



REVIEW

Diagnosing and Treating Depression in Patients with Alzheimer's Disease

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ABSTRACT

Although cognitive and functional impairment are the hallmark features of Alzheimer's disease (AD), neuropsychiatric symptoms associated with AD account for increased rates of disability and profoundly impact the quality of life of both patients and their caregivers. This narrative review of current evidence provides practical guidance in diagnosing and managing depression in patients with AD using pharmacological and nonpharmacological interventions. After apathy, depression is the second most common neuropsychiatric symptom in AD. Diagnosing late-life depression (LLD), particularly in those affected by AD, is complicated because older patients may not meet the criteria for a major depressive disorder. Clinically, late-life depression and dementia can be indistinguishable. Although these two entities are now

thought to be related, the pathologic mechanisms remain unclear. Evidence suggests that LLD may be a prodromal symptom of neurodegenerative disease. The various geropsychiatric measures currently used to diagnose, rate the severity of, and monitor the progress of treatment for depression are imperfect. Neuroimaging represents a promising avenue toward understanding the complex pathophysiologic relationships between dementia and LLD, and will support the pursuit of biomarker-driven diagnosis and treatment. Nonpharmacologic interventions to relieve depression in persons with cognitive impairment and dementia include emotion-oriented therapies, behavioral and cognitive-behavioral modification programs, and structured activity programs. Sensory-stimulation therapies and multisensory approaches show some promise for successfully treating depression in patients with dementia, but further rigorous research is needed to establish their validity. Clinical consensus and research appear to support selective serotonin reuptake inhibitors as a first choice for the pharmacological treatment of depression in patients with dementia. However, initial support for these therapies remains variable, and further investigation is needed. Extra care is required in prescribing to this population because of the generally high level of medical and psychiatric comorbidity and the potential difficulty in assessing the cognitively impaired patient's response.

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Abbreviations

AD	Alzheimer's disease
CBT	Cognitive behavioral therapy
CSDD	Cornell Scale for Depression in Dementia
CSF	Cerebrospinal fluid
CT	Computed tomography
DMN	Default mode network
DSM	Diagnostic and Statistical Manual of Mental Disorders
FDG	Fluorodeoxyglucose
GDS	Geriatric Depression Scale
LLD	Late-life depression
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
NACC	National Alzheimer's Coordinating Center
NIMH-dAD	National Institute of Mental Health diagnostic criteria for depression in AD
NPS	Neuropsychiatric symptom
NREM	Non-rapid eye movement
PET	Positron emission tomography
REM	Rapid eye movement
SCN	Suprachiasmatic nucleus
SPECT	Single-photon emission computerized tomography
SSRI	Selective serotonin reuptake inhibitor
SWS	Slow-wave sleep
WML	White matter lesion

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia. This disorder currently affects an estimated 5.6 million Americans; a figure that is expected to increase to nearly 16 million by 2050 [1]. Although the hallmark

cognitive and functional impairment features of the disorder are most often emphasized, the neuropsychiatric symptoms associated with the disease account for increased rates of disability and profoundly decrease the quality of life of both patients and their caregivers.

Neuropsychiatric symptoms (NPS) affect nearly all patients with AD (97%) [2]. These symptoms are associated with impairment in activities of daily living [3], poor quality of life [4], earlier institutionalization [5], accelerated disease progression, increased mortality [6], caregiver stress [7], and increased costs of care [8].

Apathy and depression are the most common forms of NPS in Alzheimer's disease. Although many geropsychiatric measures are available to diagnose, rate the severity of, and monitor the progress of treatment for depression, these measures remain imperfect. Additionally, numerous pharmacological and nonpharmacological treatments are used for depression in patients with AD. The purpose of this narrative review is to provide practical guidance in diagnosing and managing depression in patients with AD using both pharmacological and nonpharmacological interventions. The data for the narrative were compiled from the Medline and Pubmed databases using the terms "depression," "Alzheimer's disease," "dementia," "neuropsychiatric symptoms," and "behavioral and psychological symptoms in dementia." The data were collected from 2/1/2019 to 5/15/2019.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

DEPRESSION IN PATIENTS WITH ALZHEIMER'S DISEASE

Depression is second to apathy as the most common NPS in patients with AD. Depression is common in mild cognitive impairment (MCI)

stages. A meta-analysis of 57 studies found a prevalence of 32% in patients with MCI, with depressive symptoms being more prevalent in clinical (40%) versus community-based (25%) samples [9].

Depression is also a predictor of progression from normal cognition to MCI and from MCI to dementia. One study showed that 16% of patients in population-based AD studies and 44% of patients in hospital-based studies suffer from depression [10]. There is evidence that depression may be an early manifestation of AD [11]. The presence of MCI in depression has been shown to predict later development of AD [11].

Patients with AD and depression appear to have more severe neuropathology (tau, amyloid, and vascular burden) than those without depression and show more severe loss of serotonin receptors and serotonin transporter binding, which may have implications for treatment [12].

Older adults with late-onset depression are more likely to have vascular risk factors (including a history of cerebrovascular disease) [13]. Neuroimaging changes such as white matter hyperintensities or leukoencephalopathy, particularly those affecting the frontal-striatal and frontal-limbic brain pathways, are common among patients with late-onset depression [14]. Other risk factors for the development of depression in patients with AD include a previous history of depression [15], ApoE4 positivity [14, 16], a family history of depression, and female sex [3]. The use of certain medications such as beta-blockers, corticosteroids, and benzodiazepines as well as prolonged exposure to dopamine agonists, stimulants, anticonvulsants, hormone-altering drugs, proton pump inhibitors and H2 blockers, statins or lipid-lowering drugs, and anticholinergic medications such as dicyclomine also increase the likelihood of developing a depressive disorder.

The stage of dementia may also impact the risk of developing depression. Forsell et al. suggested that depression becomes more frequent as AD progresses from mild to moderate dementia, and becomes less common in severe dementia [17]. However, Lyketsos et al. found

no significant differences in the frequencies of major and minor depression among the stages of mild, moderate, and severe AD [3]. Starkstein et al. [18] and Lopez et al. [19] found that major depression was less frequent in AD patients with severe cognitive deficits than in those with mild or moderate cognitive deficits. These differences may be related to the challenges involved in diagnosing depression in the context of AD.

DIAGNOSIS OF DEPRESSION

Prevalence

Approximately 52% of patients have their first onset of depression at age 60 or older [20]. According to some epidemiological studies, the point prevalence of major depression is 4.6%–9.3% in patients older than 75 years, which increases to 27% in those older than 85 years [21, 22].

