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Efficacy of Antidepressants in the Treatment of Depression Associated with Alzheimer's Dementia

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Abstract: *Alzheimer's dementia is a progressive degenerative brain disease marked by cognitive decline and often accompanied by psychiatric symptoms, with depression being one of the most prevalent non-cognitive symptoms. Various antidepressants have been investigated for their efficacy in treating depression in dementia patients. This study analyses the outcomes of randomised clinical trials (RCTs) regarding the use of antidepressants to treat depression associated with Alzheimer's dementia (AD). As method, a comprehensive search was conducted for randomised, placebo-controlled, double-blind studies with a minimum duration of 4 weeks. The search included studies evaluating one or more antidepressants. Keywords used were "RCT, depression, dementia," supplemented by terms for each specific antidepressant or class of antidepressant drugs.*

Keywords: *RCT; depression; dementia.*

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1. Introduction

Alzheimer's dementia is a degenerative brain disease characterised by progressive cognitive decline. Frequently, associated psychiatric symptoms are also recorded. Clinical studies have identified four categories of non-cognitive psychiatric symptoms in dementias: symptoms of depression, psychosis, sleep difficulties (including insomnia and wandering), and qualitative disturbances of perception and thought (delusions, hallucinations) all of which can severely impact the quality of life and care management for dementia patients (Hayer, & Tadros, 2024; Vinaşi, Buciuta, & Coman, 2021). Non-cognitive symptoms contribute to increased morbidity and mortality among patients with dementia, often leading to extended hospital stays and the need for specialised care units (Nagata et al., 2023). These symptoms can manifest at any stage of dementia. Typically, some symptoms, like depression, appear soon after the onset, whereas others, such as behavioural disturbances, emerge in the more advanced stages (Geda et al., 2013).

Depression (both major and minor) is one of the most common non-cognitive symptoms of dementia. The prevalence of depression is estimated at 30 - 50% in most studies of patients with AD at different stages of progression (Lee & Lyketsos, 2003). Non-cognitive symptoms in Alzheimer's dementia and other forms of dementia make the care of these patients more difficult. Moreover, the therapeutic approach to these symptoms must consider the advanced age of the patients, which limits therapeutic options. Depression associated with dementia exacerbates cognitive decline, which can be partly reversible with effective treatment.

Treatments for depressive problems in dementia include pharmacological healing procedures, psychosocial interventions, and electroconvulsive therapy (ECT). Behavioural interventions have verified effectiveness in lowering depressive symptoms in dementia-affected people (Teri et al., 1997). ECT has shown advantageous results in treating depression associated with dementia, although it carries an increased hazard of delirium overlapping with dementia (Coman & Nemeş, 2017; Rao & Lyketsos, 2000).

The efficacy and tolerability of antidepressants in depression associated with AD have been studied for more than 30 years. Although most initial studies had a proper design (randomised, placebo-controlled, double-blind), they included a relatively small number of patients. As a result, the findings were often controversial or even contradictory.

A wide range of antidepressants have been included in clinical studies, including Tricyclic or related (Tetracyclics); Selective Serotonin Reuptake Inhibitors (SSRIs); Reversible Inhibitors of Monoamine Oxidase (RIMAs); Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs); and Noradrenaline and Specific Serotoninergic Antidepressants (NaSSAs). Initially, some antidepressants were compared with placebo in studies. Later, research expanded to compare the efficacy and tolerability of two or even three antidepressants, sometimes including a placebo arm. With the accumulation of a significant number of studies, the results have been synthesised in multiple systematic reviews and a few meta-analyses (Bains, Birks, & Dening, 2002; Siarkos, Katirtzoglou, & Politis, 2015).

Despite these advances, the available results are currently not consistent enough to fully clarify the utility of antidepressants in depression associated with AD or other forms of dementia. For example, a systematic review found limited evidence supporting the efficacy of antidepressants in treating depression in dementia (Bains, Birks, & Dening, 2002).

The primary objective of this study is to reanalyse the statements from randomised, double-blind, placebo-controlled clinical trials (RCTs) published in the literature, mainly inspecting the efficacy of antidepressants in treating depression associated with Alzheimer's dementia. Additionally, as a secondary objective, we aimed to compare our findings with those reported in recent meta-analyses.

2. Method

2.1. Selection of Articles

The present study is a systematic review with network meta-analysis. The article search was carried out using the **PubMed**, **Cochrane**, **Embase,** and **CINAHL databases**, covering January 1989 – June 2020. The search terms included "RCT, depression, dementia," supplemented by additional terms specific to each antidepressant or antidepressant class. Randomised, double-blind, controlled trials of a minimum duration of 4 weeks comparing the effectiveness of antidepressants with placebo or between them for the treatment of depression associated with Alzheimer's dementia were eligible.

