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# Efficacy and safety of ketamine for unipolar refractory depression: an overview of systematic reviews

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## Abstract

**Purpose:** To analyze the evidence of efficacy and safety of the use of intravenous ketamine for adults with refractory unipolar major depression. **Methods:** This is an overview of systematic reviews performed according to the PRISMA (*Preferred Reporting Items for Systematic reviews and Meta-Analyses*) *check-list* and Cochrane Collaboration recommendations, in which the literature searches were executed in Medline (via Pubmed) and Embase databases. Systematic reviews of randomized clinical trials of adults with refractory unipolar major depression were included, using other drugs as comparators. The methodological quality was evaluated according to the AMSTAR-2 tool (*A measurement tool to assess systematic reviews*- 2). **Results:** A total of 445 records, in which 73 studies were selected for full-text reading and 21 fully met the eligibility criteria. The most prevalent dosage was 0.5mg/kg in single dose and in multiple doses. Compared to control, ketamine promoted beneficial effect by reducing the depressive symptoms and suicidal ideation, and improving the depression tools scores. The effects were observed for 3-7 days after the ketamine infusion; in a single dose, these effects restricted the first hours (between 30-40 minutes). Additionally, the studies revealed that the adverse effects were predominantly mild, and only two studies showed serious events, such as bradycardia and hypotension, but did not result in discontinuation of the studies. The methodological quality was considered "critically low" in most cases (62%). **Conclusion:** The intravenous ketamine showed a significant improvement or non-inferiority in comparison to other treatments, and a reduction of depressive symptoms, including suicidal ideation, with an appropriate safety profile. Therefore, besides the low quality of the included systematic reviews, intravenous ketamine can represent an effective and safe option for refractory unipolar major depression. Higher quality studies about this topic are needed to guarantee more robust evidence, especially related to the ideal dosage of intravenous ketamine.

**Keywords:** Ketamine; Major depressive disorder; Suicidal Ideation; Adverse drug events.

# Eficácia e segurança da cetamina para o tratamento de depressão unipolar refratária: uma overview de revisões sistemáticas

## Resumo

**Objetivo:** Analisar as evidências relacionadas a eficácia e a segurança da cetamina intravenosa para o tratamento de pacientes adultos com transtorno unipolar depressivo maior refratário a tratamentos prévios. **Metodologia:** Trata-se de uma *overview* de revisões sistemáticas realizada conforme o *check-list* PRISMA (*Preferred Reporting Items for Systematic reviews and Meta-Analyses*) e as recomendações da Colaboração Cochrane, cuja busca foi efetuada nas bases de dados Medline (via PubMed) e Embase. Foram incluídas revisões sistemáticas de ensaios clínicos randomizados de pacientes adultos com o diagnóstico de depressão unipolar refratária ao tratamento, tendo outros fármacos como comparador. A qualidade metodológica dos estudos foi avaliada de acordo com a ferramenta AMSTAR-2 (*A measurement tool to assess systematic reviews* - 2). **Resultados:** Foram identificados 445 trabalhos, dos quais, 73 estudos foram selecionados para a leitura na íntegra e 21 atenderam aos critérios de inclusão. A posologia mais prevalente foi de 0,5mg/kg administrado tanto em dose única quanto em mais administrações. Os pacientes que receberam a cetamina apresentaram boa resposta através da redução dos sintomas depressivos, melhora dos escores de instrumentos da depressão e dos sintomas de ideação suicida. Os efeitos da cetamina foram observados por um período de até 3 a 7 dias; em dose única, esse efeito permaneceu mais restrito às primeiras horas após uma infusão (entre 30 e 40 minutos). Adicionalmente, os estudos demonstraram que os efeitos adversos foram em sua maioria leves e apenas dois casos de reações graves foram descritos, como bradicardia e hipotensão, mas que não resultaram em abandono dos ensaios. A qualidade metodológica da maioria dos estudos foi considerada criticamente baixa (62%). **Conclusão:** A cetamina intravenosa demonstrou melhora ou não inferioridade a outros tratamentos dentro dos parâmetros avaliados, com redução dos sintomas da depressão, incluindo de ideação suicida, aliado a um perfil de segurança adequado. Portanto, apesar da qualidade reduzida das evidências encontradas, a cetamina intravenosa pode representar uma opção eficaz e segura para o tratamento de depressão unipolar refratária. Estudos de maior qualidade são necessários a fim de promover evidências mais robustas, especialmente acerca do regime posológico ideal da cetamina intravenosa.

**Descritores:** Cetamina; Transtorno depressivo maior; Ideação suicida; Efeitos adversos.

## Introduction

Understanding and addressing mental disorders are fundamental to promoting mental health and providing appropriate treatment. In Brazil, the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) serves as a reference for current clinical practice, shaping therapeutic approaches and intervention strategies. In this context, it defines Major Depressive Disorder (MDD) or Unipolar Major Depression as a neurological disorder characterized by melancholic feelings, fatigue, sleep disturbances, feelings of worthlessness or guilt, and, in some cases, suicidal ideation, without association with episodes of mania or hypomania[1,2].

