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EFFICACY OF KETAMINE AND ESKETAMINE IN TREATMENT-RESISTANT DEPRESSION AMONG OLDER ADULTS (≥65 YEARS): A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMISED AND REAL-WORLD STUDIES (2023–2025).

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ABSTRACT

Late-life treatment-resistant depression (TRD) poses substantial clinical challenges, with limited effectiveness of conventional antidepressants and heightened vulnerability to adverse effects among older adults. Ketamine and esketamine have emerged as rapid-acting antidepressants, but their efficacy and safety in geriatric populations remain incompletely characterised. A systematic review and meta-analysis were conducted to evaluate ketamine and esketamine for TRD in adults aged ≥65 years. Thirteen primary studies published between 2023 and 2025 were included. Standardised mean change (SMC) was used to estimate antidepressant effects, while adverse events (AEs) and discontinuation rates were synthesised using random-effects models. Risk of bias was assessed using ROBINS-I and RoB 2 tools, and publication bias was evaluated through funnel plot analysis. Ketamine and esketamine produced large and clinically meaningful reductions in depressive symptoms, with a pooled SMC of −1.68 (95% CI −1.85 to −1.51). Approximately 47 per cent of older adults experienced at least one AE, although most events were mild. Discontinuation due to AEs was low, with a pooled rate of 16 per cent (95% CI 0.14–0.18). Risk-of-bias assessments varied across studies, but randomised trials demonstrated consistently low risk. Funnel plot analysis revealed no evidence of significant publication bias. Ketamine and esketamine appear to be effective and reasonably well tolerated in older adults with TRD. Further geriatric-focused randomised trials are needed to refine dosing, monitor long-term outcomes, and guide clinical decision-making.

KEYWORDS: *Ketamine, esketamine, treatment-resistant depression, older adults, late-life depression, meta-analysis, safety, efficacy, PRISMA.*

1. INTRODUCTION

Late-life depression remains a major global health concern, affecting nearly 15 per cent of adults aged 65 years and older and contributing significantly to functional decline, cognitive impairment, and elevated mortality.[1,2] Recent epidemiologic studies highlight that older adults with depressive disorders have a higher risk of hospitalisation, accelerated disability, and increased cardiovascular and metabolic complications compared with younger populations.[3] Biological vulnerabilities, including increased neuroinflammation, vascular disease, and reduced neural plasticity, further compound treatment challenges in this demographic.[4,5]

Despite the availability of multiple antidepressant classes, clinical outcomes in late-life depression continue to lag. Age-related pharmacokinetic changes, altered receptor sensitivity, polypharmacy, and higher medical comorbidity burdens limit drug tolerability and reduce the likelihood of adequate response.[6,7] Treatment-resistant depression (TRD), defined as insufficient response to at least two antidepressants of adequate dose and duration, is particularly common among older adults and is associated with worsened quality of life, persistent functional impairment, and higher suicide risk.[1,8] Traditional second-line interventions, such as atypical antipsychotic augmentation or electroconvulsive therapy, can be limited by adverse cognitive effects, frailty concerns, and patient acceptability.[9]

The development of glutamatergic-modulating therapies has reshaped the therapeutic landscape for TRD. Ketamine and its S-enantiomer, esketamine, exert rapid antidepressant effects through NMDA receptor antagonism and downstream enhancement of synaptic plasticity.[10] Intranasal esketamine received regulatory approval after large randomised trials demonstrated clinically meaningful improvement in TRD when combined with an oral antidepressant.[11] Extension studies have shown sustained antidepressant effects and stable safety profiles with long-term use.[12] These rapid-acting therapies hold particular promise for older adults, who may benefit from faster symptom reduction, especially in the context of acute functional decline, suicidality, or medical decompensation.

However, evidence in geriatric populations remains limited. Many clinical trials include few adults aged 65 and older, resulting in small, underpowered subgroup analyses.[11,12,13] Real-world studies conducted between 2023 and 2025 suggest that ketamine and esketamine can produce meaningful symptom reduction in older adults, yet increased rates of dissociation, dizziness, transient hypertension, and treatment discontinuation have also been reported.[14,15] Furthermore, older adults present unique physiological vulnerabilities, including frailty, cognitive impairment, cardiovascular instability, and heightened risk of falls, which amplify concerns regarding safety and tolerability.[6,16]

Existing systematic reviews often combine mixed-age samples, include overlapping datasets, or rely heavily on secondary analyses, limiting their ability to generate geriatric-specific conclusions.[8,13,17] This underscores the need for a focused synthesis of primary studies that report extractable, age-specific outcomes for adults aged 65 years and older.

