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Highlights

- What is the primary question addressed by this study? This study sought to provide the most comprehensive systematic review of the role of ketamine in treating depression in older adults, given the paucity of current evidence.

- What is the main finding of this study? Ketamine shows potential efficacy in reducing depressive symptoms in older adults across intranasal, intravenous, subcutaneous, oral, and ECT-combination routes, with varying response and remission rates. Cognitive outcomes were generally stable or improved, though some studies reported transient slowing of reaction time with repeated intranasal dosing. Adverse effects were typically mild and transient, including dizziness, nausea, and blood pressure elevations, with few treatment discontinuations.

- What is the meaning of the finding? Ketamine may be a viable antidepressant option for older adults, with individualized risk-benefit.

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

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Ketamine for Late-Life Depression: A Systematic Review of Efficacy, Safety, and Tolerability

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Abstract

Ketamine has emerged as a promising treatment for major depression, though its efficacy and safety remain incompletely characterized in older adults. This systematic review synthesizes current evidence for ketamine in geriatric depression. A search of PubMed, EMBASE, and PsycINFO was conducted. Prospective clinical trials were included, with age restriction to participants ≥60 years applied at full-text review to capture subgroup data. Thirteen studies met inclusion criteria, comprising 757 adults. Studies

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examined intranasal (n=5), intravenous (n=4), subcutaneous (n=1), and oral (n=1) ketamine formulations, as well as ketamine combined with ECT (n=2). Antidepressant efficacy findings were mixed, with some studies demonstrating improvement, while others showed no benefit. Adverse events were generally mild to moderate and discontinuation due to side effects was rare. Cognitive outcomes were mostly stable or improved, though long-term studies noted small declines in reaction time. Ketamine as an ECT anesthetic did not enhance antidepressant outcomes. Evidence certainty was very low to low; findings were limited by small samples, open-label designs, and inconsistent age-stratified reporting.

Introduction

Major depressive disorder (MDD) is one of the leading causes of disability worldwide.[1,2] Geriatric depression, defined as major depression in individuals aged ≥60, has a 12-month prevalence of 5.4% and is associated with reduced quality of life, functional impairment, and suicide risk.[3–5] Management of geriatric depression is complicated by medical comorbidities, polypharmacy, age-related pharmacodynamic and pharmacokinetic changes, and sensitivity to medication side effects.[6,7] Guidelines for geriatric depression recommend psychotherapy, antidepressants, antidepressant augmentation strategies, ECT, and rTMS.[8–10] Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has drawn widespread interest in adult populations due to its rapid antidepressant and potential pro-cognitive effects.[11–16] To our knowledge, two prior systematic reviews have focused on the use of ketamine in geriatric depression, both published in 2021.[17,18] Gupta *et al*. included two randomized controlled trials (RCTs) investigating ketamine in geriatric depression, with equivocal findings.[17] Di Vincenzo *et al.* assessed ketamine in treating depression in both younger and older adults, including case studies and series.[18] This systematic review aims to synthesize and update current evidence on ketamine in the treatment of geriatric depression.

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

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Methods

Search Strategy

PubMed, Embase, and PsycINFO databases were searched from inception to December 22, 2024. Search criteria were modelled after a prior systematic review.[18] A research librarian was involved in conducting the original search. Keywords included “ketamine” (including “esketamine,” “arketamine,” “ketalar,” and “spravato”) and “depress*”, linked with Boolean operators (AND/OR) where necessary. Complete search criteria are presented in Supplemental Table 1.

Study Selection and Eligibility Criteria

Studies were eligible if they included participants aged ≥60 with major depression receiving any ketamine formulation, and reported outcomes on depression severity, cognition, or safety/tolerability. Inclusion criteria were later refined to focus on prospective clinical trials. Non-English publications, editorials, conference abstracts, pre-prints, and pooled analyses were excluded. Age criteria were applied at full-text review, allowing inclusion of studies with older adult sub-analyses not specified in the abstract. This review followed PRISMA guidelines.[19]

Data Extraction

Abstract and full-text screening were conducted in duplicate (RS, JKT) using Covidence. Data extraction was performed in duplicate (RS, JKT) using a standardized spreadsheet. Data consensus exercises were performed ahead of formal extraction. Discrepancies were resolved through discussion. The following data were collected: study characteristics (country of publication, total sample size, sample size of participants ≥60 years old, average age of participants ≥60 years old, concomitant medications),

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intervention details (route, dose, titration schedule, control), depression scores, cognition, suicidality, and treatment-emergent adverse events (TEAEs).

Risk of Bias and Evidence Certainty

Risk of bias (ROB) for RCTs was performed according to the Cochrane ROB2 guideline with ROBVIS for visualization.[20] The Joanna Briggs Institute (JBI) critical appraisal tool for the assessment of risk of bias for quasi-experimental studies was used for all other studies.[21]. GRADE evidence certainty was assessed by two independent reviewers (RS, JKT).

Results

The literature search yielded 3,436 articles. After deduplication, 2831 articles remained. Following abstract screening, 437 underwent full-text review, and 13 met inclusion criteria (Figure 1): seven RCTs[22–28], four open-label trials[29–32], and two post-hoc analyses[33,34]. These included five intranasal (IN) [22,23,29,31,34], four intravenous (IV)[24,30,32,33], 1 subcutaneous (SC),[28] one oral,[25] and 2 ketamine combined with ECT studies.[26,27] The total sample comprised 757 adults. Common exclusion criteria included psychiatric or substance use comorbidities, elevated suicide risk, cardiovascular disease, and dementia. Study characteristics are in Table 1, key findings in Table 2, risk of bias in Figure 2 and Table 3, and GRADE assessments in Table 4. Herein, “response” will be defined as a ≥50% reduction in Montgomery–Åsberg Depression Rating Scale (MADRS) score and remission will be defined as MADRS ≤10 unless otherwise specified. “Treatment-resistant depression” (TRD) will be defined as failure of ≥2 adequate antidepressant trials, unless otherwise specified.[35]

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Intranasal Ketamine

Gálvez *et al.* (2018) conducted an RCT of IN ketamine in adults with a treatment-resistant MDE in the context of MDD. Participants' existing antidepressant medications were continued; however, no dose changes were permitted four weeks prior to, and during, the trial. The study terminated early after enrolling five of the planned 10 participants due to coordination impairment affecting medication self-administration. Two participants were aged ≥60 ("k1", age 64; "k3", age 60). Participants were randomized to IN ketamine or midazolam, administered three times weekly for two weeks, then weekly for two weeks. Each ketamine dose consisted of 10 sprays of 10 mg, administered at 5-minute intervals. Participant k1 showed an antidepressant response maintained at one-month follow-up. Participant k3 experienced slowed reaction time from baseline to treatment end. Numerical data were not reported for these outcomes. Safety and tolerability measures were not reported separately for older adults.

