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REVIEW ARTICLE

Short-term efficacy and safety of intravenous ketamine for major depressive disorder in adolescents: a systematic review and meta-analysis of randomized and open-label studies

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ABSTRACT

Background: Adolescent major depressive disorder (MDD) is associated with substantial impairment, suicide risk, and limited response to standard treatments. Intravenous ketamine has rapid antidepressant effects in adults, but pediatric evidence remains limited. This systematic review and meta-analysis evaluated the short-term efficacy and safety of intravenous ketamine for adolescents with MDD, including treatment-resistant depression (TRD).

Methods: This Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020-based review was registered in PROSPERO (CRD420251123304). PubMed, Web of Science, and Google Scholar were searched from inception to October 2025. Eligible studies included patients aged 18 years or younger treated with intravenous ketamine for MDD or TRD. Outcomes included changes in Montgomery–Åsberg Depression Rating Scale (MADRS), Children's Depression Rating Scale–Revised (CDRS-R), Children's Depression Inventory (CDI), and adverse events. Risk of bias (RoB) was assessed using RoB 2 and methodological index for non-randomized studies. Random-effects meta-analyses were performed where appropriate.

Results: Four prospective studies were included: two randomized controlled trials and two open-label studies, involving 77 adolescents. Intravenous ketamine was associated with significant reductions in depressive symptoms. Pooled MADRS scores decreased by 15.90 points [95% confidence interval (CI), -19.16 to -12.64; $p < 0.001$; $I^2 = 5.9\%$]. CDRS-R scores decreased by 21.17 points (95% CI, -29.11 to -13.24; $p < 0.001$; $I^2 = 0\%$), and CDI scores decreased by 6.55 points (95% CI, -11.78 to -1.31; $p = 0.01$; $I^2 = 0\%$). Improvements occurred within 2 hours and persisted up to 14 days in controlled studies. Adverse events were mild and transient, including dissociation, dizziness, nausea, headache, and brief hemodynamic changes. No serious adverse events were reported.

Conclusion: Intravenous ketamine may produce antidepressant effects in adolescents with MDD or TRD. Evidence remains limited by small samples, functional unblinding, open-label designs, and brief follow-up. Larger randomized trials with standardized suicidal ideation outcomes and longer safety monitoring are required before clinical adoption.

Keywords: Ketamine, pediatric depression, adolescent depression, treatment-resistant depression, systematic review, meta-analysis.

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Introduction

Major depressive disorder (MDD) in children and adolescents is a significant public health problem, affecting development, functioning, and safety. Depression during adolescence, when neurodevelopment, social demands, and identity are rapidly changing, can disrupt school performance, increase family conflict, and raise the risk of suicidal ideation and suicide attempts. Mental disorders affect many adolescents. Depression is a leading cause of illness and disability, and suicide is among the top causes of death in older adolescents and young adults [1].

Because this study was conducted in Saudi Arabia, the local and regional epidemiology is essential. The Saudi National Mental Health Survey found lifetime prevalence of suicidal ideation (4.9%), suicide planning (1.8%), and suicide attempts (1.5%), with 12-month rates of 1.8%, 0.9%, and 0.6% [2]. In the Middle East and North Africa (and Turkey), a recent meta-analysis reported a pooled prevalence of 25% for suicidal ideation and 12% for suicide attempts in people ≤25 years, noting heterogeneity and measurement differences [3]. These data support the need for interventions to reduce depressive burden and shorten acute suicide risk in adolescents.

Stigma around suicidal ideation and suicide attempts can significantly affect patient experiences and care quality, especially during crises like emergency department (ED) visits. Stigma includes public stigma (negative stereotypes), internalized stigma (self-stigma), and structural stigma (institutional) forms [4,5]. In EDs, stigma can make patients feel judged or dismissed, reducing engagement in psychosocial assessment and follow-up. Patient and caregiver accounts show that respectful, empathetic interactions are central to helpful encounters and future help-seeking [6]. Communication style also matters, as closed, yes/no questions about self-harm can limit disclosure and affect assessment and safety planning [7].

Healthcare providers may have unconscious biases, such as attribution bias (over-attributing suicidal behavior to intent), perceptions of manipulative or "attention-seeking" behavior, and emotional detachment from burnout in high-pressure ED settings. ED staff attitudes and team norms can shape responses to patients who self-harm, leading to varied care [8]. When these biases occur, especially under time pressure, they may narrow psychosocial assessment, weaken therapeutic alliance, and reduce patient disclosure, increasing the risk of missed warning signs and poorer safety planning [6,7].

