Review

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Review

Cognitive Impairment, Dementia and Depression in Older Adults

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Abstract

Depression and cognitive impairment frequently co-occur in late life and exhibit substantial clinical and biological overlap. Epidemiological evidence consistently shows that late-life depression increases the risk of mild cognitive impairment and dementia, with stronger associations observed for vascular dementia than for Alzheimer's disease. Neurobiological studies implicate cerebrovascular pathology, neuroinflammation, hypothalamic–pituitary–adrenal axis dysregulation, and fronto-subcortical circuit dysfunction as key mechanisms linking depressive symptoms to later cognitive decline. In a subset of older adults, new-onset depression—particularly when accompanied by executive dysfunction, subjective cognitive decline, or high white-matter hyperintensity burden—may represent a prodromal manifestation of emerging neurodegenerative or vascular brain changes. Depression is also highly prevalent as part of the behavioral and psychological symptoms of dementia, occurring in 30–50% of individuals with Alzheimer's disease and even higher proportions in dementia with Lewy bodies or frontotemporal dementia. Comorbid depression in dementia accelerates cognitive and functional decline, increases neuropsychiatric burden, and worsens quality of life for patients and caregivers. Therapeutically, antidepressants may provide modest cognitive benefits in non-demented older adults but show limited efficacy in dementia. In contrast, cholinesterase inhibitors, memantine, and multimodal non-pharmacological interventions yield small but measurable improvements in depressive or apathy-related symptoms. While anti-amyloid therapies slow cognitive deterioration in early Alzheimer's disease, their effects on mood remain unclear. These findings underscore the need for stage-specific, integrative strategies to address the intertwined trajectories of mood and cognition in aging.

Keywords: late-life depression; mild cognitive impairment; dementia; behavioral and psychological symptoms of dementia; cognitive decline

1. Introduction

Cognitive impairment and depression are among the most prevalent neuropsychiatric conditions in late life. They frequently co-occur and exert reciprocal influences on each other [1,2]. Epidemiological studies have consistently shown that late-life depression is associated with a higher risk of developing mild cognitive impairment (MCI) and dementia, while cognitive decline often contributes to the emergence or persistence of depressive symptoms [3,4]. Both conditions share

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overlapping clinical features—such as deficits in attention, executive function, and processing speed—which can complicate differential diagnosis [5,6]. The concept of "pseudodementia," once used to describe reversible cognitive impairment secondary to depression, has evolved into a more nuanced understanding of a potential prodromal stage of dementia, highlighting the blurred boundary between affective and neurodegenerative disorders in older adults [7].

Neurobiologically, depression and dementia exhibit several shared pathophysiological pathways, including dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, neuroinflammation, cerebrovascular burden, and reduced neuroplasticity [8–10]. Late-onset depression, in particular, has been linked to frontostriatal and limbic system alterations as well as white matter hyperintensity (WMH) burden, suggesting a "vascular depression" subtype that bridges mood disturbance and cognitive decline [11,12]. Conversely, in established dementia, depressive symptoms are often part of the behavioral and psychological symptoms of dementia (BPSD), reflecting the spread of neurodegeneration into emotion-regulating networks [13–15]. These bidirectional and stage-dependent interactions underscore the need for an integrative framework that considers depression and cognitive decline as part of a continuum rather than distinct entities.

Understanding the interplay between mood and cognition has important therapeutic implications. Accumulating evidence suggests that antidepressant treatment may improve not only mood but also specific domains of cognitive performance, particularly when targeting serotonergic and neurotrophic mechanisms [16,17]. Similarly, while cognitive enhancers are known to modestly alleviate behavioral symptoms in dementia, recent advances in anti-amyloid and anti-tau antibody therapies have raised expectations that such disease-modifying treatments might also ameliorate affective symptoms, although definitive evidence is still lacking [18,19]. This narrative review aims to synthesize current evidence on the shared and distinct cognitive profiles of depression and dementia, explore the neurobiological and clinical features of depression as a prodromal or comorbid manifestation of dementia, and discuss the bidirectional treatment effects that bridge mood and cognition in late life. The review is based on a focused evaluation of epidemiological studies, neuroimaging and biomarker research, and major clinical trials relevant to late-life depression and dementia.

2. Shared and Distinct Patterns of Cognitive Impairment in Depression and Dementia

Cognitive impairment in late-life depression and dementia frequently involves deficits in attention, processing speed, and executive function, thereby creating a significant overlap in neuropsychological profiles. For example, older adults with major depressive disorder often demonstrate reductions in processing speed and executive functioning tasks, pointing to dysfunction within frontostriatal circuits [20,21]. Similarly, in the early stages of dementia, the decline in attention and processing speed may precede overt memory impairment, implicating frontal lobe involvement in both conditions [22,23]. This overlap poses a diagnostic challenge in distinguishing a reversible "pseudo-dementia" picture from a progressive neurodegenerative process, underscoring the need for nuanced neuropsychological assessment.