Ochs-Ross et al. (2020) conducted TRANSFORM-3, a double-blind RCT comparing IN esketamine plus oral antidepressant (Esk+Oral AD) to oral antidepressant plus placebo nasal spray in 138 participants aged ≥65 (mean age 70.0, SD 4.52) with treatment-resistant MDE in MDD. All participants started a new oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR), and esketamine was flexibly dosed (28–84 mg) twice weekly for four weeks. There was no significant difference in mean MADRS score changes from baseline (Esk+Oral AD: 35.5, SD: 5.91; Placebo+Oral AD: 34.8, SD: 6.44) to Day 28 (Esk+Oral AD: 25.4, SD: 12.70); Placebo+Oral AD: 28.7, SD: 10.11; difference of LS means: -3.6, 95%

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CI: [-7.20, 0.07]; p-value: 0.059) between groups. However, a sub-analysis showed greater MADRS reduction in participants aged 65–74 (difference of LS mean: -4.9, 95% CI: [-8.96, -0.89]; p-value: 0.017) compared to ≥75 (difference of LS mean: -0.4, 95% CI: [-10.38, 9.50]; p-value: 0.930). Response and remission rates were higher in the Esk+Oral AD group (27.0% and 17.5%) than placebo (13.3% and 6.7%). TEAEs occurred in 70.8% of Esk+Oral AD and 60.0% of Placebo+Oral AD participants. Most were mild to moderate, with dizziness and nausea being most common. Transient BP elevations occurred in 12.5% of Esk+Oral AD group and UTI in 8.3%. Discontinuation due to severe TEAEs was 5.6% (Esk+Oral AD) vs. 3.1% (Placebo+Oral AD). The only TEAE leading to discontinuation with possible relation to esketamine or the Oral AD was a transient BP increase in 2 participants.

Wajs *et al.* (2020) conducted SUSTAIN-2, an open-label trial of IN esketamine plus oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR) in treatment-resistant MDE in the context of MDD. Of 802 participants, 178 were ≥65, including 111 who were transferred from TRANSFORM-3. Esketamine was flexibly dosed (28, 56, or 84 mg) twice weekly. The study had four phases: 4-week screening, 4-week induction, 48-week optimization/maintenance, and 4-week follow-up. Participants ≥65 showed stable or improved performance in verbal and visual learning, memory, working memory, and executive function, but demonstrated reaction time slowing, starting at study week 20 (simple reaction time change: –0.03, SD 0.14; choice reaction time change: –0.01, SD 0.08), though this was no longer noted at the end of the optimization/maintenance phase. Antidepressant efficacy, suicidality, and safety

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outcomes were assessed but not reported separately for older adults. One death occurred in a participant ≥65, though this was deemed unrelated to treatment.

Ochs-Ross et al. (2022) conducted a post-hoc analysis of SUSTAIN-2 comparing outcomes in adults ≥65 and <65. No significant differences were observed in MADRS score changes during induction (baseline: older 32.8, younger 31.4; Day 28: older 14.8, younger 13.2; LS mean difference: 0.5, 95% CI: [-0.90, 1.86]; p-value: 0.492) or during the 48-week optimization/maintenance phase (baseline: older 32.9, younger 31.2; end: older 10.9, younger 11.0; LS mean difference: -0.7, 95% CI: [-1.95, 0.54]; p-value:0.265). During the induction phase, response rates were 74% in older adults and 87% in younger adults, while remission rates were 51% in both groups. In the optimization/maintenance phase, response rates were 79% in older adults and 81% in younger adults, with corresponding remission rates of 61% and 56%, respectively. Frequency of TEAEs in younger and older adults were similar at induction (86.1% vs. 74.8%) and optimization/maintenance (86.8% vs. 81.0%) with common TEAEs generally consistent between groups (i.e., dizziness, dissociation, nausea, headache). Falls, aminotransferase elevations, and cystitis occurred in ≤2% of both groups. Discontinuation due to severe TEAEs in younger and older adults at induction (7.53% vs. 3.87%) and optimization/maintenance (3.77% vs. 3.97%) were also similar. Reasons for discontinuation included transient BP elevation.

Zaki *et al.* (2023) conducted SUSTAIN-3, an open-label trial of IN esketamine plus oral antidepressant (commonly fluoxetine, venlafaxine, or sertraline) in 1148 participants aged ≥18, with 122 participants

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aged ≥65. Participants were diagnosed with treatment-resistant MDE in the context of MDD. Dosing was flexible (28, 56, or 84 mg) twice weekly during a 4-week acute phase, followed by individualized maintenance dosing. Reaction time slowing occurred in the maintenance phase, worsened until week 100, and stabilized in week 160. Mean within-group changes from baseline to study endpoint indicated small declines, with z-scores of –0.195 for simple reaction time and –0.368 for choice reaction time. Other cognitive domains remained stable, including learning, working memory, and executive function. Antidepressant efficacy, suicidality, and safety/tolerability outcomes were not reported separately for participants ≥65.

Intravenous Ketamine

Rasmussen *et al.* (2013) conducted an open-label trial of IV ketamine in 10 participants with treatment-resistant MDE in the context of MDD or Bipolar Disorder Type II (BDII), including two aged ≥60 (“Patient 2”, age 61; “Patient 10”, age 74). Ketamine was administered at 0.5 mg/kg over 100 minutes, twice weekly, until remission or four infusions. Follow-up measures were obtained weekly for four weeks. Patient 2, who increased their venlafaxine dose during the study, showed a MADRS decrease from 26 to 2 after one infusion and remained in remission at one month. Patient 10, who received no concurrent medications, showed a MADRS increase from 38 to 45 after four infusions. Patient 2 reported visual hallucinations; Patient 10 experienced no AEs. SSI scores were not reported for older adults. No TEAEs led to discontinuation in participants ≥60.

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Lai *et al.* (2014) conducted a double-blind, placebo-controlled crossover trial of IV ketamine in four adults with two aged ≥60 ("Subject 1", aged 62; "Subject 3", aged 66). Participants were diagnosed with treatment-resistant MDD; treatment-resistance was defined as an inadequate response to ≥1 medication trial in the current MDE. Participants' existing antidepressant medications were continued. No changes to medication dosing or ECT exposure were permitted four weeks prior to trial entry. Participants received weekly infusions at ascending doses (0.1–0.4 mg/kg) over 2–5 minutes, with one randomly inserted saline placebo infusion. Subject 1 showed a dose-response and achieved remission at 0.4 mg/kg, though effects waned by Day 7. Subject 3 did not respond. Subject 1 experienced transient dissociation, prompting extension of infusion time to improve tolerability. Subject 3 experienced transient sedation after each ketamine infusion, thought to be dose-related in context of high BMI and weight-based ketamine dosing. No significant changes in reaction times were observed at 4 hours post-infusion.

