Systematic Review

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The Era of Rapid-Acting Antidepressants: Clinical Insights Into Ketamine, Esketamine, and Scopolamine

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Background: Treatment-resistant depression (TRD) represents a major clinical challenge, being associated with high morbidity, increased suicide risk, and substantial socioeconomic burden. The need for rapidly acting interventions has driven the development of rapid-acting antidepressants (RAADs), such as ketamine, esketamine, and scopolamine. This study aimed to systematically review the efficacy, safety, and clinical applicability of these agents in TRD.

Methods: Systematic review conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Searches were performed in PubMed/MEDLINE, Embase, Cochrane Library, and Scopus, including randomized clinical trials (RCTs) published between January 2000 and September 2025. Randomized clinical trials involving adults with TRD were included. The scopolamine trials enrolled patients with depressive disorders and were not restricted to protocol-defined TRD. Risk of bias was assessed using the Cochrane RoB 2 tool. The screening and data extraction processes were independently performed by two reviewers, with disagreements resolved by consensus or consultation with a third reviewer.

Results: Seven clinical trials were included (2 ketamine, 3 esketamine, 2 scopolamine). Intravenous ketamine (0.5 mg/kg over 40 minutes) demonstrated onset of effect at approximately 110 minutes, with response rates up to 70% at 24 hours, although with limited duration (1–2 weeks). Intranasal esketamine (56 mg or 84 mg twice weekly), combined with oral antidepressants such as escitalopram, sertraline, duloxetine, or venlafaxine extended release (XR), significantly reduced Montgomery–Åsberg Depression Rating Scale (MADRS) scores over four weeks and lowered relapse risk (hazard ratio [HR] = 0.49). Intravenous scopolamine (4 µg/kg) showed effects within 1–3 days but with less consistency in larger samples.

Conclusion: RAADs provide rapid antidepressant responses in TRD. Evidence is more consistent for acute intravenous ketamine use and for maintenance treatment with intranasal esketamine. Intravenous ketamine demonstrated the fastest onset of action, whereas esketamine presented stronger evidence for long-term maintenance and relapse prevention. Scopolamine remains experimental.

Keywords: treatment-resistant depressive disorder; ketamine; esketamine; scopolamine; antidepressants

Introduction

Major depressive disorder (MDD) is a highly prevalent psychiatric condition, affecting more than 280 million people worldwide and representing one of the leading causes of disability according to global estimates [1]. Although conventional antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), are widely used, their effectiveness remains limited, with approximately 30% to 40% of patients failing to achieve adequate remission even after multiple therapeutic trials [2]. Furthermore, these medications exhibit significant therapeutic latency, often requiring several weeks to produce clinical response, which contributes to an increased risk of suicide during the early phases of treatment [3]. This combination of insufficient response and delayed clinical improvement has driven the search for innovative interventions capable of providing rapid and sustained relief from depressive symptoms.

In recent years, the traditional neurobiological paradigm of depression, primarily based on monoaminergic dysfunction, has been expanded by evidence highlighting alterations in synaptic plasticity, glutamatergic signaling, and functional connectivity within cortico-limbic circuits [4,5]. In this context, ketamine, a noncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonist, emerged as the first agent to demonstrate rapid antidepressant effects, with responses observed within hours after subanesthetic administration [6]. These findings stimulated the investigation of other rapid-acting antidepressant classes, including esketamine, the S-enantiomer of ketamine developed for intranasal administration, and scopolamine, a muscarinic antagonist that also exhibits synaptic modulatory properties [7,8]. These agents, collectively known as rapid-acting antidepressants (RAADs), challenge the classical view of depression treatment and have the potential to transform clinical practice, particularly in emergency settings such as acute suicidal ideation.