This disorder impacts various dimensions of life, necessitating comprehensive care for the individual. Among the available treatments, pharmacotherapy with antidepressants plays a fundamental role in symptom remission and the restoration of baseline[3] functioning. The antidepressants used to manage this condition include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), atypicals, serotonin modulators, tricyclics, and monoamine oxidase[4] inhibitors (MAOIs).

Despite advances in antidepressant therapies, some cases present specific challenges, such as Treatment-Resistant Depression (TRD), a complex condition requiring comprehensive and individualized strategies. TRD is characterized by the individual's lack of response to conventional[5] treatments. Approximately 70% of MDD cases achieve symptom[9,10] remission, while the remaining 30% do not respond to optimized therapies. In the United States, the percentage of patients who do not achieve remission can reach 20% of cases[7,8].

In this context, ketamine, a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, has gained prominence due to its efficacy and safety, particularly in achieving rapid symptom improvement. However, evidence regarding the use of ketamine for TRD remains sparse and heterogeneous, particularly concerning selected populations and dosing regimens.

Thus, the objective of this study was to analyze systematic reviews related to the efficacy and safety of ketamine in treating adult patients with unipolar major depressive disorder resistant to conventional pharmacological interventions.

## Methods

A systematic review of systematic reviews was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[11] checklist and the recommendations of the Cochrane[12] Collaboration. All stages of the study were carried out by two independent reviewers, and in cases of disagreement, a third reviewer was consulted. The study was registered on the PROSPERO platform under the ID CRD42023478958 (https://www.crd.york.ac.uk/prospero/).

### Information Sources

A systematic search was performed in the Medline (via PubMed) and Embase databases on October 25, 2024, using the search strategies described in Appendix 1 of the Supplementary Material. No restrictions were applied regarding the publication date or language. A manual search was also conducted by reviewing the references of included studies and exploring gray literature (websites and society guidelines). Search filters, such as language or publication date filters, were not applied.

### Study Selection

The PICOS acronym (Population/Intervention/Comparators/Outcomes/Study Design) guided the study selection process. Systematic reviews of randomized clinical trials, with or without meta-analyses, were evaluated for inclusion. These studies involved patients aged 18 years or older who received intravenous (IV) ketamine compared to other medications used in the treatment of unipolar depression or placebo. Only the IV formulation was considered due to its greater accessibility in healthcare institutions, as the intranasal formulation was only approved in Brazil in 2020 and is associated with higher[13] costs.

#### Eligibility Criteria

Studies that met the criteria outlined by the PICOS framework were included. However, the following exclusion criteria were applied: articles published in non-Roman characters; comparisons of ketamine with non-pharmacological therapies; studies that did not include primary studies in their analyses.

#### Data Extraction

Data were extracted using a table created in Microsoft Excel® by the authors. General study information was collected, including the author, year of publication, number of studies reviewed, number of patients involved, comparators, and dosing regimens. For efficacy outcomes, the following were evaluated: treatment response, remission rates, improvement in depressive symptoms, improvement in depression scale scores, and reduction in suicidal ideation symptoms. For safety outcomes, general and severe adverse events and discontinuation rates due to adverse effects were assessed. Statistical data, such as effect measures with their respective confidence intervals and I-squared values, were also extracted.

