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REVIEW

Use of ketamine and esketamine for depression: an overview of systematic reviews with meta-analyses

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Abstract

Purpose To summarize the evidence of efficacy and safety of the use of ketamine and esketamine for depression.

Methods A literature search was performed in Medline, the Cochrane Library, LILACS, and CRD until November 2020. We included systematic reviews with meta-analyses of randomized controlled trials on the use of ketamine and esketamine in adult patients with depression. Two authors independently performed the study selection and data extraction. The AMSTAR-2 tool was used to appraise the quality of included reviews.

Results A total of 118 records were identified, and 11 studies fully met the eligibility criteria. Compared to control, ketamine improved the clinical response at 40 min to 1 week and clinical remission at 80 min to 72 h, and esketamine improved both outcomes at 2 h to 4 weeks. Ketamine and esketamine also had a beneficial effect on the depression scales score and suicidality. For adverse events, oral ketamine did not show significant change compared to control, while intranasal esketamine showed difference for any events, such as dissociation, dizziness, hypoesthesia, and vertigo. Most reviews were classified as "critically low quality," and none of them declared the source of funding of the primary studies and assessed the potential impact of risk of bias in primary studies.

Conclusion Ketamine and esketamine showed a significant antidepressant action within a few hours or days after administration; however, the long-term efficacy and safety are lacking. In addition, the methodological quality of the reviews was usually critically low, which may indicate the need for higher quality evidence in relation to the theme.

Keywords Mental disorders · Depression · Ketamine · Esketamine · Overview · Systematic review

Introduction

Depression is a complex psychiatric disorder characterized by the presence of depressed mood, anhedonia, loss of interest, low energy, and fatigue for a minimum 2-week period. Other symptoms can be noted, such as insomnia or hyposomnia, diminished ability to concentrate, significant weight alteration, low self-esteem, and suicidal ideation [1]. Its etiology is not yet fully understood, and one of the pathophysiological mechanisms involved is the functional deficiency of the monoamine neurotransmitters serotonin, noradrenaline, and/or dopamine in the brain synapses. However, other multiple interactions with other brain systems are also involved [1, 2].

According to the World Health Organization, more than 300 million people of all ages suffer from depression, being considered a leading cause of disabling worldwide — 7.5% of all years lived with disability [3]. The economic burden of depression was estimated at $210.5 billion in the USA (increase of 21.5% between 2005 and 2010), with practically half of this amount being due to direct medical costs and the other half being attributed to indirect costs related to absenteeism, presentism, and suicide [4]. In addition, depression has an important impact on activities of daily living and quality of life and affects individuals, often in early life and for sustained periods, thereby causing many disease years [5]. Therefore, depression is a public health problem.

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Treatment for depression includes the use of antidepressants, electroconvulsive therapy (ECT), and psychosocial interventions. Antidepressant medications, such as the selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors, can be used for treatment of mild, moderate, and severe depression [6]. However, current treatments require a considerable time to induce a response or remission of depression. The average time for antidepressant action of the standard antidepressants is 13 days, which can reach 20 days, considering the response criteria. Still, when patients have a clinical response, it is generally considered suboptimal [7].

At the beginning of this century, Berman et al. (2000) reported that ketamine was able to inhibit the *N*-methyl-D-aspartate (NMDA) receptor (i.e., the main receptor of the glutamatergic system that plays an important role in the antidepressant effect) [8]. In addition, current evidence suggests that ketamine's acute antidepressant effect requires opioid system activation [9]. In this context, a growing number of clinical trials have shown that subanesthetic doses of esketamine (S-ketamine) and ketamine (RS-ketamine, a racemic mixture of R-ketamine and S-ketamine) have a rapid antidepressant effect [10, 11]. From that, the off-label use of ketamine and esketamine for depression (except for intranasal esketamine approved by FDA in the USA and EMA in Europe) has increased, giving great concern for the patient's health and the healthcare system, since the efficacy and safety of these drugs are not yet fully established [12, 13].

In order to deliver accurate estimates of key outcomes of ketamine and esketamine in depression, some systematic reviews with meta-analyses have been published recently — considered the gold standard of evidence in health care [14]. In this sense, it is important to understand the diversity present in the extant systematic review literature. Also, the methodological quality of these systematic reviews is unknown, which is an indispensable step before treatment recommendations can be safely translated into clinical practice. Currently, there is no overview on the use of ketamine/esketamine in patients with depression. Therefore, this overview aimed to summarize the evidence of efficacy and safety of ketamine and esketamine for adult patients with depression from systematic reviews with meta-analyses.

Methods

The search strategy, eligibility criteria, and method of analysis for this overview were specified in advance and documented in a protocol available in Appendix 1.

Literature search

A comprehensive literature search was performed in the Medline (via PubMed), Latin American and Caribbean Health Sciences Literature (LILACS), Cochrane Library, and the Centre for Reviews and Dissemination (CRD) databases until November 29, 2020. The search strategy included the use of Medical Subject Headings (MeSH) terms and keywords related to the health condition (depression), intervention (ketamine and esketamine), and the study design (systematic reviews with meta-analysis). The detailed search strategy of all databases is shown in Appendix 2; keywords were searched in any fields unless otherwise specified. Also, we screened the reference lists of the appraised articles to identify any studies that might have been missed.

Study selection

The selection process was performed in three stages: (1) exclusion of repeated records, (2) analysis of the titles and abstracts, and (3) analysis of the full-text articles. The studies were independently selected by two authors (MBV and TML). Any disagreements were resolved by a third author (PMA). When the full-text article could not be obtained, the corresponding authors were contacted via ResearchGate (www.researchgate.net) or e-mail or both.

To be included in the present overview, the articles had to meet the following criteria: (1) be a systematic review with pairwise meta-analysis of randomized controlled trials (RCT); (2) be published in English, Spanish, or Portuguese; (3) have evaluated the use of ketamine or esketamine or both (monotherapy or associated with other drugs, any route of administration and frequency of use) in comparison with placebo or other drugs; (4) report any efficacy and safety outcomes; and (5) in adults with major depressive disorder or bipolar disorder. Articles were excluded if they were (1) narrative reviews; (2) systematic reviews without meta-analysis; (3) meta-analyses not from systematic reviews; (4) network meta-analysis; (5) systematic reviews including concomitant use of ECT and ketamine or esketamine as intervention; (6) systematic reviews with meta-analysis including another target population, intervention, or primary study design; (7) systematic reviews that did not have the full-text article available.

Data extraction

Data extraction was using a spreadsheet preformatted in Microsoft Excel® by two independent researchers (MBV and TML), and any disagreement was resolved by a third author (PMA). The following information was collected: author(s), year of publication, literature search period,

databases used in literature search, target population, intervention (dose and route of administration), comparators, outcome measures, number of RCTs and patients included in the meta-analysis, statistical model for meta-analysis, pooled effect size, heterogeneity, publication bias, quality of evidence by the GRADE approach [15], and funding source.

Quality assessment

The methodological quality of included systematic reviews was assessed using the AMSTAR-2 (Assessment of Multiple Systematic Reviews) tool [16]. The AMSTAR-2 is a 16-item questionnaire, with the majority of questions being judged as "yes," "partial yes," or "no." The overall rating was based on weaknesses in critical domains (items: 2, 4, 7, 9, 11, 13, and 15) as following: "high," no or one non-critical weakness; "moderate," more than one non-critical weakness but no critical flaws; "low," one critical flaw with or without non-critical weaknesses; and "critically low," more than one critical flaw with or without non-critical weaknesses. One investigator (TML) conducted the evaluation of the studies, and a second one (PMA) verified this evaluation.

Data synthesis

The characteristics of systematic reviews and their methodological quality were descriptively summarized using systematically structured tables. The estimates of effect size from meta-analyses (and their 95% confidence intervals [95% CI]) were expressed as mean difference (MD), standardized mean difference (SMD), relative risk (RR), and odds ratio (OR), depending on what the authors had reported.

Results

Search results

The electronic search identified 118 potentially relevant records. After removing duplicates and screening titles and abstracts, 21 studies were selected for full-text reading. Of these, 11 systematic reviews with pairwise meta-analysis on use of ketamine or esketamine or both for treatment depression fully met the eligibility criteria and were included in the present overview [17–27]. All included systematic reviews were found for full-text examination. A flowchart of the literature search is shown in Fig. 1. The excluded studies and the reasons for their exclusion are detailed in Appendix 3.

Characteristics of systematic reviews

Characteristics of the 11 reviews included in this overview are shown in Table 1. All included systematic reviews were published in English between 2015 and 2020. Most reviews included primary studies evaluating patients with major depression disorder or bipolar disorder [18, 20–22, 24, 26]. Two reviews included patients with bipolar depression [19, 23], and three reviews included patients with major depression disorder [17, 25, 27].

Almost all reviews involved ketamine as monotherapy in the intervention arm [17–25]. One review involved ketamine

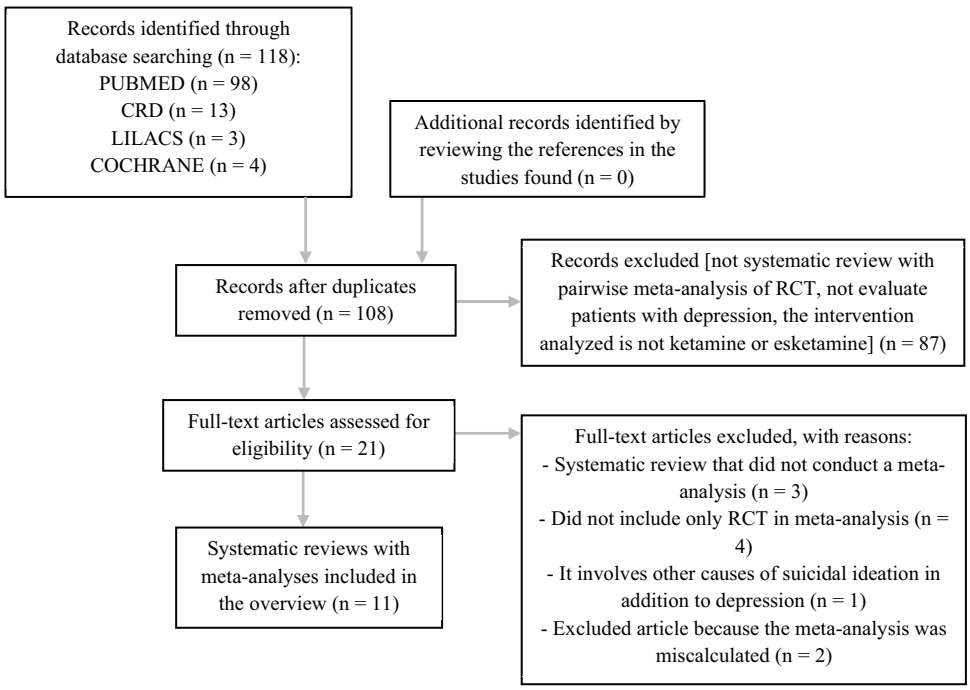

Fig. 1 Study selection flowchart through literature search. RCT randomized controlled trials