Following the search process, 4211 articles were initially identified based on general terms. After removing duplicates, 2844 articles were subjected to an initial evaluation of titles and abstracts. Of these, 2676 articles were excluded, based on the criteria of relevance to the objectives of the study. The specific reasons for excluding articles were documented in detail and classified as follows: population inadequate for the objectives of the study (no=1043); the lack of a control arm or a relevant comparison (no=876); insufficient sample sizes for robust analyses (no=527); use of non-validated instruments to measure depression (no=230).

For the remaining 168 articles, the full texts were analysed, taking into account the homogeneity of the sample size and the validity of the instruments used to measure efficacy and tolerability. Of these, 144 articles were eliminated due to non-fulfillment of the mentioned methodological criteria, leaving a total of 24 articles included in the analysis of the present study (Figure 1).

The selection process was carried out independently by two reviewers, each applying inclusion and exclusion criteria to assess the relevance and quality of the studies. In the case of discrepancies, they were discussed and resolved by consensus. To ensure a high degree of methodological rigour, the **Cochrane Risk of Bias** tool was used to assess the risk of bias, and the results of this assessment were documented for each study.

2.2. Outcome

The outcomes measured included the effect of antidepressants on depression, as objectified by established evaluation scales (Hamilton Depression Rating Scale – HAM-D, Montgomery-Asberg Depression Rating Scale – MADRS, and Cornell Scale for Depression in Dementia – CSDD) and response rates (50% reduction in initial depression score) or remission (decrease in depression score below threshold).

2.3. Data Extraction

From the selected studies, the mean and standard deviation of the scores obtained on the scales used pre- and post-intervention, as well as the number of participants included in each study, were extracted.

2.4. Data Analysis

A Bayesian network meta-analysis using random effects models was conducted to compare antidepressants with placebo and with each other, both directly and indirectly. We used Markov Chains Monte Carlo methods with 100,000 samples, with a burn-in of 20,000. Inconsistency was analysed using the node-splitting method. For the convergence analysis of the simulated model, we used Gelman-Rubin convergence assessment plots. All statistical calculations were performed using the R application with the netmeta, gemtc (Generalised Evidence Synthesis for Mixed Treatment Comparisons), and BUGSnet packages through the MetaInsight interface.