#### Quality Assessment

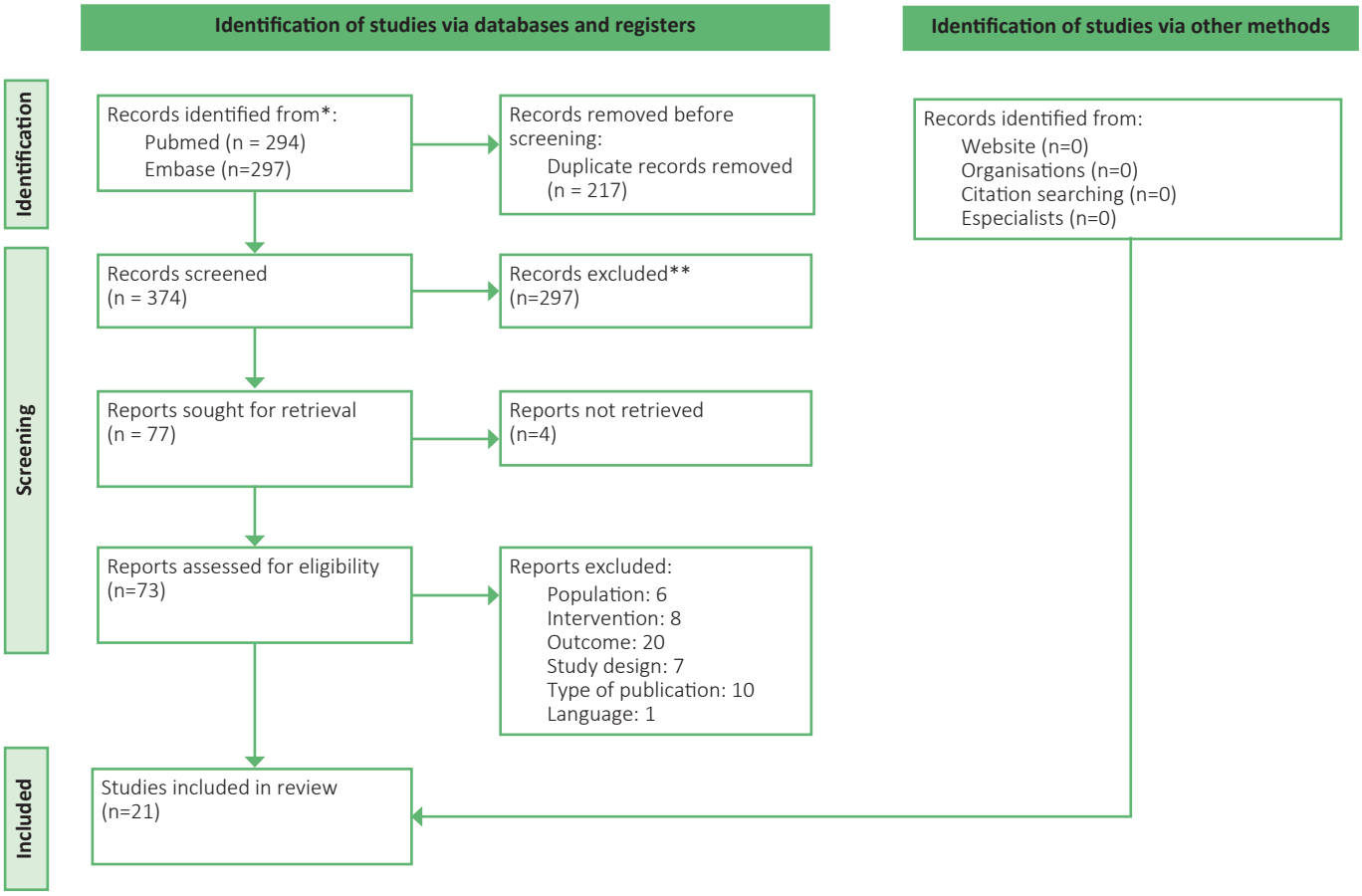
The quality of the selected articles was evaluated using the AMSTAR-2 tool (*A Measurement Tool to Assess Systematic Reviews - 2*). This instrument consists of 16 questions related to the methodological process and conduct of systematic reviews, classifying quality as high, moderate, low, or critically low depending on the responses[14].

## Results

### Article Selection

A total of 591 articles were identified in the databases, with no additional records found through manual searches or gray literature. Of these, 374 articles were selected for initial screening. After abstract screening, 73 studies were selected for full-text review, and 21 articles met the eligibility criteria (Figure 1).

**Figure 1.** Diagram of studies included in the review.




Characteristics of the Systematic Reviews

Twenty-one systematic reviews of randomized clinical trials were included, comprising five studies without meta-analyses and 16 with direct meta-analyses. These reviews included between 41 and 2,914 participants. The comparators varied across studies, with placebo being the most commonly tested (n = 15/21, 71%). The ketamine dose ranged from 0.1 to 1 mg/kg, with dosing regimens categorized as single-dose (n = 9/21, 43%) or single or multiple doses (n = 10/21, 47.6%). However, the dosing intervals for studies with multiple-dose regimens were not reported in most cases (n = 9/10, 43%). Additionally, two studies did not provide detailed information on the ketamine[15,16] dosing regimens. More details on the general characteristics of the selected systematic reviews are presented in Table 1.

Effectiveness and Safety Assessment

The outcomes for efficacy and safety were evaluated over periods ranging from 30 minutes post-infusion to more than one month. Of the 21 included studies, 11 assessed treatment response to intravenous ketamine using direct meta-analyses. Ten of these studies demonstrated statistically significant results, highlighting the superior efficacy of ketamine compared to the tested comparators. However, it is worth noting that the heterogeneity of these meta-analyses was reported as high or not reported in most cases (n = 8/11, 72.7%) (Table 2). The study by Levinta et al., 2022, showed ketamine's superiority in treatment response; however, the findings were based on a single systematic review without robust statistical data to strengthen this conclusion.

Only eight studies reported remission rates through direct meta-analyses, all of which showed statistically significant differences favoring the ketamine group, with odds ratios or relative risks ranging from 2.0 to 9.89. Regarding the improvement in depressive symptoms, four studies evaluated this outcome through meta-analyses. Among them, two reported statistical superiority of ketamine[17,18], while the others found similar effects between the comparators[19,20] (Table 2). For these two outcomes, three additional studies qualitatively analyzed ketamine's superiority. One study demonstrated an advantage in depressive[19] symptom improvement, while the other two showed superiority in depression remission rates[21,22].