Esketamine received approval from the U.S. Food and Drug Administration (FDA) in 2019 for the treatment of treatment-resistant depression (TRD), based on robust evidence from multicenter clinical trials demonstrating significant efficacy when combined with oral antidepressants, as well as reduced relapse risk in maintenance regimens [9,10]. In contrast, scopolamine remains experimental; however, early studies suggest rapid reductions in depressive symptoms following short-interval intravenous administration [11]. Nevertheless, the integration of these therapies into clinical practice requires a comprehensive understanding of their efficacy, safety, administration protocols, and adverse effects, as well as direct comparisons of outcomes across different clinical contexts.

Given the growing importance of RAADs in the management of treatment-resistant depression, this study aims to systematically review the available scientific literature on ketamine, esketamine, and scopolamine, summarizing findings from key clinical trials, including methodological characteristics, primary and secondary outcomes, safety profiles, and limitations. The goal is to provide a critical and comparative analysis to assist mental health professionals in therapeutic decision-making and to identify gaps for future research.

Methods

This review was conducted following the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [12], aiming to ensure transparency, reproducibility, and methodological rigor. A systematic literature search was performed in the PubMed/MEDLINE, Embase, Cochrane Library, and Scopus databases, covering articles published between January 2000 and September 2025. Controlled MeSH (Medical Subject Headings) descriptors and free-text terms related to the main topics were used, including “ketamine”, “esketamine”, “scopolamine”, “treatment-resistant depression”, “rapid-acting antidepressants”, and “major depressive disorder”. Search strategies were adapted for each database using Boolean operators such as AND, OR, and NOT. Gray literature was not included. The complete search strategies for each database are provided in the **Supplementary Material**. The **PRISMA 2020 checklist** is provided as a separate supplementary file.

Eligibility Criteria

Randomized clinical trials involving adults (≥18 years) diagnosed with MDD or TRD were included. TRD was defined as failure to respond to at least two antidepressants administered at adequate dose and duration. Nonrandomized studies, case series, reviews, and anesthetic use without depressive outcomes were excluded. Studies evaluating alternative routes of ketamine administration (e.g., intramuscular, buccal, or sublingual) were excluded to reduce excessive methodological and clinical heterogeneity and to focus on the routes with the strongest regulatory and clinical evidence in TRD.

The screening process was conducted in two stages by two independent reviewers. Initially, titles and abstracts were assessed for eligibility, followed by full-text evaluation of selected studies. Disagreements between reviewers during study selection and risk-of-bias assessment were resolved through discussion and consensus, with consultation of a third reviewer when necessary.

Risk of Bias Assessment

Risk of bias was independently evaluated by two reviewers using the Cochrane RoB 2 tool, covering the following domains:

D1: randomization process.
D2: deviations from intended interventions.
D3: missing outcome data.
D4: outcome measurement.
D5: selective reporting.

The overall judgment followed the algorithm recommended by the tool.

Data Synthesis

Results were synthesized narratively. A meta-analysis was not performed due to substantial clinical and methodological heterogeneity among studies, including differences in study design, sample characteristics, routes of administration, dosing regimens, concomitant antidepressant therapies, outcome measures, and follow-up duration. Although random-effects models were considered, the degree of heterogeneity was judged sufficiently high to compromise the interpretability and validity of pooled estimates.

Data were organized into comparative tables and summarized narratively. Interpretation of the results was guided not only by statistical magnitude but also by clinical relevance and applicability to real-world psychiatric practice.

Results

Study Selection and Characteristics

The systematic search identified 347 records across the consulted databases. After removal of 89 duplicates, 258 titles and abstracts were screened for eligibility. Of these, 32 articles underwent full-text assessment, resulting in the final inclusion of seven randomized clinical trials that met the inclusion criteria (Table 1, Ref. [6,7,8,9,10,11,13]): two involving intravenous ketamine, three involving intranasal esketamine, and two involving intravenous scopolamine. Reasons for exclusion included nonrandomized design, absence of treatment-resistant depression criteria, anesthetic use without antidepressant outcomes, and insufficient clinical outcome reporting. The scopolamine trials enrolled patients with depressive disorders and were not restricted to protocol-defined TRD. The included studies comprised a total of 1332 participants (range: 18–676 per study), with a predominance of female participants (61–70% across all studies).