Managing adolescent depression in practice is often more difficult than guidelines suggest. Psychotherapy and selective serotonin reuptake inhibitors (SSRIs) are first-line, but many adolescents have only a partial response or persistent symptoms. A large meta-analysis found most antidepressants have limited efficacy over placebo in this group, with fluoxetine showing the most consistent benefit [9]. Safety concerns add complexity. Meta-analyses show a modest increase in suicidality risk with antidepressants in pediatric patients, highlighting the need for careful monitoring and shared decision-making [10]. A clinically important subgroup does not respond to first-line treatment and has limited evidence-based alternatives [11].

Interest in ketamine has grown, especially when high-risk makes waiting for symptom improvement unsafe. Ketamine, originally a dissociative anesthetic, works through N-methyl-D-aspartate (NMDA) receptor antagonism, different from standard antidepressants. In adults, meta-analyses show rapid antidepressant effects within hours to days [12,13]; esketamine shows rapid reduction in depressive symptoms in severely ill adults with active suicidal ideation [14], and continuation strategies help prevent relapse in treatment-resistant patients [15]. A single ketamine dose can rapidly reduce suicidal ideation, with effects within 1 day and lasting up to a week in many trials [16].

On the contrary, evidence in adolescents is limited and heterogeneous. Few prospective studies have evaluated intravenous ketamine in adolescent depression, including randomized and open-label trials. A randomized midazolam-controlled trial found greater improvement in depressive symptoms at 24 hours with ketamine and no serious adverse events [17]. Another trial found short-term symptom improvement but noted challenges to blinding due to ketamine's psychoactive effects [18]. Open-label studies also report short-term reductions in depressive symptoms but are limited by small samples, lack of control groups, and short follow-up [19,20].

Preclinical studies support a biological basis for ketamine's rapid effects, showing NMDA receptor blockade can activate the mechanistic target of rapamycin (mTOR) pathway and promote synaptogenesis. Rapid antidepressant-like effects may depend on fast neuroplasticity mechanisms [21,22]. However, whether these mechanisms apply to adolescents, whose brains are still developing, remains uncertain.

Given the burden of adolescent depression, the urgency of suicidal crises, and limited first-line treatment response, careful synthesis is needed instead of extrapolating from adult data. A recent systematic review and meta-analysis of ketamine/esketamine in adolescents [four randomized controlled trials (RCTs), 272 adolescents] found no significant reduction in depressive symptoms at 24 hours versus placebo, but higher rates of suicidal ideation remission with ketamine [23]. This mixed result highlights the need for a focused review to distinguish supported findings from remaining uncertainties.

This review aims to synthesize evidence from randomized and open-label prospective studies of intravenous ketamine in adolescents with MDD, focusing on short-term changes in depressive symptoms, suicidal ideation, safety, and tolerability, to clarify evidence strength and identify priority gaps for future trials and longer follow-up.

Methods

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [24] and were prospectively registered in the PROSPERO database (ID: CRD420251123304).

A comprehensive literature search was performed in PubMed, Web of Science, and Google Scholar without date restrictions, including all studies published through October 2025. Only articles published in the English language were considered eligible. The search strategy incorporated both Medical Subject Headings and free-text terms, including "ketamine," "pediatric depression," "adolescent depression," "MDD," "treatment-resistant depression (TRD)," "intravenous ketamine," "psychopharmacology," "child psychiatry," "Montgomery–Åsberg Depression Rating Scale (MADRS)," "Children's Depression Rating Scale–Revised (CDRS-R)," "Children's Depression Inventory (CDI)," and "adverse events." Additional studies were identified through manual screening of reference lists, citation tracking, and searches of trial registries and dissertations. The detailed PubMed search strategy is provided in the Supplementary Material 1.

Eligibility criteria

The inclusion criteria were as follows: (a) studies enrolling children and adolescents (≤18 years) diagnosed with MDD or TRD using standardized diagnostic criteria; (b) studies evaluating intravenous ketamine at sub-anesthetic doses for the treatment of major depressive episodes; (c) studies including a comparator such as placebo, midazolam, usual or supportive care, or baseline symptoms in uncontrolled designs; and (d) outcomes of interest, including changes in depressive symptom severity measured with validated scales (such as the MADRS, CDRS-R, or CDI), remission rates, adverse events, cognitive outcomes, and quality of life. Eligible study designs included RCTs, cohort studies, case–control studies, open-label trials, and case series published in peer-reviewed journals, with no minimum sample size requirement.

The exclusion criteria were as follows: (a) studies involving adults (>18 years) or mixed populations where pediatric data could not be extracted separately, (b) studies not evaluating intravenous ketamine (e.g., oral, intranasal, or intramuscular administration, or studies exclusively evaluating esketamine without a ketamine arm), (c) studies not reporting relevant clinical outcomes related to depressive symptoms, suicidality, or safety, (d) non-original research articles, including narrative reviews, systematic reviews, meta-analyses, editorials, commentaries, and letters, (e) conference abstracts, posters, protocols, or unpublished data without accessible full text, (f) animal or *in vitro* studies, (g) duplicate publications or overlapping datasets (in which case the most comprehensive or recent dataset was included), and (h) studies not published in English.

