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Review

Current Diagnostic Challenges in Late-Life Depression and Neurocognitive Disorders

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Abstract: The comorbidity between late-life depression and neurocognitive disorders (NCDs) in the elderly is a subject of increasing interest within the scientific and medical community. We conducted a narrative review of clinical studies focused on depression and NCDs, primarily covering articles published over the past 25 years. Compared with younger adults, depression in the elderly is often characterized by difficulties in expressing sadness, more pronounced somatic, anxiety, and psychotic symptoms, as well as a heightened risk of suicide and cognitive impairment. Depressive symptoms in the elderly may mimic NCDs, act as prodromal signs of future NCDs, or represent a clinical dimension of dementia. NCDs and late-life depression share specific clinical similarities, particularly at illness onset, emphasizing the importance of early differential diagnosis to guide the development of precise, integrated, and tailored interventions.

Keywords: depressive disorders; mental disorders; brain disorders; vascular depression; dementia; frail elderly; neurocognitive disorders; differential diagnosis

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1. Introduction

Late-life depression (LLD) and neurocognitive disorders (NCDs) are common in the elderly and present significant challenges in differential diagnosis and treatment.

Depression that occurs in old age is referred to as LLD when its onset is after the age of 65. LLD is often underestimated and underdiagnosed, with an average expected prevalence of 31.8% [1]. NCDs, on the other hand, are classified in the DSM-5 under the section "Neurocognitive Disorders", alongside delirium, and are subdivided into major and mild NCDs. The term "major NCD" has replaced the former term "dementia." LLD presents with the classic depressive symptoms [2] but is more frequently accompanied by atypical symptoms such as physical pain, sleep disturbances, and cognitive impairment [3–5].

NCDs encompass a variety of syndromes that affect one or more cognitive functions, with a variable impact on functioning, independence, and daily activities [6]. The prevalence of NCDs in the population over 60 years of age is reported to be as high as 6% [7]. A major challenge in differential diagnosis arises from the frequent overlap between NCDs and LLD, although several studies have emphasized the importance of distinguishing between these two disorders, as they may differ significantly in treatment approaches and long-term outcomes [8–10]. The relationship between LLD and NCDs is so close that a

specific term, pseudodementia, was coined by Kiloh in 1961 to describe syndromes that resemble dementia but are caused by other conditions, most commonly depression [11,12]. However, the term pseudodementia has not been formally incorporated into the nosological classification of these disorders, and research on pseudodementia has gradually declined. Nonetheless, the validity of this concept remains a subject of debate [13], indicating that the issue of differential diagnosis in this field is far from being resolved. Depression has been associated with an increased risk of developing mild cognitive impairment (MCI) and NCDs [14]. Furthermore, in individuals with MCI, a high prevalence of neuropsychiatric symptoms, such as psychosis, mood disturbances, apathy, agitation, and other behavioral disturbances, has been reported. These symptoms are also associated with an increased rate of conversion from MCI to Alzheimer's disease (AD) [14].

Despite potential similarities, LLD and NCDs may differ significantly in terms of prognosis, as NCDs are mostly characterized by irreversible and progressive cognitive decline. The relationship between depression and NCDs, however, is complex. Research has shown that depression can serve as a risk factor for the development of both major and mild NCDs, often preceding the onset of cognitive impairment by several years [15]. Additionally, depression can complicate the course of NCDs and negatively impact the quality of life in elderly patients. Some emerging evidence suggests that psychotherapeutic interventions aimed at improving both cognition and depression may enhance the quality of life in elderly patients with major NCDs [16]. When a depressive episode occurs in the elderly, distinguishing between depression and NCDs is crucial, as depression may be an early indication of an underlying neurodegenerative condition. Conversely, the depressive symptoms present in dementia should be carefully assessed and treated to potentially improve the course of the disorder and enhance the patient's quality of life. We summarized the main diagnostic criteria for Major NCDs and MDD in Table 1.

Table 1. Main diagnostic criteria for major NCDs and major depressive disorders [2].

Major Neurocognitive Disorder		**Major Depressive Disorder**	
A. Evidence of Cognitive Decline	Significant cognitive decline in one or more domains (e.g., attention, memory, language, social cognition) based on the following: • Concern from the individual, informant, or clinician about cognitive decline. Documented impairment through standardized neuropsychological testing or another clinical assessment.	A. Core Symptoms	Five or more symptoms over a 2-week period, representing a change from previous functioning, with at least one being (1) depressed mood or (2) loss of interest/pleasure: 1. Depressed mood most of the day, nearly every day (reported by self or observed by others). 2. Diminished interest or pleasure in most activities. 3. Significant weight change or appetite disturbance. 4. Insomnia or hypersomnia. 5. Psychomotor agitation or impairment (observable by others). 6. Fatigue or loss of energy. 7. Feelings of worthlessness or excessive guilt. 8. Diminished ability to think or concentrate, or indecisiveness. 9. Recurrent thoughts of death or suicidal ideation/attempt.

Table 1. *Cont.*

Major Neurocognitive Disorder		**Major Depressive Disorder**	
B. Impact on Daily Independence	Cognitive deficits interfere with independence, requiring help with complex daily activities (e.g., paying bills, managing medications).	B. Functional Impact	Symptoms cause significant distress or impairment in social, occupational, or other important areas of functioning.
C. Absence of Delirium	Cognitive deficits do not occur exclusively during episodes of delirium.	C. Exclusion of Substance or Medical Condition	Symptoms are not due to the physiological effects of a substance or another medical condition.
D. Exclusion of Other Disorders	Cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).	D. Exclusion of Other Mental Disorders	The episode is not better explained by another mental disorder (e.g., schizoaffective disorder, schizophrenia, delusional disorder).
		E. No History of Mania/Hypomania	There has never been a manic or hypomanic episode.

Currently, there is a gap in the literature regarding the interplay between these two conditions. The aim of this narrative review is to provide a comprehensive overview of the recent literature on the differential diagnosis and comorbidity of depression and NCDs, offering essential evidence to guide personalized treatments and preventive strategies.

2. Materials and Methods

We began our research on 9 January 2024, exploring the interconnection between depressive disorders and NCDs in elderly patients. We searched the PubMed database with the title/abstract specification using the terms "depress*", "neurocognitive", and "pseudodementia".

Our narrative review focused on summarizing the main findings from research conducted over the past 25 years. We included original studies and reviews published from January 2000 to April 2024 focusing on differential diagnosis and clinical aspects of depressive disorders and NCDs in elderly patients (>65 years old). We excluded studies on biological markers such as neurochemical alterations [17], genetic polymorphisms of APOE ε4 [18], inflammatory biomarkers [19], and HPA axis dysregulation [18] to maintain a focus on the clinical aspects of LLD and NCDs. Two authors independently screened all retrieved articles, and a third author was involved in the solution of discrepancies between the first two authors' decisions.

3. Results

This review identified a significant clinical overlap between LLD and NCDs in certain symptomatic aspects, particularly during the early stages of both conditions, which could complicate differential diagnosis in some cases [20]. LLD often presents with cognitive symptoms, such as memory deficits, impaired attention, and executive dysfunction, resembling early signs of NCD [21]. The overlap in symptomatology leads to a risk of misdiagnosis, where depressive episodes may be mistaken for neurodegenerative conditions like AD. However, LLD typically shows a positive response to antidepressants, whereas a cognitive decline in NCDs is progressive and irreversible. Moreover, LLD may act as a prodrome or risk factor for future NCDs, with depression preceding cognitive impairment by several years in some patients [22]. Early detection and treatment of depressive symptoms in the elderly could mitigate cognitive decline [22]. Additionally, comorbid depression can exacerbate NCD progression, resulting in poorer outcomes and reduced quality of life [23]. Multimodal treatments, including psychotherapeutic and pharmacologic interventions, have been effective in enhancing mood and cognitive function in patients with LLD and NCDs. These findings underscore the need for an integrated clinical approach that addresses both affective and cognitive symptoms, supporting long-term patient outcomes.