Oughli *et al.* (2023) conducted a pilot open-label trial of IV ketamine in 25 participants aged ≥65 (mean 71.5, SD 4.9) with treatment-resistant MDE in the context of MDD. Participants' existing antidepressant medications were continued, and no changes were permitted four weeks prior to trial entry. Clonidine was used prophylactically or as a rescue medication for dissociation and hypertension. Participants received 0.5 mg/kg ketamine over 40 minutes twice weekly for 4 weeks in the acute phase; 15 continued with weekly infusions for an additional 4 weeks in the continuation phase. Mean MADRS scores decreased by 9.4 points (95% CI: [6.46, 12.32], p-value: <0.01) after the acute phase and increased by 3.5 points (95% CI: [0.38, 6.56], p-value: 0.03) after the continuation phase (Cohen's d = 0.95, p-value: 0.03). Response and remission rates were 48% and 24% at acute phase end, and 47% and 27% at continuation phase end, respectively. AEs included mild nausea and headache (8%) and transient hypertension (25%).

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Clonidine was used in 32% of participants. No TEAEs led to discontinuation. Global cognition (Cohen's d = 0.61) and executive function (Dimensional Change Card Sort Test d = 0.48; Flanker d = 0.61; List Sorting d = 0.55) improved significantly during the acute phase, with gains preserved into the continuation phase.

Vanderschelden *et al.* (2023) conducted a secondary analysis of the Oughli et al. trial (NCT04504175), examining SSI scores. Six participants met the inclusion criteria with SSI ≥2 at baseline. Of these participants, four showed reduced SSI scores after the acute phase, including two reaching SSI zero. One participant's score increased (9 to 11), and one withdrew from the study. The two participants who reached an SSI score of zero maintained this score through the continuation phase.

Subcutaneous Ketamine

George *et al.* (2017) conducted a double-blind crossover trial of SC ketamine in 16 adults aged ≥60 (mean 65.6, SD 5.7) with treatment-resistant MDE in the context of MDD or BDII. Treatment resistance was defined as inadequate response to ≥1 medication in the current MDE. Participants continued prior psychiatric medications with no changes to dosing four weeks prior to and during the trial. During the RCT phase, each participant received ascending doses (0.1–0.5 mg/kg) at least one week apart, with one randomly inserted midazolam control. Participants with MADRS ≥20 at the end of the RCT phase entered an open-label phase with flexible dosing twice weekly for four weeks, then weekly for four weeks. The

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overall remission rate was 68.8%, with 50% maintaining remission beyond 7 days. A dose response relationship was observed; two remitted at 0.1 mg/kg, and four at doses <0.5 mg/kg. MADRS scores were significantly lower than midazolam at 0.2 mg/kg (p-value: 0.01), 0.3 mg/kg (p-value: 0.001), and 0.4 mg/kg (p-value: 0.001), but not 0.1 mg/kg (p-value:0.06). In the open-label phase, two of seven non-remitters achieved remission.The most common TEAEs were transient dizziness, fatigue, and blurred vision. Mild transient BP increases occurred, with maximum changes noted at 4 hours post-infusion (baseline: 94.9 mm Hg, SD 12.7; 4 hours: 96.2 mm Hg, SD: 12.1). Reaction times remained within 1 SD of baseline; other cognitive scores were stable. Mild aminotransferase elevations occurred in three participants, and one reported urinary frequency.

Oral Ketamine

Glue *et al.* (2024) conducted an RCT of oral ketamine in 168 adults aged 18–80 with treatment-resistant MDE in the context of MDD, including 12 participants aged ≥65 (mean age of randomized participants ≥65: 68.67, SD 3.96). Participants received 120 mg/day of open-label oral ketamine for 5 days. On Day 8, responders were randomized to double-blind oral ketamine (30, 60, 120, or 180 mg daily), or placebo, twice weekly for 12 weeks. By Day 92, MADRS scores declined more in participants <65 (−6.9; 95% CI [−12.3, −1.6]) than in those ≥65 (0.1; 95% CI: [−23.4, 23.7]). A 65-year-old male in the 180 mg group died by suicide on Day 42; the authors attributed this to the participant's depression. TEAEs and cognitive

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outcomes were not reported separately for participants ≥65. However, there were no notable changes in Montreal Cognitive Assessment (MoCA) scores nor vital signs across all participants.

Ketamine and ECT

Fernie *et al.* (2017) conducted the KANECT study, a double-blind RCT comparing ketamine and propofol anesthetics for ECT in 40 participants aged 18-75 with MDD and current MDE, including three participants aged ≥65. No restrictions were placed on medications participants received during ECT aside from benzodiazepines. Participants received up to 2 mg/kg of ketamine or 2.5 mg/kg propofol with ECT twice weekly. Mean Hamilton Depression Rating Scale (HDRS) scores decreased over time in younger adults (26.50 to 14.91) but not older adults (19.33 to 19.0). Although ANCOVA analysis did not find a main effect of anesthetic, subanalysis of participants ≥65 was not performed. Cognitive outcomes were not reported separately for participants ≥65.

Zou *et al.* (2021) conducted a double-blind RCT comparing propofol alone versus propofol plus ketamine ("ketofol") anesthesia for ECT in 157 adults aged ≥60 with MDD. Mean ages were 65.76 (SD 3.98) in the ketofol group and 65.2 (SD 3.92) in the propofol group. Ketofol participants received 0.3 mg/kg ketamine and 1.5 mg/kg propofol; the propofol group received propofol only. Bilateral ECT was given three times weekly for 8-12 sessions or until remission (HAMD-24 <10 after two consecutive ECT sessions). Final response (ketamine: 82.09%, control: 81.43%; p: 0.90) and remission (ketamine: 73.13%, control:

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68.57%; p-value:0.69) rates did not differ significantly between groups. Cognitive impairment (MMSE <24) incidence was significantly (p: 0.04) lower with ketofol (10.4%) than with propofol alone (25.7%). However, effects were transient and MMSE scores in both groups returned to baseline values after treatment. TEAEs were common, including hallucination, myalgia, headache, nausea/vomiting, and delirium. However, there were no significant differences in TEAE frequency between groups. Discontinuation due to AEs was not reported.

Discussion

This review updates current evidence on the efficacy, safety, and tolerability of ketamine in geriatric depression. It builds on prior reviews by incorporating GRADE certainty assessments and applying age restrictions at full-text review, allowing inclusion of studies with sub-analyses not specified in abstracts.[17,18] Across 13 studies, encompassing 757 participants aged ≥60, ketamine showed potential antidepressant effects.