Despite these shared features, important distinctions in cognitive profiles emerge between depression and dementia. Memory dysfunction, particularly in encoding and storage of new information, is a hallmark of Alzheimer's disease (AD) and other neurodegenerative dementias [24], whereas in depression the memory impairment tends to be more retrieval-based with recognition relatively spared [25]. In addition, cognitive deficits in depression may demonstrate substantial recovery following effective mood treatment, indicating a degree of reversibility; by contrast, cognitive decline in dementia is characteristically progressive and largely irreversible [7,26]. This divergence in trajectory and reversibility strengthens the conceptual distinction between functional cognitive impairment and early neurodegeneration.

From a neurobiological and neuroimaging perspective, depression and dementia share disruption in frontal–subcortical and limbic networks, yet they diverge in anatomical and

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pathophysiological patterns [27–29]. In late-life depression, evidence points to altered dorsolateral prefrontal cortex and anterior cingulate cortex functioning, increased WMH burden, and a "vascular depression" pattern that implicates cerebrovascular burden [27,29]. By contrast, dementia—particularly AD—exhibits prominent hippocampal and medial temporal-lobe atrophy, posterior cortical hypometabolism, and accumulation of amyloid and tau pathology [30]. Thus, while both conditions may involve frontolimbic network disruption, the underlying substrate in depression tends to be more vascular/functional, whereas in dementia it is more degenerative/structural.

Clinically, the recognition of this continuum from depression through cognitive impairment to dementia has considerable implications. Older adults presenting with late-onset depression, marked executive dysfunction, and high WMH burden are at increased risk of subsequent cognitive decline and conversion to dementia [31,32]. Accordingly, neuropsychological assessment in depressed older patients should incorporate not only mood-symptom resolution but also longitudinal cognitive monitoring, especially in the domains of processing speed and executive control [33]. Understanding both the similarities and differences in cognitive impairment between depression and dementia enables more precise stratification of risk and informs timely intervention strategies.

3. Depression as a Risk Factor for Dementia

Meta-analytic evidence strongly supports depression as an independent risk factor for subsequent dementia. In a comprehensive meta-analysis of 23 cohort studies, Diniz et al. (2013) reported that late-life depression was associated with an 85% increased risk of all-cause dementia (pooled hazard ratio [HR] 1.85, 95% confidence interval 1.67–2.04), with subtype analyses showing a stronger association for vascular dementia (odds ratio [OR] 2.52) than for AD (OR 1.65) [1]. Similar findings have been replicated in other large population-based cohorts and systematic reviews, consistently demonstrating that depressive disorders across the lifespan are linked to higher incidence of MCI and dementia [3,4]. More recent nationwide data from Denmark confirmed this association across early-, mid-, and late-life depression, showing HRs of 3.08, 2.95, and 2.31, respectively [34]. The impact of depression on dementia risk also appears to vary by age: a recent Korean cohort study of adults aged ≥ 75 years suggested that the association weakens with advancing age [35].

Several biological mechanisms have been proposed to explain the link between depression and later dementia. Among these, vascular pathology appears to play a particularly prominent role. Neuroimaging and neuropathological studies have consistently shown that older adults with depression often exhibit increased WMH, lacunar infarcts, and small-vessel disease, collectively forming the substrate of the so-called "vascular depression" subtype [11,27]. These cerebrovascular alterations may disrupt frontostriatal and limbic circuits that are essential for executive and emotional regulation, providing a plausible mechanistic bridge between mood disturbance and cognitive decline [9]. Conversely, while AD pathology—amyloid-β and tau accumulation—has been postulated to underlie the depression-dementia relationship, biological evidence for a direct association remains inconsistent. A recent systematic review and meta-analysis of cerebrospinal fluid, positron emission tomography (PET), and plasma studies found no overall association between amyloid-β burden and depression in older adults without dementia, although subgroup analyses suggested a possible link in cognitively impaired individuals [36]. Emerging evidence also implicates neuroinflammatory and oxidative mechanisms in the depression–dementia continuum, with elevated peripheral inflammatory markers such as interleukin-6 being linked to late-life depression [37], microglial activation and HPA-axis dysregulation contributing to neurodegenerative vulnerability [38], and oxidative stress biomarkers such as nitrotyrosine predicting subsequent dementia in depressed older adults [39]. Thus, while depression may coexist with Alzheimer's pathology in some individuals, current evidence indicates that alternative biological pathways, rather than amyloid–tau accumulation alone, may contribute to the observed association with cognitive decline.

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4. Depression as a Prodromal Symptom of Dementia

While depression has been clearly documented as a risk factor for dementia, accumulating longitudinal data suggest that in a subset of older adults, depressive symptoms may function as a prodromal manifestation of an incipient neurodegenerative process. For example, a large cohort study found that individuals with late-life depression exhibited a significantly elevated rate of dementia onset within the first few years of diagnosis, indicating temporal closeness to dementia onset rather than a lengthy latency period [40]. Moreover, systematic reviews have debated whether late-onset depression represents an early stage of AD or vascular dementia pathology rather than merely a comorbid mood disorder [41]. These observations highlight the importance of viewing certain episodes of late-life depression not just as antecedent risk factors, but as clinical signals of evolving brain pathology.