Among the eight studies that reported depression scale score reductions through quantitative analyses, only two did not reveal statistically significant results favoring ketamine[23,24]. Notably, Witt et al., 2020, identified a significant improvement in symptoms, reflected by reduced depression scale scores within 24 to 72 hours post-infusion. However, for subsequent evaluation periods, statistical similarity was observed between the groups (Table 2).

Additionally, four meta-analyses assessed the improvement of suicidal ideation symptoms. Of these, only Chen et al., 2023, reported statistical similarity between intravenous ketamine

**Table 1.** Characteristics of the systematic reviews evaluated.

| Author, Year | Type of Meta-Analysis | Study Type | Number of Included Studies | Number of Patients | Comparators | Dosage Regimen | |
|---|---|---|---|---|---|---|---|
| | | | | | | Dose | Frequency |
| Bahji, 2021 | Direct | ECR | 24 | 1877 | Ketamine vs esketamine nasal preparations | 0.1 a 1 mg/kg | Single and Multiple Doses |
| Bahji, 2022 | Direct | ECR | 36 | 2914 | Ketamine vs esketamine nasal preparations | 0.1 a 1 mg/kg e 28 a 100mg[1] | Single Dose |
| Chen, 2023 | Direct | ECR | 17 | 1224 | Ketamine vs esketamine nasal preparations | 0.5 a 1 mg/kg | NA |
| Fond, 2014 | Direct | ECR | 9 | 192 | Ketamine vs Placebo/ midazolam/ propofol | 0.5 mg/kg | Single Dose |
| Hochschild, 2021 | Absent | ECR | 21 | 611 | Ketamine vs placebo/midazolam | 0.5 mg/kg | Single Dose and Weekly Infusions |
| Kishimoto, 2016 | Direct | ECR | 9 | 234 | Ketamine vs placebo/ pseudo-placebo | 0.1 mg/kg e 0.5 mg/kg | Single and Multiple Doses |
| Lee, 2015 | Direct | ECR | 5 | 134 | Ketamine vs Psychotropic drug in use by the patient | 0.5 mg/kg e 0.27 mg/kg | Single Dose |
| Levinta, 2022 | Absent | ECR | 18 | 1362 | Ketamine vs placebo | 0.1 a 1 mg/kg | 2 to 3 Times per Week for 4 Weeks, Single Dose and 6 Doses |
| Maguire, 2020 | Absent | ECR | 3 | 77 | Ketamine vs placebo | 0.2 mg/kg | Single Dose |
| Marcantoni, 2020 | Direct | ECR | 19 | 818 | Ketamine vs placebo placebo | 0.5 mg/kg | Single and Multiple Doses |
| McGirr, 2015 | Direct | ECR | 7 | 183 | Ketamine vs sodium chloride/midazolam | 0.5 mg/kg | Single Dose |
| Memon, 2020 | Absent | ECR | 19 | 2183 | Ketamine vs Placebo/ midazolam/ propofol | 0.1 a 1mg/kg | 1 or 3 Doses |
| Price, 2022 | Direct | ECR | 17 | 720 | Ketamine vs sodium chloride/ midazolam/ remifentanil | 0.2 a 1mg/kg | 1, 4, and 6 Doses |
| Romeo, 2015 | Direct | ECR | 6 | 110 | Ketamine vs placebo | 0.5 mg/kg | Single Dose |
| Wilkinson, 2018 | Direct | ECR | 10 | 298 | Ketamine vs sodium chloride | NA | Single Dose |
| Witt, 2020 | Direct | ECR | 15 | 572 | Ketamine vs sodium chloride/ midazolam/ propofol/ | 0.27 a 1.0 mg/kg | 1, 5 and 6 Doses |
| Xiong, 2021 | Direct | ECR | 9 | 341 | Ketamine vs sodium chloride/midazolam | 0,2 a 0.5mg/kg | Single Dose |
| Xu, 2016 | Direct | ECR | 9 | 201 | Ketamine vs sodium chloride/midazolam | 0.1 a 0.5mg/kg | 1 and 2 Doses |
| Yuan, 2020 | Direct | ECR | 9 | 334 | Ketamine vs antidepressants/ placebo | NA | NA |
| Newport, 2015 | Direct | ECR | 12 | 352 | Ketamine vs placebo/ Lithium/ Valproic acid | 0.5 mg/kg | Single Dose |
| Dias, 2022 | Absent | ECR | 6 | 41 | Ketamine vs placebo | 0.2 mg/kg e 0.5 mg/kg | 2 and 3 Doses |

Note: [1]Fixed dose, other doses were evaluated according to weight. NA: Not assessed.