4. Discussion

4.1. Late-Life Depression

Depression is a mental disorder ranked by the World Health Organization (WHO) as the third leading cause of disease burden worldwide. It is characterized by a variable combination of symptoms, ranging from persistent and disabling mood disturbances, low self-esteem, and anhedonia, to neurovegetative symptoms such as changes in appetite and circadian rhythms [24]. Depression affects both the affective and cognitive domains and significantly impairs social, relational, and occupational or academic functioning. Furthermore, it can greatly reduce an individual's quality of life, especially when it co-occurs with other medical conditions [25–29].

In the elderly, the relationship between depression and age-related illnesses is bidirectional, suggesting specific pathophysiological mechanisms unique to this age group. These mechanisms may influence the response to treatment and contribute to the so-called vascular depression syndromes, which are peculiar to the elderly [30].

The diagnostic criteria for a depressive episode in late life are no different from those in adults [2]. However, when depression occurs after the age of 65, it is classified as LLD [31]. The prevalence of depressive disorders increases progressively with age, reaching 46% in adults over 91 years of age [10,32].

The main symptoms of geriatric depression are shown in Box 1 [10,33–35].

Box 1. Main symptomatic dimensions of LLD.

- Depressed mood and psychomotor impairment
- Anxiety and prominently irritable mood
- Coexistence of physical and psychological complications
- Hypochondria
- Sleep disorders
- Suicide attempts and higher suicide risk
- Propensity for developing a recurrent condition

From a clinical perspective, LLD is often described as "depression without sadness" due to the less pronounced affective symptoms, with predominant disturbances in the domains of interest and pleasure, such as anhedonia [36]. Additionally, LLD is characterized by a greater expression of somatic symptoms, anxiety, and psychotic features (e.g., delusions of guilt), as well as pain, sleep disturbances, cognitive impairment, psychomotor impairment, and an elevated suicide risk [5,8,37].

Cognitive symptoms are an area of growing interest in LLD. These include deficits in attention, executive function, memory, and processing speed. Cognitive impairments tend to persist throughout the depressive episode and may continue for up to half of the remission period [38]. In terms of healthcare management, LLD is commonly associated with excessive use of medical resources and increased mortality [20].

LLD etiology is currently understood as the result of a complex interaction of biological, psychological, social, and personality factors, as summarized in Table 2 [3,20,39–47].

Table 2. Key elements involved in LLD and depression-related cognitive decline.

Biological factors	• Cardiovascular disease and risk factors (vascular depression hypothesis) • Impairment of verbal and visual memory, psychomotor impairment, deficits in verbal fluency, working memory • HPA axis dysregulation, reduction in brain/cognitive reserve, hippocampal atrophy (possibly related to HPA axis dysfunction) • Disruption in emotion regulation and cognitive processing brain networks
Psychological and social factors	• Childhood abuse and mistreatment, childhood financial hardship, adverse life events, physical inactivity, loneliness

Table 2. *Cont.*

Personality aspects	• Individual capacity to withstand trauma • Role of our personal beliefs, so important that believing and religious individuals are less likely to develop depression

Depressive symptoms are prevalent among older adults, yet they often remain inadequately treated. This may be due, in part, to underdiagnosis, as symptoms are frequently misattributed to normal age-related changes such as sadness or existential concerns. Additionally, concerns about the potential adverse effects of psychotropic medications in this population may further contribute to the undertreatment of depression in the elderly [48]. However, paying attention to them is crucial, because in the elderly the spheres of affectivity and cognitive function are deeply intertwined. Depressed elderly patients score lower at cognitive performance tasks and show a poorer quality of life, highlighting how this deep correlation could be targeted by appropriate treatments [48,49]. Treating depression can at some level improve the course of NCDs, and an interdisciplinary therapeutic approach [8] should be focused on affectivity considering the beneficial effects on both quality of life and the course of the underlying NCD [50].

Depression has been observed as a potential prodrome for various types of NCDs, often preceding the diagnosis by approximately 4.8 years. It can complicate the course of NCDs and may serve as an early indicator of these conditions [10,51,52]. In particular, the more the cognitive deficits are pronounced, the greater is the risk for developing subsequent dementia [53].

Key clinical elements should be considered when a depressive episode occurs in a patient with an NCD, which affects up to 30% of individuals with these disorders. For instance, in AD, depression often presents in an atypical manner, with mood disturbances being very brief (lasting even only minutes) and recurrent (occurring every few hours). Frank sadness is less prominent than irritability, worry, anxiety, and even acute fear [54]. Additionally, depression associated with AD is characterized by a higher frequency of psychotic symptoms (e.g., delusions, hallucinations) compared with depression linked with other NCDs, with suicidal thoughts being infrequent but highly specific for an ongoing depressive episode [54].

Finally, the key elements to focus on when a depressive episode in the elderly is suspected are cognitive dysfunction/mental state examination, cardiovascular diseases/cardiovascular risk factors, and a history of previous mental disorders. These elements should be prioritized in the assessment. Differential diagnoses to consider during an initial medical examination include mood disorders related to other medical conditions, substance-induced depressive disorders, adjustment disorders, simple sadness, and major NCDs [55,56]. Additionally, the role of commonly prescribed medications (e.g., antihypertensives [57], benzodiazepines, and z-drugs [58]), and lifestyle factors (e.g., current smoking) [57] should also be considered.

Furthermore, certain epidemiological factors related to LLD can aid in differential diagnosis. For instance, substance addiction has been more commonly reported among men with LLD, whereas women with LLD are more likely to have a history of major depressive disorder and be diagnosed with a major NCD. Moreover, male subjects with LLD are associated with a higher risk of suicide, which is linked to higher depression scores, lower quality of life scores, and increased feelings of loneliness. It is important to emphasize that the risk of suicide is higher in the elderly compared with younger individuals, highlighting the need for prompt and effective management of depressive episodes [20]. Finally, accurate characterization of a depressive syndrome in the elderly is essential for implementing targeted treatment, which should account for age and gender-specific considerations [59], especially considering that some pharmacologic treatments may worsen cognitive function [41]. Certain types of cognitive dysfunction, such as executive dysfunction, may be present in patients with a poor response to antidepressants, underlining once again the importance of this dimension. This observation supports

the rationale for considering augmentation strategies with targeted pharmacological and non-pharmacological interventions (e.g., psychotherapies) [60].

4.2. Neurocognitive Disorders

Brain structure and cognitive function are interdependent. Brain weight reaches its peak between the ages of 20 and 40, followed by a gradual decline, with a more pronounced degeneration occurring after age 60 [10]. As this process progresses, certain individuals may exhibit more prominent impairments in cognitive functions [20,51]. Within the spectrum of NCDs, the DSM-5 categorizes major NCDs, mild NCDs, and delirium [61]. Mild NCDs, often referred to as MCIs, are considered a precursor to AD in 14.49% to 87% of cases [62], and these conditions are often regarded as overlapping constructs within different nosological frameworks [61]. The four diagnostic criteria for NCDs focus on the presence of cognitive changes, alterations in daily functioning, and the exclusion of delirium or competing mental disorders. The primary distinction between major and mild NCDs is the degree of impact on quality of life and social functioning, with mild NCDs presenting a modest decline that has a lesser effect on quality of life [2]. However, psychiatric conditions such as schizophrenia, psychosis, dissociative disorders, and mania can mimic dementia, and these should be ruled out during diagnosis [11].