Table 1 Characteristics of systematic reviews with meta-analyses on ketamine and esketamine for depression

Authors, year	Literature search	Target population	Intervention	Dose	Comparator	Outcome measure	Funding source
Caddy et al. (2015) [17]	1950 to 9 January, 2015 (MEDLINE), 1974 to 9 January, 2015 (EMBASE), 1967 9 to January, 2015 (PSYCINFO), until 9 January, 2015 (Cochrane)	Adult patients with unipolar major depressive disorder	Ketamine	0.5 mg/kg or 0.54 mg/kg (intravenous)	Placebo	Clinical remission, clinical response, and depression rating scales scores (MADRS and HDRS)	NIHR Cochrane Incentive Award Scheme 2013
Lee et al. (2015) [18]	January 1990 to September 2013	Patients with treatment-refractory major depressive disorder or bipolar affective disorder depression	Ketamine	0.5 mg/kg or 0.54 mg/kg (intravenous)	Placebo or active-control	Depression rating scales scores (MADRS and HDRS)	NR
McCloud et al. (2015) [19]	1950 to 9 January, 2015 (MEDLINE), 1974 to 9 January, 2015 (EMBASE), 1967 to 9 January, 2015 (PSYCINFO), until 9 January, 2015 (Cochrane)	Adult patients with bipolar disorder	Ketamine	0.5 mg/kg (intravenous)	Placebo	Clinical remission, clinical response, depression rating scales scores (MADRS), acceptability — total dropouts, and acceptability — lack of efficacy	NIHR Cochrane Incentive Award Scheme 2013
McGirr et al. (2015) [20]	Until 14 January, 2014	Patients aged 18–75 years with a diagnosis of primary major depressive episode (unipolar or bipolar)	Ketamine	0.5 mg/kg or 0.54 mg/kg (intravenous) or 50 mg (intranasal)	Placebo or active-control	Clinical remission, clinical response, depression rating scales scores (MADRS and HDRS), psychotomimetic effects scores (BPRS), and dissociative symptoms scores (CADSS)	No funding source
Newport et al. (2015) [21]	Until May 2015	Patients with major depression (including major depressive episodes of bipolar disorder)	Ketamine	0.5 mg/kg or 0.54 mg/kg (intravenous) or 50 mg (intranasal)	Placebo or active-control	Clinical remission, clinical response, psychotomimetic effects scores (BPRS), and dissociative symptoms scores (CADSS)	NR

Table 1 (continued)

Authors, year	Literature search	Target population	Intervention	Dose	Comparator	Outcome measure	Funding source
Xu et al. (2016) [22]	Until August 2014	Patients with major depressive episode (unipolar or bipolar affective disorder)	Ketamine	0.5 mg/kg or 0.54 mg/kg (intravenous) or 50 mg (intranasal) or 0.1–0.4 mg/kg (intravenous) or 0.1–0.5 mg/kg (intravenous, intramuscular, or subcutaneous)	Placebo or active-control	Clinical remission, clinical response, depression rating scales (MADRS and HDRS), and suicidality (MADRS and HDRS)	NR
Fornaro et al. (2020) [23]	Until 25 May, 2020	Adult in-/outpatients with a diagnosis of bipolar depression	Ketamine	0.5 mg/kg (intravenous)	Placebo	Clinical response and acceptability	No funding source
Marcatoni et al. (2020) [24]	Publications from 2000 to 3 or 4, January, 2019. Grey literature and online sources were searched in April 2019	Adults (≥ 18 years) diagnosed with major depressive or bipolar disorder and presenting treatment resistant depression	Ketamine	0.5 mg/kg or 0.54 mg/kg* (intravenous)	Placebo or active-control	Clinical remission, clinical response, depression rating scales scores (MADRS and HDRS)	No funding source
Nuñez et al. (2020) [25]	Until 7 April, 2020	Adult patients (≥ 18 years) with major depression disorder	Ketamine	1 mg/kg or 25 mg or 50 mg (oral)	Placebo or active-control	Clinical remission, clinical response, depression rating scales scores (MADRS and HDRS), and adverse events	No funding source
Witt et al. (2020) [26]	Until 12 December, 2018	Adult patients (i.e., 18 years and over) with a primary diagnosis of major depression or bipolar depression	Ketamine or esketamine	Ketamine: 0.1–0.5 mg/kg (intravenous, intramuscular, or subcutaneous) or 0.2 mg/kg (intravenous) or 0.5 mg/kg (intravenous) Esketamine: up to 84 mg (intranasal)	Placebo or active-control	Suicidality (suicidal ideation measured by MADRS, HDRS, C-SSRS, BSSI, QIDS-SR, and SSI)	(NIHR) Oxford Cognitive Health Clinical Research Facility and NIHR Oxford Health Biomedical Research Centre

Table 1 (continued)

Authors, year	Literature search	Target population	Intervention	Dose	Comparator	Outcome measure	Funding source
Zheng et al. (2020) [27]	Until 1 August, 2019	Adult patients with major depression disorder (18–65 years) with treatment refractory symptoms and/or suicidal ideation	Esketamine	28 mg or 56 mg or 84 mg or 42–84 mg or 56–84 mg (intranasal)	Placebo	Clinical remission, clinical response, depression rating scales scores (MADRS and PHQ-9), socio-occupational disability (SDS), discontinuation rate (due to any reason, due to inefficacy, and due to intolerability), and adverse events	University of Macau, the Affiliated Brain Hospital of Guangzhou Medical University, and Science and Technology Department of Guangdong Province major science and technology

BPRS Brief Psychiatric Rating Scale, *BSSI* Beck Scale for Suicidal Ideation, *CADSS* Clinician-Administered Dissociative States Scale, *C-SSRS* Columbia Suicide Severity Rating Scale, *ECT* electro-convulsive therapy, *HDRS* Hamilton Depression Rating Scale, *MADRS* Montgomery-Åsberg Depression Rating Scale, *NR* not reported, *PHQ-9* Patient Health Questionnaire-9, *QIDS-SR* Quick Inventory of Depressive Symptomatology-Self Report, *SDS* Sheehan Disability Scale, *SSI* Scale for Suicidal Ideation

or esketamine [26], and another review involved only esketamine in the intervention arm [27]. Seven reviews included studies whose comparator was placebo or active-control [18, 20–22, 24–26], and four reviews included studies that used placebo as comparator [17, 19, 23, 27].

Nine reviews assessed clinical remission or clinical response or both [17, 19–25, 27], and all of them assessed the severity of depressive symptoms through validity scales, except the review by Fornaro et al. (2020) [23]. Most reviews used the Montgomery-Åsberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HDRS/HAM-D) [17, 18, 20, 22, 24–27], two reviews used the Brief Psychiatric Rating Scale (BPRS) and Clinician-Administered Dissociative States Scale (CADSS) [20, 21], two reviews used MADRS [19, 27], and one review used 9-Item Patient Health Questionnaire (PHQ-9) [27]. Six reviews assessed other outcomes, such as suicidality [22, 26], acceptability [19, 23, 27], disability [27], and adverse events [25, 27].

Three reviews did not report a source of support [18, 21, 22], four received research funding from institute organization [17, 19, 26, 27], and four declared no support from any organization [20, 23–25].

Results on clinical response

Ketamine produced a significant clinical response compared to placebo at 40 min, 80 min, 2 h, and 4 h after intervention [21]. Seven reviews showed a significant effect of ketamine in the clinical response at 24 h compared to placebo or active-control or both [17, 19–24]. However, very-low-dose ketamine for patients with major depression disorder did not show significant difference in the clinical response at the same time compared to placebo and active-control [22]. In addition, one review reported that ketamine was significantly better than placebo and active-control in the clinical response at 48 h [21].

Regarding clinical response at 72 h, ketamine produced a significant clinical response compared to placebo or active-control or both in four reviews [17, 20–22]. On the other hand, one study did not show a significant effect of ketamine in the clinical response at the same time compared to placebo for patients with bipolar disorder (very low-quality evidence) [19]. In addition, very-low-dose ketamine for patients with major depression disorder was not significantly better than placebo and active-control in the clinical response at 72 h [22].

Four reviews showed significant effect of ketamine in the clinical response at 1 week compared to placebo or active-control or both [20–22, 24]. However, it is important to note that there was no significant difference between ketamine and placebo at the same time in patients with bipolar depression [22]. One review showed a tendency to

significant difference between ketamine and placebo in the clinical response at 2 weeks [21]. In addition, one systematic review showed a significant effect of ketamine in the clinical response overall compared to placebo and active-control [24]. The only review that evaluated oral ketamine did not present a significant result [25].

Finally, esketamine was statistically superior compared to placebo in the clinical response at 2 h, 1 week, 4 weeks, by 2 to 28 days and by 8 to 28 days (high-quality evidence) [27]. The results on clinical response are displayed in Table 2.

Results on clinical remission

Ketamine produced a significant clinical remission of symptoms compared to placebo at 80 min, 2 h, and 4 h after intervention [21]. Regarding the clinical remission at 24 h, four reviews showed significant effect of ketamine compared to placebo or active-control or both [20–22, 24]. On the other hand, two reviews involving a smaller number of patients did not report significant differences in the clinical remission of symptoms between groups at the same time [17, 19]. In addition, ketamine was significantly better than placebo and active-control in the clinical remission at 48 h [21].

Data on clinical remission of symptoms at 72 h was presented by five reviews. Ketamine produced a significant clinical remission compared to placebo or active-control or both in most of them [17, 20–22]. However, very-low-dose ketamine for patients with major depression disorder did not show significant difference in the clinical remission at the same time compared to placebo and active-control [22].

Two reviews showed significant effect of ketamine in the clinical remission of symptoms at 1 week compared to placebo and active-control [20, 22], and two reviews did not present a significant difference between groups [21, 24]. One review assessed the clinical remission of symptoms at 2 weeks and did not show a significant difference between ketamine and placebo [21]. In addition, two reviews did not show a significant difference between ketamine versus placebo and active-control in the clinical remission overall [24, 25].

Finally, esketamine was statistically superior compared to placebo in the clinical remission at 2 h, 4 h, 24 h, 1 week, 4 weeks, and by 8 to 28 days (high-quality evidence) [27]. The results on clinical remission are displayed in Table 3.

