REVIEW ARTICLE

Alzheimer Disease

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Dr McDade has received personal compensation in the range of $500 to $4999 for serving as a consultant for Lilly and for serving on a scientific advisory or data safety monitoring board for Alector, Inc and Lilly. Dr McDade has received personal compensation in the range of $5000 to $9999 for serving on a scientific advisory or data safety monitoring board for Fondation Alzheimer and in the range of $10,000 to $49,999 for serving on a scientific advisory or data safety monitoring board for Alzamend Neuro Inc. Dr McDade has received intellectual property interests from a discovery or technology relating to health care and publishing royalties from a publication relating to health care. The institution of Dr McDade has received research/grant support from F. Hoffmann-LaRoche, Lilly, and the National Institute on Aging. The blood-based amyloid test is licensed by C2N and was cofounded by colleagues of Dr McDade. Washington University will receive royalties from this test, but Dr McDade will not receive personal compensation from it.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr McDade discusses the unlabeled/investigational use of atypical antipsychotics for the treatment of behavioral symptoms of dementia.

ABSTRACT

PURPOSE OF REVIEW: Alzheimer disease (AD) is the most common cause of dementia in adults (mid to late life), highlighting the importance of understanding the risk factors, clinical manifestations, and recent developments in diagnostic testing and therapeutics.

RECENT FINDINGS: Advances in fluid (CSF and blood-based) and imaging biomarkers are allowing for a more precise and earlier diagnosis of AD (relative to non-AD dementias) across the disease spectrum and in patients with atypical clinical features. Specifically, tau- and amyloid-related AD pathologic changes can now be measured by CSF, plasma, and positron emission tomography (PET) with good precision. Additionally, a better understanding of risk factors for AD has highlighted the need for clinicians to address comorbidities to maximize prevention of cognitive decline in those at risk or to slow decline in patients who are symptomatic. Recent clinical trials of amyloid-lowering drugs have provided not only some optimism that amyloid reduction or prevention may be beneficial but also a recognition that addressing additional targets will be necessary for significant disease modification.

SUMMARY: Recent developments in fluid and imaging biomarkers have led to the improved understanding of AD as a chronic condition with a protracted presymptomatic phase followed by the clinical stage traditionally recognized by neurologists. As clinical trials of potential disease-modifying therapies continue, important developments in the understanding of the disease will improve clinical care now and lead to more effective therapies in the near future.

INTRODUCTION

The burden of Alzheimer disease (AD) on individuals and society and the increase in longevity of humans have resulted in an increasing emphasis on diagnosis and treatment of this neurodegenerative disease. With the development over the past 3 decades of specific biomarkers that identify the molecular pathology of AD, it is now clear that AD dementia is a chronic condition that develops silently for well over 10 years before the appearance of symptoms. An important consequence of these biomarker developments, however, is that AD, having been defined for more than a century by its clinical features, is increasingly being identified before the onset of clinical features as codified by abnormal biomarkers of the AD pathophysiologic process.[1] These biomarkers are expanding the toolkit for neurologists to accurately diagnose AD at the earliest stage of clinical symptoms

and to more precisely differentiate AD dementia from non-AD dementia syndromes. This article discusses the diverse clinical AD phenotypes, although the focus is on the most common amnestic-predominant form of AD. Updates on risk factors, diagnostics, and treatments apply to all forms of AD.

KEY POINT

● Women have nearly double the lifetime risk of developing Alzheimer disease relative to men.

EPIDEMIOLOGY AND RISK FACTORS

Understanding the sex and racial prevalence by age of onset of AD and knowing the most common risk factors for the disease allow the clinician to better determine the probability of AD, relative to another neurodegenerative disorder, as the likely cause for an individual's cognitive impairment.

Epidemiology

AD remains the leading neurodegenerative cause of dementia in the United States and the developed countries of the world.[2] In the United States, the incidence increases significantly after the seventh decade (from an annual incidence of 0.4% in those 65 to 74 years of age to 7.6% in those 85 years of age and older).[2] With the increase in the number of individuals living past 65 years of age, it is estimated that the total number of people with AD and related dementias will double in the next 30 years. However, in the United States and developed Western European countries, evidence exists of a decrease in the prevalence and incidence rates of dementia over the past 2 decades, attributed to a decrease in health-related risk factors such as cardiovascular and cerebrovascular disease and an increase in educational attainment.[3,4] Women have nearly double the lifetime risk of developing AD compared to men, but other than the greater life expectancy for women, the specific reasons for this remain uncertain. Likewise, most studies suggest Black and Hispanic American populations have a higher incidence and prevalence of AD and related dementias than non-Hispanic White populations, even when taking into account the decreased incidence across people of all backgrounds in the United States over the recent decades.[3-5] However, when taking into account body mass index and the presence of the *APOE* ε4 allele, Black older adults may have a decreased incidence of AD when compared with White older adults.[6] Recent studies of AD-related CSF biomarkers have shown differences in the levels of soluble amyloid, tau, and phosphorylated tau (p-tau) in Black people compared to non-Hispanic White populations[7,8] as well as markers of microglial activity[9] that may point toward potential biological-genetic differences as one contributor to the identified differences in AD risk, along with the probable social determinants of health that result along racial lines in the United States. However, as race increasingly is recognized as a social rather than biological construct, the understanding that social determinants of health likely play an important role in health disparities is growing. For more information on social determinants of health and heath disparities, refer to the article "Health Disparities in Dementia" by Joyce (Joy) E. Balls-Berry, PhD, MPE, and Ganesh M. Babulal, PhD, OTD, MSCI, MOT[10], in this issue of *Continuum*.

Although AD remains the most likely cause for a dementia with onset before the age of 65 (in the fifth or sixth decade), the relative proportion of non-AD causes, particularly frontotemporal dementia, increases in people younger than age 65 such that frontotemporal dementia is an important diagnosis to consider in middle-aged adults with dementia. With increasing age, the relative proportion of cases of dementia that are attributable to AD pathology alone decreases, and comorbid pathologies such as α-synuclein (Lewy bodies), transactive response

DNA-binding protein 43 (TDP-43), and vascular lesions increase.[11-13] This is particularly important when considering the use of biomarkers in the assessment of patients based on their age (CASE 1-1), as evidence exists of substantially higher rates of abnormal amyloid biomarkers for non-AD dementias from the sixth to ninth decades[1,15-16] and in cognitively normal individuals. For practical purposes, this means that the older an individual is, the less likely a positive biomarker for AD is to represent the sole cause of the dementia syndrome, but negative AD biomarkers strongly suggest a non-AD dementia syndrome.

