

**American Journal of Geriatric Psychiatry**  
**Ketamine for Late-Life Depression: A Systematic Review of Efficacy, Safety, and Tolerability**  
--Manuscript Draft--

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<b>Additional Information:</b>	
<b>Question</b>	<b>Response</b>
Please provide the word count for your submission. The word count applies to only the main manuscript text; it should not include the abstract, references, figure legends, or tables.	5112
Please indicate the number of figures, if	2

any, that are included with this submission.	
Please indicate the number of tables, if any, that are included with this submission.	5

Dear Editor,

We kindly request you reconsider our original article entitled **Ketamine for Late-Life Depression: A Systematic Review of Efficacy, Safety, and Tolerability** for publication in the American Journal of Geriatric Psychiatry after we have edited our manuscript according to the peer-review comments from our original submission. We have responded to each peer-review feedback point-by-point and have also highlighted changes in the manuscript with comments to make reading easier. We confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere.

Ketamine has emerged as a new and promising treatment for major depression. In light of evidence for ketamine in the general adult population, there has been increasing interest in the applications of ketamine in geriatric populations. To our knowledge, the most recent systematic reviews investigating ketamine and depression in older adults from 2021. In addition, these systematic reviews have limitations such as including case reports/series or only including randomized controlled trials.

To that end, we aimed to create the most comprehensive systematic review by implementing an age cut-off ( $\geq 60$  years old) at full-text review instead of abstract screening to capture subgroup analyses. Through this method, we have reported results of multiple studies that would be missed with a conventional screening approach. Our results show ketamine to have some effectiveness in treating depression and its largely safe and tolerably side effect profile. As the most popular geriatric psychiatry journal, we believe this publication to be of great interest to your readers.

Please address all correspondence concerning this manuscript to:

Dr. Roger S. McIntyre, e-mail: [roger.mcintyre@bcdf.org](mailto:roger.mcintyre@bcdf.org)

Thank you for your time and consideration of this manuscript.

Sincerely,

Ronesh Sukhdeo

Submitting author, on behalf of all co-authors

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## Reviewer 1

General Comment: This is a timely and relevant review examining the use of ketamine - intranasal, subcutaneous, and intravenous- in older adults with depression. A notable strength of this review is the adherence to PRISMA guidelines. They also included the major studies and the results were clearly highlighted. Limitations include that their studies focused on younger older adults that limits the generalizability of the finding to older old adults.

**[Feedback 1] Can the authors clarify how they determined treatment resistance in the samples? It is unclear whether the sample included older adults with treatment resistant depression.**

Authors' Response: Thank you for this suggestion. A general definition for "treatment resistance" is included in the first paragraph of our Results section, and it is indicated where studies' diverged from this definition in each study-specific paragraph. Definitions of treatment resistance for each study are also included now in Table 1. *Please see associated highlights for changes made.*

**[Feedback 2] Minor edits: can the authors spell out: LFT, IV, IN, SC**

Authors' Response: Thank you for this suggestion. We have spelled out LFTs in every instance, and have spelled out IV, IN, and SC in their first respective instances. *Please see associated highlights for changes made.*

## Reviewer 2

I thank the authors for the opportunity to review the manuscript titled : "Ketamine for Late-Life Depression: A Systematic Review of Efficacy, Safety, and Tolerability" by Sukhdeo et al. This is a very relevant and well written review of the current state of the literature on the use of ketamine in older adults. The authors completed a systematic review of the available literature. Their results suggest that ketamine may be a good treatment option for depression in older adults and it is generally well tolerated with minimal side effects.

A few suggestions for the authors to consider:

**[Feedback 3] Per the PRISMA guidelines, please present the full search strategies for all databases, registers and websites, including any filters and limits used. This can sometimes be added as an Appendix. Did a research librarian conduct the search?**

Authors' Response: Thank you for this suggestion. We have included the full search strategy for all databases and the corresponding filters, limits, and resulting numbers in Appendix 1. A research librarian was involved in creating the original search strings/criteria; this is now indicated in the paper. *Please see associated highlights for changes made.*

**[Feedback 4] Throughout the manuscript, both terms MDD and TRD are used. In the results section, please clarify which studies had participants with MDD and which had TRD and how TRD was defined for each study (when applicable). Some of the studies seem to make that distinction and it would be helpful the highlight that since those with TRD would be expected to have a lower response and remission rate. And for those with TRD, please add a descriptor of severe the treatment resistance was ( e.g mean score of the ATHF or other scale used).**

Authors' Response: Thank you for this suggestion. We have indicated whether or not studies included treatment resistant depression populations and, if so, the definitions of treatment resistance used. This information was updated in the Results section and in Table 1. In addition, we have included the descriptor of severity of treatment response (e.g., ATHF, ATRQ, MSM) where available and applicable. *Please see associated highlights for changes made.*

**[Feedback 5] Were the exclusion criteria uniform among most studies (e.g history of psychosis, dementia, Bipolar disorder, substance use). This is useful to comment on relating the generalizability of this treatment. How many studies assessed cognitive status as baseline?**

Authors' Response: Thank you for this suggestion. A summary of common exclusion criteria of the included studies is included in the Results section, and a comment on how this limits generalizability is included now in the Discussion section. In some studies, baseline diagnoses of cognitive impairment or dementia were exclusion criteria, further limiting generalizability of cognitive outcomes. This is explored further in the discussion section. *Please see associated highlights for changes made.*

**[Feedback 6] Also in the results section, please clarify which studies used ketamine as an augmenting agent vs monotherapy. How many required participants to be on a stable dose of an antidepressant vs the studies that had participants start a new antidepressant while starting with esketamine.**

Authors' Response: Thank you for this suggestion. We have clarified in each study's respective results summary if ketamine was a monotherapy or used alongside an antidepressant or other psychotropic medications. *Please see associated highlights for changes made.*

**[Feedback 7] Since this is a review of late-life depression, can you please comment on which studies looked at geriatric focused negative outcomes or adverse events such as falls and cognition. The authors may want to consider this in their discussion about future studies.**

Authors' Response: Thank you very much for this suggestion. Studies which assessed geriatric-focused treatment emergent adverse events are now more clearly showcased in the results section. Cognition was assessed in multiple studies; falls were only assessed in one study (Ochs-Ross, 2022). A suggestion to focus on outcomes relevant to geriatric populations is now included in the discussion section. *Please see associated highlights for changes made.*

**[Feedback 8] The authors describe some cognitive changes that occur with use of ketamine in its various forms. For example, in the studies that reported slowed RT among other cognitive changes, please indicate the duration of these effects- was it just for a few hours or did it last for days. In fact, there is evidence that the neuroplastic or precognitive effects of ketamine can help improved overall cognitive and executive function .**

Authors' Response: Thank you for this suggestion. A more detailed discussion of the impact of ketamine on cognition is included in the discussion. Higher level cognitive functions including executive function and learning were preserved or improved. Small, but persistent, reaction time changes were noted with longer-term ketamine treatment. *Please see associated highlights for changes made.*

**[Feedback 9] The authors may want to consider discussing where ketamine treatments may fall in the general treatment algorithm for TRD - after oral antidepressants? Before ECT? Same as TMS? As they expand on the risk benefit of this treatment.**

Authors' Response: Thank you for this suggestion. While we agree this would be clinically useful, providing recommendations regarding a treatment algorithm for TRD falls outside the scope of this review.

## **Reviewer 3**

The goal of this manuscript is to review evidence for the efficacy, safety, and tolerability of ketamine (intravenous, subcutaneous, intranasal, and oral) in persons age 60 years or older with a diagnosis of depression, which is a topic of relevance to readers of this journal. Included studies were not limited to those with exclusively older patients; if a study included a mixed age group, but included persons aged 60 years or older, it could also be included in the review if age-related data were reported in the original study. The senior author previously published a systematic review of ketamine for the treatment of depression in older adults, in the Journal of Psychiatric Research in 2021. The current manuscript provides an updated review.

#### GENERAL COMMENTS

**[Feedback 10] Was a protocol completed and registered prior to conducting this systematic review? I could not find a protocol registered in PROSPERO and there is no mention of protocol registration in the manuscript.**

Authors' Response: We thank the authors for this point. PROSPERO registration was not completed for this paper.

**[Feedback 11] While a meta-analysis based on a systematic review would be ideal, there are too few data (and the studies are too heterogeneous) to perform a meta-analysis. The authors therefore present the findings qualitatively, in the text and tables. There are parts of the text where more data could be provided. For example, in the section on ketamine and ECT, when reporting the results of the Zou et al. study, the authors write "Final response and remission rates did not differ significantly between groups.", without supporting data---it would be informative and important to report the actual response and remission rates in the text, as well as the table. The same comment applies to some other parts of the text and tables. In addition, there are sections of the Results (e.g studies by Wajs et al. and Zaki et al.) where there is no mention of efficacy findings. It would be helpful to systematically report when efficacy was not assessed, so that the reader isn't left guessing.**

Authors' response: We are grateful to this reviewer for this suggestion. We agree that including more supporting data is important and have done a review of each study for their respective results section paragraph and table row, and have filled in more data where available. If efficacy findings were not reported for a study, we have mentioned this. *Please see changes implemented throughout the Results section; some examples are highlighted in the updated manuscript.*

3) There are some additional things that could strengthen this systematic review:

**[Feedback 12] Risk of bias can also be assessed for observational and cohort studies (using a different tool than Cochrane; e.g. JBI tool) and I suggest that this be done;**

Authors' response: Thank you for this suggestion. The JBI risk tool was used to evaluate risk of bias for the other studies and summarized in Table 3. *Please see associated highlights for changes made.*

**[Feedback 13] In addition to a comprehensive assessment of risk of bias, there should also be an assessment of the certainty of evidence, for example using the GRADE tool. Evaluating and discussing the certainty of evidence would be very helpful---I suspect that the certainty of evidence is low.**

Authors' response: Thank you for this suggestion. The GRADE tool was used to assess the certainty of evidence. Results of this assessment are summarized in Table 4. Indeed, the certainty of evidence is very low to low for most studies.

**[Feedback 14] Where important data are missing, I suggest contacting the authors of those studies to obtain the data. For example, the Glue et al. article reports that efficacy of oral ketamine differs between younger and older adults, but the article doesn't report the number of older and younger participants in the study---obtaining this information would be very helpful in interpreting this age-related finding.**

Authors' response: Thank you for this suggestion. Authors were contacted where available data were missing. We have confirmed the number of older and younger participants in the Glue et al. article.

**[Feedback 15] There is a lack of clarity about the types of studies that were included in the review. The Abstract states that "Only primary, peer-reviewed studies were included; case reports and case series were excluded." It isn't clear what the word 'primary' means, from an operational point of view, in this sentence. The Methods (page 3) state "primary, peer-reviewed research articles", so it is not clear whether it was the study or the published article that was the focus of eligibility. The authors include data from the naturalistic, retrospective REAL-ESK study, but don't include the study by Lipsitz et al. 2021, which was also naturalistic and retrospective. Both were published in journals as 'peer-reviewed research articles'. I suggest that the authors confine their review to clinical trials, that is studies where participants were prospectively assigned to treatment with ketamine in order to evaluate its effect on health outcomes. -**

Authors' response: Thank you very much for this thoughtful suggestion. We updated our inclusion criteria to focus on prospective clinical trials and revised our article discussion based on this adjustment. This adjustment to inclusion criteria was also reflected in our methods section. *Please see associated highlights for changes made.*

**[Feedback 16]** I suggest reorganizing tables 1 and 2, so that the studies are grouped according to the route of administration (intravenous, subcutaneous, intranasal, and oral), using subheadings in the tables for each grouping. In addition, within each grouping, I suggest that studies are systematically organized according to their design, starting with open-label studies and followed by RCTs.