Results on depression scales

Four reviews showed significant beneficial effects of ketamine in the HAM-D/HDRS and MADRS scores at 24 h compared to placebo or active-control or both [17, 18, 20, 22]. However, one systematic review did not show significant effect in the same time compared to placebo and active-control [24]. Two reviews showed a beneficial effect at 72 h [17, 22]. However, Xu et al. (2016) reported that very-low-dose ketamine did not improve the HAM-D/HDRS and MADRS scores at the same time compared to placebo and active control [22].

Three reviews showed data of HAM-D/HDRS and MADRS scores at 1 week [18, 22, 24]. All of them showed significant beneficial effects of ketamine compared to placebo or active-control or both. However, Lee et al. (2015) did not show significant difference between ketamine and placebo for patients with bipolar depression [18], and Xu et al. (2016) did not show significant difference between ketamine (normal or very-low-dose) compared to placebo and active-control [22]. In addition, Nuñez et al. (2020) showed a significant effect of oral ketamine compared to placebo or active-control or both at 2 and 3 weeks [25], and two studies showed superior effect of ketamine compared to placebo and active-control in the overall scores [24, 25].

Regarding the MADRS score, one review showed that ketamine produced a significant beneficial effect compared to placebo at 24 h and 72 h [19]. However, the superior result was not observed at 1 and 2 weeks (very low-quality evidence) [19]. In addition, Zheng et al. (2020) showed a significant beneficial effect of esketamine compared to placebo (high-quality evidence) [27].

Finally, two reviews assessed the use of ketamine through BPRS and CADSS score [20, 21] and one assessed the use of esketamine through PHQ-9 score (high-quality evidence) [27]. All reviews showed the intervention arm was significantly better than placebo or active-control or both to improve these scores. The results on depression scales are shown in Table 4.

Results on suicidality, acceptability, disability, and adverse events

One review presented the results of the suicidal ideation at 4 h, 24 to 72 h, 2 to 4 weeks, and more than 4 weeks, observing a significant difference between ketamine or esketamine or both compared to placebo and active control at 4 h and 24 to 72 h (low-quality evidence) [26]. Xu et al. (2016) presented a significant difference between ketamine versus placebo and active control at 24 and 72 h. However, this result was not observed at 1 week [22].

Three reviews did not show a significant difference between ketamine or esketamine versus placebo in the acceptability of the treatment (total dropout and dropout due to lack of efficacy) [19, 23, 27]. In contrast, Zheng et al. (2020) showed a significant difference between esketamine and placebo on acceptability (dropout due to adverse events) (high-quality evidence) [27]. In addition, only one review evaluated disability and showed a significant difference between esketamine and placebo (high-quality evidence) [27].

Table 2 Results on clinical response in systematic reviews with meta-analyses on ketamine and esketamine for depression

Authors, year	Comparisons	Diagnosis	No of RCT/ patients	Statistical model	Pooled effect [95% CI] (P value)*	Heterogeneity I^2 (P value)**	Publication bias	Quality of evidence
Clinical response at 40 min								
Newport et al. (2015) [21]	Ketamine vs. saline	MDD and BD	4/65	NR	OR = 13.2 [3.2 to 53.7] **(< 0.001)**	NR (NR)	NR	NR
Clinical response at 80 min								
Newport et al. (2015) [21]	Ketamine vs. saline	MDD and BD	3/47	NR	OR = 24.7 [5.0 to 122.5] **(< 0.001)**	NR (NR)	NR	NR
Clinical response at 2 h								
Newport et al. (2015) [21]	Ketamine vs. saline	MDD and BD	3/47	NR	OR = 24.7 [5.0 to 122.5] **(< 0.001)**	NR (NR)	NR	NR
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/133	RE	RR = 2.77 [1.62 to 4.76] **(0.0002)**	0% (0.78)	Not performed	High
Clinical response at 4 h								
Newport et al. (2015) [21]	Ketamine vs. saline	MDD and BD	4/65	NR	OR = 24.4 [6.0 to 99.5] **(< 0.001)**	NR (NR)	NR	NR
Clinical response at 24 h								
Caddy et al. (2015) [17]	Ketamine vs. saline	MDD	3/56	RE	OR = 10.77 [2.00 to 58.00] **(0.006)**	0% (0.46)	NR	Low
McCloud et al. (2015) [19]	Ketamine vs. saline	BD	2/33	RE	OR = 11.61 [1.25 to 107.74] **(0.03)**	0% (0.91)	NR	Low
McGirr et al. (2015) [20]	Ketamine vs. saline and midazolam	MDD and BD	7/183	RE	OR = 8.81 [4.16 to 18.68] **(0.000)**	NR (0.25)	Asymmetry in the funnel plot p Egger ≤ **0.05**	NR
	Ketamine vs. saline	MDD and BD	6/110	RE	OR = 18.73 [6.39 to 54.87] **(0.000)**	NR **(0.06)**	NR	NR
Newport et al. (2015) [21]	Ketamine vs. saline and midazolam	MDD and BD	6/164	NR	OR = 9.9 [4.4 to 22.3] **(< 0.001)**	0% (0.51)	NR	NR
	Ketamine IV vs. saline and midazolam	MDD and BD	5/146	NR	OR = 4.58 [1.82 to 11.49] **(0.001)**	NR (NR)	NR	NR
	Ketamine vs. saline and midazolam	MDD	4/134	NR	OR = 8.42 [3.47 to 20.39] **(< 0.001)**	NR (NR)	NR	NR
	Ketamine vs. saline	BD	2/30	NR	OR = 24.05 [2.96 to 195.56] **(0.003)**	NR (NR)	NR	NR
Xu et al. (2016) [22]	Ketamine vs. saline and midazolam	MDD and BD	8/192	RE	RR = 2.6 [1.6 to 4.4] **(0.0003)**	NR (NR)	NR	NR
	Ketamine (low dose) vs. saline and midazolam	MDD and BD	5/153	RE	RR = 2.9 [1.6 to 5.2] **(0.0004)**	NR (NR)	NR	NR
	Ketamine (very low dose) vs. saline and midazolam	MDD	3/39	RE	RR = 1.8 [0.6 to 5.7] (0.3)	NR (NR)	NR	NR

Table 2 (continued)

Authors, year	Comparisons	Diagnosis	No of RCT/ patients	Statistical model	Pooled effect [95% CI] (P value)*	Heterogeneity I^2 (P value)**	Publication bias	Quality of evidence
Fornaro et al. (2020) [23]	Ketamine vs. saline	BD	2/33	RE	OR = 10.68 [2.14 to 53.27] **(< 0.005)**	0% (NR)	NR	NR
Marcatoni et al. (2020) [24]	Ketamine vs. saline and midazolam	MDD and BD	7/373	RE	OR = 7.39 [2.50 to 21.83] (NR)	12% (0.34)	Asymmetry in the funnel plot p Egger = 0.0013	NR
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/344	RE	RR = 5.42 [1.38 to 21.20] **(0.02)**	63% **(0.04)**	Not performed	High
Clinical response at 48 h								
Newport et al. (2015) [21]	Ketamine vs. saline and midazolam	MDD and BD	5/137	NR	OR = 8.4 [3.4 to 20.4] **(< 0.001)**	NR (NR)	NR	NR
Clinical response at 72 h								
Caddy et al. (2015) [17]	Ketamine vs. saline	MDD	3/56	RE	OR = 12.59 [2.38 to 66.73] **(0.003)**	0% (0.89)	NR	Low
McCloud et al. (2015) [19]	Ketamine vs. saline	BD	2/33	RE	OR = 8.24 [0.84 to 80.61] (0.07)	0% (0.55)	NR	Very low
McGirr et al. (2015) [20]	Ketamine vs. saline and midazolam	MDD and BD	7/183	RE	OR = 6.63 [3.33 to 13.18] **(0.000)**	NR (0.42)	No asymmetry in the funnel plot p Egger = 0.17	NR
	Ketamine vs. saline	MDD and BD	6/110	RE	OR = 8.19 [3.36 to 19.94] **(0.000)**	NR (0.51)	NR	NR
Newport et al. (2015) [21]	Ketamine vs. saline and midazolam	MDD and BD	7/172	NR	OR = 7.1 [3.3 to 14.9] **(< 0.001)**	NR (NR)	NR	NR
Xu et al. (2016) [22]	Ketamine vs. saline and midazolam	MDD and BD	8/192	RE	RR = 2.4 [1.4 to 4.1] **(0.002)**	NR **(0.02)**	NR	NR
	Ketamine (low dose) vs. saline and midazolam	MDD and BD	5/153	RE	RR = 3.1 [1.7 to 5.9] **(0.0004)**	NR (NR)	NR	NR
	Ketamine (very low dose) vs. saline and midazolam	MDD	3/39	RE	RR = 1.1 [0.4 to 3.1] (0.9)	NR (NR)	NR	NR
Clinical response at 1 week								
McGirr et al. (2015) [20]	Ketamine vs. saline and midazolam	MDD and BD	6/174	RE	OR = 4.80 [2.22 to 10.38] **(0.000)**	NR (0.94)	No asymmetry in the funnel plot p Egger = 0.53	NR
	Ketamine vs. saline	MDD and BD	5/101	RE	OR = 5.35 [1.97 to 14.58] **(0.001)**	NR (0.51)	NR	NR
Newport et al. (2015) [21]	Ketamine vs. saline and midazolam	MDD and BD	6/164	NR	OR = 4.6 [2.1 to 10.2] **(< 0.001)**	0% (0.95)	NR	NR
	Ketamine vs. saline and midazolam	MDD	4/134	NR	OR = 4.72 [1.95 to 11.38] **(0.001)**	NR (NR)	NR	NR
	Ketamine vs. saline	BD	2/30	NR	OR = 4.16 [0.64 to 27.22] (0.137)	NR (NR)	NR	NR

Table 2 (continued)

Authors, year	Comparisons	Diagnosis	No of RCT/ patients	Statistical model	Pooled effect [95% CI] (P value)*	Heterogeneity I^2 (P value)**	Publication bias	Quality of evidence
Xu et al. (2016) [22]	Ketamine vs. saline and midazolam	MDD and BD	5/153	RE	RR = 3.4 [1.6 to 7.1] **(0.001)**	NR (NR)	NR	NR
	Ketamine (low dose) vs. saline and midazolam	MDD and BD	4/138	RE	RR = 3.4 [1.6 to 7.3] **(0.002)**	NR (NR)	NR	NR
Marcatoni et al. (2020) [24]	Ketamine vs. saline and midazolam	MDD and BD	4/205	RE	OR = 5.09 [1.88 to 13.76] (NR)	0% (0.80)	Asymmetry in the funnel plot p Egger = 0.0013	NR
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/133	RE	RR = 3.87 [1.37 to 10.93] **(0.01)**	0% (NR)	Not performed	High
Clinical response at 2 weeks								
Newport et al. (2015) [21]	Ketamine vs. saline	MDD and BD	4/55	NR	OR = 4.4 [1.0 to 18.8] (0.05)	NR (NR)	NR	NR
Clinical response at 4 weeks								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/626	RE	RR = 1.36 [1.16 to 1.58] **(0.0001)**	0% (0.97)	Not performed	High
Clinical response by 2 to 28 days								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/678	RE	RR = 3.17 [1.40 to 7.18] **(0.006)**	15% (0.31)	Not performed	High
Clinical response by 8 to 28 days								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	3/759	RE	RR = 1.39 [1.18 to 1.64] **(0.0001)**[a]	5% (0.39)	Not performed	High
Clinical response overall								
Marcatoni et al. (2020) [24]	Ketamine vs. saline and midazolam	MDD and BD	7/578	RE	OR = 6.33 [3.33 to 12.05] **(< 0.0001)**	0% (0.64)	Asymmetry in the funnel plot p Egger = 0.0013	NR
Nuñez et al. (2020) [25]	Ketamine vs. placebo and diclofenac	MDD	3/161	RE	RR = 2.58 [0.94 to 7.08] (0.065)	65.85% **(0.05)**	Not performed	NR