Table 1. Main clinical studies with ketamine, esketamine, and scopolamine in the treatment of treatment-resistant depression.

Drug	Author (Year) ref	Country/ Centers	Population	Total N	Sex (%F)	Design	Dose/ Route	Frequency/ Duration	Cointervention	Primary outcome	Outcome timepoint	Response/ Remission	Duration of effect	Common adverse events
Ketamine (IV)	Zarate et al. (2006) [6]	USA, single center (NIMH)	Drug-free TRD	18	61% F	Double-blind, crossover, placebo-controlled	0.5 mg/kg IV over 40 min	Single dose, 1-week crossover	None	HDRS-21	110 min and days 1–7	Response ≈70% at 24 h; transient partial remission	~7 days without maintenance	Mild dissociation, dizziness, transient BP elevation
Ketamine (IV)	Murrough et al. (2013) [7]	USA, multicenter (2 sites)	TRD (resistant MDD)	73	65% F	Double-blind, parallel, active control (midazolam)	0.5 mg/kg IV over 40 min	Single dose	None	MADRS (24 h)	24 hours	Response 64% vs 28% (ketamine vs midazolam)	Effect attenuates without maintenance	Dissociation, nausea, dizziness
Esketamine (IN)	Popova et al. (2019) [9]	Multicenter, international	TRD, failure ≥2 ADs	227	66% F	Double-blind, parallel	56 or 84 mg intranasal (flexible)	Twice weekly for 4 weeks	New oral AD (escitalopram, sertraline, venlafaxine XR, or duloxetine)	MADRS change (day 28)	Week 4	Mean difference ≈ –4 points vs placebo	Maintained with continued use	Dissociation, nausea, vertigo, dysgeusia, transient BP elevation
Esketamine (IN)	Daly et al. (2019) [10]	Multicenter, international	TRD stabilized after induction	297	68% F	Randomized withdrawal	56 or 84 mg intranasal	Maintenance phase (weekly/biweekly)	Oral AD maintained	Time to relapse	During maintenance	Relapse HR = 0.49 (continuation vs withdrawal)	Reduced relapse while on treatment	Typical monitored events, no new safety signals
Esketamine (IN)	Vieta et al. (2025) [13]	Europe and Latin America	TRD vs quetiapine XR	676	64% F	Open-label, randomized, rater-blinded	56 or 84 mg intranasal	Up to 32 weeks	Concomitant oral AD	Functionality and productivity	32 weeks	Better occupational performance vs quetiapine XR	Sustained long-term benefit	Transient dissociation, dizziness, nausea
Scopolamine (IV)	Furey and Drevets (2006) [8]	USA, NIMH	Recurrent MDD or bipolar disorder	19	68% F	Double-blind, crossover, placebo-controlled	4 µg/kg IV	3 infusions, 3–5-day interval	None	MADRS and HARS	1–3 days after infusion	Rapid and significant symptom reduction	Days to a few weeks	Somnolence, dry mouth, dizziness
Scopolamine (IV)	Drevets and Furey (2010) [11]	USA, NIMH	MDD	22	70% F	Double-blind, crossover, placebo-controlled	4 µg/kg IV	3 infusions, 3–5-day interval	None	MADRS	1–3 days	≈30% MADRS reduction after first block	Days to a few weeks	Somnolence, dry mouth, mild hypotension

Abbreviations: TRD, Treatment-Resistant Depression; MDD, Major Depressive Disorder; NIMH, National Institute of Mental Health; AD, antidepressant; MADRS, Montgomery–Åsberg Depression Rating Scale; HDRS, Hamilton Depression Rating Scale; HR, hazard ratio; XR, extended release; BP, blood pressure.