Major Neurocognitive Disorders

Major NCDs are characterized by a significant decline in at least one of the core cognitive domains, which include executive function, complex attention, language, learning, memory, perceptual-motor abilities, or social cognition [63,64], as well as neuropsychiatric symptoms [65]. This cognitive decline reflects a change from the individual's previous cognitive abilities, is persistent, and progresses over time [64]. According to the DSM-5-TR, there are 13 subtypes of major neurocognitive disorders (NCDs), which are categorized in Table 3 based on their etiology [2,66]. It is important to emphasize that multiple aetiologies may coexist in a single patient, collectively resulting in a full neurocognitive disorder [2].

Table 3. Principal Major NCDs grouped for etiology [2,66].

Neurodegenerative Processes	Other Medical Conditions
• Alzheimer's disease • Vascular disease • Frontotemporal lobar degeneration • Dementia with Lewy bodies • Parkinson's disease • Huntington's disease	• Substance-related and/or medication-related • Traumatic brain injury • HIV infection • Prion diseases • Another medical conditions (e.g., multiple sclerosis)

Symptoms of major NCDs may vary depending on the cause and severity of the disease. It is possible to identify some clinical presentations often suggestive of a specific diagnosis (Table 4) [6,67,68].

Table 4. Key clinical features for differential diagnosis of NCDs due to neurodegenerative causes.

Key Clinical Elements	Diagnosis
Progressiveness in memory loss	Alzheimer's disease
Stepwise cognitive decline	Vascular cognitive impairment
Hallucinations, mental status fluctuations, parkinsonism	Dementia with Lewy bodies
Behavioral disinhibition, loss of empathy, hyperphagia/ ;hyperorality, with or without aphasia	Behavioral variant frontotemporal dementia
Psychiatric symptoms, chorea, personality changes	Huntington's disease
Bradykinesia, rigidity, rest tremor, excellent response to levodopa	Parkinson's disease

Diagnosis of major NCDs involves more than just clinical features; it requires a thorough evaluation that includes the patient's medical history, physical and neurological examinations, and cognitive testing. Additionally, brain imaging techniques such as magnetic resonance imaging (MRI), computed tomography (CT), and nuclear medicine neuroimaging may be necessary for a comprehensive assessment [6,69].

Treatment for major NCDs primarily focuses on non-pharmacological approaches, including occupational therapy and targeted activities, which can enhance the quality of life for both patients and caregivers. These methods may also be utilized when pharmacological therapies are ineffective [70]. In cases where non-pharmacological interventions fail, pharmacological treatments can help alleviate the behavioral and psychological symptoms associated with NCDs [70]. However, no current medications can alter the progressive and debilitating course of NCDs, and available drugs must be selected with caution due to their tolerability profiles [70,71]. Among the various forms of major NCDs, AD is the most prevalent, characterized by the accumulation of amyloid plaques, neurofibrillary tangles, and significant cholinergic deficits [72]. To date, the most commonly used drugs approved by the FDA for the treatment of AD are acetylcholinesterase inhibitors (AChEIs), such as donepezil, rivastigmine, and galantamine, and N-methyl-D-aspartate (NMDA) antagonists such as memantine [71]. These treatments do not modify the disease course but may modestly delay the progression of AD [73]. In the past two years, the U.S. FDA has approved two monoclonal antibodies, lecanemab and donanemab, for the treatment of AD. These drugs aim to slow the progression of cognitive decline by targeting and reducing amyloid plaques in the brain. Clinical trials have shown that both lecanemab and donanemab are most effective in early stages of AD, offering a promising new therapeutic option for patients [74–76].

4.3. Differential Diagnosis: Overlapping Symptoms and Clinical Approach

Considering the bidirectional relationship between depression and NCDs, some depressive episodes with prominent cognitive symptoms may be misdiagnosed as dementia and up to one-third of elderly patients initially diagnosed with a psychiatric condition will later reveal NCDs [11]. Currently, these conditions should be pictured as a spectrum of clinical manifestations ranging from depression to cognitive decline [39].

Depression may be the presenting feature of dementia, particularly AD [77]. Defining the underlying cause is crucial to interfere with this vicious cycle that can lead to the worsening of the elderly's conditions. In general, when evaluating a depressive episode in the elderly, detailed cognitive and mental status examinations should be conducted first. In this population, a depressive episode with a prominent dysphoric mood may mimic a manic episode and should be promptly ruled out. Additionally, for depressive episodes that do not meet all the diagnostic criteria, adjustment disorder should be considered, especially in elderly individuals exposed to recent stressful events. A general medical examination is also essential to identify possible underlying medical conditions (e.g., stroke, multiple sclerosis, hyperthyroidism) or pharmacological factors (e.g., medications, substance use disorders) [20].

Cerebrovascular diseases may contribute to the onset and exacerbation of depression in geriatric patients, as explained by the "vascular depression hypothesis" [31,78]. Vascular dementia is typically characterized by a stepwise progression, fluctuating course, and a primary decline in cognitive function with relative preservation of personality [79]. Vascular disease can be present in LLD or represent a worsening factor, often resulting in a reduced response to antidepressants [30]. Non-pharmacological treatment strategies are generally preferred, while tricyclic antidepressants should be used with caution due to their potential for causing arrhythmias, heart failure, myocardial infarction, and anticholinergic effects [80]. Selective serotonin reuptake inhibitors (SSRIs) are better tolerated, though they are metabolized by cytochrome P450, as many cardiac drugs [81]. In such cases, individualized treatment plans based on a drug–drug interactions evaluation, as well as

psychotherapeutic and endocrinological interventions, may represent an effective treatment strategy [82].

In AD, depressive symptoms may vary in intensity and are often less consistent compared with primary depression. Patients with AD may exhibit mood fluctuations, with irritability and anxiety being more prominent than a sustained depressed mood [83–85]. However, when depressive symptoms persist, particularly with features such as guilt, suicidal thoughts, and significant distress, they may indicate a more severe state of depression. These persistent depressive symptoms, especially when accompanied by neurovegetative signs (e.g., changes in sleep or appetite), can align more closely with a diagnosis of LLD rather than typical AD-related mood disturbances [86–89].

From a clinical perspective, patients with NCDs often present with memory disturbances [90–93]. To assess memory impairment, tools such as the Verbal Associative Learning and Memory Test (VALMT) can be useful. The VALMT is a learning and memory test which is useful to identify accelerated long-term forgetting in healthy individuals that may be an early marker for the development of AD [92].

Accurate differential diagnosis also requires particular attention for focus disturbances. Depressed individuals often exhibit abulia, may need additional time to complete tasks, and frequently report disturbances in focus and concentration, along with appearing apathetic [94]. Both LLD and NCD patients present with memory difficulties and distressing phenomena [94,95]. Reliable information from family members is crucial for evaluating these aspects, as some individuals may display a predominantly negative and depressive cognitive style that does not constitute a formal depressive episode [94].

Regarding cognitive functioning, when depressive symptoms in LLD are associated with cognitive impairment, there is a greater reported risk of progression to dementia [96–98]. In general, cognitive impairments have been associated with depression, anxiety, agitation, and apathy, with a stronger relationship between anxiety, agitation, and progressive cognitive decline [96]. In general, patients with LLD tend to show patchy memory loss, provide more subjective reports, exhibit minimal effort to cope with their dysfunction, and frequently respond with "I don't know" to questions about orientation, memory, abstraction, or judgment, even without attempting to answer [13]. Mood symptoms in major NCDs are more likely to be situation-dependent and fluctuate based on time, place, and company, whereas in depression the psychopathological features are generally less responsive to environmental changes [99].