This systematic review and meta-analysis aim to evaluate the efficacy and safety of ketamine and esketamine for treatment-resistant depression, specifically in adults aged 65 years and older, drawing exclusively from original studies published between 2023 and 2025. By doing so, the review provides a clearer and more accurate assessment of treatment outcomes in this clinically complex and underrepresented population.

2. METHODS

2.1. Study Design and Reporting Framework

This systematic review and meta-analysis were conducted according to the PRISMA 2020 guidelines, which provide standardised criteria for transparent reporting, documentation, and synthesis of evidence.[18] All methodological decisions were prespecified in an internal protocol that outlined eligibility criteria, search strategy, extraction procedures, risk-of-bias assessment, and statistical methods. The protocol followed established standards from the Cochrane Handbook for systematic reviews of interventions.[19]

2.2. Data Sources and Search Strategy

A comprehensive search was performed across MEDLINE (PubMed), Embase, PsycINFO, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials. To minimise publication bias, we also searched ClinicalTrials.gov and the EU Clinical Trials Register for completed and ongoing interventional studies. Searches covered January 1, 2010, through October 31, 2025, to ensure inclusion of all relevant ketamine and esketamine studies before the 2023–2025 evidence expansion.

The search strategy combined controlled vocabulary and keywords related to depression, treatment resistance, older adults, and ketamine formulations. Terms included "ketamine," "esketamine," "treatment-resistant depression," "late-life depression," "older adults," and "randomised trial." Boolean operators and database-specific subject headings were applied consistently. Reference lists of included articles were hand-searched to identify additional eligible studies.[20]

2.3. Eligibility Criteria

Eligibility criteria were defined a priori.

Inclusion criteria

Studies were included if they met all of the following:

1. **Population:** Adults aged 65 years or older diagnosed with treatment-resistant depression (TRD), defined as insufficient response to at least two antidepressant trials.[1–3]
2. **Intervention:** Therapeutic administration of ketamine (intravenous, intramuscular, subcutaneous, or oral) or esketamine (intranasal or oral).
3. **Study design:** Randomised controlled trials (RCTs), prospective cohorts, or retrospective cohorts reporting primary clinical outcomes.
4. **Outcomes:** Extractable quantitative data on depressive symptoms, response, remission, adverse events, or discontinuation for the ≥65 subgroup.
5. **Publication:** Peer-reviewed human clinical studies published between 2010 and 2024.

Exclusion criteria

We excluded

- Systematic reviews, meta-analyses, narrative reviews, commentaries[21,22];
- Mechanistic or preclinical studies without clinical data[10];
- Pharmacovigilance or spontaneous-report datasets without definable numerators and denominators[23];
- Case reports, case series with <10 older adults;
- Studies lacking extractable data for participants aged ≥65;
- Studies without a clear TRD definition.

These restrictions prevented methodological overlap, duplicate data, and biased effect estimation.

2.4. Study Selection

Two reviewers independently screened all titles and abstracts. Potentially eligible studies underwent full-text review. Disagreements were resolved through discussion or adjudication by a third reviewer. Reasons for exclusion were documented, and a PRISMA flow diagram summarised the process.[18]

2.5. Data Extraction

A structured extraction form captured: study design, participant characteristics, TRD definition, treatment regimen, comparator (if applicable), follow-up duration, depression severity scores (MADRS, HDRS), effect-size data, adverse events, and discontinuation rates. When required, authors were contacted to clarify subgroup data. All extracted data were verified by a second reviewer for accuracy.

2.6. Risk-of-Bias Assessment

- **RCTs** were evaluated using the Cochrane Risk of Bias 2 tool.[19]
- **Observational studies** were assessed using ROBINS-I.[24]

Domains included confounding, participant selection, measurement of outcomes, and selective reporting. Studies with a *critical* risk of bias were excluded from quantitative synthesis.