Regarding methodological design, five studies were double-blind placebo-controlled, one used an active comparator (midazolam), and one was an open-label randomized trial with blinded raters. All studies were published between 2006 and 2025, with a greater concentration of robust evidence emerging in the past decade. Table 1 summarizes methodological characteristics, administration protocols, primary outcomes, and safety profiles of the included trials.

The study selection process is summarized in Fig. 1.

Risk of Bias Assessment

Evaluation using the RoB 2 tool revealed low risk of bias in the domains of randomization (D1) and deviations from intended interventions (D2) across most studies. The domain most frequently rated as "some concerns" was missing outcome data (D3), reflecting incomplete reporting of attrition and adherence.

The ESCAPE-TRD study was classified as having high overall risk of bias due to its open-label design with potential influence from deviations from intended interventions. Fig. 2 presents the graphical summary of the risk-of-bias assessment.

The included trials converge on the concept of rapid-acting antidepressants capable of inducing clinical improvement within hours to a few days, with peak effects during the first week and maintenance dependent on continued treatment regimens when available. In treatment-resistant depression, intravenous ketamine (0.5 mg/kg over 40 min) demonstrated clear superiority over placebo and active comparator in 24-hour outcomes; intranasal esketamine (56 mg or 84 mg) added to a new oral antidepressant achieved additional symptom reduction over four weeks and reduced relapse risk during maintenance; intravenous scopolamine (4 µg/kg) produced rapid decreases in depressive scores in proof-of-concept crossover studies. Overall, adverse events were transient and predictable (e.g., dissociation and transient blood pressure elevation with glutamatergic agents; anticholinergic effects with scopolamine), requiring supervised administration and post-dose monitoring.

Efficacy of Intravenous Ketamine

Zarate et al. (2006) [6] conducted a seminal study evaluating ketamine in TRD using a double-blind crossover design involving 18 antidepressant-free patients. A single infusion of 0.5 mg/kg over 40 minutes resulted in significant reductions in HDRS-21 scores as early as 110 minutes, with effects maintained for up to 7 days. The response rate (defined as ≥50% reduction in scores) reached 71% (12/17 evaluable patients) at 24 hours compared with 0% in the placebo group ($p < 0.001$). Full remission (HDRS-21 ≤7) occurred in 29% of patients at 24 hours but was transient.

Murrough et al. (2013) [7], in a multicenter study including 73 patients, confirmed the superiority of ketamine over an active control (midazolam). Response at 24 hours was 64% (23/36) in the ketamine group versus 28% (10/37) in the midazolam group (odds ratio = 3.86; 95% CI: 1.39–10.7; $p = 0.01$). The magnitude of antidepressant effect, measured by mean reduction in MADRS scores, was –7.95 points in the ketamine group versus –3.59 in controls (difference: –4.36; 95% CI: –7.24 to –1.48; $p = 0.003$). The effect gradually attenuated after day 3 without maintenance therapy.

Efficacy of Intranasal Esketamine

Popova et al. (2019) [9], in the TRANSFORM-2 study, evaluated 227 patients with TRD who had failed at least two antidepressants. Intranasal esketamine (56 or 84 mg, flexible dosing, twice weekly) combined with a new oral antidepressant demonstrated superiority over intranasal placebo plus oral antidepressant. The mean difference in MADRS scores at day 28 was –4.0 points (95% CI: –7.31 to –0.64; $p = 0.020$), with detectable effects as early as 24 hours (–3.2 points; $p = 0.015$).

Daly et al. (2019) [10], in the SUSTAIN-1 trial, investigated relapse prevention in 297 patients who had responded to the induction phase with esketamine. After 16 weeks of stabilization, participants were randomized to continue esketamine (weekly or biweekly) or discontinue treatment. The hazard ratio for relapse was 0.49 (95% CI: 0.29–0.84; $p = 0.003$), indicating a 51% reduction in relapse risk with continued esketamine treatment.