Because of the prolonged asymptomatic period of time during which AD pathology develops and because amyloid-lowering therapies in symptomatic AD may not demonstrate a clear cognitive benefit, efforts to identify at-risk individuals (ie, cognitively normal with evidence of abnormal AD biomarkers) are increasing. One goal of these efforts is to then enroll eligible individuals into amyloid-targeting trials to test the effect of amyloid reduction for the prevention of cognitive decline[17-19] and for disease modification. However, because no obvious cognitive or functional deficits are seen during the presymptomatic stages of disease, it is only through the use of AD biomarkers that these individuals can be identified. Estimates of the prevalence of abnormal amyloid in cognitively normal individuals are driven primarily by age (approximately 10% in the sixth decade to approximately 45% in the tenth decade) and the presence of an *APOE* ε4 allele, which increases the prevalence by 2 to 3 times, meaning that *APOE* ε4 allele carriers are likely to have abnormal amyloid biomarkers at an earlier age.[16,20] Although the testing of AD biomarkers in cognitively normal individuals is not currently supported as standard clinical practice, if current prevention studies prove beneficial, it is likely that the use of these biomarkers for the screening of at-risk individuals will become more common.

Risk Factors

Major risk factors of AD can be divided into nonmodifiable and modifiable. The following section reviews the most consistently supported risk factors from both categories.

NONMODIFIABLE RISK FACTORS. Age is the strongest risk factor for AD. Beyond age, approximately 80% of the variance of AD risk appears to be attributed to genetic factors, with the *APOE* ε4 allele by far the strongest genetic risk factor.[21] *APOE* ε4 heterozygotes have a 2 to 3 times greater lifetime risk than non-ε4 carriers, and ε4 homozygotes have greater than 10 times the risk relative to *APOE* ε3/ε3 homozygotes (the most common *APOE* allele combination in US adults). In contrast to *APOE* ε4 carriers, *APOE* ε2 carriers have a substantially lower lifetime risk of developing AD.[22]

Given the role of the *APOE* allele in AD risk, therapeutic developments that specifically target this pathway are under way.[23] In less than 1% of all AD cases, dominantly inherited mutations of the amyloid beta precursor protein (*APP*) gene, presenilin 1 (*PSEN1*) gene, or presenilin 2 (*PSEN2*) gene result in early-onset AD. However, in the vast majority of individuals with late-onset AD, the genetic contribution to AD is likely multifactorial as more than 30 genetic loci have currently been identified and are related to a number of different processes (eg, cholesterol metabolism, lysosomal pathways and endocytosis, immune pathways). In the future, a polygenic risk score or hazard risk score could be used to identify an individual's risk of developing AD as part of the vision of precision

medicine applications to AD,[24] although currently the clinical application of the polygenic risks remains limited (CASE 1-2).

MODIFIABLE RISK FACTORS. The evidence on modifiable risk factors is based on both observational studies and interventional studies (ie, randomized clinical trials). Although discrepancies remain in the magnitude of specific risk factors on developing AD, relatively consistent evidence exists for a number of protective factors and detrimental health and lifestyle risk factors across the life cycle (FIGURE 1-2[25]).

Based on a 2020 meta-analysis of nearly 400 studies published worldwide, the strongest evidence for protective factors was found for length of childhood education, a higher body mass index in older adults, and participation in cognitively active activities.[25] Eight factors were found to have the strongest negative effects: diabetes, orthostatic hypotension, hypertension in midlife, head trauma, stress, depression, midlife obesity, and coronary artery bypass grafting surgery. Additionally, midlife exercise may decrease the risk of developing AD in a dose-dependent manner,[26] and interventional studies in those older than 65 years of age suggest that exercise may decrease the likelihood of developing dementia. It has been suggested that hyperhomocysteinemia may increase the risk of late-life dementia and that treatment with a combination of folic acid and vitamins B_6 and B_{12} may decrease the risk of developing AD.[27]

As most neurologists will encounter patients who are symptomatic, the impact of many of these risk factors at that stage of the disease is likely minimal. However, a knowledge of the modifiable risk factors is important for counseling adult children who often accompany their parents for evaluations.

Although links exist between alterations in the circadian system and AD, the causality between sleep disorders and neurodegeneration remains uncertain. It is clear that disruptions of sleep rhythm can be detected in those at risk of developing AD based on changes in CSF biomarkers[28,29] and that obstructive sleep apnea likely contributes to an acceleration of changes in AD biomarkers in cognitively normal and mildly cognitively impaired individuals.[30,31] Preliminary evidence indicates that treatment of obstructive sleep apnea may improve AD biomarkers.[31] At a minimum, the currently available data support the need for screening of sleep-related disorders in the evaluation of patients with cognitive impairment.

An infectious etiology of AD has been proposed by some researchers over the past 2 decades. A number of population-based studies from Asia[32,33] and Europe[34] have suggested that infection with herpesvirus type 1 or type 2 or varicella-zoster virus may increase the risk of late-life dementia and that treatment with antiviral medications may reduce the risk, but the strength of this association remains unclear. Current trials of antiviral therapies in patients with AD are under way and may provide more direct evidence of the role of neurotropic viruses and dementia progression.[35]

CLINICAL SYNDROME AND DIAGNOSTIC APPROACH

The diagnosis of AD remains grounded in the clinical evaluation, with supporting and confirmatory evidence coming from diagnostic studies. The focus in this article is primarily on the amnestic-predominant symptoms and how best to determine whether or not AD-related neuropathologic changes are the likely cause. Key to an accurate diagnosis is access to an informant who knows the patient well and can provide observations of the temporal course of

KEY POINTS

- The older an individual is, the less likely a positive biomarker for Alzheimer disease (AD) is to represent the sole cause of the dementia syndrome, but negative AD biomarkers strongly suggest a non-AD dementia syndrome.
- The positive predictive value of positive AD biomarkers in determining AD as the primary cause for dementia increases when used in people in their fifth to seventh decades compared to when used in people their eighth to tenth decades.
- The currently available data support the need for screening of sleep-related disorders in the evaluation of patients with cognitive impairment.

CASE 1-1

A 52-year-old right-handed woman with 16 years of education was referred because of an 18-month history of difficulty with occupational performance in her job as a high school teacher (eg, difficulties in preparing lessons, problems with learning students' names) and difficulties with focus (eg, problems with filling out tax documents and college aid paperwork, misplacing items). She had good insight into her cognitive changes and provided a number or specific examples of where she had noted changes from prior abilities. However, she was still working, shopping, cooking, and managing her schedule and reported no difficulties with navigation when driving or problems with forgetting conversations or events. She was healthy and had no family history of neurodegenerative diseases and no history of head injuries. She was initially diagnosed with adult-onset attention-deficit disorder and started on methylphenidate with no improvement. Following the initial dementia evaluation, a fludeoxyglucose positron emission tomography (FDG-PET) was obtained, which showed prominent hypometabolism of the parietal regions bilaterally and asymmetric left hemisphere temporal and frontal lobes (FIGURE 1-1A). She was referred for a second opinion for possible frontotemporal dementia due to temporal and frontal hypometabolism.