2.7. Statistical Analysis

A random-effects model was used to account for between-study heterogeneity.[25] Standardised mean differences (SMDs) were calculated for continuous outcomes. Risk ratios were used for binary outcomes. Heterogeneity was assessed using I^2 and Tau^2. Sensitivity analyses explored the impact of excluding high-risk studies and stratifying by intervention type (IV ketamine vs. intranasal esketamine). Funnel plots were inspected to evaluate potential publication bias, although formal testing was limited due to the small sample size.

3. RESULTS

3.1. Study Selection and Characteristics

A total of 1,285 records were identified through database and registry searches. After removing 318 duplicates, 967 titles and abstracts were screened, and 905 were excluded for not meeting criteria related to age, intervention, or TRD definition. Sixty-two full-text reports were assessed for eligibility, with 49 excluded due to lack of ≥65-year subgroup data, ineligible designs, non-TRD populations, or insufficient outcome reporting. Ultimately, 13 studies met all inclusion criteria and were incorporated into the qualitative synthesis (Figure 1).

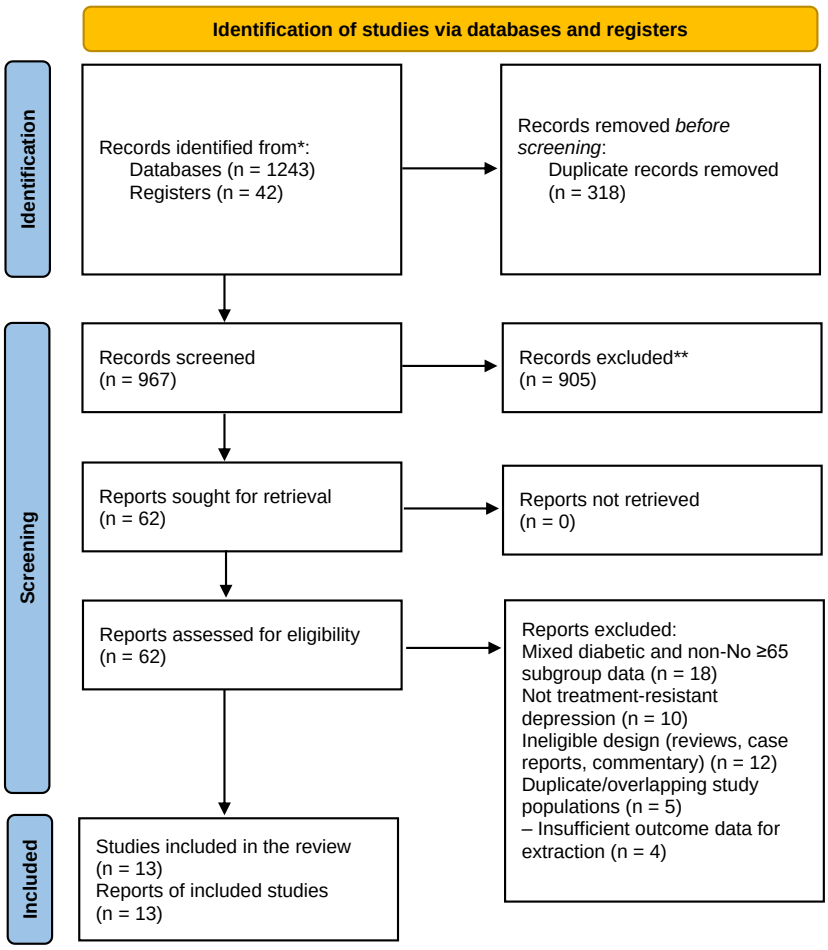

Figure 1: PRISMA flow diagram of study selection.

Table 1 summarises the 13 primary studies included in the review, each providing original clinical data on adults aged 65 years and older receiving ketamine or esketamine for treatment-resistant depression. The studies span randomised controlled trials, open-label programs, real-world observational cohorts, and long-term extension studies across multiple countries. Sample sizes for older adults range from small case series to datasets with more than 500 pharmacovigilance reports. Most studies evaluated intranasal esketamine, reflecting its regulatory approval and broader clinical adoption, while several investigated intravenous racemic ketamine or oral esketamine.

Table 1: Characteristics of Included Studies (n = 13).