Vieta et al. (2025) [13], in the ESCAPE-TRD study including 676 patients, demonstrated that intranasal esketamine plus oral antidepressant resulted in improved occupational functioning and productivity over 32 weeks compared with quetiapine XR plus oral antidepressant. Although detailed quantitative analyses are ongoing, the study highlighted sustained functional benefits beyond symptomatic improvement.

In the TRANSFORM studies, esketamine showed significant MADRS reductions by day 28, with improvements detectable within the first 24–48 hours. SUSTAIN-1 demonstrated reduced relapse risk during maintenance treatment [9,10].

Efficacy of Intravenous Scopolamine

Furey and Drevets (2006) [8] evaluated 19 patients with MDD or anxiety disorders with depressive symptoms in a double-blind crossover study. Intravenous scopolamine (4 µg/kg) administered in three infusions at 3–5-day intervals produced rapid and significant reductions in MADRS and HARS scores, with effects detectable within 1–3 days after the first infusion. The duration of effect ranged from several days to a few weeks.

Drevets and Furey (2010) [11] partially replicated these findings in 22 patients with MDD. Mean MADRS reductions were approximately 30% after the first infusion block. However, heterogeneity of results and small sample sizes limit the generalizability of these findings.

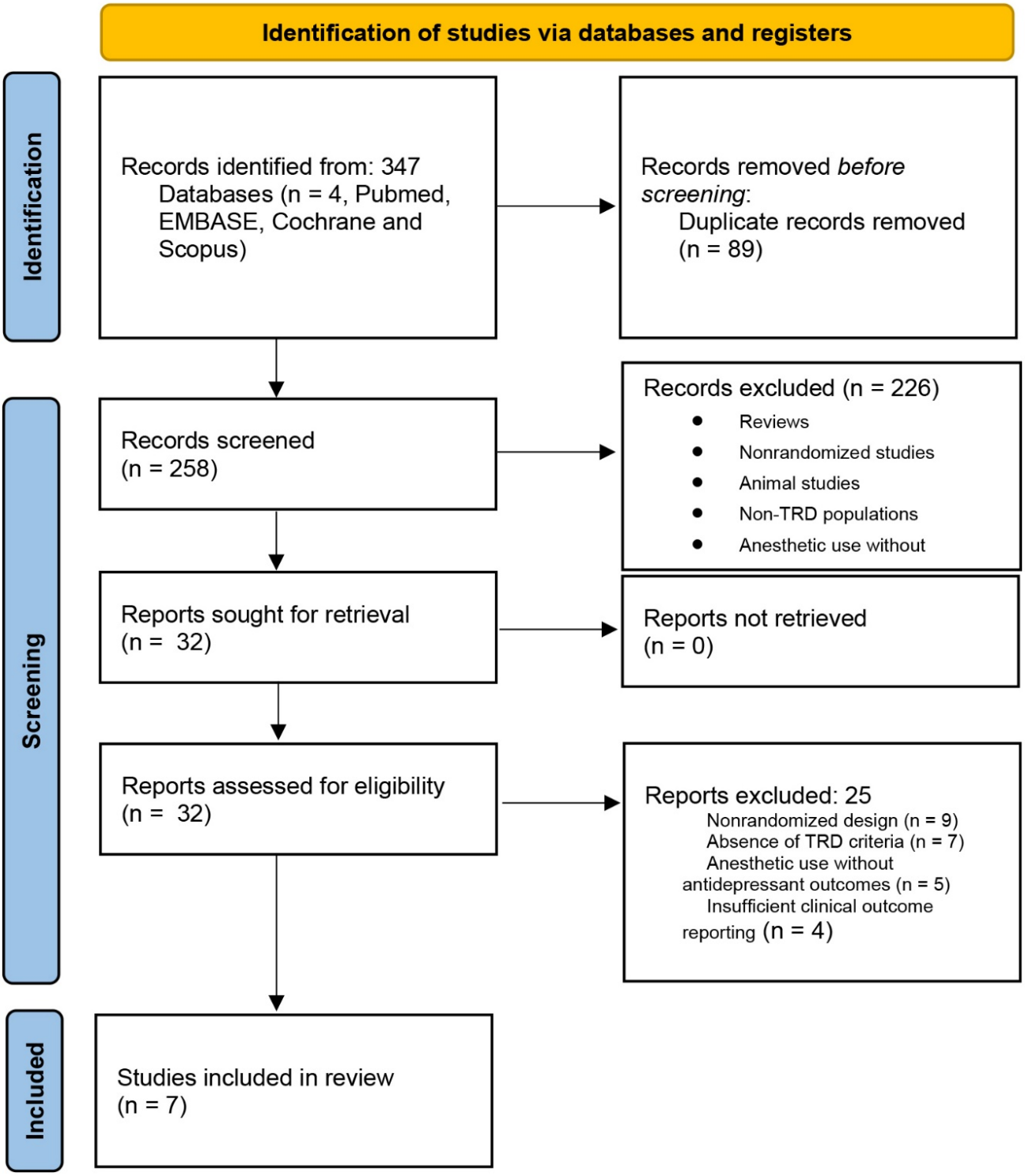

Fig. 1. PRISMA 2020 flow diagram of study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Safety Profile

Adverse events were consistent across studies. For ketamine/esketamine, the most frequent effects included transient dissociation (reported in 30–60% of patients), dizziness, nausea, and mild, transient elevations in blood pressure (generally <20 mmHg), resolving spontaneously within 1–2 hours. For scopolamine, anticholinergic effects predominated, including somnolence, dry mouth, blurred vision, and mild orthostatic hypotension. Serious adverse events and discontinuations due to adverse events occurred in some included trials; however, most reported adverse events were transient.