Authors' Response: Thank you for this suggestion, we have reorganized the tables and grouped them per route of administration. We did not organize according to study design, as we felt that having a chronological order to be more readable and consistent with the order of paragraphs in the results section describing each study. *Please see associated highlights in Tables 1 and 2 for changes made.*

#### SPECIFIC COMMENTS

**[Feedback 17]** Abstract: "Results suggest that ketamine is effective in treating major depression in older adults, although findings were mixed." I suggest that this interpretation of the findings is too enthusiastic and that an alternative interpretation would be: "Results of some studies suggest that ketamine may be effective in treating major depression in older adults, although other studies did not find it to be efficacious". In addition, once the certainty of evidence has been assessed, I suggest that a sentence is added to the abstract that reports on the certainty of evidence, so as to provide context for recommending (or not) ketamine as an intervention for treatment resistant depression in older adults.

Authors' Response: Thank you for this suggestion. We have incorporated the recommended edits, and have also included a sentence for the certainty of evidence that has been assessed. Our abstract reflects these changes. *Please see associated highlights for changes made.*

**[Feedback 18]** The Introduction describes the goal of the review as examining the efficacy, safety, and tolerability of ketamine in treatment-resistant depression in older adults. However, the search term and inclusion criterion is simply a diagnosis of depression, not necessarily treatment-resistant depression. Please revise the Introduction and goal of the review to reflect the search.

Authors' Response: Authors' response: We thank the reviewer for this suggestion. We agree that initially describing the review to be specifically for treatment-resistant depression to be misleading. We have made changes to the Abstract and Introduction to better reflect our search criteria for this study and focus on geriatric depression, as opposed to treatment-resistant depression. Of note, given the clinical indication for ketamine, many of our studies include patients with treatment-resistant depression. *Please see associated highlights for changes made.*

**[Feedback 19] Discussion, Limitations (page 12).** The authors note that several of the studies informing the review were open-label. I suggest that they expand upon this point, specifically that open-label studies may over-estimate efficacy of the drug because of expectancy effects, as well as the non-pharmacologic effects of participating in a research study (e.g., support and encouragement by research personnel). In addition, another limitation worth mentioning is that even the placebo controlled studies may have had a less than optimal placebo intervention (e.g. studies by Lai et al. and George et al. are reported to have administered a single dose of placebo).

Authors' response: We thank the reviewer for this insightful suggestion. We have expanded on the limitations section of our review and provided additional commentary into the limitations of open-label studies and limitations to placebo interventions used. *Please see associated highlights for changes made.*

**[Feedback 20] Discussion.** There needs to be discussion of the certainty of evidence.

Authors' response: We thank the reviewer for this suggestion. The findings and implications of the GRADE certainty of evidence assessment is included in the discussion of the paper. *Please see associated highlights for changes made.*

**[Feedback 21] Discussion.** I suggest that future directions be discussed in more detail. Clearly there is a need for an adequately powered, adequately blinded, parallel-design randomized controlled trial of ketamine in older adults (including both 'young old' and 'old old'). If such a trial was to be conducted, which route of ketamine administration would be recommended based on the existing evidence and why? What is the evidence that midazolam would offer effective blinding and are there concerns about this approach in older adults, who are vulnerable to cognitive impairment with benzodiazepines? if such a study was to find ketamine to be effective acutely, a continuation RCT to examine relapse prevention would then be indicated.

Authors' response: We thank the reviewer for this insightful suggestion. We have added to our discussion per the above suggestion and provide a discussion on what future RCTs may look like given the current

evidence with respect to routes of administration of ketamine and comparators of ketamine in controlled studies.

## Reviewer 4

This is a manuscript entitled Ketamine for Late-Life Depression: A Systematic Review of Efficacy, Safety, and Tolerability, which aims to systematically organize and update the currently available evidence related to this topic. The following comments are intended to strengthen the authors' publication process:

Background:

**[Feedback 22] The definition of "geriatric depression" should be explicitly framed in epidemiological terms (e.g., ICD/DSM criteria if used in referenced studies).**

Authors' Response: Thank you for this suggestion. DSM definitions of depression (e.g., "major depressive episode in the context of MDD or BDII") were specified where indicated, including the Introduction and in the Results section. *Please see associated highlights for changes made.*

**[Feedback 23] Consider differentiating late-onset vs. early-onset depression in later life, as they may differ in pathophysiology and treatment response.**

Authors' Response: Thank you for this suggestion. While only one study examined subgroups based on late onset and early onset in our review, this is now included as a suggestion for future studies in our Discussion section. *Please see associated highlights for changes made.*

**[Feedback 24] Include global disability metrics (e.g., DALYs, burden by region or age group from GBD data).**

Authors' Response: Thank you. We have included a comment on the burden of disability of MDD to the introduction; however, we were unable to provide greater details (e.g., burden by region or age group) due to word-count limitations. *Please see associated highlights for changes made.*

**[Feedback 25] Emphasize why TRD in geriatric populations represents a unique clinical and public health challenge (e.g., multimorbidity, polypharmacy, frailty).**

Authors' response: We thank the reviewer for this suggestion. We have expanded our introduction to include the above point. *Please see associated highlights for changes made.*

**[Feedback 26]** The sentence "To our knowledge, two prior systematic reviews..." is vague. Were these reviews recent? What were their key limitations? Clarifying these would better justify the need for an updated review.

Authors' Response: Thank you for this suggestion, we have updated our introduction to reflect the value in providing an updated review. *Please see associated highlights for changes made.*

**[Feedback 27]** "Ketamine demonstrates rapid onset effects..." → Consider: "Ketamine has been shown to produce rapid antidepressant effects..."

Authors' Response: Thank you for this suggestion. We agree that this phrasing strengthens the writing of this paper and have updated the Introduction accordingly. *Please see associated highlights for changes made.*

**[Feedback 28]** Replace "we endeavour to update..." with a more academic phrase, such as: "This systematic review aims to synthesize and update current evidence regarding..."

Authors' Response: Thank you for this suggestion. *Please see associated highlights for changes made.*

Methods:

**[Feedback 29] General: expand the information with more details**

Authors' Response: We have included more details in the methods with respect to the data extraction process, risk of bias assessments, and study inclusion and exclusion criteria.

**[Feedback 30] Separate the methods section including subsections**

Authors' Response: We have separated the methods into subsections accordingly.

**[Feedback 31] Ideally, include the full search strings as a supplementary table or appendix.**

Authors' Response: Thank you for this suggestion, we have included a Supplementary Table that details our full search string and resulting numbers from each database. *Please see Supplementary Table 1.*

**[Feedback 32]** Indicate that a PRISMA flow diagram was used to describe the screening process. This is a standard expectation. For example: "The selection process is detailed in the PRISMA flow diagram (Figure X)."

Authors' Response: We thank the reviewer for this suggestion, we have included a direct reference to Figure 1 in the method section which includes the PRISMA diagram. *Please see associated highlights for changes made.*

**[Feedback 33]** Data Extraction Process Omitted:

- \* There is no mention of how data were extracted
- \* Was a standardized extraction form used?
- \* Was data extraction conducted independently by two reviewers?
- \* What variables were extracted (study design, sample size, dose, formulation, outcomes, etc.)?

Authors' Response: Thank you for these insightful points. We have expanded our methods section to include the above points. *Please see associated highlights for changes made.*

**[Feedback 34]** Discussion: What additional strength was identified in updating the systematic review compared to the two previous reviews? Briefly explain this in the strengths section of your manuscript.

Authors' response: We thank the author for this suggestion. We have included a section of the strengths of the systematic review in the Discussion section. *Please see associated highlights for changes made.*

## 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.

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Word count: 5112

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

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

## 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  $\geq 60$  years applied at full-text review to capture subgroup data. Thirteen studies met inclusion criteria, comprising 757 adults. Studies 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.

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

## Introduction

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

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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.<sup>18</sup> 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.

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

## 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.<sup>19</sup>

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

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## Risk of Bias and Evidence Certainty

Risk of bias (ROB) for RCTs was performed according to the Cochrane ROB2 guideline with ROBVIS for visualization.<sup>20</sup> 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.<sup>21</sup> GRADE evidence certainty was assessed by two independent reviewers (RS, JKT).

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## 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<sup>22–28</sup>, four

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

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open-label trials<sup>29–32</sup>, and two post-hoc analyses<sup>33,34</sup>. These included five intranasal (IN)<sup>22,23,29,31,34</sup>, four intravenous (IV)<sup>24,30,32,33</sup>, 1 subcutaneous (SC),<sup>28</sup> one oral,<sup>25</sup> and 2 ketamine combined with ECT studies.<sup>26,27</sup> 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.<sup>35</sup>

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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.

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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

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

Word count: 5112

(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% 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  $\geq 75$  (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  $\geq 65$ , 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  $\geq 65$  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 outcomes were assessed but not reported separately for older adults. One death occurred in a participant  $\geq 65$ , though this was deemed unrelated to treatment.

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Ochs-Ross *et al.* (2022) conducted a post-hoc analysis of SUSTAIN-2 comparing outcomes in adults  $\geq 65$  and  $< 65$ . No significant differences were observed in MADRS score changes during induction (baseline:

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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.

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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 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",

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

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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  $\geq 60$ .

Lai *et al.* (2014) conducted a double-blind, placebo-controlled crossover trial of IV ketamine in four adults with two aged  $\geq 60$  ("Subject 1", aged 62; "Subject 3", aged 66). Participants were diagnosed with treatment-resistant MDD; treatment-resistance was defined as an inadequate response to  $\geq 1$  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  $\geq 65$  (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,

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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%). 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  $\geq 2$  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  $\geq 60$  (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  $\geq 1$  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  $\geq 20$  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 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

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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.

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## 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 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.

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Zou *et al.* (2021) conducted a double-blind RCT comparing propofol alone versus propofol plus ketamine ("ketofol") anesthesia for ECT in 157 adults aged  $\geq 60$  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 (HAM-D-24 <10 after two consecutive ECT sessions). Final response (ketamine: 82.09%, control: 81.43%; p: 0.90) and remission (ketamine: 73.13%, control: 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.

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## 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.<sup>17,18</sup> Across 13 studies, encompassing 757 participants aged  $\geq 60$ , ketamine showed potential antidepressant effects.

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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.<sup>23</sup> Factors potentially limiting efficacy included suboptimal dosing and 4-week duration, which may have been insufficient to capture delayed responses.<sup>36</sup> Long-term open-label studies of IN ketamine (SUSTAIN-2 and SUSTAIN-3) suggest durable responses lasting up to 160 weeks.<sup>29,31</sup> IV

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ketamine demonstrated antidepressant effects in open-label and crossover trials, with response and remission rates comparable to younger populations in some cases.<sup>30</sup>

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.<sup>28</sup> The sole oral ketamine study in older adults showed no significant effect, though was limited by small sample.<sup>25</sup> Two RCTs of ketamine as an ECT adjunct did not find superiority over placebo.<sup>26,27</sup> However, Zou et al. observed reduced post-ECT cognitive impairment with ketofol compared to propofol, suggesting that ketamine may mitigate ECT cognitive side effects.<sup>27</sup>

Ketamine was generally well tolerated. AEs were mostly mild and transient (e.g., dizziness, nausea, hypertension, dissociation), consistent with findings in younger populations.<sup>23,29</sup> In Oughli et al., prophylactic use of clonidine reduced dissociative and hypertensive AEs, suggesting a strategy to enhance tolerability.<sup>30</sup> 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.<sup>30</sup> 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.<sup>29,31</sup> Notably, several trials excluded individuals with baseline cognitive impairment or major neurocognitive disorder, limiting generalizability.<sup>25,26,30,32</sup>

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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.<sup>23,25,34,37</sup> Additionally, Ochs-Ross et

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al. (2022) found that response appears to decline progressively with increasing age, with the oldest patients ( $\geq 75$ ) showing the least benefit, though findings in this group were limited by small sample sizes.<sup>34</sup>

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.