Study selection

All records were imported into Rayyan (Rayyan Systems Inc., Qatar) for screening. Two reviewers independently screened titles, abstracts, and full texts against the inclusion criteria. Discrepancies were resolved through discussion or, if unresolved, by a third reviewer. The selection process is summarized in a PRISMA 2020 flow diagram [24].

Data extraction

Two reviewers independently extracted data using a standardized, pilot-tested form. Variables included study characteristics (author, year, country, and design), sample size, participant demographics, diagnostic criteria, and intervention details (formulation, dose, and route of administration). We also noted comparators; outcomes (MADRS, CDRS-R, CDI); response and remission rates; adverse events; follow-up; and funding or conflict-of-interest statements. For quantitative synthesis, we extracted pre- and post-treatment means, standard deviations, and group sample sizes.

Quality assessment

The risk of bias (RoB) was assessed according to study design: for RCTs, we used the Cochrane RoB 2 tool to evaluate randomization, deviations from intended interventions, missing data, outcome measurements, and selective reporting [25], while for non-randomized studies, we used the Methodological Index for Non-Randomized Studies (MINORS) tool [26]. Two reviewers independently assessed the studies, resolving disagreements by consensus or consulting a third reviewer if necessary. The overall certainty of evidence for each outcome was evaluated using the grading of recommendations assessment, development and evaluation (GRADE) approach [27], which considers study limitations, consistency, directness, precision, and publication bias.

Statistical analysis and meta-analysis

Continuous outcomes were analyzed as mean differences (MD) with 95% confidence intervals (CI). Pooled analyses used a random-effects model to account for variability between studies. We assessed heterogeneity using the χ^2 test and I^2 statistic, defining substantial heterogeneity as $I^2 > 50\%$ or χ^2 $p < 0.10$. Statistical significance was set at $p < 0.05$. Analyses were conducted using Stata/BE 18.5 (StataCorp, College Station, TX). Where possible, we planned subgroup analyses according to study design, age subgroup, and outcome measures. Sensitivity analyses were used to test robustness. When data pooling was not possible due to an insufficient number of studies, findings were described narratively.

Results

Literature findings

A total of 1,288 records were identified through a systematic search in PubMed ($n = 644$), Web of Science ($n = 445$), and Google Scholar ($n = 199$). After removing 269 duplicates, 1,019 records were screened by title and abstract. Of these, 860 were excluded, leaving 159 full-text reports for eligibility assessment. One hundred fifty-five were excluded (78 due to an ineligible study design, 45 ineligible population, 19 inaccessible full texts, 12 irrelevant outcomes, and 1 for another reason). Finally, four studies were included in this systematic review and meta-analysis: two RCTs and two open-label non-randomized studies. The study selection process is summarized in the PRISMA 2020 flowchart (Figure 1).

Characteristics of included studies

The four included studies enrolled a total of 77 participants aged 18 years or younger with MDD or TRD, all of whom received intravenous ketamine. Among the RCTs, Dwyer et al. [17] conducted a crossover (RCT comparing intravenous ketamine to midazolam in adolescents with TRD, finding a rapid and clinically meaningful reduction in depressive symptoms, with improvements persisting for up to 2 weeks in trials with longer follow-up. Macejova et al. [18] conducted a RCT in adolescent females with TRD, reporting clinically meaningful improvements in depressive severity compared to midazolam; however, blinding was a significant limitation. Regarding open-label studies, Cullen et al. [19] evaluated intravenous ketamine in adolescents with TRD and reported substantial symptom reduction during the short follow-up period. Kovacova et al. [20] conducted a small-scale open-label study showing symptomatic improvement following ketamine infusion but noted limitations due to small sample size and brief (2-hour) follow-up period. Collectively, these studies demonstrated the consistent short-term efficacy of ketamine across designs (Table 1).

Across all included studies, ketamine demonstrated a favorable tolerability profile. Reported adverse events