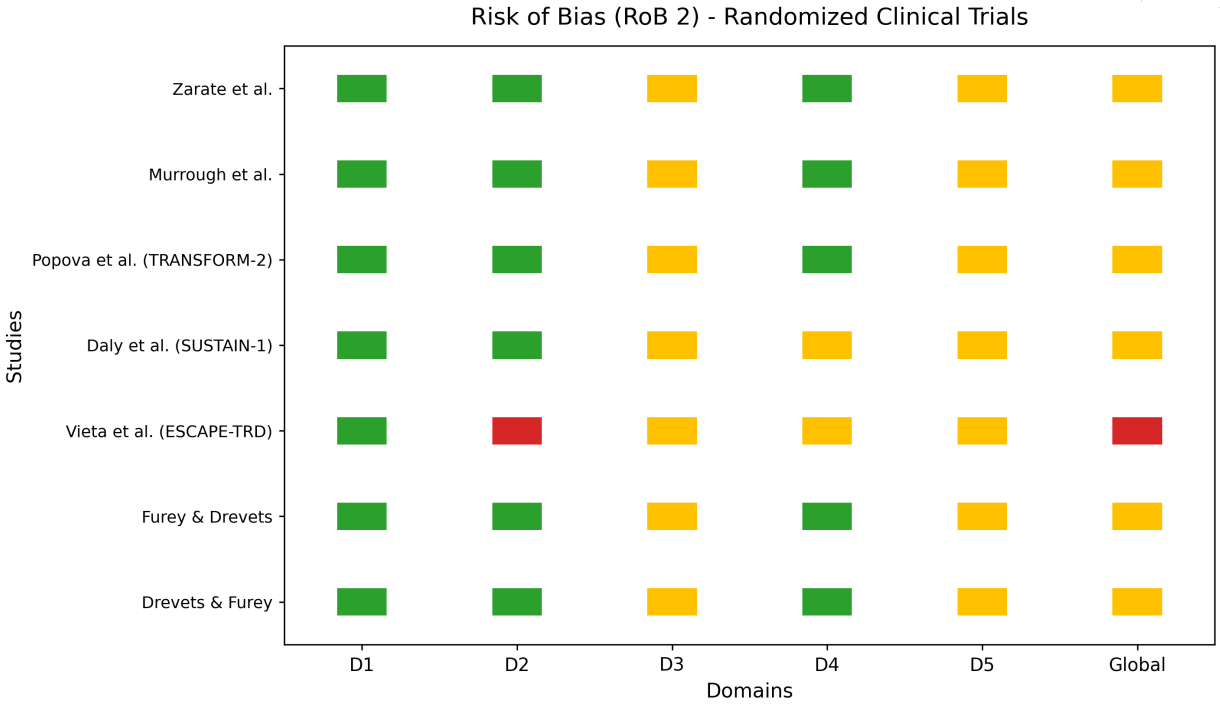

Fig. 2. Risk of bias assessment of included randomized clinical trials using the Cochrane RoB 2 tool. The risk-of-bias assessment of the included randomized clinical trials according to the Cochrane Risk of Bias 2 (RoB 2) tool. Green squares indicate low risk of bias; yellow squares indicate some concerns; red squares indicate high risk of bias. The evaluated domains were: D1, randomization process; D2, deviations from intended interventions; D3, missing outcome data; D4, outcome measurement; and D5, selective reporting. Overall risk-of-bias judgments were determined according to the RoB 2 algorithm recommendations.

Discussion

Comparative Efficacy of Rapid-Acting Antidepressants

The findings of this review consistently indicate rapid antidepressant effects with intravenous ketamine and intranasal esketamine in patients with TRD. However, important differences emerge regarding onset time, maintenance efficacy, administration logistics, and strength of evidence.

Intravenous ketamine demonstrated the fastest onset of antidepressant action, with significant symptom reduction occurring within approximately 110 minutes after infusion in the study by Zarate et al. [6]. Response rates approached 70% during the first 24 hours, highlighting ketamine's potential role in acute psychiatric emergencies, particularly in patients with severe suicidal ideation. Nevertheless, antidepressant effects were frequently transient, with gradual loss of efficacy after several days in the absence of maintenance treatment.

In contrast, intranasal esketamine exhibited a slightly slower onset of action, generally within 24–48 hours, but demonstrated stronger evidence regarding maintenance treatment and relapse prevention [9,10]. The intranasal route also offers greater outpatient feasibility compared with intravenous infusion protocols, although supervised administration remains necessary because of transient dissociative and cardiovascular effects.