Most available evidence pertains to IN and IV ketamine. IN ketamine demonstrated mixed efficacy; in the large RCT TRANSFORM-3, there was a trend toward statistical significance over placebo, though significance was not achieved.[23] Factors potentially limiting efficacy included suboptimal dosing and 4-week duration, which may have been insufficient to capture delayed responses.[36] Long-term open-label studies of IN ketamine (SUSTAIN-2 and SUSTAIN-3) suggest durable responses lasting up to 160 weeks.[29,31] IV ketamine demonstrated antidepressant effects in open-label and crossover trials, with response and remission rates comparable to younger populations in some cases.[30]

Evidence for SC, oral ketamine, and ketamine as an adjunct in ECT remains limited. George et al. reported favourable remission rates in SC ketamine, suggesting even low doses (0.1 mg/kg) may be effective.[28] The sole oral ketamine study in older adults showed no significant effect, though was limited

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by small sample.[25] Two RCTs of ketamine as an ECT adjunct did not find superiority over placebo.[26,27] However, Zou et al. observed reduced post-ECT cognitive impairment with ketofol compared to propofol, suggesting that ketamine may mitigate ECT cognitive side effects.[27]

Ketamine was generally well tolerated. AEs were mostly mild and transient (e.g., dizziness, nausea, hypertension, dissociation), consistent with findings in younger populations.[23,29] In Oughli et al., prophylactic use of clonidine reduced dissociative and hypertensive AEs, suggesting a strategy to enhance tolerability.[30] Discontinuation due to AEs was rare (<8%), and serious AEs were infrequent. No study reported increased rates of cystitis or hepatotoxicity in older versus younger adults.

Cognitive effects were generally neutral or positive. Several studies noted preserved memory, executive function, and working memory, with one trial reporting improvements in global cognition and executive function during acute treatment.[30] Reaction time results were mixed; small declines were observed in some long-term studies, persisting up to 160 weeks in SUSTAIN-3, though the clinical relevance of this finding remains unclear.[29,31] Notably, several trials excluded individuals with baseline cognitive impairment or major neurocognitive disorder, limiting generalizability.[25,26,30,32]

Evidence suggests that ketamine's antidepressant efficacy may change with age. Glue et al. and both Ochs-Ross et al. studies suggest that while older adults can respond to treatment, they may require longer durations to achieve comparable benefits seen in younger individuals.[23,25,34,37] Additionally, Ochs-Ross et al. (2022) found that response appears to decline progressively with increasing age, with the oldest patients (≥75) showing the least benefit, though findings in this group were limited by small sample sizes.[34]

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There are several limitations to this review. Most included studies were small, open-label, or exploratory, with limited power to detect age-specific effects. Many excluded common geriatric comorbidities or high suicide risk, limiting generalizability. Adjunctive treatments confounded ketamine's independent effects. Open-label designs raise concerns about expectancy effects and observer bias. Some studies used randomly-inserted placebo controls, designed primarily to mitigate expectancy bias rather than serve as robust comparators for treatment efficacy.[24,28] Saline and midazolam controls also posed challenges; while midazolam better mimics ketamine to protect blinding, its use in older adults requires caution due to potential cognitive and safety concerns.[38,39] In light of these limitations, GRADE evidence certainty was very low to low (Table 4).

This review underscores the need for well-powered RCTs focused on older adults. Future trials should designate older adults as prespecified analytic subgroups, include individuals ≥75, and measure geriatric safety outcomes (e.g., falls). Studies may consider late- vs. early-onset depression, given potential pathophysiological differences.[34,40] While IV and IN routes are most studied, SC ketamine warrants further exploration based on promising early data. Tailored approaches, including dose titration, adjunctive agents (e.g., clonidine), and monitoring of BP, cognition, and laboratory indices, may enhance tolerability.[41]

In conclusion, ketamine shows modest but promising antidepressant efficacy in older adults, with generally favorable safety and tolerability. Well-powered, age-stratified RCTs are needed to optimize dosing and clarify antidepressant efficacy.

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Word count: 5112

Author contributions:

Ronesh Sukhdeo: Conceptualization, Methodology, Investigation, Writing - Original Draft, Writing - Review and Editing, Visualization. Jocelyn K. Tamura: Conceptualization, Methodology, Investigation, Writing - Original Draft, Writing - Review and Editing, Visualization. Christine E. Dri: Writing - Review & Editing. Roger S. McIntyre: Conceptualization, Writing - Review & Editing.

Data statement:

This data has not been previously presented orally or by poster at scientific meetings.

Conflicts of Interest and Source of Funding:

Dr. Roger S. McIntyre has received research grant support from CIHR/GACD/National Natural Science Foundation of China (NSFC) and the Milken Institute; speaker/consultation fees from Lundbeck, Janssen, Alkermes, Neumora Therapeutics, Boehringer Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Neurawell, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Viatris, Abbvie, Bristol Myers Squibb (BMS) and Atai Life Sciences. For the remaining authors none were declared.

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Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

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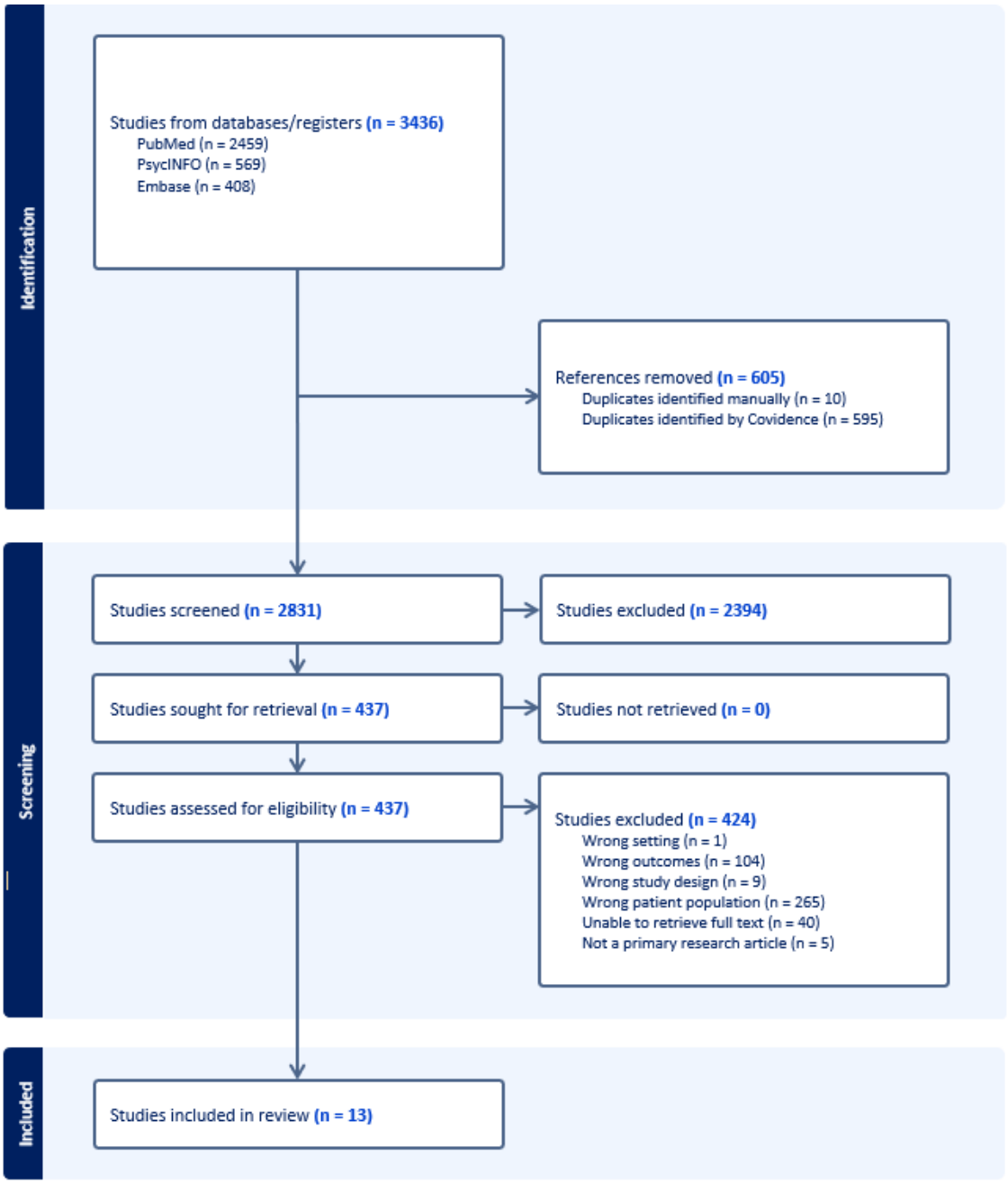
Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Figures

