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Review article

Antidepressants for treating depression among older adults with dementia: A systematic review and meta-analysis

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ABSTRACT

Background: Depression and dementia represent significant health challenges in older adults. Despite guidelines recommending antidepressants, their efficacy in depressed patients with dementia remains undetermined.
Objective: This review, in following a *living systematic review approach*, primarily aims to determine the effect of any-type antidepressant on the level of depressive symptoms in older adults with dementia and secondly if there is an effect of any-type antidepressants on cognitive state, quality of life, and functionality in the old-age population with dementia.
Methods: Systematic review and meta-analysis of RCTs from *Medline, Embase,* and *Cochrane Register*. Participants were ≥65 years, with both depression and any type of dementia. Certainty-of-Evidence was assessed through the Cochrane Risk-of-Bias tool and GRADE. Analysis involved standardized mean difference, with 95 % confidence-intervals (CIs).
Findings: Of the 27,771 screened articles, 8 studies (617 participants), treated with SSRI, SSNRI, atypical, and tricyclic antidepressants were retained for quantitative synthesis. No evidence for an effect was found (SMD −0.10 [−0.26, 0.07]), nor when subgrouped based on depression severity or dementia level, nor for secondary outcomes.
Interpretation: This review did not find evidence of a clinical effect of antidepressants for treating depression in older adults with dementia. Methodological challenges might contribute to this finding.

1. Introduction

Depression and dementia profoundly affect older adults (those 65 years and older), leading to diminished quality of life and independence (Luppa et al., 2012; Voros et al., 2020; Wang et al., 2021). Approximately 22.1 % of older adults with mild dementia and 11.6 % of those with moderate dementia also experience major depressive disorder (Asmer et al., 2018). Depression is both associated with a higher risk of developing dementia, as well as being considered a neuropsychiatric symptom of dementia (Aalten et al., 2008; Ownby et al., 2006). Furthermore, depression might be part of the first clinical symptoms heralding the onset of dementia, highlighting the complex relationship between these two disorders (Kitching, 2015).

The choice of treatment in depression is usually based on severity; mild depression is usually treated with psycho-education, self-management, and psychotherapy, whereas moderate to severe depression with psychotherapy and antidepressant therapy (Kennedy et al., 2016). Antidepressant use for depression has long been the mainstay of managing depression, and their benefits versus placebo for reducing symptoms of depression are well established (Cipriani et al., 2018).

The effectiveness of antidepressants for treating depression in dementia is not well established. Some research suggests antidepressants

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might worsen symptoms, while a recent Cochrane Review found inconclusive evidence supporting their effectiveness due to a lack of comprehensive studies (Muliyala, 2010; Dudas et al., 2018). This uncertainty contrasts with the common practice of prescribing antidepressants for major depression in the elderly, and the high nursing home prevalence of psychotropic polypharmacy (Jester et al., 2021). Given the global trend of an aging population and the increasing prevalence of dementia, the need to effectively diagnose and treat depression in dementia patients becomes increasingly critical.

Recent developments in depression research suggest a renewed interest in the field (Wang et al., 2021). An update of current research is therefore warranted to identify new research to provide updated evidence for using antidepressants for depression in dementia. This study follows a *living systematic review approach*, where new evidence is continuously synthesised, ensuring that the findings remain current and relevant (Covidence Systematic Review Software, n.d.). This review primarily aims to determine the effect of any-type antidepressants on the level of depressive symptoms and secondly on cognitive state, quality of life, and functionality in older adults with dementia.

2. Methods

The study protocol to this systematic review and meta-analysis is listed in PROSPERO (CRD42019126323). Any deviations from the protocol are stated in the supplementary material.

2.1. Search methods

A systematic review and meta-analysis was conducted of randomly controlled studies (RCTs), using a tailored search of electronic databases *Medline, Embase,* and *Cochrane Central Register of Controlled Trials databases* (search strategy was designed by VM and conducted by ST and EL). Search criterion was based on various terms and synonyms of *depression, dementia, antidepressants,* and *pharmacotherapy* in various combinations, with no limits to time. Although there were no language limitations during the initial search, only English and German language articles were retained. Searches were also conducted on retained article reference lists for potential additional relevant studies. The search protocols are listed in the supplemental material. Duplicates *between Medline, Embase, Cochrane Central Register of Controlled Trials databases* were screened out using Covidence systematic review software de-duplication (Cochrane, 2019).

2.2. Selection criteria

2.2.1. Study type

Studies were included when they were RCTs, whose primary focus was on treating depression using a psychotropic treatment. All forms of pharmacotherapy for depression were considered. Non-RCT study designs, such as quasi-experimental studies, case-control studies, case series, expert opinion, and animal experiments were excluded.