Her neurologic examination was remarkable for dyscalculia, mild left/right confusion with normal praxis, and fluent speech with frequent paraphasic errors and difficulty with repetition but normal naming. Cognitive testing demonstrated severe executive cognitive difficulties, impaired verbal fluency, and only mild verbal and visual learning and memory difficulties. Brain MRI showed mild atrophy and significant microhemorrhages in cortical areas suggestive of cerebral amyloid angiopathy (FIGURE 1-1B), thus inferring the additional presence of fibrillar amyloid-β plaques.

COMMENT

This case illustrates a nonamnestic-predominant cognitive pattern seen more commonly (but not exclusively) in early-onset Alzheimer disease. The patient exhibited a pattern referred to as the frontal-executive or dysexecutive pattern[14] that is frequently misdiagnosed as an attention-deficit disorder or anxiety disorder. The lack of changes in behavior and personality along with the patient's retained insight distinguish this from typical behavioral variant frontotemporal dementia, and the presence of MRI findings consistent with cerebral amyloid angiopathy in a 52-year-old with no history of head injuries, bleeding disorder, or hypertension is strongly suggestive of amyloid-β pathology, supporting a diagnosis of Alzheimer disease as the likely cause of her symptoms and abnormal FDG-PET scan.

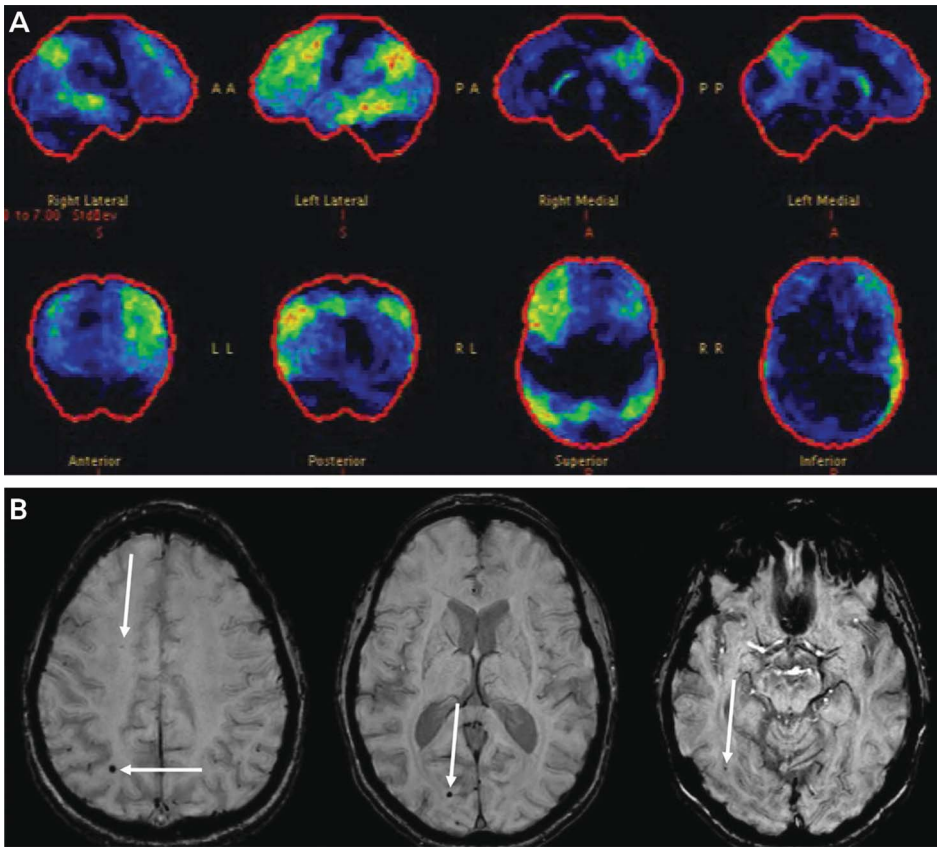

FIGURE 1-1

Imaging of the patient in CASE 1-1. *A*, Fludeoxyglucose positron emission tomography (FDG-PET) scan shows prominent hypometabolism of the parietal regions bilaterally and asymmetric left hemisphere temporal and frontal lobes. Color represents difference relative to normal population, *yellow-red* indicating more severe hypometabolism. *B*, Axial susceptibility-weighted imaging (SWI) shows cerebral microbleeds (*arrows*) in a cortical distribution, supportive of cerebral amyloid angiopathy in an early-onset Alzheimer disease presentation.

symptom development and the degree of functional impairment resulting from the cognitive impairment. The American Academy of Neurology (AAN) guidelines for the diagnosis of dementia recommend a cognitive screen, structural brain imaging (MRI or CT), screening for depression, and assessment of serum thyroid-stimulating hormone (TSH) and vitamin B_{12} levels.[36] Although these recommendations capture the minimum that should be performed, a thorough review of medications, potential toxic exposures (eg, excessive alcohol, occupational exposure), and modifiable factors that may contribute to cognitive decline should be included as part of any assessment of a patient with possible dementia. Additionally, a thorough review of the family history, particularly of first-degree relatives, should be performed for the ascertainment of dementia or related neurodegenerative diseases. As part of the initial assessment and follow-up, a review of legal and safety issues should also be performed. For more information on fluid-based biomarkers, refer to the article "Fluid Biomarkers in Dementia Diagnosis" by Suzanne E. Schindler, MD, PhD,[37] and for more information on imaging-based biomarkers, refer to the article "The Value of Neuroimaging in Dementia Diagnosis" by Cyrus A Raji, MD, PhD, and Tammie L. S. Benzinger, MD, PhD,[38] in this issue of *Continuum*.

CASE 1-2

A 53-year-old woman presented for consultation for memory problems. She worked as a project manager and reported difficulty in recalling names of new team members and keeping track of timelines and that she had recently missed a meeting because she had forgotten about it. Her partner reported no difficulties with activities at home and no consistent memory problems. Her past medical history was notable only for untreated obstructive sleep apnea and prediabetes. Her 83-year-old mother had been diagnosed with dementia 3 years earlier, and her maternal grandfather had dementia in his midseventies. The patient had been told that her mother carried an *APOE* ε4 allele when she had taken part in a research study.

Her examination was normal, including performance on detailed neuropsychological testing. Thyroid-stimulating hormone (TSH) and vitamin B_{12} levels were normal. Although she was reassured about her normal test results, she asked about purchasing a direct-to-consumer genetic test for Alzheimer disease (AD). She was advised to begin treatment of her obstructive sleep apnea and to consult with a dietitian about treating her prediabetic state.

COMMENT

Although commercial testing for AD genetic risk is available, mostly based on the *APOE* gene, the benefit of testing in adults with no clear cognitive symptoms is limited. The lack of an early-onset pattern of dementia would not support referral to genetic counseling for possible autosomal dominant AD. In adults with a family history of late-onset AD, information on modifiable risk factors should be provided as the current best practice. If disease-modifying therapies are identified, genetic testing for AD risk genes may have utility.