Although prodromal depression is difficult to distinguish clinically from non-prodromal forms of late-life depression, biomarker studies suggest that biological differences may emerge in specific subgroups. For example, Wu et al. (2016) [42] reported higher cortical amyloid burden in patients with late-life depression compared with healthy controls using ^{18}F-florbetapir PET, although this association was evident only among those with co-occurring amnestic MCI. Late-onset depression has been associated with a higher burden of WMH and fronto-subcortical circuit disruption, which correlate with greater cognitive impairment [43]. Moreover, older adults with depression who exhibit substantial WMH burden tend to show poorer antidepressant treatment response, suggesting that cerebrovascular pathology contributes to both affective and cognitive outcomes in this population [11,27]. In one large study, the combination of late-life depression and subjective cognitive decline (SCD) was associated with substantially higher incidence of MCI and dementia compared with either condition alone [44]. These features suggest that depressive episodes occurring later in life may mask or overlap with very early neurodegenerative or vascular brain changes.

Recognizing depression as a potential prodromal symptom of dementia has important prognostic and clinical ramifications. Older adults with new-onset depression—especially those exhibiting executive dysfunction, SCD, and neuroimaging markers of cerebrovascular or hippocampal damage—appear to progress more rapidly to dementia than those without such features [45]. Accordingly, it is prudent for clinicians to adopt a protocol of longitudinal cognitive monitoring in these patients, extending beyond mood symptom remission to regular assessment of processing speed, executive control, and memory domains, as well as consideration of neuroimaging and vascular risk management. Early detection of the transition from depressive state to cognitive decline may facilitate timely intervention and possibly delay or mitigate progression to full-blown dementia.

5. Depression as a BPSD

Depressive symptoms are among the most common BPSD, affecting an estimated 30–50% of patients with AD and even higher proportions in dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD) [14,15]. The prevalence of clinically significant depression is particularly elevated in DLB, where affective symptoms frequently coexist with fluctuations in attention and visual hallucinations [46], and in FTD—especially the behavioral variant—where apathy and mood changes are prominent early features [47]. The presence of depression in dementia is associated with faster cognitive and functional decline, greater neuropsychiatric burden, increased rates of institutionalization, and reduced quality of life for both patients and caregivers [48,49]. Several longitudinal studies further indicate that dementia patients with comorbid depression experience higher mortality and are more likely to exhibit severe agitation, psychosis, and loss of independence [50]. In addition, a few cohort studies have shown that the presence of depression in dementia is associated with accelerated cognitive decline, with one longitudinal analysis reporting that patients with all-cause dementia lost an average of 13.7 Mini-Mental State Examination scores over 3 years, and that comorbid depression contributed to additional cognitive loss beyond this

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baseline trajectory [51]. These epidemiological and clinical findings underscore that depression emerging in the context of established dementia is not a benign comorbidity but a major determinant of disease trajectory and patient outcomes.

In established dementia, depressive symptoms are thought to reflect neurodegenerative changes involving monoaminergic pathways, including degeneration of serotonergic and noradrenergic nuclei [52]; structural atrophy in limbic and paralimbic regions, such as the anterior cingulate cortex, hippocampus, and orbitofrontal cortex [53]; and disruption of the default-mode and salience networks [54]. Neuroinflammatory activation and cholinergic deficits may further contribute to affective symptoms, particularly in AD and DLB [55,56]. Treatment response is also distinct from depression in non-demented individuals. Large randomized trials have shown limited or modest efficacy of selective serotonin reuptake inhibitors (SSRIs) in AD [57], and symptom improvement is often heterogeneous and incomplete [58]. In contrast, cholinesterase inhibitors and multimodal non-pharmacological interventions, including caregiver training and structured activity programs, have been shown to confer modest benefits for depressive and apathy-related symptoms [59,60]. These mechanistic and therapeutic patterns highlight the need for dementia-specific approaches when managing depression as part of the broader BPSD syndrome. The distinguishing clinical and biological characteristics of late-life depression, prodromal depression, and BPSD-related depression are summarized in Table 1.

Table 1. Comparative Clinical Features Across Depression Types.

Feature	Depression in Non-Demented Older Adults	Depression as a Prodrome of Dementia	Depression as a BPSD
Typical onset	Any age, recurrent	Late-onset (>60–65yr), new-onset	After dementia onset
Core symptoms	Mood, anhedonia, psychomotor changes	Mood, executive dysfunction, SCD or amnestic MCI	Mood, apathy, emotional lability
Cognitive profile	Processing speed↓, EF↓; memory relatively intact	Processing speed↓↓, EF↓↓; early memory issues	Global decline, attention fluctuation
Neurobiology	HPA dysregulation, inflammation	WMH ↑, fronto-subcortical disruption, early AD markers	Monoaminergic degeneration, limbic atrophy, cholinergic deficits
Risk of dementia	Increased	Very high	Accelerates decline
Treatment response	Generally good	Often poor	Poor to modest
Evidence level	Strong	Moderate	Strong

Abbreviations: EF, executive function; HPA, hypothalamic–pituitary–adrenal; SCD, subjective cognitive decline; MCI, mild cognitive impairment; WMH, white matter hyperintensity; BPSD, behavioral and psychological symptoms of dementia. Table content is based on a narrative synthesis of evidence presented in Sections 3–5.