Scopolamine demonstrated rapid antidepressant effects in proof-of-concept studies, with symptom improvement occurring within 1–3 days. However, the available evidence remains limited by small sample sizes, crossover designs, and lack of large confirmatory trials. Consequently, its clinical applicability remains experimental.

Safety and Tolerability Profile

In terms of safety, ketamine/esketamine are associated with dissociation, nausea, dizziness, and transient increases in blood pressure, which are generally self-limited; scopolamine is characterized by anticholinergic effects such as dry mouth, blurred vision, and constipation. Regarding critical outcomes such as suicidal ideation, robust evidence supports acute reduction following ketamine administration [14]. For esketamine, antidepressant benefits translate into functional improvements and relapse prevention during maintenance treatment [9,10,13].

Neurobiological Mechanisms and Therapeutic Implications

Mechanistically, these agents act as psychoplastogens, promoting rapid restoration of synaptic connectivity in prefrontal and limbic circuits. Ketamine activates mTORC1 signaling, increases BDNF expression, and promotes synaptogenesis, mechanisms that appear to be associated with rapid antidepressant responses following NMDA

receptor blockade [15,16]. Scopolamine enhances glutamatergic release via muscarinic M1 receptor blockade in GABAergic interneurons, converging on mTOR and BDNF pathway activation [17]. These mechanisms help explain the rapid onset of clinical effects and represent promising targets for novel therapeutic strategies.