2.2.2. Population

Study participants were older adults, 65 years and older, that had been diagnosed with both depressive disorders and dementia. The age criterion of 65 years was chosen to align with commonly accepted definitions of the older adult population used by major health organizations such as the World Health Organization. The depressive episode or recurrent depressive disorder had to be diagnosed according to ICD or DSM diagnostic criteria, regardless of their respective versions, or levels of depression (mild, moderate, severe according to ICD or mild or major according to DSM), or the *Olin Diagnosis Criteria for Depression in Alzheimer's Disease*. Dementia diagnosis had to fulfill the ICD or DSM criteria, irrespective of their version. No exclusions were made based on the dementia type. All levels of dementia were included (mild, moderate, and severe).

Studies were excluded when the investigated population had non-major depression mood disorders (e.g. bipolar depression or dysthymia), co-occurring severe psychiatric disorders (e.g. schizophrenia, substance dependency), or due to treatable somatic causes (e.g. hypothyroidism). Studies where brain stimulation treatments were used (e.g. electro-convulsive therapy (ECT) or repetitive trans-cranial magnetic stimulation (rTMS)), or where participants had pre-dementia diagnoses (e.g. mild cognitive impairment (MCI)) were excluded. MCI was not included to ensure consistency with similar systematic reviews reviewing only dementia populations.

2.2.3. Outcomes

Outcome measures were any quantitative assessments using standardized rating scales, which are usually self-administered or physician administered questionnaires for measuring depression symptoms, such as the geriatric depression inventory (GDI).

The primary outcome was depression. Secondary outcomes were cognitive state, quality of life, and functional decline. The secondary outcomes were selected due to their common associations with depression and clinical importance. When primary and secondary outcomes were measured by more than one standardized rating scale, one scale was selected for inclusion, based on the consistency of use across included trials, and based on their psychometric properties. When several time points were available in a study, the time-point closest to 12 weeks was selected, as peak observable effect of most antidepressants is expected at this time point.

2.2.4. Identification and selection of studies, data extraction, assessment of study quality

Two authors (ST and EL), blinded to each other, reviewed retained study titles and abstracts, against the inclusion and exclusion criteria. Full texts of retained articles were obtained for full text review. Data was manually extracted by ST and EL. All discrepancies were resolved by a third author (VM). Risk of bias was assessed for each study, following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence, and using the Cochrane Risk of Bias version 1 (RoB-1) tool. The systematic review screening and data extraction tool, Covidence, was used for both screening and data extraction.

2.3. Analysis

Meta-analysis was conducted using a random-effects model on the pooled continuous data, using the *RevMan 5.4 systematic analysis software.* All levels of depression severity, types of dementia, and antidepressant classes were pooled together. When different continuous measures were used, outcomes were reported as the standardized mean difference (SMD) with 95 % confidence interval (CI). When studies had multiple arms, over estimation of effect was avoided by dividing the control group participant number by the number of pooled investigative groups. Effect sizes were considered small, medium and large when SMD outcomes showed values of $\geq$0.2, $\geq$0.5, and $\geq$0.8 (Deeks et al., 2023). Random-effect models were selected when different studies were pooled, as heterogeneity was expected (Kraemer and Kupfer, 2006). Random-effect models allow for a more conservative estimate of effect, when heterogeneity exists, however, if there was no heterogeneity between studies, than effect sizes nor their CIs do not change between random or fixed-effect models (Kraemer and Kupfer, 2006).

Clinical and methodological diversity was evaluated by comparing participant characteristics and methodologies. Consistency of intervention effects was assessed using overlapping 95 % CIs in forest plots. No unit of analysis adjustments were needed as all studies were RCTs. Publication bias was tested with funnel plots for asymmetry when there were about 10 studies. The overall primary outcome's effect size was re-expressed as number-needed-to-treat (NNT) using the Kraemer et al. method (2006) (Rohatgi, 2022).