Therapeutic trial plays a crucial role in determining whether the primary underlying cause of a clinical presentation is a mood disorder or an NCD. Typically, LLD responds positively to an adequate trial of antidepressant medication, whereas antidepressants may be ineffective or even exacerbate anxiety and irritability in NCD [10]. In such cases, neurodegenerative etiology should be more strongly suspected. This underscores the potential benefit of combined therapies, such as antipsychotics, in treating depression occurring alongside NCDs. The recent literature emphasizes the use of SSRIs, considering that antidepressants with anticholinergic properties (e.g., tricyclic antidepressants) may worsen cognitive symptoms and exacerbate cognitive decline [100,101]. Sertraline and vortioxetine have been shown to improve episodic memory and processing speed. The most selective SSRIs, such as citalopram and escitalopram, have minimal cognitive benefits, and citalopram has been associated with adverse effects in treatment refractory patients [102–104]. Serotonin–norepinephrine reuptake inhibitors (SNRIs), particularly duloxetine, may positively affect memory symptoms [105].

Findings on the effects of cholinesterase inhibitors and NMDA antagonists on cognitive and depressive symptoms in patients with LLD and MCI are sometimes inconsistent. For instance, the use of donepezil in depression shows variable results concerning mood disorders [106–108], and there is no evidence supporting the use of memantine for treating NCDs with comorbid depressive disorders [109–111]. Despite these findings, one study suggests that the combined use of citalopram and memantine may reduce depressive

symptoms and improve cognitive outcomes in elderly individuals with major depressive disorders and memory issues [112].

Ultimately, recent advancements in blood biomarkers could offer a promising new tool for diagnosing AD in both primary and secondary care. This non-invasive test can differentiate AD from LLD, which often share overlapping symptoms. Its availability is a potential "game changer", allowing for earlier and more accurate diagnoses of neurodegenerative diseases. This breakthrough could significantly improve patient care by guiding more targeted interventions based on precise diagnoses [113].

Limits. This review is limited by the heterogeneity in diagnostic criteria for LLD and NCDs across studies, which may limit the result comparison. However, the comprehensive analysis of studies spanning over the last 25 years can offer a broad perspective on the interplay between LLD and NCDs [9,114].

5. Conclusions

Differential diagnosis between LLD and NCDs presents significant challenges. The relationship between depression and major NCDs in the elderly is an area of growing interest within the scientific and medical communities, though the underlying mechanisms and causal relationships remain unclear. It has been hypothesized in the literature that depression, cognitive impairment, and dementia exist on intersecting continuums, with depression-related cognitive impairment ranging from reversible to irreversible. This dynamic perspective suggests a spectrum from depression without dementia symptoms to dementia without depression. Understanding this correlation is crucial for developing more effective diagnostic, preventive, and therapeutic strategies.

Moreover, evidence supports the long-term impact of depression on cognitive functioning, highlighting the importance of addressing depression promptly in the elderly. Early intervention aimed at supporting cognitive functioning when impairments are detected can significantly improve both physical and mental health outcomes in this population. Symptoms such as depressed mood, irritability, and early deficits in executive function, memory, or attention should not be underestimated. An integrated approach to screening for cognitive impairment (e.g., Mini-Mental State Examination), psychopathological dimensions (psychiatric evaluation), and functional capacity is essential for identifying targets for personalized, non-pharmacological, and pharmacological interventions.

Further research and clinical interest in this area should be encouraged to improve the overall mental and physical health of elderly patients. Considering the deep interconnection between cognitive and emotional dimensions in this population, these aspects should not be treated as exclusive elements. A personalized and multidisciplinary approach, aimed at identifying integrated therapeutic interventions, is strongly recommended.

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References

1. Zenebe, Y.; Akele, B.; W/Selassie, M.; Necho, M. Prevalence and Determinants of Depression among Old Age: A Systematic Review and Meta-Analysis. *Ann. Gen. Psychiatry* **2021**, *20*, 55. [CrossRef] [PubMed]
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*; DSM-5-TR; American Psychiatric Association Publishing: Washington, DC, USA, 2022; ISBN 978-0-89042-575-6.
3. Muniswamy, N.R.; Mukku, S.S.R.; Sivakumar, P.T.; Rajur, S.; Rajeswaran, J.; Mehta, U.M.; Thirthalli, J.; Kumar, K.J.; Varghese, M. Study of Neuropsychological Deficits in Late Onset Depression. *Asian J. Psychiatry* **2020**, *54*, 102435. [CrossRef] [PubMed]
4. Chen, R.-A.; Lee, C.-Y.; Lee, Y.; Hung, C.-F.; Huang, Y.-C.; Lin, P.-Y.; Lee, S.-Y.; Wang, L.-J. Defining Cognitive Profiles of Depressive Patients Using the Brief Assessment of Cognition in Affective Disorders. *PeerJ* **2019**, *7*, e7432. [CrossRef] [PubMed]