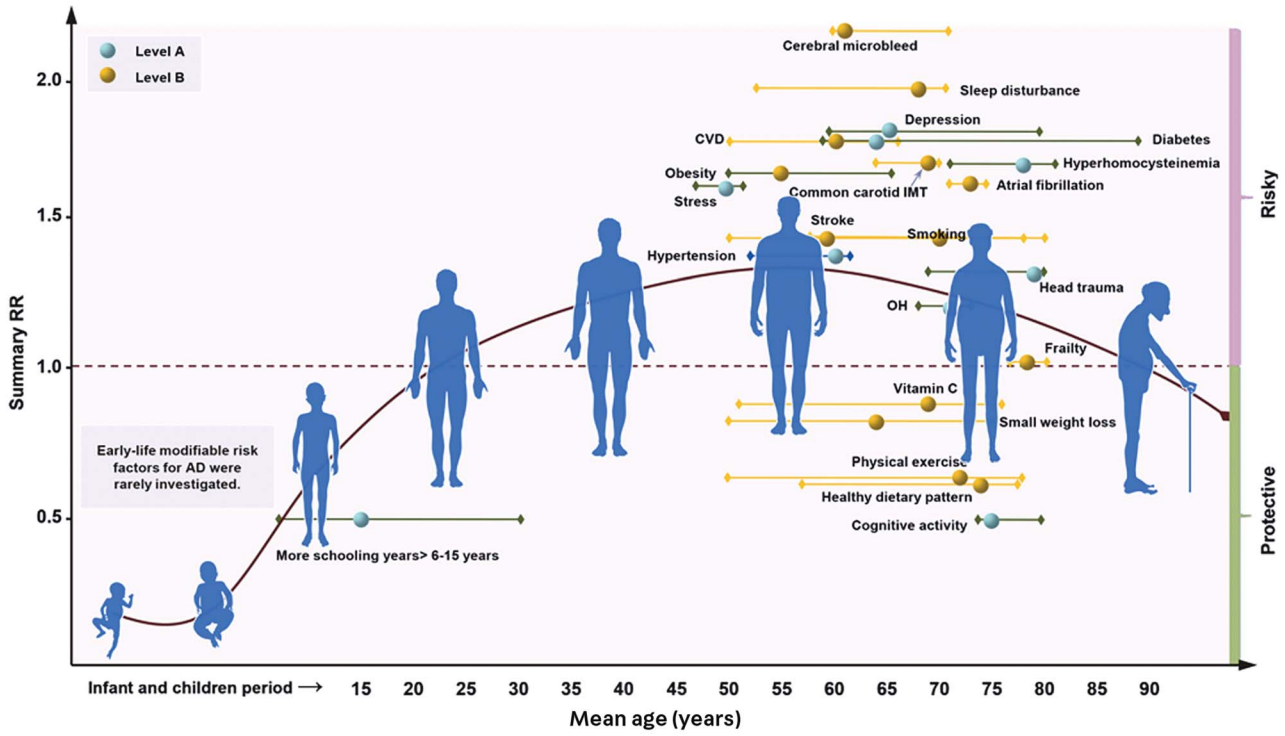

FIGURE 1-2

A life course Alzheimer disease (AD) risk estimate (relative risk [RR]) of potential modifiable risk factors based on evidence (Level A or Level B) from publications. The lower half represents potential protective factors, and the upper half represents potential risk factors. The length of the horizontal lines indicates the age at which each risk factor may have the greatest impact and therefore the point of intervention.

CVD = cardiovascular disease; IMT = intima-media thickness; OH = orthostatic hypotension.

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Clinical Approach

Because the process of neurodegeneration in AD evolves over many years during which synaptic and neuronal loss occurs, the symptomatic phase represents the end stage of a 1- to 2-decade process that once fully established is inexorably progressive. Once symptoms appear, the time to death is most commonly in the range of 7 to 10 years.[39,40]

Additionally, a period of time of mild to moderate synaptic dysfunction likely exists before severe neuronal loss, during which symptoms are inconsistent and/or very mild. Likewise, at an individual level, the expression of the disease can vary significantly between patients. Nonetheless, patterns of cognitive decline occur that are more common in AD and likely reflect regional vulnerability that is intrinsic to the aging human brain[41-43]; in AD, this is typically visual and verbal memory. Additionally, it is important to recognize that the progression of AD is associated frequently with noncognitive symptoms (eg, mood disorders, motor changes, circadian rhythm alterations).

Prodromal/Early Alzheimer Disease/Mild Cognitive Impairment

At the earliest stages of AD, before significant functional impairment (ie, impairment of instrumental activities of daily living that eventually result in the loss of independent function), subtle cognitive changes can often be detected by

patients or their collateral source. Multiple terms are used for the earliest detectable stages of cognitive decline, including prodromal AD; very early AD; mild cognitive impairment (MCI); and cognitively impaired, with no dementia. The major distinguishing factor between these terms is the establishment of the underlying cause (ie, a neurodegenerative or non-neurodegenerative cause), which should be the goal as it has significant implications for determining the likelihood of progression. The evaluation of a patient with mild cognitive changes should answer four key questions:

- **Is the cognitive symptom clearly a decline from the patient's previous cognitive level?**
- **Is the cognitive symptom consistent?**
- **Does the symptom have a clear effect on the patient's day-to-day function?**
- **Does the patient show clear evidence of impairment on cognitive assessment?**

CASE 1-3

A 71-year-old man presented for evaluation of concerns from his family over inconsistent memory problems (eg, repeating himself, misplacing items) and depressive symptoms. Two years earlier, he had a right subcortical stroke with mild motor symptoms. The family reported mild depressive symptoms only partially responsive to sertraline. He continued to complete projects around the home and had no driving issues, but he required increased reminders for appointments and medications and had been more withdrawn from family activities. He was a retired plumber.

His neurologic examination was remarkable for subtle left upper extremity pronator drift only. His Montreal Cognitive Assessment (MoCA) score was 26/30 (>26/30 normal) (-2 on recall, -1 on serial 7s, -1 on clock drawing), and he endorsed 7/15 (<5 normal) items on the Geriatric Depression Scale short form. MRI demonstrated a right internal capsule lacune and mild periventricular fluid-attenuated inversion recovery (FLAIR) hyperintensities. CSF analysis found a decreased amyloid-β42 level and elevated phosphorylated tau at position 181 (p-tau181) and total tau levels consistent with a biomarker pattern of Alzheimer disease (AD) as the probable cause for the patient's mild cognitive changes.

COMMENT

The availability of commercial platforms for testing AD CSF biomarkers has increased the number of diagnostic tools for neurologists. This case highlights a scenario in which biomarkers can be especially helpful in determining whether subtle cognitive changes are attributable to AD, particularly when other potential causes for cognitive problems are identified. The patient's relatively young age at symptom onset increases the probability that the AD biomarker results represent a true positive test result and are the likely cause of the patient's symptoms.