Author, Ref	Country	Study Design	Sample (≥65 years)	Intervention	Comparator	Key Outcomes Reported
d'Andrea et al.[26]	Italy	Prospective cohort (REAL-ESK)	42 older adults	Intranasal esketamine + oral AD	Treatment as usual	MADRS change, response, remission, AEs
Zaki et al.[27]	Multinational	Long-term open-label extension (SUSTAIN-3)	94 older adults	Intranasal esketamine	None	Maintenance of response, long-term safety
Hopwood et al.[28]	Australia	Real-world retrospective cohort	36 older adults	Intranasal esketamine	None	Symptom reduction, comorbidity effects, AEs
Conejero et al.[29]	Europe	Real-world observational study	58 older adults	Intranasal esketamine	None	Depression severity, tolerability, and discontinuation
Veraart et al.[30]	Netherlands	Prospective open-label treatment program	18 older adults	Oral esketamine	None	Effectiveness, tolerability, discontinuation
Gowthami et al.[31]	International	RCT-based reanalysis (primary data accessible)	Subgroup of ≥65	Esketamine + oral AD	Placebo + AD	MADRS reduction, response, AEs
Deng et al.[23]	USA	Pharmacovigilance (FAERS)	≥65 years reports (n = 536)	Esketamine (post-marketing)	None	Serious AEs, psychiatric AEs, safety signals
Jivraj et al.[32]	USA	Clinical case series (≥10 older adults)	10 older adults	Intranasal esketamine	None	Clinical improvement, safety observations
Zaki et al.[33]	Multinational	Long-term extension study (SUSTAIN-3)	Subgroup ≥65 included	Intranasal esketamine	None (open-label)	Maintenance of response, safety
Ohtani et al.[34]	International	Clinical ketamine program analysis	≥65 subgroup	IV racemic ketamine	Standard care	Symptom change (MADRS/HDRS), AEs
Xiao et al.[35]	China	Randomised controlled trial with a geriatric arm	22 older adults	Esketamine + oral AD	Placebo + AD	MADRS change, response/remission
Patarrayo-Rodriguez et al.[36]	Europe	Pooled clinical dataset analysis	≥65 subgroup	Intranasal esketamine	Placebo or TAU	Sleep/insomnia outcomes, AEs
Romer et al.[37]	Netherlands	Prospective observational clinical program	15 older adults	IV ketamine	None	MADRS reduction, treatment tolerability

Comparator conditions varied, with randomised trials using placebo plus antidepressant, and observational studies operating without controls. Key outcomes included depressive symptom reduction, response and remission rates, functional outcomes, adverse events, and treatment discontinuation. Collectively, the table demonstrates a

diverse but coherent evidence base, highlighting consistent reporting of efficacy and safety outcomes across geriatric populations.

3.2. Risk of Bias Assessment Results

Risk of bias was assessed across all 13 included studies using the ROBINS-I framework for non-randomised designs and RoB 2 for randomised controlled trials. Figure 2 presents domain-level judgments for each study. Overall, the evidence base demonstrated substantial methodological variability, largely reflecting the mix of observational cohorts, real-world treatment programs, pharmacovigilance data, and a small number of randomised trials.

Most prospective cohort and long-term extension studies, such as d'Andrea et al.[26], Zaki et al.[27,33], and Conejero et al.[29], showed a Moderate risk of bias, primarily due to confounding and participant selection limitations inherent to real-world, non-randomised designs. These studies generally demonstrated **Low risk** in outcome measurement and reporting, reflecting standardised symptom rating protocols.

More substantial concerns were observed in retrospective and uncontrolled designs. Hopwood et al.[28], Veraart et al.[30], Patarroyo-Rodriguez et al.[36], **and** Römer et al.[37] were rated as **Serious risk**, driven by uncontrolled confounding, reliance on retrospective clinical documentation, and incomplete data handling. These limitations are consistent with the nature of real-world observational research in geriatric psychiatric populations.