The diagnosis of depression in seniors, and in particular, in those affected by AD, is complicated by additional challenges. Elderly patients may not meet full Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 [23] criteria for a major depressive disorder (Table 1). They frequently do not report a depressed mood, but instead present with less specific symptoms such as insomnia, anorexia, treatment-resistant pain symptoms, and fatigue. Older patients, particularly women, may have vegetative symptoms and cognitive dysfunction that overlap with symptoms of AD [24]. Some features that suggest depression include frequent office visits or use of medical services; persistent reports of pain, fatigue, insomnia, and headache; changes in sleep or appetite; unexplained gastrointestinal symptoms; and signs of social isolation and increased dependency. Elderly individuals may also dismiss less severe depression as an acceptable response to life stressors or a normal part of aging.

Impact of Depression

Late-life depression (LLD) remains underdiagnosed and inadequately treated—in late life,

Table 1 DSM-5 diagnostic criteria for depression

Criteria	The individual must be experiencing five or more symptoms during the same 2-week period, and at least one of the symptoms should be either (1) depressed mood or (2) loss of interest or pleasure
Symptoms	<ol style="list-style-type: none"> 1. Depressed mood most of the day, nearly every day 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day 3. Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day 4. A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down) 5. Fatigue or loss of energy nearly every day 6. Feelings of worthlessness or excessive or inappropriate guilt nearly every day 7. Diminished ability to think or concentrate, or indecisiveness, nearly every day 8. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
Diagnosis	To receive a diagnosis of depression, these symptoms must cause the individual clinically significant distress or impairment in social, occupational, or other important areas of functioning. The symptoms must also not be a result of substance abuse or another medical condition

Adapted from [23]

this is associated with higher rates of morbidity and mortality. The rates of cognitive, social, and physical impairment, as well as the resulting decrease in independence, significantly impact the lives of seniors suffering from depression [25, 26]. Compared to non-depressed counterparts, severely depressed older adult patients have elevated rates of mortality (controlling for sex, preexisting chronic health problems, socioeconomic status, and fitness) [25–28].

Diagnostic Criteria

In 2001, the National Institute of Mental Health convened an expert panel that developed a provisional set of diagnostic criteria for depression in AD (NIMH-dAD; Table 2) [29, 30]. These criteria were derived from DSM-IV criteria for major depression, with a few modifications. The number of symptoms required for a diagnosis of depression was decreased from five to three. The duration and frequency of depressive symptoms were also decreased; symptoms need only be present together within the same 2-week

period, as compared with the DSM-IV requirement that symptoms be present “most of the day, nearly every day” for at least 2 weeks. Cognitive complaints such as a decreased ability to think and to concentrate were eliminated. Anhedonia criteria were modified to focus on decreased affect and pleasure associated with social and other activities. Symptoms distinct to this population, including withdrawal, social isolation, and irritability, were added as new symptoms. These changes were believed to reflect the clinical features of depression in patients with AD better [29, 30].

Teng et al. evaluated a cohort of 101 patients, diagnosing depression at baseline and after 3 months using NIMH-dAD criteria and the Structured Clinical Interview for DSM-IV Axis I Disorders [31]. Depressive symptoms also were assessed with the Cornell Scale for Depression in Dementia (CSDD), the Geriatric Depression Scale (GDS), and the Neuropsychiatric Inventory Questionnaire. The use of NIMH-dAD criteria allowed the investigators to identify a greater proportion of AD patients as depressed than when several other established

Table 2 National Institute of Mental Health Diagnostic Criteria for Depression in AD**Criteria**

- A. Three (or more) of the following symptoms must be present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms must either be (1) depressed mood or (2) decreased positive affect or pleasure
1. Clinically significant depressed mood
 2. Decreased positive affect or pleasure in response to social contacts and usual activities
 3. Social isolation or withdrawal
 4. Disruption in appetite
 5. Disruption in sleep
 6. Psychomotor changes
 7. Irritability
 8. Fatigue or loss of energy
 9. Feelings of worthlessness, hopelessness, or excessive or inappropriate guilt
 10. Recurrent thoughts of death, suicidal ideation, plan or attempt
- B. All criteria are met for dementia of the Alzheimer type (DSM-IV)
- C. The symptoms cause clinically significant distress or disruption in functioning
- D. The symptoms do not occur exclusively in the course of delirium
- E. The symptoms are not due to the direct physiological effects of a substance
- F. The symptoms are not better accounted for by other conditions such as major depressive disorder, bipolar disorder, bereavement, schizophrenia, schizoaffective disorder, psychosis of Alzheimer disease, anxiety disorders, or substance-related disorders

Adapted from [29]

assessment tools for depression were applied. These results are consistent with the results from a previous study that interpolated NIMH-dAD diagnoses from data collected using a structured interview from another diagnostic instrument [31].

Variants of Depression

The validity of existing criteria for geriatric depressive disorders, particularly the DSM-5, continues to be questioned. Data suggest that there are qualitative differences in the clinical presentation of depression in younger and older adults and that the different presentations of depression in older adults are not fully assessed

by the current measures of depression [26, 32, 33]. These differences are even further potentiated in cognitively impaired seniors.

In a study comparing major depressive features between patients with AD and cognitively normal older adults, several significant differences were noted. Patients with AD had more prominent difficulties with concentration and indecisiveness, fewer sleep disturbances, and fewer reports of feelings of worthlessness or excessive guilt. However, patients with AD were noted to have higher rates of psychotic symptoms, such as delusions and hallucinations. There was also a trend toward higher rates of psychomotor agitation/retardation and fatigue/

loss of energy in patients with more advanced AD [34].

The variability in the cognitive profile of geriatric depression also suggests that this syndrome represents a heterogeneous group of disorders requiring careful neuropsychiatric assessment and treatment planning [35]. Attempts have been made to define and categorize the different presentations of depression in seniors. Several geriatric-specific variants of depression have been proposed. One of these, the “depletion syndrome,” is characterized by hopelessness, loss of appetite, thoughts of death, and lack of interest [36, 37]. Another variant is the “depression-executive dysfunction syndrome” [38]. In this syndrome, cognitive performance is typically impaired on measures of verbal fluency, naming, and initiation/perseveration; psychomotor retardation and anhedonia are included, but vegetative symptoms, agitation, and guilt are less severe than in other types of depression.

Diagnostic Assessment Tools

Although a structured clinical interview remains the cornerstone of diagnosis, a variety of geropsychiatric measures have been developed to help diagnose depression, rate the severity of the disease, and monitor treatment progress (Table 3).

In general, current test measures were found to underestimate the depletion syndrome, although they generally inflated the extent to which depression was found in older adults. Therefore, current measures may underestimate depression in older adults because they do not measure the most common subtype of geriatric depression [39].