Outcomes were sub-grouped *a priori* based on baseline study population depression severity; mild and moderate-to-severe. Moderate and severe depression were sub-grouped together, as various guidelines recommend starting pharmacotherapy as opposed to psychotherapy alone as of moderate depression. Categorisation of depression severity groups was based on the average established severity scores at baseline between intervention and control groups. Due to a lack of information, the a priori analysis based on frailty was not conducted. No *post hoc* subgroup analyses were conducted. Sensitivity analysis was performed where studies showed considerable heterogeneity (outliers), trials with a high risk of bias, and comparing fixed-effect, random-effect estimates, and only studies investigating selective-serotonin-reuptake-inhibitors

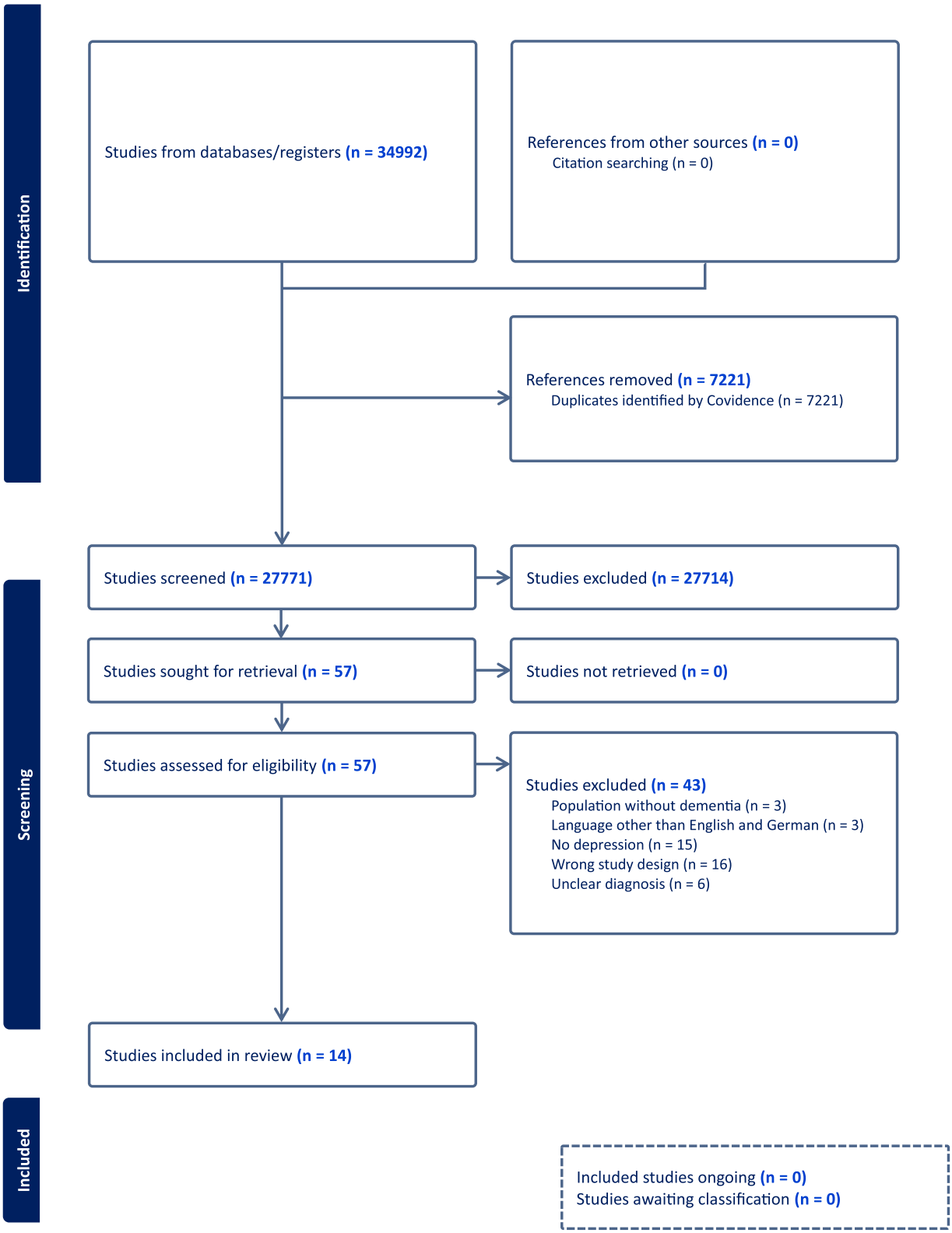

Fig. 1. PRISMA flow diagram.

(SSRIs).

When studies published data only in figures, a computer program, WebPoltDigitizer 4.6, selected due to its adaptability to non-linear graphs, was used to extract data for inclusion in meta-analysis (An et al., 2017).