(IV) and intranasal (IN) ketamine groups. The remaining studies demonstrated the superiority of IV ketamine. Wilkinson et al., 2018, which compared IV ketamine to saline solution, showed improvement in suicidal ideation symptoms favoring the intervention at 3 days (Cohen's d = 0.67 [95% CI 0.35–0.99]) and 7 days (Cohen's d = 0.61 [95% CI 0.27–0.94]) post-infusion (Table 2).

Regarding safety outcomes, three studies reported the relevant results[24,27,28]. Among these, Bahji et al., 2022, did not identify statistically significant differences in the incidence of general adverse events between groups. However, the study highlighted a higher discontinuation rate in the ketamine group (RR 1.56 [95% CI 1–2.45]) (Table 3). In studies that did not conduct meta-analyses[17,21,22,29,30], ketamine did not demonstrate superiority over comparator groups in terms of adverse event occurrence or severity. These findings suggest that ketamine is generally well-tolerated as a treatment option.

Methodological Quality of Systematic Reviews (AMSTAR-2)

Most studies were rated as having critically low (n = 13/21, 61.9%) or low (n = 6/21, 28.5%) quality according to the AMSTAR-2 tool (Table 4). The primary reasons for methodological quality downgrades included: a) Lack of a list of excluded articles (n = 19/21, 90.4%), b) Absence of discussion and interpretation of results considering the risk of bias in primary studies (n = 12/21, 57%), c) Unavailability of search strategies (n = 12/21, 57%). Of the 21 included studies, only two (9.5%) demonstrated moderate quality, and none were rated as having high methodological quality.

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**Table 2.** Effectiveness outcome measures.

| Author, Year, Evaluation Period[1] | | Treatment Response RR[2] or OR[3] (95% CI) I² (%) | Remission Rate RR or OR (95% CI) I² (%) | Improvement in Depression Symptoms G[4] or SMD[5] (95% CI) I² (%) | Improvement in Depression Instrument Scores SMD (95% CI) I² (%) | Improvement in Suicidal Ideation Symptoms SMD or D[6] (95% CI) I² (%) |
|---|---|---|---|---|---|---|
| Bahji, 2021 | | RR 2.04 (1.57; 2.64), 63 | RR 2 (1.5; 2.7), 38 | NA | SMD -1.1 (-1.5; -0.8), 90 | SMD –0.3867 (-0.7082; -0.0653), 71.3 |
| Bahji, 2022 | | RR 2,14 (1.62; 2.66), 65 | RR 1.64 (1.33; 2.02), 39 | NA | SMD -0.63 (-0.80; -0.45), 78 | NA |
| Chen, 2023 | | D 0.72 (0.36; -1.07), 87 | NA | NA | NA | D 0.81 (0.41; 1.21), 88 |
| Fond, 2014 | | SMD -1,1 (-1.39; -0.81), 6,3 | NA | NA | SMD 0.99 (0.75; -1.23), 2.9 | NA |
| Hochschild, 2021 | | NA | NA | NA | NA | NA |
| Kishimoto, 2016 | 40-60 min | RR 13.6 (2.67; 69.6), 0 | RR 6.63 (1.23; 35.7), 0 | G -0.5 (−1.0; 0), 44.3 | NA | NA |
| | 4h-1 dia | RR 14.7 (3.72; 58.3), 0 | RR 9.89 (2.4; 40.5), 0 | G –1 (−1.28; −0.73), 0 | NA | NA |
| | 5-8 dias | RR 3.43 (1.77; 6.63), 0 | RR 5.22 (1.20; 22.6), 0 | G -0.38 (-0.73; -0.03), 9.38 | NA | NA |
| Lee, 2015 | | NA | NA | SMD 1.01 (0.69; 1.34), 30 | NA | NA |
| Levinta, 2022 | | NA | NA | SMD 0.41 (0.14; 0.68), 0 | NA | NA |
| Maguire, 2020 | | NA | NA | NA | NA | NA |
| Marcantoni, 2020 | | OR 6.33 (3.33; 12.05), 0 | OR 5.11 (2.15; 12.17), 0 | NA | SMD 0.68 (0.46; 0.90), 9 | NA |
| McGirr, 2015 | 24h | OR 9.1 (4.28; 19.34), NA | OR 7.06 (2.50; 19.95), NA | NA | SMD 0.9 (0.66; 1.13), NA | NA |
| | 3 dias | OR 6.77 (3.40; 13.50), NA | OR 3.86 (1.53; 9.74), NA | NA | NA | NA |
| | 7 dias | OR 4.87 (2.24; 10.55), NA | OR 4 (1.52; 10.51), NA | NA | NA | NA |
| Memon, 2020 | | NA | NA | NA | NA | NA |
| Price, 2022 | Rápido | OR 3.2 (2.27; 4.54), NA | OR 2.51 (1.68; 3.79), NA | NA | SMD 0.58 (0,44; 0,72), NA | NA |
| | Pós-rápido | OR 2.85 (1.89; 4.36), NA | OR 2.4 (1.51; 3.88), NA | NA | SMD 0.38 (0,23; 0,54), NA | NA |
| Romeo, 2015 | | NA | NA | NA | SMD 0.38 (-0,87; -0,11), 0 | NA |
| Wilkinson, 2018 | 1 dia | NA | NA | NA | NA | D 0.85 (0.53; 1.17), NA |
| | 2 dias | NA | NA | NA | NA | D 0.85 (0.52; 1.17), NA |
| | 3 dias | NA | NA | NA | NA | D 0.67 (0.35; 0.99), NA |
| | 7 dias | NA | NA | NA | NA | D 0.61 (0.27; 0.94), NA |
| Witt, 2020 | <4h | NA | NA | NA | SMD -0.51 (-1.0; -0.03), 73 | NA |
| | 4-12h | NA | NA | NA | NA | NA |
| | 12-24h | NA | NA | NA | SMD -0.63 (-0.99; 0.26), 63 | NA |
| | 24-72h | NA | NA | NA | SMD -0.57 (-0.99; -0.14), 50 | NA |
| | 72h-2 sem | NA | NA | NA | SMD -0.16 (-0.41; 0.03), 2 | NA |
| | 2-4 sem | NA | NA | NA | SMD -0.24 (-0.53; 0.05), 0 | NA |
| | >1 mês | NA | NA | NA | SMD -0.21 (-0.58; 0.16), 3 | NA |
| Xiong, 2021 | | NA | NA | G 1.096 (0.576; 1.617), NA | NA | NA |
| Xu, 2016 | 1 dia | RR 2.6 (1.6; 4.4), NA | RR 5.2 (2.1; 12.9), NA | NA | NA | NA |
| | 7 dias | RR 3.43 (1.6; 7.1), NA | RR 2.6 (1.2; 5.7), NA | NA | NA | NA |
| Yuan, 2020 | Grupo 1[2] | OR 0.21 (1.68; 22.89), 0 | OR 6.68 (2.23; 20.01), 0 | NA | NA | NA |
| | Grupo 2[3] | OR 2.99 (1.58; 5.67), 26 | OR 3.28 (1.89; 5.68), 63 | NA | NA | NA |
| Newport, 2015 | | OR 9.87 (4.37; 22.29), 0 | NA | NA | NA | NA |
| Dias, 2022 | | NA | NA | NA | NA | NA |