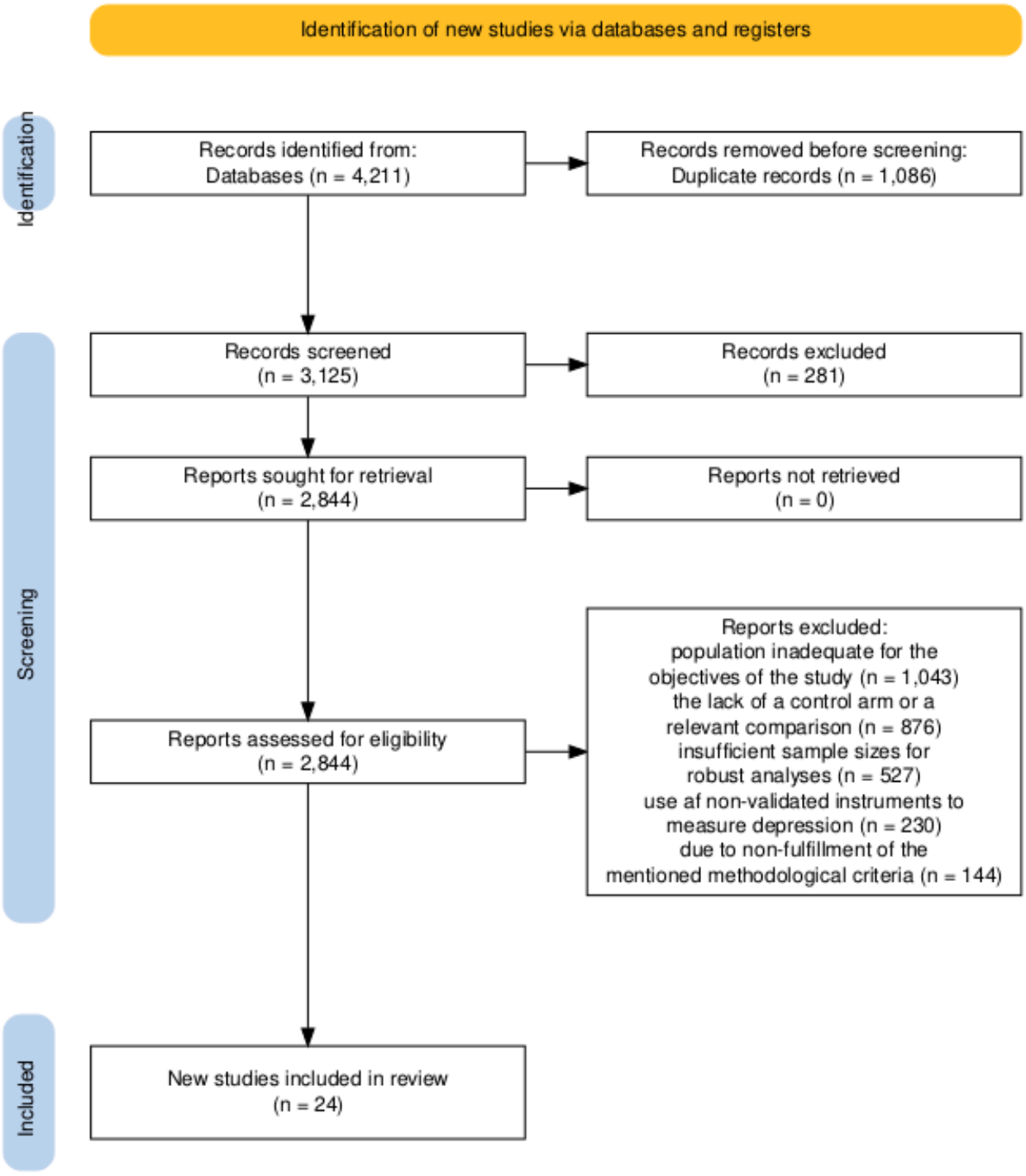

Figure 1. PRISMA flow diagram of the study selection process.

3. Results

3.1. Study Characteristics

In total, 24 studies were analysed. Of these, 8 were considered relevant after the initial evaluation of titles and abstracts. Sixteen studies were analysed in detail and included in the analysis.

From the articles included in the analysis, 9 compared antidepressants with placebo, and 7 compared antidepressants with each other. In total, 3 studies had three arms. The most studied antidepressant was sertraline, analysed in 7 studies. The other SSRIs studied include citalopram/escitalopram, fluoxetine, and paroxetine. Among other classes of antidepressants, the review included tricyclics and related (imipramine, amitriptyline, clomipramine, desipramine, maprotiline, and mianserine), SNRIs (venlafaxine), NaSSAs (mirtazapine), RIMAs (moclobemide), and miscellaneous antidepressants (vortioxetine) and NDRIs (bupropion). Detailed characteristics of the studies can be found in Table 1 and Table 2.

Table 1. Characteristics and Efficacy Results of Single Antidepressant Studies in Treating Depression Associated with Alzheimer's Dementia.

Author (Year)	Antidepressants (daily doses)	Duration (weeks)	Sample size Total (antidepressant/placebo)	Depressive symptoms outcome measure	Efficacy results
Nyth, & Gottfries, 1990	Citalopram 20 mg	4	N=89 (N=44 / N=45)	MADRS	Citalopram > placebo (p=0.358 – not significant)
Teri, 1991	Imipramine 83 mg (mean dose)	8	N=28 (N=13 / N=15)	HAM-D	Imipramine = placebo (not significant)
Fuchs, & Schlaepfer, 1993	Maprotiline 50 mg (mean dose)	8	N=127 (N=64 / N= 63)	GDS	Maprotiline > placebo (p=0.09 – significant at the 10% level)
Petracca & Chemerinski, 1996	Clomipramine 100 mg	6	N=21 (N=11 /N=10)	HAM-D	Clomipramine > placebo (p<0.05 - significant)
Roth, Mountjoy, & Amrein, 1996	Moclobemide 400 mg	6	N=511 (N=259 / N=252)	HAM-D, CGI	Moclobemide > placebo (p<0.001 - significant)
Magai, et al., 2000	Sertraline 100 mg	8	N=31 (N=17 / N=14)	CSDD, GS	Sertraline > placebo (p<0.001 - significant)
Petracca, Chemerinski, & Starkstein, 2001	Fluoxetine 40 mg	6	N=35 (N=15 / N=20)	HAM, CGI	Fluoxetine > placebo (not significant)
de Vasconcelos Cunha, Tavares, & Caramelli, 2007	Venlafaxine 131.25 mg	6	N=31 (N=14 / N=17)	MADRS, CGI	Venlafaxine > placebo (p=0.19 – not significant)
Weintraub, & Stern, 2010	Sertraline 100 mg	24	N=131 (N=67 / N=64)	CSDD	Sertraline > placebo (p=0.26 – not significant)

HAM-D - Hamilton Depression Rating Scale; MADRS - Montgomery-Asbeg Depression Rating Scale; CSDD - Cornell Scale for Depression in Dementia; GS - Gestalt Scale (GS)16; CGI - Clinical Global Impression; GDS - Geriatric Depression Scale.