3. Results

3.1. Result of the systematic search

The electronic search of databases yielded 34,992 hits, which after de-duplication yielded 27,771 articles for title and abstract screening. The search was conducted up to 18.07.2023. Of the screened articles, 57 studies were classified as relevant based on title and abstract review, and the associated full texts were obtained. Of the 57 articles whose full text was examined, 14 studies, totaling 1909 participants, met the pre-specified criteria for inclusion (Banerjee et al., 2013; de Vasconcelos Cunha et al., 2007; Fuchs et al., 1993; Katona et al., 1998; Lyketsos et al., 2003; Magai et al., 2000; Petracca et al., 1996; Reifler et al., 1989; Rosenberg et al., 2010; Jeong et al., 2022; Roth et al., 1996; Petracca et al., 2001; Taragano et al., 1997; Rosenberg 2012; Page et al., 2021). However, only 8 studies were included for quantitative synthesis (Banerjee et al., 2013; de Vasconcelos Cunha et al., 2007; Fuchs et al., 1993; Magai et al., 2000; Petracca et al., 1996; Taragano et al., 1997; Rosenberg et al., 2010; Jeong et al., 2022). Unfortunately, individual data was not available for Fuchs et al. (1993), Roth et al. (1996), Taragano et al. (1997), Katona et al. (1998), Jeong et al. (2022), and Rosenberg (2012), so that they could not be included in the pooled analysis. The population of the studies included in quantitative synthesis consisted of a population with Alzheimer's dementia.

The selection process is summarized in Fig. 1: *Study flow diagram* using PRISMA criteria (Hieronymus et al., 2021). The included studies are summarized in the *Characteristics of Included Studies* found in the *Supplementary material.* There were 43 excluded studies, of which 3 did not have dementia populations, 3, had languages other than English and German, 15 did not have depression, 16 had a study design other than RCT, and 6 did not have clear diagnosis of depression. The reasons for exclusion of are listed in the *Supplementary material, Table 4: Characteristics of Excluded Studies.*

3.2. Effects of intervention: primary outcome

3.2.1. Efficacy of any-type antidepressant on depression

Data was pooled in a meta-analysis using a random-effects model. No study was clustered, and therefore did not require adjustment for clustering. A total of 339 patients were included in the study group and 278 subjects in the control group for the outcome depression. Banerjee et al. (2013) had two intervention groups and one control. To prevent over-estimation of effect size, the control group was halved between each intervention group. When pooled using the SMD, we did not find evidence that antidepressants reduced the level of depression in older adults with dementia for mild depression (SMD −0.23, 95 % CI −0.54 to 0.09; $I^2 = 0$ %; 4 studies, 160 participants; Fig. 2) nor for moderate to severe depression (SMD −0.06, 95 % CI −0.28 to 0.16; $I^2 = 22$ %; 4 studies, 457 participants; Fig. 2). Publication bias was not suspected, as the *Funnel Plot* did not reveal asymmetry (Fig. 2, Supplementary Material). The effect sizes correspond to an NNT of 8 (95 % CI −3 to 20) and 30 (95 % CI −4 to 20) respectively.

When studies with mild to severe depression were pooled using SMD, we did not find evidence of a reduction of the level of depression in older adults with dementia (SMD −0.10, 95 % CI −0.26 to 0.07; $I^2 = 1$ %; 8 studies, 617 participants, Fig. 2). The effect size for mild to severe level of depression corresponds to an NNT of 18 (95 % CI −7 to 26). We are moderately certain of the evidence, downgrading due to imprecision.

Subgroup analysis based on severity of dementia could not include two studies (Petracca et al., 1996; Fuchs et al., 1993), and no studies with a severe level of dementia were included in the quantitative synthesis. No evidence was found for a reduction of the severity of depression in mild dementia (SMD −0.11 95 % CI −0.73 to 0.51, 1 study, 41 participants, Fig. 2) nor for moderate dementia (SMD −0.09, 95 % CI −0.31 to 0.13; $I^2 = 22$; 5 studies, 514 participants, Fig. 2). Of note, An 2017 was included in the mild depression subgroup, as the baseline of the Mini Mental Status Examination (MMSE) suggested a moderate level of dementia (Banerjee et al., 2013). Sensitivity analyses, while slightly altering heterogeneity, did not affect our interpretation of the effect (see *supplementary material*, Table 2). Of note, when pooling only for SSRI interventions, the maximum CI value touches the line of no effect (−0.19 (95 % CI −0.38 to 0.00).

