

The Interface between Depression and Alzheimer's Disease. A Comprehensive Approach

Pedro J. Modrego, Leyre D. de Cerio, Antonio Lobo¹

Servicio de Neurología, Hospital Miguel Servet de Zaragoza, ¹Department of Psychiatry, University of Zaragoza, Spain

Abstract

Depression and Alzheimer's disease (AD) are frequent interacting diseases in the elderly with a negative impact on the quality of life of patients and caregivers. Late-life depression may be regarded either as an early symptom of AD or a risk factor for AD, depending on the context. This review was focused on the latest developments in the fields of the neurobiological basis and treatment of depression in AD. We found that some plausible hypotheses are emerging to correlate with depression in AD, such as neuroinflammation and dysimmune regulation. It seems that depression is not related to amyloid deposition, but this issue is not completely resolved. The response to antidepressants is controversial according to the evidence from 10 small double-blind randomized placebo-controlled clinical trials with antidepressants in AD patients with depression: four with sertraline, one with three arms (sertraline, mirtazapine, placebo), one with fluoxetine, one with imipramine, one with clomipramine, one with escitalopram, and one with vortioxetine. The total number of treated patients completing the trials was 638. The main criterion of a positive response was a reduction in the scores of clinical scales for depression of at least 50%. The weighted OR (odds ratio) was calculated with the method of Mantel-Haenszel: 1.29; 95% CI: 0.77–2.16. No significant differences were found compared with placebo. Antidepressants did not have a meaningful negative influence on cognition, which was measured with the mini-mental state examination (MMSE) in 18 clinical trials. Alternatives other than drugs are also discussed. Although there have been important advances in this field, pathophysiology and treatment deserve further research.

Keywords: Alzheimer disease, depression, randomized trials

EPIDEMIOLOGIC BACKGROUND

Late-life depression has been frequently associated with Alzheimer's disease (AD), both as a risk factor and as a clinical symptom that develops before dementia or in its clinical course. Many symptoms are common in major depression and in AD-related depression, which gives rise to some difficulties in the differential diagnosis. In addition, depression has a meaningful impact on the quality of life of patients and caregivers. It is recommended to include depression in the systematic approach for patients with AD. The majority of behavioral scales include relevant items to be detected and scored, and some treatment may be offered when needed.

The issue of late-onset depression as a risk factor for developing AD has been the focus of large community-based studies. However, this relationship has been controversial. Some studies found that depression increases the risk of either dementia,^[1-4] or cognitive decline.^[5] Late-onset depression has been especially associated with cognitive impairment and AD.^[6-8] However, other cohort studies reported no association.^[9-13] A meta-analysis of 28 community-based cohort studies found that late-life depression is associated with an increased risk for AD; pooled OR: 2.46 (1.81–3.35).^[14]

From a comprehensive overview, it was hypothesized that depression is an early manifestation rather than a risk factor for dementia and that there is a continuum between late-life depression, mild cognitive impairment (MCI), and dementia.^[15]

MCI is defined as a transitional state between normal aging and dementia.^[16] Although this condition is regarded as a precursor of AD, it does not apply equally to all forms of MCI, but only to MCI patients with the amnesic form. In MCI patients, depression tends to increase the risk of progression to AD.^[17-19] However, other studies found stronger predictors such as anxiety^[20,21] and apathy^[22,23] but not depression as predictors of progression to dementia in MCI.

The prevalence of major depression in AD ranges from 4.8% to 50%,^[24-30] depending on the diagnostic instrument used. The incidence of depression varies among studies. It was 1.8% and 6.4% at 6- and 12-months follow-up, respectively, in one study, with decreasing rates 1 year after admission.^[31] In another study, the incidence was below 2% per year over 3 years.^[20] However,

Address for correspondence: Dr. Pedro J. Modrego,
Servicio de Neurología, Hospital Universitario Miguel Servet, Zaragoza,
Spain.
E-mail: pmpjmp@gmail.com

Submitted: 14-Apr-2023 **Revised:** 04-Jul-2023 **Accepted:** 04-Jul-2023

Published: 11-Sep-2023

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

DOI: 10.4103/aian.aian_326_23

rates as high as 85% were seen in a cohort of 181 patients with AD, with a high incidence of agitation and psychosis.^[32] Major depression also had a negative impact on daily living activities and was associated with behavioral disturbances such as aggression and wandering.^[31] The degree of cognitive impairment was higher in AD patients with depression than in non-depressed AD patients.^[26] The progression of cognitive deterioration was not dependent on the presence/absence of depression over a period of 12 or 17 months.^[33,34]

METHODS

Apart from epidemiologic considerations, the purpose of this review is to provide the audience with the latest evidence in the field of the interface between depression and AD, especially with regard to the neurobiological basis and treatment. The sources used are the Medline database and the Cochrane Library. With the words “depression in Alzheimer's disease,” we could find over 10,000 articles.

We selected mostly original articles dealing with new developments in the field of depression in AD, especially focused on prevalence, clinical criteria, neurobiological basis, and treatment. We searched original papers that reported the role of monoamines, amyloid burden, and neuroinflammation. We focused our attention on neuropathology-based articles. Finally, we included 130 papers that were judged to be more informative and that provided knowledge for a better understanding of the interface between AD and depression. The effect of antidepressants on depression and cognition was assessed in a quantitative manner by meta-analysis from randomized placebo-controlled trials and in a qualitative manner when it comes to non-randomized trials and cohort studies.

Neurobiological basis of depression in Alzheimer's disease

The clinical association of depression with AD may suggest that there is a common pathophysiological basis for both conditions.^[28] Both cognitive impairment and neuropsychiatric symptoms such as agitation, psychosis, depression, apathy, disinhibition, anxiety, eating disorders, sleep disorders, and purposeless behavior have been linked with the loss of cholinergic transmission in the brain. This fact is also endorsed by the improvement of these symptoms, to some degree, with cholinesterase inhibitors.^[35] Given the modest response to these agents, the dysfunction of other neurotransmission systems must be involved. New developments in this field have given rise to new hypotheses. As in depression in non-demented patients, the impairment of monoaminergic and serotonergic systems has been claimed to be causative of AD-associated depression. However, we found conflicting reports. On the one hand, some studies found significant impairment in the serotonergic system.^[36-38] A neuropathological exam in 25 patients with AD and 12 age-matched controls showed loss of neurons in the locus ceruleus and the dorsal raphe nucleus; the brains of the AD patients with depression showed a decreased density of neurons at the mid-level of the locus

ceruleus and the rostral level of the raphe nucleus when compared with the non-depressed patients.^[39] On the other hand, another neuropathological study that included 14 patients with major depression, 8 with AD and depression, 7 with AD but not depression, and 10 elderly subjects without depression or dementia found no differences in the neuronal loss in these nuclei between demented patients with and without depression. However, the differences were significant when compared between demented and non-demented subjects, with demented patients having fewer serotonergic neurons than controls.^[40]

Interestingly, noradrenergic and serotonergic transmitters have been investigated in demented patients with major depression, and it was found that there was a meaningful reduction of norepinephrine in the cortex as deep as 10–20 fold in comparison with the non-depressed ones and a reduction of serotonin levels as well in all studied areas of the brain.^[41] A PET analysis revealed a significant decrease in cortical serotonin receptors 5-HT₂ in almost all of the areas of the brain of nine AD patients in comparison to 37 age-matched controls.^[42] Reduced levels of serotonin have been reported in the following cortical areas: superior frontal gyri, anterior and inferior temporal lobes, and fusiform gyri in the brains of 17 AD patients in comparison with 18 controls.^[43] All of these abnormalities found in relation to neurotransmitters have led to the use of tricyclics or serotonin reuptake inhibitors (SRI s) in AD-associated depression.

The hallmarks of AD are neuritic cortical plaques and neurofibrillary tangles. Therefore, the relationship between amyloid/tangle burden and depression has been worthy of investigation. However, the reports have given contradictory findings. Two studies found that AD patients with either comorbid depression or a history of major depression have a greater amyloid and neurofibrillary tangle burden in their brains than AD patients without depression.^[44,45] However, this relationship was not confirmed after examining four cortical areas of the brains of 130 older religious people. Depression and AD were related, but this association was independent of the density of plaques and tangles.^[46] Moreover, depression was not associated with neuritic plaque score or Braak stages in an autopsy study conducted in 120 controls, 77 MCI patients, and 93 AD patients.^[47] In another postmortem study of 83 individuals, the association between depression and AD was independent of AD pathology, as patients with AD pathology but not clinical AD were less likely to have depression than cognitively normal controls and individuals with clinical and pathological diagnoses of AD.^[48] For non-demented patients, this relationship is also controversial. By means of PET with beta-amyloid ligand, greater β -amyloid deposition was observed in the left parietal cortex in patients with late-life depression compared with controls,^[49] but this association was not confirmed in a larger study based on the ADNI cohort, from which it was found the opposite.^[50] No association was found between major depressive disorder and the density of brain neuritic plaques in a community sample-based autopsy study.^[51] Therefore,

the link between depression and the pathological hallmarks of AD is unclear.