BP bipolar disorder, *MDD* major depressive disorder, *NR* not reported, *RE* random effects

*Bolded P value: $P < 0.05$ is considered statistically significant; **It tells us what the proportion of variation in observed effects would remain if we could somehow get rid of the sampling error. Bolded P value: $P < 0.1$ is considered statistically significant

[a]RR = 1.37 [1.15 to 1.64] (NR) — value recalculated by David S (2020) [Response to a recently published systematic review on intranasal esketamine for major depressive disorder. J Affect Disord. 2020;273:16–17]

In terms of adverse events, one systematic review on oral ketamine reported this outcome and did not show a significant difference between ketamine versus placebo and active-control [25]. Finally, Zheng et al. (2020) showed significant difference between esketamine and placebo in the dissociation, dissociative disorder, dizziness postural, feeling abnormal, feeling drunk, hypoesthesia, oral hypoesthesia, lethargy, nausea, paresthesia, sedation, somnolence, throat irritation, vertigo, vision blurred, and vomiting (high-quality evidence) [27]. The results on suicidality, acceptability, disability, and adverse events are displayed in Table 5.

Methodological quality of systematic reviews

Methodological quality of 11 systematic reviews based on the AMSTAR-2 tool is shown in Table 6. Three reviews presented "low quality" [17, 19, 24] while eight reviews presented "critically low quality" [18, 20–23, 25–27].

All reviews included the components of PICO (Population, Intervention, Control, and Outcomes) in their research questions. Moreover, only three reviews did not perform study selection and data extraction in duplicate [20, 21, 25], two reviews did not provide a satisfactory explanation for

Table 3 Results on clinical remission in systematic reviews with meta-analyses on ketamine and esketamine for depression

Authors, year	Comparisons	Diagnosis	No of RCT/ patients	Statistical model	Pooled effect [95% CI] (*P* value)*	Heterogeneity I^2 (*P* value)**	Publication bias	Quality of evidence
Clinical remission at 40 min								
Newport et al. (2015) [21]	Ketamine vs. saline	MDD and BD	4/65	NR	OR = 2.6 [0.5 to 13.8] (0.26)	NR (NR)	NR	NR
Clinical remission at 80 min								
Newport et al. (2015) [21]	Ketamine vs. saline	MDD and BD	3/47	NR	OR = 7.3 [1.4 to 39.3] **(0.02)**	NR (NR)	NR	NR
Clinical remission at 2 h								
Newport et al. (2015) [21]	Ketamine vs. saline	MDD and BD	3/47	NR	OR = 10.3 [1.9 to 55.8] **(0.007)**	NR (NR)	NR	NR
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/133	RE	RR = 7.71 [2.16 to 27.55] **(0.002)**	0% (0.97)	Not performed	High
Clinical remission at 4 h								
Newport et al. (2015) [21]	Ketamine vs. saline	MDD and BD	4/65	NR	OR = 11.8 [2.2 to 64.1] **(0.004)**	NR (NR)	NR	NR
Clinical remission at 24 h								
Caddy et al. (2015) [17]	Ketamine vs. saline	MDD	2/48	RE	OR = 6.6 [0.96 to 45.09] (0.05)	0% (0.97)	NR	NR
McCloud et al. (2015) [19]	Ketamine vs. saline	BD	2/33	RE	OR = 5.16 [0.51 to 52.3] (0.16)	0% (0.72)	NR	NR
McGirr et al. (2015) [20]	Ketamine vs. saline and midazolam	MDD and BD	5/154	RE	OR = 7.07 [2.50 to 19.95] **(0.000)**	NR (0.61)	No asymmetry in the funnel plot *p* Egger = 0.23	NR
Newport et al. (2015) [21]	Ketamine vs. saline and midazolam	MDD and BD	6/164	NR	OR = 14.5 [2.7 to 78.5] **(< 0.002)**	NR (NR)	NR	NR
	Ketamine vs. saline	BD	2/30	NR	OR = 14.01 [51.73 to 111.70] **(0.013)**	NR (NR)	NR	NR
Xu et al. (2016) [22]	Ketamine vs. saline and midazolam	MDD and BD	6/173	RE	RR = 5.2 [2.1 to 12.9] **(0.0003)**	NR (NR)	NR	NR
	Ketamine (low dose) vs. saline and midazolam	MDD and BD	5/153	RE	RR = 5.1 [2.0 to 13.1] **(0.0008)**	NR (NR)	NR	NR
Marcatoni et al. (2020) [24]	Ketamine vs. saline and midazolam	MDD and BD	4/205	RE	OR = 6.53 [1.13 to 37.62] (NR)	0% (0.69)	Asymmetry in the funnel plot *p* Egger = 0.0013	NR
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/199	RE	RR = 6.87 [1.55 to 30.35] **(0.01)**	44% (0.15)	Not performed	High
Clinical remission at 48 h								
Newport et al. (2015) [21]	Ketamine vs. saline and midazolam	MDD and BD	5/137	NR	OR = 8.4 [1.6 to 45.0] **(< 0.01)**	NR (NR)	NR	NR
Clinical remission at 72 h								
Caddy et al. (2015) [17]	Ketamine vs. saline	MDD	3/56	RE	OR = 6.69 [1.25 to 35.71] **(0.03)**	0% (0.92)	NR	NR
McCloud et al. (2015) [19]	Ketamine vs. saline	BD	2/33	RE	OR = 3.62 [0.34 to 38.6] (0.29)	0% (0.95)	NR	NR
McGirr et al. (2015) [20]	Ketamine vs. saline and midazolam	MDD and BD	5/154	RE	OR = 3.87 [1.54 to 9.75] **(0.004)**	NR (0.54)	No asymmetry in the funnel plot *p* Egger = 0.10	NR
Newport et al. (2015) [21]	Ketamine vs. saline and midazolam	MDD and BD	7/172	NR	OR = 5.6 [1.2 to 27.1] **(< 0.03)**	NR (NR)	NR	NR

Table 3 (continued)

Authors, year	Comparisons	Diagnosis	No of RCT/ patients	Statistical model	Pooled effect [95% CI] (*P* value)*	Heterogeneity I^2 (*P* value)**	Publication bias	Quality of evidence
Xu et al. (2016) [22]	Ketamine vs. saline and midazolam	MDD and BD	8/192	RE	RR = 2.5 [1.2 to 5.0] **(0.01)**	NR (NR)	NR	NR
	Ketamine (low dose) vs. saline and midazolam	MDD and BD	5/153	RE	RR = 3.4 [1.5 to 7.5] **(0.003)**	NR (NR)	NR	NR
	Ketamine (very low dose) vs. saline and midazolam	MDD	3/39	RE	RR = 0.9 [0.2 to 3.8] (0.9)	NR (NR)	NR	NR
Clinical remission at 1 week								
McGirr et al. (2015) [20]	Ketamine vs. saline and midazolam	MDD and BD	5/154	RE	OR = 4.00 [1.53 to 10.51] **(0.005)**	NR (0.58)	No asymmetry in the funnel plot *p* Egger = 0.75	NR
Newport et al. (2015) [21]	Ketamine vs. saline and midazolam	MDD and BD	6/164	NR	OR = 3.1 [0.6 to 15.4] (< 0.17)	NR (NR)	NR	NR
	Ketamine vs. saline	BD	2/30	NR	OR = 1.51 [0.22 to 10.49] (0.674)	NR (NR)	NR	NR
Xu et al. (2016) [22]	Ketamine vs. saline and midazolam	MDD and BD	5/153	RE	RR = 2.6 [1.2 to 5.7] **(0.02)**	NR (NR)	NR	NR
	Ketamine (low dose) vs. saline and midazolam	MDD and BD	4/138	RE	RR = 2.6 [1.2 to 6.0] **(0.02)**	NR (NR)	NR	NR
Marcatoni et al. (2020) [24]	Ketamine vs. saline and midazolam	MDD and BD	4/205	RE	OR = 4.18 [0.71 to 24.64] (NR)	0% (0.68)	Asymmetry in the funnel plot *p* Egger = 0.0013	NR
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/133	RE	RR = 4.66 [1.12 to 19.42] **(0.03)**	0% (NR)	Not performed	High
Clinical remission at 2 weeks								
Newport et al. (2015) [21]	Ketamine vs. saline	MDD and BD	4/55	NR	OR = 1.5 [0.3 to 7.9] (< 0.65)	NR (NR)	NR	NR
Clinical remission at 4 weeks								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/626	RE	RR = 1.38 [1.11 to 1.72] **(0.004)**	9% (0.33)	Not performed	High
Clinical remission by 8 to 28 days								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	4/825	RE	RR = 1.42 [1.17 to 1.72] **(0.0004)**[a]	0% (0.49)	Not performed	High
Clinical remission overall								
Marcatoni et al. (2020) [24]	Ketamine vs. saline and midazolam	MDD and BD	4/410	RE	OR = 5.11 [2.15 to 12.17] (0.003)	0% (0.86)	Asymmetry in the funnel plot *p* Egger = 0.0013	NR
Nuñez et al. (2020) [25]	Ketamine vs. placebo and diclofenac	MDD	3/161	RE	RR = 2.77 [0.96 to 8.00] (0.06)	35.89% (0.21)	Not performed	NR

BP bipolar disorder, *IV* intravenous, *MDD* major depressive disorder, *NR* not reported, *RE* random effects

*Bolded *P* value: $P < 0.05$ is considered statistically significant; **It tells us what the proportion of variation in observed effects would remain if we could somehow get rid of the sampling error. Bolded *P* value: $P < 0.1$ is considered statistically significant

[a]RR = 1.45 [1.16 to 1.80] (NR) — value recalculated by David S (2020) [Response to a recently published systematic review on intranasal esketamine for major depressive disorder. J Affect Disord. 2020;273:16–17]