The higher the number of positive responses to these questions, the higher the probability that the patient's symptoms represent the earliest stages of a progressive neurogenerative disease (regardless of the term used to define it). The most common diagnostic term currently used for patients in the earliest stages of cognitive decline is MCI. MCI is meant to identify a transition state between normal cognition in older adults and dementia (which requires an associated functional decline) and represents a risk state for developing dementia, particularly in the case of amnestic MCI. A limitation of MCI as a diagnosis is that it is agnostic to the underlying cause; subsequently, a wide range of prevalence and risks of progression has been reported. Moreover, the diagnosis of MCI as most commonly used has relied on a distinction between normal or impaired function to distinguish MCI from dementia. However, in most instances, the point at which mild cognitive changes begin to impact day-to-day function, even subtly, is when individuals are likely to seek medical guidance. Therefore, a strict reliance on normal function but impaired cognitive abilities to make a diagnosis of MCI or dementia, particularly in a progressive neurodegenerative disorder with a high level of interindividual variability, may become somewhat arbitrary. For example, a 2018 meta-analysis from the AAN Practice Guidelines[44] found a risk of progression from MCI to dementia over 2 years of 14.9% (95% confidence interval, 11.6%-19.1%) but a chance of reversion to normal of 14% to 39%. However, in those with evidence of a positive amyloid-β (Aβ) biomarker (as determined by amyloid PET), the risk of conversion to dementia in 2 years is likely between 22% and 50%.[45,46] Therefore, in addition to assessing for reversible causes of cognitive changes, efforts to identify a neurodegenerative source should be the primary goal if a diagnosis of MCI is considered. If access to specific CSF- or PET-based biomarkers is limited, the use of MRI to evaluate for evidence of global or hippocampal atrophy can provide support for both a probable underlying neurodegenerative cause and for risk of progression. However, a recent Cochrane Review of the use of MRI measures of hippocampal volumes did not find strong enough evidence to suggest the use of MRI alone in predicting a neurodegenerative cause for MCI.[47]

When AD is the probable cause of early cognitive decline/MCI, the most frequently reported symptoms are related to changes in episodic memory, both verbal and nonverbal (**CASE 1-3**). In addition to asking about specific examples (eg, misplacing items, forgetting appointments, repeating questions, getting lost, forgetting to pay bills), it can be helpful to inquire about autobiographical events from the past 1 to 4 weeks, corroborated by an informant.[48]

Basic cognitive screening assessments (eg, the Mini-Mental State Examination [MMSE], the Montreal Cognitive Assessment [MoCA]) may be normal but in the case of early AD will typically demonstrate some difficulties with memory. Following amnestic deficits, dysexecutive problems are commonly reported in the early stages of AD (eg, poor decisions while operating a motor vehicle or in managing complex paperwork/financial decisions). Although no appropriately powered studies have directly compared all cognitive screening tests, evidence indicates that the MoCA (with a cutoff of 24 or 25) is likely more sensitive and specific in detecting the earliest stages of cognitive impairment than the MMSE.[49] In the case of very mild symptoms, a comprehensive neuropsychological assessment, if available, can be helpful in confirming and quantifying the level of impairment. Screening for a mood disorder, such as depression, anxiety, or apathy, can provide information supportive of an

KEY POINTS

- The American Academy of Neurology guidelines for the diagnosis of dementia recommend a cognitive screen, structural brain imaging, screening for depression, and assessment of serum thyroid-stimulating hormone and vitamin B_{12} levels. Although these recommendations capture the minimum that should be performed, a thorough review of medications, potential toxic exposures, and modifiable factors should be included as part of any assessment of a patient with possible dementia.
- Although not definitive, the presence of AD-specific biomarkers increases the likelihood of progression to dementia in patients with mild symptoms.
- The presence of hippocampal atrophy on brain MRI is insufficient to diagnose AD as the cause of mild cognitive impairment.
- The most common core cognitive domain affected in AD is episodic memory.

underlying neurodegenerative cause for the mild cognitive symptoms. Mild behavioral impairment is considered a risk state for neurodegenerative dementia and is defined as the emergence of mild neuropsychiatric symptoms in late life in cognitively normal individuals.[50,51]

During the early stages of the disease, it is also important to review legal issues related to health and financial decisions (eg, durable power of attorney, end-of-life medical decisions) with patients and their supporters to best ensure the patient's autonomy is respected by allowing them to inform these decisions.

Mild to Moderate Symptoms

When a patient is evaluated at the stage at which a clear decline in cognitive function relative to previous levels is seen and the decline results in impairment of independent function (ie, meeting the criteria for dementia), beyond ensuring a nonreversible cause, the focus is to determine the probable cause. As AD progresses to the mild to moderate stages, the overall clinical picture remains primarily a cognitive-predominant syndrome (worsening memory, increasing language problems, and greater visuospatial decline). A pattern of early and progressive episodic memory remains the most common core symptom in typical AD. The appearance of significant movement disorders, behavioral changes, pronounced hallucinations, or severe hypersomnia, even at the moderate stage, should prompt consideration of another diagnosis or at least pronounced copathology. However, mild motor symptoms, mood disorders (primarily affective disorders), and circadian rhythm changes emerge during the moderate stages of AD dementia (FIGURE 1-3).