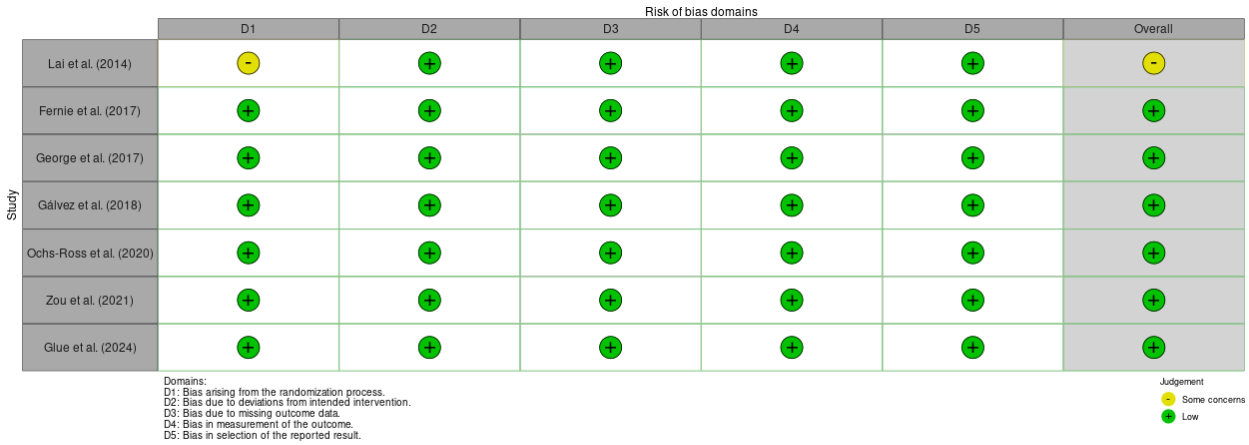
Figure 1: PRISMA flow chart



Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Figure 2: Risk-of-Bias of Randomized Controlled Trials



Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Table 1: Summary of Study Design and Participant Characteristics

Study Name	Study Design	Total Sample	Sample Age ≥60	Age (years)	Diagnosis	Definition of Treatment-Resistance	Severity of Treatment-Resistance	Total Study Duration
Intravenous								
Rasmussen *et al.* (2013)	Open-label trial	10	2	Patient 2: 61 Patient 10: 74	Treatment-resistant MDE in the context of MDD or BDII	Inadequate response to ≥2 medication trials in the current MDE	Not reported	Variable
Lai *et al.* (2014)	Randomized, double-blind, placebo-controlled, crossover trial	4	2	Subject 1: 62 Subject 2: 66	Treatment-resistant MDE in the context of MDD	Inadequate response to ≥1 medication trial in the current MDE	MSM scores: Subject 1: 11 Subject 3: 13	Variable

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Oughli *et al.* (2023); post-hoc analysis done by Vandersche lden *et al.* (2023)	Open-label trial	25	25	Mean (SD) = 71.5 (4.9)	Treatment-resistant MDE in the context of MDD	Inadequate response to ≥2 medication trials in the current MDE	Mean ATHF (SD) = 3.3 (1.4)	Acute phase of biweekly dosing for 4 weeks with partial responders eligible to receive weekly dosing for 4 more weeks
Intranasal								
Gálvez *et al.* (2018)	RCT	5	2	k1: 60 k3: 64	Treatment-resistant MDE in the context of MDD	Inadequate response to ≥2 medication trials in the current MDE	Not reported	4 weeks
Wajs *et al.* (2020); post-hoc analysis done by	Open-label	802	178	Mean (SD) = 69.7 (4.18)	Treatment-resistant MDE in the context of MDD	Inadequate response to ≥2 medication trials in the current MDE	Not reported	Induction phase of biweekly dosing for 4 weeks followed by optimization/maintena nce phase of 4 weeks

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Ochs-Ross *et al.* (2022)								of weekly dosing with additional weekly or biweekly dosing
Ochs-Ross *et al.* (2020)	RCT	138	138	Mean (SD) = 70.0 (4.52)	Treatment-resistant MDE in the context of MDD	Inadequate response to ≥2 medication trials in the current MDE	MGH-ATRQ (n): 1: 21 2: 63 3: 30 4: 16 ≥5: 7	Biweekly dosing for 4 weeks
Zaki *et al.* (2023)	Open-label trial	1148	122	Mean (SD) = 49.6 (12.28)[a]	Treatment-resistant MDE in the context of MDD	Inadequate response to ≥2 medication trials in the current MDE	Not reported	A portion of patients received biweekly dosing for 4 weeks in the acute phase followed by a variable optimization/maintenance phase
Subcutaneous								

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

George *et al.* (2017)	Randomized, double-blind, placebo-controlled, crossover trial	16	16	Mean (SD) = 65.6 (5.7)	Treatment-resistant MDE in the context of MDD or BDII	Inadequate response to ≥1 medication trial in the current MDE	Mean MGH-ATRQ (SD) = 4.3 (4.7)	Variable
Oral								
Glue *et al.* (2024)	RCT	168	12	Not reported	Treatment-resistant MDE in the context of MDD	Inadequate response to ≥2 medication trial in the current MDE	MSM = 4.8 for entire sample; not reported separately for participants ≥60	Biweekly dosing for 12 weeks with 4 weeks follow-up
Ketamine with ECT								
Fernie *et al.* (2017)	RCT	40	3	Intervention: Mean (SD) = 51.76 (9.97)	MDD with current MDE	N/A	N/A	Variable

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

				Control: Mean (SD) = 49.88 (12.53)[a]				
Zou *et al.* (2021)	RCT	157	157	Intervention: mean (SD) = 65.76 (3.98) Placebo: mean (SD) = 65.62 (3.92)	MDD	N/A	N/A	Variable

