Low risk	High risk	Low risk	High risk	Low risk	Low risk
Cao 2019	Low risk	Low risk	Low risk	High risk	High risk	Low risk
Chen 2018	Low risk	Low risk	Low risk	High risk	High risk	Low risk
Correia-Melo 2020	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Daly 2018	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Diazgranados 2010	Low risk	High risk	Low risk	High risk	Low risk	Low risk
Domany 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Downey 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Fava 2018	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Fedgchin 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Fu 2020	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Gálvez 2018	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
George 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Grunebaum 2017	Low risk	Low risk	Low risk	High risk	High risk	Low risk
Grunebaum 2018	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Hu 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ionescu 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ionescu 2021	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Lai 2014	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
Lapidus 2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Li 2016	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Loo 2016	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Murrough 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Murrough 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Nugent 2019	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Ochs-Ross 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Phillips 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Popova 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Singh 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sos 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Su 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Zarate 2006	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Zarate 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

APPENDIX C. Supplementary Data

Attached electronically.