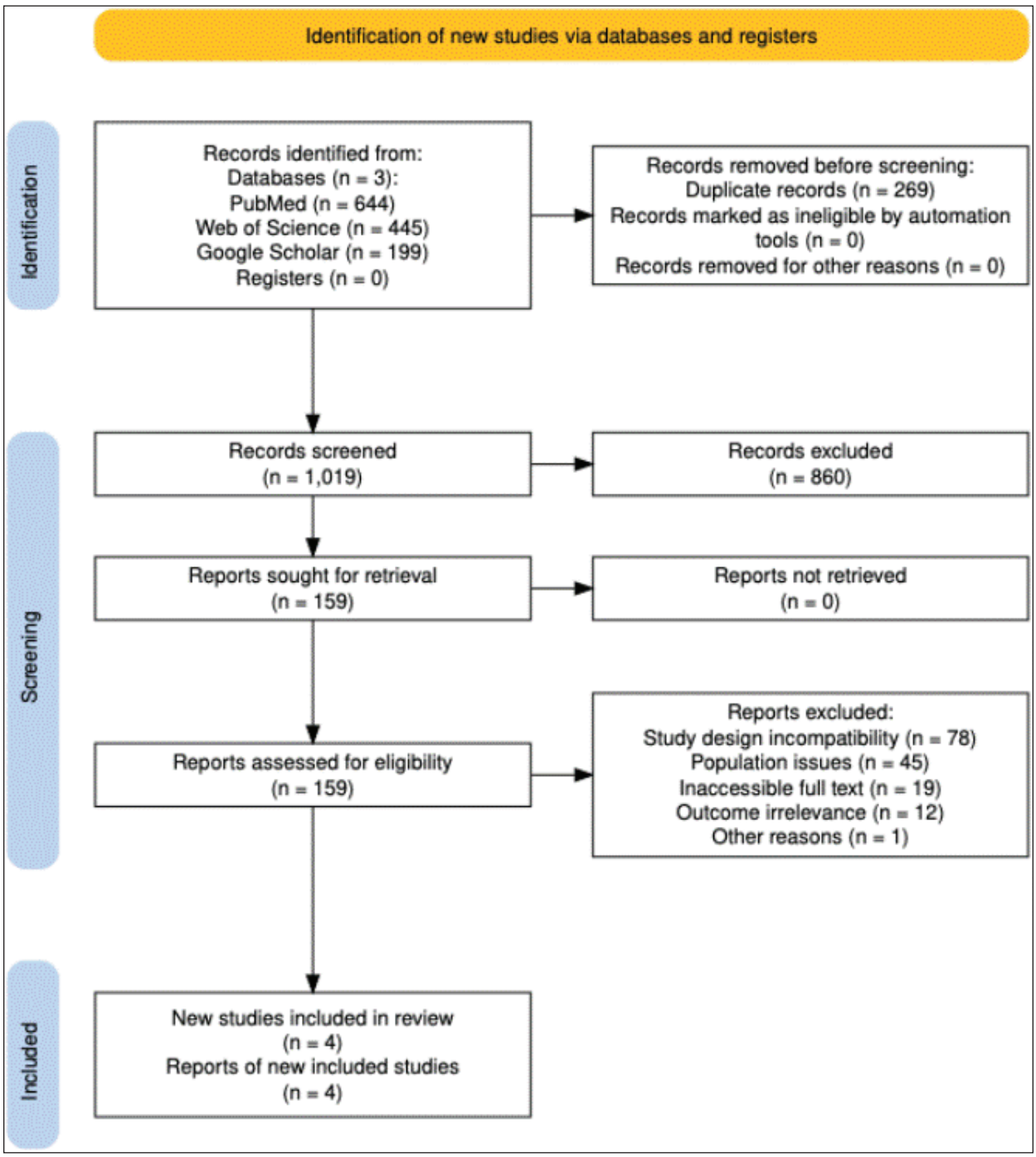

Figure 1. *PRISMA 2020 flow diagram of study selection.*

Table 1. *Characteristics of included studies.*

Study (Author, Year)	Country	Design	Population (*n*)	Intervention	Comparator	Primary outcomes	Follow-up	Key findings
Kovacova et al., 2024 [20]	Slovak Republic	Open-label	20	Intravenous ketamine	None	MADRS; CDI	2 hours	Symptomatic improvement noted; limited by short follow-up
Cullen et al., 2018 [19]	USA	Open-label	13	Intravenous ketamine	None	MADRS; CDRS-R	Post-treatment (1 day after final infusion)	Marked reduction in depressive severity; well tolerated
Macejova et al., 2024 [18]	Slovakia	RCT (parallel-group)	27	Intravenous ketamine	Midazolam	MADRS; CDI	1-2 weeks	Significant improvement versus midazolam; blinding challenges
Dwyer et al., 2021 [17]	USA	RCT (crossover)	17	Intravenous ketamine	Midazolam	MADRS; CDRS-R	Up to 14 days	Rapid and significant reduction versus midazolam; effect sustained to 14 days

MADRS, Montgomery–Åsberg Depression Rating Scale; **CDRS-R**, Children's Depression Rating Scale–Revised; **CDI**, Children's Depression Inventory; **RCT**, randomized controlled trial.