[a] Mean age and SD provided of entire sample size if ≥60 data not available

Abbreviations: SD, standard deviation; MDD, major depression disorder; MDE, major depressive episode; BDII, Bipolar Disorder Type II; MADRS, Montgomery–Asberg Depression Rating Scale; MSM, Maudsley Staging Method; ATHF, Antidepressant Treatment History Form; MGH-ATRQ, Massachusetts General Hospital, Antidepressant Treatment Response Questionnaire

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Table 2: Summary of Key Results

Study Name	**Intervention**	**Placebo/ Control**	**Outcome Measures**		**Safety and Tolerability**
			Pre-Treatment	**Post-Treatment**	
Intravenous					
Rasmussen *et al.* (2013)	IV ketamine, 0.5 mg/kg over 100 min., twice weekly until remission or 4 infusions completed	None	**MADRS Scores** Patient 2: 26 Patient 10: 38	**MADRS Scores** Patient 2: 2 Patient 10: 45	Patient 2: visual hallucinations Patient 10: no side effects
Lai *et al.* (2014)	IV ketamine, ascending dosing of 0.1, 0.2, 0.3, and 0.4 mg/kg over 2-5 min., weekly	Saline placebo	**MADRS Scores** Subject 1: 29 Subject 3: 29 **Simple and Complex Reaction Time** Not reported	**MADRS Scores** Subject 1: Remission after 0.4 mg/kg dose Subject 3: No response nor remission **Simple and Complex Reaction Time** No significant differences between pre- and post-	Subject 1: Dissociation symptoms when dose given over 2 min.; prompting revision of study protocol to 5 min. infusions Subject 3: transient sedation post-infusion with stable vital signs

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Study Name	**Intervention**	**Placebo/ Control**	**Outcome Measures**		**Safety and Tolerability**
			Pre-Treatment	**Post-Treatment**	
				treatment	
Fernie *et al.* (2017)	IV ketamine, up to 2 mg/kg bolus, used as anesthetic during twice weekly ECT	IV propofol, up to 2.5 mg/kg bolus, used as anesthetic during twice weekly ECT	**-**	**-**	No significant difference detected in cognition between the IV ketamine and control group
Zou *et al.* (2021)	IV ketamine, 0.3 mg/kg, before receiving 1.5 mg/kg propofol for ECT anesthesia	Placebo saline in addition to 1.5 mg/kg propofol	**Mean HAMD Scores (SD)** Ketamine: 30.91 (3.67) Control: 31.03 (4.11)	**Mean HAMD Scores (SD)** End of sixth ECT Ketamine: 14.18 (3.65) Control: 16.03 (4.66) P-value (ketamine vs control): 0.01 <u>Response rate</u>	No significant difference in adverse events between ketamine and control groups. Most common side effects were myalgia or headache (21% in the ketamine group) and nausea and vomiting (10% in the ketamine group)

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				Ketamine: 76.12% Control: 58.57% P-value: 0.04 End of ECT Ketamine: 8.69 (4.15) Control: 8.97 (4.82) P-value (ketamine vs control): 0.71 <u>Response rate</u> Ketamine: 82.09% Control: 81.43% P-value: 0.90 <u>Remission rate</u> Ketamine: 73.13%	

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Study Name	**Intervention**	**Placebo/ Control**	**Outcome Measures**		**Safety and Tolerability**
			Pre-Treatment	**Post-Treatment**	
				Control: 68.57% P-value: 0.69	
Oughli *et al.* (2023); post-hoc analysis done by Vanderschelden *et al.* (2023)	IV ketamine, 0.5 mg/kg over 40 minutes twice weekly for 4 weeks (acute phase) followed by of weekly infusions for 4 weeks (continuation phase)	None	**Mean MADRS Scores (SD)** Acute phase: 24.4 (7.9) Continuation phase: Not reported **Cognition** NIH Toolbox Cognitive Battery: Not reported **Scale for Suicide Ideations** Mean 11.2	**MADRS Scores** Acute phase: Mean change -9.4 from baseline, 95% CI [6.46, 12.32] P-value: <0.01 Continuation phase: Mean change +3.5 from end of acute phase 95% CI [0.38, 6.56] P-value: 0.03 <u>Response Rates</u> Acute phase: 48% Continuation phase: 47%	No treatment-related severe adverse events

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Study Name	**Intervention**	**Placebo/ Control**	**Outcome Measures**		**Safety and Tolerability**
			Pre-Treatment	**Post-Treatment**	
				<u>Remission Rates</u> Acute phase: 24% Continuation phase: 27% **Cognition*** Dimensional Change Card Sort Test: Mean change +6.61 (95% CI [1.43, 11.78], Cohen's d = 0.48, t = 2.65, p-value: 0.02 Flanker: Mean change +5.43 (95% CI [2.25, 8.61], Cohen's d = 0.61 , t	

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				= 3.54 , P-value: ≤ 0.01) List Sorting: Mean change +8.63 (95% CI [2.40, 14.86], Cohen's d = 0.55, t = 2.91 , P-value: ≤ 0.01) Fluid Cognition Composite: Mean change +7.59 (95% CI [2.85, 12.32], Cohen's d = 0.61 , t = 3.40 , P-value: ≤ 0.01)	

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Study Name	**Intervention**	**Placebo/ Control**	**Outcome Measures**		**Safety and Tolerability**
			Pre-Treatment	**Post-Treatment**	
				Scale for Suicide Ideations Mean 8.0	
Intranasal					
Gálvez *et al.* (2018)	IN ketamine, 10 sprays of 10 mg, administered at 5-minute intervals, three times weekly for the first two weeks, followed by weekly administration for two weeks	Midazolam 4.5 mg	**MADRS Scores** K1: Not reported K3: Not reported **Reaction time** K3: Not reported	**MADRS Scores** K1: Demonstrated antidepressant response; however, not reported numerically K3: Did not demonstrate antidepressant response; however, not reported numerically **Reaction time**	All participants experienced motor coordination difficulties impairing ability to self administer sprays

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				K3: Demonstrated slower reaction time from baseline; however, not reported	
Wajs *et al.* (2020); post-hoc analysis done by Ochs-Ross *et al.* (2022)	Induction phase: IN ketamine, initially 28 mg (for (≥65), 56 mg or 84 mg twice a week for 4 weeks, flexibly dosed based on efficacy and tolerability Optimization/maintenance phase: IN ketamine, weekly dosing with end of induction phase dose,	None	**Mean MADRS Scores (SD)** IND baseline Older adults: 32.8 (5.98) Young adults: 31.4 (5.04) OP/MAINT (week 12) Older adults: 32.9 (6.06) Young adults: 31.2 (4.76)	**Mean MADRS Scores (SD)** End of IND (day 28) Older adults: 14.8 (8.81), change of -18.1 (9.37) Young adults: 13.2 (7.11), change of -18.0 (7.19) Difference of LS means (older minus younger) [95% CI]: 0.5 [-0.90, 1.86] P-value: 0.49	Side effects were similar between young and older adults. Older, but not younger participants, demonstrated prolongation of simple and choice reaction times during the OP/MAINT phase. Higher cognitive functions were preserved