Many of the available geropsychiatric tests remain imperfect. Most existing depression self-report scales used for older adults (e.g., Beck Depression Inventory-II, Center for Epidemiologic Studies Depression Scale, Zung Self-Rating Depression Scale) fail to consider the level of cognitive impairment along with visual deficits of older patients. The validity of certain depression rating scales is considerably decreased in patients with a Mini-Mental State

Examination (MMSE) score equal to or less than 15 [40].

With the exceptions of the GDS and CSDD, which were specifically developed for use in geriatric patients and contain fewer somatic items, most existing depression rating scales currently used for older adults have been developed and validated in younger populations. No current self-report assessment tools discriminate between subtypes of geriatric depression [41].

Most self-report depression scales currently used for older adults, e.g., the Beck Depression Inventory-II, contain items tapping somatic symptoms. When there is considerable overlap between depressive symptoms and physical conditions, failure to take the physical illness into account may result in an overestimation of depression in such populations [41]. This overlap may affect the assessment of treatment efficacy.

Cognitively impaired patients also underreport symptoms on patient-focused depression scales such as the GDS, as they are unable to recall or are not aware of the depressive symptoms reported by the caregivers [34]. As the reliability of GDS diminishes with MMSE scores below 15, input from caregivers becomes more important as the patient’s cognitive status declines [40]. Therefore, an assessment tool that incorporates caregiver input, such as the CSDD, may be more appropriate in patients with dementia [42]. Patients with CSDD scores above 12 require treatment, and those with scores above 8 require close follow-up and possibly treatment [43].

NEUROIMAGING IN AD AND DEPRESSION

The clinical picture of LLD can be indistinguishable from that of dementia. There is increasing awareness of a relationship between these two entities, yet the pathologic mechanisms remain unclear. Evidence is growing that suggests that LLD may be a prodromal symptom of neurodegenerative disease. The ability to distinguish between LLD and dementia, particularly early in the disease course, has significant

Table 3 Depression scales used in geriatric psychiatry

Scales	Description
Geriatric Depression Scale (GDS)	Self-report questionnaire with “yes” or “no” responses. Different versions are available, with the number of questions ranging from 30 to 4. The 5-item GDS is reported to be as effective as the 15-item GDS for the screening of depression in cognitively intact older individuals
Cornell Scale for Depression in Dementia (CSDD)	Developed specifically for the assessment of depression in dementia. It is a 19-item comprehensive interview of both patient and informant and includes the clinician’s impression Assesses signs and symptoms during the week preceding the interview
NIMH-dAD	The NIMH Provisional Diagnostic Criteria for Depression in Alzheimer’s Disease, a provisional set of diagnostic criteria for depression in AD, developed in 2001 in order to better reflect the clinical features of depression in AD
Center for Epidemiologic Studies Depression Scale (CES-D), NIMH	A 20-item self-report questionnaire on symptom frequency during the past week. Responses range from rarely or none to most or all the time
Neuropsychiatric Inventory (NPI)	Useful to assess 10 behavioral areas and 2 neurovegetative areas. Assessment is based on informant (caregiver) observations. Scores for the areas reveals frequency and severity and caregiver distress
Hamilton Rating Scale of Depression (HAM-D)	Gold standard of observer-rated depression rating scales. Requires training to administer. Is helpful in assessing the severity of depression
Montgomery-Asberg Depression Rating Scale (MADRS)	Administered by a trained interviewer. Helpful to measure progress. Useful for assessment of depression in individuals with physical illness
Beck Depression Inventory (BDI)	A 21-item, self-report, multiple choice inventory. Revised version is BDI-II. Helps to assess severity of depression
Patient Health Questionnaire (PHQ)	PHQ-9—self-report questionnaire: helps screen, diagnose, monitor, and measure severity of depression. PHQ-2—“first step” approach: enhances routine enquiry
Zung Self-Rating Depression Scale (SDS)	A 20-item self-report questionnaire to screen affective, psychological, and somatic symptoms associated with depression

implications for clinical care, along with our understanding of the neurobiological systems implicated. Neuroimaging represents a promising avenue to elucidate these two potentially overlapping pathologies.

Various imaging techniques, structural and functional, are currently used in research and clinical settings for the evaluation of dementia, LLD, or both. Clinical consensus guidelines [44]

recommend the use of structural brain imaging—either magnetic resonance imaging (MRI) (preferred) or computed tomography (CT)—for the evaluation of a cognitive/dementia syndrome in order to rule out structural and potentially treatable causes and to assess atrophy. The most characteristic structural imaging biomarker of AD is hippocampal atrophy [45, 46]; however, this finding is not specific for

AD and is seen in other neurodegenerative diseases. Smaller hippocampal volumes are associated with memory performance [47].

MRI

MRI morphometric studies in LLD demonstrate atrophy of various brain structures including lower gray matter volumes in the frontal–temporal lobes, hippocampus, parahippocampal gyrus, amygdala, putamen, pallidum, and thalamus compared to controls [48]. Another study showed that LLD is associated with cortical thinning, which is associated with age at depression onset, sex, and level of cognitive functioning [49]. Volumetric hippocampal changes in LLD can reflect one or more pathophysiological processes, including early neurodegenerative disease, vascular disease, and (duration-related) treatment of depressive illness [50, 51]. Based on an imaging meta-analysis, patients with LLD and AD both demonstrate abnormalities in hippocampal volume and ventricular enlargement [52].

One potential shared pathway to dementia and depression is vascular disease. Neuroimaging is essential to our understanding of this complex relationship. Alexopoulos et al. first described the vascular hypothesis for LLD, positing that cerebrovascular disease plays a critical role in provoking and perpetuating depressive symptoms as a result of structural damage to frontal–subcortical circuits [53]. However, the diagnosis of vascular depression remains controversial, without definitive biological or neuroanatomical substrates, and the term is used more often in research than in the clinical setting. The diagnosis is driven largely by neuroimaging findings of white matter hyperintensities on T2-weighted or fluid-attenuated inversion recovery MRI, subcortical lacunes, microinfarcts, and microhemorrhages along with frontal and hippocampal gray matter atrophy [54]. LLD with these imaging findings has been termed “MRI-defined vascular depression” [55].

Functional Imaging

Functional imaging is used in the clinical dementia evaluation in atypical cases, early-onset cases, or other uncertain cases where further specificity is warranted despite standard structural imaging [44]. The most commonly used functional scans in this setting are fluorodeoxyglucose positron emission tomography (FDG-PET) or single-photon emission computed tomography (SPECT). FDG-PET technology demonstrates glucose metabolism, which is a surrogate for neuronal and synaptic activity along with neurodegeneration. SPECT incorporates CT with a radioactive tracer to demonstrate cerebral blood flow or perfusion.