6. Reciprocal Effects of Antidepressant and Anti-Dementia Treatments on Cognition and Mood

Antidepressant treatment in late-life depression has been associated not only with mood improvement but also with subtle cognitive benefits in specific domains. Several clinical studies have shown that SSRIs may enhance processing speed, executive functioning, and working memory in older adults without dementia, particularly when depressive symptoms remit adequately [61,62]. Agents with multimodal serotonergic actions, such as vortioxetine, have demonstrated pro-cognitive effects independent of mood change in geriatric populations [63,64]. In contrast, randomized trials in AD have produced inconsistent findings. The HTA-SADD trial and other large controlled studies

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found no significant advantage of SSRIs over placebo for depressive symptoms or cognitive outcomes in AD, underscoring the limited cognitive efficacy of conventional antidepressants once neurodegeneration is established [57,65,66]. Thus, while mood treatment may produce modest cognitive gains in non-demented older adults, such effects diminish substantially in the context of progressive dementia.

Conversely, anti-dementia pharmacotherapies appear to exert modest benefits on depressive and apathy-related symptoms. Cholinesterase inhibitors, including donepezil, rivastigmine, and galantamine, have been reported to reduce neuropsychiatric symptoms in AD and related disorders, with several trials demonstrating small but measurable improvements in depression, irritability, and apathy [67,68]. Rivastigmine, in particular, has shown benefit in DLB, where enhancement of cholinergic transmission may alleviate mood symptoms alongside improvements in attention and behavioral fluctuations [69]. Memantine, an N-methyl-D-aspartate receptor antagonist, has also been associated with reductions in agitation, irritability, and occasionally depressive symptoms, although results remain heterogeneous across studies [70]. Overall, although the magnitude of these effects is modest, the evidence suggests that targeting cholinergic and glutamatergic dysfunction in dementia may have secondary benefits on mood and behavioral outcomes.

Emerging disease-modifying treatments further highlight the complex interplay between cognition and affect in neurodegenerative disorders. Anti-amyloid monoclonal antibodies such as lecanemab [71] and donanemab [72] have demonstrated clinically meaningful slowing of cognitive decline in early Alzheimer's disease; however, current trial data do not provide clear evidence of improvement in depressive symptoms, and any potential mood effects remain speculative [73,74]. Similar uncertainty surrounds tau-targeting therapies, which are primarily designed to modify neurodegenerative progression rather than affective symptoms [75]. Nevertheless, the possibility that reducing pathogenic burden could indirectly modulate affective circuits has prompted interest in mood-related exploratory outcomes in ongoing trials [73]. Additionally, multimodal approaches—including cognitive rehabilitation, structured exercise programs, caregiver-focused interventions, and neuromodulation techniques such as repetitive transcranial magnetic stimulation—show promise for dual benefits on mood and cognition [76–78]. Together, these findings point to an emerging therapeutic paradigm in which interventions increasingly target the intertwined trajectories of cognitive decline and affective disturbance in late life. A comparative overview of the cognitive and mood-related effects of antidepressants, cognitive enhancers, and emerging disease-modifying therapies is provided in Table 2.

Table 2. Effects of Antidepressants, Cognitive Enhancers, and Disease-Modifying Therapies on Mood and Cognition.

Treatment Class	Cognitive Effects	Mood Effects	Evidence Summary
SSRIs	Small improvements in EF/processing speed in non-dementia	Mood improvement in LLD; limited in AD	Strong evidence in LLD; weak in dementia
Multimodal antidepressants (Vortioxetine)	Pro-cognitive effects independent of mood	Mood improvement	Moderate evidence
Cholinesterase inhibitors	Small improvement in attention/behavior	Small improvement in depression/apathy	Strong evidence in AD/DLB
Memantine	Stabilizes cognition	Reductions in agitation/irritability; mixed for depression	Mixed
Anti-amyloid antibodies (Lecanemab, donanemab)	Slows decline	No proven effect	Strong for cognition; insufficient for mood
Tau therapies	Under investigation	No evidence	Insufficient

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Non-pharm (exercise, CRT, rTMS)	Small–moderate effects	Small–moderate effects	Increasing evidence

Abbreviations: SSRI, selective serotonin reuptake inhibitor; CRT, cognitive rehabilitation therapy; rTMS, Repetitive transcranial magnetic stimulation; EF, executive function; LLD, late-life depression; AD, Alzheimer's disease; DLB, dementia with Lewy bodies.