Table 2. *Intervention parameters and safety outcomes of included studies.*

Study (Author, Year)	Dose / route	Frequency / duration	Depression scales	Response / remission	Common adverse events	Serious adverse events
Kovacova et al., 2024 [20]	IV ketamine 0.5 mg/kg over 40 minutes	Single infusion; follow-up 2 hours	MADRS; CDI	Not reported (acute change only)	Transient dissociation, dizziness, mild blood pressure elevation	None reported
Cullen et al., 2018 [19]	IV ketamine 0.5 mg/kg over 40 minutes	Six infusions over 2 weeks	MADRS; CDRS-R	38% response (≥50% CDRS-R reduction); mean reduction 42.5%	Nausea, dizziness, transient dissociation	None reported
Macejova et al., 2024 [18]	IV ketamine 0.5 mg/kg over 40 minutes	Six infusions over 2 weeks (Days 1, 3, 5, 8, 10, 12); follow-up 2 and 24 hours	MADRS; CDI	33% at 2 hours; 59% at 24 hours versus 14% and 46% (midazolam)	Mild dissociation, headache, transient blood pressure changes	None reported
Dwyer et al., 2021 [17]	IV ketamine 0.5 mg/kg over 40 minutes	Two infusions (Days 0 and 14, crossover); follow-up to 14 days	MADRS; CDRS-R	77% response versus 35% (midazolam) within Days 1-3	Dissociation, nausea, dizziness, mild blood pressure increase	None reported

IV, intravenous; **MADRS**, Montgomery–Åsberg Depression Rating Scale; **CDRS-R**, Children's Depression Rating Scale–Revised; **CDI**, Children's Depression Inventory.

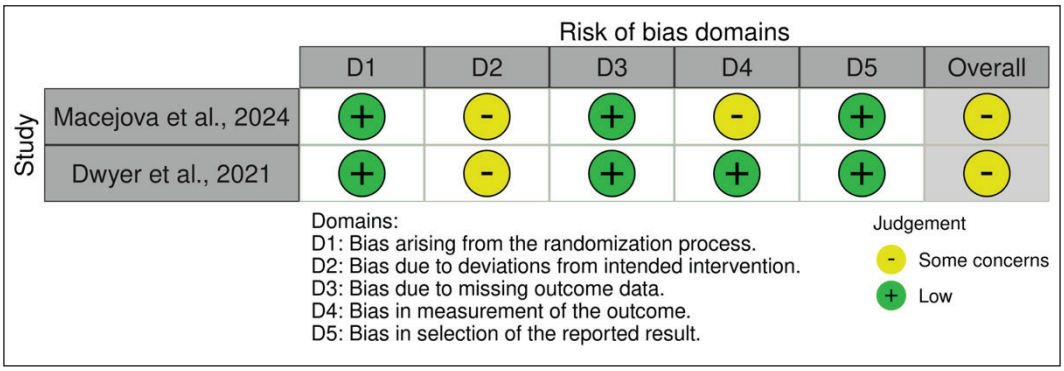

Figure 2. *RoB assessment using the cochrane RoB 2 tool.*

included transient dissociation, dizziness, and mild hemodynamic changes, all of which were self-limited. No serious adverse events or discontinuations were documented (Table 2).

RoB assessment

RCTs: The RoB was assessed using the Cochrane RoB 2 tool. Both RCTs were rated as having some concerns. Randomization and outcome reporting were adequate, but both trials experienced difficulties with blinding. In Dwyer et al. [17], functional unblinding was noted due to ketamine's psychoactive effects, while Macejova et al. [18] provided insufficient details regarding blinding procedures. The RoB assessment for the two RCTs was conducted using the Cochrane RoB 2 tool (Figure 2).

Non-randomized studies: The two open-label studies were assessed using the MINORS tool, yielding scores of 11-12 out of 16, consistent with moderate

Table 3. *MINORS quality assessment for non-randomized studies.*

Study ID	D1: Aim	D2: Consecutive	D3: Prospective	D4: Endpoints	D5: Unbiased	D6: Follow-up	D7: <5% Loss	D8: Sample Size	D1: Aim	Total (Max 16)	RoB
Cullen et al. [19]	Prospective open-label, non-randomized	2	1	2	2	1	2	2	0	12/16	Moderate risk (open-label, no control, no sample size calculation)
Kovacova et al. [20]	Prospective open-label, non-randomized	2	1	2	2	1	1	2	0	11/16	Moderate–high risk (short follow-up, no blinding, no sample size calculation)

D, domain; **MINORS**, Methodological Index for Non-Randomized Studies.