Table 2. Characteristics and Efficacy Results of Studies Comparing Multiple Antidepressants in Treating Depression Associated with Alzheimer's Dementia.

Author (Year)	**Antidepressants (daily doses)**	**Duration**	**Sample size**	**Depressive symptoms outcome measure**	**Efficacy results**
Taragano, et al., 1997	Amitriptyline 25 mg, Fluoxetine 10 mg	45 days	Amitriptyline, N=19; Fluoxetine, N=18	HAM-D	Amitriptyline (Baseline – Day 45 ($p<0.000$ – significant) Fluoxetine (Baseline – Day 45 ($p<0.0001$ – significant) Amitriptyline < Fluoxetine (not significant)
Katona, Livingston, & Cooper, 1998	Imipramine 50-100 mg, Paroxetine 20-40 mg	8 weeks	**Imipramine**, N=98 (50 mg, N=65; 75 mg, N=24; 100 mg, N=9); **Paroxetine**, N= 99 (20 mg, N=60; 30 mg, N=29; 40 mg, N=10)	MADRS, CGI S, CGI I, GBS Scale, CSDD	Imipramine < Paroxetine (MADRS $p=0.368$ – not significant; CSDD $p=0.049$ – significant)
Karlsson, & Hallgren, 2000	Mianserin 30-60 mg, Citalopram 20-40 mg	12 weeks	Mianserin, N=26; Citalopram, N=24	MADRS, CGI I	Mianserin > Citalopram (MADRS $p=0.25$ – not significant; CGI $p<0.04$ - significant)
Banerjee, et al., 2011	Sertraline 95 mg (mean dose), Mirtazapine 30 mg (mean dose)	13 weeks, 39 weeks	Sertraline week 13, N=78; week 39, N= 68; Mirtazapine week 13, N= 85; week 39, N= 76; Placebo week 13, N= 95; week 39, N= 82;	CSDD	13 weeks: Placebo > Mirtazapine > Sertraline (not significant) 30 weeks: Mirtazapine > Placebo > Sertraline (not significant)
Mokhber, & Abdollahi, 2014	Desipramine 150 mg, Sertraline 150 mg, Venlafaxine 150 mg	12 weeks	Desipramine, N= 19; Sertraline, N=20; Venlafaxine, N= 20;	HAM-D	Sertraline > Venlafaxine > Desipramine (not significant)
Jeong et al., 2022	Vortioxetine 15 mg, Control group: Escitalopram, Paroxetine, Bupropion, Venlafaxine, Sertraline	12 months	Vortioxetine, N= 36; Control group, N=72;	HAM-D, CSDD	Vortioxetine > control group (HAM-D $p=0.05$ – significant, CSDD $p=0.04$ – significant)
Takemoto, Suzuki, & Matsumoto, 2020	Sertraline 31.8 mg (mean dose), Escitalopram 7.3 mg (mean dose), Nicergoline 14.5 mg (mean dose)	3 months	Sertraline, N=11; Escitalopram, N=13; Nicergoline, N= 9;	GDS, AS	Escitalopram (baseline-3 months: GDS $p=0.04$ – significant, AS – not significant) Sertraline (baseline-3 months: GDS – not significant, AS $p=0.05$ – significant) Escitalopram > Sertraline (not significant)

HAM-D: Hamilton Depression Rating Scale; MADRS: Montgomery-Asbeg Depression Rating Scale, CGI: Clinical Global Impression; Gottfries, Brane, Steen (GBS) Scale; CSDD: Cornell Scale for Depression in Dementia; GDS: Geriatric Depression Scale; AS: Apathy Scale

The inconsistency test shows that there are no significant differences between the results obtained through indirect and direct comparisons of the medications. The inter-study standard deviation is 3.48 (95% CI 1.88-6.25).