Note: [1] Evaluation during different periods for some studies.; [2]Ketamine vs Antidepressants; [3]Ketamine vs Placebo; D: Cohen's D; G: Glass's Delta; I²: Measurement of heterogeneity; NA: Not assessed; OR: odds ratio RR: Rate Ratio; SMD: Standardized Mean Difference

**Table 3.** Safety outcome measures.

| Author, Year | Adverse Events RR or OR (95% CI) $I^2$ (%) | Serious Adverse Events RR or OR (95% CI) $I^2$ (%) | Discontinuation Due to Adverse Events RR or OR (95% CI) $I^2$ (%) |
|---|---|---|---|
| Bahji, 2021 | RR 1.87 (1.0271; 3.4076), 0 | NA | RR 0.96 (0.7234; 1.291), 40.5 |
| Bahji, 2022 | OR 2.14 (0.82; 5.60), 62 | NA | RR 1.56 (1.0; 2.45), <1 |
| Chen, 2023 | NA | NA | NA |
| Fond, 2014 | NA | NA | NA |
| Hochschild, 2021 | NA | NA | NA |
| Kishimoto, 2016 | NA | NA | NA |
| Lee, 2015 | NA | NA | NA |
| Levinta, 2022 | NA | NA | NA |
| Maguire, 2020 | NA | NA | NA |
| Marcantoni, 2020 | NA | NA | NA |
| McGirr, 2015 | NA | NA | OR 1.95 (0.86; 4.42), NA |
| Memon, 2020 | NA | NA | NA |
| Price, 2022 | NA | NA | NA |
| Romeo, 2015 | NA | NA | NA |
| Wilkinson, 2018 | NA | NA | NA |
| Witt, 2020 | NA | NA | NA |
| Xiong, 2021 | NA | NA | NA |
| Xu, 2016 | NA | NA | NA |
| Yuan, 2020 | NA | NA | NA |
| Newport, 2015 | NA | NA | NA |
| Dias, 2022 | NA | NA | NA |

Note: $I^2$: Measurement of heterogeneity; NA: Not assessed; OR: odds ratio RR: Rate Ratio;