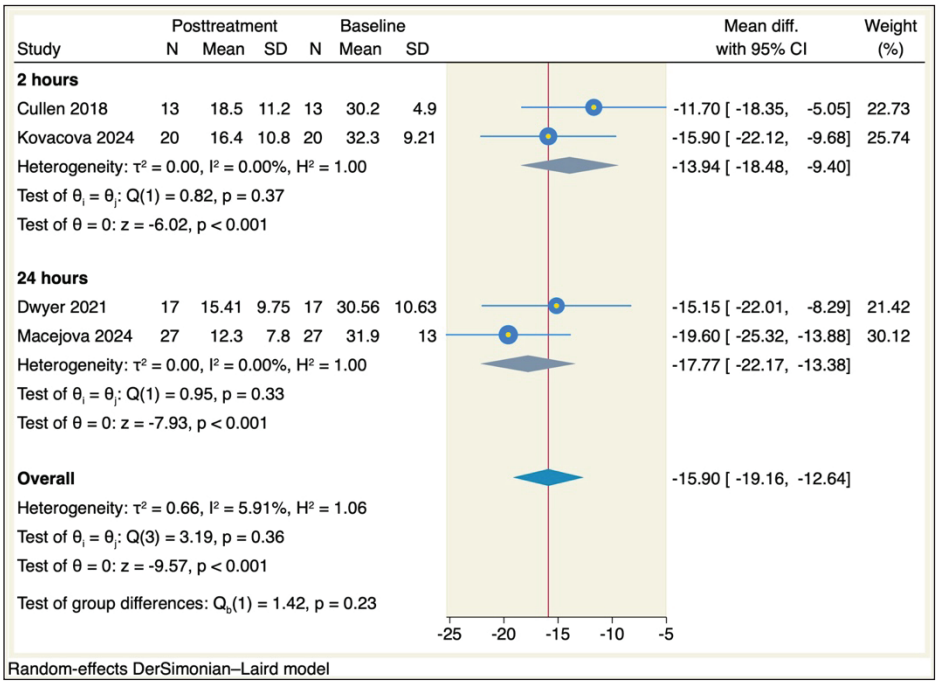

Figure 3. *Forest plot of change in MADRS scores following ketamine treatment CDRS-R.*

methodological quality. Strengths included prospective data collection and relevant outcomes, but both studies lacked blinding, sample size calculation, and adequate follow-up. Kovacova et al. [20] were particularly limited by a very short observation duration (Table 3).

Quantitative synthesis

Montgomery–Åsberg Depression Rating Scale

All four studies (n = 77) reported baseline and post-treatment MADRS scores. Pooled MADRS scores declined after ketamine administration (MD = -15.90, 95% CI [-19.16 to -12.64], p < 0.001). Statistical heterogeneity was low and nonsignificant (I^2 = 5.9%, p = 0.36). Subgroup analysis confirmed consistent improvement across time points, with significant reductions observed at 2 hours (MD = -13.94, 95% CI [-18.48 to -9.40], p < 0.001) and 24 hours (MD = -17.77, 95% CI [-22.17 to -13.38], p < 0.001), and no evidence of subgroup heterogeneity (p = 0.23). The pooled effect is illustrated in Figure 3.

Two studies reported outcomes using the CDRS-R. CDRS-R scores also decreased after ketamine infusion compared with baseline (MD = -21.17, 95% CI [-29.11 to -13.24], p < 0.001). No heterogeneity was detected (I^2 = 0%, p = 0.72). The pooled effect is shown in Figure 4.

Children's depression inventory

Two studies assessed depressive symptoms using the CDI. Ketamine treatment resulted in a significant reduction in CDI scores compared with baseline (MD = -6.55, 95% CI [-11.78 to -1.31], p = 0.01). The studies were homogeneous (I^2 = 0%, p = 0.37). The pooled effect is shown in Figure 5.

A summary of the certainty of evidence for each outcome, assessed using the GRADE approach, is provided in Supplementary Material 2. The evaluation showed that the evidence supporting intravenous ketamine infusion