Table 4 Results on depression scales score in systematic reviews with meta-analyses on ketamine and esketamine for depression

Authors, year	Comparisons	Diagnosis	No of RCT/ patients	Statistical model	Pooled effect [95% CI] (*P* value)*	Heterogeneity I^2 (*P* value)**	Publication bias	Quality of evidence
HAM-D/HDRS and MADRS score at 24 h								
Caddy et al. (2015) [17]	Ketamine vs. saline	MDD	3/54	RE	SMD = −1.42 [−2.26 to −0.57] **(0.001)**	35.93% (0.21)	NR	NR
Lee et al. (2015) [18][a]	Ketamine vs. saline and midazolam	MDD and BD	5/150	RE	SMD = −1.01 [−1.34 to −0.69] **(< 0.001)**	30.0% (0.27)	No asymmetry in the funnel plot	NR
	Ketamine vs. saline and midazolam	MDD	3/117	RE	SMD = −0.90 [−1.35 to −0.46] **(< 0.001)**	NR (NR)	NR	NR
	Ketamine vs. saline	BD	2/33	RE	SMD = −1.29 [−1.89 to −0.75] **(< 0.001)**	NR (NR)	NR	NR
McGirr et al. (2015) [20][a]	Ketamine vs. saline and midazolam	MDD and BD	7/183	RE	SMD = −0.76 [−0.92 to −0.60] **(0.000)**	57.63% **(≤ 0.05)**	Asymmetry in the funnel plot	NR
	Ketamine IV vs. saline and midazolam	MDD and BD	6/163	RE	SMD = −0.83 [−0.98 to −0.68] **(0.000)**	NR (NR)	NR	NR
	Ketamine vs. saline and midazolam	MDD	5/150	RE	SMD = −1.07 [−1.42 to −0.72] **(0.000)**	NR (NR)	NR	NR
	Ketamine vs. saline	BD	2/36	RE	SMD = −0.68 [−0.86 to −0.51] **(< 0.001)**	NR (NR)	NR	NR
Xu et al. (2016) [22]	Ketamine vs. saline and midazolam	MDD and BD	6/116	RE	SMD = −1.1[−1.7 to −0.6) (NR)	43.5% (NR)	NR	NR
	Ketamine (low dose) vs. saline	MDD and BD	4/81	RE	SMD = −1.4 [−2.0 to −0.9] (NR)	0.0% (NR)	NR	NR
	Ketamine (very low dose) vs. saline and midazolam	MDD	2/35	RE	SMD = −0.5 [−1.5 to 0.5] (NR)	54.0% (NR)	NR	NR
Marcatoni et al. (2020) [24][a]	Ketamine vs. saline and midazolam	MDD and BD	7/NR	RE	SMD = −0.77 [−1.08 to −0.46] (NR)	24% (0.25)	Asymmetry in the funnel plot *p* Egger = 0.0013	NR
	Ketamine vs. Saline and Midazolam	MDD	6/NR	RE	SMD = −0.79 [−1.17 to −0.41] (NR)	36% (0.17)	Asymmetry in the funnel plot *p* Egger = 0.0013	NR
MADRS score at 24 h								
McCloud et al. (2015) [19]	Ketamine vs. saline	BD	2/32	FE	MD = −11.81[−20.01 to −3.61] **(0.005)**	0% (0.47)	NR	Very low
HAM-D/HDRS and MADRS score at 72 h								
Caddy et al. (2015) [17]	Ketamine vs. saline	MDD	3/54	RE	SMD = −1.21 [−1.82 to −0.59] **(0.0001)**	0% (1.00)	NR	NR
Xu et al. (2016) [22]	Ketamine vs. saline and midazolam	MDD and BD	6/116	RE	SMD = −0.8 [−1.4 to −0.3) (NR)	41.6% **(0.02)**	NR	NR
	Ketamine (low dose) vs. saline	MDD and BD	4/81	RE	SMD = −1.2 [−1.7 to −0.7] (NR)	0.0% (NR)	NR	NR

Table 4 (continued)

Authors, year	Comparisons	Diagnosis	No of RCT/ patients	Statistical model	Pooled effect [95% CI] (*P* value)*	Heterogeneity I^2 (*P* value)**	Publication bias	Quality of evidence
	Ketamine (very low dose) vs. saline and midazolam	MDD	2/35	RE	SMD = −0.1 [−0.8 to 0.6] (NR)	0.0% (NR)	NR	NR
MADRS score at 72 h								
McCloud et al. (2015) [19]	Ketamine vs. saline	BD	2/31	FE	MD = −9.10 [−16.00 to −2.21] **(0.010)**	0% (0.60)	NR	NR
HAM-D/HDRS and MADRS score at 1 week								
Lee et al. (2015) [18][a]	Ketamine vs. saline and midazolam	MDD and BD	5/150	RE	SMD = −0.41 [−0.68 to −0.14] **(0.003)**	0% (0.87)	NR	NR
	Ketamine vs. saline and midazolam	MDD	3/117	RE	SMD = −0.46 [−0.78 to −0.14] **(0.004)**	NR (NR)	NR	NR
	Ketamine vs. saline	BD	2/33	RE	SMD = −0.28 [−0.76 to 0.21] (<0.26)	NR (NR)	NR	NR
Xu et al. (2016) [22]	Ketamine vs. saline and midazolam	MDD and BD	6/116	RE	SMD = −0.5[−1.0 to 0.1] (NR)	47.5% (NR)	NR	NR
	Ketamine (low dose) vs. saline	MDD and BD	4/81	RE	SMD = −0.7 [−1.3 to −0.1] (NR)	35.9% (NR)	NR	NR
	Ketamine (very low dose) vs. saline and midazolam	MDD	2/35	RE	SMD = −0.1 [−1.2 to 1.1] (NR)	65.7% (NR)	NR	NR
Marcatoni et al. (2020) [24][a]	Ketamine vs. saline and midazolam	MDD and BD	3/NR	RE	SMD = −0.49 [−0.78 to −0.20] (NR)	0% (0.83)	Asymmetry in the funnel plot *p* Egger = 0.0013	NR
HAM-D/HDRS and MADRS score at 2 weeks								
Nuñez et al. (2020) [25]	Ketamine vs. placebo	MDD	2/NR	RE	SMD = −0.71 [−1.08 to −0.35] **(0.001)**	0% (0.75)	Not performed	NR
HAM-D/HDRS and MADRS score at 3 weeks								
Nuñez et al. (2020) [25]	Ketamine vs. placebo and diclofenac	MDD	2/NR	RE	SMD = −0.79 [−1.40 to −0.17] **(0.012)**	43.76% (0.18)	Not performed	NR
HAM-D/HDRS and MADRS score								
Marcatoni et al. (2020) [24][a]	Ketamine vs. saline and midazolam	MDD and BD	7/NR	RE	SMD = −0.68 [−0.90 to −0.46] **(0.0001)**	9% (0.36)	Asymmetry in the funnel plot *p* Egger = 0.0013	NR
	Ketamine vs. saline and midazolam	MDD	6/NR	RE	SMD = −0.69 [−0.94 to −0.44] **(0.0002)**	19% (0.27)	Asymmetry in the funnel plot *p* Egger = 0.0013	NR
Nuñez et al. (2020) [25]	Ketamine vs. placebo and diclofenac	MDD	3/NR	RE	SMD = −0.75 [−1.08 to −0.43] **(<0.0001)**	0% (0.44)	Not performed	NR
MADRS score at 1 week								
McCloud et al. (2015) [19]	Ketamine vs. saline	BD	2/28	FE	MD = −0.88 [−5.88 to 4.12] (0.73)	0% (0.88)	NR	Very low

Table 4 (continued)

Authors, year	Comparisons	Diagnosis	No of RCT/ patients	Statistical model	Pooled effect [95% CI] (*P* value)*	Heterogeneity I^2 (*P* value)**	Publication bias	Quality of evidence
MADRS score at 2 weeks								
McCloud et al. (2015) [19]	Ketamine vs. saline	BD	2/26	FE	MD = −1.14 [−6.30 to 4.01] (0.66)	0% (0.63)	NR	NR
MADRS score								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	2/518	RE	SMD = −0.30 [−0.48 to −0.13] **(0.0008)**	0% (0.96)	Not performed	High
BPRS score								
McGirr et al. (2015) [20][a]	Ketamine vs. saline and midazolam	MDD and BD	7/183	RE	SMD = −1.43 [−2.07 to −0.80] **(0.000)**	NR (0.87)	NR	NR
Newport et al. (2015) [21][a]	Ketamine vs. saline and midazolam	MDD and BD	5/127	NR	MD = −0.74 [−1.01 to −0.46] **(< 0.001)**	NR (NR)	NR	NR
CADSS score								
McGirr et al. (2015) [20][a]	Ketamine vs. saline and midazolam	MDD and BD	4/126	RE	SMD = −3.70 [−5.91 to −1.49] **(0.001)**	NR (NR)	NR	NR
Newport et al. (2015) [21][a]	Ketamine vs. saline and midazolam	MDD and BD	3/102	NR	MD = −23.75 [−25.37 to −22.13] **(< 0.001)**	NR (NR)	NR	NR
PHQ-9 score								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	2/521	RE	SMD = −0.32 [−0.50 to −0.15] **(0.0004)**	0% (0.77)	Not performed	High

BPRS Brief Psychiatric Ratin Scale, *CADSS* Clinician-Administered Dissociative States Scale, *FE* fixed effects, *HDRS* Hamilton Depression Rating Scale, *IV* intravenous, *MADRS* Montgomery-Åsberg Depression Rating Scale, *NR* not reported, *PHQ-9* Patient Health Questionnaire-9, *RE* random effects

*Bolded *P* value: $P < 0.05$ is considered statistically significant; **It tells us what the proportion of variation in observed effects would remain if we could somehow get rid of the sampling error. Bolded *P* value: $P < 0.1$ is considered statistically significant

[a]An inversion was made on the side of the forest graph (signs of effect size) to harmonize the presentation of the results

any heterogeneity observed in their results [21, 25], and one review did not use a satisfactory technique for assessing the risk of bias (RoB) in primary studies, did not use appropriate methods for statistical combination of their results, and did not report any potential sources of conflict of interest [21].

In contrast, no review reported on the sources of funding for the studies included in their review and assessed the potential impact of risk of bias in individual studies on their results. Five reviews did not report an "a priori" design and indicated the existence of a protocol [18, 20–22, 27]. Furthermore, only five reviews provided a list of excluded studies and justify their exclusions [17, 19, 20, 23, 24], four of the reviews conducted an adequate investigation of publication bias and discuss its likely impact on the results of the review [18, 20, 24, 26], and two of them considered the risk of bias in individual studies when interpreting/discussing their results [17, 19].