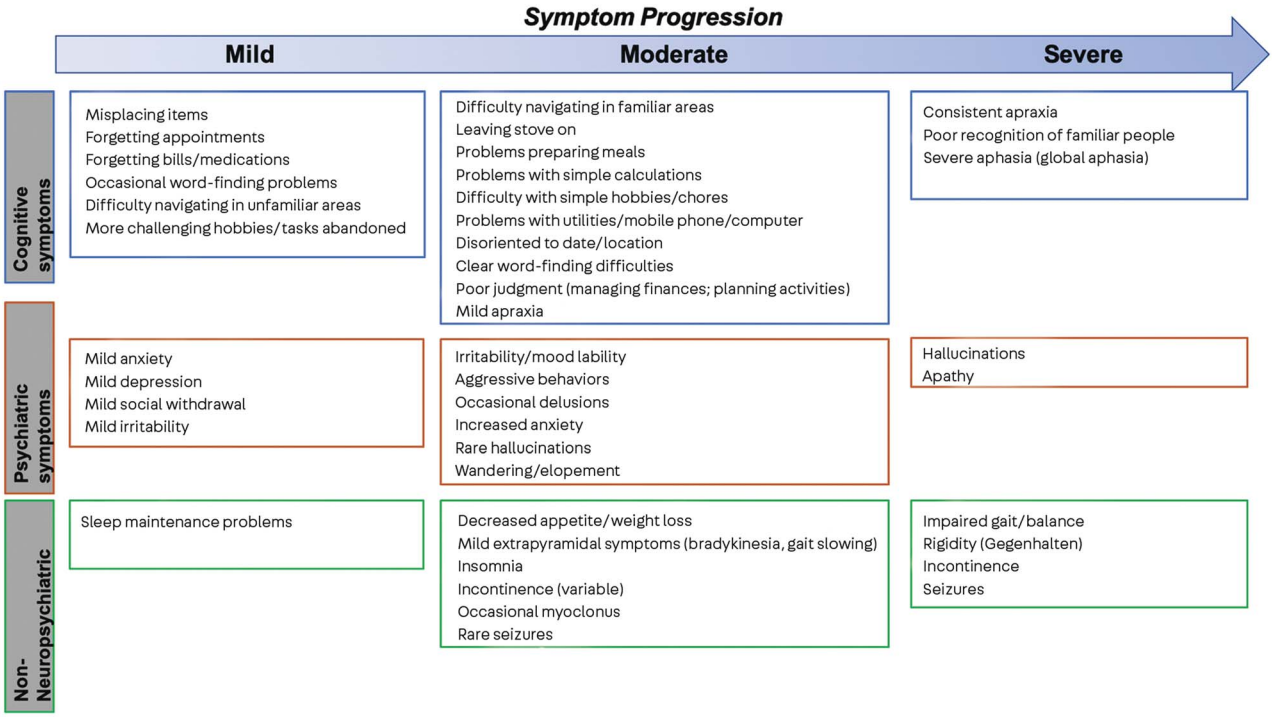

FIGURE 1-3
Cognitive and noncognitive symptoms associated with Alzheimer disease progression.

It is also during the moderate stages of disease that judgment and decision-making abilities may begin to be significantly affected, resulting in a decline in independent function (eg, driving, managing financial decisions, shopping and cooking unaided, difficulty with using appliances/television/computer/mobile phone). Therefore, a careful review of safety is important during each assessment. It is the loss of independent function that typically marks the transition to the moderate stages of AD. The loss of independence in basic activities of daily living (eg, dressing, personal hygiene, preparation of simple meals, and chores) that results in a major increase in burden for those caring for patients with AD typically begins during the moderate stages of the disease (MMSE <18). Moreover, the decline in judgment that occurs increases the risk of issues of safety, necessitating a review of driving performance, prohibiting access to firearms, and an assessment of an individual's ability to be left unsupervised. Social workers, geriatric case managers, and memory care day programs can be instrumental in dealing with the loss of function that occurs with AD and relieving caregiver stress.

KEY POINTS

- Mild behavioral impairment is considered a prodromal dementia syndrome of newly developed neuropsychiatric symptoms in cognitively normal older adults.
- The presence of noncognitive problems characteristic of the moderate to severe stages of AD in patients with only mild cognitive symptoms should raise concern for an alternative diagnosis.

Behavioral and Noncognitive Symptoms

In most instances, as the neurodegeneration progresses to the moderate AD stage, the frequency of noncognitive symptoms increases significantly. Although the transition from mild to moderate to severe symptoms is more fluid than outlined in FIGURE 1-3, the presence of noncognitive problems characteristic of the moderate to severe stages in patients with only mild cognitive symptoms should raise concern for an alternative diagnosis. During the stage of mild to moderate disease, problems with incontinence may begin to develop and continue to worsen into the more severe stages. Because of the impact incontinence can have on patients getting out of the home, it is important to evaluate for this and provide options for management or referral to an appropriate health care provider.

PSYCHIATRIC SYMPTOMS. Although mild irritability and mood changes are common during the initial stages of AD, the frequency and magnitude of these increases during the moderate stages. Agitation, depressive symptoms, and anxiety are more common and may impact patient safety. Moreover, with progression of cognitive decline, particularly when MMSE scores fall below 20, the frequency of psychotic symptoms, primarily delusions (eg, paranoia, accusations of infidelity of spouses, misidentification of familiar individuals or environments) but also hallucinations (eg, simple visual hallucinations of objects or people), increase significantly and may reach as high as 50% of patients.[52,53] From a prognostic standpoint, the presence of psychotic symptoms is also associated with a more rapid progression and higher rate of entering an institutional setting (CASE 1-4).[53]

NONCOGNITIVE SYMPTOMS. Like psychiatric and behavioral symptoms, the development of non-neuropsychiatric symptoms increases significantly during the moderate to severe stages of disease. These symptoms can be classified as motor or nonmotor. In moderate AD during the stage of significant functional impairment, extrapyramidal symptoms, mild tremor, and myoclonus develop in approximately 30% to 50% of patients, and clinical seizures range from 2% to 15%.[54-57] Relative to non-AD and non–Lewy body dementias, myoclonus and seizures are likely less common in vascular and frontotemporal dementia,[57]

which can be used as a clinical symptom to help differentiate AD from non-AD dementias.

DISORDERS OF HOMEOSTASIS/HYPOTHALAMIC FUNCTION. Both circadian rhythm disorders (particularly insomnia and increased sleep fragmentation) and weight loss tend to increase as AD progresses. These changes are suggested to reflect degeneration of the hypothalamus.[58] As sleep disorders are not uncommon in most neurodegenerative disorders at some point, patterns of circadian disruption may be used to help distinguish between the different disorders. For example, dementia with Lewy bodies is commonly associated with sleep disorders, but evidence suggests greater daytime sleepiness (more than 2 hours) and more frequent fluctuations of arousal and orientation are seen in dementia with Lewy bodies than in AD.[59] For more information on dementia with Lewy bodies, refer

CASE 1-4

A 73-year-old healthy right-handed man presented for evaluation of a 1-year history progressive cognitive and functional decline and psychiatric symptoms. During a vacation 1 year earlier, he became lost while driving back to his hotel. His wife reported that in the 12 months since, he had demonstrated difficulties with managing home finances and the schedule for a club he was involved in and now needed reminders to take his medications. Five months before this evaluation, he had developed anxiety and paranoid delusions without hallucinations, which required a brief psychiatric hospitalization seemingly precipitated by an acute medical issue experienced by his wife. His wife reported that he had no significant motor problems, sleep problems (eg, hypersomnia or rapid eye movement [REM] sleep behavior disorder symptoms). He was otherwise healthy but had a long-standing history of anxiety. He was taking clonazepam 0.5 mg/d and quetiapine 50 mg at night. His family history was remarkable for mild dementia in his mother in her late eighties. The patient was a retired computer programmer.

The neurologic examination was remarkable for subtle left upper extremity rigidity and mild slowing of gait but no apraxia, neglect, agnosia, tremor, or micrographia. Cognitive testing identified impaired verbal memory and executive function with normal semantic memory and visuoconstruction (as demonstrated by clock drawing and intersecting pentagons). Brain MRI brain was remarkable for mild cortical atrophy.

The motor findings suggested the possibility of a Lewy body dementia. However, amyloid positron emission tomography (PET) was obtained, and the patient was found to have moderate to severe amyloid-β plaques suggestive of Alzheimer disease (AD) pathology as the cause of his symptoms (FIGURE 1-4).