5. Marazziti, D.; Consoli, G.; Picchetti, M.; Carlini, M.; Faravelli, L. Cognitive Impairment in Major Depression. *Eur. J. Pharmacol.* **2010**, *626*, 83–86. [CrossRef]
6. Gale, S.A.; Acar, D.; Daffner, K.R. Dementia. *Am. J. Med.* **2018**, *131*, 1161–1169. [CrossRef]
7. Jia, L.; Du, Y.; Chu, L.; Zhang, Z.; Li, F.; Lyu, D.; Li, Y.; Li, Y.; Zhu, M.; Jiao, H.; et al. Prevalence, Risk Factors, and Management of Dementia and Mild Cognitive Impairment in Adults Aged 60 Years or Older in China: A Cross-Sectional Study. *Lancet Public Health* **2020**, *5*, e661–e671. [CrossRef]
8. Altamura, A.C.; Cattaneo, E.; Pozzoli, S.; Bassetti, R. Inquadramento diagnostico e gestione farmacologica della depressione senile Assessment and pharmacological management of elderly depression. *Ital. J. Psychopathol.* **2006**, *12*, 85–92.
9. Beekman, A.T.F.; Deeg, D.J.H.; Van Tilburg, T.; Smit, J.H.; Hooijer, C.; Van Tilburg, W. Major and Minor Depression in Later Life: A Study of Prevalence and Risk Factors. *J. Affect. Disord.* **1995**, *36*, 65–75. [CrossRef]
10. Tetsuka, S. Depression and Dementia in Older Adults: A Neuropsychological Review. *Aging Dis.* **2021**, *12*, 1920. [CrossRef]
11. Mouta, S.; Fonseca Vaz, I.; Pires, M.; Ramos, S.; Figueiredo, D. What Do We Know about Pseudodementia? *Gen. Psychiatry* **2023**, *36*, e100939. [CrossRef]
12. Kiloh, L.G. PSEUDO-DEMENTIA. *Acta Psychiatr. Scand.* **1961**, *37*, 336–351. [CrossRef] [PubMed]
13. Brodaty, H.; Connors, M.H. Pseudodementia, Pseudo-pseudodementia, and Pseudodepression. *Alzheimers Dement. Diagn. Assess. Dis. Monit.* **2020**, *12*, e12027. [CrossRef]
14. Radue, R.; Walaszek, A.; Asthana, S. Neuropsychiatric Symptoms in Dementia. In *Handbook of Clinical Neurology*; Elsevier: Amsterdam, The Netherlands, 2019; Volume 167, pp. 437–454. ISBN 978-0-12-804766-8.
15. Boyle, L.L.; Porsteinsson, A.P.; Cui, X.; King, D.A.; Lyness, J.M. Depression Predicts Cognitive Disorders in Older Primary Care Patients. *J. Clin. Psychiatry* **2010**, *71*, 74–79. [CrossRef] [PubMed]
16. Cammisuli, D.M.; Cipriani, G.; Giusti, E.M.; Castelnuovo, G. Effects of Reminiscence Therapy on Cognition, Depression and Quality of Life in Elderly People with Alzheimer's Disease: A Systematic Review of Randomized Controlled Trials. *J. Clin. Med.* **2022**, *11*, 5752. [CrossRef]
17. Remes, O.; Mendes, J.F.; Templeton, P. Biological, Psychological, and Social Determinants of Depression: A Review of Recent Literature. *Brain Sci.* **2021**, *11*, 1633. [CrossRef] [PubMed]
18. Joseph, C.; Wang, L.; Wu, R.; Manning, K.J.; Steffens, D.C. Structural Brain Changes and Neuroticism in Late-Life Depression: A Neural Basis for Depression Subtypes. *Int. Psychogeriatr.* **2021**, *33*, 515–520. [CrossRef]
19. Matsushima, J.; Kawashima, T.; Nabeta, H.; Imamura, Y.; Watanabe, I.; Mizoguchi, Y.; Kojima, N.; Yamada, S.; Monji, A. Association of inflammatory biomarkers with depressive symptoms and cognitive decline in a community-dwelling healthy older sample: A 3-year follow-up study. *J. Affect. Disord.* **2015**, *173*, 9–14. [CrossRef]
20. Sekhon, S.; Patel, J.; Sapra, A. Late-Life Depression. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2024.
21. Steffens, D.C.; Fahed, M.; Manning, K.J.; Wang, L. The Neurobiology of Apathy in Depression and Neurocognitive Impairment in Older Adults: A Review of Epidemiological, Clinical, Neuropsychological and Biological Research. *Transl. Psychiatry* **2022**, *12*, 525. [CrossRef]
22. Oberlin, L.E.; Respino, M.; Victoria, L.; Abreu, L.; Hoptman, M.J.; Alexopoulos, G.S.; Gunning, F.M. Late-Life Depression Accentuates Cognitive Weaknesses in Older Adults with Small Vessel Disease. *Neuropsychopharmacology* **2022**, *47*, 580–587. [CrossRef]
23. Kwak, S.; Kim, H.; Oh, D.J.; Jeon, Y.-J.; Oh, D.Y.; Park, S.M.; Lee, J.-Y. Clinical and Biological Subtypes of Late-Life Depression. *J. Affect. Disord.* **2022**, *312*, 46–53. [CrossRef]
24. Malhi, G.S.; Mann, J.J. Depression. *Lancet* **2018**, *392*, 2299–2312. [CrossRef] [PubMed]
25. Aarsland, D.; Påhlhagen, S.; Ballard, C.G.; Ehrt, U.; Svenningsson, P. Depression in Parkinson Disease—Epidemiology, Mechanisms and Management. *Nat. Rev. Neurol.* **2012**, *8*, 35–47. [CrossRef] [PubMed]
26. Kochar, B.; Barnes, E.L.; Long, M.D.; Cushing, K.C.; Galanko, J.; Martin, C.F.; Raffals, L.E.; Sandler, R.S. Depression Is Associated With More Aggressive Inflammatory Bowel Disease. *Am. J. Gastroenterol.* **2018**, *113*, 80–85. [CrossRef] [PubMed]
27. Moussavi, S.; Chatterji, S.; Verdes, E.; Tandon, A.; Patel, V.; Ustun, B. Depression, Chronic Diseases, and Decrements in Health: Results from the World Health Surveys. *Lancet* **2007**, *370*, 851–858. [CrossRef]
28. Fraser, I.S.; Shearman, R.P. Gynaecological Importance of Unusual Pituitary Tumours. *Aust. N. Z. J. Obstet. Gynaecol.* **1985**, *25*, 44–49. [CrossRef]
29. Xu, Y.; Zheng, R.; Guo, H.; Wei, Y.; Wen, B.; Dai, S.; Han, S.; Cheng, J.; Zhang, Y. Structural and Functional Deficits and Couplings in Severe and Moderate OCD. *J. Psychiatr. Res.* **2023**, *160*, 240–247. [CrossRef]
30. Alexopoulos, G.S. Mechanisms and Treatment of Late-Life Depression. *Transl. Psychiatry* **2019**, *9*, 188. [CrossRef]
31. Alexopoulos, G.S. Depression in the Elderly. *Lancet* **2005**, *365*, 1961–1970. [CrossRef]
32. Van't Veer-Tazelaar, P.J.; van Marwijk, H.W.; Jansen, A.P.; Rijmen, F.; Kostense, P.J.; van Oppen, P.; van Hout, H.P.; Stalman, W.A.; Beekman, A.T. Depression in Old Age (75+), the PIKO Study. *J. Affect. Disord.* **2008**, *106*, 295–299. [CrossRef]
33. Fiske, A.; Wetherell, J.L.; Gatz, M. Depression in Older Adults. *Annu. Rev. Clin. Psychol.* **2009**, *5*, 363–389. [CrossRef]
34. Mitchell, A.J.; Subramaniam, H. Prognosis of Depression in Old Age Compared to Middle Age: A Systematic Review of Comparative Studies. *Am. J. Psychiatry* **2005**, *162*, 1588–1601. [CrossRef] [PubMed]
35. Sözeri-Varma, G. Depression in the Elderly: Clinical Features and Risk Factors. *Aging Dis.* **2012**, *3*, 465–471. [PubMed]