Overlap of primary studies across the systematic reviews

In this overview, there are two pairs of systematic reviews on ketamine that included the same RCT (Appendix 4). McGirr et al. [20] (critically low-methodological quality) and Newport et al. [21] (critically low-methodological quality) included the same seven RCT; however, in common comparisons on clinical response and remission at 24 h, 72 h, and 1 week as well as BPRS score and CADSS score, they did not use the same RCT or considered different sample sizes. Other than that, they performed other comparisons that did not overlap, either by outcome, time measured, or subgroup analyses. Moreover, McCloud et al. [19] (low-methodological quality) and Fornaro et al. [23] (critically low-methodological quality) included the same two RCT, performed meta-analyses for response rate at 24 h and drop-out rate with both RCT, and used the same statistical model

Table 5 Results on suicidality, acceptability, disability, and adverse events in systematic reviews with meta-analyses on ketamine and esketamine for depression

Authors, year	Comparisons	Diagnosis	No of RCT/ patients	Statistical model	Pooled effect [95% CI] (*P* value)*	Heterogeneity I^2 (*P* value)**	Publication bias	Quality of evidence
Suicidality at 4 h								
Witt et al. (2020) [26]	Ketamine and esketamine vs. saline and midazolam	MDD and BD	9/332	RE	SMD = −0.51 [−1.00 to −0.03] **(0.04)**	73.0% **(< 0.0001)**	*p* Egger = 0.616	Low
Witt et al. (2020) [26]	Ketamine vs. saline and midazolam	MDD and BD	5/144	RE	SMD = −0.82 [−1.72 to 0.08] (0.07)	81% **(< 0.0001)**	NR	NR
Suicidality at 24 h								
Xu et al. (2016) [22]	Ketamine vs. saline and midazolam	MDD and BD	7/120	RE	SMD = −0.4 [−0.7 to −0.2] (NR)	0.0% (NR)	NR	NR
Suicidality by 24 at 72 h								
Witt et al. (2020) [26]	Ketamine vs. saline and midazolam	MDD and BD	6/195	RE	SMD = −0.61 [−1.10 to −0.12] **(0.02)**	57% **(0.03)**	NR	Low
Suicidality at 72 h								
Xu et al. (2016) [22]	Ketamine vs. saline and midazolam	MDD and BD	7/120	RE	SMD = −0.4 [−0.7 to −0.1] (NR)	2.0% (NR)	NR	NR
Suicidality at 1 week								
Xu et al. (2016) [22]	Ketamine vs. saline and midazolam	MDD and BD	7/120	RE	SMD = −0.1 [−0.4 to 0.1] (NR)	0.0% (NR)	NR	NR
Suicidality by 2 at 4 weeks								
Witt et al. (2020) [26]	Ketamine vs. saline and midazolam	MDD and BD	4/193	RE	SMD = −0.24 [−0.53 to 0.05] (0.1)	0% (0.70)	NR	Moderate
Witt et al. (2020) [26]	Ketamine vs. saline	MDD	2/67	RE	SMD = −0.19 [−0.61 to 0.23] (0.38)	1% (0.37)	NR	NR
Suicidality more than 4 weeks								
Witt et al. (2020) [26]	Ketamine vs. saline and midazolam	MDD and BD	3/122	RE	SMD = −0.21 [−0.58 to 0.16] (0.27)	3% (0.36)	NR	Moderate
Acceptability—total dropouts								
McCloud et al. (2015) [19]	Ketamine vs. saline	BD	2/33	RE	OR = 3.48 [0.56 − 21.74] (0.18)	0% (0.66)	NR	Very low
Fornaro et al. (2020) [23]	Ketamine vs. saline	BD	2/33	RE	OR = 4.14 [0.79 to 21.78] (0.093)	0% (NR)	NR	NR
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/887	RE	RR = 1.53 [0.90 to 2.61] (0.12)	32% (NR)	Not performed	High
Acceptability – dropouts due to lack of efficacy								
McCloud et al. (2015) [19]	Ketamine vs. saline	BD	2/33	RE	OR = 5.65 [0.76 − 41.87] (0.09)	0% (0.93)	NR	NR
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/798	RE	RR = 1.75 [0.41 to 7.52] (0.45)	22% (NR)	Not performed	High

Table 5 (continued)

Authors, year	Comparisons	Diagnosis	No of RCT/ patients	Statistical model	Pooled effect [95% CI] (*P* value)*	Heterogeneity I^2 (*P* value)**	Publication bias	Quality of evidence
Acceptability – dropouts due to adverse events								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/798	RE	RR = 3.50 [1.38 to 8.86] **(0.008)**	0% (0.44)	Not performed	High
Disability								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	2/436	RE	SMD = −0.37 [−0.56 to −0.17] **(0.0002)**	0% (0.53)	Not performed	High
Adverse events—overall								
Nuñez et al. (2020) [25]	Ketamine vs. placebo and diclofenac	MDD	3/NR	RE	RR = 1.28 [0.89 to 1.83] (0.19)	0% (0.42)	Not performed	NR
Adverse events—anxiety								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/746	RE	RR = 1.70 [1.00 to 2.91] (0.05)	0% (NR)	Not performed	High
Adverse events—blood pressure increased								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/680	RE	RR = 2.46 [0.87 to 6.97] (0.09)	42% (NR)	Not performed	High
Adverse events—diarrhea								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/680	RE	RR = 1.35 [0.72 to 2.52] (0.36)	0% (NR)	Not performed	High
Adverse events—dissociation								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/901	RE	RR = 5.70 [3.53 to 9.21] **(< 0.00001)**	1% (NR)	Not performed	High
Adverse events—dissociative disorder								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/155	RE	RR = 9.25 [1.64 to 52.11] **(0.01)**	0% (NR)	Not performed	High
Adverse events—dizziness								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/901	RE	RR = 3.49 [2.41 to 5.05] **(< 0.00001)**	0% (NR)	Not performed	High
Adverse events—dizziness postural								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/680	RE	RR = 10.67 [2.53 to 45.13] **(0.001)**	0% (NR)	Not performed	High
Adverse events—dysgeusia								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/901	RE	RR = 1.28 [0.94 to 1.75] (0.12)	8% (NR)	Not performed	High
Adverse events—euphoric mood								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/523	RE	RR = 2.10 [0.80 to 5.52] (0.13)	0% (NR)	Not performed	High
Adverse events—fatigue								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/680	RE	RR = 1.50 [0.81 to 2.80] (0.20)	0% (NR)	Not performed	High
Adverse events—feeling abnormal								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/155	RE	RR = 6.24 [1.05 to 37.19] **(0.04)**	0% (NR)	Not performed	High

Table 5 (continued)

Authors, year	Comparisons	Diagnosis	No of RCT/ patients	Statistical model	Pooled effect [95% CI] (*P* value)*	Heterogeneity I^2 (*P* value)**	Publication bias	Quality of evidence
Adverse events—feeling drunk								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/680	RE	RR = 9.35 [2.19 to 39.85] **(0.003)**	0% (NR)	Not performed	High
Adverse events—gastrointestinal								
Nuñez et al. (2020) [25]	Ketamine vs. placebo and diclofenac	MDD	3/NR	RE	RR = 0.90 [0.40 to 2.03] (0.80)	0% (0.46)	Not performed	NR
Adverse events—headache								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/901	RE	RR = 1.29 [0.98 to 1.70] (0.07)	0% (NR)	Not performed	High
Adverse events—hypertension								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/155	RE	RR = 1.03 [0.28 to 3.82] (0.97)	0% (NR)	Not performed	Moderate
Adverse events—hypoesthesia								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/680	RE	RR = 7.39 [2.95 to 18.53] **(< 0.0001)**	0% (NR)	Not performed	High
Adverse events—hypoesthesia oral								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/835	RE	RR = 7.54 [3.34 to 17.01] **(< 0.00001)**	0% (NR)	Not performed	High
Adverse events—insomnia								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/835	RE	RR = 1.05 [0.64 to 1.72] (0.85)	0% (NR)	Not performed	High
Adverse events—lethargy								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/457	RE	RR = 5.81 [1.31 to 25.75] **(0.02)**	0% (NR)	Not performed	High
Adverse events—mental impairment								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/457	RE	RR = 4.25 [0.92 to 19.73] (0.06)	0% (NR)	Not performed	High
Adverse events—nasal discomfort								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/835	RE	RR = 0.88 [0.47 to 1.66] (0.69)	3% (NR)	Not performed	High
Adverse events—nausea								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/901	RE	RR = 2.95 [2.10 to 4.13] **(< 0.00001)**	0% (NR)	Not performed	High
Adverse events—neurological								
Nuñez et al. (2020) [25]	Ketamine vs. placebo and diclofenac	MDD	3/NR	RE	RR = 1.51 [0.77 to 2.94] (0.23)	0% (0.56)	Not performed	NR
Adverse events—oropharyngeal pain								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/155	RE	RR = 1.06 [0.29 to 3.93] (0.93)	0% (NR)	Not performed	Moderate
Adverse events—paresthesia								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/746	RE	RR = 5.51 [2.63 to 11.55] **(< 0.00001)**	0% (NR)	Not performed	High

Table 5 (continued)

Authors, year	Comparisons	Diagnosis	No of RCT/ patients	Statistical model	Pooled effect [95% CI] (*P* value)*	Heterogeneity I^2 (*P* value)**	Publication bias	Quality of evidence
Adverse events—paresthesia oral								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/680	RE	RR = 3.08 [0.70 to 13.56] (0.14)	42% (NR)	Not performed	High
Adverse events—pollakiuria								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/457	RE	RR = 3.64 [0.75 to 17.60] (0.11)	0% (NR)	Not performed	High
Adverse events—psychiatric								
Nuñez et al. (2020) [25]	Ketamine vs. placebo and diclofenac	MDD	3/NR	RE	RR = 1.44 [0.42 to 4.95] (0.56)	17.49% (0.30)	Not performed	NR
Adverse events—sedation								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/678	RE	RR = 4.75 [1.91 to 11.82] **(0.0008)**	0% (NR)	Not performed	High
Adverse events—somnolence								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/746	RE	RR = 1.76 [1.20 to 2.59] **(0.004)**	0% (NR)	Not performed	High
Adverse events—tremor								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/457	RE	RR = 2.43 [0.77 to 7.66] (0.13)	0% (NR)	Not performed	High
Adverse events—throat irritation								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/782	RE	RR = 1.93 [1.02 to 3.65] **(0.04)**	0% (NR)	Not performed	High
Adverse events—vertigo								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/901	RE	RR = 9.78 [4.96 to 19.27] **(< 0.00001)**	0% (NR)	Not performed	High
Adverse events—vision blurred								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/730	RE	RR = 6.73 [2.52 to 18.00] **(0.0001)**	0% (NR)	Not performed	High
Adverse events—vomiting								
Zheng et al. (2020) [27]	Esketamine vs. placebo	MDD	NR/746	RE	RR = 5.49 [2.40 to 12.53] **(< 0.0001)**	0% (NR)	Not performed	High

BP bipolar disorder, *MDD* major depressive disorder, *NR* not reported, *RE* random effects

*Bolded *P* value: $P < 0.05$ is considered statistically significant; **It tells us what the proportion of variation in observed effects would remain if we could somehow get rid of the sampling error; Bolded *P* value: $P < 0.1$ is considered statistically significant

for meta-analyses (random effects model); however, the number of events they reported for the outcomes was different and, therefore, they showed slightly distinct results. In both cases, it was not possible to identify whether there was an error in data extraction by the review authors or whether data were extracted from different sources for the same primary study (e.g., different reports, unpublished data). There was no overlap of RCT across the systematic reviews that evaluated esketamine (Appendix 5).