**Table 4.** Methodological quality assessment.

| Author, Year | Q1[1] | Q2 | Q3 | Q4[1] | Q5 | Q6 | Q7[1] | Q8 | Q9[1] | Q10 | Q11[1] | Q12 | Q13[1] | Q14 | Q15[1] | Q16 | AG |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bahji, 2021 | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | M |
| Bahji, 2022 | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | M |
| Chen, 2023 | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | CB |
| Fond, 2014 | Yes | Yes | No | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | No | B |
| Hochschild, 2021 | Yes | Yes | Yes | No | No | No | No | Yes | Yes | Yes | NA | NA | Yes | NA | NA | Yes | CB |
| Kishimoto, 2016 | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | CB |
| Lee, 2015 | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | No | Yes | Yes | B |
| Levinta, 2022 | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | yes | Yes | NA | NA | No | NA | NA | Yes | CB |
| Maguire, 2020 | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | No | No | NA | NA | No | NA | NA | Yes | CB |
| Marcantoni, 2020 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | B |
| McGirr, 2015 | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | B |
| Memon, 2020 | No | Yes | No | Yes | Yes | Yes | No | Yes | Yes | Yes | NA | NA | Yes | NA | Yes | Yes | CB |
| Price, 2022 | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | B |
| Romeo, 2015 | No | Yes | Yes | Yes | Yes | Yes | No | Yes | No | No | Yes | No | No | No | Yes | No | CB |
| Wilkinson, 2018 | No | Yes | Yes | Yes | Yes | No | No | Yes | No | Yes | Yes | No | No | No | No | Yes | CB |
| Witt, 2020 | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | CB |
| Xiong, 2021 | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | CB |
| Xu, 2016 | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | CB |
| Yuan, 2020 | No | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | CB |
| Newport, 2015 | Yes | Yes | No | No | No | No | No | Yes | No | Yes | Yes | No | No | No | No | Yes | CB |
| Dias, 2022 | Yes | Yes | No | Yes | Yes | Yes | No | No | NA | Yes | NA | NA | No | NA | NA | Yes | CB |

Note: [1]Critical Issues; AG: Global Assessment; B: Low; CB: Critically Low; M: Moderate; NA: Not applicable. Q1: Did the research questions and inclusion criteria for the review include the components of PICO? Q2: Did the review report explicitly state that the review methods were established prior to conducting the review, and did the report justify any significant deviations from the protocol? Q3: Did the authors of the review explain the selection of study designs for inclusion in the review? Q4: Did the authors of the review use a comprehensive literature search strategy? Q5: Did the reviewers perform study selection in duplicate? Q6: Did the reviewers perform data extraction in duplicate? Q7: Did the authors of the review provide a list of excluded studies and justify the exclusions? Q8: Did the authors of the review describe the included studies with adequate detail? Q9: Did the authors of the review use a satisfactory technique to assess the risk of bias in individual studies included in the review? Q10: Did the authors of the review report the funding sources for the studies included in the review? Q11: If a meta-analysis was performed, did the authors of the review use appropriate methods for the statistical combination of results? Q12: If a meta-analysis was performed, did the authors of the review assess the potential impact of risk of bias in individual studies on the meta-analysis or other evidence synthesis results? Q13: Did the authors of the review consider the risk of bias in primary studies when interpreting/discussing the review results? Q14: Did the authors of the review provide a satisfactory explanation and discussion of any heterogeneity observed in the review results? Q15: If a quantitative synthesis was performed, did the authors of the review conduct an adequate investigation of publication bias (small-study bias) and discuss its likely impact on the review results? Q16: Did the authors of the review report any potential sources of conflict of interest, including any funding they received to conduct the review?

## Discussion

The present overview revealed that intravenous ketamine at doses ranging from 0.1 to 1 mg/kg demonstrated superior efficacy compared to the tested comparators for the treatment of refractory major unipolar depression. This superiority was particularly evident in terms of treatment response, remission rates, and improvements in depression scale scores. Although only a small proportion of systematic reviews explored the safety profile (n=3/21, 14.2%), intravenous ketamine was associated with similar rates of adverse reactions and treatment discontinuation compared to control groups in most cases.

The dosing regimens employed in the studies were largely homogeneous, with a single dose of 0.5 mg/kg being particularly notable. This dose was associated with a rapid reduction in depressive symptoms in patients resistant to conventional[18,19,31] treatment. Ketamine's effects were sustained for up to 72 hours[25] and, in some cases, extended for up to one week[32].

In the context[26] of suicidal ideation, ketamine was shown to be equivalent to intranasal esketamine, suggesting that both formulations may be effective. However, when compared to midazolam, a study without meta-analysis showed no superiority of ketamine in reducing suicidal ideation within 24 hours. Nonetheless, ketamine demonstrated significant improvement in symptoms after 48 hours, indicating its most pronounced effects occur shortly after administration[29]. Additionally, short-term benefits, including a marked reduction in suicidal ideation within the first three days post-administration, highlight ketamine's potential for rapid symptom alleviation. Further research is required to determine optimal dosing[29] intervals, especially for long-term efficacy in severe cases.