Over the next 3 years, his delusions persisted and required increasing treatment; he also had significant cognitive and functional decline (with Mini-Mental State Examination [MMSE] score declining from 25 to 10 in 3 years) and developed generalized tonic-clonic seizures. He died 5 years after diagnosis.

to the article "Cognitive Syndromes Associated With Movement Disorders" by Jennifer G. Goldman, MD, MS, FAAN, and Samantha K. Holden, MD, MS,[60] in this issue of *Continuum*. Disorders of sleep can be distressing for caregivers of patients with AD and require a comprehensive approach to treatment.

Age of Onset in Alzheimer Disease

Although AD incidence begins to increase substantially in the eighth decade, AD also is the most common cause of dementia with onset in the fifth to seventh decades of life. Some important points should be considered when evaluating those younger than 65 years of age. First, a nonamnestic (focal variant) presentation is more common in early-onset AD, often leading to an initial misdiagnosis (eg, anxiety disorder, adult attention-deficit disorder). The focal variants of AD typically fall into three broad categories: a visuospatial variant, a

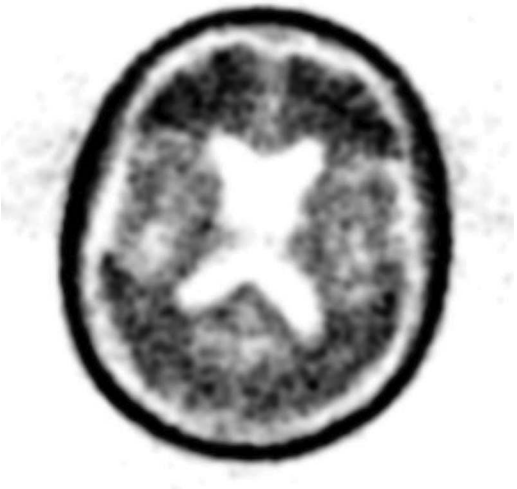

FIGURE 1-4
Imaging of the patient in CASE 1-4. Amyloid positron emission tomography (PET) shows reduced gray-white matter differentiation of the bilateral frontal, parietal, and posterior-lateral temporal areas on florbetapir PET scan suggestive of moderate to severe amyloid-β neuritic plaques. Dark (*black*) regions in frontal and parietal cortices indicate retention of florbetapir tracer to amyloid plaques.

COMMENT

This case represents a patient with AD with severe psychiatric symptoms. Although a combination of AD and dementia with Lewy bodies cannot be ruled out, the patient's relatively young age (72 at symptom onset), lack of significant parkinsonism and other supportive signs of dementia with Lewy bodies, and presence of confirmatory AD biomarkers suggests a high probability of AD as the primary cause. The patient's relatively rapid progression highlights a more aggressive phenotype than is typical in patients with AD.

language variant, and a frontal-executive/behavioral variant.[14] For more information on AD variants, refer to the article "Atypical Alzheimer Disease Variants" by Angelina J. Polsinelli, PhD, and Liana G. Apostolova, MD, MSc, FAAN,[61] in this issue of *Continuum*. However, in the majority of cases, cognitive assessments of patients with early-onset AD will still identify a clear amnestic pattern (FIGURE 1-5).[62]

Second, the rate of progression in patients with early onset may be more rapid than the typical amnestic-predominant pattern most common in later ages of onset. However, postmortem studies suggest that rather than the age of onset as the determinant of the rate of progression, it more likely the pattern of regional neurofibrillary tau pathology burden that determines the rate of progression[63]; specifically, patients with evidence of a greater ratio of neurofibrillary tau pathology outside of the temporal lobes to that in the hippocampus (hippocampal sparing) had evidence of a significantly faster rate of progression than those with neurofibrillary tau pathology limited to the hippocampus and, as a group, were younger. In the clinical setting, this may be approximated with cognitive testing demonstrating a greater ratio of nonmemory test impairment to memory impairment and MRI patterns of atrophy demonstrating greater cortical-to-hippocampal atrophy (FIGURE 1-6).

Third, an important consideration in patients with early-onset AD, particularly those younger than 55 years of age, is the increased possibility of a dominantly inherited mutation. In the presence of a family history with two or more generations of early age of onset, particularly with multiple family members

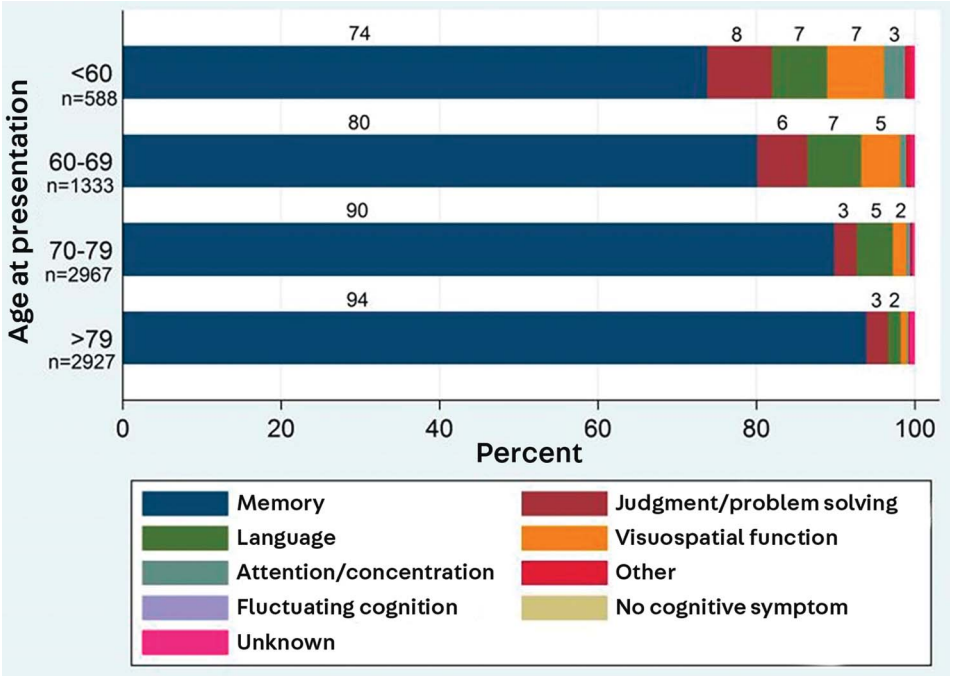

FIGURE 1-5
Initial pattern of cognitive syndrome for patients with autopsy-proven Alzheimer disease based on age of onset. Of patients with onset before the age of 60, 26% initially manifested with nonamnestic-predominant symptoms compared to 10% in those between the ages of 70 and 79 and 6% in those older than 79 years of age.