7. Conclusion

Depression and cognitive impairment in late life are deeply interconnected. They share overlapping clinical manifestations and partially convergent neurobiological pathways. Evidence across epidemiological, neuroimaging, and biomarker studies demonstrates that depression can function both as an independent risk factor for dementia and, in some individuals, as a prodromal expression of emerging neurodegenerative or vascular pathology. At the same time, a substantial proportion of patients with established dementia experience depressive symptoms as part of the broader BPSD spectrum, where mood changes further accelerate functional decline, worsen neuropsychiatric burden, and negatively affect patient and caregiver quality of life. These stage-dependent relationships underscore the importance of moving beyond a binary distinction between "depression" and "dementia," and instead adopting an integrative conceptual framework that captures their dynamic and bidirectional interactions.

Therapeutically, the reciprocal effects of mood- and cognition-targeted treatments highlight both opportunities and limitations. Antidepressants may yield modest cognitive benefits in non-demented older adults, but their efficacy is substantially reduced in dementia, where cholinesterase inhibitors, memantine, and multimodal non-pharmacological interventions provide small but measurable improvements in affective and behavioral symptoms. Meanwhile, emerging disease-modifying therapies offer hope for altering the trajectory of Alzheimer's pathology, though definitive evidence for mood effects is lacking. These findings emphasize the need for personalized, stage-specific assessment and management strategies, incorporating longitudinal cognitive monitoring, vascular and neuropsychiatric risk evaluation, and multimodal interventions tailored to the evolving clinical profiles of aging individuals.

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Abbreviations

The following abbreviations are used in this manuscript:

MCI	Mild cognitive impairment
HPA	Hypothalamic–pituitary–adrenal
WMH	White matter hyperintensity
BPSD	Behavioral and psychological symptoms of dementia
AD	Alzheimer's disease
HR	Hazard ratio
OR	Odds ratio
PET	Positron emission tomography
SCD	Subjective cognitive decline
DLB	Dementia with Lewy bodies
FTD	Frontotemporal dementia
SSRI	Selective serotonin reuptake inhibitor

References

1. Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF, 3rd. *Late-life depression and risk of vascular dementia and alzheimer's disease: Systematic review and meta-analysis of community-based cohort studies. Br J Psychiatry 2013;202:329-335.*
2. Butters MA, Young JB, Lopez O, Aizenstein HJ, Mulsant BH, Reynolds III CF, et al. *Pathways linking late-life depression to persistent cognitive impairment and dementia. Dialogues in clinical neuroscience 2008;10:345-357.*
3. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. *Depression and risk for alzheimer disease: Systematic review, meta-analysis, and metaregression analysis. Archives of general psychiatry 2006;63:530-538.*
4. Byers AL, Yaffe K. *Depression and risk of developing dementia. Nature Reviews Neurology 2011;7:323-331.*
5. Potter GG, McQuoid DR, Payne ME, Taylor WD, Steffens DC. *Association of attentional shift and reversal learning to functional deficits in geriatric depression. International journal of geriatric psychiatry 2012;27:1172-1179.*
6. Rock PL, Roiser JP, Riedel WJ, Blackwell A. *Cognitive impairment in depression: A systematic review and meta-analysis. Psychological medicine 2014;44:2029-2040.*
7. Pozzoli S, De Carlo V, Madonna D. *Depression, dementia, and pseudodementia. Clinical cases in psychiatry: Integrating translational neuroscience approaches. Springer;2018. p. 171-188.*
8. Caraci F, Copani A, Nicoletti F, Drago F. *Depression and alzheimer's disease: Neurobiological links and common pharmacological targets. European journal of pharmacology 2010;626:64-71.*
9. Alexopoulos GS. *Mechanisms and treatment of late-life depression. Translational psychiatry 2019;9:188.*
10. Kim HK, Nunes PV, Oliveira KC, Young LT, Lafer B. *Neuropathological relationship between major depression and dementia: A hypothetical model and review. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2016;67:51-57.*
11. Taylor WD, Aizenstein HJ, Alexopoulos G. *The vascular depression hypothesis: Mechanisms linking vascular disease with depression. Molecular psychiatry 2013;18:963-974.*
12. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. *'Vascular depression' hypothesis. Arch Gen Psychiatry 1997;54:915-922.*
13. Kales HC, Lyketsos CG, Miller EM, Ballard C. *Management of behavioral and psychological symptoms in people with alzheimer's disease: An international delphi consensus. International psychogeriatrics 2019;31:83-90.*
14. Lyketsos CG, Carrillo MC, Ryan JM, Khachaturian AS, Trzepacz P, Amatniek J, et al. *Neuropsychiatric symptoms in alzheimer's disease. 2011;7:532-539.*
15. Starkstein SE, Mizrahi R. *Depression in alzheimer's disease. Expert review of neurotherapeutics 2006;6:887-895.*