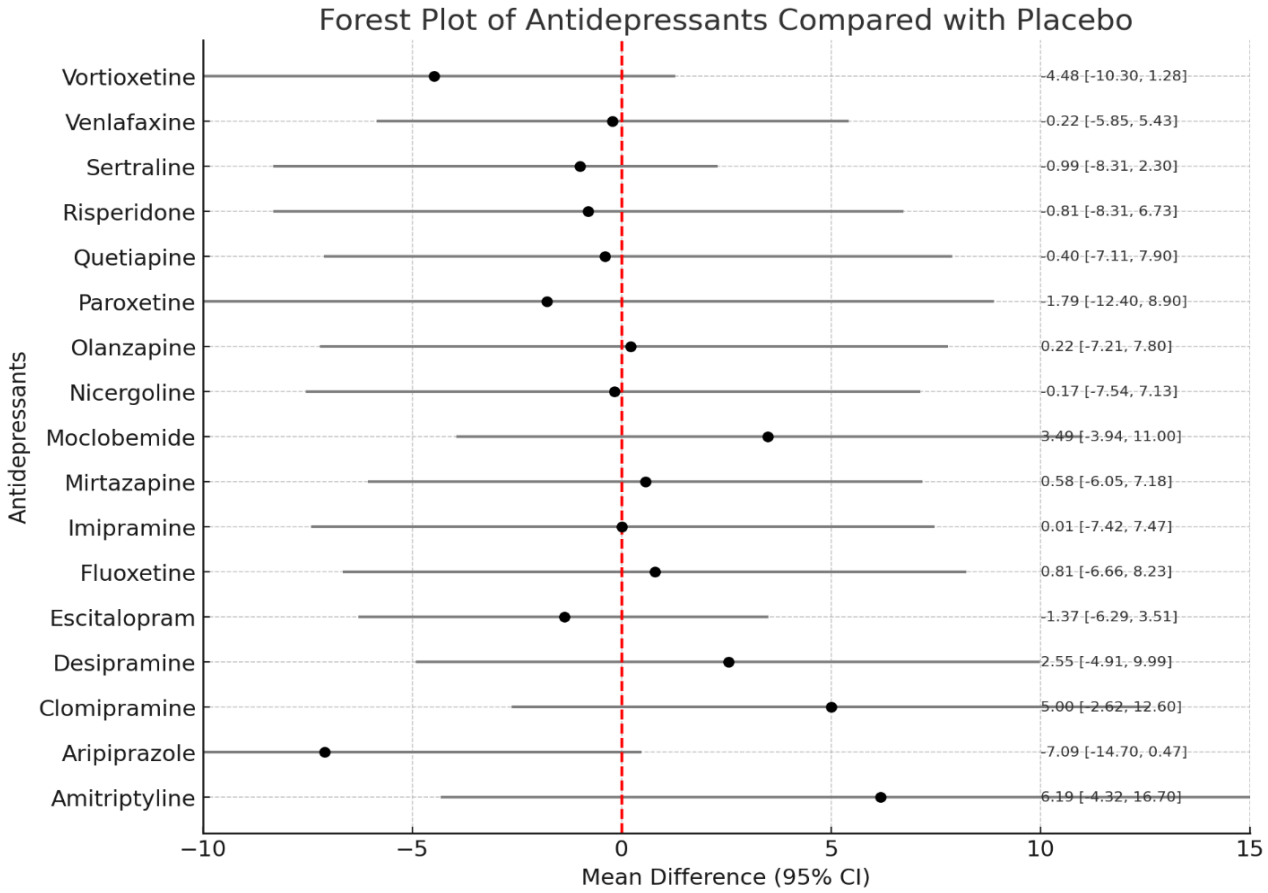

Figure 2. Inconsistency test results.

Figure 2 shows the standardised mean (SD) differences between antidepressants and placebo in the reduction of depression symptoms, including the confidence intervals for each estimate. This graph allows the direct and indirect comparison of each drug's effectiveness, highlighting the differences between the classes of antidepressants.

Vortioxetine demonstrated significantly higher efficacy than placebo (SD -4.48; 95% CI [-10.30; -1.28]), showing a consistent reduction in depressive symptoms. It ranks first in the efficiency ranking, being suitable for patients with moderate to severe depression associated with Alzheimer's dementia.

Paroxetine and **escitalopram,** with SDs of -1.79 and -1.37, respectively, showed high efficacy but lower than vortioxetine. These medicines may be viable options for patients at higher risk of adverse effects due to their better tolerability profile.

Sertraline, although included in several studies, had inconsistent results, with an SD of -0.99, suggesting moderate efficacy, especially suitable for older patients, due to the minimal cognitive side effects.