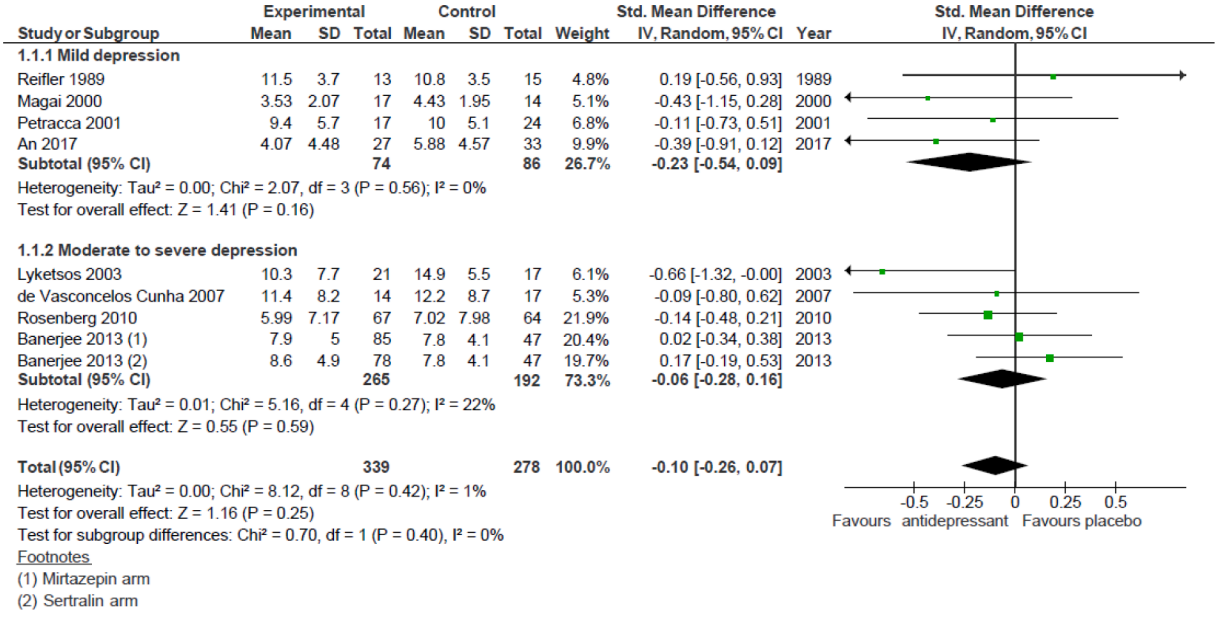

Fig. 2. Forest Plot of Antidepressant versus Placebo on Mean Depression Scores at 6–13 Weeks.

3.3. Effects of intervention: secondary outcomes

3.3.1. Cognitive state

Four studies reported post-intervention MMSE measures (Banerjee et al., 2013; Magai et al., 2000; Taragano et al., 1997; Rosenberg et al., 2010), of which only Lyketsos et al. (2000) evaluated individuals with moderate to severe depression. When pooled using mean difference (MD), we did not find evidence to demonstrate the effect of antidepressants on cognitive state for mild to severe depression (MD −0.38, 95 % CI −2.11 to 1.35; $I^2 = 0$ %; 4 studies, 167 participants; Fig. 3) nor only for mild depression (MD −0.53, 95 % CI −2.37 to 1.32; $I^2 = 0$ %; 3 studies, 129 participants; Fig. 3) or moderate to severe depression (MD 0.7, 95 % CI −4.26 to 5.66; 1 study, 38 participants; Fig. 3). We are moderately certain of the evidence, downgrading for imprecision.

3.3.2. Quality of life

Only one study reported explicitly on quality of life, using the Euro Quality of Life - 5 Dimension questionnaire (EQ-5D). When each arm of the Banerjee study was pooled using mean difference (MD), we did not find evidence to demonstrate the effect of antidepressants on quality of life in older adults with moderate to severe depression (MD −0.04, 95 % CI −0.09 to 0.02; 1 study, 111 participants; Fig. 4). We are moderately certain of the evidence, downgrading for imprecision.

3.3.3. Functionality

Four studies reported on functionality, based on the Sunnaas Index of Activities of Daily Living (SIADL) scale, Psychogeriatric Dependency Rating Scale—ADL subscale (PGDRS-ADL), Functional Independence Measure (FIM), and Older Americans Resources and Services (OARS-ADL). When pooled using SMD, we did not find evidence to demonstrate the effect of antidepressants on functionality in older adults with mild depression (SMD −0.22, 95 % CI −0.57 to 0.13; 3 studies, 129 participants; Fig. 5) or moderate to severe depression (SMD −0.39, 95 % CI −1.03 to 0.26; 1 study, 38 participants; Fig. 5), nor when mild to severe depression were pooled together (SMD −0.26, 95 % CI −0.56 to 0.05; 4 studies, 167 participants; Fig. 5).