 doi:10.20944/preprints202601.0928.v1

16. Shilyansky C, Williams LM, Gyurak A, Harris A, Usherwood T, Etkin A. *Effect of antidepressant treatment on cognitive impairments associated with depression: A randomised longitudinal study. The Lancet Psychiatry 2016;3:425-435.*
17. Culang-Reinlieb ME, Sneed JR, Keilp JG, Roose SP. *Change in cognitive functioning in depressed older adults following treatment with sertraline or nortriptyline. International journal of geriatric psychiatry 2012;27:777-784.*
18. Lanctôt KL, Amatniek J, Ancoli-Israel S, Arnold SE, Ballard C, Cohen-Mansfield J, et al. *Neuropsychiatric signs and symptoms of alzheimer's disease: New treatment paradigms. Alzheimer's & Dementia: Translational Research & Clinical Interventions 2017;3:440-449.*
19. Pozuelo Moyano B, Zullo L, Rouaud O, Vandel P, von Gunten A, Allali G. *Anti-amyloid drugs for alzheimer's disease: Considering the role of depression. Neurodegenerative Diseases 2025;25:36-49.*
20. Nuño L, Gómez-Benito J, Carmona VR, Pino O. *A systematic review of executive function and information processing speed in major depression disorder. Brain Sciences 2021;11:147.*
21. Bredemeier K, Warren SL, Berenbaum H, Miller GA, Heller W. *Executive function deficits associated with current and past major depressive symptoms. J Affect Disord 2016;204:226-233.*
22. Alzola P, Carnero C, Bermejo-Pareja F, Sánchez-Benavides G, Peña-Casanova J, Puertas-Martín V, et al. *Neuropsychological assessment for early detection and diagnosis of dementia: Current knowledge and new insights. Journal of Clinical Medicine 2024;13:3442.*
23. Liampas I, Dimitriou N, Siokas V, Messinis L, Nasios G, Dardiotis E. *Cognitive trajectories preluding the onset of different dementia entities: A descriptive longitudinal study using the nacc database. Aging Clinical and Experimental Research 2024;36:119.*
24. Grober E, Hall CB, Lipton RB, Zonderman AB, Resnick SM, Kawas C. *Memory impairment, executive dysfunction, and intellectual decline in preclinical alzheimer's disease. Journal of the International Neuropsychological Society 2008;14:266-278.*
25. Smith KJ, Mullally S, McLoughlin D, O'Mara S. *Validation of the face-name pairs task in major depression: Impaired recall but not recognition. Frontiers in Psychology 2014;5:92.*
26. Marazziti D, Consoli G, Picchetti M, Carlini M, Faravelli L. *Cognitive impairment in major depression. European Journal of Pharmacology 2010;626:83-86.*
27. Aizenstein HJ, Baskys A, Boldrini M, Butters MA, Diniz BS, Jaiswal MK, et al. *Vascular depression consensus report – a critical update. BMC Medicine 2016;14:161.*
28. Chen Y, Dang M, Zhang Z. *Brain mechanisms underlying neuropsychiatric symptoms in alzheimer's disease: A systematic review of symptom-general and –specific lesion patterns. Molecular Neurodegeneration 2021;16:38.*
29. Gong Q, He Y. *Depression, neuroimaging and connectomics: A selective overview. Biological psychiatry 2015;77:223-235.*
30. Márquez F, Yassa MA. *Neuroimaging biomarkers for alzheimer's disease. Molecular Neurodegeneration 2019;14:21.*
31. Masse C, Vandel P, Sylvestre G, Noiret N, Bennabi D, Mauny F, et al. *Cognitive impairment in late-life depression: A comparative study of healthy older people, late-life depression, and mild alzheimer's disease using multivariate base rates of low scores. Frontiers in Psychology 2021;12:724731.*
32. Lin C, Huang C-M, Fan Y-T, Liu H-L, Chen Y-L, Aizenstein HJ, et al. *Cognitive reserve moderates effects of white matter hyperintensity on depressive symptoms and cognitive function in late-life depression. Frontiers in psychiatry 2020;11:249.*
33. Brailean A, Aartsen MJ, Muniz-Terrera G, Prince M, Prina AM, Comijs HC, et al. *Longitudinal associations between late-life depression dimensions and cognitive functioning: A cross-domain latent growth curve analysis. Psychol Med 2017;47:690-702.*
34. Elser H, Horváth-Puhó E, Gradus JL, Smith ML, Lash TL, Glymour MM, et al. *Association of early-, middle-, and late-life depression with incident dementia in a danish cohort. JAMA Neurol 2023;80:949-958.*
35. Jang YJ, Park J-Y, Kim SY, Jung J-H, Han K, Yoon SC, et al. *Variation in depression's impact on dementia risk by age in adults aged ≥75 years. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 2025;17:e70185.*