3.2. Participants

In total, the studies included in the meta-analysis involved 1736 participants, with 1069 treated with antidepressants and 667 with a placebo.

3.3. Efficacy of Antidepressants

The analysis of the efficacy of antidepressants used for the treatment of depression associated with Alzheimer's dementia revealed significant variations between the classes of drugs studied, highlighting the importance of balancing efficacy and tolerability, especially for elderly populations, vulnerable to the side effects of pharmacological treatments.

From the results obtained, three antidepressants showed greater efficacy than placebo: Vortioxetine (SD -4.49), Paroxetine (SD -1.80), and Escitalopram (SD -1.38). Weaker results compared to placebo were observed for the following tricyclic antidepressants: Clomipramine (SD 4.99); Amitriptyline (SD 6.20); Desipramine (SD 2.53); Moclobemide (SD 3.49). The rest of the antidepressants had effects comparable to placebo.

The tolerability profile varied significantly between drugs. For example, sertraline, evaluated in seven studies, demonstrated a favorable profile with no notable adverse effects on cognitive functions. In contrast, for vortioxetine, although efficacy was high, there is a lack of data on long-term side effects, which underlines the need for further investigation.

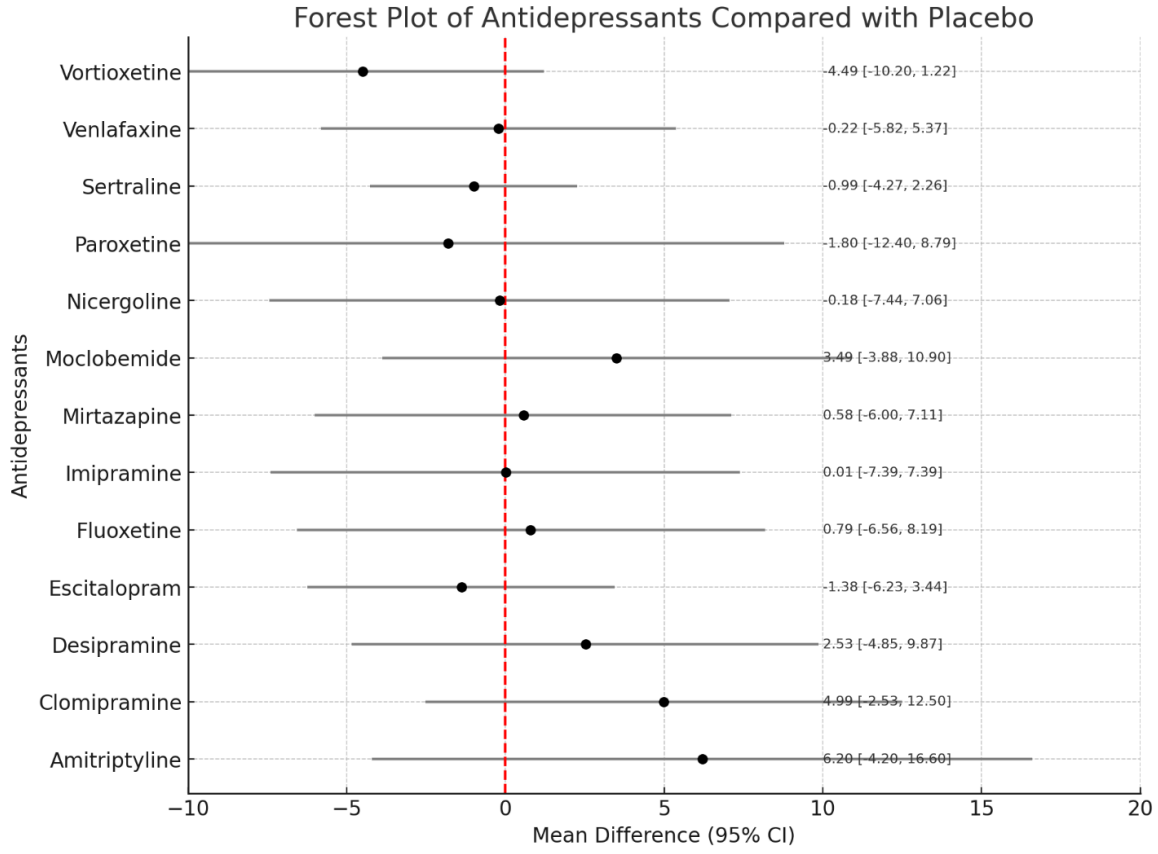

Figure 2. Inconsistency test results.