Patients exhibited good tolerability to ketamine, with only two cases of severe adverse events (suicidal ideation and bradycardia followed by hypotension) that did not lead to trial[33] discontinuation. Mild[18,27,28,32,33] adverse events included symptoms such as anxiety, blurred vision, dissociation, dizziness, headache, decreased appetite, nausea, and restlessness, most of which resolved within 80[17] to 90 minutes. Higher doses (1–2 mg/kg) were associated with prolonged emergence from anesthesia in over 10% of cases. Post-marketing data have also reported rare adverse events such as cholangitis[34], sialorrhea[34], laryngospasm[35], hypertension or hypotension[36], arrhythmias[36], dysuria[37], urinary urgency[37], and hallucinations[35]. Cardiovascular effects (e.g., bradycardia and hypotension) and psychiatric effects (e.g., agitation and irritability) were among the most frequently reported in studies on refractory depression, with resolution typically occurring within 90 minutes[38].

The included systematic reviews exhibited considerable heterogeneity, particularly regarding comparators, which ranged from medications of different classes (e.g., midazolam, propofol) to placebo or saline. However, ketamine is primarily considered an adjunct therapy to conventional antidepressants, providing an alternative for treatment-resistant cases[39,40]. Notably, patients randomized to placebo or saline groups were not excluded from receiving concurrent antidepressant therapy.

This evidence supports the role of intravenous ketamine as a valuable therapeutic option in managing refractory major unipolar depression, offering rapid and sustained antidepressant effects while being generally well-tolerated. However, further studies are warranted to optimize its long-term use and to address remaining uncertainties regarding its safety and efficacy.

Additionally, the instruments used for monitoring depression varied across studies, with the most common tools being the Montgomery-Åsberg Depression Rating Scale (MADRS)[41] and its adaptations, the Hamilton Depression Rating Scale (HDRS)[42] and its adaptations, the Modified Scale for Suicidal Ideations (MSSI)[43], the Columbia-Suicide Severity Rating Scale (C-SSRS)[44], the Beck Scale for Suicide Ideation (BSS)[45], the Beck Hopelessness Scale (BHS)[46], and the Mini-Mental Status Examination (MMSE)[47].

Another significant contributor to heterogeneity among the systematic reviews and the included primary studies was the lack of consensus in defining outcomes. For instance, Marcantoni et al., 2020 defined treatment response as a 50% reduction in depression scores from baseline, while Bahji et al., 2022 defined it as the percentage improvement in the MADRS score associated with ketamine's rapid effect (approximately one day post-infusion) without specifying the exact reduction rate.

In 2020, Lima et al. conducted a similar review, identifying comparable results. However, their study evaluated the efficacy and safety of all ketamine formulations (intravenous, oral, intranasal) for both unipolar and bipolar depression, rather than exclusively focusing on intravenous ketamine for unipolar depression. Lima et al. reinforced ketamine's efficacy alongside its tolerability. Despite broader eligibility criteria, their review included fewer studies (n=11) compared to the present overview. This review opted to focus solely on intravenous ketamine due to its greater accessibility in healthcare settings. Similar to the present findings, Lima et al. highlighted a scarcity of statistical data regarding adverse effects of intravenous ketamine, with most data relating to oral ketamine or esketamine. Moreover, the systematic reviews included in their study were predominantly rated as low or critically low quality using the AMSTAR-2 tool, mirroring the results of the present overview.

The quality of the included systematic reviews underscores the need for greater methodological rigor in the execution and reporting of studies. Researchers, reviewers, and journal editors must prioritize methodological standards to ensure reliability and inform clinical decision-making effectively. Similar shortcomings have been noted in other healthcare-related systematic reviews, which can compromise both the credibility of the findings and their practical applications[49-51].

This overview is not without limitations. Despite the systematic search strategy, some relevant records might not have been captured; however, manual searches did not identify additional studies. Significant heterogeneity was observed across the selected studies, alongside reduced methodological quality, highlighting the need for new primary and secondary research to provide more robust and definitive answers on this topic. Outcome definitions varied among studies due to the lack of standardization in the literature, complicating comparisons. Furthermore, the poor reporting of adverse events in many studies limits the ability to draw definitive conclusions regarding the safety of intravenous ketamine. Finally, the methodological limitations of the included studies within each systematic review caNot be overlooked. These findings underscore the importance of addressing these gaps in future research to strengthen the evidence base for the use of intravenous ketamine in treating refractory unipolar depression.

## Conclusion

The systematic reviews included in this overview generally revealed greater efficacy of intravenous ketamine for the treatment of major unipolar depression refractory to conventional treatment compared to the tested comparators, particularly in

terms of treatment response, remission rate, and improvement in depression scale scores, combined with a favorable safety profile. However, the clinical benefits observed were immediate or occurred within a few days after the drug infusion, highlighting the need for large, high-quality methodological trials to determine the optimal dosing interval to ensure prolonged effects with acceptable tolerability. Additionally, the low quality of the included studies demands cautious interpretation of the results and underscores the necessity of careful consideration in their evaluation.

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**Conflict of Interest Statement**

The authors declare no conflicts of interest.

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