Although the ApoE4 allele's presence is clearly linked with the risk of AD, the relationship with depression has not been completely elucidated. Two studies reported a positive association between the ApoE4 allele and late-onset depression.^[52,53] However, other studies found no association between the ApoE-4 allele and depression in AD.^[54-56]

Additional hypotheses are at the forefront and deserve more attention. Neuroinflammation is in the spotlight of the underlying pathology in AD, as there is evidence of activation of inflammatory pathways in the brain of people with dementia, and that correlates with neuropsychiatric symptoms in AD.^[57-59] An interesting hypothesis has been raised by a cascade of events: chronic stress (1) cytokine production (2) inflammation (3) increased vascular permeability (4) microglial activation (5) white matter damage (6) neuronal loss.^[60] A new possible mechanism might be based on the modulation of microglia activation by different pathways such as Kappa-B Nuclear factor and the NLRP3 inflammasome.^[61] However, further research is needed in this field before implementing appropriate therapies. The glutamatergic pathway also deserves attention, as it is involved in both depression and AD.^[62] In fact, the glutamate levels measured by MR spectroscopy are lower in AD patients than in controls.^[63] Another hypothesis points to the role of hypothalamic-pituitary-adrenal axis dysregulation in the development of both AD and major depression. This may result in an excess of brain glucocorticoids, with glucocorticoid receptors being a possible target for therapy.^[64]

Interesting hypotheses have arisen with regard to neurotrophic factors. Variations in the gene regulating the synthesis of transforming growth factor (TGF), which is neuroprotective against β -amyloid toxicity, have been associated with AD-related depression.^[65] In addition, fluoxetine and vortioxetine may increase TGF levels in the hippocampus of A β -injected mice, leading to improvements in memory and mobility.^[66] Brain-derived neurotrophic factor may also be involved in the pathogenesis of late-life depression, as reduced levels have been found in the CSF of patients with depression and MCI compared with healthy controls. However, no differences were found in the CSF AD-related biomarkers.^[67]

Key points

There is not enough evidence pointing to monoamine or serotonin reduction as the cause of depression in AD. Although the reports are conflicting, the amyloid burden does not seem to be associated with depression in AD. The hypothesis of neurodegeneration, inflammation, and glutamatergic pathway dysfunction is emerging as an alternative to the classic hypothesis.

Diagnosis pitfalls of depression in AD

Clinicians face difficulties not only in distinguishing dementia from major depression but also in diagnosing depression in AD. In AD patients, the clinical interview poses several challenges derived from other co-existing behavioral symptoms, for

example, apathy, loss of insight, and decreased language fluency. In addition, some symptoms may appear in both AD and major depression. Detecting and diagnosing depression in AD may pose a challenge in the clinical setting for several reasons. The demented patients have a limited awareness of their symptoms and language disturbances and, therefore, have difficulties expressing their feelings. In addition, there may be problems with overlapping symptoms that may appear in major depression, dementia, and MCI. Moreover, it may be difficult to differentiate apathy from depression.

In clinical settings, the criteria used to diagnose AD have improved a lot by incorporating biomarkers evidence (those of the NIA-AA work group).^[68] The DSM-IV criteria are useful too if biomarkers are not available.^[69] Detecting depression is mostly based on the clinical interview with the patient and caregivers. The clinical scales containing depression-specific items are widely used, such as Behavioral Pathology in AD Rating Scale,^[70] Behavioral Rating Scales for the CERAD,^[71] and the Neuropsychiatric Inventory.^[72] However, given the special characteristics of depression in AD, these scales are appropriate to quantify the symptoms but not sensitive enough for detection. There are other scales, such as the Montgomery-Asberg Depression Rating Scale,^[73] the Hamilton Depression Rating Scale,^[74] and the Cornell Scale for Depression in Dementia, that are more suitable to detect, rate, and quantify response to treatment.^[75] The Cornell Scale seems to be excellent for several reasons: (a) it elicits information from patients and caregivers; (b) it makes it easier to distinguish symptoms of dementia from those derived from depression; and (c) it has high inter-rater reliability and responsiveness to treatment.^[75]

The differential diagnosis between AD-related depression and depressive pseudo-dementia remains sometimes challenging. Apart from the specific criteria, there are some clinical features underpinning AD-related depression.^[76] The classic symptoms of depression, such as a sad mood and feelings of guilt or worthlessness, are less prominent in AD-related depression. Depression is perceived better by caregivers than by the patient himself. Some disturbances of mood tend to be short-lived and recurrent. Sleep disturbances, loss of appetite and weight, and apathy are also more prominent in depressed AD patients. Suicidal ideation is uncommon in AD. Furthermore, behavioral symptoms such as agitation, apathy, delusions, and hallucinations are frequent in AD, whereas they occur rarely in depression without dementia.^[29]

Apathy is a common symptom in AD, but it may also appear in major depression. According to the DSM-V criteria, apathy is defined by decreased motivation, reduced goal-directed behavior, and decreased emotional responsiveness. Distinguishing pure apathy from AD-related depression poses no major challenge, as pure apathy does not present the clinical criteria required for AD-related depression.

Therefore, the final diagnosis of depression should be based on an extensive clinical interview with patients and caregivers and on fulfilling ad hoc appropriate criteria.

The DSM-IV and V criteria for major depression are also useful instruments, but some shortcomings have been argued. These criteria were created to diagnose depression in non-demented patients. Given the particular clinical features of depression in AD, requiring the presence of at least five depressive symptoms in these patients might result in an infradiagnosis of depression. In this regard, a group of experts elaborated specific criteria for depression in AD,^[77] which derived from the DSM-IV-TR criteria. The adapted criteria may be summarized as follows: the required number of symptoms is three or more, and the presence of symptoms nearly every day is not necessary. The presence of irritability and social isolation is required. The loss of interest or pleasure was changed for decreased positive affect or pleasure in response to social contact and usual activities. These criteria were endorsed by the NIMH (National Institute of Mental Health) and validated in a cohort of 101 AD patients.^[78] The authors detected depression more frequently (44% of cases) with this tool than with other instruments such as the DSM-IV criteria (36%), the Cornell Scale (30%), and the Geriatric Depression Scale (33%). The use of self-reported scales alone is not encouraged as it may overlook symptoms of depression and should be reserved for screening purposes only or when the information provided by caregivers is incomplete or unreliable. For example, the Geriatric Depression Scale is widely used, but it has the caveat of omitting several items such as guilt, sexuality, and suicide ideation.^[79]

Key points

Specific criteria for AD-related depression are available in order to distinguish it from major depression and depressive pseudo-dementia. The Cornell scale for depression is especially useful to evaluate responses to treatment.

Treatment of depression in Alzheimer's disease. Evidence from clinical trials

The response to antidepressants has been analyzed separately for AD patients with depression and depression in non-demented patients. A previous extensive meta-analysis, based on the data of 245 elderly patients treated with tricyclic antidepressants (TCA; 223 with placebo), 365 treated with Selective Serotonin Reuptake Inhibitors (SSRIs) (372 with placebo), and 58 treated MAOIs monoamine oxidase inhibitors (63 with placebo), showed that all three groups of antidepressants were effective for depression in the elderly in comparison to placebo, recommending at least 6 weeks of duration to see the effect.^[80] In demented patients, the conclusions are different. To begin with, the number of randomized placebo-controlled trials with antidepressants in patients with cognitive impairment and the sample size are small. According to a meta-analysis of 107 demented subjects from four different trials, there was unclear evidence of the efficacy of antidepressants for depression, let alone the significant heterogeneity seen in these trials.^[81]

We searched for available information published from randomized placebo-controlled clinical trials on patients with

AD-related depression. Among the 825 abstracts reviewed in MEDLINE and searched with the key words "Clinical trials for depression in AD". To date, we have encountered only 10 small randomized double-blind placebo-controlled trials, including a total of 638 (completers) patients with AD and depression, that have been published specifically designed to detect differences in effect between placebo and the antidepressant (class I evidence).^[82-91] Sertraline was tested in five trials^[82-86]; in the rest of the trials, the following antidepressants were used: fluoxetine,^[87] clomipramine,^[88] mirtazapine,^[86] imipramine,^[89] escitalopram, and^[90] vortioxetine.^[91] In Table 1, the main data of the trials are reported, including the number of patients who completed at least 6 weeks of treatment and their respective numbers and proportions of responders and non-responders in the treated group and the placebo group. In two trials, only the mean differences in the Cornell Scale were reported.^[90,91] In the trial with vortioxetine, the standard deviations of the Cornell Scale scores were not provided, nor was the number of patients with improvement.^[91] We considered a positive response when the improvement was at least 50% on clinical scales. The pooled data from the selected clinical trials were included in the meta-analysis. We did not include data from unpublished trials. The meta-analysis was made with the method of Mantel-Hansel. We used *the MedCalc Statistical Software version 19.1.5 (MedCalc Software Bv, Ostend, Belgium; https://www.medcalc.org;2020)*.

Initially, we included nine trials for meta-analysis. The difference in the number of respondents was not significant (OR: 1, 32; 95% CI: 0.76–2, 13). To avoid heterogeneity, we excluded three very small trials from the analysis.^[83,88,89] According to the final meta-analysis from six trials,^[82,84-87] we conclude that antidepressants are not better than placebo (weighted OR: 1.29, 95% CI: 0.77–2.15 (see Figure 1, random effects model). The inclusion of these very small trials did not change the results. The evaluation of response to treatment was similar in all of the trials. There was no heterogeneity according to a Q-value of 10 ($P = 0.07$) and an I^2 index = 50%. Publication bias was excluded by Egger's test ($P = 0.07$).

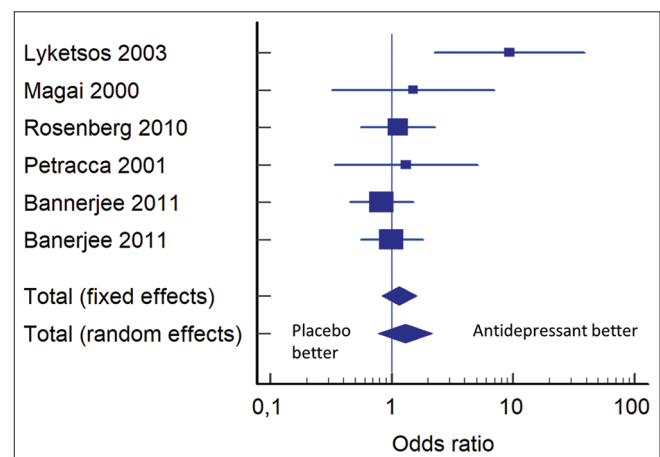


Figure 1: A forest plot representing the odds of response to antidepressants in randomized controlled clinical trials and the overall value with 95% CIs

We performed another meta-analysis with the trials, giving the changes in the Cornell Scale at 12 weeks. The differences were not significant according to a meta-analysis from seven trials^[82,84-87,89,90] [see Figure 2]; weighted OR: 0.12; 95% CI: -0.42–0, 07; $P=0,18$. The Q value was 10.5; $P=0.10$. The I index was 42.7%. There was no publication bias according to Edger and Begg's tests ($P=0.25$ and 0.88 respectively). In the trial not included in the meta-analysis,^[91] the differences in the

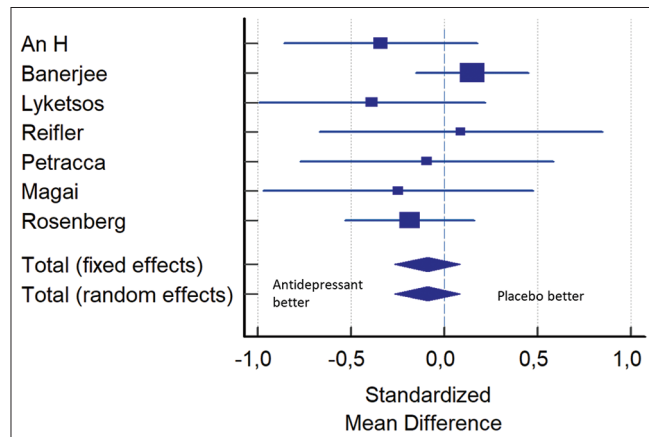


Figure 2: A forest plot pooled standardized mean differences in the Cornell Scale in placebo-controlled trials. The I^2 index was 0.00%

Cornell Scale were also not significant between vortioxetine and placebo.

However, there are some drawbacks to bear in mind to better interpret the results. The rate of responders was lower in the two largest trials, trials 1 and 2,^[85,86] than in the remainder of the trials. In addition, the rate of responders in the placebo group was high in all of the trials. In one trial,^[89] all patients on either imipramine or placebo improved. In the two largest trials that used sertraline,^[85,86] this drug was not superior to placebo according to the differences found in the Cornell scale scores and the mADCS-CGIC for improvement, and its use was associated with more side effects. The differences remained non-significant at 24 and 54 weeks, respectively. In one trial, the placebo group improved even more than the groups on either sertraline or mirtazapine.^[86]

Therefore, our meta-analysis does not provide evidence of the efficacy of antidepressants in AD-related depression. However, we cannot exclude the possible benefit of antidepressants in determined patients. For conclusive evidence, we need larger and more inclusive randomized placebo-controlled trials.

There are more clinical trials with different designs and evidence levels. A large placebo-controlled trial conducted in 694 patients with some degree of cognitive decline (511 with dementia) and depression concluded that

Table 1: Data from 10 randomized double-blind placebo-controlled trials with antidepressants in AD-related depression. OR means odds ratio. HDRS means the Hamilton Depression Rating Scale. YES means 50% improvement or more on clinical scales. NO means no improvement

Author	Drug, dose, and duration	Drug treated Patients Improvement Yes vs. No	Placebo treated patients Improvement Yes vs No	Response evaluation as the primary end point	Odds Ratio	95% CI
Lyketsos et al., 2003 ^[82]	Sertraline, 95 mg/day 12 weeks	20 vs. 4 (n=24)	7 vs. 13 (n=20)	Cornell Scale HDRS	9.28	2.26–38.1
Lyketsos et al., 2000 ^[83]	Sertraline 100 mg/day 12 weeks	9 vs. 3 (n=12)	2 vs. 8 (n=10)	Cornell Scale HDRS	12	1.17–170
Magai et al., 2000 ^[84]	Sertraline, 100 mg/day 8 weeks	8 vs. 7 (n=15)	6 vs. 6 (n=12)	Cornell Scale	1.14	0.25–5.22
Rosenberg et al., 2010 ^[85]	Sertraline 100 mg, 12 weeks	27 vs. 40 (n=67)	24 vs. 40 (n=64)	mADCS-CGIC Cornell Scale	1.12	0.55–2.27
Petracca et al., 2001 ^[87]	Fluoxetine, 40 mg, 6 weeks	7 vs. 8 (n=15)	8 vs. 12 (n=20)	HDRS	1.31	0.35–5.07
Petracca et al., 1996 ^[88]	Clomipramine 100 mg, 6 weeks	9 vs. 2 (n=11)	8 vs. 12 (n=20)	HDRS	6.75	1.14–39.7
Banerjee et al., 2011 ^[86]	Sertraline 150 mg or mirtazapine 45 mg, 12 weeks	38 vs. 47 n=85 42 vs. 43 n=85	47 vs. 48 n=95	Cornell Scale	0.97 0.99	0.53–1.76 0.55–1.79
Reifler et al., 1989 ^[89]	Imipramine 83 mg, 8 weeks	13 vs. 0 (n=13)	15 vs. 0 (n=15)	HDRS	Undefined	Undefined
An et al., 2017 ^[90]	Escitalopram for 12 weeks	n=27	N=33	Cornel Scale mean difference	1.81	NS
Jeong et al., 2022 ^[91]	Vortioxetine for 12 weeks	n=22	n=24	Cornell Scale mean difference	1.62	NS
Meta-analysis from trials 82-89				Weighted Overall OR	1.32	0.76–2.13

For analysis purposes, one trial with three arms: sertraline, mirtazapine, and placebo^[86] was factored out as two trials with the same placebo arm

meclobemide (MAOI) was an effective antidepressant, with significant improvement (more than 50 reductions in the Hamilton Scale in 56% of patients) in comparison with 37% of patients in the placebo group.^[92] Some other small trials with antidepressants have been published. A Scandinavian trial was conducted to assess response to citalopram in 149 elderly patients with depression, but only 94 completed the 6-week trial and were included in the analysis. A small number of 29 patients with major depression also had dementia: 15 were treated with citalopram and 8 with placebo. Significant improvement in cognitive and emotional function was seen in the citalopram group in comparison to the placebo group on three clinical scales.^[93] Another small clinical trial compared donepezil (5 mg/day) alone with donepezil plus 20 mg/day of citalopram in 50 AD patients, with improvement in depression and a positive impact on the quality of life of patients and caregivers.^[94] Other small, non-placebo-controlled trials yielded a positive effect on depression with several antidepressants: sertraline,^[95] trazodone,^[96] L-deprenyl,^[97] and escitalopram.^[98]

Given their anticholinergic side-effects and cardiotoxicity, TCA are prescribed less than SSRIs in the elderly. Nevertheless, three double-blind clinical trials compared SSRI and TCA and concluded that both drug types were similar in terms of clinical response, with better tolerance of the SSRI drugs: fluoxetine vs. amitriptyline,^[99] paroxetine vs. imipramine,^[100] and paroxetine vs. nortriptyline.^[101] The trial of paroxetine vs. imipramine included 198 depressed and demented patients for 8 weeks, and all of them improved equally on the Montgomery-Asberg

depression scale, the Clinical Global Impression scale, and the Cornell scale. The frequency of anticholinergic effects was twice as high in the group treated with imipramine as that observed in the paroxetine group (13.1% vs. 6.1%). In the study of paroxetine vs. nortriptyline, including 116 non-demented depressed patients, the rate of response in the intent-to-treat analysis was similar: 57% in the nortriptyline group in comparison to 55% in the paroxetine group. The proportion of side effects was twice as high in the group of patients treated with nortriptyline as that observed in the paroxetine group (33% vs. 16%).

In a larger trial, mianserin was compared with citalopram in 336 elderly depressed patients with and without dementia, with similar rates of response; however, the changes in the Montgomery-Asberg scale were smaller in demented patients.^[102]

Key point

The newest and older antidepressants are not superior to placebo in AD-related depression, according to the evidence found in randomized placebo-controlled trials.

Impact of antidepressants on cognitive function

There is a fear that antidepressants have negative effects on cognition in demented patients. This issue has also been addressed in most clinical trials, which report results and make comments with regard to the possible negative or positive influence of antidepressants on cognitive function. Some of them were designed to detect changes in cognitive function. Table 2 summarizes all of the 19 trials that mention this

Table 2: Data from studies with antidepressants in AD-related depression that reported the effects on cognition

Author	Number of patients	Drugs and duration	Effect on cognition
Munro <i>et al.</i> , 2004 ^[104]	41	Sertraline, 12 weeks	Women improved; men worsened
Lyketsos <i>et al.</i> , 2003 ^[82]	44	Sertraline, 12 weeks vs. placebo	No significant changes
Lyketsos <i>et al.</i> , 2000 ^[83]	22	Sertraline, 12 weeks vs. placebo	No significant changes
Petracca <i>et al.</i> , 2001 ^[87]	41	Fluoxetine, 6 weeks vs. placebo	No significant changes
Petracca <i>et al.</i> , 1996 ^[88]	21	Clomipramine, 6 weeks vs. placebo	Lower MMSE scores, but no changes on FIM
Roth <i>et al.</i> , 1996 ^[92]	511	Meclobemide, 6 weeks	Significant improvement
Nyth <i>et al.</i> , 1992 ^[93]	149	Citalopram, 6 weeks	Improvement
Reifler <i>et al.</i> , 1989 ^[89]	61	Imipramine, 8 weeks vs. placebo	Subtle decrement in DRS and ADLS.
Teri <i>et al.</i> , 1991 ^[105]			Improvement on MMSE
Magai <i>et al.</i> , 2000 ^[84]	31 female	Sertraline, 8 weeks vs. Placebo	No significant changes
Caballero <i>et al.</i> , 2006 ^[106]	58 on cholinesterase inhibitors	SSRI (sertraline and citalopram) for 9 months	Similar cognitive decline
Rozzini <i>et al.</i> , 2010 ^[107]	150 on cholinesterase inhibitors	SSRIs For 9 months	Small protective effect
Rosenberg <i>et al.</i> , 2010 ^[85]	131	Sertraline 100 mg or placebo for 12/24 weeks	No significant changes
Banerjee <i>et al.</i> , 2013 ^[86]	138	Sertraline or mirtazapine vs. placebo for 13/39 weeks	No significant changes
Cumbo <i>et al.</i> , 2019 ^[103]	108	Vortioxetine vs. other antidepressants for 12 months	Improvement
Mokhber <i>et al.</i> , 2014 ^[108]	59	Sertraline vs. desipramine and venlafaxine for 12 weeks	Sertraline is better for depression
Choe <i>et al.</i> , 2015 ^[109]	54	Escitalopram vs. placebo for 54 weeks	No significant changes
An <i>et al.</i> , 2017 ^[90]	60	Escitalopram vs. placebo for 12 weeks	No significant changes
Jeong <i>et al.</i> , 2022 ^[91]	46	Vortioxetine vs. placebo for 12 weeks	No significant changes

MMSE means Mini-Mental state examination, and FIM means functional independence measure. ADLS means activities of daily living scale. DRS: dementia rating scale

influence. Most of them did not yield significant changes in cognitive function. A meta-analysis of 7 placebo-controlled randomized trials is given in Figure 3. The pooled mean difference on the MMSE was 0.05 points; 95% CI: -0.08–0.21. There was neither heterogeneity nor publication bias according to the Q value and Edger's test ($P = 0.9$ and 0.91 , respectively).^[82,85-87,89,90,103] Some trials deserve comments. In one trial including 41 patients treated with sertraline as an antidepressant, the authors found no changes in cognitive function, but a post-hoc analysis suggested a sex-specific difference in the response to sertraline versus placebo for women but not in men.^[104] Another trial assessed in detail the effect of imipramine on cognition in depressed AD patients included in a previous study.^[105] In general, the effect was not meaningful, as there was a 1.9-point improvement in imipramine-treated patients in comparison with 1.3 points in the placebo group, but no changes in memory were seen. However, on the dementia rating scale, the patients on imipramine declined, especially in conceptualization, although the differences were not statistically significant.

In the largest randomized trial using either sertraline or mirtazapine vs. placebo, there were no significant changes on the MMSE scores.^[86] Although there was a small trend to worsen cognitive function with antidepressants, the impact on cognition was not significant.

It is worth mentioning the largest clinical trial, which included 694 patients with cognitive decline, of whom 511 were demented.^[92] It was a randomized placebo-controlled trial with Meclobemide compared with placebo. Apart from a >50% reduction in the Hamilton scale score, meclobemide also improved cognition significantly. This finding might suggest a neuroprotective effect, but the trial was limited to 42 days, which is not sufficient to draw this conclusion.

A retrospective study of 99 AD patients with depression showed that those treated with SSRIs (58 patients, mainly on sertraline or citalopram) did not decline cognitively faster than those without antidepressants.^[106] However, a

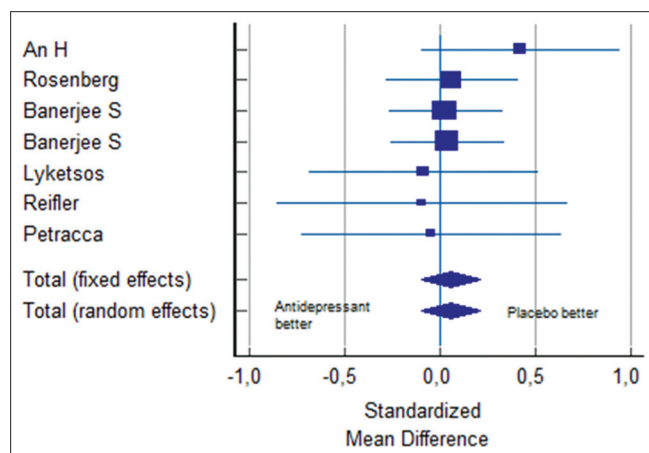


Figure 3: A forest plot representing the standardized mean differences on the MMSE scores in antidepressant-treated patients vs. placebo

multi-center trial designed for this purpose showed that the depressed AD patients treated with an SSRI drug for 9 months remained stable in mini-mental in comparison with the untreated ones, who declined 0.8 points on average.^[107] Vortioxetine has been associated with a procognitive effect compared with other antidepressants,^[103] but this effect was not seen in a placebo-controlled clinical trial.^[91] Escitalopram was specifically tested to assess its possible neuroprotective effect on AD progression, with negative results.^[109] Sertraline was superior to both venlafaxine and desipramine in terms of depression, cognition, and behavioral symptoms.^[108] Tianeptine was reported to improve depression and cognition in a retrospective study, even more than other antidepressants.^[110] In a longitudinal cohort composed of 225 patients with MCI and 31 with AD, depressed patients treated with SSRI drugs ($n = 24$) compared with those depressed but not treated with SSRI ($n = 49$) showed less cognitive deterioration and reduced gray-matter atrophy.^[111]

Although antidepressants have not been associated with increased mortality or faster cognitive decline in AD patients,^[112] their use increases the risk of osseous fractures.^[113]

Key point

Antidepressants have no impact on cognition in patients with AD-related depression.

Other pharmacological and non-pharmacological approaches to treat depression in AD

Cholinesterase inhibitors have been the standard of care in AD with improvements in cognitive function but also to reduce behavioral disturbances and the distress of caregivers, but this does not happen for depression. A large trial involving 978 patients treated with either galantamine or placebo for 21 weeks showed a global improvement in the NPI scale in comparison to placebo in the items of aberrant motor behavior and anxiety but not in depression.^[114] The same was reported in another trial with donepezil for 24 weeks, with significant improvement on NPI subscales such as anxiety, apathy, and irritability but not on the depression subscale.^[115] An open-label retrospective study with 86 AD patients treated with donepezil and based on NPI measures reported improvement of behavioral symptoms in 41% of patients and worsening in 28%, but higher scores in depression.^[116]

Given the limited efficacy and side effects of antidepressants, behavioral treatment of depression in AD patients has emerged as a possible alternative. A randomized controlled clinical trial tried two active behavioral treatments: one oriented toward patient pleasant events and another emphasizing caregiver problem-solving, in comparison with the usual care condition or waiting list controls. Patients and caregivers on behavioral treatment improved significantly in their depressive symptoms in comparison with controls.^[117] In another clinical trial based on 153 community-dwelling AD patients, the patient-caregiver dyads were randomly assigned to receive either a combined exercise and caregiver training program or routine medical care for three months. The patients on behavioral treatment

improved their quality of life and depression according to the SF-36 questionnaire and the Cornell Scale for Depression, respectively, in comparison with controls.^[118]

Cognitive therapy may be offered as a feasible option. In an inclusive randomized trial of depressed patients from the general population and with a wide age range, cognitive therapy was as effective as antidepressants in terms of clinical response and remission rate after 16 weeks of treatment.^[119] After a 12-month follow-up, the same authors observed that patients withdrawn from cognitive therapy were significantly less likely to relapse than patients withdrawn from medications (30.8% vs. 76.2%), which means higher efficacy in relapse prevention.^[120] In AD, there is limited experience with cognitive therapy for depression and cognition. The efficacy was summarized in a meta-analysis of 17 controlled studies. Cognitive therapy based on restorative strategies not only obtained a medium-sized effect on multiple functional domains but also on depression and daily living activities.^[121] Reminiscence therapy has also proven useful in a randomized controlled trial of 95 patients with AD and depression who were assessed at 12 and 24 weeks by means of the Cornell scale for depression.^[122]

Electro Convulsive Therapy (ECT) is seldom used due to its potential side effects and unlikely benefit. It is restricted to some patients in experienced centers. In the John Hopkins Hospital, 31 patients with several types of dementia were treated with ECT (mean: nine treatments) with some improvement in mood and cognition, but 15 patients developed delirium.^[123]

Anticonvulsant mood stabilizers (carbamazepine, valproic acid, lamotrigine, gabapentin, and topiramate) have been used before, but there is no evidence of a beneficial effect in demented patients with depression, according to an extensive review focused on randomized trials and open-labeled studies.^[124] The same conclusion was drawn for atypical antipsychotics such as olanzapine, quetiapine, and risperidone. In the CATIE-AD trial, which included 421 patients, no improvement was seen on the item depression with these drugs compared with placebo. In addition, olanzapine had negative effects on depressive symptoms.^[125]

Exercise is also a potential therapy thanks to its effect on hippocampal neurogenesis in major depression and Alzheimer's disease,^[126] but large trials are needed to evaluate improvement.

Key points

Cholinesterase inhibitors, anti-psychotics, and mood stabilizers do not improve depression in AD. Cognitive therapy is emerging with promising results.

DISCUSSION AND CONCLUSIONS

Depression is a frequent co-morbid condition in AD, and the mechanism of causation remains elusive. Although no major advances have occurred in the field of treatment, new developments have emerged in neurobiology. Depressive symptoms seem to be independent of the amyloid burden. Interestingly, in a cohort of 1524 β -amyloid-positive patients

with either MCI or AD, depressive symptoms appeared at different stages of the disease and independently of cognitive status.^[127] This fact points toward some differences in relation to pathophysiology. The diagnosis poses some challenges because of impaired cognition. Amyloid-PET may be a good instrument to distinguish AD-related depression from depressive pseudo-dementia.^[128]

Given the lack of large randomized trials, optimal treatment and the real degree of efficacy remain undetermined. Nonetheless, most authors prefer to use SSRI drugs. In addition, the high rates of response to placebo undermine the possible efficacy of antidepressants. In a recently published meta-analysis, the authors found a small benefit from mirtazapine and sertraline, but they included patients with other types of dementia and non-placebo-controlled trials.^[129] To date, there are no predictors of response to antidepressants. Cognitive and behavioral therapies are promising, but further research is needed to determine what patients will benefit from them and what treatment programs will be useful.

There are many unmet needs with regard to treatment for AD-related depression, with some glimpses of hope on the horizon. Along with education, hypertension, and job status, depression was a predictor of cognitive status in AD in a Bayesian model, so intervention on these factors might result in slower cognitive deterioration.^[130]

In conclusion, the interactions between depression and AD are not well understood. Depression appears independently of cognitive function status and brain pathology, and it is little responsive to antidepressants.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Wilson RS, Mendes de Leon CF, Bennet DA, Bienias JL, Evans DA. Depressive symptoms and cognitive decline in a community population of older persons. *J Neurol Neurosurg Psychiatry* 2004;75:126-9.
2. Devanand DP, Sano M, Tang MX, Taylor S, Gurland BJ, Wilder D, et al. Depressed mood and the incidence of Alzheimer's disease in elderly living in the community. *Arch Gen Psychiatry* 1996;53:175-82.
3. Wilson RS, Barnes LL, Mendes de Leon CF, Aggarwal NT, Schneider JS, Bach J, et al. Depressive symptoms, cognitive decline, and risk of AD in older persons. *Neurology* 2002;59:364-70.
4. Fuhrer R, Dufouil C, Dartigues JF; PAQUID Study. Exploring sex differences in the relationship between depressive symptoms and dementia incidence: Prospective results from the PAQUID Study. *J Am Geriatr Soc* 2003;51:1055-63.
5. Rosenberg PB, Mielke MM, Xue QL, Carlson MC. Depressive symptoms predict incident cognitive impairment in cognitive healthy older women. *Am J Geriatr Psychiatry* 2010;18:204-11.
6. Green CR, Cupples LA, Kurz A, Auerbach R, Go R, Sadovnick D, et al. Depression as a risk factor for Alzheimer disease: The MIRAGE study. *Arch Neurol* 2003;60:753-9.
7. van Reekum R, Simard M, Clarke D, Binns MA, Conn D. Late-life depression as a possible predictor of dementia: Cross-sectional and short term follow-up results. *Am J Geriatr Psychiatry* 1999;7:151-9.

8. Gracia-García P, de la Camara C, Santabàrbara J, López-Antón R, Quintanilla MA, Ventura T, *et al.* Depression and incident Alzheimer Disease: The impact of disease severity. *Am J Geriatr Psychiatry* 2015;23:119-29.
9. Lindsay J, Laurin D, Verreault R, Hebert R, Helliwell B, Hill GB, *et al.* Risk factors for Alzheimer's disease: A prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol* 2002;156:445-53.
10. Vinkers DJ, Gussekloo J, Stek ML, Westendorp RG, van der Mast RC. Temporal relation between depression and cognitive impairment in old age: Prospective population based study. *BMJ* 2004;329:881.
11. Amieva H, Le Goff M, Millet X, Orgogozo JM, Peres K, Barberger-Gateau P, *et al.* Prodromal Alzheimer's disease: Successive emergence of the clinical symptoms. *Ann Neurol* 2008;64:479-80.
12. Ganguly M, Du Y, Dodge HH, Ratcliff GG, Chang CH. Depressive symptoms and cognitive decline in late-life. A prospective epidemiological study FREE. *Arch Gen Psychiatry* 2006;63:153-60.
13. Wilson RS, Hoganson GM, Rajan KB, Barnes LL, Mendes de Leon CF, Evans DA. Temporal course of depressive symptoms during the development of Alzheimer disease. *Neurology* 2010;78:121-8.
14. Saiz-Vazquez O, Gracia-García P, Ubillós-Landa S, Puente-Martínez A, Casado-Yusta S, Olaya B, *et al.* Depression as a risk factor for Alzheimer's disease: A systematic review of longitudinal meta-analyses. *J Clin Med* 2021;10:1809.
15. Panza F, Frisardi V, Capurso C, D'Introno A, Colacicco AM, Imbimbo BP, *et al.* Late-life depression, mild cognitive impairment, and dementia: Possible continuum? *Am J Geriatr Psychiatry* 2010;18:98-116.
16. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: Clinical characterization and outcome. *Arch Neurol* 1999;56:303-8.
17. Li YS, Meyer JS, Thornby J. Longitudinal follow-up of depressive symptoms among normal versus cognitively impaired subjects. *Int J Geriatr Psychiatry* 2001;16:718-27.
18. Copeland MP, Daly E, Hines V, Mastromauro C, Zaitchik C, Gunther J, *et al.* Psychiatric symptomatology and prodromal Alzheimer's disease. *Alzheimer Dis Assoc Disord* 2003;17:1-8.
19. Modrego PJ, Ferrández J. Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: A prospective cohort study. *Arch Neurol* 2004;61:1290-3.
20. Teng E, Lu PH, Cummings JL. Neuropsychiatric symptoms are associated with progression from mild cognitive impairment to Alzheimer's disease. *Dement Geriatr Cogn Disord* 2007;24:253-9.
21. Palmer K, Berger AK, Monastero R, Winblad B, Bäckman L, Fratiglioni L. Predictors of progression from mild cognitive impairment to Alzheimer's disease. *Neurology* 2007;68:1596-602.
22. Robert PH, Berr C, Volteau M, Bertogliati C, Benoit M, Sarazin M, *et al.* Apathy in patients with mild cognitive impairment and the risk of developing Alzheimer's disease. A one-year follow-up study. *Clin Neurol Neurosurg* 2006;108:733-6.
23. Chilovi BV, Conti M, Zanetti M, Mazzu I, Rozzini L, Padovani A. Differential impact of apathy and depression in the development of dementia in mild cognitive impairment patients. *Dement Geriatr Cogn Disord* 2009;27:390-8.
24. Weiner MF, Doody RS, Sairson R, Foster B, Liao TY. Prevalence and incidence of major depressive disorder in Alzheimer disease: Findings from two databases. *Dement Geriatr Cogn Disord* 2002;13:8-12.
25. Forsell Y, Winblad B. Major depression in a population of demented and non-demented old people: Prevalence and correlates. *J Am Geriatr Soc* 1998;46:27-30.
26. Rovner BW, Broadhead J, Spencer M, Carson K, Folstein MF. Depression and Alzheimer's disease. *Am J Psychiatry* 1989;146:350-3.
27. Lyketsos CG, Steele C, Baker L, Galik E, Kopunek S, Steinberg M, *et al.* Major and minor depression in Alzheimer's disease: Prevalence and impact. *J Neuropsychiatry Clin Neurosci* 1997;9:556-61.
28. Heun R, Kockler M, Ptók U. Depression in Alzheimer's disease: Is there a temporal relationship between the onset of depression and the onset of dementia? *Eur Psychiatry* 2002;17:254-8.
29. Zubenko GS, Zubenko WN, McPherson S, Spoor E, Marin DB, Farlow MR, *et al.* A collaborative study of the emergence and clinical features of the major depressive syndrome of Alzheimer's disease. *Am J Psychiatry* 2003;160:857-966.
30. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: Results from the cardiovascular health study. *JAMA* 2002;288:1475-83.
31. Payne J, Sheppard JM, Steinberg M, Warren A, Baker A, Steele C, *et al.* Incidence, prevalence, and outcomes of depression in residents of a long term care facility with dementia. *Int J Geriatr Psychiatry* 2002;17:247-53.
32. Levy ML, Cummings JL, Fairbanks LA, Bravi D, Calvani M, Carta A. Longitudinal assessment of symptoms of depression, agitation, and psychosis in 181 patients with Alzheimer's disease. *Am J Psychiatry* 1996;153:1438-43.
33. Garre-Olmo J, Lopez-Pousa S, Vilalta-Franch J, Turon-Estrada A, Hernandez-Ferrandiz M, Lozano-Gallego M, *et al.* Evolution of depressive symptoms in Alzheimer disease: One-year follow-up. *Alzheimer Dis Assoc Disord* 2003;17:77-85.
34. Reifler BV, Larson E, Teri L, Poulsen M. Dementia of the Alzheimer's type and depression. *J Am Geriatr Soc* 1996;34:855-9.
35. Cummings JL, Back C. The cholinergic hypothesis of neuropsychiatric symptoms in Alzheimer's disease. *Am J Geriatr Psychiatry* 1988;6:S64-78.
36. Whitford GM. Alzheimer's disease and serotonin: A review. *Neuropsychobiology* 1986;15:133-42.
37. Meltzer CC, Smith G, DeKosky ST, Pollock BG, Mathis CA, Moore RY, *et al.* Serotonin in aging, late-life depression, and Alzheimer's disease: The emerging role of functional imaging. *Neuropsychopharmacology* 1998;18:407-30.
38. Gareri P, De Fazio P, Sarro G. Neuropharmacology of depression in aging and age-related diseases. *Ageing Res Rev* 2002;1:113-34.
39. Zweig RM, Ross CA, Hedreen JC, Steele C, Cardillo JE, Whitehouse PJ, *et al.* The neuropathology of aminergic nuclei in Alzheimer's disease. *Ann Neurol* 1988;24:233-42.
40. Hendricksen M, Thomas AJ, Ferrer IN, Ince P, O'Brien JT. Neuropathological study of the dorsal raphe nuclei in late-life depression and Alzheimer's disease with and without depression. *Am J Psychiatry* 2004;161:1096-102.
41. Zubenko GS, Moossy J, Kopp U. Neurochemical correlates of major depression in primary dementia. *Arch Neurol* 1990;47:209-14.
42. Blin J, Baron JC, Dubois B, Cruzel C, Fiorelli M, Attar-Lévy D, *et al.* Loss of brain 5-HT₂ receptors in Alzheimer's disease: *In vivo* assessment with positron emission tomography and 18F setoperone. *Brain* 1993;116:497-510.
43. Palmer AM, Stratmann GC, Procter AW, Bowen DM. Possible neurotransmitter basis of behavioral changes in Alzheimer's disease. *Ann Neurol* 1988;23:616-20.
44. Rapp MA, Schneider-Beeeri M, Purohit DP, Perl DP, Haroutunian V, Sano M. Increased neurofibrillary tangles in patients with Alzheimer's disease with comorbid depression. *Am J Geriatr Psychiatry* 2008;16:168-74.
45. Rapp MA, Schneider-Beeeri M, Groszman HT, Sano M, Perl DP, Purohit DP, *et al.* Increased hippocampal in plaques and tangles patients with Alzheimer disease with a lifetime history of major depression. *Arch Gen Psychiatry* 2006;63:161-7.
46. Wilson RS, Schneider JA, Bienias JL, Arnold SE, Evans DA, Bennett DA. Depressive symptoms, clinical AD, and cortical plaques and tangles in older persons. *Neurology* 2003;61:1102-7.
47. McCutcheon ST, Han D, Troncoso J, Koliatsos VE, Albert M, Lyketsos CG, *et al.* Clinicopathological correlates of depression in Alzheimer's disease in the NACC. *Int J Geriatr Psychiatry* 2016;31:1301-11.
48. Morgan MD, Mielke MM, O'Brian R, Troncoso JC, Zonderi AB, Lyketsos CG. Rates of depression in individuals with pathologic but not clinical Alzheimer disease are lower than those in individuals without the disease: Findings from the Baltimore Longitudinal Study on Aging (BLSA). *Alzheimer Dis Assoc Disord* 2007;21:199-204.
49. Smith GS, Kuwabara H, Nandi A, Gould NF, Nassery N, Savonenko A, *et al.* Molecular imaging of beta-amyloid deposition in late-life depression. *Neurobiol Aging* 2021;101:85-93.
50. Mackin RS, Insel PS, Landau S, Bickford D, Morin R, Rhodes E, *et al.* Late-life depression is associated with reduced cortical amyloid