Discussion

Main findings

To the best of our knowledge, this is the first overview of systematic reviews with meta-analyses evaluating efficacy and safety of ketamine and esketamine in adult patients with depression. Ketamine showed a significantly greater clinical response compared to control in most results between 24 h

Table 6 The quality assessment results of systematic reviews with meta-analyses included using the AMSTAR-2 tool

Author, year	Amstar-2 item																Overall quality
	1	**2***	**3**	**4***	**5**	**6**	**7***	**8**	**9***	**10**	**11***	**12**	**13***	**14**	**15***	**16**	
Caddy et al. (2015) [17]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	N	Y	Low
Lee et al. (2015) [18]	Y	N	Y	PY	Y	Y	N	PY	Y	N	Y	N	N	Y	Y	Y	Critically low
McCloud et al. (2015) [19]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	N	Y	Low
McGirr et al. (2015) [20]	Y	N	Y	PY	N	Y	Y	PY	Y	N	Y	N	N	Y	Y	Y	Critically low
Newport et al. (2015) [21]	Y	N	Y	N	N	N	N	PY	N	N	N	N	N	N	N	N	Critically low
Xu et al. (2016) [22]	Y	N	Y	PY	Y	Y	N	Y	Y	N	Y	N	N	Y	N	Y	Critically low
Fornaro et al. (2020) [23]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	N	Y	Critically low
Marcatoni et al. (2020) [24]	Y	PY	Y	Y	Y	Y	Y	Y	PY	N	Y	N	N	Y	Y	Y	Low
Nuñez et al. (2020) [25]	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	N	N	N	N	Y	Critically low
Witt et al. (2020) [26]	Y	Y	Y	PY	Y	Y	N	Y	Y	N	Y	N	N	Y	Y	Y	Critically low
Zheng et al. (2020) [27]	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	N	N	Y	N	Y	Critically low

Item 1: Did the research questions and inclusion criteria for the review include the components of PICO? **Item 2**: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? **Item 3**: Did the review authors explain their selection of the study designs for inclusion in the review? **Item 4**: Did the review authors use a comprehensive literature search strategy? **Item 5**: Did the review authors perform study selection in duplicate? **Item 6**: Did the review authors perform data extraction in duplicate? **Item 7**: Did the review authors provide a list of excluded studies and justify the exclusions? **Item 8**: Did the review authors describe the included studies in adequate detail? **Item 9**: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? **Item 10**: Did the review authors report on the sources of funding for the studies included in the review? **Item 11**: If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? **Item 12**: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? **Item 13**: Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? **Item 14**: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? **Item 15**: If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? **Item 16**: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

*Critical domains

Y yes, *N* no, *PY* partial yes

and 1 week post-intervention, except for very low doses for patients with major depression disorder at 24 h and 72 h, for patients with bipolar disorder at 72 h and 1 week, and for oral ketamine. Esketamine was statistically superior compared to placebo in the clinical response at all results evaluated between 2 h and 4 weeks.

For clinical remission, ketamine was significantly superior compared to control in most results between 80 min and 72 h post-intervention. The findings were inconsistent from 1 week after the intervention and not significant for oral ketamine. In addition, esketamine showed significant beneficial effects compared to placebo in the clinical remission at all results evaluated between 2 h and 4 weeks. When compared to control, ketamine showed significant reduction on scores of BPRS, CADSS, MADRS until 72 h, and in most results between at 24 h and 3 weeks post-intervention for the HAM-D/HDRS and MADRS depression scales. Esketamine was significantly better than placebo to improve the PHQ-9 score.

A recent systematic review with network meta-analysis compared the efficacy of 21 antidepressants for the acute treatment of adults with major depressive disorder [28]. The analyses were performed about 8 weeks post-intervention and the pooled effect size for clinical response, and clinical remission for antidepressants was frequently smaller than reported by the systematic reviews on the efficacy of ketamine and esketamine included in this overview. Therefore, ketamine and its isomer produce a rapid, powerful, and persistent action in adult patients with depression. Despite ketamine and esketamine presenting a faster onset of action and more likely to sustain it having clear therapeutic advantages [11, 29, 30], it is important to note that little is known about their long-term efficacy.

The effects of ketamine and esketamine on suicidal ideation were apparent up to 72 h post-intervention, but not at longer time points compared to control. According to the recent literature, there is no scientific evidence to support the use of suicide risk assessment tools to predict suicidal acts. However, they can complement the clinical assessment and be the starting point of the suicide prevention process [31]. Considering that patients using antidepressants have a higher risk of suicide in the first week of treatment compared to subsequent weeks, the use of medications with antidepressant effects within hours or a few days might have a positive impact on the patient's prognosis [32, 33].

Finally, only two systematic reviews with meta-analysis reported adverse events. Compared to control, the use of oral ketamine did not cause more adverse events, while intranasal esketamine showed significantly more dropouts due to adverse events and any events, such as dissociative disorder, dizziness, oral hypoesthesia, and vertigo. The main justification for not pooling data on ketamine used in different routes of administration is that many RCTs did not present data on adverse events; then, acute (up to 2 weeks) and long-term adverse events are lacking. In the absence of data, it would be imprudent to assume that there are no serious safety concerns [12]. Even because a systematic review (including different types of study designs) showed a qualitative summary of the adverse events from the use of ketamine. According to Short et al. (2018), acute adverse events associated with ketamine are common and include mainly psychiatric, psychotomimetic, cardiovascular, and neurological changes. Moreover, these authors suggest a selective reporting bias with limited assessment of long-term safety [34].

Methodological quality of systematic reviews

All systematic reviews included in this overview were classified as "low quality" or "critically low quality" according to the AMSTAR-2 critical appraisal criteria. This result is consistent with overviews that also used the AMSTAR-2 instrument to assess the methodological quality of systematic reviews on various treatments for depression [35, 36].

About the items of the AMSTAR-2 tool, all reviews did not report on the sources of funding for the studies included in their study (item 10). This finding is very worrying, since studies that receive industry funding can favor sponsored products, and they are less likely to be published compared to financially independent studies [37–39]. The failure to evaluate this item seems to be common in systematic reviews on treatments for mental disorders [35, 36, 40, 41].

In this overview, no systematic review assessed how their results varied in relation to the inclusion or exclusion of individual studies with a high risk of bias (item 12). A justification of the authors of the reviews was the small number of RCTs included in the combined effect estimates that made this analysis unfeasible. Non-adherence to this item was less frequent in the literature on systematic reviews of treatments for mental disorders [35, 36, 41].

The development of a research protocol prior to conducting a review is considered a critical item by the AMSTAR-2 (item 2). Nevertheless, only a few reviews have fully adhered to this item, which is like the findings of other overviews on treatments for mental disorders [35, 36, 40, 41]. Adherence to a well-developed protocol promotes transparency of the review process and can help avoid the biased post hoc decisions, for example selective outcome reporting [42].

Opportunities for future research

This overview revealed that there is room for improvement in the future studies. Though the number of RCT evaluating ketamine and its esketamine isomer in depression has grown in recent years, the evidence summarized is from 20 RCTs including ketamine (Appendix 4) and four RCTs including esketamine (Appendix 5). From that, it was noted that more evidence is needed on the effects of these drugs on a treatment period longer than 2–4 weeks (i.e., able to elucidate long-term efficacy and safety), head-to-head trials (directly comparing ketamine and esketamine or using active-control with antidepressant drugs), and also on the use of different doses and routes of administration of both drugs (ketamine was frequently administered by intravenous route and esketamine by intranasal route).

In addition, future systematic reviews with meta-analyses on this theme should be appropriately designed and conducted, primarily in reporting an explicit statement that the methods were established prior to conducting the review and justifying any significant deviations from the protocol, reporting on the sources of funding for the RCT included in the systematic review, assessing the potential impact of risk of bias in RCT on the results of the meta-analysis; accounting for risk of bias in RCT when interpreting/discussing the results of the review, and conducting an adequate investigation of publication bias and discuss its likely impact on the results of the review.

Strengths and limitations of the overview

To our knowledge, this is the first overview to summarize evidence on the use of ketamine and esketamine in adult patients with depression. In addition, the study assessed the methodological quality of systematic reviews using the validated AMSTAR-2 tool. However, this study also presents some limitations. Only systematic reviews with meta-analysis were included in this overview. Reviews including simultaneous use of ECT and ketamine or esketamine were excluded, and this may have excluded important reviews on the theme and decreased the number of reviews to compose the new evidence generated from this overview. We did not conduct searches for unpublished reviews from thesis repositories and conference proceedings, or ongoing reviews. In addition, the quality of evidence for the outcomes was extracted based on the assessment of this parameter by the review authors, and not all reviews performed this analysis. Finally, we do not provide the prediction interval, which would be helpful to assess whether the between-study variation was clinically significant.

Conclusion

The findings of this overview showed a significant superiority of ketamine and esketamine in most results for clinical response, clinical remission, depression scales scores, and suicidal ideation compared to control. No systematic review performed a meta-analysis for adverse events of ketamine (except for oral ketamine and esketamine). It is very important to note that the data came from the first 2 weeks of treatment with ketamine and 4 weeks for esketamine, and the long-term efficacy and safety are lacking. In addition, most reviews showed a critically low methodological quality, which limits the reliability of the evidence. Thus, it is necessary to carry out more primary studies, and future systematic reviews should follow the quality assessment tools so that best evidence can be used in the decision-making for the use of ketamine and its isomer in adult patients with depression.