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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.<sup>24,28</sup> 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.<sup>38,39</sup> In light of these limitations, GRADE evidence certainty was very low to low (Table 4).<sup>1</sup>

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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  $\geq 75$ , and measure geriatric safety outcomes (e.g., falls). Studies may consider late- vs. early-onset depression, given potential pathophysiological differences.<sup>34,40</sup> 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.<sup>41</sup>

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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.

**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.

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

**Data statement:**

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

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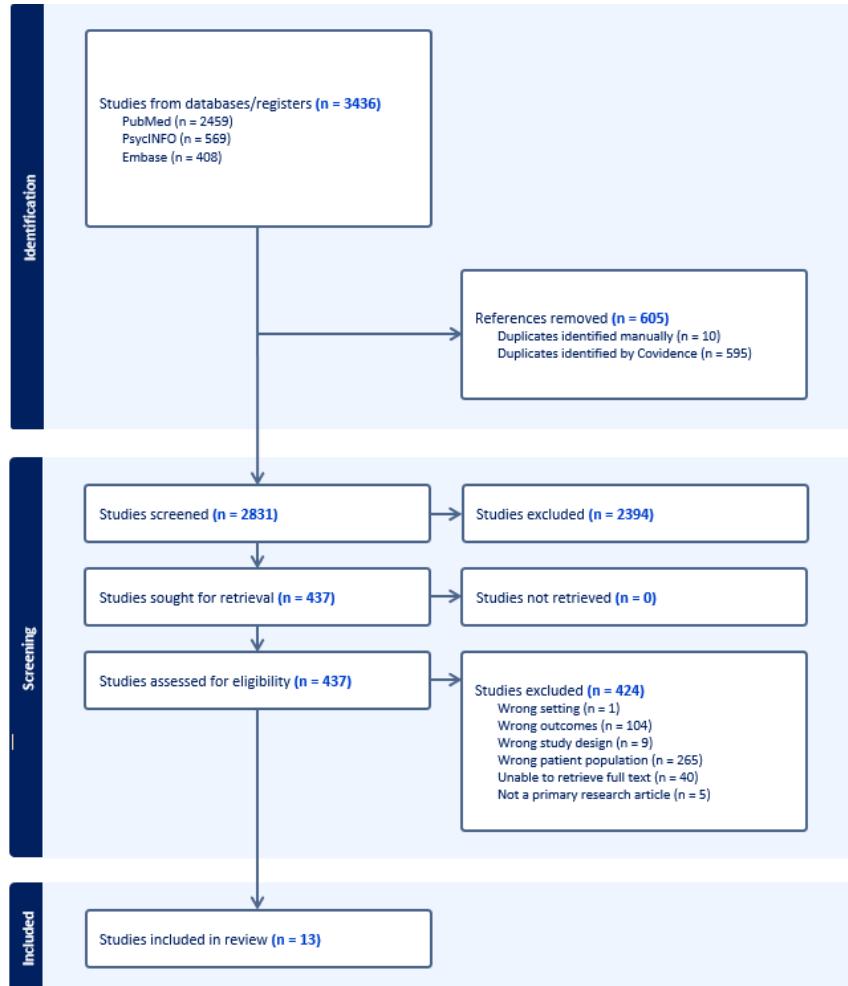
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Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

## Figures

Figure 1: Figure 1. PRISMA flow chart



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

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

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

**Table 1: Summary of Study Design and Participant Characteristics**

Study Name	Study Design	Total Sample	Sample Age $\geq 60$	Age (years)	Diagnosis	Definition of Treatment-Resistance	Severity of Treatment-Resistance	Total Study Duration
<b>Intravenous</b>								
Rasmussen <i>et al.</i> (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 $\geq 2$ medication trials in the current MDE	Not reported	Variable
Lai <i>et al.</i> (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 $\geq 1$ medication trial in the current MDE	MSM scores: Subject 1: 11 Subject 3: 13	Variable
Oughli <i>et al.</i> (2023); post-hoc analysis	Open-label trial	25	25	Mean (SD) = 71.5 (4.9)	Treatment-resistant MDE in the context of MDD	Inadequate response to $\geq 2$ 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

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

done by Vandersche lden <i>et al.</i> (2023)								receive weekly dosing for 4 more weeks
<b>Intranasal</b>								
Gálvez <i>et al.</i> (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 <i>et al.</i> (2020); post-hoc analysis done by Ochs-Ross <i>et al.</i> (2022)	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 of weekly dosing with additional weekly or biweekly dosing
Ochs-Ross <i>et al.</i> (2020)	RCT	138	138	Mean (SD) = 70.0	Treatment-resistant MDE in the context	Inadequate response to ≥2 medication trials	MGH-ATRQ (n): 1: 21	Biweekly dosing for 4 weeks

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

				(4.52)	of MDD	in the current MDE	2: 63 3: 30 4: 16 ≥5: 7	
Zaki <i>et al.</i> (2023)	Open-label trial	1148	122	Mean (SD) = 49.6 (12.28) <sup>a</sup>	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
<b>Subcutaneous</b>								
George <i>et al.</i> (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
<b>Oral</b>								

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

Glue <i>et al.</i> (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
<b>Ketamine with ECT</b>								
Fernie <i>et al.</i> (2017)	RCT	40	3	Intervention: n: Mean (SD) = 51.76 (9.97)  Control: Mean (SD) = 49.88 (12.53) <sup>a</sup>	MDD with current MDE	N/A	N/A	Variable
Zou <i>et al.</i> (2021)	RCT	157	157	Intervention: n: mean (SD) =	MDD	N/A	N/A	Variable

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

				65.76 (3.98)  Placebo: mean (SD) = 65.62 (3.92)				
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<sup>a</sup> 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

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**Table 2: Summary of Key Results**

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
<b>Intravenous</b>					
Rasmussen et al. (2013)	IV ketamine, 0.5 mg/kg over 100 min., twice weekly until remission or 4 infusions completed	None	<b>MADRS Scores</b> Patient 2: 26 Patient 10: 38	<b>MADRS Scores</b> 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	<b>MADRS Scores</b> Subject 1: 29 Subject 3: 29  <b>Simple and Complex Reaction Time</b> Not reported	<b>MADRS Scores</b> Subject 1: Remission after 0.4 mg/kg dose Subject 3: No response nor remission  <b>Simple and Complex Reaction Time</b> 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

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
			treatment		
Fernie <i>et al.</i> (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 <i>et al.</i> (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	<b>Mean HAMD Scores (SD)</b> Ketamine: 30.91 (3.67) Control: 31.03 (4.11)	<b>Mean HAMD Scores (SD)</b> 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

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

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	
				Control: 68.57%  P-value: 0.69	
Oughli <i>et al.</i> (2023); post-hoc analysis done by Vandershelden <i>et al.</i> (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	<b>Mean MADRS Scores (SD)</b> Acute phase: 24.4 (7.9) Continuation phase: Not reported  <b>Cognition</b> NIH Toolbox Cognitive Battery: Not reported  <b>Scale for Suicide Ideations</b> Mean 11.2	<b>MADRS Scores</b> 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

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				<u>Remission Rates</u> Acute phase: 24% Continuation phase: 27%  <b>Cognition*</b> 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 = 3.54 , P-value: ≤ 0.01)	

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	
				<p>List Sorting: Mean change +8.63 (95% CI [2.40, 14.86], Cohen's d = 0.55, <math>t = 2.91</math> , P-value: <math>\leq 0.01</math>)</p> <p>Fluid Cognition Composite: Mean change +7.59 (95% CI [2.85, 12.32], Cohen's d = 0.61 , <math>t = 3.40</math> , P-value: <math>\leq 0.01</math>)</p> <p><b>Scale for Suicide Ideations</b> Mean 8.0</p>	
<b>Intranasal</b>					

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	
Gálvez <i>et al.</i> (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	<b>MADRS Scores</b>  K1: Not reported  <b>Reaction time</b>  K3: Not reported	<b>MADRS Scores</b>  K1: Demonstrated antidepressant response; however, not reported numerically  K3: Did not demonstrate antidepressant response; however, not reported numerically  <b>Reaction time</b>  K3: Demonstrated slower reaction time from baseline; however, not reported	All participants experienced motor coordination difficulties impairing ability to self administer sprays
Wajs <i>et al.</i> (2020);	Induction phase: IN ketamine, initially 28 mg (for ( $\geq$ 65), 56 mg	None	<b>Mean MADRS Scores (SD)</b>	<b>Mean MADRS Scores (SD)</b>	Side effects were similar between young and older adults.

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	
post-hoc analysis done by Ochs- Ross <i>et al.</i> (2022)	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, followed by weekly or biweekly dosing that could be changed every 4 weeks		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)	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  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, 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

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				<p>(older minus younger)  [95% CI]: -0.7 [-1.95, 0.54]  P-value: 0.26</p> <p><u>Response rates</u>  IND phase  Older adults: 74%  Young adults: 87%</p> <p>OP/MAINT phase  Older adults: 79%  Young adults: 81%</p> <p><u>Remission rates</u>  IND phase  Older adults: 51%</p>	

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	
				<p>Young adults: 51%</p> <p>OP/MAINT phase</p> <p>Older adults: 61%</p> <p>Young adults: 56%</p>	
Ochs-Ross <i>et al.</i> (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, sertraline, or venlafaxine XR)	<b>Mean MADRS Scores (SD)</b> Ketamine: 35.5 (5.91) Control: 34.8 (6.44)	<b>Mean MADRS Scores (SD)</b> Ketamine: 25.4 (12.70), change of -10.0 (12.74) Control: 28.7 (10.11), change of -6.3 (8.86) Difference of LS means [95% CI]: -3.6 [-7.20, 0.07], P-value: 0.06 <u>Response rates</u> Ketamine: 27.0%	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	
				<p>Control: 13.3%</p> <p><u>Remission rates</u></p> <p>Ketamine: 17.5%</p> <p>Control: 6.7%</p> <p><u>Sub-analysis of young old (65-74) and older old (≥75) participants</u></p> <p>Young old:</p> <p>Difference of LS means [95% CI]: -4.9 [-8.96, -0.89]</p> <p>P-value: 0.02</p> <p>Older old:</p> <p>Difference of LS means</p>	