Perfusion imaging techniques, such as SPECT, may provide a promising approach to differentiating depression from dementia. Amen et al. evaluated perfusion neuroimaging using SPECT in more than 4500 subjects with a diagnosis of depression, dementia, or both [56]. Subjects with dementia had lower regional cerebral blood flow, specifically seen in the amygdala and hippocampus, compared to subjects with depression, and these changes were magnified in those with both depression and dementia. Overall, SPECT distinguished between depression and dementia with 86% accuracy.

White Matter Lesions

The pathophysiology of white matter lesions (WMLs) has not been fully elucidated. It is generally accepted that WMLs are caused, at least in part, by small-vessel ischemia. However, given that WMLs are found in some individuals with no major vascular risk factors (hypertension, hyperlipidemia, diabetes, heart disease, smoking, and obesity), other non-vascular factors must play a role [50]. One autopsy study compared 20 older subjects with a history of major depression to age-matched controls. At autopsy, deep WMLs were found to be ischemic in nature for all depressed subjects compared to less than one-third of control subjects. Furthermore, in the depressed subjects, ischemic lesions were significantly more present in the

dorsolateral prefrontal cortex compared with the non-depressed group. Of note, the non-depressed group had more clinical vascular disease during life than the depressed group. On histopathologic analysis, ischemic deep WMLs revealed infarction, gliosis, axonal loss, ischemic demyelination, or a combination of these, supporting the vascular hypothesis of depression [57].

One multimodal imaging study evaluated brain MRI features associated with late-life depressive symptoms in older community-dwelling adults, analyzing whole-brain variables including white matter hyperintensity burden, fractional anisotropy (a measure of water movement), and gray matter volume. The loss of gray matter volume was most significant in the bilateral insula and anterior cingulate cortex. The insula has been previously implicated in major depressive disorder [58] and, furthermore, is a brain region known to be sensitive to hypoperfusion, supporting a cerebrovascular pattern for depressive symptoms in older adults.

The causal relationship between WML burden, cognitive changes, and LLD remains unclear. One population-based study of older adults [59] analyzed the relationship between WMLs and cortical atrophy on CT and later development of depression or dementia in community-dwelling adults over a 10-year period. The authors found that WML and temporal lobe atrophy independently predicted later development of depression and dementia, possibly suggesting shared pathogenetic pathways. There remains a considerable debate, regarding whether shared versus distinct pathophysiologic pathways exist between dementia and LLD. While evidence supports the presence of hippocampal atrophy in LLD, one study showed a lack of identifiable A β pathology in LLD based on [¹⁸F]flutemetamol amyloid PET findings [60]. Another study assessed cortical A β with ¹⁸F-florbetapir PET and showed that depressed patients with moderate-to-severe treatment resistance had higher ¹⁸F-florbetapir standardized uptake value ratios than healthy controls in the parietal regions [61, 62]. As well, the elevated amyloid burden in depressed older patients with moderate-to-severe treatment

resistance was seen in the precuneus, parietal, temporal, and occipital regions. Overall amyloid PET findings in the more treatment-resistant depressed group were similar to typical findings in confirmed AD subjects. Hence, treatment-refractory depression in older individuals may represent early changes in AD-related pathophysiology.

CSF Biomarkers

Liguori et al. sought to evaluate whether cerebrospinal fluid (CSF) AD biomarkers and ¹⁸F-FDG PET findings in older adults ($n = 256$) with concomitant dementia and untreated depression could differentiate AD from LLD [63]. CSF was collected, and FDG-PET was completed at baseline and after a 2-year interval. The authors found that CSF A β 42 levels were significantly higher in LLD (range, 550–1204 pg/mL) compared to AD patients (range, 82–528 pg/mL). Furthermore, CSF AD biomarkers (A β 42 and tau proteins) in LLD patients were similar to those of controls. Regarding ¹⁸F-FDG PET, patients with AD showed a significant reduction in ¹⁸F-FDG PET uptake in temporoparietal regions compared to both controls and LLD subjects, whereas the LLD and control groups had similar ¹⁸F-FDG PET findings. It should be noted that LLD subjects showed nonspecific, heterogeneous patterns of glucose hypometabolism involving various cortical and subcortical brain areas.

Neural Networks

While structural and functional neuroimaging studies have elucidated gray matter volumetric changes (network nodes), white matter tract disruptions (network edges), and rest- and task-related changes in network dynamics, increasing evidence points to the importance of disrupted functional neural network connectivity in the pathophysiology and symptomatology of both cognitive impairment and LLD [64, 65]. Intrinsic neural networks found to be involved in LLD include the default mode network (DMN), executive control network, and salience network. These networks become active in the

resting state (not doing a task) and inactive when a person is engaged in any attention-demanding tasks, which is called task-induced deactivation [59]. Imaging these intrinsic networks requires either functional PET scans or resting-state functional MRI to evaluate regional cerebral blood flow. During the resting state, functional MRI shows an increased regional blood flow or blood oxygenation level dependent signal within the set of brain regions, while there is a decrease in this signal during attention-demanding tasks.

Increasing evidence suggests that the DMN could be the neural basis of the connection between LLD and AD [66]. The DMN, first described by Raichle et al. [65], is involved in wakeful rest, mind-wandering, and self-referential thinking, and is considered to involve certain spatially distributed brain regions with synchronized activity patterns, including the posterior cingulate cortex/precuneus, superior frontal gyrus, medial prefrontal cortex, inferior parietal lobule, lateral temporal cortex, angular gyrus, hippocampus, and cerebellum [64, 66].

Sheline et al. proposed that a failure to deactivate the DMN during cognitive or emotional tasks is a network-based mechanism in depression [67]. DMN overactivity has been linked to negative rumination in depression [68]. Negative ruminations are a type of self-referential thinking, which is common in depression in both early and late life. Though not a core diagnostic feature, higher levels of rumination are predictive of more severe depressive symptoms in depressed individuals [69]. Increased functional connectivity between the subgenual prefrontal cortex and the DMN has been shown in major depressive disorder, and is posited to be a neural substrate of depressive rumination [70].

It is hypothesized that DMN activity correlates with increased neuronal and synaptic activity along with increased A β and possibly tau release, which, in a vulnerable individual, could predispose to and propagate AD pathology. One study of cognitively normal individuals with Pittsburgh compound B PET-confirmed A β deposition found that elevated A β disrupted DMN functional connectivity even in the absence of a task. Connectivity between the

precuneus and hippocampus was significantly lower in nondemented older adults with A β deposition compared to those without A β plaques [71]. Hence, there appears to be a bidirectional relationship between abnormal DMN functional connectivity and AD pathology, where one begets the other.