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
	followed by weekly or biweekly dosing that could be changed every 4 weeks			OP/MAINT (week 12) Older adults: 10.9 (7.20), change of -22.2 (9.50) Young adults: 11.0 (6.08), change of -19.9 (7.03) Difference of LS means (older minus younger) [95% CI]: -0.7 [-1.95, 0.54] P-value: 0.26 <u>Response rates</u> IND phase Older adults: 74% Young adults: 87% OP/MAINT phase	

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Study Name	**Intervention**	**Placebo/ Control**	**Outcome Measures**		**Safety and Tolerability**
			Pre-Treatment	**Post-Treatment**	
				Older adults: 79% Young adults: 81% <u>Remission rates</u> IND phase OIder adults: 51% Young adults: 51% OP/MAINT phase Older adults: 61% Young adults: 56%	
Ochs-Ross *et al.* (2020)	IN esketamine at 28 mg, 56 mg, or 84 mg, twice weekly for 4 weeks, with new oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine XR)	Placebo nasal spray with new oral antidepressant (duloxetine, escitalopram,	**Mean MADRS Scores (SD)** Ketamine: 35.5 (5.91) Control: 34.8 (6.44)	**Mean MADRS Scores (SD)** Ketamine: 25.4 (12.70), change of -10.0 (12.74) Control: 28.7 (10.11), change of -6.3 (8.86)	Most common side effects were dizziness (21% in ketamine vs 8% in the control group) and nausea (13% in ketamine vs 5% in the control group)

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
		sertraline, or venlafaxine XR)		Difference of LS means [95% CI]: -3.6 [-7.20, 0.07], P-value: 0.06 <u>Response rates</u> Ketamine: 27.0% Control: 13.3% <u>Remission rates</u> Ketamine: 17.5% Control: 6.7% <u>Sub-analysis of young old (65-74) and older old (≥75) participants</u> Young old:	

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Study Name	**Intervention**	**Placebo/ Control**	**Outcome Measures**		**Safety and Tolerability**
			Pre-Treatment	**Post-Treatment**	
				Difference of LS means [95% CI]: -4.9 [-8.96, -0.89] P-value: 0.02 Older old: Difference of LS means [95% CI]: -0.4 [-10.38, 9.50] P-value: 0.93	
Zaki *et al.* (2023)	Induction phase: IN esketamine, initially 28 mg (for (≥65), 56 mg or 84 mg twice a week for 4	None	-	**Mean change in Z-scores from baseline to end of OP/MAINT in Z-score (SD)** **Cogstate**	No treatment-related cystitis or psychosis reported. Long-term ketamine exposure showed no concern for dependence. Most common side effects were dissociation, dizziness, nausea,

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
	weeks, flexibly dosed based on efficacy and tolerability, combined with an antidepressant Optimization/maintenance phase: IN esketamine, weekly flexible dosing			Simple reaction time ≥65: -0.200 (1.36) <65: -0.05 (1.25) Choice reaction time ≥65: -0.37 (1.36) <65: -0.22 (1.31) One card learning ≥65: 0.31 (1.20) <65: 0.28 (1.34) One-Back ≥65: 0.02 (1.18) <65: 0.16 (1.08)	vertigo, and

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Study Name	**Intervention**	**Placebo/ Control**	**Outcome Measures**		**Safety and Tolerability**
			Pre-Treatment	**Post-Treatment**	
				Groton maze learning test ≥65: 0.14 (0.96) <65: 0.17 (1.03) HVLT-R, word recall ≥65: 0.11 (1.18) <65: 0.12 (1.12) HVLT, delayed recall ≥65: 0.10 (1.15) <65: 0.11 (1.02)	
Subcutaneous					
George *et*	SC ketamine, 0.1, 0.2, 0.3, 0.4,	Midazolam 0.01	**Mean MADRS Scores**	**MADRS Scores**	Transient increases in BP

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Study Name	**Intervention**	**Placebo/ Control**	**Outcome Measures**		**Safety and Tolerability**
			Pre-Treatment	**Post-Treatment**	
al. (2017)	0.5 mg/kg with ascending regimen and weekly dosing. Midazolam control was randomly used instead of ketamine in the first 3 weeks.	mg/kg	**(SD)** 34.8 (3.5) **Simple and Complex Reaction Time** Not reported	Not reported Significance of changes in MADRS in ketamine compared with midazolam by dose: 0.1 mg/kg (p-value: 0.06) 0.2 mg/kg (p-value: 0.01) 0.3 mg/kg (p-value: 0.001) 0.4 mg/kg (p-value: 0.001) 0.5 mg/kg statistical analysis was not done **Simple and Complex Reaction Time**	Psychomimetic effects Liver function tests: mild AST, ALT, or GGT elevation in 3/16 participants

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				Performance was within 1 SD of baseline means	
Oral					
Glue *et al.* (2024)	RCT phase: Oral extended-release ketamine, 30 mg, 60 mg, 120 mg, or 180 mg twice weekly	Placebo tablet with polyethylene oxide	-	**Mean MADRS Scores** Authors remarked greater reduction in MADRS scores from baseline to Day 92 among participants aged <65 years (−6.9 [95% CI] [−12.3, −1.6]) compared with participants ≥65	

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				years (0.1 [95% CI] [−23.4 to 23.7])	

*Only significant values reported

Treatment outcomes included only for patients ≥60 years old. Values rounded to two decimal places. Abbreviations: IV, intravenous; CI: confidence interval; MADRS, Montgomery and Asberg Depression Rating Scale; LS: least square SC: subcutaneous; ECT, electroconvulsive therapy; IN, intranasal; SD, standard deviation; IND, induction phase; OP/MAINT, optimization/maintenance phase; HAMD, Hamilton Depression Rating Scale; HVTL-R, Hopkins Verbal Learning Test Revised

Table 3: Risk of Bias of Quasi-Experimental Studies

STUDY INFORMATION	INTERNAL VALIDITY BIAS RELATED TO:						STATISTICAL CONCLUSION VALIDITY:
	Temporal Precedence	Selection and Allocation	Confounding Factors	Administration of Intervention	Assessment, Detection, and Measurement of Outcome	Participant Retention	

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

NAME	OUTCOME	1	2	3	4	5	6	7	8	9
Rasmussen *et al.* (2013)	Depression Score	Y	N	Y	N	Y	Y	U	Y	Y
	Safety and Tolerability					Y	Y	U		
Wajs *et al.* (2020)	Cognition	Y	N	Y	N	Y	Y	U	Y	Y
Ochs-Ross *et al.* (2022)	Depression Score	Y	N	Y	Y	Y	Y	U	Y	Y
	Cognition					Y	Y	U		Y
	Safety and Tolerability					Y	Y	U		Y
Oughli *et al.* (2023)	Depression Score	Y	N	Y	Y	Y	Y	U	Y	Y
	Cognition					Y	Y	U		Y
	Safety and Tolerability					Y	Y	U		Y