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	
				[95% CI]: -0.4 [-10.38, 9.50]  P-value: 0.93	
Zaki <i>et al.</i> (2023)	Induction phase: IN esketamine, initially 28 mg (for $\geq 65$ ), 56 mg or 84 mg twice a week for 4 weeks, flexibly dosed based on efficacy and tolerability, combined with an antidepressant  Optimization/maintenance phase: IN esketamine, weekly flexible dosing	None	-	<b>Mean change in Z-scores from baseline to end of OP/MAINT in Z-score (SD)</b>  <b>Cogstate</b> Simple reaction time $\geq 65$ : -0.200 (1.36) $< 65$ : -0.05 (1.25)  Choice reaction time $\geq 65$ : -0.37 (1.36) $< 65$ : -0.22 (1.31)	No treatment-related cystitis or psychosis reported. Long-term ketamine exposure showed no concern for dependence. Most common side effects were dissociation, dizziness, nausea, vertigo, and

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	
				<p>One card learning  <math>\geq 65</math>: 0.31 (1.20)  <math>&lt; 65</math>: 0.28 (1.34)</p> <p>One-Back  <math>\geq 65</math>: 0.02 (1.18)  <math>&lt; 65</math>: 0.16 (1.08)</p> <p>Groton maze learning test  <math>\geq 65</math>: 0.14 (0.96)  <math>&lt; 65</math>: 0.17 (1.03)</p> <p>HVLT-R, word recall  <math>\geq 65</math>: 0.11 (1.18)  <math>&lt; 65</math>: 0.12 (1.12)</p>	

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	
			HVLT, delayed recall ≥65: 0.10 (1.15) <65: 0.11 (1.02)		
<b>Subcutaneous</b>					
George <i>et al.</i> (2017)	SC ketamine, 0.1, 0.2, 0.3, 0.4, 0.5 mg/kg with ascending regimen and weekly dosing.  Midazolam control was randomly used instead of ketamine in the first 3 weeks.	Midazolam 0.01 mg/kg	<b>Mean MADRS Scores (SD)</b> 34.8 (3.5)  <b>Simple and Complex Reaction Time</b> Not reported	<b>MADRS Scores</b> 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:	Transient increases in BP  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

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				<p>0.001)</p> <p>0.5 mg/kg statistical analysis was not done</p> <p><b>Simple and Complex Reaction Time</b></p> <p>Performance was within 1 SD of baseline means</p>	
<b>Oral</b>					
Glue <i>et al.</i> (2024)	RCT phase:  Oral extended-release ketamine, 30 mg, 60 mg, 120 mg, or 180 mg twice weekly	Placebo tablet with polyethylene oxide	-	<p><b>Mean MADRS Scores</b></p> <p>Authors remarked greater reduction in MADRS scores from baseline to Day 92 among participants aged &lt;65 years (<math>-6.9</math> [95% CI]</p>	

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	
			[-12.3, -1.6]) compared with participants ≥65 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; HVLT-R, Hopkins Verbal Learning Test Revised

**Table 3: Risk of Bias of Quasi-Experimental Studies**

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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		
NAME	OUTCOME	1	2	3	4	5	6	7	8	9

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

Rasmussen <i>et al.</i> (2013)	Depression Score	Y	N	Y	N	Y	Y	U	Y	Y
	Safety and Tolerability					Y	Y	U		
Wajs <i>et al.</i> (2020)	Cognition	Y	N	Y	N	Y	Y	U	Y	Y
Ochs-Ross <i>et al.</i> (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 <i>et al.</i> (2023)	Depression Score	Y	N	Y	Y	Y	Y	U	Y	Y
	Cognition					Y	Y	U		Y
	Safety and Tolerability					Y	Y	U		Y
Vanderschelden	Suicidality	Y	N	Y	Y	Y	Y	U	Y	Y

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

et al. (2023)									
Zaki et al. (2023)	Cognition	Y	N	Y	N	Y	Y	U	Y

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

**Table 4: GRADE Summary of Findings Table**

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Outcome	Number of Participants; Study designs	Findings Summary	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Certainty (GRADE)
<b>Intranasal Ketamine</b>								
<b>Change in Depression Symptom Severity</b>	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
<b>Cognition</b>	1 RCT (Gálvez et al., 2018)	Wajs and Zaki showed mild improvement in cognition.	Serious	Not Serious	Not Serious	Serious	Not Serious	●●○ Low

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

	al., 2018); 2 open-label studies (Wajs et al., 2020, Zaki et al., 2023)	reaction time slowing; other cognitive domains were largely stable. Gálvez interpretation limited by early discontinuation and small sample size.						
<b>Frequency of TEAEs</b>	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	 Moderate				
<b>Discontinuation due to TEAEs</b>	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
<b>Intravenous Ketamine</b>								
<b>Change in Depression</b>	2 open-label studies	Oughli et al., found mean MADRS decreased by 9.4 points (95% CI:	Serious	Serious	Not Serious	Serious	Not Serious	 Low

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

<b>Symptom</b>	(Rasmussen et al., 2013, Oughli et al., 2023), 1 placebo-controlled crossover trial (Lai et al., 2014)	6.5 to 12.3, p-value: 0.01). Rasmussen and Lai reported mixed results.						
<b>Cognition</b>	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
<b>Frequency of TEAEs</b>	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
<b>Discontinuation</b>	2 open-label	No participants aged ≥60	Serious	Not Serious	Serious	Serious	Not Serious	●○○ Very

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

<b>due to TEAEs</b>	studies (Rasmussen et al., 2013, Oughli et al., 2023), 1 placebo-controlled crossover trial (Lai et al., 2014)	discontinued treatment due to TEAEs across all three studies (n=29).						Low
<b>Subcutaneous Ketamine</b>								
<b>Change in Depression Symptom Severity</b>	1 placebo-controlled crossover trial (George et al., 2017)	SC ketamine significantly reduced MADRS scores compared to midazolam at doses $\geq 0.2$ mg/kg. A dose-response relationship was observed, and overall remission rate was 68.8%.	Serious	N/A	Not Serious	Serious	Not Serious	●○○ Low
<b>Cognition</b>	1 placebo-controlled crossover trial (George et al., 2017)	Neurocognitive test scores (e.g., simple/complex reaction times) remained within 1 SD of baseline. No significant cognitive decline was reported.	Serious	N/A	Not Serious	Serious	Not Serious	●○○ Low
<b>Frequency of</b>	1 placebo-	Most common TEAEs were	Serious	N/A	Not Serious	Serious	Not Serious	●○○ Low

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

<b>TEAEs</b>	controlled crossover trial (George et al., 2017)	transient dizziness, fatigue, and blurred vision. Mild, transient BP elevations and LFT abnormalities were noted.						
<b>Discontinuation due to TEAEs</b>	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
<b>Oral Ketamine</b>								
<b>Change in Depression Symptom Severity</b>	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
<b>Cognition</b>	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
<b>Frequency of TEAEs</b>	1 RCT (Glue et al., 2024)	TEAEs were measured but not reported separately for older adults. One participant ≥65 died by	Serious	N/A	Serious	Serious	Not Serious	●○○ Very Low

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

		suicide. Authors noted no notable change in vital signs overall.						
<b>Ketamine + ECT</b>								
<b>Change in Depression Symptom Severity</b>	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
<b>Cognition</b>	2 RCTs (Fernie et al., 2017, Zou et al., 2021)	Zou et al., suggests less transient post-ECT cognitive impairment with ketofol.	Serious	Serious	Serious	Serious	Not Serious	●○○ Very Low
<b>Frequency of TEAEs</b>	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

**Supplemental Table 1: Full search strategy****Commented [39]: Feedback 3**

	#	Search	Results
PsycInfo	1	(ketamine or arketamine or esketamine or ketalar or sprawato).ti,ab.	5198
	2	(depress* adj3 diagnos*).ti,ab.	14887
	3	(major adj3 depress*).ti,ab.	54137
	4	2 or 3	63781
	5	1 and 4	776
	6	Limit 5 to (human and English language)	569
EMBASE	1	(ketamine or arketamine or esketamine or ketalar or sprawato).ti,ab,du.	75552
	2	(depress* adj3 diagnos*).ti,ab.	27005
	3	(major adj3 depress*).ti,ab.	87045
	4	2 or 3	105986
	5	1 and 4	2295

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

Word count: 5112

	6	Limit 5 to (human and English language and (clinical trial or randomized controlled trial or controlled clinical trial or multicentre study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial))	408
PubMed	1	Search: (((((ketamine[Title/Abstract]) OR (esketamine [Title/Abstract])) OR (arketamine[Title/Abstract])) OR (ketalar[Title/Abstract])) OR (spravato[Title/Abstract])) AND (depress*[Title/Abstract])	2459
		Filters: Humans, English	

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

# 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  $\geq 60$  years applied at full-text review to capture subgroup data. Thirteen studies met inclusion criteria, comprising 757 adults. Studies 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.<sup>1,2</sup> Geriatric depression, defined as major depression in individuals aged  $\geq 60$ , has a 12-month prevalence of 5.4% and is associated with reduced quality of life, functional impairment, and suicide risk.<sup>3–5</sup> Management of geriatric depression is complicated by medical comorbidities, polypharmacy, age-related pharmacodynamic and pharmacokinetic changes, and sensitivity to medication side effects.<sup>6,7</sup> Guidelines for geriatric depression recommend psychotherapy, antidepressants, antidepressant augmentation strategies, ECT, and rTMS.<sup>8–10</sup> 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.<sup>11–16</sup> To our knowledge, two prior systematic reviews have focused on the use of ketamine in geriatric depression, both published in 2021.<sup>17,18</sup> Gupta *et al.* included two randomized controlled trials (RCTs) investigating ketamine in geriatric depression, with equivocal findings.<sup>17</sup> Di Vincenzo *et al.* assessed ketamine in treating depression in both younger and older adults, including case studies and series.<sup>18</sup> This systematic review aims to synthesize and update current evidence on ketamine in the treatment of geriatric depression.

# 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.<sup>18</sup> 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  $\geq 60$  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.<sup>19</sup>

## **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  $\geq 60$  years old, average age of participants  $\geq 60$  years old, concomitant medications), 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.<sup>20</sup> 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.<sup>21</sup> 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<sup>22-28</sup>, four

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

open-label trials<sup>29–32</sup>, and two post-hoc analyses<sup>33,34</sup>. These included five intranasal (IN) <sup>22,23,29,31,34</sup>, four intravenous (IV)<sup>24,30,32,33</sup>, 1 subcutaneous (SC),<sup>28</sup> one oral,<sup>25</sup> and 2 ketamine combined with ECT studies.<sup>26,27</sup> 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.<sup>35</sup>

## 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

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(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% 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 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:

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

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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 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",

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

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  $\geq 60$ .