Future of Neuroimaging in AD and Depression

Many questions remain unanswered, but neuroimaging represents a promising and vital avenue toward understanding the complex pathophysiologic relationships between dementia and LLD and for supporting the pursuit of biomarker-driven diagnosis and treatment.

SLEEP AND DEPRESSION

Causes of Sleep Disruption

Numerous sleep changes occur with normal aging, including advanced sleep timing, increased sleep fragmentation, more fragile sleep, and less time in deeper non-rapid eye movement (NREM) sleep [72]. Aging leads to changes in the structures involved in generating or entraining circadian rhythms, and contributes to altered circadian rhythm timing with advancing age. Characteristic age-related changes in rest-activity circadian rhythms include lower amplitude [73, 74], fragmentation of loss of rhythms, and decreased sensitivity to suprachiasmatic nucleus (SCN) time cues such as light exposure [75]. In dementing neurodegenerative diseases, these sleep and circadian changes are magnified along with others such as decreased rapid eye movement (REM) sleep [72], all of which contribute to worsening dementia symptoms and brain pathology.

While the sleep-wake cycle is the best-characterized circadian rhythm, many other forms of circadian disruption are also common. In dementia, circadian dysfunction worsens as the disease progresses, which often results in sleep-wake rhythm disorders, such as irregular

sleep–wake rhythm disorder [76]. The pathophysiology of circadian disruption in dementia is yet to be fully elucidated; however, internal and external factors have been implicated, including SCN dysfunction, abnormal SCN input, and disrupted environmental factors (so-called zeitgebers). The integrity of the SCN (the central pacemaker) and the monosynaptic pathway from the retina to the SCN (known as the retinohypothalamic tract) are essential for proper circadian function. SCN degeneration results in an inability to consolidate wakefulness and the development of an abnormal 24-h rhythm. Autopsy studies of brains from patients with severe AD reveal SCN degeneration, namely neuronal loss and neurofibrillary tangle formation [77].

Disrupted environmental factors, such as light exposure, social cues, activity, and meal-times, influence the period, phase, and amplitude of circadian rhythms. Without sufficient exposure to timed light, the biological clock becomes desynchronized with the solar day, resulting in deleterious effects on various physiological functions, neurobehavioral performance, and sleep [78]. Older adults and, to a greater extent, those institutionalized are more likely to be exposed to less robust daytime light [79]. Ancoli-Israel and colleagues demonstrated that lower daytime light levels contribute to increasingly abnormal circadian rhythms as measured by actigraphy and were associated with an increase in night-time awakenings, even after controlling for the level of dementia [80]. Gehrman et al. hypothesized that in the early stages of dementia, SCN damage results in a decline in circadian rhythmicity, at which point environmental cues take on a larger role, contributing to a resynchronization of circadian rhythms [81]. When dementia becomes severe, environmental cues lose their potency.

Sleep Disruption and Depression

Meanwhile, sleep disruption is a core feature of depression, with up to 90% of depressed individuals having subjective sleep complaints [82]. Depressed patients often show altered circadian rhythms, sleep disturbances, and diurnal mood

variation. Sleep disruption is a risk factor in the development of depression [83, 84], is often the first subjective symptom, and is associated with an increased risk of relapse along with an increased risk of suicide [85]. In polysomnographic studies, individuals with major depressive disorder have prolonged sleep latency (longer time to fall asleep), frequent nocturnal awakenings, and poor sleep efficiency (percentage of time sleeping while in bed) [86]. Additionally, sleep architecture in depressed individuals shows decreased REM latency (time from sleep onset to first epoch of REM) and an increased proportion of REM sleep overall [87]. Paradoxically, some studies have demonstrated that sleep deprivation interventions can acutely reverse depressive symptoms in approximately 50–60% of patients with major depression, but this remission was temporary, and disease relapsed following subsequent rebound sleep [88, 89].

Biochemical Factors in Sleep Dysfunction

It is established that soluble A β levels fluctuate diurnally—they increase during awake time and decrease during sleep [90]. These fluctuations are thought to be related to neuronal activity and metabolic demand. Sleep disruption and deprivation, specifically decreased NREM slow-wave sleep (SWS) at < 1 Hz, is associated with aggregation of A β and tau neurofibrillary tangles [91, 92]. Decreased NREM SWS is associated with impaired overnight memory consolidation and weaker hippocampal-neocortical memory transformation [91]. Lucey and colleagues recently demonstrated elevated tau levels in both CSF and PET analysis in cognitively asymptomatic or mildly impaired subjects with decreased NREM SWS [93].

Evidence increasingly supports the role of dysfunctional A β and tau clearance systems in the development of AD. A sleep-dependent brain clearance system has been described, which is a whole-brain perivascular network facilitating the clearance of interstitial solutes, including A β and tau. The CSF-interstitial fluid system is also known as the glymphatic system because of its hypothetical reliance on glial cells

for interstitial transport [94, 95]. In rodent studies, Xie and colleagues found that the CSF-interstitial fluid clearance system was mainly active during sleep, specifically SWS [96]. The authors theorize that this occurs because, during sleep, neurons are less active and shrink in size, which results in a 60% increase in the interstitial space volume relative to the awake state. With more volume and less resistance, CSF flow and clearance is hypothetically greater.

Functional neuroimaging studies demonstrate that DMN connectivity is decreased during sleep [97]. Specific brain regions that show a decrease in activity with progression from wakefulness to SWS include the posterior cingulate cortex, parahippocampal gyrus, and medial prefrontal cortex [98]. The DMN becomes less active during SWS, indicating a drop in neuronal activity and metabolic demand. Ju et al. posit that poor sleep quality results in increased neuronal activity, contributing to chronically increased soluble A β , which leads to an increased risk of amyloid plaque formation over time [99].

Links Among Sleep Dysfunction, Depression, and Dementia

The relationship between sleep dysfunction, depression, and dementia appears to be dynamic and synergistic, though the pathomechanisms remain unclear. Both sleep disruption and depression are common in dementia, independently and co-occurring, and both can be prodromal symptoms of neurodegenerative disease. While the relationship between sleep dysfunction and AD is often described as bidirectional, bringing depression into the equation could lead to a tridirectional relationship, which is challenging to disentangle [99].