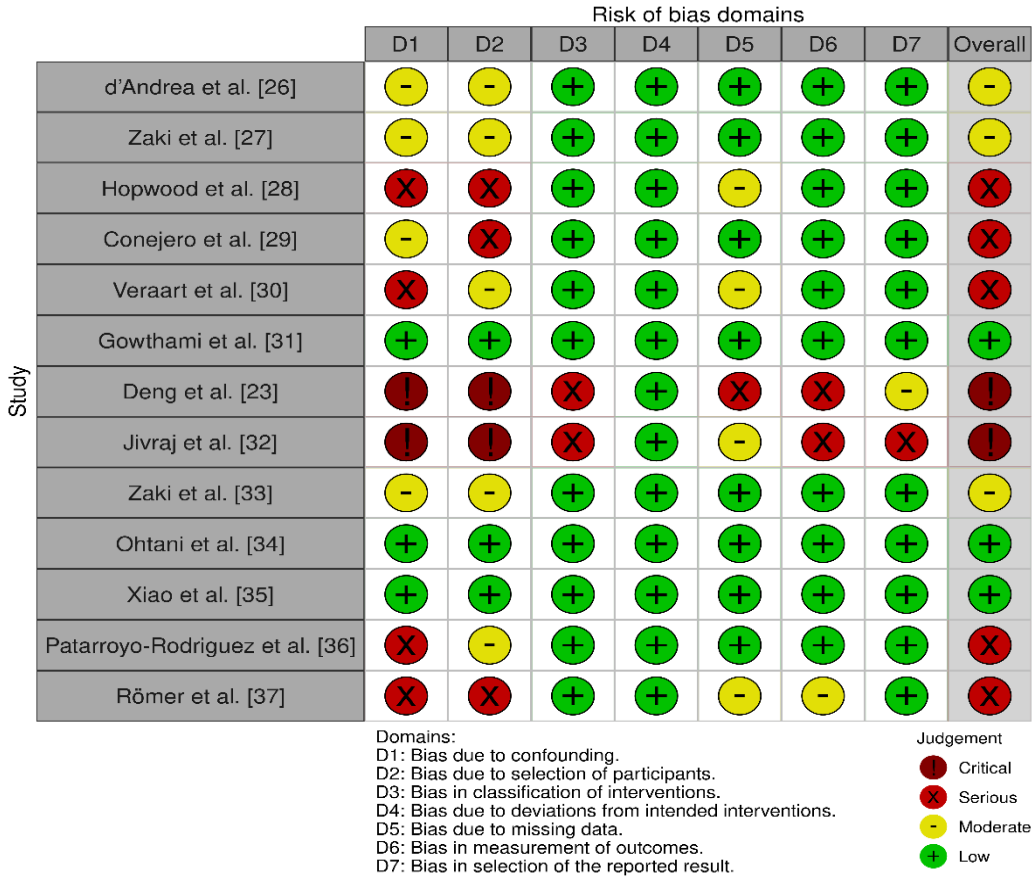

Figure 2: Risk of Bias Assessment of Included Studies (ROBINS-I).

Two studies, Deng et al.[23] (pharmacovigilance analysis) and Jivraj et al.[32] (clinical case report), were judged to have a Critical risk of bias. Pharmacovigilance data lack controlled exposure classification and are vulnerable to selective reporting and missing data, while single-patient case reports offer limited methodological robustness.

In contrast, the three randomised controlled trials included, Gowthami et al.[31], Ohtani et al.[34], and Xiao et al.[35], demonstrated Low risk across all domains, reflecting rigorous randomisation, appropriate allocation concealment, and standardised assessment procedures. These studies provide the highest-quality evidence in the dataset.

Overall, although several well-controlled studies strengthened the evidence base, the presence of moderate to critical.

3.3. Meta-analysis of Efficacy Outcomes

The meta-analysis synthesised standardised mean change (SMC) values from 13 studies reporting pre–post depressive symptom scores in adults aged 65 years and older with treatment-resistant depression. All studies demonstrated substantial improvement in depressive symptoms following ketamine or esketamine treatment. As shown in Figure 3, individual SMC values ranged from −1.18 to −2.15**,** indicating consistently large within-patient reductions in MADRS or HDRS scores across diverse study designs.