Lai *et al.* (2014) conducted a double-blind, placebo-controlled crossover trial of IV ketamine in four adults with two aged  $\geq 60$  ("Subject 1", aged 62; "Subject 3", aged 66). Participants were diagnosed with treatment-resistant MDD; treatment-resistance was defined as an inadequate response to  $\geq 1$  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  $\geq 65$  (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%). 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  $\geq 2$  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  $\geq 60$  (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  $\geq 1$  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  $\geq 20$  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 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 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  $\geq 60$  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: 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.<sup>17,18</sup> Across 13 studies, encompassing 757 participants aged  $\geq 60$ , 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.<sup>23</sup> Factors potentially limiting efficacy included suboptimal dosing and 4-week duration, which may have been insufficient to capture delayed responses.<sup>36</sup> Long-term open-label studies of IN ketamine (SUSTAIN-2 and SUSTAIN-3) suggest durable responses lasting up to 160 weeks.<sup>29,31</sup> IV

ketamine demonstrated antidepressant effects in open-label and crossover trials, with response and remission rates comparable to younger populations in some cases.<sup>30</sup>

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.<sup>28</sup> The sole oral ketamine study in older adults showed no significant effect, though was limited by small sample.<sup>25</sup> Two RCTs of ketamine as an ECT adjunct did not find superiority over placebo.<sup>26,27</sup> However, Zou et al. observed reduced post-ECT cognitive impairment with ketofol compared to propofol, suggesting that ketamine may mitigate ECT cognitive side effects.<sup>27</sup>

Ketamine was generally well tolerated. AEs were mostly mild and transient (e.g., dizziness, nausea, hypertension, dissociation), consistent with findings in younger populations.<sup>23,29</sup> In Oughli et al., prophylactic use of clonidine reduced dissociative and hypertensive AEs, suggesting a strategy to enhance tolerability.<sup>30</sup> 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.<sup>30</sup> 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.<sup>29,31</sup> Notably, several trials excluded individuals with baseline cognitive impairment or major neurocognitive disorder, limiting generalizability.<sup>25,26,30,32</sup>

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.<sup>23,25,34,37</sup> Additionally, Ochs-Ross et

al. (2022) found that response appears to decline progressively with increasing age, with the oldest patients ( $\geq 75$ ) showing the least benefit, though findings in this group were limited by small sample sizes.<sup>34</sup>

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.<sup>24,28</sup> 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.<sup>38,39</sup> 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  $\geq 75$ , and measure geriatric safety outcomes (e.g., falls). Studies may consider late- vs. early-onset depression, given potential pathophysiological differences.<sup>34,40</sup> 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.<sup>41</sup>

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.

**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.

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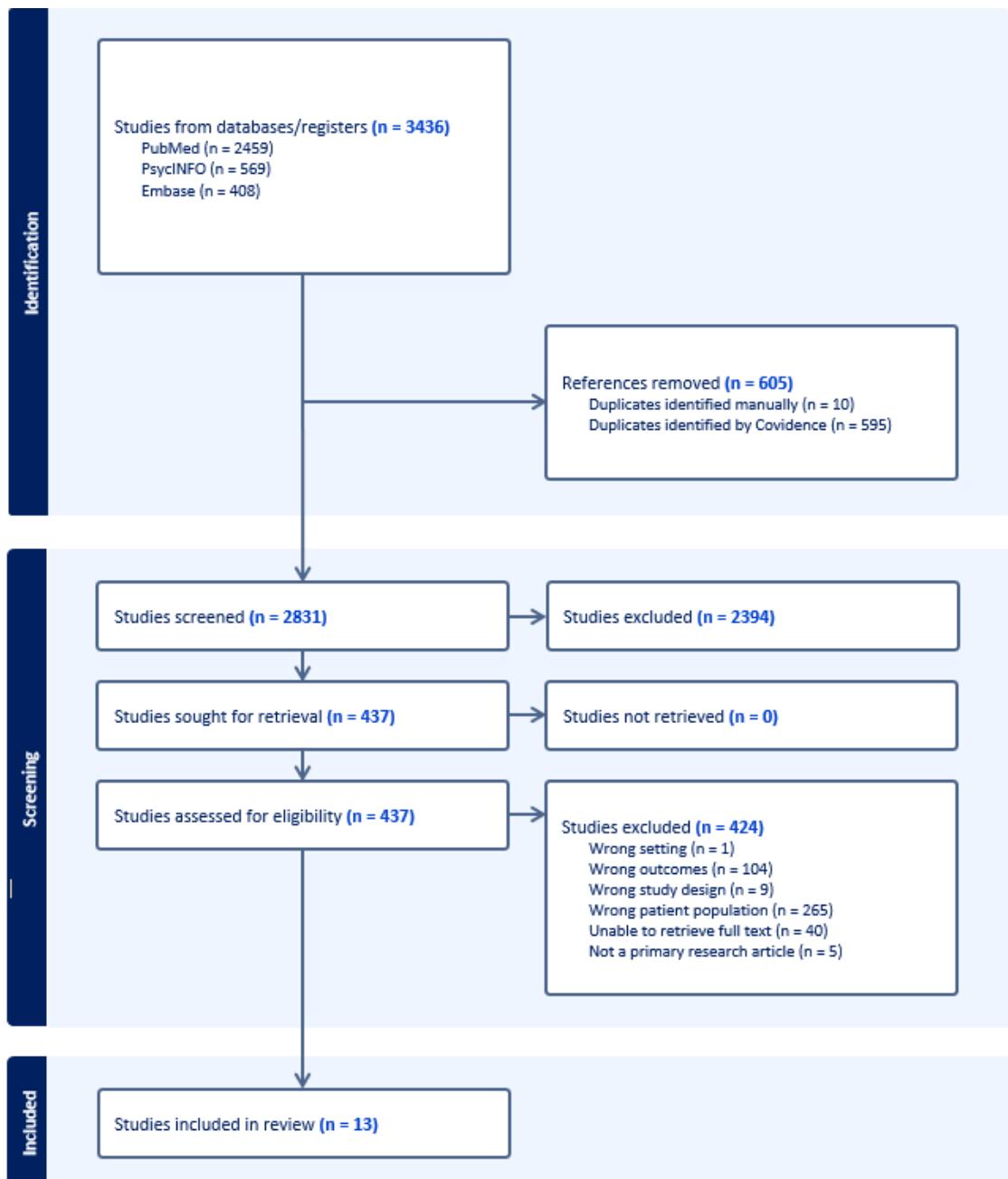
Key words: ketamine, esketamine, treatment-resistant depression, geriatric, cognitive function, dementia

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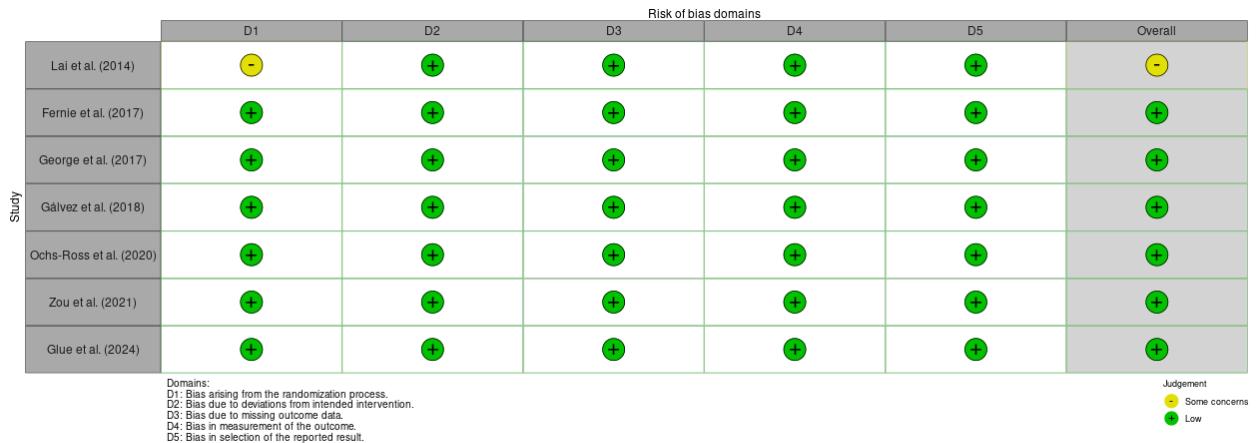
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# Figures

Figure 1: PRISMA flow chart



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

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

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

**Table 1: Summary of Study Design and Participant Characteristics**

<b>Study Name</b>	<b>Study Design</b>	<b>Total Sample</b>	<b>Sample Age ≥60</b>	<b>Age (years)</b>	<b>Diagnosis</b>	<b>Definition of Treatment-Resistance</b>	<b>Severity of Treatment-Resistance</b>	<b>Total Study Duration</b>
<b>Intravenous</b>								
Rasmussen <i>et al.</i> (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 <i>et al.</i> (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
Oughli <i>et al.</i> (2023); post-hoc analysis	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

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

Word count: 5112

done by Vandersche Iden <i>et al.</i> (2023)								receive weekly dosing for 4 more weeks
<b>Intranasal</b>								
Gálvez <i>et al.</i> (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 <i>et al.</i> (2020); post-hoc analysis done by Ochs-Ross <i>et al.</i> (2022)	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 of weekly dosing with additional weekly or biweekly dosing
Ochs-Ross <i>et al.</i> (2020)	RCT	138	138	Mean (SD) = 70.0	Treatment-resistant MDE in the context	Inadequate response to ≥2 medication trials	MGH-ATRQ (n): 1: 21	Biweekly dosing for 4 weeks

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

				(4.52)	of MDD	in the current MDE	2: 63 3: 30 4: 16 ≥5: 7	
Zaki <i>et al.</i> (2023)	Open-label trial	1148	122	Mean (SD) = 49.6 (12.28) <sup>a</sup>	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/maintena- nce phase
<b>Subcutaneous</b>								
George <i>et</i> <i>al.</i> (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
<b>Oral</b>								

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

Word count: 5112

Glue <i>et al.</i> (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
<b>Ketamine with ECT</b>								
Fernie <i>et al.</i> (2017)	RCT	40	3	Intervention: Mean (SD) = 51.76 (9.97)  Control: Mean (SD) = 49.88 (12.53) <sup>a</sup>	MDD with current MDE	N/A	N/A	Variable
Zou <i>et al.</i> (2021)	RCT	157	157	Intervention: mean (SD) =	MDD	N/A	N/A	Variable

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

				65.76 (3.98)  Placebo:  mean (SD)  = 65.62 (3.92)				
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<sup>a</sup>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

**Table 2: Summary of Key Results**

Study Name	Intervention	Placebo/Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
<b>Intravenous</b>					
Rasmussen et al. (2013)	IV ketamine, 0.5 mg/kg over 100 min., twice weekly until remission or 4 infusions completed	None	<b>MADRS Scores</b> Patient 2: 26 Patient 10: 38	<b>MADRS Scores</b> 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	<b>MADRS Scores</b> Subject 1: 29 Subject 3: 29  <b>Simple and Complex Reaction Time</b> Not reported	<b>MADRS Scores</b> Subject 1: Remission after 0.4 mg/kg dose Subject 3: No response nor remission  <b>Simple and Complex Reaction Time</b> 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

Study Name	Intervention	Placebo/Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				treatment	
Fernie <i>et al.</i> (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 <i>et al.</i> (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	<b>Mean HAMD Scores (SD)</b> Ketamine: 30.91 (3.67) Control: 31.03 (4.11)	<b>Mean HAMD Scores (SD)</b> End of sixth ECT Ketamine: 14.18 (3.65) Control: 16.03 (4.66) <u>P-value (ketamine vs control): 0.01</u> <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

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

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	
				Control: 68.57% P-value: 0.69	
Oughli <i>et al.</i> (2023); post-hoc analysis done by Vanderschelden <i>et al.</i> (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	<b>Mean MADRS Scores (SD)</b> Acute phase: 24.4 (7.9) Continuation phase: Not reported  <b>Cognition</b> NIH Toolbox Cognitive Battery: Not reported  <b>Scale for Suicide Ideations</b> Mean 11.2	<b>MADRS Scores</b> 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	No treatment-related severe adverse events

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	
				<p><u>Remission Rates</u></p> <p>Acute phase: 24%</p> <p>Continuation phase: 27%</p> <p><b>Cognition*</b></p> <p>Dimensional Change</p> <p>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</p> <p>Flanker: Mean change +5.43 (95% CI [2.25, 8.61], Cohen's d = 0.61 , t = 3.54 , P-value: ≤ 0.01)</p>	

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	
				<p>List Sorting: Mean change +8.63 (95% CI [2.40, 14.86], Cohen's d = 0.55, <math>t = 2.91</math> , P-value: <math>\leq 0.01</math>)</p> <p>Fluid Cognition Composite: Mean change +7.59 (95% CI [2.85, 12.32], Cohen's d = 0.61 , <math>t = 3.40</math> , P-value: <math>\leq 0.01</math>)</p> <p><b>Scale for Suicide</b></p> <p><b>Ideations</b></p> <p>Mean 8.0</p>	
<b>Intranasal</b>					

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
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	<b>MADRS Scores</b>  K1: Not reported  <b>Reaction time</b>  K3: Not reported	<b>MADRS Scores</b>  K1: Demonstrated antidepressant response; however, not reported numerically  <b>Reaction time</b>  K3: Did not demonstrate antidepressant response; however, not reported numerically  <b>Reaction time</b>  K3: Demonstrated slower reaction time from baseline; however, not reported	All participants experienced motor coordination difficulties impairing ability to self administer sprays
Wajs et al. (2020);	Induction phase: IN ketamine, initially 28 mg (for ( $\geq$ 65), 56 mg	None	<b>Mean MADRS Scores (SD)</b>	<b>Mean MADRS Scores (SD)</b>	Side effects were similar between young and older adults.