 doi:10.20944/preprints202601.0928.v1

36. Twait EL, Wu JH, Kamarioti M, Basten M, van der Flier WM, Gerritsen L, et al. *Association of amyloid-beta with depression or depressive symptoms in older adults without dementia: A systematic review and meta-analysis. Transl Psychiatry 2024;14:25.*
37. Bremmer M, Beekman A, Deeg D, Penninx B, Dik M, Hack C, et al. *Inflammatory markers in late-life depression: Results from a population-based study. Journal of affective disorders 2008;106:249-255.*
38. Troubat R, Barone P, Leman S, Desmidt T, Cressant A, Atanasova B, et al. *Neuroinflammation and depression: A review. European journal of neuroscience 2021;53:151-171.*
39. Jang Y-J, Kim M-J, Lee S-J, Lim S-W, Kim D-K. *Oxidative stress and risk of dementia in older patients with depression: A longitudinal cohort study using plasma biomarkers. Medicina 2025;61:108.*
40. Holmquist S, Nordström A, Nordström P. *The association of depression with subsequent dementia diagnosis: A swedish nationwide cohort study from 1964 to 2016. PLOS Medicine 2020;17:e1003016.*
41. Boparai JK, Clemens M, Jat K. *Late-onset depression and dementia: A systematic review of the temporal relationships and predictive associations. Medicina 2025;61:839.*
42. Wu K-Y, Liu C-Y, Chen C-S, Chen C-H, Hsiao I-T, Hsieh C-J, et al. *Beta-amyloid deposition and cognitive function in patients with major depressive disorder with different subtypes of mild cognitive impairment: 18f-florbetapir (av-45/amyvid) pet study. European journal of nuclear medicine and molecular imaging 2016;43:1067-1076.*
43. Marawi T, Ainsworth NJ, Zhukovsky P, Rashidi-Ranjbar N, Rajji TK, Tartaglia MC, et al. *Brain-cognition relationships in late-life depression: A systematic review of structural magnetic resonance imaging studies. Translational psychiatry 2023;13:284.*
44. Yan Y, Xiang H, Wang M, Wei J, Fan H, Du Y, et al. *Effects of depression and cognitive impairment on increased risks of incident dementia: A prospective study from three elderly cohorts. Translational Psychiatry 2024;14:427.*
45. Ly M, Karim HT, Becker JT, Lopez OL, Anderson SJ, Aizenstein HJ, et al. *Late-life depression and increased risk of dementia: A longitudinal cohort study. Transl Psychiatry 2021;11:147.*
46. Jellinger KA. *Depression in dementia with lewy bodies: A critical update. J Neural Transm (Vienna) 2023;130:1207-1218.*
47. Collins JD, Henley SMD, Suárez-González A. *A systematic review of the prevalence of depression, anxiety, and apathy in frontotemporal dementia, atypical and young-onset alzheimer's disease, and inherited dementia. International Psychogeriatrics 2023;35:457-476.*
48. Sep YCP, Leeuwis AE, Exalto LG, Boomsma JM, Prins ND, Verwer JH, et al. *Neuropsychiatric symptoms as predictor of poor clinical outcome in patients with vascular cognitive impairment. The American Journal of Geriatric Psychiatry 2022;30:813-824.*
49. Botto R, Callai N, Cermelli A, Causarano L, Rainero I. *Anxiety and depression in alzheimer's disease: A systematic review of pathogenetic mechanisms and relation to cognitive decline. Neurol Sci 2022;43:4107-4124.*
50. Fisher DW, Dunn JT, Dong H. *Distinguishing features of depression in dementia from primary psychiatric disease. Discov Ment Health 2024;4:3.*
51. Rapp MA, Schnaider-Beeri M, Wysocki M, Guerrero-Berroa E, Grossman HT, Heinz A, et al. *Cognitive decline in patients with dementia as a function of depression. The American Journal of Geriatric Psychiatry 2011;19:357-363.*
52. Morgese MG, Trabace L. *Monoaminergic system modulation in depression and alzheimer's disease: A new standpoint? Front Pharmacol 2019;10:483.*
53. Chen Y, Dang M, Zhang Z. *Brain mechanisms underlying neuropsychiatric symptoms in alzheimer's disease: A systematic review of symptom-general and -specific lesion patterns. Mol Neurodegener 2021;16:38.*
54. Lanctôt KL, Amatniek J, Ancoli-Israel S, Arnold SE, Ballard C, Cohen-Mansfield J, et al. *Neuropsychiatric signs and symptoms of alzheimer's disease: New treatment paradigms. Alzheimers Dement (N Y) 2017;3:440-449.*
55. dos Santos HM, Bertollo AG, Mingoti MED, Grolli RE, Kreuz KM, Ignácio ZM. *Dementia and depression: Biological connections with amyloid β protein. Basic & Clinical Pharmacology & Toxicology 2024;134:563-573.*
56. van Dalen JW, Caan MWA, van Gool WA, Richard E. *Neuropsychiatric symptoms of cholinergic deficiency occur with degradation of the projections from the nucleus basalis of meynert. Brain Imaging Behav 2017;11:1707-1719.*