3.4. Rankings of efficiency

Median rankings were generated to classify the medications included in the meta-analysis based on their potential efficacy. Cluster 1: Includes vortioxetine and aripiprazole, which have demonstrated the greatest therapeutic benefits. These medications are suitable for patients with

severe depression, especially in the advanced stages of dementia. Cluster 2: Drugs such as fluoxetine and mirtazapine, with similar efficacy to placebo, are more suitable for patients with mild depression or as adjunctive therapy. Cluster 3: Drugs such as amitriptyline and clomipramine, which have shown limited or no efficacy, should be used with caution, due to the increased risks of adverse effects.

Table 3: Rankings of Antidepressant Efficacy in Treating Depression Associated with Alzheimer's Dementia.

Rank	Drug
1	Vortioxetine
4	Paroxetine
5	Escitalopram, Sertraline
7	Nicergoline, Venlafaxine
8	Imipramine
8	Fluoxetine, Mirtazapine
13	Moclobemide
14	Clomipramine
15	Amitriptiline

Note: Ranks 2, 3, 6, 10, 11, and 12 are not assigned due to ties or gaps in the efficacy data.

Table 3 provides a detailed classification of the antidepressants analysed in this meta-analysis, based on the medians of their effectiveness in reducing depressive symptoms associated with Alzheimer's dementia. The rankings highlight important differences between drug classes. It is considered a useful tool to guide clinical decision-making in selecting appropriate treatment methods.

4. Discussions

The analysis of the studies included in this systematic review and network meta-analysis highlights conflicting results and significant variability in the efficacy and tolerability of antidepressants used to treat depression associated with Alzheimer's dementia (AD). These discrepancies are due to both the heterogeneity of the included studies and methodological limitations, such as small sample sizes and varied assessment tools.

Tricyclic and Tetracyclic Antidepressants: Imipramine, clomipramine, and maprotiline were each examined in one of the individual studies as the only antidepressant. Amitriptyline, desipramine, and mianserin have been included in comparative research that did not include a placebo arm. Regarding their effectiveness on depression related to dementia, it has been tested in almost all research. As for the effect on cognitive overall performance, there was either a decline during treatment or no effect, which is predictable considering the anticholinergic consequences of those antidepressants.

Among selective serotonin reuptake inhibitors (**SSRIs)**, sertraline was the most studied: three studies as the only antidepressant and two comparative studies, one of which used a placebo arm. In three out of five studies, it was effective in improving depression, while in two, the effect was comparable to that of a placebo. However, in all studies, there was no negative influence on cognition and no reduced tolerability. Citalopram and fluoxetine were each studied in one study as a single antidepressant and in a second comparative study with other antidepressants. In one study, each antidepressant showed a significant improvement effect on depression associated with dementia, while in the remaining two studies, the two antidepressants did not significantly influence depression. However, in all four studies, the effects on cognition were absent.

Serotonin-norepinephrine reuptake inhibitors (SNRIs): Several studies have examined the use of venlafaxine in treating hopelessness associated with AD. One review compared

venlafaxine and placebo; however, it was easy to cover only 31 patients and other comparators. All looked at venlafaxine, desipramine, and sertraline which were placed again. Overall, the results challenge the efficacy of venlafaxine in treating these patients. And if there is anything Tolerability profile of the drug is also not as good as sertraline.

Noradrenergic and specific serotonergic antidepressants (NaSSAs): Mirtazapine was evaluated in a single comparative study with sertraline, a placebo-controlled study that included a representative number of patients (326). The results showed that both antidepressants improved depression less than the placebo.

Reversible inhibitor of monoamine oxidase (RIMAs): Moclobemide proved effective in treating depression associated with dementia and had a favourable cognitive outcome. Although the results are based on a single study, considering the large number of cases included (694), the degree of confidence can be considered significant.

Our results are supported by statistical studies or meta-analyses published in recent years. A review published in 2015 concluded that antidepressants studied to date no longer show any real efficacy in treating AD-related depression (Siarkos, Katirtzoglou, & Politis, 2015). A 2017 meta-analysis found that there was no conclusive evidence to support the efficacy of antidepressants in treating AD-related depression (Orgeta et al, 2017). Although depression is prevalent, data from 2018 indicates that there will likely be an increase in the number of people with mental health problems and more patients taking antidepressants. However, there is limited evidence to support the effectiveness of antidepressants in treating these patients. Additionally, some evidence suggests that antidepressant treatment may prolong metabolic syndrome, associated with increased risk of cardiometabolic diseases. (Dudas et al, 2018).