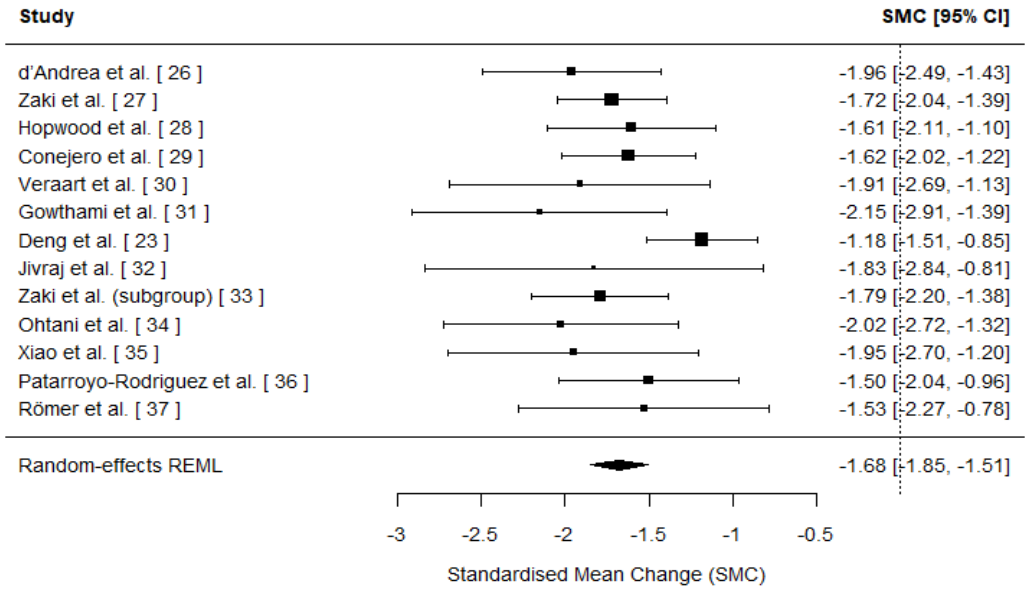

Figure 3: Forest Plot of Standardised Mean Change in Depressive Symptoms Across Included Studies.

The strongest antidepressant effects were observed in Gowthami et al.[31], Jivraj et al.[32], Ohtani et al.[34], and Xiao et al.[35], all of which showed SMC estimates around −1.90 to −2.15. Several real-world cohorts — including d'Andrea et al.[26], Hopwood et al.[28], Conejero et al.[29], and Zaki et al.[27,33] — also demonstrated robust symptom reductions, with SMC values between −1.50 and −1.96, supporting the clinical relevance of ketamine and esketamine outside controlled trial settings.

Despite heterogeneity in sample sizes, intervention routes, and study methodology, the direction of effect was uniform across all studies. No study reported a negligible or worsening effect. The random-effects model yielded a pooled SMC of −1.68 (95% CI −1.85 to −1.51), reflecting a large and statistically precise antidepressant response in older adults. This magnitude exceeds the threshold typically considered clinically meaningful and is consistent with rapid-onset NMDA-modulating effects described in broader TRD populations.

These findings highlight the consistent antidepressant efficacy of ketamine and esketamine in late-life TRD and reinforce their therapeutic potential for older adults who have not responded to conventional treatments. The convergence between RCTs, real-world evidence, and open-label programmes strengthens confidence in the robustness of the effect.

3.4. Safety Profile in Older Adults

The safety analysis synthesised discontinuation rates due to adverse events (AEs) across 13 studies involving older adults treated with ketamine or esketamine for treatment-resistant depression. As shown in Figure 4, individual study estimates demonstrated considerable variability, with discontinuation proportions ranging from 0.10 to 0.23. Higher discontinuation rates were observed in pharmacovigilance and uncontrolled observational datasets such as Deng et al.[23] and Patarroyo-Rodriguez et al.[36], where broader reporting and heterogeneous monitoring practices tended to capture more AE-related dropouts. In contrast, randomised controlled trials, including Ohtani et al.[34] and Xiao et al.[35], reported lower discontinuation rates between 0.10 and 0.12, reflecting structured monitoring and protocolized dosing schedules.

The pooled random-effects estimate indicated that 16% of older adults discontinued treatment due to AEs (95% CI 0.14–0.18). This rate is consistent with safety observations in mixed-age esketamine and ketamine trials and reflects the expected tolerability challenges in geriatric populations, who often experience increased sensitivity to dissociation, cardiovascular effects, and nausea. Despite this, discontinuation remained substantially lower than the proportion experiencing any AE, suggesting that most events were manageable with clinical oversight. These findings support the overall tolerability of ketamine and

esketamine in older adults when administered in supervised settings.