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Word count: 5112

Vanderschelden et al. (2023)	Suicidality	Y	N	Y	Y	Y	Y	U	Y	Y
Zaki *et al.* (2023)	Cognition	Y	N	Y	N	Y	Y	U	Y	Y

Abbreviations: Y, Yes; N, No; U, Unknown

Table 4: GRADE Summary of Findings Table

Outcome	**Number of Participants; Study designs**	**Findings Summary**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Certainty (GRADE)**
Intranasal Ketamine								
Change in Depression Symptom Severity	2 RCTs (Ochs-Ross et al., 2020, Gálvez et al., 2018); 1 open-label study (Wajs et al., 2020)	TRANSFORM-3 found no statistically significant difference in MADRS change at Day 28 between ketamine and placebo. Other studies were open-label or underpowered.	Serious	Not Serious	Not Serious	Serious	Not Serious	⨁◯◯◯ Low

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

Cognition	1 RCT (Gálvez et al., 2018); 2 open-label studies (Wajs et al., 2020, Zaki et al., 2023)	Wajs and Zaki showed mild reaction time slowing; other cognitive domains were largely stable. Gálvez interpretation limited by early discontinuation and small sample size.	Serious	Not Serious	Not Serious	Serious	Not Serious	⨁⨁◯◯ Low
Frequency of TEAEs	1 RCT (Ochs-Ross et al., 2020); 1 post-hoc analysis (Ochs-Ross et al., 2022)	TEAEs were common across both studies, occurring in approximately 70–86% of participants. Most adverse events were mild to moderate, with dizziness, nausea, and dissociation being the most frequently reported.	Not Serious	Not Serious	Not Serious	Not Serious	Not Serious	⨁⨁⨁◯ Moderate
Discontinuation due to TEAEs	1 RCT (Ochs-Ross et al., 2020); 1 post-hoc analysis (Ochs-Ross et al., 2022)	Discontinuation due to TEAEs was uncommon across both studies. Rates ranged from ~3–7%, with similar proportions in older and younger adults.	Not Serious	Not Serious	Not Serious	Serious	Not Serious	⨁⨁◯◯ Low
Intravenous Ketamine								
Change in	2 open-label	Oughli et al., found mean MADRS	Serious	Serious	Not Serious	Serious	Not Serious	⨁⨁◯◯ Low

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Word count: 5112

Depression Symptom Severity	studies (Rasmussen et al., 2013, Oughli et al., 2023), 1 placebo-controlled crossover trial (Lai et al., 2014)	decreased by 9.4 points (95% CI: 6.5 to 12.3, p-value: 0.01). Rasmussen and Lai reported mixed results.						
Cognition	1 open-label study (Oughli et al., 2023), 1 placebo-controlled crossover trial (Lai et al., 2014)	Oughli et al. found significant improvements in cognitive composite and executive function; Lai et al. found no decline in reaction times post-infusion.	Serious	Not Serious	Not Serious	Serious	Not Serious	⨁⨁◯◯ Low
Frequency of TEAEs	2 open-label studies (Rasmussen et al., 2013, Oughli et al., 2023), 1 placebo-controlled crossover trial (Lai et al., 2014)	Across 29 older adults, no serious TEAEs or discontinuations were reported. Common TEAEs were transient hypertension (25%) and nausea/vomiting (8%, Oughli).	Serious	Not Serious	Serious	Serious	Not Serious	⨁◯◯◯ Very Low

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Discontinuation due to TEAEs	2 open-label studies (Rasmussen et al., 2013, Oughli et al., 2023), 1 placebo-controlled crossover trial (Lai et al., 2014)	No participants aged ≥60 discontinued treatment due to TEAEs across all three studies (n=29).	Serious	Not Serious	Serious	Serious	Not Serious	⨁◯◯◯ Very Low
Subcutaneous Ketamine								
Change in Depression Symptom Severity	1 placebo-controlled crossover trial (George et al., 2017)	SC ketamine significantly reduced MADRS scores compared to midazolam at doses ≥0.2 mg/kg. A dose-response relationship was observed, and overall remission rate was 68.8%.	Serious	N/A	Not Serious	Serious	Not Serious	⨁⨁◯◯ Low
Cognition	1 placebo-controlled crossover trial	Neurocognitive test scores (e.g., simple/complex reaction times) remained within 1 SD of baseline.	Serious	N/A	Not Serious	Serious	Not Serious	⨁⨁◯◯ Low

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	(George et al., 2017)	No significant cognitive decline was reported.						
Frequency of TEAEs	1 placebo-controlled crossover trial (George et al., 2017)	Most common TEAEs were transient dizziness, fatigue, and blurred vision. Mild, transient BP elevations and LFT abnormalities were noted.	Serious	N/A	Not Serious	Serious	Not Serious	⨁⨁◯◯ Low
Discontinuation due to TEAEs	1 placebo-controlled crossover trial (George et al., 2017)	No participants discontinued due to adverse events in this small sample.	Serious	N/A	Not Serious	Serious	Not Serious	⨁⨁◯◯ Low
Oral Ketamine								
Change in Depression Symptom Severity	1 RCT (Glue et al., 2024)	No clinically meaningful change in MADRS by Day 92 (mean change: 0.1; 95% CI: [−23.4, 23.7]) in older adults	Serious	N/A	Serious	Serious	Not Serious	⨁◯◯◯ Very Low

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Cognition	1 RCT (Glue et al., 2024)	No notable changes reported in cognition for all participants; no separate data for ≥65	Serious	N/A	Serious	Serious	Not Serious	⨁◯◯◯ Very Low
Frequency of TEAEs	1 RCT (Glue et al., 2024)	TEAEs were measured but not reported separately for older adults. One participant ≥65 died by suicide. Authors noted no notable change in vital signs overall.	Serious	N/A	Serious	Serious	Not Serious	⨁◯◯◯ Very Low
Ketamine + ECT								
Change in Depression Symptom Severity	2 RCTs (Fernie et al., 2017, Zou et al., 2021)	Response and remission rates did not differ significantly between ketofol and propofol only groups; HRSD scores decreased more in younger than older adults.	Not Serious	Serious	Serious	Serious	Not Serious	⨁◯◯◯ Very Low
Cognition	2 RCTs (Fernie et al., 2017, Zou et	Zou et al., suggests less transient post-ECT cognitive impairment	Serious	Serious	Serious	Serious	Not Serious	⨁◯◯◯ Very Low

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	al., 2021)	with ketofol.						
Frequency of TEAEs	1 RCT (Zou et al., 2021)	Hallucination, headache, nausea, delirium were common; no significant difference between ketofol vs. propofol groups.	Not Serious	N/A	Not Serious	Serious	Not Serious	⨁⨁◯ Moderate

Abbreviations: RCT, randomized controlled trial; MADRS, Montgomery and Asberg Depression Rating Scale; TEAE, treatment-emergent adverse event; CI, confidence interval; SC, subcutaneous; SD, standard deviation; BP, blood pressure; LFT, liver function test; HRSD, Hamilton Depression Rating Scale; ECT, electroconvulsive therapy;

Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia