Biological Psychiatry

Review

Depression in Alzheimer's Disease: Epidemiology, Mechanisms, and Treatment

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ABSTRACT

Depression and Alzheimer's disease (AD) are substantial public health concerns. In the past decades, a link between the 2 disease entities has received extensive acknowledgment, yet the complex nature of this relationship demands further clarification. Some evidence indicates that midlife depression may be an AD risk factor, while a chronic course of depression in late life may be a precursor to or symptom of dementia. Recently, multiple pathophysiological mechanisms have been proposed to underlie the bidirectional relationship between depression and AD, including genetic predisposition, immune dysregulation, accumulation of AD-related biomarkers (e.g., amyloid-β and tau), and alterations in brain structure. Accordingly, numerous therapeutic approaches, such as pharmacology treatments, psychotherapy, and lifestyle interventions, have been suggested as potential means of interfering with these pathways. However, the current literature on this topic remains fragmented and lacks a comprehensive review characterizing the association between depression and AD. In this review, we aim to address these gaps by providing an overview of the co-occurrence and temporal relationship between depression and AD, as well as exploring their underlying mechanisms. We also examine the current therapeutic regimens for depression and their implications for AD management and outline key challenges facing the field.

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Alzheimer's disease (AD) and depression are recognized as the most common and challenging mental disorders throughout society. In addition to the core feature of cognitive impairment, AD is also accompanied by neuropsychiatric symptoms including depression. Depression is primarily characterized by mood disturbances, decreased attention and concentration, and feelings of low self-worth. While depression and dementia are generally recognized as distinct clinical entities, they share some common features, which makes the interrelationship between depression and dementia complex and makes it difficult to distinguish between the 2 conditions when they co-occur. One recent study found that depression and cognitive impairment exhibit a bidirectional relationship (1). Specifically, midlife or late-life depression elevates AD risk, and patients with AD are more prone to develop depression. Despite significant advances having been made in understanding the neurobiology of and treatment strategies for depression in AD, the biological connection between depression and AD remains unclear. Uncovering this link may open novel ways of treatment and prevention to tackle both diseases while also improving patient health care. In this review, we update the current knowledge on epidemiology, on mechanisms that may underlie the link between depression and dementia, and the therapeutic implications of depression in AD (Figure 1).

EPIDEMIOLOGY

Prevalence of AD With Comorbid Depression

The prevalence of depression in dementia varies widely due to differences in symptom evaluation methods and regions of the studies conducted. To identify patients with comorbid depression in the context of AD, the utilization of standardized neuropsychological tests continues to hold significant value within clinical assessment protocols. The results of a recent meta-analysis led to the conclusion that the Rey Auditory Verbal Learning Test-Delayed Recognition; the Boston Naming Test; the Dementia Rating Scale's memory, conceptualization, and construction subscales; and the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) constructional praxis are neuropsychological tests that appear to be useful for differentiating between AD and late-life depression (2). The overall pooled prevalence of depressive symptoms in dementia is approximately 38% to 40% and varies with the severity of dementia (3). The differential effects of depression are greater for vascular dementia than for AD (3,4). Overall, depression occurs less frequently in patients with AD, with an overall pooled prevalence of 38%, compared with a prevalence of 50% among individuals with vascular dementia (3). Similarly, the prevalence of major depressive disorder (MDD) was lower among individuals with AD (14.8%) compared with those with vascular dementia (24.7%) (5). However, additional research is needed to explore these differences in more detail.

Depression Increases the Risk of Subsequent AD

Plenty of research has explored the relationship between a history of depression and greater cognitive decline (6), as well as an increased risk of both all-cause dementia and AD (6–8). In one study, the association between depression and dementia was the strongest during the first 6 months after a depression diagnosis and persisted over a follow-up period of more than 20 years (9). The severity of depression, but not the

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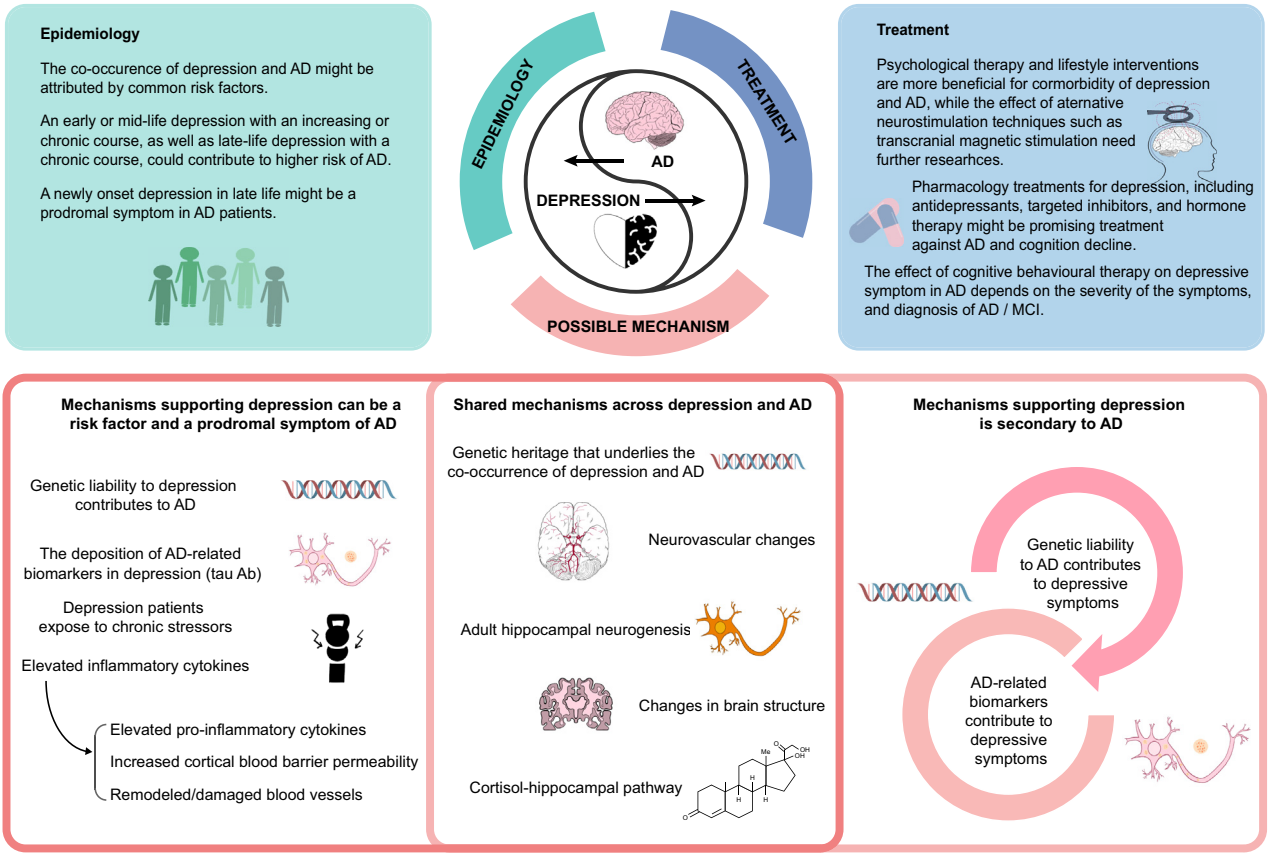

Figure 1. Graphical abstract. In this review, we discuss the following 3 aspects of depression–Alzheimer's disease (AD) comorbidity: epidemiology, possible mechanisms, and treatments. Aβ, amyloid-β; MCI, mild cognitive impairment.

frequency of depressive episodes, has been found to have a dose-response association with the risk of dementia (9–11).

Late-life depression is associated with dementia (12) and AD (13). In one study, older adults who experienced their first lifetime depressive episodes after the age of 60 exhibited more severe cognitive impairment and faster decline in verbal skills and memory ability (14). In contrast, depressive symptoms in midlife, even when they are chronic or recurring, may not increase the risk of dementia (15). The study of depression trajectories in relation to the risk of dementia is necessary due to the remitting and relapsing character of depression. A substudy within the Rotterdam Study revealed that continued worsening of depressive symptoms, but not the trajectory typical of remitting depression, were predictive of dementia (16). To investigate the relationships between depression treatments and the risk of incident dementia, a prospective cohort study from the UK Biobank discovered that participants with untreated depression had a 30% higher risk of developing dementia than participants who had received the appropriate antidepressants or psychotherapy, highlighting the need for prompt interventional strategies (17).

Depressive Symptoms as a Neuropsychiatric Symptom of AD

Approximately 16% and 32% of individuals with dementia will experience depressive symptoms with and without a formal diagnosis of MDD, respectively (5,18). During the early stages of AD, depression can manifest as psychological reactions, while in the later stages, severe cognitive impairment hampers emotional responses. Notably, patients with early-onset AD are more susceptible to heightened levels of depression, which can be attributed to significant lifestyle alterations, difficulties in social adjustment, and a faster progression of the disease. In contrast, patients with late-onset AD may encounter more persistent depression, which is likely influenced by contextual factors such as physical disability (19). Meanwhile, depression can accelerate the progression of AD at any stage (20).

The evidence summarized above demonstrates that depression and AD are no doubt connected, although the exact nature of the relationship remains unclear. We hypothesize that earlier-life depression, especially with persistent or recurrent depressive symptoms, is one of the risk factors for subsequent AD, whereas depression that occurs in later life may be a prodrome of AD. To assess the probable causal or prodromal nature of this relationship, it is essential to conduct longitudinal studies that span across adulthood.

MECHANISMS OF THE ASSOCIATION BETWEEN AD AND DEPRESSION

Several models have been generated to explain how depression and AD are associated, including shared risk factors and

bidirectional relationships. Based on the current understanding of disease mechanisms and temporal associations, we propose a framework of putative mechanisms linking dementia and depression (Figure 2). Such mechanism models are not mutually exclusive, and there could be multiple factors that contribute to the association between depression and dementia, even within the same individual. The strong heterogeneity of depression phenotypes, which encompasses a wide range of signs, symptoms, and subtypes, likely contributes to the mixed directions of effects between the 2 disorders. This may explain why depressive disorders are regarded as an important predictor of AD pathology while the opposite is less definite (21).

Mechanisms Supporting Depression Can Be a Risk Factor and a Prodromal Symptom of AD

Genetic Liability to Depression Contributes to AD. A previous study found no evidence to support a common polygenic structure for AD and MDD (22). However, another study found that 3 common variants and 6 rare variants of major MDD risk genes were associated with the risk of developing AD (23). By quantifying the messenger RNA expression alterations of these risk genes in AD mouse models, the study identified 18 MDD risk genes that were differentially expressed in AD brain tissues and 7 genes that were significantly correlated with number of amyloid plaques or tau tangles, indicating that MDD risk genes may play an active role in AD pathology (23). In a recent large-scale study, researchers found that depression may causally contribute to AD, identifying 46 brain transcripts and 7 brain proteins associated with this relationship (24).

The Deposition of AD-Related Biomarkers in Depression. The deposition of cerebral amyloid-β (Aβ) in depression is controversial. A systematic review including 15 cross-sectional studies has substantiated a possible link between amyloid and MDD in older adults (25). Even minimal depressive symptoms were found to be associated not only with greater cerebrospinal fluid (CSF) amyloid markers but also with an 83% increased probability of developing AD dementia in elderly adults without dementia (26). The connection between minimal depressive symptoms and amyloid pathology was bidirectional, whereas the influence of minimal depressive symptoms on both cognitive impairment and AD risk was partially mediated by amyloid pathology (26). However, some studies did not find a statistically significant association between cognitive decline in patients with depression and either CSF concentrations of Aβ (27) or cortical Aβ accumulation (28,29). Among Aβ-negative patients with MDD, deceased ^{18}F-florbetapir uptakes were observed in most cortical regions (28), indicating an underlying nonamyloid-mediated pathogenesis linking depression and AD. In terms of tau pathology, a previous meta-analysis found that CSF total tau levels were similar in individuals with MDD and healthy control participants. Given the restrictive nature of the available data, definitive conclusions currently elude us (30).

Stress Condition and Inflammation Linking Depression and AD. Dysregulation of the immune system has been regarded as one of the most prominent mechanisms linking depression to cognitive decline (31). Exposure to chronic stressors may accelerate the onset of dementia among patients with depression via the actions of cytokines. Elevated levels of interleukin 6 and tumor necrosis factor α have been found in serum, CSF, and brain cortices, especially in the prefrontal (32) and orbitofrontal (33) cortices, among patients with depression, along with increased translocator protein in the anterior cingulate cortex and temporal cortex (34). Increased levels of proinflammatory cytokines may lead to damage to brain structure and further impaired cognitive function through 3 pathways, including reduced brain serotonin leading to the accumulation of toxic byproducts of oxidative stress like quinolinic acid and further neural and glial damage (35), increased cortical blood-brain barrier (BBB) permeability, and remodeling or damage of blood vessels (31). The influence can be reversed by anti-inflammatory medication like minocycline (36). It was also suggested that antidepressants may reduce the incidence of AD via increased levels of the anti-inflammatory cytokine transforming growth factor β1 (37) (Figure 3).

Mechanisms Supporting Depression as Secondary to AD

Genetic Liability to AD Contributes to Depression. Despite the fact that earlier research using Mendelian randomization could not reach a consistent conclusion regarding the causal effect of the genetic predisposition to AD on the risk of depression (24,38), individuals with higher polygenic risk scores for AD were shown to have an elevated risk of depression beyond the age of 50 (39). By performing pleiotropy analyses using a genome-wide association study of the 2 disorders, several risk genes for late-onset AD that were strongly related to the risk of MDD have been identified (38). The principal functions of the discovered genes are immune response and regulation of endocytosis (38), which could be interpreted to mean that the influence of these AD risk genes on depression prevalence may be exerted via immune deregulation.

AD-Related Biomarkers Contribute to Depressive Symptoms. In one study, among cognitively normal older adults, those with elevated positron emission tomography tau levels were twice as likely to experience depression (40). Moreover, the level of plasma total tau levels has shown a significant association with symptoms of depression, apathy, anxiety, worry, and sleep quality (41), and a higher level of CSF tau has been associated with an increased risk of depression and apathy over time (42,43). However, the role of Aβ is controversial. Administration of Aβ oligomers through intracerebroventricular injection in 3-month-old mice has been shown to result in an elevation of depressive-like behaviors, suggesting that amyloid pathology has a direct effect on depressive-like behaviors (44–46). These behaviors were subsequently ameliorated by the administration of the antidepressant fluoxetine or neuropeptide Y (45,46). One cross-sectional study suggested a relationship between depressive symptoms and higher amyloid load as assessed by neuroimaging in patients with subjective cognitive decline (47). A study conducted during COVID-19 confinement showed that under the same stressors, amyloid-positive individuals were more likely to have greater depressive symptoms, suggesting

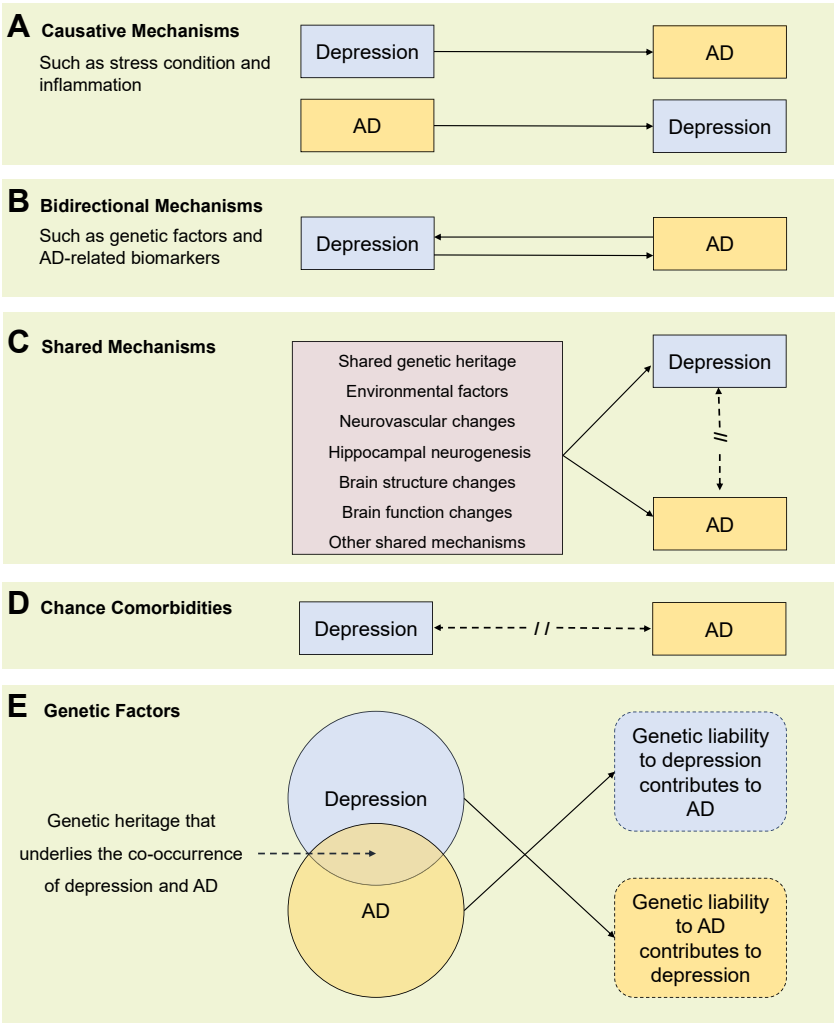

Figure 2. Mechanisms of the association between depression and Alzheimer's disease (AD). The graphic briefly summarizes a framework of putative mechanisms linking AD and depression that we proposed in this review. **(A)** Causal mechanisms such as stress condition and the inflammation it induces, which participate in the depression-to-AD association. **(B)** Some factors, such as AD-related biomarkers, work bidirectionally, and the specific AD pathology is different in the 2 directions of the relationship. **(C)** Commonly shared risk factors discussed in this review include genetic heritage, neurovascular changes, hippocampal neurogenesis, changes in brain structure, and the cortisol-hippocampal pathway. **(D)** Chance comorbidities. **(E)** The genetic factor is quite complex in this association. Genetic liability to depression contributes to AD, whereas genetic liability to AD contributes to depression. Other genetic heritage can lead to co-occurrence of the 2 disorders. Arrows with a solid line represent causal association, while arrows with dashed lines represent noncausal associations.

that AD pathology may increase the occurrence and extent of depressive symptoms in response to stressors (48). However, the A4 (Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease) Study did not find a significant association between elevated positron emission tomography amyloid and the development of depression in adults with normal cognition (49).

Shared Mechanisms Across Depression and AD

Commonly shared risk factors can be genetic, environmental, structural, or neurochemical. These overlapping pathophysiological substrates may explain the comorbidity of both syndromes and provide potential overlapping biomarkers for the identification of the 2 disorders.

Genetic Heritage That Underlies the Co-Occurrence of Depression and AD. The pathogenesis of both depression and AD is complex and involves polygenic risk factors. As anticipated, recent findings suggest that depression shares certain genetic factors with AD. A study using UK Biobank genome-wide association study summary statistics investigated the impact of 98 overlapping genetic variants on both depression and AD and identified a significant association between a single nucleotide polymorphism in the *TMEM106B* gene and both disorders (21). The single nucleotide polymorphism was also associated with higher volume of the posterior, mid-posterior, and anterior sections of the corpus callosum; lower volume of the third ventricle; and larger area of the inferior temporal gyrus (21). AD and other neurodegenerative diseases may share at least 13 causal proteins with several psychiatric disorders. This accounts for 30% of the total of 44 identified causal proteins associated with neurodegenerative disorders. These findings support the hypothesis of a shared genetic and molecular basis between the psychiatric and neurodegenerative groups (50) and inspire further investigation into the genetic mechanisms that underlie the co-occurrence of AD and depression.

Environmental Factors. Environmental factors such as lifestyle, diet, physical activity, and social support have been

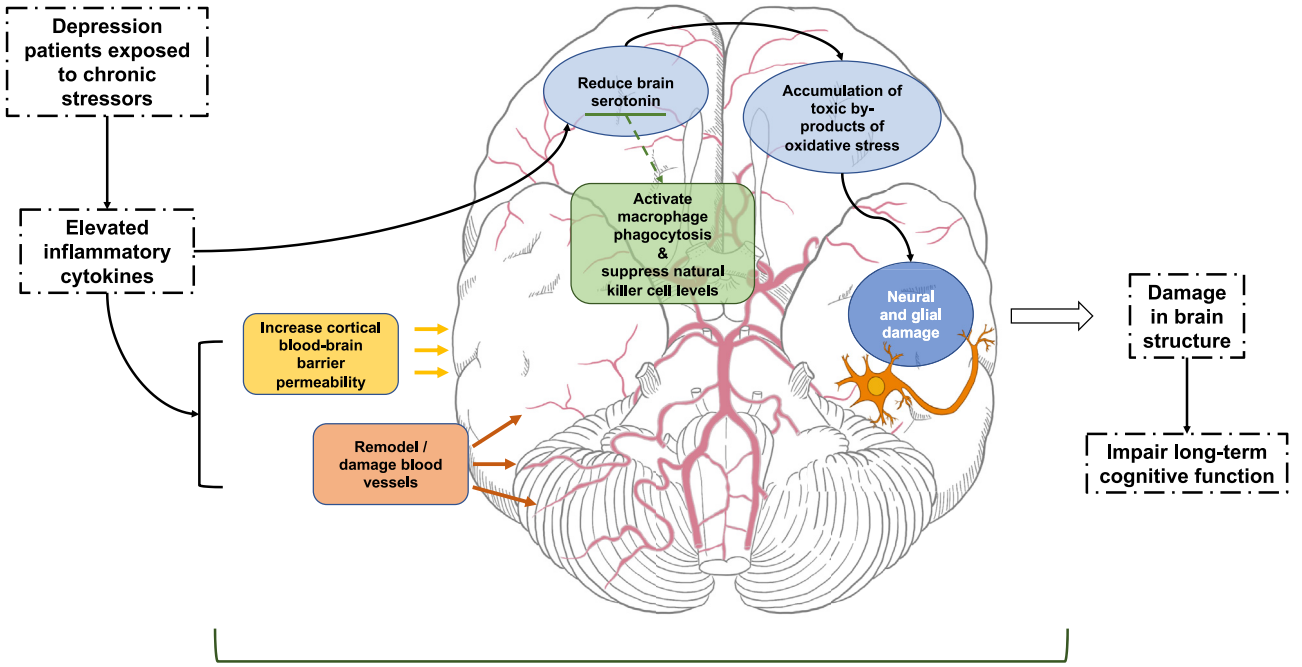

Figure 3. Stress condition and inflammation linking depression and Alzheimer's disease. The graphic shows the possible mechanisms by which inflammation dysregulation induced by chronic stressors participates in the association between depression and Alzheimer's disease. Current evidence indicates that elevated proinflammatory cytokines lead to damage in brain structure and further cognition impairment via reduced brain serotonin, which then causes accumulation of toxic byproducts of oxidative stress, increased cortical blood-brain barrier permeability, and blood vessel remodeling or damage.

implicated in increasing the risk of AD as well as depression. Individuals exposed to a harmful biophysical environment, such as air pollution and heavy metals, have a higher risk of developing both depression and AD later in life (51–53). These factors can interact with genetic and neurochemical factors, influencing the pathophysiological substrates that underlie both disorders. It should be noted that most environmental exposures have multiple, linked, or unrelated impacts on various mental health conditions beyond the specific disorders of AD and depression.

Neurovascular Changes. Neurovascular dysfunction in mood-related brain regions, which is associated with increased BBB permeability, may link chronic stress and psychiatric disorders like depression (54–56) via the VEGF/VEGFR2 pathway (55), abnormal blood vessel morphology, and peripheral cytokine infiltration into the brain parenchyma (56). Brain endothelial-specific Lrp1 deletion in brain capillaries of the BBB reduced plasma Aβ levels, driving AD pathology and aggravating cognitive impairment (57,58). However, the brain capillary damage and BBB breakdown in the hippocampus were revealed to be unrelated to Aβ and tau biomarkers in individuals with early cognitive dysfunction (58).

Hippocampal Neurogenesis May Display a Converging Link Between Depression and AD. The hippocampus plays a key role in both AD and depression. Adult hippocampal neurogenesis (AHN) is functionally linked to cognitive and neural plasticity in humans and animal models (59). Multiple studies have investigated the role of AHN in patients with MDD (60) and in AD pathology (61,62). Patients with Lewy body dementia who use selective serotonin reuptake inhibitors (SSRIs) to treat depression have been found to have increased numbers of DCX+ cells and experience less cognitive decline, supporting the hypothesis that antidepressant-induced enhanced AHN not only improves mood but also has the potential to prevent neurodegeneration and preserve memory. In AD mouse models, activation of supramammillary, nucleus-enhanced adult-born neurons improves AHN and rescues memory and emotion deficits. This activation not only promotes robust hippocampal plasticity but also augments the phagocytic capacity of microglia toward plaques (63).

Changes in Brain Structure. Both late-life depression and AD are frequently associated with changes in brain structure, particularly decreased hippocampus volume and increased white matter lesion volume (64). Hippocampal atrophy and late-life depression may be independent predictors of AD occurrence. White matter lesion volume was found to grow over time and was discovered to partially mediate the relationship between dementia and late-life depression (65). Compared with healthy older adults, a significant difference in total hippocampal volume was observed among depressed older adults, although the underlying mechanism may not be the same as amyloid pathology (66). Notwithstanding the fact that depression and AD show comparable changes in brain

structure, a typical mode of cortical atrophy is believed to exist in the 2 disorders. In both patients with MDD and patients with AD, pronounced atrophy is observed in the temporal lobe regions and the anterior cingulate cortex, whereas exclusive atrophy of the posterior cingulate cortex and precuneus is uniquely evident in patients with AD (67).

Changes in Brain Function. The impairment of brain networks differs between depression and AD. Research has shown that patients with MDD had lower functional connectivity (FC) than patients with subthreshold depression in the frontal, cortical, and limbic areas, while those with amyloid deposition showed greater FC reduction, particularly in the hippocampus, parahippocampus, and frontal and temporal cortices (68). The default mode network (DMN) is not only involved in the mechanism of depression but is also considered as a potential network for cognitive deficits in late-onset depression (69). Compared with healthy control participants, patients with major depression exhibited increased FC in the anterior DMN and between the anterior DMN and the salience network (70) but decreased FC in the posterior DMN and between the posterior DMN and the central executive network (71). The dissociation pattern may be due to reduction in the white matter integrity of the cingulate bundle which links the 2 parts (72). The abnormal FC in patients with late-onset depression was found to be related not only to the severity of depression but also the cerebral Aβ accumulation (73) and the dysfunctional overall cognition (74). Altered connectivity in the DMN may be a potential neural mechanism that links depression, Aβ pathology, and disease progression in the trajectory of AD (70,75).

Cortisol-Hippocampal Pathway Underlying the Onset of Depression and AD. A pathophysiological pathway linking depression and dementia may be mediated by a dysregulation of the hypothalamic-pituitary-adrenal axis (76). Comparing the cortisol levels of individuals with either depression or dementia and the reference group, individuals with dementia and comorbid depression showed the highest cortisol ratio. Moreover, among patients with depression and dementia, cortisol level was found to be associated with cognitive function (77). Hypothalamic-pituitary-adrenal dysfunction in AD may be a consequence of disease progression. However, currently, plasma cortisol concentration may not be a reliable biomarker to differentiate the 2 disorders (76).

TREATMENTS

The Effect of Depression Treatment on Prevention of AD

Pharmacological Interventions. Although existing evidence shows that depression is associated with dementia, the effect of successful control of depressive symptoms on dementia prevention is still not quite clear. The antidementia effect of antidepressants may differ by the specific type of drug. Antidepressants are classified into 3 main categories: SSRIs, serotonin and norepinephrine reuptake inhibitors, and tricyclic antidepressants. SSRIs have been shown to be more efficient than other types of antidepressants (78). Long-term treatment over 4 years with SSRIs can lead to delayed progression to AD by approximately 3 years in patients with mild cognitive impairment who have a history of depression compared with short-term SSRI treatment or no treatment, despite the absence of difference in CSF biomarker levels (78). In another study with cognitively normal older adults, escitalopram-treated patients showed an overall 9.4% greater reduction in CSF Aβ42 than the placebo groups (79,80), which is consistent with the function of SSRIs in reducing Aβ levels observed in animal studies. Many previous studies have demonstrated that antidepressants, particularly SSRIs, aid in the prevention of dementia; however, some of the investigations revealed no discernible differences between antidepressant-treated patients and nontreated patients (81–85). The use of paroxetine (81), an SSRI, or trazodone (82), a tricyclic antidepressant, was found to be related to a higher risk of dementia among adults in middle or older age than in nonusers. This may be a result of the fact that patients at the prodromal stage of dementia who have clinical symptoms of depression are more likely to be prescribed such medications.

In addition to classic antidepressants, other kinds of pharmacological treatment may also change the outcome of whether AD develops among patients with depression. For example, both lifetime oral contraceptive use and hormone replacement therapy after menopause were reported to be associated with a decreased risk of AD in female patients (86).

Psychological Interventions. Although commonly used antidepressant treatments act well in vitro and in animal experiments, results of some population-based studies have called their protective effect against AD into question, as discussed above. Both clinicians and patients may also be concerned about the balance between potential benefit and possible adverse events (87,88). As another effective first-line therapy for depression, psychological therapies are not only preferred more by patients (89) but also provide longer-term depression relapse prevention benefits (90). Reliable improvement in depression across psychological therapies was associated with a 12% reduced rate of a future dementia diagnosis (91).

The Effect of Treating Depressive Symptoms in AD

Pharmacological Interventions. Antidepressants remain the mainstay of pharmacotherapy in depression with AD; however, most meta-analyses have not shown a clear benefit of antidepressants for depression comorbid with AD (92,93). A recent network meta-analysis based on 25 studies including 14 medications found that only mirtazapine and sertraline showed a slightly better effect in treating symptoms of depression (94). However, the limitations of the network meta-analysis approach should not be ignored because the efficacy of medications may be overestimated. Recent Delphi consensuses recommended that multimodal antidepressants (duloxetine, venlafaxine/desvenlafaxine, vortioxetine, tianeptine, and mirtazapine) (20,95) and SSRI antidepressants are valid therapeutic choices for clinicians treating depression (96), a conclusion that is consistent with most guidelines (93).

Table 1. Randomized Clinical Trials and Meta-Analyses of the Effect of Antidepressants on Depressive Symptoms in Alzheimer's Disease

Participants	Study Sample	Primary Outcome	Intervention, mg/day	Treatment Duration, Weeks	Main Results	Reference	Study Design
AD Patients With Depression	Fluoxetine (*n* = 17), placebo (*n* = 24)	HAMD, CGI	Fluoxetine (SSRI): 10–40	6	No significant difference was observed between fluoxetine and placebo in mood improvement in AD patients with depression.	Petracca *et al.*, 2001 (101)	DB-RCT
AD Patients With Major Depression	Amitriptyline (*n* = 19), fluoxetine (*n* = 18)	HAMD, MMSE, dropout rates	Fluoxetine (SSRI): 10; amitriptyline (TCA): 25	6	Both amitriptyline and fluoxetine led to reduction in HAMD and MMSE scores. Efficacy was similar for fluoxetine and amitriptyline, but fluoxetine was better tolerated.	Taragano *et al.*, 1997 (102)	DB-RCT
AD Patients With Depression	Escitalopram (*n* = 42), placebo (*n* = 42)	CSDD	Escitalopram (SSRI): 5–15	12	No significant difference in depression and cognition was observed between the 2 groups.	An *et al.*, 2017 (103)	DB-RCT
Dementia Patients With Depression	Paroxetine (*n* = 99), imipramine (*n* = 99)	MADRS, CGI	Paroxetine (SSRI): 20–40; imipramine (TCA): 50–100	8	Paroxetine and imipramine were effective at treating depression in patients with dementia.	Katona *et al.*, 1998 (104)	DB-RCT
AD Patients With Depression or Apathy	Sertraline (*n* = 11), escitalopram (*n* = 13), nicergoline (*n* = 9)	MMSE, HDSR, GDS, AS	Sertraline (SSRI): mean dosage of 31.8; escitalopram (SSRI): mean dosage of 7.3; nicergoline mean dosage of 14.5	12	Escitalopram group showed a significant improvement in GDS score. Sertraline group showed a significant improvement in AS score.	Takemoto *et al.*, 2020 (105)	Randomized, single-blind, multicenter, prospective, observational study
AD Patients With Depression	Sertraline (*n* = 107), mirtazapine (*n* = 108), placebo (*n* = 111)	CSDD	Sertraline (SSRI): 150; mirtazapine (NaSSA): 45	39	Sertraline and mirtazapine were no more effective than placebo. There were more adverse reactions in those treated with antidepressants compared to placebo.	Banerjee *et al.*, 2011 (106)	DB-RCT
AD Patients With Major Depression	Sertraline hydrochloride (*n* = 24), placebo (*n* = 20)	Response rate, CSDD, HAMD, MMSE, Psychogeriatric Depression Rating Scale-ADL, NPIQ	Sertraline (SSRI): mean dosage of 95	12	Sertraline was superior to placebo in depression reduction, lessened behavior disturbance, and improved ADL, but did not improve cognition.	Lyketsos *et al.*, 2003 (107)	RCT
Patients With Mild-to-Moderate AD and Depression	Sertraline (*n* = 67), placebo (*n* = 64)	mADCS-CGIC, CSDD, remission	Sertraline (SSRI): 25–125	24	Sertraline treatment was not associated with delayed improvement between 12 and 24 weeks of treatment.	Weintraub *et al.*, 2010 (108)	DB-RCT
Moderate AD Patients With Major Depressive Disorder	Sertraline (*n* = 20), venlafaxine (*n* = 20), desipramine (*n* = 19)	HAMD, MMSE, BI	Sertraline (SSRI): 25–150; venlafaxine (SNRI): 37.5–150; desipramine (TCA): 25–150	12	Results improved significantly for: 1) HAMD, MMSE, and BI in the sertraline group. 2) MMSE and BI in the venlafaxine group. 3) BI scores only in the desipramine group.	Mokhber *et al.*, 2014 (109)	DB-RCT

Table 1. Continued

Participants	Study Sample	Primary Outcome	Intervention, mg/day	Treatment Duration, Weeks	Main Results	Reference	Study Design
Probable AD Patients With Depression	Clomipramine (*n* = 11), placebo (*n* = 10)	HAMD, MMSE, FIM	Clomipramine (TCA): 25–100	6	1) Clomipramine showed a significant effect in mood improvement compared with placebo. 2) Patients treated with clomipramine showed significantly lower MMSE scores overall than placebo-treated patients.	Petracca *et al.*, 1996 (110)	DB-RCT
AD Patients With and Without Depression	Depressed: imipramine (*n* = 13), placebo (*n* = 15); not depressed: imipramine (*n* = 14), placebo (*n* = 19)	HAMD, MMSE	Imipramine (TCA): mean dosage of 83	8	No significant difference was observed between imipramine and placebo in improvement of depression scale scores.	Reifler *et al.*, 1989 (111)	DB-RCT
Dementia Patients With Depression	Maprotiline (*n* = 64), placebo (*n* = 63)	GDS, MMSE, video rating of the global impression	Maprotiline (TCA): 25–75	8	Maprotiline showed significant beneficial effect compared with placebo in GDS but not in cognition or global impression.	Fuchs *et al.*, 1993 (112)	DB-RCT
Dementia Patients or Cognitive Decline Patients With Depression	Dementia with depressive symptoms (*n* = 511), depression with cognitive decline (*n* = 183)	HAMD, MMSE, SCAG, CGAE, BGP	Moclobemide (MAOI): 400	6	Moclobemide reduced HAMD scores significantly compared with placebo, and also improved cognitive function measured by the SCAG factor 1.	Roth *et al.*, 1996 (113)	DB-RCT
Mild AD Patients With Depression	Vortioxetine (*n* = 36), other common antidepressants (*n* = 72)	MMSE, AM, RCPM, Digit Span, HAMD, CSDD	Vortioxetine: 15; other antidepressants	48	1) Vortioxetine-treated patients scored better on baseline-to-end point MSME, AM, RCPM, and Digit Span. 2) Vortioxetine reduced HAMD and CSDD scores.	Cumbo *et al.*, 2019 (114)	Prospective, randomized, parallel-group study
Patients With AD	*N* = 1374	Overall NPS, depressive symptoms, cognition, care burden	15 pharmacological interventions (SSRIs, non-SSRIs)	8–13	1) Serotonergic antidepressants improved cognitive function and overall NPS and alleviated agitation, depressive symptoms, and care burden. 2) SSRIs and non-SSRIs reduced agitation and depressive symptoms, whereas only SSRIs reduced overall NPS and care burden.	Hsu *et al.*, 2021 (97)	Meta-analysis including 8 RCTs
Dementia Patients With Depression	*N* = 1592	Depressive symptoms and rates of response or remission, cognitive function, ADLs, quality of life	8 antidepressants (escitalopram, sertraline, venlafaxine, maprotiline, clomipramine, fluoxetine, imipramine, and moclobemide)	12.7	Antidepressants showed little or no effect on a test of cognitive function including attention, memory, and language.	Dudas *et al.*, 2018 (93)	Meta-analysis including 10 DB-RCTs

Table 1. Continued

Participants	Study Sample	Primary Outcome	Intervention, mg/day	Treatment Duration, Weeks	Main Results	Reference	Study Design
AD Patients With Depression	*N* = 599	CSDD, HDRS, MADRS, GDS, DSM, MMSE	14 antidepressants (escitalopram, sertraline, mirtazapine, venlafaxine, maprotiline, paroxetine, imipramine, fluoxetine, citalopram, venlafaxine, desipramine, minaprine, clomipramine, and amitriptyline)	6–13	1) Only mirtazapine and sertraline showed better effect in treating symptoms of depression compared with placebo. 2) No significant effect of antidepressants on cognitive function.	He *et al.,* 2021 (94)	Meta-analysis including 25 RCTs
Patients With AD	*N* = 1616	MMSE, ADAS-cog, CSDD, HAMD, MADRS	7 SGAs (trazodone, fluoxetine, citalopram, sertraline, bupropion, ascitalopram, and mirtazapine)	2–48	Treatment with SGAs showed little benefit for both cognition and depression.	Qin *et al.,* 2022 (115)	Meta-analysis including 15 RCTs
AD Patients With Depression	*N* = 165	Number of patients responding to treatment, number of patients with remission of depression, MMSE, AEs, dropout for any reason, and dropout due to AEs	4 antidepressants (imipramine, clomipramine, sertraline, and fluoxetine)	6–12	1) Antidepressants showed superiority in reducing depressive symptoms, response, and remission. 2) No significant differences in cognition were observed between the antidepressant- and placebo-treated groups.	Thompson *et al.,* 2007 (116)	Meta-analysis including 5 DB-RCTs

Both primary and secondary outcomes are listed for meta-analyses.

AD, Alzheimer's disease; ADAS-cog, Alzheimer Disease Cooperative Study-Activities of Daily Living Scale; ADL, activity of daily living; AE, adverse event; AM, Attentive Matrices; AS, Apathy Scale; BGP, Behavioral Rating Scale for Geriatric Patients; BI, Barthel Index of Activities of Daily Living; CGAE, Clinical Global Assessment of Efficacy; CGI, Clinical Global Impression scale; CSDD, Cornell Scale for Depression in Dementia; DB-RCT, double-blind randomized clinical trial; FIM, Functional Independence Measure; GDS, Geriatric Depression Scale; HAMD, Hamilton Depression Rating Scale; HDSR, Hasegawa Dementia Rating Scale-Revised; mADCS-CGIC, modified Alzheimer's Disease Cooperative Study Clinical Global Impression of Change; MADRS, Montgomery–Åsberg Depression Rating Scale; MAOI, monoamine oxidase inhibitor; MMSE, Mini-Mental State Examination; NaSSA, noradrenergic and specific serotonergic antidepressant; NPIQ, Neuropsychiatric Inventory Questionnaire; NPS, neuropsychiatric symptoms; RCPM, Raven Coloured Progressive Matrices; SCAG, Sandoz Clinical Assessment-Geriatric Scale; SGA, second-generation antipsychotic; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Despite the minor effect, increased cognitive performance, along with alleviated depressive symptoms and overall neuropsychiatric symptoms, were reported in a recent meta-analysis of AD patients with depression treated with serotonergic antidepressants (97). Both SSRIs and non-SSRIs can considerably reduce agitation and depressive symptoms, but only SSRIs can decrease overall neuropsychiatric symptoms and care burden (97). For example, vortioxetine plays a critical role in the regulation of both mood and cognitive performance (98–100). Table 1 summarizes the randomized clinical trials and meta-analyses that have examined the impact of antidepressants on depressive symptoms in individuals with AD (93,94,97,101–116).

Besides traditional antidepressants, a great number of novel pharmacological treatments that target the comorbidity of depression and AD such as PDE4 inhibitors (117–119) and novel medications that fuse the key pharmacophore of antidepressant and anti-AD drugs (120,121) are also under development.

Nonpharmacological Interventions. Feasible nonpharmacological interventions such as psychological treatments and psychosocial and environmental modifications are recommended as first-line treatments for neuropsychiatric symptoms in dementia, in addition to situations where symptoms are extremely distressing or pose potential danger to self or others (122). Individual psychological interventions consisting of cognitive behavioral therapy, cognitive rehabilitation, and reminiscence have been proven to reduce the depressive symptoms of patients with mild cognitive impairment or dementia, the effect of which persisted for 6 months after the intervention (123). Cognitive behavioral therapies (behavioral activation and problem-solving therapy) are effective in reducing depressive symptoms, increasing depression remission, and improving patient quality of life and activities of daily living at the end of treatment (124). Also, computerized cognitive training and cognitive stimulation therapy were found to have medium-to-large effects in the reduction of depressive symptoms (125). It has been indicated that compared with usual care, a combination of psychological interventions may be more efficient (126).

Social interventions, including long-term exercise, sleep hygiene, patient and caregiver education, and arts-based therapies (visual or music), as well as neurostimulation such as transcranial magnetic stimulation are also in practice (127). Music-based therapeutic interventions for dementia can effectively reduce depressive symptoms and alleviate behavioral disturbances (128) and have been listed in a recent consensus statement as one of the most promising nonpharmacological approaches for neuropsychiatric symptoms in dementia (129). Patients receiving treatment that integrates neuronavigated repetitive transcranial magnetic stimulation with cognitive training have shown improvements in cognitive function (130,131). A systematic review suggested that frontal repetitive transcranial magnetic stimulation could exert procognitive effects on executive function and attention in some patients with depression but inconsistent cognitive impacts in patients with AD.

CONCLUSIONS AND FUTURE DIRECTIONS

The heterogeneity of both depression and AD poses challenges for understanding their underlying mechanisms. Future research should concentrate on characterizing subgroups to gain insights into their unique characteristics and develop personalized intervention strategies. Genetic studies also face challenges in unraveling the complex genetic architecture of depression and AD. Larger sample sizes, cleaner phenotype definitions, and further improvements of biostatistical tools are needed to increase statistical power and identify additional risk variants. Both disorders exhibit overlapping neuropsychiatric symptoms, suggesting potential common pathways. Exploring shared pathological hallmarks, such as neurofibrillary tangles, inflammation, and neurovascular pathology, may offer new therapeutic avenues. In addition, identifying reliable biomarkers can help monitor individuals at risk, facilitate early detection, track disease progression, and guide treatment decisions. This may involve exploring genetic, epigenetic, proteomic, or metabolomic markers, as well as neuroimaging and neurophysiological measures, to better understand the underlying pathophysiology and identify potential therapeutic targets. The current research situation also calls for future prospective studies with antidepressive treatments and cognitive decline and dementia as primary outcomes to contribute to the prevention of AD.

To summarize, patients with both AD and depression may exhibit accelerated cognitive decline and could potentially benefit from the use of antidepressants. Exploring the epidemiological and biological relationships between depression and AD offers valuable insights into disease prevention, early detection, and intervention strategies. The clinical implications of the mechanisms linking depression and AD highlight the need for a comprehensive and multidimensional approach to future research.

Search Strategy and Selection Criteria

We performed a systematic search of the PubMed, ClinicalTrials.gov, and PsycINFO databases to identify studies that reported associations between depression and dementia. We used the search terms "depress*" OR "dysthymia*" OR "adjustment disorder*" OR "mood disorder*" OR "affective disorder" OR "affective symptoms" AND "dementia" OR "Alzheimer Disease." The literature search was limited to the English language and limited to the dates up to June 4, 2023, with a primary focus on dates between May 2018 and June 2023.

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