Functional and Socioeconomic Impact

The rapid action of these agents may carry important clinical and functional implications, particularly by accelerating symptom improvement and potentially reducing hospitalization time in severe depressive episodes. Trials such as ESCAPE-TRD demonstrated improvements in occupational functioning and productivity over 32 weeks with esketamine [13]. However, the interpretation of socioeconomic benefits should remain cautious, since formal pharmacoeconomic analyses and direct cost-per-treatment calculations were beyond the scope of the included studies, although previous pharmacoeconomic models have suggested potential cost-effectiveness of esketamine in treatment-resistant depression [18].

Strengths and Limitations of This Review

Limitations of this review include heterogeneity among analyzed studies, differences in diagnostic criteria, assessment instruments, routes of administration, concomitant antidepressant therapies, and follow-up duration, as well as the limited number of scopolamine trials. Additional limitations include the relatively small sample sizes of several studies, short-term follow-up in most trials, and the absence of standardized maintenance protocols, which restrict direct comparisons between interventions. Conversely, the strength of this study lies in integrating clinical evidence, biological mechanisms, and functional outcomes, providing a comprehensive and critical overview of the use of these agents in clinical practice.

The findings indicate consistent rapid antidepressant effects for IV ketamine and IN esketamine, with more robust evidence supporting esketamine in maintenance regimens. Interpretation should consider methodological limitations identified by RoB 2, particularly regarding missing data and selective reporting. Furthermore, long-term safety issues, including abuse potential, cognitive effects, and durability of antidepressant response, remain incompletely understood and require further investigation in larger pragmatic studies. Scopolamine shows promising results but requires replication in larger samples.

Overall certainty of evidence should be interpreted cautiously due to small sample sizes, short follow-up duration, methodological heterogeneity, and potential selective reporting bias in some included trials. Therefore, although evidence for ketamine and esketamine appears promising, confidence in long-term effectiveness and safety remains limited.

Future research should prioritize: (1) identification of clinical, neurobiological, and genetic biomarkers capable of reliably predicting individual treatment response; (2) optimization of maintenance protocols balancing long-term efficacy and safety; (3) development of new psychoplastogenic compounds with lower dissociative potential; and (4) pragmatic cost-effectiveness evaluations in resource-limited settings, particularly in low- and middle-income countries.

Conclusion

Ketamine, esketamine, and scopolamine represent a new paradigm in the treatment of depression, offering rapid antidepressant responses; ketamine has also shown evidence of short-term reductions in suicidal ideation. Intravenous ketamine shows stronger evidence for acute use, whereas intranasal esketamine combines efficacy with outpatient feasibility and relapse prevention. Intravenous scopolamine, although promising, still requires confirmatory studies.

The careful integration of these therapies into clinical practice, combined with monitoring protocols and maintenance strategies, has the potential to transform the management of a disorder historically marked by high morbidity, functional impairment, and substantial socioeconomic burden.

In conclusion, intravenous ketamine and intranasal esketamine present consistent evidence of rapid antidepressant action in TRD. Scopolamine remains an experimental intervention requiring further confirmatory studies.

Availability of Data and Materials

All data analyzed during this study are included in this published article and its **Supplementary Material**. No additional datasets were generated or analyzed during the current study.

Author Contributions

JFC conceived the study, designed the review protocol, performed the literature search, analyzed and interpreted the data, and drafted the manuscript. EPS contributed to study selection, methodological review, interpretation of findings, and critical revision of the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

Jozélio Freire de Carvalho was a member of the Editorial Board of this journal at the time of acceptance. Jozélio Freire de Carvalho had no involvement in the peer review of this article and has no access to information regarding its peer review. The other author declares no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

The artificial intelligence-assisted tool (ChatGPT) was used exclusively for language refinement, grammatical review, and assistance in the translation of the manuscript from Portuguese into English. After its use, the authors thoroughly reviewed, verified, and revised all content to ensure accuracy and originality.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202638212.235

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