Burke et al. used a syndemic approach to analyze the associative effects of depression, anxiety, and sleep disturbance on the risk of later development of symptomatic AD in a cognitively asymptomatic cohort of more than 11,000 individuals in the National Alzheimer's Coordinating Center (NACC) [100]. The authors describe the syndemic approach as "reaching

beyond a person's biology and takes account of stress, inequality, the community, and the environment, all over time, as potential cofactors in the exacerbation of illnesses" [100]. The authors showed strong independent hazards of AD development for depression, sleep disturbance, and anxiety independently. The additive interaction and risk of eventual AD diagnosis were significant for those experiencing recent depression symptoms and sleep disturbances, current or lifetime, as compared to those without either symptom. Those with clinician-verified depression and sleep disturbance showed three times greater risk of eventual AD diagnosis than those without these symptoms. Another study by the same group using NACC data showed that these independent risk relationships between sleep, dementia, and depression were even stronger for APOE4 carriers, indicating a genetic role [101].

Treatment for Sleep Dysfunction in Patients with Dementia and Depression

Sleep represents a promising area for the discovery of diagnostic markers and novel treatment approaches in dementia and LLD. Pharmacologic and nonpharmacologic approaches to improve NREM SWS may serve to decrease or delay the aggregation of toxic A β and tau proteins. One recent retrospective study evaluated whether the use of trazodone, a commonly used sleep medication in older adults, resulted in less cognitive decline compared to non-trazodone users. Trazodone was originally developed as an antidepressant, though it was found to be less effective for that indication [102]. Trazodone has been previously shown to significantly increase NREM SWS on polysomnography [103]. Analyzing NACC data, a study showed that trazodone non-users declined 2.6-fold faster on the MMSE than trazodone users over 4 years. Other hypnotics, including melatonin, ramelteon, and mirtazapine, have not produced such an improvement in NREM SWS [104].

Beyond medications, sleep and circadian dysfunction in older adults can be targeted through nonpharmacologic and behavioral

approaches. Such therapies include cognitive behavioral therapy, chronotherapies such as bright-light exposure, and social rhythm therapies for the illness. Evidence suggests that addressing sleep impairment in older adults, particularly before the development of cognitive symptoms, could have disease-modifying effects. However, more research is needed.

TREATMENT OF DEPRESSION IN PATIENTS WITH AD

Currently, no clearly established consensus guidelines exist regarding the treatment of depression in patients with AD. However, a large body of literature has documented the different approaches and medications that have been investigated. Both pharmacological and nonpharmacological interventions have been shown to help reduce depressive symptoms in cognitively impaired patients and in improving their quality of life. These interventions can broadly be divided into nonpharmacological therapies and lifestyle interventions and psychopharmacology.

Nonpharmacological Therapies and Lifestyle Interventions

The National Institute for Health and Care Excellence (NICE) guideline published in June 2018 regarding the assessment and management of dementia has a section on managing noncognitive symptoms [105]. It suggests considering psychological treatments for people with mild-to-moderate dementia who have mild-to-moderate depression. Per these recommendations, antidepressants should not be routinely offered unless they are indicated for a preexisting severe mental health problem. Good clinical practice requires the use of nonpharmacological approaches for NPS, including depression, before the initiation of pharmacological interventions [106, 107]. Nonpharmacological therapies that specifically target depression or its symptoms include emotion-oriented therapies, brief psychotherapies, and sensory-stimulation therapies. Regardless of the

specific therapy chosen, it is advised that these be used as an acute and short-term intervention [108, 109].

Emotion-Oriented Therapies

Emotion-oriented therapies aim to fit the therapy to the emotional needs of people with dementia by utilizing approaches such as validation, reminiscence, reality, and simulated-presence therapy. Reminiscence therapy uses memory aids such as old family photos and personal objects while encouraging patients to talk about their pasts [110]. Reality-orientation therapy hypothesizes that confusion can be reduced by giving repeated orientation clues, such as the date, time of day, season, or names. It is based on the theory that the inability to orient one's self reduces the ability of those with dementia to function. Validation therapy adopts the concept that cognitively impaired individuals withdraw to an inner reality based on emotions, rather than trying to face the challenges of their faltering cognitive abilities. The therapist accepts the subsequent disorientation of the patient and validates his or her feelings, providing a background for meaningful conversations addressing their emotions [111]. Simulated-presence therapy involves exposing a patient to audio or videotaped recordings of loved ones [112].

Despite several positive clinical reports of efficacy for these interventions, there is currently insufficient evidence for their effectiveness in reducing any NPS, and almost no research providing data on their effects on depression. However, numerous anecdotal and research reports of clinical effectiveness and the patient-centered nature of these individualized therapies suggest that they might yet prove to be of value [113–119].

Brief Psychotherapies

Several brief psychotherapeutic interventions have also been shown to be particularly effective in this population [120, 121]. Behavioral therapies are more commonly applied in the later stages of dementia, while modified cognitive-behavioral strategies appear to be more successful with those in the earlier stages of

cognitive decline [122]. Cognitive behavioral therapy (CBT) requires a period of detailed assessment to identify the triggers, behaviors, and reinforcers (also known as ABC: antecedents, behaviors, and consequences). Their relationships are discussed with the patient. Interventions are then based on an analysis of these findings. CBT in AD patients with depression focuses on identifying and reframing negative thoughts and increasing participation in social and pleasurable activities.

Although CBT is more commonly used with caregivers of patients with dementia than with the patients themselves, a few studies have tested the effects of individual or group CBT on NPS, and on depression in particular. Teri et al. used cognitive therapy in adults with mild dementia to challenge the patients' negative cognitions in order to reduce distortions and enable the patients to generate more adaptive ways of viewing specific situations and events [123, 124].

Most CBT programs for persons with dementia involve their caregivers, both as CBT coaches for the care recipient and as treatment partners who frequently benefit from the intervention as well [123–125]. Implementing CBT with persons suffering from dementia requires a highly structured format and continuous monitoring of the person's understanding of the therapeutic material. The strongest evidence is for short-term CBT and problem-solving therapy [109].

Sensory Stimulation Therapies

Sensory stimulation therapies, including music therapy, art therapy, pet therapy, aromatherapy, activity therapies, and multisensory approaches (such as Snoezelen), have the potential for benefit in depressed patients with cognitive impairment. Similar to the emotion-oriented therapies, few rigorous studies have been performed, and efficacies are mixed, although reports from clinical observers are generally very positive [126].

Lifestyle Modifications

Other lifestyle modifications, such as an increase in physical activity, may provide

additional benefits through nonpharmacological means. A meta-analysis of eight studies found that moderate daily exercise was effective at reducing symptoms of depression in the elderly [127]. Exercise has also been associated with a decrease in hippocampal atrophy, which is believed to be related to improved cerebral perfusion as well as the release of brain-derived nerve growth factor [127]. These studies did not exclusively focus on AD, but it is reasonable to extrapolate these results to depression in patients with AD.

Psychopharmacology

Recent guidelines for pharmacotherapy in geriatric patients with depression (Table 4) have been recommended by the French Association for Biological Psychiatry and Neuropsychopharmacology and the foundation *FondaMental* [128].