The results highlight the need for a personalised approach to the use of antidepressants for depression associated with AD. Vortioxetine and escitalopram, due to their documented efficacy and safety profile, may be suitable options for patients with moderate or severe depression. Instead, tricyclic antidepressants should be avoided because of the risks associated with severe side effects, such as sedation and cognitive decline.

Although some antidepressants have shown therapeutic benefits in the studies analysed, the lack of consistent effectiveness can be explained by several factors. The variability in the severity of depression, the stage of Alzheimer's dementia, and associated comorbidities complicate the evaluation of the effectiveness of treatments. This diversity can dilute the results and mask the real effectiveness of medicines. The studies also used different doses of the same drug, which influenced the results. Too low doses could underestimate the effectiveness, while too high doses can increase the risk of adverse effects. Depression associated with AD often requires long-term treatment to see clear benefits. Some studies had intervals too short to demonstrate extensive efficacy. Patients with AD often receive concomitant medication for different conditions, that may have an impact on the effectiveness of antidepressants and increase the risk of side effects, in addition to the dearth of analysis by way of subgroups, together with variations in gender, age, or severity of the disease, can conceal unique blessings of some drugs for sure classes of patients.

An essential aspect of the use of antidepressants in patients with AD is tolerability. Although modern drugs such as vortioxetine and escitalopram have a favorable profile, data on their long-term effects are limited. **Sertraline**, due to its minimal impact on cognitive function and a low risk of side effects, can be a useful option for milder cases. In stark contrast, tricyclic antidepressants have been associated with an increased risk of severe adverse effects, such as excessive sedation and cognitive decline, due to their anticholinergic properties. These data suggest that treatment selection should take into account each patient’s safety profile.

The selected studies included a relatively small number of cases. Moreover, the patients were divided into two or more study arms. Due to the less restrictive nature of the selection criteria, the volume of the patient cohort was not considered a criterion for inclusion.

The cases included in the selected studies and the assessment tools used are, to some extent, heterogeneous, making a quantitative analysis of the results difficult and rendering qualitative

analysis more feasible. One of the causes affecting the homogeneity of the patients is due to variation in diagnostic labels: "Alzheimer's disease"/"Alzheimer's dementia", "probable Alzheimer's disease", "mixed dementia", "dementia", and "cognitive decline in the elderly". Considering that the most common form of dementia is Alzheimer's, the homogeneity of the patients becomes acceptable. Thus, the Alzheimer's Dementia Study Society mentions the following prevalences corresponding to the main forms of dementia: Alzheimer's dementia at 55%, vascular dementia at 20%, Lewy body dementia at 15%, and frontotemporal dementia at 5% (Gearing, et al., 1995).

Another source is that the patients with or without cognitive decline included in the selected studies mostly presented "major depressive episodes", but in others, those with "minor depression" or even "emotional disorders" were also included.

Finally, another aspect that raises difficulties in the quantitative evaluation of study results is due to the use of different instruments for assessing depression. Among the clinical scales, the HAM-D was found in several studies, but in different versions: with 17, respectively, 24 items, the CDSS, and MADRS were found in most but not in all the studies.

5. Conclusions

This systematic review and network meta-analysis of randomised controlled trials (RCTs) evaluating the efficacy of antidepressants in treating depression associated with Alzheimer's dementia (AD) underscores significant challenges in establishing definitive conclusions. Although a broad spectrum of antidepressants, including SSRIs, SNRIs, NaSSAs, RIMAs, and tricyclic antidepressants, was assessed, the overall evidence for their effectiveness in ameliorating depressive symptoms in AD patients remains inconclusive and methodologically constrained.

Our analysis identified **vortioxetine**, **paroxetine**, and **escitalopram** as the most promising antidepressants, demonstrating superior efficacy compared to placebo. However, these results were inconsistent across studies, reflecting variability in sample characteristics, study designs, and outcome measures. Conversely, tricyclic antidepressants, such as **clomipramine**, **amitriptyline**, and **desipramine**, not only failed to demonstrate benefits but also yielded outcomes inferior to placebo. These findings align with previous systematic reviews and meta-analyses that highlighted the limited evidence supporting the efficacy of antidepressants in managing depression in dementia.

While certain antidepressants may offer potential benefits for managing depression in Alzheimer's dementia, the current body of evidence is insufficient to support their widespread use. Future studies must adopt enhanced methodological rigour to provide clearer guidance for clinicians addressing the complex needs of this vulnerable patient population. Until such data are available, the use of antidepressants in AD should remain cautious, individualised, and guided by a thorough assessment of risks and benefits.

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