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	
post-hoc analysis done by Ochs-Ross <i>et al.</i> (2022)	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, followed by weekly or biweekly dosing that could be changed every 4 weeks		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)	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  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, 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

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				<p>(older minus younger)  [95% CI]: -0.7 [-1.95,  0.54]  P-value: 0.26</p> <p><u>Response rates</u>  IND phase  Older adults: 74%  Young adults: 87%</p> <p>OP/MAINT phase  Older adults: 79%  Young adults: 81%</p> <p><u>Remission rates</u>  IND phase  Older adults: 51%</p>	

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	
				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, sertraline, or venlafaxine XR)	<b>Mean MADRS Scores (SD)</b>  Ketamine: 35.5 (5.91) Control: 34.8 (6.44)	<b>Mean MADRS Scores (SD)</b>  Ketamine: 25.4 (12.70), change of -10.0 (12.74) Control: 28.7 (10.11), change of -6.3 (8.86)  Difference of LS means [95% CI]: -3.6 [-7.20, 0.07], P-value: 0.06  <u>Response rates</u>  Ketamine: 27.0%	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	
				<p>Control: 13.3%</p> <p><u>Remission rates</u></p> <p>Ketamine: 17.5%</p> <p>Control: 6.7%</p> <p><u>Sub-analysis of young old (65-74) and older old (≥75) participants</u></p> <p>Young old:</p> <p>Difference of LS means</p> <p>[95% CI]: -4.9 [-8.96, -0.89]</p> <p>P-value: 0.02</p> <p>Older old:</p> <p>Difference of LS means</p>	

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	
				[95% CI]: -0.4 [-10.38, 9.50] P-value: 0.93	
Zaki <i>et al.</i> (2023)	Induction phase: IN esketamine, initially 28 mg (for $\geq 65$ ), 56 mg or 84 mg twice a week for 4 weeks, flexibly dosed based on efficacy and tolerability, combined with an antidepressant  Optimization/maintenance phase: IN esketamine, weekly flexible dosing	None	-	<b>Mean change in Z-scores from baseline to end of OP/MAINT in Z-score (SD)</b>  <b>Cogstate</b> Simple reaction time $\geq 65$ : -0.200 (1.36) $< 65$ : -0.05 (1.25)  Choice reaction time $\geq 65$ : -0.37 (1.36) $< 65$ : -0.22 (1.31)	No treatment-related cystitis or psychosis reported. Long-term ketamine exposure showed no concern for dependence. Most common side effects were dissociation, dizziness, nausea, vertigo, and

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	
				<p>One card learning  <math>\geq 65</math>: 0.31 (1.20)  <math>&lt; 65</math>: 0.28 (1.34)</p> <p>One-Back  <math>\geq 65</math>: 0.02 (1.18)  <math>&lt; 65</math>: 0.16 (1.08)</p> <p>Groton maze learning test  <math>\geq 65</math>: 0.14 (0.96)  <math>&lt; 65</math>: 0.17 (1.03)</p> <p>HVLT-R, word recall  <math>\geq 65</math>: 0.11 (1.18)  <math>&lt; 65</math>: 0.12 (1.12)</p>	

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	
				HVLT, delayed recall ≥65: 0.10 (1.15) <65: 0.11 (1.02)	
<b>Subcutaneous</b>					
George et al. (2017)	SC ketamine, 0.1, 0.2, 0.3, 0.4, 0.5 mg/kg with ascending regimen and weekly dosing. Midazolam control was randomly used instead of ketamine in the first 3 weeks.	Midazolam 0.01 mg/kg	<b>Mean MADRS Scores (SD)</b> 34.8 (3.5)  <b>Simple and Complex Reaction Time</b> Not reported	<b>MADRS Scores</b> 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:	Transient increases in BP 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

Study Name	Intervention	Placebo/Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				<p>0.001)</p> <p>0.5 mg/kg statistical analysis was not done</p> <p><b>Simple and Complex Reaction Time</b></p> <p>Performance was within 1 SD of baseline means</p>	
<b>Oral</b>					
Glue <i>et al.</i> (2024)	RCT phase: Oral extended-release ketamine, 30 mg, 60 mg, 120 mg, or 180 mg twice weekly	Placebo tablet with polyethylene oxide	-	<p><b>Mean MADRS Scores</b></p> <p>Authors remarked greater reduction in MADRS scores from baseline to Day 92 among participants aged &lt;65 years (-6.9 [95% CI]</p>	

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	
				[-12.3, -1.6]) compared with participants ≥65 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; HVLT-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		
NAME	OUTCOME	1	2	3	4	5	6	7	8	9

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

Word count: 5112

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
Vanderschelden	Suicidality	Y	N	Y	Y	Y	Y	U	Y	Y

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

et al. (2023)										
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)
<b>Intranasal Ketamine</b>								
<b>Change in Depression Symptom Severity</b>	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
<b>Cognition</b>	1 RCT (Gálvez et	Wajs and Zaki showed mild	Serious	Not Serious	Not Serious	Serious	Not Serious	●●○ Low

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

Word count: 5112

	al., 2018); 2 open-label studies (Wajs et al., 2020, Zaki et al., 2023)	reaction time slowing; other cognitive domains were largely stable. Gálvez interpretation limited by early discontinuation and small sample size.						
<b>Frequency of TEAEs</b>	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	●●● Moderate				
<b>Discontinuation due to TEAEs</b>	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
<b>Intravenous Ketamine</b>								
<b>Change in Depression</b>	2 open-label studies	Oughli et al., found mean MADRS decreased by 9.4 points (95% CI:	Serious	Serious	Not Serious	Serious	Not Serious	●●○ Low

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

Word count: 5112

<b>Symptom</b>	(Rasmussen et al., 2013, Oughli et al., 2023), 1 placebo-controlled crossover trial (Lai et al., 2014)	6.5 to 12.3, p-value: 0.01). Rasmussen and Lai reported mixed results.						
<b>Cognition</b>	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
<b>Frequency of TEAEs</b>	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
<b>Discontinuation</b>	2 open-label	No participants aged ≥60	Serious	Not Serious	Serious	Serious	Not Serious	●●●● Very

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

Word count: 5112

<b>due to TEAEs</b>	studies (Rasmussen et al., 2013, Oughli et al., 2023), 1 placebo-controlled crossover trial (Lai et al., 2014)	discontinued treatment due to TEAEs across all three studies (n=29).							Low
<b>Subcutaneous Ketamine</b>									
<b>Change in Depression Symptom Severity</b>	1 placebo-controlled crossover trial (George et al., 2017)	SC ketamine significantly reduced MADRS scores compared to midazolam at doses $\geq 0.2$ mg/kg. A dose-response relationship was observed, and overall remission rate was 68.8%.	Serious	N/A	Not Serious	Serious	Not Serious	●●○○	Low
<b>Cognition</b>	1 placebo-controlled crossover trial (George et al., 2017)	Neurocognitive test scores (e.g., simple/complex reaction times) remained within 1 SD of baseline. No significant cognitive decline was reported.	Serious	N/A	Not Serious	Serious	Not Serious	●●○○	Low
<b>Frequency of</b>	1 placebo-	Most common TEAEs were	Serious	N/A	Not Serious	Serious	Not Serious	●●○○	Low

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

<b>TEAEs</b>	controlled crossover trial (George et al., 2017)	transient dizziness, fatigue, and blurred vision. Mild, transient BP elevations and LFT abnormalities were noted.						
<b>Discontinuation due to TEAEs</b>	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
<b>Oral Ketamine</b>								
<b>Change in Depression Symptom Severity</b>	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
<b>Cognition</b>	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
<b>Frequency of TEAEs</b>	1 RCT (Glue et al., 2024)	TEAEs were measured but not reported separately for older adults. One participant ≥65 died by	Serious	N/A	Serious	Serious	Not Serious	●○○ Very Low

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

Word count: 5112

		suicide. Authors noted no notable change in vital signs overall.						
<b>Ketamine + ECT</b>								
<b>Change in Depression Symptom Severity</b>	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
<b>Cognition</b>	2 RCTs (Fernie et al., 2017, Zou et al., 2021)	Zou et al., suggests less transient post-ECT cognitive impairment with ketofol.	Serious	Serious	Serious	Serious	Not Serious	●●○ Very Low
<b>Frequency of TEAEs</b>	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