Pharmacokinetics and Pharmacodynamics

Pharmacological treatment of depression in cognitively impaired patients presents unique challenges due to physiologic changes that accompany normal aging as well as the neurodegenerative process itself. Significant changes in pharmacokinetics and pharmacodynamics dictate that vigilance be exercised to avoid drug–drug interactions and accidental overdoses. The presence of medical comorbidities also influences both the therapeutic and adverse effects of antidepressant medications.

Hepatic metabolism and renal clearance decrease with advancing age. The decrease in mesenteric blood flow also decreases gastrointestinal absorption. Neurodegenerative changes also lead to decreased production of acetylcholine as well as a decreased number of cholinergic neurons in the basal forebrain, which leads older individuals to show marked sensitivity to developing anticholinergic adverse effects.

Given their physical and cognitive frailty, individuals with dementia may be particularly susceptible to the adverse effects of medications; therefore, the old adage “start low and go slow” applies when dosing the elderly. Comorbid

Table 4 Therapeutic strategies in geriatric depression

Clinical features	First intention	Second intention	Contraindications
Mild to moderate intensity	SSRI	SNRI	Irreversible MAOI
	α 2 Antagonist	Agomelatine	Bupropion Association with an ATD from the same pharmacological class Anticonvulsant ECT
Moderate to severe intensity	SSRI	Imipramine	Bupropion
	SNRI		Association with an ATD from the same pharmacological class
Severe cognitive impairments	α 2 Antagonist	α 2 Antagonist	Anticonvulsant
	SSRI	Agomelatine	First-generation antipsychotic
Severe psychomotor agitation	SNRI	SNRI	Bupropion
	α 2 Antagonist	Potentialiation with AAP	Tianeptine Irreversible MAOI Association with an ATD from the same pharmacological class
Severe psychomotor retardation	SSRI	α 2 Antagonist	Tianeptine
	SNRI	Imipramine	Bupropion
Severe sleep disorders	ECT in association	SNRI	Association with an ATD from the same pharmacological class First-generation antipsychotic
	SSRI	α 2 Antagonist	Tianeptine
Severe anhedonia	α 2 Antagonist	Agomelatine	Irreversible MAOI Bupropion Association with an ATD from the same pharmacological class
	SSRI	α 2 Antagonist	Association with an ATD from the same pharmacological class
	SNRI	Imipramine	Anticonvulsant
		Agomelatine	First-generation antipsychotic

Table 4 continued

Clinical features	First intention	Second intention	Contraindications
Psychotic symptoms	SNRI	SSRI	Tianeptine
	Potential with AAP	$\alpha 2$ Antagonist Imipramine	Irreversible MAOI Bupropion
		ECT in association	Association with an ATD from the same pharmacological class
High suicidal risk	SSRI	$\alpha 2$ Antagonist	Tianeptine
	SNRI	Imipramine	Bupropion
		ECT in association	Association with an ATD from the same pharmacological class
		Potential with AAP	First-generation antipsychotic

Data adapted from [128]

AAP AAP gene, *ATD* antidepressant, *ECT* electroconvulsive therapy, *MAOI* monoamine oxidase inhibitor, *SNRI* dual serotonin and norepinephrine reuptake inhibitors, *SSRI* selective serotonin reuptake inhibitor

medical conditions including diabetes, history of falls, renal and hepatic insufficiency, cardiac arrhythmias, and cerebrovascular risk factors should all be considered before initiation of pharmacotherapy. It is also important to note that the patient's cognitive limitations may affect their ability to communicate regarding the emergence of adverse effects. Hence, close monitoring by the prescriber and caregivers is indicated.

Use of Antidepressants in Patients with Dementia

Antidepressants are frequently prescribed for the treatment of depression in patients with dementia. The 2007 practice guidelines issued by the Work Group on Alzheimer's Disease and Other Dementias of the American Psychiatric Association recommend selective serotonin reuptake inhibitors (SSRIs) as the first pharmacological treatment of choice for depression in dementia [129]. SSRIs tend to be better tolerated than other antidepressants because they have fewer serious adverse effects. The Work Group suggests that if patients with dementia cannot

tolerate higher dosages when needed for the remission of depression, trials of alternative antidepressants such as bupropion, venlafaxine, and mirtazapine may be considered [129].

The evidence regarding the efficacy of these agents, however, remains conflicting. Reviews of research on the pharmacological treatment of NPS in general [106, 107, 130] indicate positive effects of various antidepressants (including sertraline, fluoxetine, citalopram, trazodone, and moclobemide) on depression in patients with dementia, with citalopram and sertraline being the most commonly prescribed [131–133]. Case reports and small pilot studies indicate that other antidepressants, including trazodone, buspirone, and mirtazapine, may improve depression in patients with dementia, but no large trials have been performed in individuals with dementia to date [106, 107, 134].

Lyketsos et al. examined depressive symptoms using the CSDD in a 12-week double-blind, placebo-controlled trial of sertraline. The results were encouraging and indicated that sertraline had a clear advantage over placebo,

with the bulk of the antidepressant effect seen in the first 3 weeks after starting therapy. Improvements were also noted in activities of daily living, but no significant effect was noted in cognition [135].

Lyketsos et al. expanded this study with a larger group recruited from two different sites. Once again, the results demonstrated sertraline as being superior to placebo at 12 weeks. In addition, the researchers noted improvements in activities of daily living as well as non-mood behavioral disturbances. The improvement in activities of daily living, as well as non-mood behavioral disturbances, lagged behind the improvement in depressive symptoms. The improvement in symptoms was hypothesized to be due to an improvement in depression, rather than being a direct response to sertraline. It was also noted that there was no improvement in cognitive functioning [131].

The Depression in Alzheimer's Disease Study (DIADS)-2 work group [136, 137] continued to investigate the role of sertraline in treating depression in AD, publishing data collected at 12 weeks and again at 24 weeks. Neither of these demonstrated sertraline as being superior to placebo. They did agree that the previously proposed dose range of 90–100 mg a day was safe and appropriate.

An analysis by Dudas et al. [138] of the findings from these three studies [131, 136, 137] indicated overall little or no benefit from treatment with an antidepressant (MD – 0.10 points, 95% CI – 0.99 to 0.78; 433 participants; 3 studies).

One landmark study [139] examined 150 mg sertraline or 45 mg mirtazapine per day versus placebo. Decreases in depression scores at 13 weeks did not show a statistically significant difference between patients receiving mirtazapine or sertraline versus placebo. It was concluded that the overall effectiveness of antidepressants in patients with AD is small. However, a meta-analysis trended toward treatment response; hence, the possible clinical advantages of antidepressants could not be fully ruled out [140].