- burden: Findings from the Alzheimer's disease neuroimaging initiative depression project. *Biol Psychiatry* 2021;89:757-65.
51. Saldanha NM, Suemoto CK, Rodriguez RD, Leite REP, Nascimento C, Ferreti-Rebustini R, *et al.* β -amyloid pathology is not associated with depression in a large community sample autopsy study. *J Affect Disord* 2021;278:372-81.
 52. Krishnan KR, Tupler LA, Ritchie JC, McDonald WM, Knight DL, Nemeroff CB, *et al.* Apolipoprotein E-4 frequency in geriatric depression. *Biol Psychiatry* 1996;40:69-71.
 53. Kim DH, Payne ME, Levy RM, McFall JR, Stefens DC. APOE genotype and hippocampal volume change in geriatric depression. *Biol Psychiatry* 2002;51:426-9.
 54. Zubenko GS, Henderson R, Stiffler JS, Stabler S, Rosen J, Kaplan BB. Association of the APOE-4 allele with clinical subtypes of late-life depression. *Biol Psychiatry* 1996;6:77-93.
 55. Scarmeas N, Brandt J, Albert M, Denanand DP, Marder K, Bell K, *et al.* Association between the APOE genotype and psychopathologic symptoms in Alzheimer's disease. *Neurology* 2002;58:1182-8.
 56. Locke DE, Dueck AC, Stonnington CM, Knopman DS, Geda YE, Casselli RJ. Depressive symptoms in healthy apolipoprotein E ϵ 4 carriers and noncarriers: A longitudinal study. *J Clin Psychiatry* 2013;74:1256-61.
 57. Leonard BE, Myint A. Inflammation and depression: Is there a causal connection with dementia? *Neurotoxicity Res* 2006;10:149-60.
 58. Maes M, Kubera M, Obuchowicz E, Goehler L. Depression's multiple comorbidities explained by neuroinflammatory and oxidative and nitrosative stress pathways. *Neuroendocrinol Lett* 2011;32:7-24.
 59. Holmgren S, Hjorth E, Schultzberg M, Lärksäter M, Frenkel D, Tysen-Bäckström AC, *et al.* Neuropsychiatric symptoms in dementia -A role for neuroinflammation? *Brain Res Bull* 2014;108:88-93.
 60. Hayley S, Hakim AM, Albert PR. Depression, dementia, and immune dysregulation. *Brain* 2021;144:746-60.
 61. Thawkar BS, Kaur G. Inhibitors of NF- κ B and P2X7/NLRP3/caspase 1 pathway in microglia: Novel therapeutic opportunities in neuroinflammation induced early-stage Alzheimer's disease. *J Neuroimmunol* 2019;326:62-74.
 62. Frisardi V, Panza F, Farooqui A. Late-life depression and Alzheimer's disease: The glutamatergic system inside of this mirror relationship. *Brain Res Rev* 2011;67:344-55.
 63. Fayed N, Modrego PJ, Rojas G, Aguilar K. Brain glutamate levels are decreased in Alzheimer disease. A magnetic resonance spectroscopy study. *Am J Alzheimer Dis Other Dement* 2011;26:450-6.
 64. Canet G, Chevallier N, Zussy C, Desruma C, Givalois L. Central role of glucocorticosteroid receptors in Alzheimer's disease and depression. *Front Neurosci* 2016;12:739.
 65. Caraci F, Bosco P, Signorelli M, Spada RS, Cosentino FI, Toscano G, *et al.* The CC genotype of transforming growth factor- β 1 increases the risk of late-onset Alzheimer's disease and is associated with AD-related depression. *Eur Neuropsychopharmacol* 2012;22:281-9.
 66. Torrisi SA, Geraci F, Tropea MR, Grasso M, Caruso G, Fidilio A, *et al.* Dluoxetine and vortioxetine reverse depressive-like phenotype and memory deficits induced by A β 1-42 oligomers in mice: A key role of transforming growth factor- β 1. *Front Pharmacol* 2019;10:693.
 67. Diniz BS, Teixeira AL, Machado-Vieira R, Talib LL, Radanovic M, Gattaz WF, *et al.* Reduced cerebrospinal fluid levels of brain-derived neurotrophic factor is associated with cognitive impairment in late-life major depression. *J Gerontol* 2014;69:845-51.
 68. McKhan GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas GH, *et al.* The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:263-9.
 69. The American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington DC: American Psychiatric Association; 2013.
 70. Reisberg B, Borenstein J, Salob SP, Ferris SH, Franssen E, Georgotas A. Behavioral symptoms in Alzheimer's disease: Phenomenology and treatment. *J Clin Psychiatry* 1987;48(Suppl):9-15.
 71. Tariot PN, Mack JL, Patterson MB. The behavior rating scale for dementia of the Consortium to establish a Registry for Alzheimer's disease. *Am J Psychiatry* 1995;152:1349-57.
 72. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. *Neurology* 1994;44:2308-14.
 73. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382-9.
 74. Hamilton MA. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62.
 75. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell scale for depression in dementia. *Biol Psychiatry* 1988;23:271-84.
 76. Lyketsos CG, Lee HB. Diagnosis and treatment of depression in Alzheimer's disease. A practical update for the clinician. *Dement Geriatr Cogn Disord* 2004;17:55-64.
 77. Olin JT, Schneider LS, Katz IR, Meyers BS, Alexopoulos GS, Breitner JC, *et al.* Provisional diagnostic criteria for depression of Alzheimer's disease. *Am J Geriatr Psychiatry* 2002;10:125-8.
 78. Teng E, Ringman JM, Ross LK, Mulnard RA, Dick MB, Bartzokis G, *et al.* Diagnosing depression in Alzheimer's disease with the national institute of mental health provisional criteria. *Am J Geriatr Psychiatry* 2008;16:469-77.
 79. Spreen O, Strauss E. Geriatric depression scale. In: Spreen O, Strauss E, editors. *A Compendium of Neuropsychological Tests*. Oxford (England): Oxford University Press; 1998. p. 612-6.
 80. Mottram WK, Sivananthan A, Nightingale A. Antidepressants versus placebo for depressed elderly. *Cochrane Database Syst Rev* 2001;2:CD000561.
 81. Bains J, Birks JS, Denning TR. The efficacy of antidepressants in the treatment of depression in dementia. *Cochrane Database Syst Rev* 2002;4:CD003944.
 82. Lyketsos CG, DelCampo L, Steinberg M, Miles Q, Steele CD, Munro C, *et al.* Treating depression in Alzheimer disease: Efficacy and safety of sertraline therapy, and the benefits of depression reduction: The DIADS. *Arch Gen Psychiatry* 2003;60:737-46.
 83. Lyketsos CG, Sheppard JM, Steele CD, Kopunek S, Steinberg M, Baker AS, *et al.* Randomized, placebo-controlled, double-blind clinical trial of sertraline in the treatment of depression complicating Alzheimer's disease: Initial results from the depression in Alzheimer's disease study. *Am J Psychiatry* 2000;157:1686-9.
 84. Magai C, Kennedy G, Cohen CI, Gombert D. A controlled clinical trial of sertraline in the treatment of depression in nursing home patients with late-stage Alzheimer's disease. *Am J Geriatr Psychiatry* 2000;8:66-74.
 85. Rosenberg PB, Drye LT, Martin BK, Frangakis C, Mintzer JE, Weintraub D, *et al.*; DIADS-2 Research Group. Sertraline for the treatment of depression in Alzheimer disease. *Am J Geriatr Psychiatry* 2010;18:136-45.
 86. Banerjee S, Hellier J, Romeo M, Dewey M, Knapp M, Ballard C, *et al.* Study of the use of antidepressants for depression in dementia: The HTA-SADD trial—A multicentre, thramin. Double-blind, placebo-controlled trial of the clinical effectiveness and cost-effectiveness of sertraline and mirtazapine. *Health Technol Assess* 2013;17:1-166.
 87. Petracca GM, Chemerinski E, Starkstein SE. A double-blind, placebo-controlled study of fluoxetine in depressed patients with Alzheimer's disease. *Int Psychogeriatr* 2001;13:233-40.
 88. Petracca G, Tesón A, Chemerinski E, Leiguarda R, Starkstein SE. A double-blind placebo-controlled study of clomipramine in depressed patients with Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* 1996;8:270-5.
 89. Reifler BV, Teri L, Raskind M, Veith R, Barnes R, White E, *et al.* Double-blind trial of imipramine in Alzheimer's disease patients with and without depression. *Am J Psychiatry* 1989;146:45-9.
 90. An H, Choi B, Park KW, Kim DH, Yang DW, Hong CH, *et al.* The effect of escitalopram on mood and cognition in depressive Alzheimer's disease subjects. *J Alzheimers Dis* 2017;55:727-35.
 91. Jeong HW, Yoon KH, Lee CH, Moon YS, Kim DH. Vortioxetine treatment for depression in Alzheimer's disease: A randomized, double-blind, placebo-controlled study. *Clin Psychopharmacol Neurosci* 2022;20:311-9.
 92. Roth M, Mountjoy CQ, Amrein R. Meclobemide in elderly patients with cognitive decline and depression. An international double-blind, placebo-controlled trial. *Br J Psychiatry* 1996;168:149-57.
 93. Nyth AL, Gottfries CG, Lyby K, Smedegaard-Andersen L, Gylding-Sabroe J, Kristensen M, *et al.* A controlled multicenter clinical study of citalopram and placebo in elderly depressed patients with and