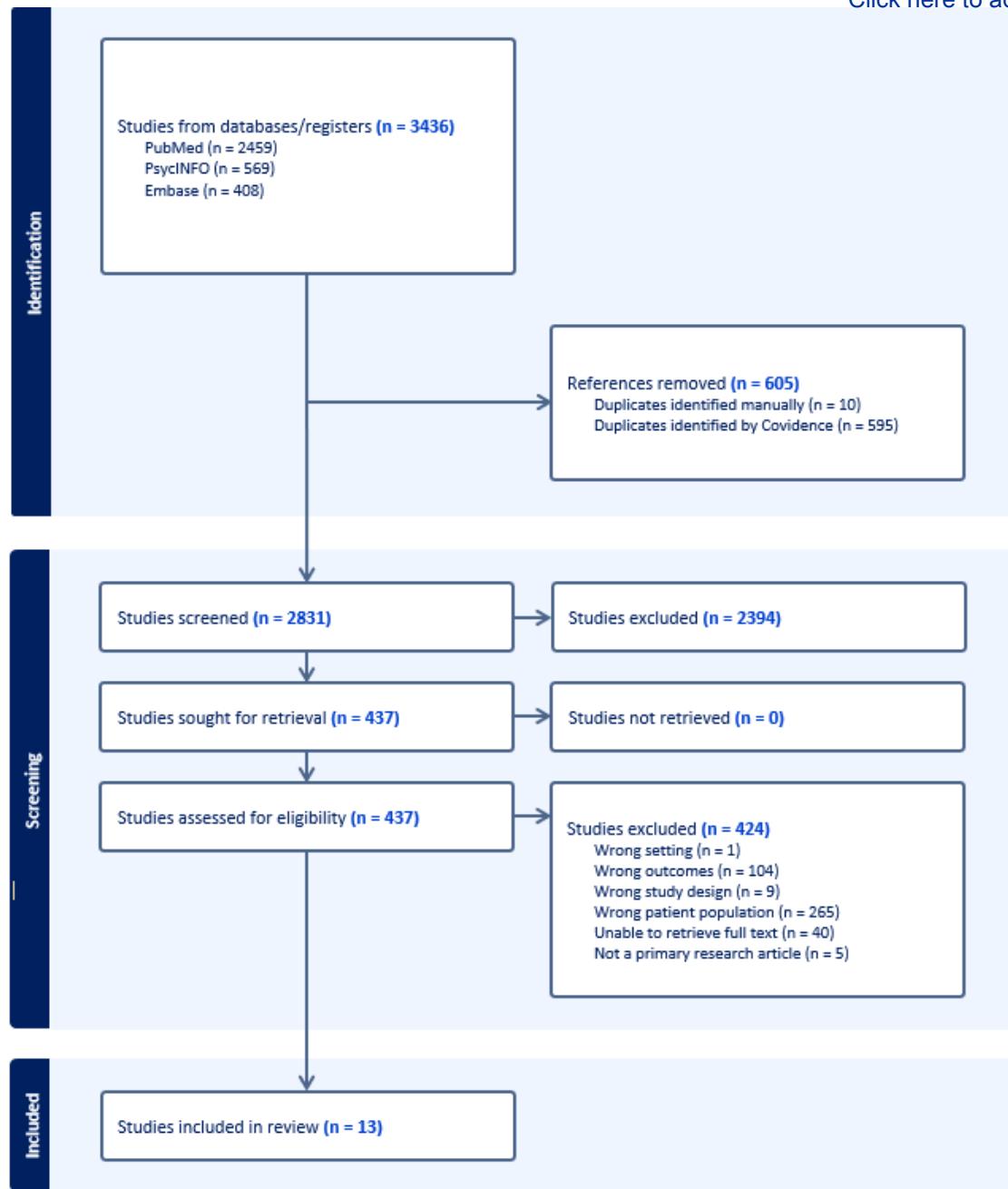
**Supplemental Table 1: Full search strategy**

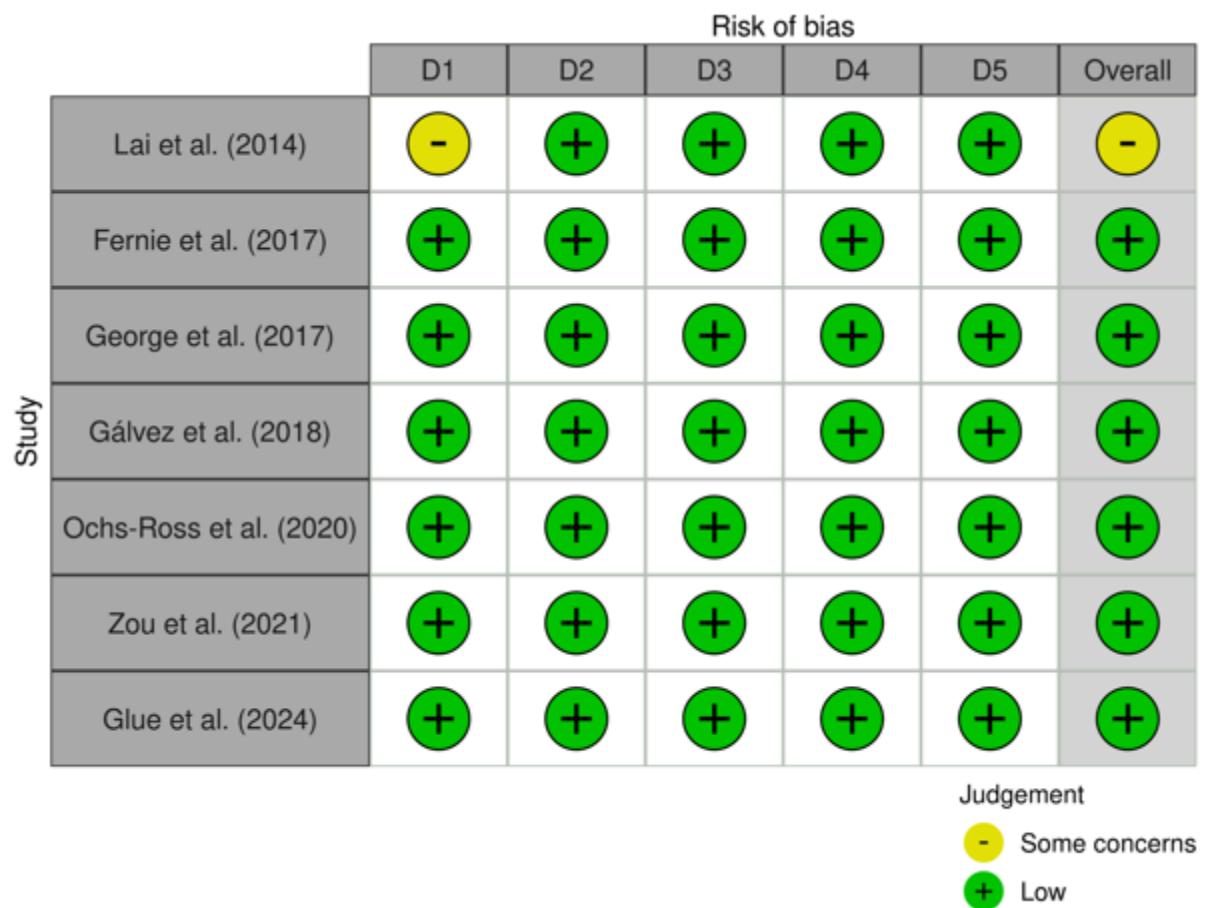
	#	Search	Results
PsyInfo	1	(ketamine or arketamine or esketamine or ketalar or spravato).ti,ab.	5198
	2	(depress* adj3 diagnos*).ti,ab.	14887
	3	(major adj3 depress*).ti,ab.	54137
	4	2 or 3	63781
	5	1 and 4	776
	6	Limit 5 to (human and English language)	569
EMBASE	1	(ketamine or arketamine or esketamine or ketalar or spravato).ti,ab,du.	75552
	2	(depress* adj3 diagnos*).ti,ab.	27005
	3	(major adj3 depress*).ti,ab.	87045
	4	2 or 3	105986
	5	1 and 4	2295

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

		Limit 5 to (human and English language and (clinical trial or randomized controlled trial or controlled clinical trial or multicentre study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial))	408
PubMed	1	Search: (((((ketamine[Title/Abstract]) OR (esketamine [Title/Abstract])) OR (arketamine[Title/Abstract])) OR (ketalar[Title/Abstract])) OR (spravato[Title/Abstract])) AND (depress*[Title/Abstract])	2459
		Filters: Humans, English	

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





**Table 1: Summary of Study Design and Participant Characteristics**

<b>Study Name</b>	<b>Study Design</b>	<b>Total Sample</b>	<b>Sample Age ≥60</b>	<b>Age (years)</b>	<b>Diagnosis</b>	<b>Definition of Treatment-Resistance</b>	<b>Severity of Treatment-Resistance</b>	<b>Total Study Duration</b>
<b>Intravenous</b>								
Rasmussen <i>et al.</i> (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 <i>et al.</i> (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
Oughli <i>et al.</i> (2023); post-hoc analysis done by	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

Vandersche lden <i>et al.</i> (2023)								for 4 more weeks
<b>Intranasal</b>								
Gálvez <i>et al.</i> (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 <i>et al.</i> (2020); post-hoc analysis done by Ochs-Ross <i>et al.</i> (2022)	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/maintenance phase of 4 weeks of weekly dosing with additional weekly or biweekly dosing
Ochs-Ross <i>et al.</i> (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	Biweekly dosing for 4 weeks

							4: 16 ≥5: 7	
Zaki <i>et al.</i> (2023)	Open-label trial	1148	122	Mean (SD) = 49.6 (12.28) <sup>a</sup>	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/maintena- nce phase
<b>Subcutaneous</b>								
George <i>et al.</i> (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
<b>Oral</b>								
Glue <i>et al.</i> (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	Biweekly dosing for 12 weeks with 4 weeks follow-up

							separately for participants $\geq 60$	
<b>Ketamine with ECT</b>								
Fernie <i>et al.</i> (2017)	RCT	40	3	Interventio n: Mean (SD) = 51.76 (9.97)  Control: Mean (SD) = 49.88 (12.53) <sup>a</sup>	MDD with current MDE	N/A	N/A	Variable
Zou <i>et al.</i> (2021)	RCT	157	157	Interventio n: mean (SD) = 65.76 (3.98)  Placebo:	MDD	N/A	N/A	Variable

				mean (SD) = 65.62 (3.92)			
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<sup>a</sup> 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

**Table 2: Summary of Key Results**

Study Name	Intervention	Placebo/Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
<b>Intravenous</b>					
Rasmussen et al. (2013)	IV ketamine, 0.5 mg/kg over 100 min., twice weekly until remission or 4 infusions completed	None	<b>MADRS Scores</b> Patient 2: 26 Patient 10: 38	<b>MADRS Scores</b> 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	<b>MADRS Scores</b> Subject 1: 29 Subject 3: 29  <b>Simple and Complex Reaction Time</b> Not reported	<b>MADRS Scores</b> Subject 1: Remission after 0.4 mg/kg dose Subject 3: No response nor remission  <b>Simple and Complex Reaction Time</b> No significant differences between pre- and post-treatment	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

Study Name	Intervention	Placebo/Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
Fernie <i>et al.</i> (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 <i>et al.</i> (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	<b>Mean HAMD Scores (SD)</b> Ketamine: 30.91 (3.67) Control: 31.03 (4.11)	<b>Mean HAMD Scores (SD)</b> End of sixth ECT Ketamine: 14.18 (3.65) Control: 16.03 (4.66)  <u>P-value (ketamine vs control): 0.01</u>  <u>Response rate</u> Ketamine: 76.12% Control: 58.57%  <u>P-value: 0.04</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)

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				<p>End of ECT</p> <p>Ketamine: 8.69 (4.15)</p> <p>Control: 8.97 (4.82)</p> <p>P-value (ketamine vs control): 0.71</p> <p><u>Response rate</u></p> <p>Ketamine: 82.09%</p> <p>Control: 81.43%</p> <p>P-value: 0.90</p> <p><u>Remission rate</u></p> <p>Ketamine: 73.13%</p> <p>Control: 68.57%</p> <p>P-value: 0.69</p>	
Oughli <i>et al.</i> (2023);	IV ketamine, 0.5 mg/kg over 40 minutes twice weekly for 4	None	<b>Mean MADRS Scores (SD)</b>	<b>MADRS Scores</b> Acute phase: Mean	No treatment-related severe adverse events

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
post-hoc analysis done by Vanderschelden et al. (2023)	weeks (acute phase) followed by of weekly infusions for 4 weeks (continuation phase)		<p>Acute phase: 24.4 (7.9)  Continuation phase: Not reported</p> <p><b>Cognition</b>  NIH Toolbox Cognitive Battery: Not reported</p> <p><b>Scale for Suicide Ideations</b>  Mean 11.2</p>	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% <u>Remission Rates</u> Acute phase: 24% Continuation phase: 27%	

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				<p><b>Cognition*</b></p> <p>Dimensional Change</p> <p>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)</p> <p>Flanker: Mean change +5.43 (95% CI [2.25, 8.61], Cohen's d = 0.61 , t = 3.54 , P-value: ≤ 0.01)</p> <p>List Sorting: Mean change +8.63 (95% CI [2.40, 14.86], Cohen's d = 0.55, t = 2.91 , P-value: ≤ 0.01)</p>	