Effect of Antidepressants on Cognitive Decline

More recent studies have focused on duloxetine, vortioxetine, and brexpiprazole. Vortioxetine demonstrated a significant positive improvement in cognitive function compared to placebo [141]. Brexpiprazole, when used as an adjunctive agent in an open-label safety and tolerability study (26 weeks), was shown to be well tolerated in elderly patients, with improvements noted in depression and social functioning.

Earlier studies gave conflicting results regarding efficacy, safety, and effects on cognitive function. Most of the existing studies differed in study design, rating scales used, and severity of symptoms addressed. Only two comparative studies have been published. Tarango et al. [142] compared fluoxetine to amitriptyline, and Katona et al. [143] compared paroxetine to imipramine. One of the earliest studies by Roth and colleagues in 1996 [144] demonstrated that moclobemide was effective in treating symptoms of depression; however, no improvement in cognitive function was found. In 1995, Tollefson et al. [145] demonstrated the efficacy of fluoxetine versus placebo. However, in 2001, Petracca et al. [146] found that it was not superior to placebo. In contrast, in 1992, Nyth et al. [147] demonstrated that citalopram improved both cognitive and emotional functioning in a 6-week double-blind placebo-controlled trial. Tricyclic antidepressants were also studied [148, 149], and both clomipramine and imipramine were shown to be superior to placebo. Clomipramine seemed to lower scores on the MMSE. Despite inconclusive data regarding treatment, there was agreement that untreated depression in patients with AD and an impaired level of functioning resulted in increased impairment of quality of life, a higher decline in activities of daily living, an increased likelihood of being discharged from assisted living facilities, an increased likelihood of needing a nursing home level of care, and increased mortality and suicidal ideations.

Perhaps the more significant future direction of psychopharmacology is exploring the relationship between antidepressants and progression of cognitive decline. Bartels et al. [150] demonstrated that long-term SSRI treatment

might delay progression from mild cognitive impairment to AD. Zhou et al. [151] observed that fluoxetine delayed the cognitive functional decline and synaptic changes in a transgenic mouse model of early AD. However, the clinical studies published at this time are insufficient to draw conclusions.

Adverse Effects of Antidepressants in Patients with Dementia

As noted previously, the selection of a particular antidepressant should encompass the consideration of potential adverse effects.

SSRIs include fluoxetine, paroxetine, sertraline, citalopram, and escitalopram. Potential adverse effects of these agents include nausea and vomiting, agitation, anxiety, indigestion, diarrhea or constipation, dizziness, blurred vision, dry mouth, diaphoresis, loss of appetite and weight loss, insomnia or sedation, headaches, and sexual adverse effects. However, these drugs have less marked anticholinergic and antiadrenergic properties, and therefore, may be less likely to cause confusion or falls [152].

Both citalopram and escitalopram have been associated with a prolonged QTc interval, particularly if combined with other medications that prolong QTc. The risk also increases when those drugs are combined with medications (e.g., cimetidine, omeprazole) that decrease the metabolism of those drugs, thus raising their serum blood levels.

Selective serotonergic and noradrenergic reuptake inhibitors such as venlafaxine, desvenlafaxine, and duloxetine, tetracyclic antidepressants such as trazodone and maprotiline, and reversible monoamine oxidase inhibitors such as moclobemide are alternative options to SSRIs. Another often-used example of the newer antidepressants is the $\alpha 2$ antagonist mirtazapine. The adverse effect profiles of these medications are similar to that of SSRIs.

The oldest class of antidepressants is the tricyclic antidepressants. They are associated with potentially problematic adverse effects for older patients. In particular, their anticholinergic properties are associated with a negative impact on cognition [153]. Other problematic anticholinergic effects would include increased intraocular pressure, urinary retention, dry

mouth, and constipation. Because of their antiadrenergic adverse effects, they can also cause postural hypotension [154] and dizziness, thereby increasing the risk of fall. In general, this class of antidepressants should be avoided in patients with cognitive impairment.

APATHY

Although this review focuses on depression, it is important to understand the distinction between apathy and depression as the underlying causes of symptoms, and patients' responses to antidepressant treatment vary significantly. Apathy is characterized by lack of motivation, decreased initiative, akinesia, and emotional indifference. It is the most common NPS associated with AD and a primary cause of caregiver distress [155]. It frequently emerges in the pre-cognitive impairment stages of AD, increases in frequency as the disease progresses, and predicts conversion from normal cognition to MCI and from MCI to dementia [156]. In 2009, an international task force published diagnostic criteria for apathy which require that two of three dimensions of diminished motivation must be present for at least 4 weeks with identifiable associated functional impairment [157]. The Apathy Evaluation Scale is commonly used to assess apathy across the AD continuum [158]. The Neuropsychiatric Inventory also includes an apathy subscale, but it has not yet been validated for use on its own. Apathy can occur alone or as a symptom of depression [159].

In neuroimaging studies, apathy has been associated with cortical dysfunction in the posterior cingulate or inferior temporal cortex. It has also been associated with atrophy, hypometabolism, and hypoperfusion in these regions. High levels of tau and phospho-tau in the CSF and abnormalities in cholinergic, GABAergic, and dopaminergic function have also been associated with apathy [160]. Dopaminergic circuits have been targeted in treatment trials using methylphenidate, with a significant reduction in apathy symptoms and improvement in global cognition in a 6-week study [161]. Open-label studies of cholinesterase inhibitors (donepezil, galantamine, and

rivastigmine) showed improvements in apathy with all three medications [162].

In the clinical setting, patients suffering from apathy will frequently deny feeling “depressed,” and may not endorse the typical symptoms of depression. Their caregivers may report that their engagement, motivation, and interest has dwindled and, as a result of these observations, express concerns over their loved one being depressed.

CONCLUSION

When treating patients with AD, the impact of neuropsychiatric symptoms, particularly depression, on the patients’ quality of life should not be overlooked. Diagnosing depression in this patient population can be challenging. Thus, additional research and development of assessment tools focused on a geriatric population are needed. Neuroimaging may represent a promising avenue toward understanding the complex pathophysiologic relationships between dementia and LLD, and may support the pursuit of biomarker-driven diagnosis and treatment.

Additional future research into the pathological mechanisms of depression and AD will enable a better understanding of these diseases and their relationship, leading to better pharmacological and nonpharmacological treatments. Larger clinical trials assessing pharmacological and nonpharmacological interventions are necessary for the development of comprehensive consensus guidelines regarding the treatment of depression in patients with AD. Improving interventions for depression in patients with AD can help to decrease disability and improve the quality of life of patients and their caregivers.

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