Appendix 1. Protocol of overview

1. **Review question**

   To summarize the evidence of efficacy and safety of ketamine for patients with depression from systematic reviews with meta-analyses
2. **Searches**

   A comprehensive literature search will be performed until October 2019 in the Medline (via PubMed), Latin American and Caribbean Health Sciences Literature (LILACS), Cochrane Library, and the Centre for Reviews and Dissemination (CRD) databases. In addition, we will screen the reference lists of the appraised articles to identify any studies which might have been missed. A standardized search strategy will include MeSH terms or text words related to health condition (depression), intervention (ketamine), and study design (systematic review with meta-analysis)
3. **Study selection**

   The selection process will be performed in three steps: (1) exclusion of repeated records, (2) analysis of the titles and abstracts, and (3) analysis of the full-text articles. The studies will be independently selected by two authors. Any disagreements will be resolved by a third author. When the full-text article could not be obtained, the corresponding authors will be contacted via ResearchGate (www.researchgate.net) or e-mail or both

   To be included in the overview, the articles must meet the following criteria: (1) be a systematic review with meta-analysis of randomized controlled trials; (2) be published in English, Spanish or Portuguese; (3) have evaluated the use of ketamine (monotherapy or associated with other drugs, any route of administration and frequency of use) compared to placebo or other drugs; (4) report any efficacy and safety outcomes; and (5) in patients with major depressive disorder or bipolar disorder

   Articles will be excluded if they were (1) narrative reviews, (2) systematic reviews without meta-analysis; (3) meta-analyses not from systematic reviews; (4) systematic reviews including use concomitant of ECT and ketamine as intervention; (5) systematic reviews with meta-analysis including another target population, intervention, or primary study design; and (6) systematic reviews that did not have the full-text article available
4. **Data extraction**

   Data extraction will be performed by two independent authors, and any disagreement will be resolved by a third researcher. The following information will be collected on a spreadsheet preformatted in Microsoft Excel: author(s), year of publication, literature search, population, intervention, comparators, outcome measures, number of RCTs and patients included in the outcome analysis, pooled effect size, heterogeneity, publication bias, and funding source
5. **Quality assessment**

   The methodological quality of included systematic reviews will be assessed using the AMSTAR-2. The AMSTAR-2 is a 16-item questionnaire, with the majority of questions being judged as "yes," "partial yes," or "no." The items in this tool are as follows: Item 1: Did the research questions and inclusion criteria for the review include the components of PICO? Item 2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? Item 3: Did the review authors explain their selection of the study designs for inclusion in the review? Item 4: Did the review authors use a comprehensive literature search strategy? Item 5: Did the review authors perform study selection in duplicate? Item 6: Did the review authors perform data extraction in duplicate? Item 7: Did the review authors provide a list of excluded studies and justify the exclusions? Item 8: Did the review authors describe the included studies in adequate detail? Item 9: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? Item 10: Did the review authors report on the sources of funding for the studies included in the review? Item 11: If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? Item 12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies

on the results of the meta-analysis or other evidence synthesis? Item 13: Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? Item 14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? Item 15: If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? Item 16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

The overall confidence in the results of the review will be rated either high, moderate, low, or critically low. One investigator conducted the evaluation of the studies, and a second one verified this evaluation

6. **Strategy for data synthesis**

   The characteristics of systematic reviews and their methodological quality will be descriptively summarized using systematically structured tables. The estimates of effect size from meta-analyses (and their 95% confidence intervals [95% CI]) will be expressed as mean difference (MD), standardized mean difference (SMD), relative risk (RR), and odds ratio (OR), depending on what the authors had reported

7. **Funding**

   None

8. **Conflicts of interest**

   None known

Author contribution PMA and TML contributed to the development of the review protocol. MBV, TML, and PMA conducted selected articles, data extraction, and quality assessment of included reviews. PMA and TML contributed to drafting and critical revisions of the manuscript. MBV critically reviewed the manuscript. All the authors have approved the final manuscript.

Declarations

Conflict of interest The authors declare no competing interests.

Appendix 2. Search strategy by database

Database	Search strategy
Medline (via PubMed)	systematic[sb] AND (((ketamine[MeSH Terms]) OR (ketamine) OR (ketalar) OR (ketaset) OR (ketanest) OR (calipsol) OR (kalipsol) OR (calypsol) OR (esketamine) OR (spravato)) AND ((mental disorders[MeSH Terms]) OR (depression[MeSH Terms]) OR (depressive disorder[MeSH Terms]) OR (depressive disorder, major[MeSH Terms]) OR (bipolar disorder[MeSH Terms]) OR (depress*) OR (dysthymi*) OR ("affective disorder*") OR ("mood disorder*") OR (unipolar) OR (bipolar)))
LILACS	((MH:"depression") OR (MH:"depressive disorder") OR (depression) OR (depressive) OR (dysthymia) OR (dysthymic) OR ("affective disorder") OR ("affective disorders") OR ("mood disorder") OR ("mood disorders") OR (unipolar) OR (bipolar)) AND ((MH:ketamine) OR (ketamine) OR (ketalar) OR (ketaset) OR (ketanest) OR (calipsol) OR (kalipsol) OR (calypsol) OR (esketamine) OR (spravato)) AND ((MH:review) OR (MH: "review literature as topic") OR ((review OR overview) AND systematic) OR "systematic review" OR review OR (meta-analysis OR metanalysis OR metaanalysis))
The Cochrane Library	#1 MeSH descriptor: [depression] explode all trees #2 MeSH descriptor: [depressive disorder] explode all trees #3 MeSH descriptor: [depressive disorder, major] explode all trees #4 MeSH descriptor: [bipolar disorder] explode all trees #5 (depression):ti,ab,kw #6 (depressive):ti,ab,kw #7 (dysthymia):ti,ab,kw #8 (dysthymic):ti,ab,kw #9 ("affective disorder"):ti,ab,kw #10 ("affective disorders"):ti,ab,kw #11 ("mood disorder"):ti,ab,kw #12 ("mood disorders"):ti,ab,kw #13 (unipolar):ti,ab,kw #14 (bipolar):ti,ab,kw #15 (#1 OR #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) #16 MeSH descriptor: [Ketamine] explode all tree #17 ketamine:ti,ab,kw #18 Ketalar:ti,ab,kw #19 Ketaset:ti,ab,kw #20 Ketanest:ti,ab,kw #21 Calipsol:ti,ab,kw #22 Kalipsol:ti,ab,kw #23 Calypsol:ti,ab,kw #24 esketamine #25 spravato #26 (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25) #27 (#15 AND #26)

Database	Search strategy
Center for Reviews and Dissemination (CRD)	(ketamine) OR (esketamine) AND (depression)

Appendix 3. List of excluded studies

Reason for exclusion	Authors, year	Title	Reference
Systematic review that did not conduct a meta-analysis	Serafini et al. (2014)	The role of ketamine in treatment-resistant depression: a systematic review	Curr Neuropharmacol, 2014;12(5):444–61
	Short et al. (2018)	Side-effects associated with ketamine use in depression: a systematic review	Lancet Psychiatry, 2018;5(1):65–78
	Cao et al. (2019)	Pharmacological interventions targeting anhedonia in patients with major depressive disorder: a systematic review	Prog Neuropsychopharmacol Biol Psychiatry, 2019;92:109–17
Did not include only RCT in meta-analysis	Caddy et al. (2014)[a]	Ketamine as the prototype glutamatergic antidepressant: pharmacodynamic actions, and a systematic review and metaanalysis of efficacy	Ther Adv Psychopharmacol, 2014;4(2):75–99
	Fond et al. (2014)[a]	Ketamine administration in depressive disorders: a systematic review and metaanalysis	Psychopharmacology (Berl), 2014;231(18):3663–76
	Tashakkori et al. (2021)	The time course of psychotic symptom side effects of ketamine in the treatment of depressive disorders: a systematic review and meta-analysis	Australas Psychiatry. 2021;29(1):80–87
	Yuan et al. (2020)	Application of antidepressants in depression: a systematic review and meta-analysis	J Clin Neurosci. 2020;80:169–181
It involves other causes of suicidal ideation in addition to depression	Wilkinson et al. (2018)	The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis	Am J Psychiatry, 2018; 175(2):150–58
Excluded article because the meta-analysis was miscalculated	Parsaik et al. (2015)[b]	Efficacy of ketamine in bipolar depression: systematic review and meta-analysis	J Psychiatr Pract, 2015; 21(6):427–35
	Bahjie et al. (2021)[c]	Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis	J Affect Disord. 2021;278:542–555

RCT randomized controlled trials.

[a]Systematic reviews excluded during data extraction, as they included the study by Valentine et al. (2011) [43] that is not a randomized controlled trial — data confirmed with the author of the primary study.

[b]Systematic reviews retracted of scientific journal.

[c]Systematic review excluded during data extraction, as they considered data from the Singh et al. (2016) [44] in the ketamine group and Lapidus et al. (2014) [45] in the esketamine group.

Appendix 4. Randomized controlled trials included in the systematic reviews with meta-analyses on ketamine for depression

	RCT 1	RCT 2	RCT 3	RCT 4	RCT 5	RCT 6	RCT 7	RCT 8	RCT 9	RCT 10	RCT 11	RCT 12	RCT 13	RCT 14	RCT 15	RCT 16	RCT 17	RCT 18	RCT 19	RCT 20
Authors, year	Berman et al. (2000) [8]	Zarate et al. (2006) [46]	Diazgranados et al. (2010) [47]	Zarate et al. (2012) [48]	Murrough et al. (2013) [49]	Sos et al. (2013) [50]	Lai et al. (2014) [51]	Lapidus et al. (2014) [45]	Hu et al. (2016) [52]	Loo et al. (2016) [53]	Jafarinia et al. (2016) [54]	George et al. (2017) [55]	Grunebaum et al. (2017) [56]	Su et al. (2017) [57]	Arabzadeh et al. (2018) [58]	Chen et al. (2018) [59]	Grunebaum et al. (2018) [60]	Domany et al. (2019) [61]	Ionescu et al. (2019) [62]	Fava et al. (2020) [63]
Caddy et al. (2015) [17]	X	X				X														
Lee et al. (2015) [18]		X	X	X	X	X														
McCloud et al. (2015) [19]			X	X																
McGirr et al. (2015) [20]	X	X	X	X	X	X		X												
Newport et al. (2015) [21]	X	X	X	X	X	X		X												
Xu et al. (2016) [22]		X	X	X	X	X	X	X		X										
Witt et al. (2020) [26]				X	X				X	X		X	X	X			X		X	
Fornaro et al. (2020) [23]			X	X																
Marcantoni et al. (2020)		X	X		X	X										X	X			X
Nuñez et al. (2020) [25]											X				X			X		

Appendix 5. Randomized controlled trials included in the systematic reviews with meta-analyses on esketamine for depression

	RCT 1	RCT 2	RCT 3	RCT 4
Authors, year	Canuso et al. (2018) [64]	Daly et al. (2018) [65]	Fedgchin et al. (2019) [66]	Popova et al. (2019) [67]
Witt et al. (2020) [26]	X			
Zheng et al. (2020) [27]	X	X	X	X

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