36. Gallo, J.J.; Rabins, P.V. Depression without Sadness: Alternative Presentations of Depression in Late Life. *Am. Fam. Physician* **1999**, *60*, 820–826. [PubMed]
37. Enache, D.; Winblad, B.; Aarsland, D. Depression in Dementia: Epidemiology, Mechanisms, and Treatment. *Curr. Opin. Psychiatry* **2011**, *24*, 461–472. [CrossRef]
38. Perini, G.; Cotta Ramusino, M.; Sinforiani, E.; Bernini, S.; Petrachi, R.; Costa, A. Cognitive Impairment in Depression: Recent Advances and Novel Treatments. *Neuropsychiatr. Dis. Treat.* **2019**, *15*, 1249–1258. [CrossRef]
39. Kobayashi, T.; Kato, S. Depression–Dementia Medius: Between Depression and the Manifestation of Dementia Symptoms. *Psychogeriatrics* **2011**, *11*, 177–182. [CrossRef]
40. Butters, M.A.; Young, J.B.; Lopez, O.; Aizenstein, H.J.; Mulsant, B.H.; Reynolds Iii, C.F.; DeKosky, S.T.; Becker, J.T. Pathways Linking Late-Life Depression to Persistent Cognitive Impairment and Dementia. *Dialogues Clin. Neurosci.* **2008**, *10*, 345–357. [CrossRef]
41. Korten, N.C.M.; Penninx, B.W.J.H.; Kok, R.M.; Stek, M.L.; Oude Voshaar, R.C.; Deeg, D.J.H.; Comijs, H.C. Heterogeneity of Late-Life Depression: Relationship with Cognitive Functioning. *Int. Psychogeriatr.* **2014**, *26*, 953–963. [CrossRef]
42. Kim, Y.-K.; Han, K.-M. Neural Substrates for Late-Life Depression: A Selective Review of Structural Neuroimaging Studies. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2021**, *104*, 110010. [CrossRef]
43. Hegeman, A.; Schutter, N.; Comijs, H.; Holwerda, T.; Dekker, J.; Stek, M.; Van Der Mast, R. Loneliness and Cardiovascular Disease and the Role of Late-life Depression. *Int. J. Geriatr. Psychiatry* **2018**, *33*, e65–e72. [CrossRef]
44. Domènech-Abella, J.; Mundó, J.; Miret, M.; Ayuso-Mateos, J.L.; Sánchez-Niubò, A.; Abduljabbar, A.S.; Haro, J.M.; Olaya, B. From Childhood Financial Hardship to Late-Life Depression: Socioeconomic Pathways. *Aging Ment. Health* **2021**, *25*, 86–93. [CrossRef] [PubMed]
45. Naderzadeh, S.; Khoran, Z.; Khanjani, M.; Wiesmann, U. Childhood Maltreatment, Late-Life Depression, and Sense of Coherence: A Structural Equation Modeling. *Aging Ment. Health* **2023**, *27*, 965–972. [CrossRef]
46. Bonelli, R.; Dew, R.E.; Koenig, H.G.; Rosmarin, D.H.; Vasegh, S. Religious and Spiritual Factors in Depression: Review and Integration of the Research. *Depress. Res. Treat.* **2012**, *2012*, 962860. [CrossRef] [PubMed]
47. McCullough, M.E.; Larson, D.B. Religion and Depression: A Review of the Literature. *Twin Res.* **1999**, *2*, 126–136. [CrossRef]
48. Voros, V.; Fekete, S.; Tenyi, T.; Rihmer, Z.; Szili, I.; Osvath, P. Untreated Depressive Symptoms Significantly Worsen Quality of Life in Old Age and May Lead to the Misdiagnosis of Dementia: A Cross-Sectional Study. *Ann. Gen. Psychiatry* **2020**, *19*, 52. [CrossRef] [PubMed]
49. Lin, J.; Figuerado, Y.; Montgomery, A.; Lee, J.; Cannis, M.; Norton, V.C.; Calvo, R.; Sikand, H. Efficacy of Ketamine for Initial Control of Acute Agitation in the Emergency Department: A Randomized Study. *Am. J. Emerg. Med.* **2021**, *44*, 306–311. [CrossRef] [PubMed]
50. Livingston, G.; Sommerlad, A.; Orgeta, V.; Costafreda, S.G.; Huntley, J.; Ames, D.; Ballard, C.; Banerjee, S.; Burns, A.; Cohen-Mansfield, J.; et al. Dementia Prevention, Intervention, and Care. *Lancet Lond. Engl.* **2017**, *390*, 2673–2734. [CrossRef]
51. Bennett, S.; Thomas, A.J. Depression and Dementia: Cause, Consequence or Coincidence? *Maturitas* **2014**, *79*, 184–190. [CrossRef]
52. Ganguli, M.; Du, Y.; Dodge, H.H.; Ratcliff, G.G.; Chang, C.-C.H. Depressive Symptoms and Cognitive Decline in Late Life: A Prospective Epidemiological Study. *Arch. Gen. Psychiatry* **2006**, *63*, 153. [CrossRef]
53. AgeCoDe Study Group; Heser, K.; Bleckwenn, M.; Wiese, B.; Mamone, S.; Riedel-Heller, S.G.; Stein, J.; Lühmann, D.; Posselt, T.; Fuchs, A.; et al. Late-Life Depressive Symptoms and Lifetime History of Major Depression: Cognitive Deficits Are Largely Due to Incipient Dementia Rather than Depression. *J. Alzheimers Dis.* **2016**, *54*, 185–199. [CrossRef]
54. Lyketsos, C.G.; Lee, H.B. Diagnosis and Treatment of Depression in Alzheimer's Disease. *Dement. Geriatr. Cogn. Disord.* **2004**, *17*, 55–64. [CrossRef] [PubMed]
55. Rabins, P.V. Reversible Dementia and the Misdiagnosis of Dementia: A Review. *Psychiatr. Serv.* **1983**, *34*, 830–835. [CrossRef] [PubMed]
56. Wagner, G.S.; McClintock, S.M.; Rosenquist, P.B.; McCall, W.V.; Kahn, D.A. Major Depressive Disorder with Psychotic Features May Lead to Misdiagnosis of Dementia: A Case Report and Review of the Literature. *J. Psychiatr. Pract.* **2011**, *17*, 432–438. [CrossRef] [PubMed]
57. Luijendijk, H.J.; Stricker, B.H.; Hofman, A.; Witteman, J.C.M.; Tiemeier, H. Cerebrovascular Risk Factors and Incident Depression in Community-dwelling Elderly. *Acta Psychiatr. Scand.* **2008**, *118*, 139–148. [CrossRef]
58. Bourgeois, J.; Elseviers, M.M.; Van Bortel, L.; Petrovic, M.; Vander Stichele, R.H. The Impact of Chronic Benzodiazepine Use on Cognitive Evolution in Nursing Home Residents. *Hum. Psychopharmacol. Clin. Exp.* **2015**, *30*, 85–93. [CrossRef]
59. Greil, W.; De Bardeci, M.; Seifert, J.; Bernegger, X.; Cattapan, K.; Stassen, H.; Wagner, A.L.; Sieberer, M.; Grohmann, R.; Toto, S. Treatment of Depression: Are Psychotropic Drugs Appropriately Dosed in Women and in the Elderly? Dosages of Psychotropic Drugs by Sex and Age in Routine Clinical Practice. *Hum. Psychopharmacol. Clin. Exp.* **2022**, *37*, e2809. [CrossRef]
60. Pimontel, M.A.; Rindskopf, D.; Rutherford, B.R.; Brown, P.J.; Roose, S.P.; Sneed, J.R. A Meta-Analysis of Executive Dysfunction and Antidepressant Treatment Response in Late-Life Depression. *Am. J. Geriatr. Psychiatry* **2016**, *24*, 31–41. [CrossRef]
61. Stokin, G.B.; Krell-Roesch, J.; Petersen, R.C.; Geda, Y.E. Mild Neurocognitive Disorder: An Old Wine in a New Bottle. *Harv. Rev. Psychiatry* **2015**, *23*, 368–376. [CrossRef]