Study Name	Intervention	Placebo/Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				<p>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)</p> <p><b>Scale for Suicide Ideations</b> Mean 8.0</p>	
<b>Intranasal</b>					
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	<p><b>MADRS Scores</b> K1: Not reported K3: Not reported</p> <p><b>Reaction time</b> K3: Not reported</p>	<p><b>MADRS Scores</b> K1: Demonstrated antidepressant response; however, not reported numerically K3: Did not demonstrate antidepressant response;</p>	All participants experienced motor coordination difficulties impairing ability to self administer sprays

Study Name	Intervention	Placebo/Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				<p>however, not reported numerically</p> <p><b>Reaction time</b></p> <p>K3: Demonstrated slower reaction time from baseline; however, not reported</p>	
Wajs <i>et al.</i> (2020); post-hoc analysis done by Ochs-Ross <i>et al.</i> (2022)	<p>Induction phase: IN ketamine, initially 28 mg (for (<math>\geq</math>65), 56 mg or 84 mg twice a week for 4 weeks, flexibly dosed based on efficacy and tolerability</p> <p>Optimization/maintenance phase: IN ketamine, weekly dosing with end of induction phase dose,</p>	None	<p><b>Mean MADRS Scores (SD)</b></p> <p>IND baseline Older adults: 32.8 (5.98) Young adults: 31.4 (5.04)</p> <p>OP/MAINT (week 12) Older adults: 32.9 (6.06)</p>	<p><b>Mean MADRS Scores (SD)</b></p> <p>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)</p> <p>Difference of LS means (older minus younger)</p>	<p>Side effects were similar between young and older adults.</p> <p>Older, but not younger participants, demonstrated prolongation of simple and choice reaction times during the OP/MAINT phase. Higher cognitive functions were preserved</p>

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		Young adults: 31.2 (4.76)	[95% CI]: 0.5 [-0.90, 1.86]  P-value: 0.49  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%	

Study Name	Intervention	Placebo/Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				<p>OP/MAINT phase</p> <p>Older adults: 79%</p> <p>Young adults: 81%</p> <p><u>Remission rates</u></p> <p>IND phase</p> <p>Older adults: 51%</p> <p>Young adults: 51%</p> <p>OP/MAINT phase</p> <p>Older adults: 61%</p> <p>Young adults: 56%</p>	
Ochs-Ross <i>et al.</i> (2020)	IN esketamine at 28 mg, 56 mg, or 84 mg, twice weekly for 4 weeks, with new oral antidepressant (duloxetine, escitalopram, sertraline, or	Placebo nasal spray with new oral antidepressant (duloxetine,	<b>Mean MADRS Scores (SD)</b> Ketamine: 35.5 (5.91) Control: 34.8 (6.44)	<b>Mean MADRS Scores (SD)</b> Ketamine: 25.4 (12.70), change of -10.0 (12.74) Control: 28.7 (10.11),	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)

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
	venlafaxine XR)	escitalopram, sertraline, or venlafaxine XR)		<p>change of -6.3 (8.86)  Difference of LS means  [95% CI]: -3.6 [-7.20,  0.07], P-value: 0.06</p> <p><u>Response rates</u>  Ketamine: 27.0%  Control: 13.3%</p> <p><u>Remission rates</u>  Ketamine: 17.5%  Control: 6.7%</p> <p><u>Sub-analysis of young old  (65-74) and older old  (≥75) participants</u>  Young old:  Difference of LS means</p>	

Study Name	Intervention	Placebo/Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				<p>[95% CI]: -4.9 [-8.96, -0.89]  P-value: 0.02</p> <p>Older old:  Difference of LS means  [95% CI]: -0.4 [-10.38, 9.50]  P-value: 0.93</p>	
Zaki <i>et al.</i> (2023)	Induction phase: IN esketamine, initially 28 mg (for ( $\geq 65$ )), 56 mg or 84 mg twice a week for 4 weeks, flexibly dosed based on efficacy and tolerability, combined with an antidepressant	None	-	<p><b>Mean change in Z-scores from baseline to end of OP/MAINT in Z-score (SD)</b></p> <p><b>Cogstate</b></p> <p>Simple reaction time  <math>\geq 65</math>: -0.200 (1.36)</p>	<p>No treatment-related cystitis or psychosis reported. Long-term ketamine exposure showed no concern for dependence. Most common side effects were dissociation, dizziness, nausea, vertigo, and</p>

Study Name	Intervention	Placebo/ Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
	Optimization/maintenance phase:  IN esketamine, weekly flexible dosing			<p>&lt;65: -0.05 (1.25)</p> <p>Choice reaction time</p> <p>≥65: -0.37 (1.36)</p> <p>&lt;65: -0.22 (1.31)</p> <p>One card learning</p> <p>≥65: 0.31 (1.20)</p> <p>&lt;65: 0.28 (1.34)</p> <p>One-Back</p> <p>≥65: 0.02 (1.18)</p> <p>&lt;65: 0.16 (1.08)</p> <p>Groton maze learning test</p> <p>≥65: 0.14 (0.96)</p> <p>&lt;65: 0.17 (1.03)</p>	

Study Name	Intervention	Placebo/Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				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)	
<b>Subcutaneous</b>					
George et al. (2017)	SC ketamine, 0.1, 0.2, 0.3, 0.4, 0.5 mg/kg with ascending regimen and weekly dosing. Midazolam control was randomly used instead of ketamine in the first 3 weeks.	Midazolam 0.01 mg/kg	<b>Mean MADRS Scores (SD)</b> 34.8 (3.5)  <b>Simple and Complex Reaction Time</b> Not reported	<b>MADRS Scores</b> 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)	Transient increases in BP Psychomimetic effects  Liver function tests: mild AST, ALT, or GGT elevation in 3/16 participants

Study Name	Intervention	Placebo/Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				<p>0.3 mg/kg (p-value: 0.001)</p> <p>0.4 mg/kg (p-value: 0.001)</p> <p>0.5 mg/kg statistical analysis was not done</p> <p><b>Simple and Complex Reaction Time</b></p> <p>Performance was within 1 SD of baseline means</p>	
<b>Oral</b>					
Glue <i>et al.</i> (2024)	RCT phase: Oral extended-release ketamine, 30 mg, 60 mg, 120 mg, or 180 mg twice weekly	Placebo tablet with polyethylene oxide	-	<p><b>Mean MADRS Scores</b></p> <p>Authors remarked greater reduction in MADRS scores from baseline to Day 92 among</p>	

Study Name	Intervention	Placebo/Control	Outcome Measures		Safety and Tolerability
			Pre-Treatment	Post-Treatment	
				participants aged <65 years (-6.9 [95% CI] [-12.3, -1.6]) compared with participants ≥65 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; HVLT-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	

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

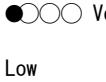
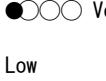
et al. (2023)										
Zaki et al. (2023)	Cognition	Y	N	Y	N	Y	Y	U	Y	Y

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)
<b>Intranasal Ketamine</b>								
<b>Change in Depression Symptom Severity</b>	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
<b>Cognition</b>	1 RCT (Gálvez et al., 2018); 2 open-label studies (Wajs	Wajs and Zaki showed mild reaction time slowing; other cognitive domains were largely	Serious	Not Serious	Not Serious	Serious	Not Serious	 Low

	et al., 2020, Zaki et al., 2023)	stable. Gálvez interpretation limited by early discontinuation and small sample size.						
<b>Frequency of TEAEs</b>	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	 Moderate				
<b>Discontinuation due to TEAEs</b>	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
<b>Intravenous Ketamine</b>								
<b>Change in Depression Symptom Severity</b>	2 open-label studies (Rasmussen et al., 2013, Oughli et al., 2023), 1 placebo-controlled	Oughli et al., found mean MADRS decreased by 9.4 points (95% CI: 6.5 to 12.3, p-value: 0.01). Rasmussen and Lai reported mixed results.	Serious	Serious	Not Serious	Serious	Not Serious	 Low

	crossover trial (Lai et al., 2014)							
<b>Cognition</b>	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
<b>Frequency of TEAEs</b>	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
<b>Discontinuation due to TEAEs</b>	2 open-label studies (Rasmussen et al., 2013, Oughli et al., 2023), 1 placebo-controlled	No participants aged ≥60 discontinued treatment due to TEAEs across all three studies (n=29).	Serious	Not Serious	Serious	Serious	Not Serious	 Very Low

	crossover trial (Lai et al., 2014)							
<b>Subcutaneous Ketamine</b>								
<b>Change in Depression Symptom Severity</b>	1 placebo-controlled crossover trial (George et al., 2017)	SC ketamine significantly reduced MADRS scores compared to midazolam at doses $\geq 0.2$ mg/kg. A dose-response relationship was observed, and overall remission rate was 68.8%.	Serious	N/A	Not Serious	Serious	Not Serious	 Low
<b>Cognition</b>	1 placebo-controlled crossover trial (George et al., 2017)	Neurocognitive test scores (e.g., simple/complex reaction times) remained within 1 SD of baseline. No significant cognitive decline was reported.	Serious	N/A	Not Serious	Serious	Not Serious	 Low
<b>Frequency of TEAEs</b>	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
<b>Discontinuation due to TEAEs</b>	1 placebo-controlled	No participants discontinued due to adverse events in this small	Serious	N/A	Not Serious	Serious	Not Serious	 Low

	crossover trial (George et al., 2017)	sample.						
<b>Oral Ketamine</b>								
<b>Change in Depression Symptom Severity</b>	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
<b>Cognition</b>	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
<b>Frequency of TEAEs</b>	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
<b>Ketamine + ECT</b>								
<b>Change in Depression Symptom Severity</b>	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	Not Serious	Serious	Serious	Serious	Not Serious	●○○○ Very Low

		younger than older adults.						
<b>Cognition</b>	2 RCTs (Fernie et al., 2017, Zou et al., 2021)	Zou et al., suggests less transient post-ECT cognitive impairment with ketofol.	Serious	Serious	Serious	Serious	Not Serious	   Very Low
<b>Frequency of TEAEs</b>	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;

**Supplemental Table 1: Full search strategy**

	#	Search	Results
PsyInfo	1	(ketamine or arketamine or esketamine or ketalar or spravato).ti,ab.	5198
	2	(depress* adj3 diagnos*).ti,ab.	14887
	3	(major adj3 depress*).ti,ab.	54137
	4	2 or 3	63781
	5	1 and 4	776
	6	Limit 5 to (human and English language)	569
EMBASE	1	(ketamine or arketamine or esketamine or ketalar or spravato).ti,ab,du.	75552
	2	(depress* adj3 diagnos*).ti,ab.	27005
	3	(major adj3 depress*).ti,ab.	87045
	4	2 or 3	105986
	5	1 and 4	2295
	6	Limit 5 to (human and English language and (clinical trial or randomized controlled trial or controlled clinical trial or multicentre study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial))	408

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

PubMed	1	Search: (((((ketamine[Title/Abstract]) OR (esketamine [Title/Abstract])) OR (arketamine[Title/Abstract])) OR (ketalar[Title/Abstract])) OR (spravato[Title/Abstract])) AND (depress*[Title/Abstract])	2459
		Filters: Humans, English	

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



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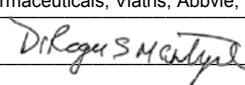
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