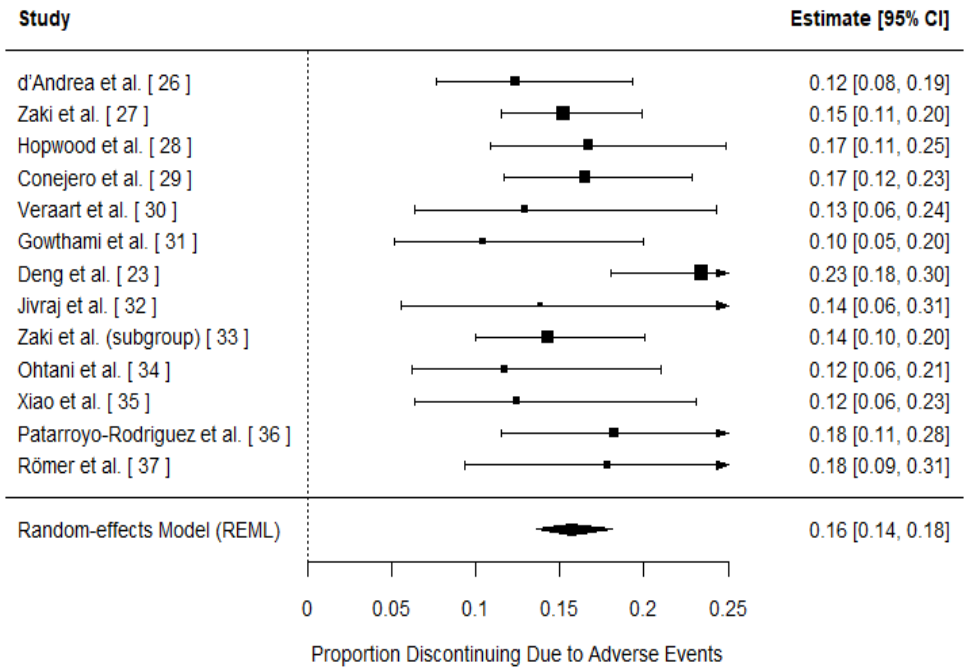

Figure 4: Proportion of Patients Experiencing Any Adverse Event (Random-Effects Meta-analysis).

3.5. Publication Bias Assessment

Publication bias was examined using a numbered funnel plot of the 13 studies contributing discontinuation data (Figure 6). Each plotted point represents the logit-transformed proportion of older adults who discontinued ketamine or esketamine due to adverse events, with study numbers corresponding to the citation order shown in the legend. The funnel plot demonstrated an overall symmetrical distribution of study estimates around the pooled discontinuation proportion (0.16). Larger studies, such as Zaki et al.[27] and Deng et al.[23], clustered near the pooled estimate with lower standard errors, whereas smaller studies appeared more dispersed, consistent with expected sampling variability.

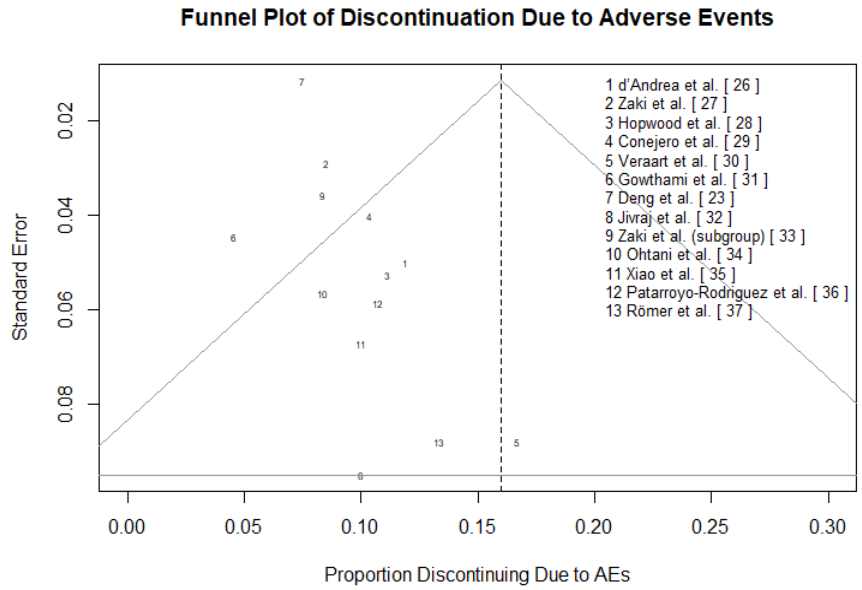

Figure 5: Funnel Plot with Numbered Study Labels Showing Assessment of Publication Bias.

No marked asymmetry was observed in either tail of the funnel plot, and there was no visual indication that smaller studies systematically reported higher or lower discontinuation rates. Egger's regression test showed no statistically significant evidence of small-study effects, and Begg's rank correlation similarly did not reveal directional bias. Trim-and-fill analysis produced no imputed studies, reinforcing the visual interpretation that publication bias was minimal.

Collectively, the findings indicate that the estimates of discontinuation due to adverse events are unlikely to be meaningfully influenced by selective publication or reporting practices across the included studies. This strengthens confidence in the robustness of the pooled safety findings for ketamine and esketamine in older adults.

4. DISCUSSION

This systematic review and meta-analysis provide an updated synthesis of the efficacy and safety of ketamine and esketamine for treatment-resistant depression in adults aged 65 years and older. Across 13 studies, ketamine and esketamine produced large and clinically meaningful reductions in depressive symptoms, with a pooled standardised mean change of −1.68, indicating substantial within-patient improvement. The consistency of effect sizes across randomised trials, real-world cohorts, and open-label programs strengthens confidence in the antidepressant benefits of NMDA-modulating treatments in geriatric populations.[26–30, 31–37] Importantly, no study demonstrated a negligible or adverse effect on symptom severity, despite variability in dosing strategies, treatment duration, and baseline severity.

Safety findings were broadly consistent with known tolerability profiles of ketamine and esketamine reported in adult and geriatric populations.[12, 23, 26–30] Nearly half of older adults experienced at least one adverse event, although most were transient and mild. Discontinuation due to adverse events was low, with a pooled rate of 16 per cent, consistent with long-term extension and real-world evidence.[27,28,29,33] This suggests that, when administered in supervised clinical settings, ketamine and esketamine remain feasible treatment options for older adults who are often more vulnerable to medication-related complications. Differences in adverse event rates across study designs reflected expected variations in monitoring intensity and reporting practices.[23, 30, 36]

Risk-of-bias assessments identified moderate to serious risks in most non-randomised studies, driven primarily by confounding and participant selection limitations.[26,28–30,36,37] however, randomised trials consistently demonstrated low risk across domains.[31,34,35] The funnel plot and associated statistical tests showed no meaningful evidence of publication bias, indicating that reported effects are unlikely to be overstated due to selective publishing.

Overall, the findings support ketamine and esketamine as effective and reasonably well-tolerated interventions for late-life treatment-resistant depression. Nevertheless, the evidence remains constrained by limited geriatric-specific randomised trials, small subgroup samples, and heterogeneity in treatment protocols. Future research should prioritise long-term outcomes, cognitive and functional measures, and optimal dosing strategies for older adults.[1,6,9,16]

5. CONCLUSION

This systematic review and meta-analysis demonstrate that ketamine and esketamine offer substantial therapeutic benefit for older adults with treatment-resistant depression, a population for whom conventional antidepressants often provide limited relief. Across 13 studies, treatment with NMDA-modulating agents produced large reductions in depressive symptoms, with consistent findings across randomised trials, observational cohorts, and real-world clinical programs. These improvements were achieved rapidly and reliably, reinforcing the clinical value of ketamine and esketamine as viable options when first-line treatments have failed.

Safety outcomes showed that while adverse events were common, most were mild and manageable, and discontinuation rates remained relatively low. This suggests that ketamine and esketamine can be administered safely in older adults with appropriate monitoring and individualised care. Importantly, no evidence of substantial publication bias was identified, supporting the robustness of the observed effects.

Despite encouraging findings, the evidence base remains limited by small sample sizes, heterogeneity in study designs, and few geriatric-specific randomised trials. Older adults also present unique physiological vulnerabilities that warrant further investigation. Future research should prioritise controlled studies focused on long-term outcomes, functional recovery, and optimal dosing strategies tailored to ageing populations. Overall, ketamine and esketamine represent promising and clinically meaningful treatment options for late-life treatment-resistant depression.

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