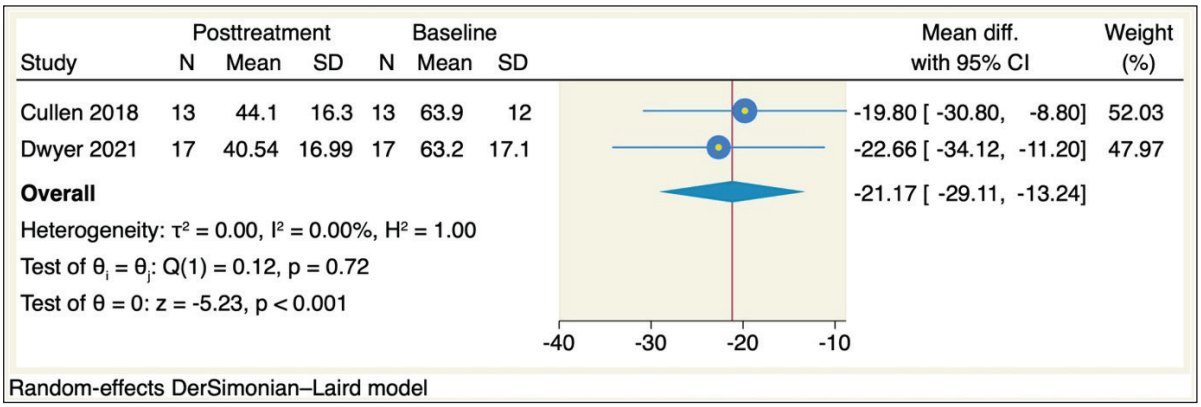

Figure 4. *Forest plot of change in CDRS-R scores.*

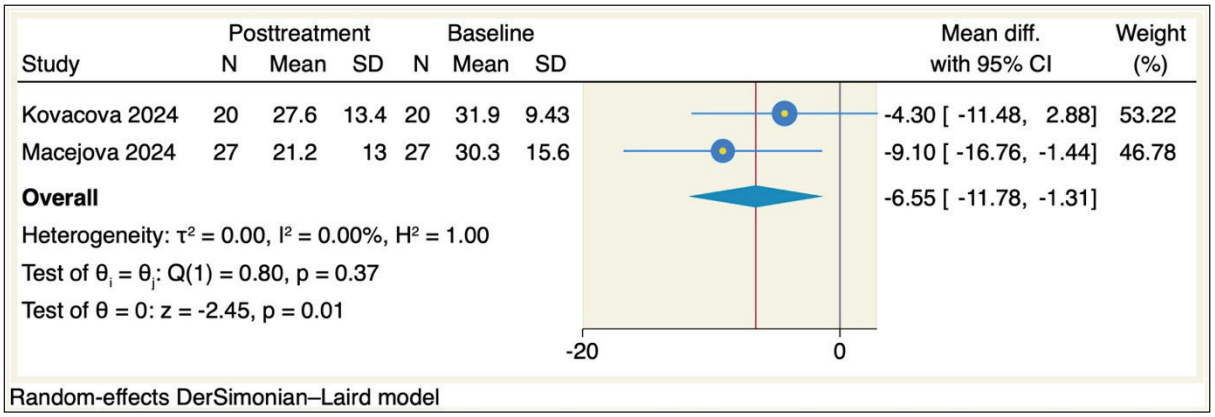

Figure 5. *Forest plot of change in CDI scores.*

in children and adolescents with MDD ranged from moderate to very low certainty. For the MADRS, scores decreased by an average of 13.94 points at 2 hours and 17.77 points at 24 hours after infusion, corresponding to very low and moderate certainty, respectively. The CDRS-R findings demonstrated mean reductions of 22.66 points in randomized data (moderate certainty) and 19.8 points in non-randomized data (very low certainty). For the CDI, the decrease was 9.1 points in randomized evidence (moderate certainty) and 4.3 points in non-randomized evidence (very low certainty). Overall, the results indicate a consistent short-term improvement in depressive symptoms across all scales, though confidence in these estimates remains limited by the small sample sizes, open-label study designs, and brief follow-up periods in the included trials.

Discussion

This systematic review and meta-analysis of four prospective studies, two RCTs, and two open-label trials, enrolling 77 adolescents with MDD or TRD, found that intravenous ketamine at 0.5 mg/kg produced rapid, statistically significant, and clinically meaningful reductions in depressive symptom severity across all three validated rating scales. The pooled MADRS declined by 15.90 points (95% CI -19.16 to -12.64; $p < 0.001$; $I^2 = 5.9\%$), the CDRS-R by 21.17 points (95% CI -29.11 to -13.24; $p < 0.001$; $I^2 = 0\%$), and the CDI by 6.55 points (95% CI -11.78 to -1.31; $p = 0.01$; $I^2 = 0\%$). Symptom reductions were detectable within 2 hours and persisted for 14 days in the controlled trials. No serious adverse events were recorded across any included study.

The direction and magnitude of these effects stretch beyond merely replicating what the Introduction established for adult populations. While adult meta-analyses have confirmed rapid antidepressant responses within hours [12,13] and antisuicidal effects lasting up to 1 week [16], the present results show that comparable short-term reductions are achievable in adolescents, a population for whom such data have largely been absent. Critically, the 77% response rate within 1–3 days in the Dwyer et al. [17] RCT substantially exceeded the midazolam comparator rate of 35%, providing controlled evidence that this effect is not attributable solely to non-specific infusion factors or natural symptom fluctuation.

The most recent adolescent-specific meta-analysis by Magalhães et al. [23], noted in the Introduction as reporting no significant symptom reduction at 24 hours versus placebo across four RCTs, appears to diverge from the present findings. This difference is methodological rather than substantive: Magalhães et al. [23] measured ketamine's advantage over an active comparator, whereas the present analysis quantified absolute within-group change across all study designs, including open-label data. The two analyses are, therefore, complementary; together, they indicate that ketamine produces meaningful

absolute symptom reduction, but that the net advantage over an active control such as midazolam, while present, is more modest than open-label estimates alone would suggest. Heterogeneity in the present pooled MADRS analysis was low (I^2 = 5.9%), indicating concordance across the four studies despite design variation.