4. Discussion

This systematic review primarily assessed the effects on the level of depression of antidepressants compared to placebo for treating depression in older adults with dementia, and secondly on cognitive state, quality of life and functionality. Of 14 identified studies, 8 contained sufficient data for quantitative synthesis, totaling 617 participants (339 in the intervention arm and 278 in the control arm). Although the general effect size trend, for both mild as well as moderate to severe depression groups, favored treatment with antidepressants, the results did not confirm an effect. The secondary outcomes assessing the effects of antidepressants on changes in cognitive state, quality of life and functionality also did not show evidence of an effect.

Additionally, the small effect sizes obtained within the margins of the confidence intervals were unlikely to lead to a minimal clinically important difference (MCID) in depression symptoms, which has been suggested to be 0.875 (Lyketsos et al., 2000). This was equally the case for the secondary analyses of the cognitive state, quality of life, and functionality. The corresponding estimated NNT for antidepressant treatment of mild depression was 8 (95 % CI −3 to 20) and moderate to severe was 30 (95 % CI −4 to 20), as well as for all levels of depression at 18 (95 % CI −7 to 26). However, these outcomes are inconclusive as their CIs cross the line of no effect.

This review updates the Thompson et al. (2007) and Dudas et al. (2018) reviews comparing antidepressants versus placebo for treating depression in dementia, screening for potential new studies since their publications, and finding none. The findings of this systematic review are comparable with the one of Dudas (2018), yet differed in that we included Magai et al. (2000), excluded Petracca et al. (1996), and presented the meta-analysis sub-grouped based on the severity of depression, rather than by antidepressant class. Magai et al. (2000) was included as we considered the study population relevant, considering that mild depression can also benefit from antidepressant treatment. The inclusion of studies with populations treating mild depression allows for a broader representation of the depression spectrum. However, unlike the Dudas (2018) review, we excluded the Petracca et al. (1996) study, as over 50 % of the study population did not fulfill the criteria of depression, but rather only dysthymia. When adding the Petracca et al. (1996) to the pooled meta-analysis, there is no significant change in the effect size (see Fig. 2: *Supplementary material*). The findings of this study contrast that of Thompson et al. (2007), who included three studies from this meta-analysis (Thompson et al., 2007; Petracca et al., 1996; Taragano et al., 1997) finding an efficacy of sertraline and fluoxetine versus placebo in reducing depression in Alzheimer's dementia (Bomasang-Layno et al., 2015). However, the effect size obtained was unlikely to lead to a MCID (Lyketsos et al., 2000). Of note, Bomasang (2015) reviewed antidepressants for treating depression in Parkinson Disease (Elliott et al., 2017). The studies included in the Bomasang (2015) review, however, did not fulfill our inclusion criteria as their population remained cognitively fit, not yet being in the phase of the disease having dementia.

Considering the persistent lack of clear evidence for antidepressant treatment of depression in older adults with dementia, despite frequent

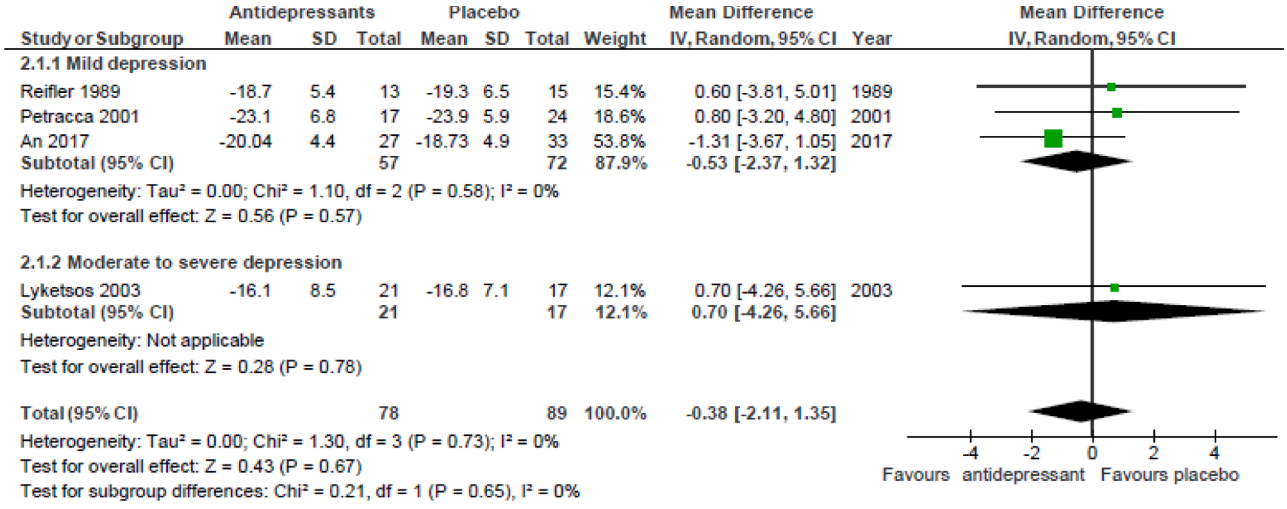

Fig. 3. Forest Plot of Antidepressant versus Placebo on Mean Cognition Scores at 6–13 Weeks.