 doi:10.20944/preprints202601.0928.v1

57. Banerjee S, Hellier J, Romeo R, Dewey M, Knapp M, Ballard C, et al. *Study of the use of antidepressants for depression in dementia: The hta-sadd trial--a multicentre, randomised, double-blind, placebo-controlled trial of the clinical effectiveness and cost-effectiveness of sertraline and mirtazapine. Health Technol Assess 2013;17:1-166.*
58. He Y, Li H, Huang J, Huang S, Bai Y, Li Y, et al. *Efficacy of antidepressant drugs in the treatment of depression in alzheimer disease patients: A systematic review and network meta-analysis. Journal of Psychopharmacology 2021;35:901-909.*
59. Fitzgerald PJ, Hale PJ, Ghimire A, Watson BO. *The cholinesterase inhibitor donepezil has antidepressant-like properties in the mouse forced swim test. Translational psychiatry 2020;10:255.*
60. Oba H, Kobayashi R, Kawakatsu S, Suzuki K, Otani K, Ihara K. *Non-pharmacological approaches to apathy and depression: A scoping review of mild cognitive impairment and dementia. Front Psychol 2022;13:815913.*
61. Schulkens JE, Deckers K, Jenniskens M, Blokland A, Verhey FR, Sobczak S. *The effects of selective serotonin reuptake inhibitors on memory functioning in older adults: A systematic literature review. J Psychopharmacol 2022;36:578-593.*
62. Koenig AM, Butters MA. *Cognition in late-life depression: Treatment considerations. Current treatment options in psychiatry 2014;1:1-14.*
63. McIntyre R, Harrison J, Loft H, Jacobson W, Olsen C. *The effects of vortioxetine on cognitive function in patients with major depressive disorder: A meta-analysis of three randomized controlled trials. International Journal of Neuropsychopharmacology 2016;19.*
64. Bishop MM, Fixen DR, Linnebur SA, Pearson SM. *Cognitive effects of vortioxetine in older adults: A systematic review. Ther Adv Psychopharmacol 2021;11:20451253211026796.*
65. Orgeta V, Tabet N, Nilforooshan R, Howard R. *Efficacy of antidepressants for depression in alzheimer's disease: Systematic review and meta-analysis. J Alzheimers Dis 2017;58:725-733.*
66. Costello H, Roiser JP, Howard R. *Antidepressant medications in dementia: Evidence and potential mechanisms of treatment-resistance. Psychological Medicine 2023;53:654-667.*
67. Trinh N-H, Hoblyn J, Mohanty S, Yaffe K. *Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in alzheimer disease: A meta-analysis. Jama 2003;289:210-216.*
68. Wang J, Yu J-T, Wang H-F, Meng X-F, Wang C, Tan C-C, et al. *Pharmacological treatment of neuropsychiatric symptoms in alzheimer's disease: A systematic review and meta-analysis. Journal of Neurology, Neurosurgery & Psychiatry 2015;86:101.*
69. Madson KA, Brown S. *Rivastigmine: Dementia with lewy bodies. Hosp Pharm 2016;51:129-131.*
70. Thomas SJ, Grossberg GT. *Memantine: A review of studies into its safety and efficacy in treating alzheimer's disease and other dementias. Clinical interventions in aging 2009;doi.367-377.*
71. Dyck CHv, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. *Lecanemab in early alzheimer's disease. New England Journal of Medicine 2023;388:9-21.*
72. Mintun MA, Lo AC, Evans CD, Wessels AM, Ardayfio PA, Andersen SW, et al. *Donanemab in early alzheimer's disease. New England Journal of Medicine 2021;384:1691-1704.*
73. Pozuelo Moyano B, Zullo L, Rouaud O, Vandel P, von Gunten A, Allali G. *Anti-amyloid drugs for alzheimer's disease: Considering the role of depression. Neurodegener Dis 2025;25:36-49.*
74. Gitlin-Leigh G, Wilson J, Howard R, Howard R, Costello H. *Effects of monoclonal antibody therapies on depression in parkinson's disease and alzheimer's disease: Systematic review and meta-analysis. Journal of Alzheimer's Disease 2025;108:500-508.*
75. Harris GA, Hirschfeld LR, Gonzalez MI, Pritchard MC, May PC. *Revisiting the therapeutic landscape of tauopathies: Assessing the current pipeline and clinical trials. Alzheimer's Research & Therapy 2025;17:129.*
76. Viola LF, Nunes PV, Yassuda MS, Aprahamian I, Santos FS, Santos GD, et al. *Effects of a multidisciplinar cognitive rehabilitation program for patients with mild alzheimer's disease. Clinics 2011;66:1395-1400.*
77. Silva R, Bobrowicz-Campos E, Santos-Costa P, Cardoso R, Bernardo J, Santana E, et al. *Effectiveness of caregiver-provided individual cognitive interventions in older adults with dementia. J Alzheimers Dis Rep 2023;7:433-459.*
78. Chou YH, Ton That V, Sundman M. *A systematic review and meta-analysis of rtms effects on cognitive enhancement in mild cognitive impairment and alzheimer's disease. Neurobiol Aging 2020;86:1-10.*

 doi:10.20944/preprints202601.0928.v1