The mTOR-mediated synaptogenesis mechanism introduced in the background [21,22] provides a plausible biological basis for the 2-hour onset observed here, but whether this pathway operates identically in the still-developing adolescent brain cannot be inferred solely from the clinical data. None of the included studies collected neuroimaging or biomarker data, a gap that the present review cannot resolve.

The 2-hour onset documented here is particularly relevant to ED settings, where clinicians face the gap between the acute need for symptom reduction in acutely suicidal adolescents and the 2-to-4-week latency of standard SSRI therapy, a class already shown to carry limited success in this age group [9] and a modest increase in pediatric suicidality risk [10]. Ketamine's acute tolerability profile, with no serious adverse events registered across all included studies, is reassuring in this context. However, any ED implementation must account for the organizational factors identified in the Introduction: stigma, attribution bias, and closed-questioning styles that reduce patient disclosure and undermine psychosocial assessment [6-8]. A pharmacological protocol alone is insufficient; it must be embedded within a care framework that addresses these communication and attitudinal barriers.

Strengths and limitations

This review was prospectively registered on PROSPERO (CRD420251123304) and conducted in full accordance with PRISMA 2020 guidelines [24], with pre-specified tools for RoB assessment, the Cochrane RoB 2 for RCTs [25], and the MINORS instrument for non-randomized studies [26], and GRADE evidence grading [27]. The low heterogeneity across all three pooled analyses and the consistency of direction across study designs and rating scales strengthen confidence in the finding. Nonetheless, the total sample of 77 participants is small, limiting statistical power and external validity. Both RCTs received 'some concerns' on the Cochrane RoB 2 tool, primarily because ketamine's prominent dissociative effects render complete blinding impractical, potentially inflating self-reported outcomes. GRADE certainty ranged from moderate for RCT-derived outcomes at 24 hours to very low for non-randomized and 2-hour data. The CDI confidence interval for non-randomized evidence crossed the null (-11.48 to +2.88), suggesting uncertainty in that subgroup. Follow-up did not exceed 14 days in any study, precluding conclusions about the durability of effect, relapse, or long-term safety. No included study reported suicidal ideation outcomes in a format amenable to meta-analysis, and none were conducted in the Middle East or North Africa, limiting relevance to the Saudi and regional context despite the documented burden of adolescent suicidality in the region [2,3].

Priority areas for future research include: adequately powered double-blind RCTs with extended follow-up of at least 4 to 8 weeks; standardized suicidal ideation endpoints (e.g., the Columbia Suicide Severity Rating Scale) reported in formats appropriate for meta-analysis; adolescent-specific dose-finding studies, as all included trials used the adult-derived 0.5-mg/kg protocol without pharmacokinetic optimization for this age group; and trials conducted in under-represented regions including the Middle East and North Africa, where the burden of adolescent depression and suicidality is documented but no regional trial evidence exists.

Conclusion

Pooled analysis of four prospective studies enrolling 77 adolescents with MDD or TRD demonstrated that intravenous ketamine at 0.5 mg/kg produced consistent, statistically significant, and clinically meaningful short-term reductions in depressive symptom severity. MADRS scores declined by a mean of 13.94 points at 2 hours and 17.77 points at 24 hours post-infusion; CDRS-R scores declined by a mean of 21.17 points; and CDI scores declined by a mean of 6.55 points. A response rate of 77% within 1-3 days was observed in the largest RCT, compared with 35% for the active comparator. No serious adverse events were documented in any included study, and transient dissociative and hemodynamic effects resolved spontaneously in all cases.

The certainty of evidence ranged from moderate for randomized outcomes at 24 hours to very low for non-randomized and acute data, reflecting the small aggregate sample, risk of functional unblinding, and very brief follow-up periods. These findings support cautious optimism regarding ketamine's short-term antidepressant efficacy in adolescents with TRD, but not definitive clinical adoption. Larger, adequately powered RCTs incorporating suicidal ideation as a primary outcome, extended follow-up, and representation from diverse global regions are required before intravenous ketamine can be recommended as a standard intervention in this population.

List of Abbreviations

CDI	Children's depression inventory
CDRS-R	Children's Depression Rating Scale–Revised
CI	Confidence interval
ED	Emergency department
GRADE	Grading of Recommendations Assessment, Development and Evaluation; IV, intravenous
MADRS	Montgomery–Åsberg Depression Rating Scale
MDD	Major depressive disorder
MD	Mean difference
MINORS	Methodological Index for Non-Randomized Studies; mTOR, mechanistic target of rapamycin
NMDA	N-methyl-D-aspartate
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomized controlled trial

RoB 2	Risk of Bias 2 tool
SSRI	Selective serotonin reuptake inhibitor
TRD	Treatment-resistant depression.

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Conflict of interest
The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Ethical approval
This systematic review and meta-analysis are based entirely on previously published studies. No new patient data were collected; therefore, no ethical approval or patient consent was required.

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Supplementary content (If any) is available online.

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