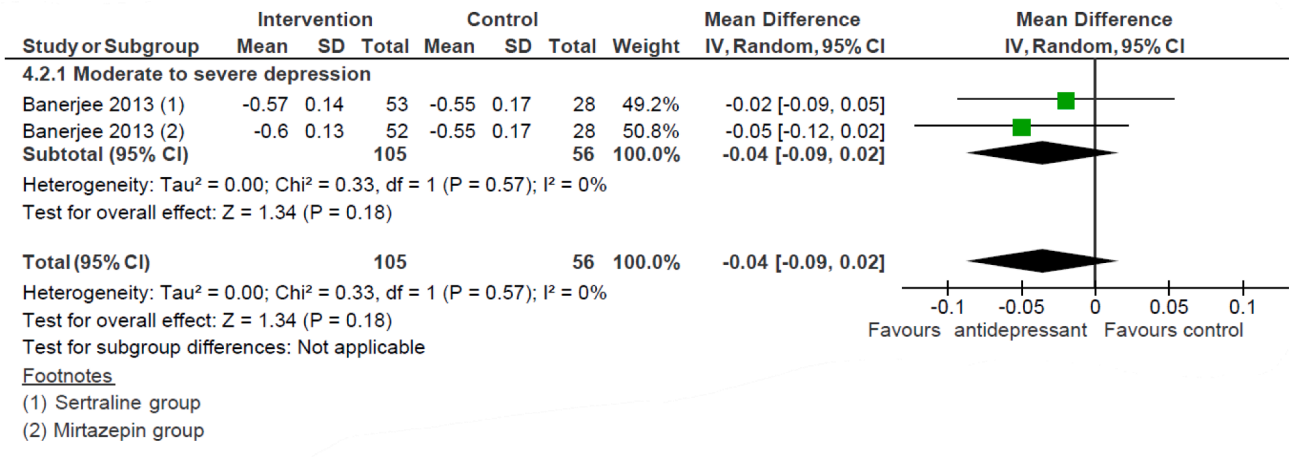

Fig. 4. Forest Plot of Antidepressant versus Placebo on Mean Quality of Life Scores at 6–13 Weeks.

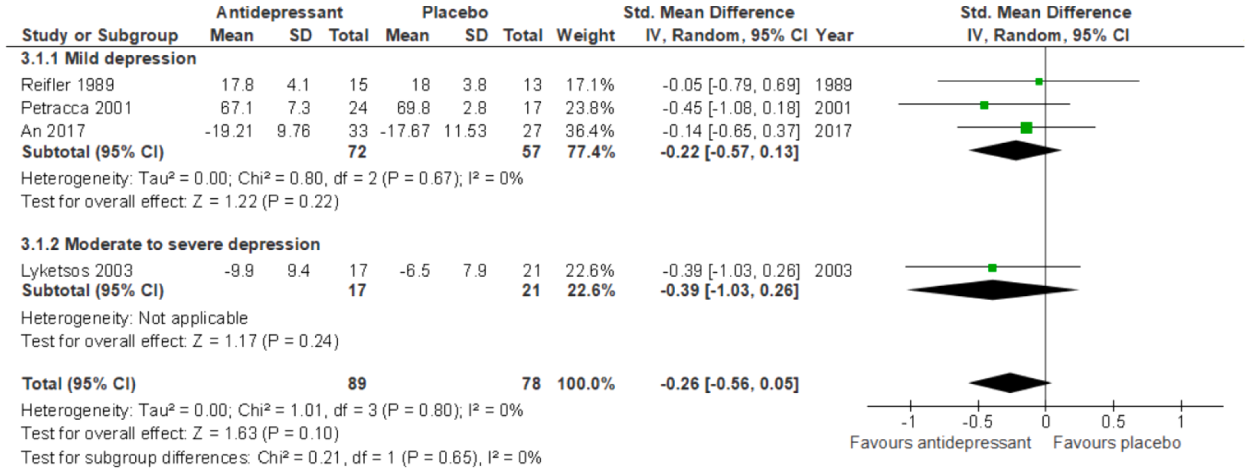

Fig. 5. Forest Plot of Antidepressant versus Placebo on Mean Functionality Scores at 6–13 Weeks.

prescribing, this updated systematic review exemplifies a *Living Systematic Review Approach* (Covidence Systematic Review Software, n.d.). It confirms ongoing gaps in the literature, guiding future research, and demonstrates a commitment to transparency by continuously monitoring and evaluating evidence; It maintains the review's clinical relevance, preventing stagnation and obsolescence; and helps avoid outdated information (Deeks et al., 2023). By preventing the dissemination of outdated information, living systematic reviews support better-informed clinical and policy decisions, ultimately contributing to improved healthcare outcomes (Covidence Systematic Review Software, n.d.).