62. Chen, Y.; Qian, X.; Zhang, Y.; Su, W.; Huang, Y.; Wang, X.; Chen, X.; Zhao, E.; Han, L.; Ma, Y. Prediction Models for Conversion From Mild Cognitive Impairment to Alzheimer's Disease: A Systematic Review and Meta-Analysis. *Front. Aging Neurosci.* **2022**, *14*, 840386. [CrossRef]
63. Ismail, Z.; Smith, E.E.; Geda, Y.; Sultzer, D.; Brodaty, H.; Smith, G.; Agüera-Ortiz, L.; Sweet, R.; Miller, D.; Lyketsos, C.G.; et al. Neuropsychiatric Symptoms as Early Manifestations of Emergent Dementia: Provisional Diagnostic Criteria for Mild Behavioral Impairment. *Alzheimers Dement.* **2016**, *12*, 195–202. [CrossRef]
64. Emmady, P.D.; Schoo, C.; Tadi, P. Major Neurocognitive Disorder (Dementia). In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2024.
65. Wolak, J.P. Chronic Brain Failure. *Emerg. Med. Clin. N. Am.* **2021**, *39*, 307–322. [CrossRef] [PubMed]
66. Sachdev, P.S.; Blacker, D.; Blazer, D.G.; Ganguli, M.; Jeste, D.V.; Paulsen, J.S.; Petersen, R.C. Classifying neurocognitive disorders: The DSM-5 approach. *Nat. Rev. Neurol.* **2014**, *10*, 634–642. [CrossRef] [PubMed]
67. Pyrgelis, E.-S.; Velonakis, G.; Papageorgiou, S.G.; Stefanis, L.; Kapaki, E.; Constantinides, V.C. Imaging Markers for Normal Pressure Hydrocephalus: An Overview. *Biomedicines* **2023**, *11*, 1265. [CrossRef] [PubMed]
68. Kalia, L.V.; Lang, A.E. Parkinson's Disease. *Lancet* **2015**, *386*, 896–912. [CrossRef]
69. Burkett, B.J.; Babcock, J.C.; Lowe, V.J.; Graff-Radford, J.; Subramaniam, R.M.; Johnson, D.R. PET Imaging of Dementia: Update 2022. *Clin. Nucl. Med.* **2022**, *47*, 763–773. [CrossRef]
70. Wang, F.; Feng, T.-Y.; Yang, S.; Preter, M.; Zhou, J.-N.; Wang, X.-P. Drug Therapy for Behavioral and Psychological Symptoms of Dementia. *Curr. Neuropharmacol.* **2016**, *14*, 307–313. [CrossRef]
71. Jones, K.C. Update on Major Neurocognitive Disorders. *Focus* **2021**, *19*, 271–281. [CrossRef]
72. Hugo, J.; Ganguli, M. Dementia and Cognitive Impairment. *Clin. Geriatr. Med.* **2014**, *30*, 421–442. [CrossRef]
73. Jones, K.C.; Han, J.Y.; Shah, A.A. Cognitive Continuum: Areas of Controversy with Cognitive Enhancers. *Psychiatr. Ann.* **2016**, *46*, 110–117. [CrossRef]
74. Ameen, T.B.; Kashif, S.N.; Abbas, S.M.I.; Babar, K.; Ali, S.M.S.; Raheem, A. Unraveling Alzheimer's: The Promise of Aducanumab, Lecanemab, and Donanemab. *Egypt. J. Neurol. Psychiatry Neurosurg.* **2024**, *60*, 72. [CrossRef]
75. Jin, M.; Noble, J.M. What's in It for Me? Contextualizing the Potential Clinical Impacts of Lecanemab, Donanemab, and Other Anti-β-Amyloid Monoclonal Antibodies in Early Alzheimer's Disease. *Eneuro* **2024**, *11*, ENEURO.0088-24.2024. [CrossRef]
76. van Dyck, C.H.; Swanson, C.J.; Aisen, P.; Bateman, R.J.; Chen, C.; Gee, M.; Kanekiyo, M.; Li, D.; Reyderman, L.; Cohen, S.; et al. Lecanemab in Early Alzheimer's Disease. *N. Engl. J. Med.* **2023**, *388*, 9–21. [CrossRef] [PubMed]
77. Moretti, M.C.; Bonfitto, I.; Nieddu, L.; Leccisotti, I.; Dimalta, S.; Moniello, G.; Lozupone, M.; Bellomo, A.; Panza, F.; Avolio, C.; et al. Association of Loneliness with Functional and Cognitive Status in Minor and Major Neurocognitive Disorders. *Life* **2024**, *14*, 1216. [CrossRef] [PubMed]
78. Muliyala, K.; Varghese, M. The Complex Relationship between Depression and Dementia. *Ann. Indian Acad. Neurol.* **2010**, *13*, 69. [CrossRef]
79. Tohgi, H. Vascular Dementia. *Tohoku J. Exp. Med.* **1990**, *161*, 39–47. [CrossRef]
80. Cohen, H.W.; Gibson, G.; Alderman, M.H. Excess Risk of Myocardial Infarction in Patients Treated with Antidepressant Medications: Association with Use of Tricyclic agents. *Am. J. Med.* **2000**, *108*, 2–8. [CrossRef]
81. Sbolli, M.; Fiuzat, M.; Cani, D.; O'Connor, C.M. Depression and Heart Failure: The Lonely Comorbidity. *Eur. J. Heart Fail.* **2020**, *22*, 2007–2017. [CrossRef]
82. Linnemann, C.; Lang, U.E. Pathways Connecting Late-Life Depression and Dementia. *Front. Pharmacol.* **2020**, *11*, 279. [CrossRef]
83. Ballard, C.; Day, S.; Sharp, S.; Wing, G.; Sorensen, S. Neuropsychiatric Symptoms in Dementia: Importance and Treatment Considerations. *Int. Rev. Psychiatry Abingdon Engl.* **2008**, *20*, 396–404. [CrossRef]
84. Geda, Y.E.; Roberts, R.O.; Mielke, M.M.; Knopman, D.S.; Christianson, T.J.H.; Pankratz, V.S.; Boeve, B.F.; Sochor, O.; Tangalos, E.G.; Petersen, R.C.; et al. Baseline Neuropsychiatric Symptoms and the Risk of Incident Mild Cognitive Impairment: A Population-Based Study. *Am. J. Psychiatry* **2014**, *171*, 572–581. [CrossRef]
85. Ismail, Z.; Gatchel, J.; Bateman, D.R.; Barcelos-Ferreira, R.; Cantillon, M.; Jaeger, J.; Donovan, N.J.; Mortby, M.E. Affective and Emotional Dysregulation as Pre-Dementia Risk Markers: Exploring the Mild Behavioral Impairment Symptoms of Depression, Anxiety, Irritability, and Euphoria. *Int. Psychogeriatr.* **2018**, *30*, 185–196. [CrossRef] [PubMed]
86. Simpson, S. Neurological Correlates of Depressive Symptoms in Alzheimer's Disease and Vascular Dementia. *J. Affect. Disord.* **1999**, *53*, 129–136. [CrossRef] [PubMed]
87. Mulsant, B.H.; Ganguli, M. Epidemiology and Diagnosis of Depression in Late Life. *J. Clin. Psychiatry* **1999**, *60* (Suppl. S20), 9–15. [PubMed]
88. Invernizzi, S.; Simoes Loureiro, I.; Kandana Arachchige, K.G.; Lefebvre, L. Late-Life Depression, Cognitive Impairment, and Relationship with Alzheimer's Disease. *Dement. Geriatr. Cogn. Disord.* **2021**, *50*, 414–424. [CrossRef] [PubMed]
89. Harwood, D.G.; Sultzer, D.L. "Life Is Not Worth Living": Hopelessness in Alzheimer's Disease. *J. Geriatr. Psychiatry Neurol.* **2002**, *15*, 38–43. [CrossRef]
90. Christensen, H.; Kopelman, M.D.; Stanhope, N.; Lorentz, L.; Owen, P. Rates of Forgetting in Alzheimer Dementia. *Neuropsychologia* **1998**, *36*, 547–557. [CrossRef]
91. Kopelman, M.D. Rates of Forgetting in Alzheimer-Type Dementia and Korsakoff's Syndrome. *Neuropsychologia* **1985**, *23*, 623–638. [CrossRef]