- without concomitant dementia. *Acta Psychiatr Scand* 1992;86:138-45.
94. Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Depression and Alzheimer's disease: Symptom or comorbidity? *Am J Alzheimer Dis Other Demen* 2002;17:338-44.
 95. Volicer L, Rheume Y, Cyr D. Treatment of depression in advanced Alzheimer's disease using sertraline. *J Geriatr Psychiatry Neurol* 1994;7:227-9.
 96. Lebert F, Pasquier F, Petit H. Behavioral effects of trazodone in Alzheimer's disease. *J Clin Psychiatry* 1994;55:536-8.
 97. Schneider LS, Pollock VE, Zemansky MF, Gleason RP, Palmer R, Sloane RB. A pilot study of low-dose L-deprenyl in Alzheimer's disease. *J Geriatr Psychiatry Neurol* 1991;4:143-8.
 98. Rao V, Spiro JR, Rosenberg PB, Lee HB, Rosenblatt A, Lyketsos CG. An open-label study of escitalopram (Lexapro) for the treatment of 'depression of Alzheimer's disease' (Dad). *Int J Geriatr Psychiatry* 2006;21:273-4.
 99. Tarangano FE, Lyketsos CG, Mangone CA, Allegri RF, Comesana-Diaz E. A double-blind, randomized, fixed-dose trial of fluoxetine vs amitriptyline in the treatment of major depression complicating Alzheimer's disease. *Psychosomatics* 1997;38:246-52.
 100. Katona CL, Hunter BN, Bray J. A double-blind comparison of the efficacy and safety of paroxetine and imipramine in the treatment of depression with dementia. *Int J Geriatr Psychiatry* 1998;13:100-8.
 101. Mulsant BH, Pollock BG, Nebes R, Miller MD, Sweet RA, Stack J, *et al.* A twelve week, double-blind, randomized comparison of nortriptyline and paroxetine in older depressed inpatients and outpatients. *Am J Geriatr Psychiatry* 2001;9:406-14.
 102. Karlson I, Godderis J, Augusto De Mendonça Lima C, Nygaard H, Simányi M, Taal M, *et al.* A thramin, double-blind comparison of the efficacy and safety of citalopram compared to mianserin in elderly, depressed patients with or without mild to moderate dementia. *Int J Geriatr Psychiatry* 2000;15:295-306.
 103. Cumbo E, Cumbo S, Torregrossa S, Migliore D. Treatment effects of vortioxetine on cognitive functions in mild Alzheimer's disease patients with depressive symptoms. A 12 month, open-label, observational study. *J Prevent Alzheimers Dis* 2019;6:192-7.
 104. Munro CA, Brandt J, Sheppard J-ME, Steele CD, Samus QM, Steinberg M, *et al.* Cognitive response to pharmacological treatment for depression in Alzheimer disease: Secondary outcomes from the depression in Alzheimer's disease study (DIADS). *Am J Geriatr Psychiatry* 2004;12:491-8.
 105. Teri L, Reifler BV, Veith RC, Barnes R, White E, McLean P, *et al.* Imipramine in the treatment of depressed Alzheimer's patients: Impact on cognition. *J Gerontol* 2001;46:372-7.
 106. Caballero J, Hitchcock M, Beversdorf D, Scharre D, Nahata M. Long-term effects of antidepressants on cognition in patients with Alzheimer's disease. *J Clin Pharm Ther* 2006;31:593-8.
 107. Rozzini L, Chilovi BV, Conti M, Bertoletti E, Zanetti M, Trabucchi M, *et al.* Efficacy of SSRIs on cognition of Alzheimer's disease patients treated with cholinesterase inhibitors. *Int Psychogeriatr* 2010;22:114-9.
 108. Mokhber N, Abdollahian E, Soltanifar A, Samadi R, Saghebi A, Haghighi MB, *et al.* Comparison of sertraline, venlafaxine, and thramine effects on depression, cognition and the daily living activities in Alzheimer's patients. *Pharmacopsychiatry* 2014;47:131-40.
 109. Choe YM, Kim KW, Jhoo JH, Ryu SH, Seo EH, Sohn BK, *et al.* Multicenter, randomized, placebo-controlled, double-blind thram trial of escitalopram on the progression-delaying effects in Alzheimer's disease. *Int J Geriatr Psychiatry* 2016;31:731-9.
 110. Garcia-Alberca JM, Gris E, de la Guia P, Mendoza S. Effects of tianeptine treatment on depression and cognitive function in patients with Alzheimer's disease: A 12-month retrospective observational study. *J Alzheimers Dis* 2022;88:707-20.
 111. Brendel M, Sauerbeck J, Greven S, Kotz S, Scheiwein F, Blautzik J, *et al.* Serotonin selective reuptake inhibitor treatment improves cognition and grey matter atrophy but not amyloid burden during two-year follow-up in mild cognitive impairment and Alzheimer's disease patients with depressive symptoms. *J Alzheimers Dis* 2018;65:793-806.
 112. Modrego PJ, Lobo A. Determinants of progression and mortality in Alzheimer's disease. A systematic review. *Neuropsychiatry (London)* 2018;8:1465-75.
 113. Wei YJ, Simoni-Wastilla L, Lucas JA, Brandt N. Fall and fracture risk in nursing home residents with moderate-to-severe behavioral symptoms of Alzheimer's disease and related dementias initiating antidepressants or antipsychotics. *J Gerontol Biol Sci Med Sci* 2017;72:695-702.
 114. Cummings JL, Schneider L, Tariot PN, Kershaw PR, Weiyng Y. Reduction of behavioural disturbances and caregiver distress by galantamine in patients with Alzheimer's disease. *Am J Psychiatry* 2004;161:532-8.
 115. Gauthier S, Feldman H, Hecker J, Vellas B, Emir B, Subbiah P; Donepezil MSAD Study Investigators Group. Functional, cognitive, and behavioral effects of donepezil in patients with moderate Alzheimer's disease. *Curr Med Res Opin* 2002;18:347-54.
 116. Mega MS, Masterman DM, O'Connor SM, Barclay TR, Cummings JL. The spectrum of behavioral responses to cholinesterase inhibitor therapy in Alzheimer disease. *Arch Neurol* 1999;56:1388-93.
 117. Teri L, Logsdon RG, Uomoto J, McCurry SM. Behavioral treatment of depression in dementia patients: A controlled clinical trial. *J Gerontol B Psychol Sci Soc* 1997;52:159-66.
 118. Teri L, Gibbons LE, McCurry SM, Logsdon RG, Buchner DM, Barlow WE, *et al.* Exercise plus behavioral management in patients with Alzheimer disease: A randomized controlled trial. *JAMA* 2003;290:2015-22.
 119. De Rubeis RJ, Hollon SD, Amsterdam JD, Shelton RC, Young PR, Salomon RM, *et al.* Cognitive therapy vs medications in the treatment of moderate to severe depression. *Arch Gen Psychiatry* 2005;62:409-16.
 120. Hollon SD, DeRubeis RJ, Shelton RC, Amsterdam JD, Salomon RM, O'Reardon JP, *et al.* Prevention of relapse following cognitive therapy vs medications in moderate to severe depression. *Arch Gen Psychiatry* 2005;62:417-22.
 121. Sitzer DI, Twamley EW, Jeste DW. Cognitive training in Alzheimer's disease: A meta-analysis of the literature. *Acta Psychiatr Scand* 2006;114:75-90.
 122. Li MO, Lyu JH, Zhang Y, Gao ML, Li R, Mao PX, *et al.* Efficacy of group reminiscence therapy on cognition, depression, neuropsychiatric symptoms, and activities of daily living for patients with Alzheimer disease. *J Geriatr Psychiatry Neurol* 2020;33:272-81.
 123. Rao V, Lyketsos CG. The benefits and risks of ECT for patients with degenerative dementia who also suffer from depression. *Int J Geriatr Psychiatry* 2000;15:729-35.
 124. Pinheiro D. Anticonvulsant mood stabilizers in the treatment of behavioral and psychological symptoms of dementia (BPSD). *Encephale* 2008;34:409-15.
 125. Sultzer DL, Davis SM, Tariot PN, Dagerman KS, Lebowitz BD, Lyketsos CG, *et al.*; CATIE-AD Study Group. Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: Phase 1 outcomes from the CATIE-AD effectiveness trial. *Am J Psychiatry* 2008;165:844-54.
 126. Freberg E, Taglialetela G. Exercise as a potential therapeutic strategy to target the clinical link between depression and Alzheimer's disease: A narrative review. *J Alzheimers Dis* 2022;89:759-67.
 127. Eikelboom WS, van den Berg E, Singleton EH, Baart SJ, Coesmans M, Leeuwis AE, *et al.* Neuropsychiatric and cognitive symptoms across the Alzheimer disease clinical spectrum: Cross-sectional and longitudinal associations. *Neurology* 2021;97:e1276-87.
 128. Leonhardi J, Barthel H, Speerforck S, Dietzel J, Schroeter ML, Saur D, *et al.* Differential diagnosis between Alzheimer disease-related depression and pseudo-dementia in depression. A new indication for amyloid- β imaging? *J Alzheimers Dis* 2022;88:1029-35.
 129. He Y, Li H, Huang J. Efficacy of antidepressant drugs in the treatment of depression in Alzheimer disease patients. A systematic review and network meta-analysis. *J Psychopharmacol* 2021;35:901-9.
 130. Han H, Qin Y, Ge X, Cui J, Liu L, Luo Y, *et al.* Risk assessment during longitudinal progression of cognition in older adults: A community-based Bayesian networks model. *Curr Alzheimer Res* 2021;18:232-42.