However, some studies support antidepressant use, such as Citalopram, in older adults with dementia, for the management of neuropsychiatric symptoms, such as agitation (Chen et al., 2023). Distinguishing primary psychiatric disorders and neuropsychiatric symptoms is difficult considering there is overlap in non-specific symptoms, such as apathy and anhedonia (Fisher et al., 2024).

The lack of clear efficacy may represent a different pathogenesis of depression in older adults with dementia, suggesting the importance of investigating older adults separately There may be a role due to the cerebral structural alterations inherent with the various forms of dementia, neurotransmitter dysregulation, metabolic changes, and changes in the blood-brain barrier (BBB) permeability inherent in older adults. Fisher et al. (2024) highlights the autoimmune hypothesis, where an aberrant immune function has been found to correlate with both depression and Alzheimer's dementia, and the vascular hypothesis, where large cerebrovascular events and disease result in cerebral injury in strategic locations. They suggest that there may be a mixed inflammatory and vascular component, resulting in BBB disruption (Fisher et al., 2024).

4.1. *Strengths and limitations*

This systematic review and meta-analysis was designed to minimize potential biases throughout the review process, including publishing a study protocol with PROSPERO. However, despite the thorough search, it is possible that potentially eligible studies were missed, such as unpublished studies, or articles published in languages other than English and German (language bias). Several databases as well as reference lists of included studies were searched, to avoid the risk of publication bias.

The certainty of evidence of the findings in this review was judged to be moderate, downgraded due to imprecision. In addition, this review does not encompass the entirety of research in the field, as several studies did not publish sufficient evidence to be included in this review, resulting in their findings not contributing to the results of quantitative synthesis. Of note, the available evidence is limited owing to a small number of research participants; a total of 617 participants, of which 160 and 457 participants had mild and moderate to severe depression respectively.

The included studies were heterogeneous, having a broad baseline of cognitive levels and severity of depression as well as different classes of antidepressants, of which tricyclic antidepressants (TCA) and

monoamine oxidase inhibitors (MAOs) are generalized avoided in this population due to the side effect profiles (Gallagher et al., 2008). The study populations included in quantitative synthesis was likely heterogeneous, however only their mean depression and cognitive levels were reported. It was therefore not possible to stratify them based on depression and dementia level.

4.2. Implications for research

Considering the lack of new publications since the 2018 Dudas review, despite a well described increase in prevalence of all-cause dementia worldwide (Avan and Hachinski, 2023), there is a need for new studies investigating the effects of antidepressant for treating depression in dementia.

The likely distinct pathogenesis of depression in dementia populations indicates a need for targeted research for an improved understanding. and for developing specific treatment guidelines considering neurocognitive status. Challenges in distinguishing between neuropsychiatric symptoms and major depressive disorder symptoms suggest a need for more nuanced screening tools for health-care professionals.

5. Conclusion

This systematic review and meta-analysis did not find evidence of an effect of antidepressants for treating depression in older adults with dementia for both mild and moderate to severe depression. Despite this, current trends in managing depression in this population continue to recommend antidepressant treatment. The lack of effect may be related to differences depending on the severity of dementia and to the distinct pathogenesis of depression, which future studies could help clarify. Psychiatric evaluation in older adults remains a challenge. There is a need for more nuanced diagnostic criteria and screening tools to better distinguish between major depression and neuropsychiatric symptoms.

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Data sharing

Data obtained is readily available for sharing upon request to EL for academic purposes.

CRediT authorship contribution statement

Eric Lenouvel: Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Sebastian Tobias:** Writing – original draft, Formal analysis, Data curation. **Viktoria Mühlbauer:** Writing – review & editing, Data curation, Conceptualization. **Dhayana Dallmeier:** Writing – review & editing, Methodology, Conceptualization. **Michael Denkinger:** Writing – review & editing, Methodology, Conceptualization. **Stefan Klöppel:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Carlos Schönfeldt-Lecuona:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

All authors declare that they have no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2024.116114.

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