92. McGibbon, T.; Jansari, A.; Demirjian, J.; Nemes, A.; Opre, A. Accelerated Forgetting in Healthy Older Samples: Implications for Methodology, Future Ageing Studies, and Early Identification of Risk of Dementia. *Q. J. Exp. Psychol.* **2023**, *76*, 1347–1367. [CrossRef]
93. Huppert, F.A.; Kopelman, M.D. Rates of Forgetting in Normal Ageing: A Comparison with Dementia. *Neuropsychologia* **1989**, *27*, 849–860. [CrossRef]
94. Kitching, D. Depression in Dementia. *Aust. Prescr.* **2015**, *38*, 209–211. [CrossRef]
95. Winter, Y.; Korchounov, A.; Zhukova, T.V.; Bertschi, N.E. Depression in Elderly Patients with Alzheimer Dementia or Vascular Dementia and Its Infl Uence on Their Quality of Life. *J. Neurosci. Rural Pract.* **2011**, *2*, 27–32. [CrossRef] [PubMed]
96. Brodaty, H.; Heffernan, M.; Draper, B.; Reppermund, S.; Kochan, N.A.; Slavin, M.J.; Trollor, J.N.; Sachdev, P.S. Neuropsychiatric symptoms in older people with and without cognitive impairment. *J. Alzheimers Dis.* **2012**, *31*, 411–420. [CrossRef] [PubMed]
97. Mukku, S.S.R.; Dahale, A.B.; Muniswamy, N.R.; Muliyala, K.P.; Sivakumar, P.T.; Varghese, M. Geriatric Depression and Cognitive Impairment—An Update. *Indian J. Psychol. Med.* **2021**, *43*, 286–293. [CrossRef] [PubMed]
98. Sekhon, S.; Marwaha, R. Depressive Cognitive Disorders. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2024.
99. Lyketsos, C.G.; Steinberg, M.; Tschanz, J.T.; Norton, M.C.; Steffens, D.C.; Breitner, J.C. Mental and Behavioral Disturbances in Dementia: Findings from the Cache County Study on Memory in Aging. *Am. J. Psychiatry* **2000**, *157*, 708–714. [CrossRef] [PubMed]
100. Khawam, E.A.; Laurencic, G.; Malone, D.A. Side Effects of Antidepressants: An Overview. *Cleve. Clin. J. Med.* **2006**, *73*, 351–353. [CrossRef]
101. Gray, S.L.; Anderson, M.L.; Dublin, S.; Hanlon, J.T.; Hubbard, R.; Walker, R.; Yu, O.; Crane, P.K.; Larson, E.B. Cumulative Use of Strong Anticholinergics and Incident Dementia: A Prospective Cohort Study. *JAMA Intern. Med.* **2015**, *175*, 401. [CrossRef]
102. Bartels, C.; Wagner, M.; Wolfsgruber, S.; Ehrenreich, H.; Schneider, A.; Alzheimer's Disease Neuroimaging Initiative. Impact of SSRI Therapy on Risk of Conversion From Mild Cognitive Impairment to Alzheimer's Dementia in Individuals With Previous Depression. *Am. J. Psychiatry* **2018**, *175*, 232–241. [CrossRef]
103. Xue, L.; Bocharova, M.; Young, A.H.; Aarsland, D. Cognitive improvement in late-life depression treated with vortioxetine and duloxetine in an eight-week randomized controlled trial: The role of age at first onset and change in depressive symptoms. *J. Affect. Disord.* **2024**, *361*, 74–81. [CrossRef]
104. Nelson, J.C.; Gandelman, J.A.; Mackin, R.S. A Systematic Review of Antidepressants and Psychotherapy Commonly Used in the Treatment of Late Life Depression for Their Effects on Cognition. *Am. J. Geriatr. Psychiatry* **2024**. [CrossRef]
105. Raskin, J.; Wiltse, C.G.; Siegal, A.; Sheikh, J.; Xu, J.; Dinkel, J.J.; Rotz, B.T.; Mohs, R.C. Efficacy of Duloxetine on Cognition, Depression, and Pain in Elderly Patients With Major Depressive Disorder: An 8-Week, Double-Blind, Placebo-Controlled Trial. *Am. J. Psychiatry* **2007**, *164*, 900–909. [CrossRef]
106. Pelton, G.H.; Harper, O.L.; Tabert, M.H.; Sackeim, H.A.; Scarmeas, N.; Roose, S.P.; Devanand, D.P. Randomized Double-blind Placebo-controlled Donepezil Augmentation in Antidepressant-treated Elderly Patients with Depression and Cognitive Impairment: A Pilot Study. *Int. J. Geriatr. Psychiatry* **2008**, *23*, 670–676. [CrossRef] [PubMed]
107. Reynolds, C.F.; Butters, M.A.; Lopez, O.; Pollock, B.G.; Dew, M.A.; Mulsant, B.H.; Lenze, E.J.; Holm, M.; Rogers, J.C.; Mazumdar, S.; et al. Maintenance Treatment of Depression in Old Age: A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Efficacy and Safety of Donepezil Combined With Antidepressant Pharmacotherapy. *Arch. Gen. Psychiatry* **2011**, *68*, 51. [CrossRef] [PubMed]
108. Holtzheimer, P.E.; Meeks, T.W.; Kelley, M.E.; Mufti, M.; Young, R.; McWhorter, K.; Vito, N.; Chismar, R.; Quinn, S.; Dey, S.; et al. A Double Blind, Placebo-controlled Pilot Study of Galantamine Augmentation of Antidepressant Treatment in Older Adults with Major Depression. *Int. J. Geriatr. Psychiatry* **2008**, *23*, 625–631. [CrossRef] [PubMed]
109. Lenze, E.J.; Skidmore, E.R.; Begley, A.E.; Newcomer, J.W.; Butters, M.A.; Whyte, E.M. Memantine for Late-life Depression and Apathy after a Disabling Medical Event: A 12-week, Double-blind Placebo-controlled Pilot Study. *Int. J. Geriatr. Psychiatry* **2012**, *27*, 974–980. [CrossRef] [PubMed]
110. Smith, M.R.; Lee, C.; Crowley, S.J.; Fogg, L.F.; Eastman, C.I. Morning Melatonin Has Limited Benefit as a Soporific For Daytime Sleep After Night Work. *Chronobiol. Int.* **2005**, *22*, 873–888. [CrossRef]
111. Zarate, C.A.; Singh, J.B.; Quiroz, J.A.; De Jesus, G.; Denicoff, K.K.; Luckenbaugh, D.A.; Manji, H.K.; Charney, D.S. A Double-Blind, Placebo-Controlled Study of Memantine in the Treatment of Major Depression. *Am. J. Psychiatry* **2006**, *163*, 153–155. [CrossRef]
112. Lavretsky, H.; Laird, K.T.; Krause-Sorio, B.; Heimberg, B.F.; Yeargin, J.; Grzenda, A.; Wu, P.; Thana-Udom, K.; Ercoli, L.M.; Siddarth, P. A Randomized Double-Blind Placebo-Controlled Trial of Combined Escitalopram and Memantine for Older Adults With Major Depression and Subjective Memory Complaints. *Am. J. Geriatr. Psychiatry* **2020**, *28*, 178–190. [CrossRef]
113. Palmqvist, S.; Tideman, P.; Mattsson-Carlgren, N.; Schindler, S.E.; Smith, R.; Ossenkoppele, R.; Calling, S.; West, T.; Monane, M.; Verghese, P.B.; et al. Blood Biomarkers to Detect Alzheimer Disease in Primary Care and Secondary Care. *JAMA* **2024**, *332*, 1245–1257. [CrossRef]
114. Zhao, Y.; Wu, X.; Tang, M.; Shi, L.; Gong, S.; Mei, X.; Zhao, Z.; He, J.; Huang, L.; Cui, W. Late-Life Depression: Epidemiology, Phenotype, Pathogenesis and Treatment before and during the COVID-19 Pandemic. *Front. Psychiatry* **2023**, *14*, 1017203. [CrossRef]