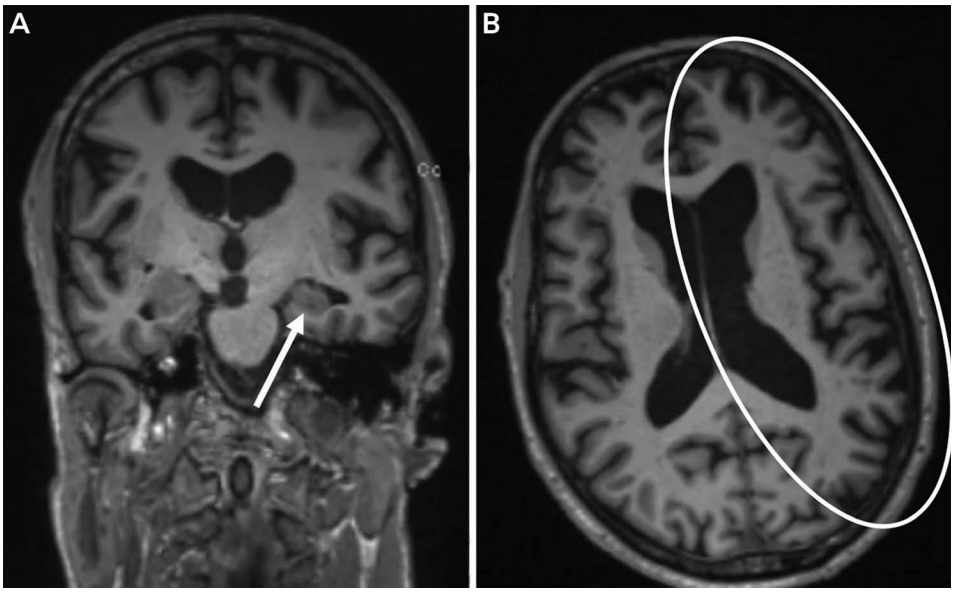

FIGURE 1-6
Disproportionate cortical-to-hippocampal atrophy. Coronal (*A*) and axial (*B*) T1-weighted images of a 67-year-old with a dysexecutive-predominant clinical phenotype. The *arrow* highlights a relatively normal left hippocampal volume relative to the significant cortical atrophy (left hemisphere greater than right, *white circle*). Of note, the coronal image highlights an oblique angle of scan, resulting in asymmetric view of hippocampi and pseudoatrophy.

KEY POINT

- The presence of atypical motor features (eg, spasticity, ataxia) in a patient with confirmed early-onset AD (with biomarker support) should raise concern for a possible dominantly inherited mutation.

per generation, a genetic cause should be considered and referral for genetic counseling discussed with patients and families. A 2019 study in France found that greater than 10% of individuals without a clear family history and an age younger than 51 at symptom onset were found to have a dominant AD mutation.[64] Additionally, the presence of atypical motor features (eg, spasticity, ataxia) in a patient with confirmed early-onset AD (with biomarker support) should also raise concern for a possible dominantly inherited mutation.

Finally, in those with a younger age of onset, AD biomarkers can be particularly helpful in confirming a diagnosis of AD over a non-AD cause. With increasing age, the probability of having evidence of AD-related neuropathologic changes, particularly Aβ plaques, in the absence of clinical symptoms increases, particularly in the eighth to tenth decades of life.[16] The likelihood of an individual with cognitive decline having evidence of abnormal Aβ–related biomarkers in the eighth to tenth decades, regardless of whether it is likely to be the primary cause, is much higher. The positive predictive value of abnormal AD-related pathologic biomarkers (CSF or PET) is therefore greater in younger patients.[15]

PATHOLOGY AND PATHOLOGY-RELATED BIOMARKERS

The core pathologies of AD are extracellular aggregated Aβ plaques and intracellular neurofibrillary tau tangles. Although neurofibrillary tau and Aβ plaques are typically conceptualized as static homogeneous hallmarks of AD pathology, recent work from postmortem tissue has elucidated the microstructural pattern of tau pathology in AD relative to non-AD tauopathies[65,66] and highlighted how individual differences in the rate of progression of AD might relate to distinct differences in the structure of both Aβ plaques and neurofibrillary tau.[67] Recent cryogenic electron microscopy has been able to identify distinct

microstructural changes related to the different tauopathies that may help us to understand some of the reasons for distinct clinical syndromes. Additionally, for tau in particular, evidence exists that differences in the phosphorylation patterns between individuals might account for differences in the rate of progression.[68] As the number of tau-related (phosphorylation, truncation) peptides that can be measured in the CSF and serum has significantly expanded,[69-72] it will be important to determine whether the developments in fluid biomarkers of tau and Aβ will be able to more accurately predict clinical progression or whether their utility will be limited to distinguishing AD from non-AD causes of dementia.

Pathology-related Biomarkers

Recently, major advances have been made in the development of imaging and fluid biomarkers that represent different components of amyloid and tau-related pathologic changes, which allow for an increase in the accuracy of diagnosis before death. For more information, refer to the section on diagnostic approach in this article and to the articles "Fluid Biomarkers in Dementia Diagnosis" by Suzanne E. Schindler, MD, PhD,[37] and "The Value of Neuroimaging in Dementia Diagnosis" by Cyrus A. Raji, MD, PhD, and Tammie L. S. Benzinger, MD, PhD,[38] in this issue of *Continuum*. Efforts have been made to integrate these biomarkers into the classification of individuals, primarily in research cohorts.[73] Recognizing the need for abnormal amyloid and tau pathology to confirm the diagnosis of AD, along with the hallmark neurodegeneration of the disease, a recent biomarker-based classification scheme was proposed to identify AD-related pathophysiologic profiles, called the A/T/N (for amyloid, tau, and neurodegeneration) criteria (TABLE 1-1).[73] Within this classification system, the use of AD-specific and nonspecific biomarkers are dichotomized as normal or abnormal to provide eight possible combinations, with A-/T-/N- suggesting very low probability of AD-related biomarker changes and A+/T+/N+ suggesting a high probability of AD-related biomarker changes and different combinations between of various levels of uncertainty. Although the A/T/N classification is

TABLE 1-1 **Current Biomarker Measurements Representing the Different Pathophysiologic Processes of Alzheimer Disease in the Amyloid/Tau/Neurodegeneration Criteria**

Pathologic process	Fluid biomarker	Brain imaging biomarker
Amyloid-β (Aβ) plaques	CSF Aβ40 and 42; plasma Aβ42/Aβ40 ratio	Amyloid PET[a]
Tau	CSF phosphorylated tau (p-tau); plasma p-tau	Tau PET[b]
Neurodegeneration	CSF total tau; CSF neurofilament light chain (NfL); plasma NfL	FDG-PET hypometabolism characteristic of Alzheimer disease; MRI (volumetric changes) characteristic of Alzheimer disease

CSF = cerebrospinal fluid; FDG-PET = fludeoxyglucose positron emission tomography; MRI = magnetic resonance imaging; PET = positron emission tomography.
[a] Currently approved amyloid tracers include florbetaben F 18, florbetapir F 18, and flutemetamol F 18.
[b] Currently approved tau tracers include flortaucipir F 18.

meant to remain distinct from a clinical diagnosis, its application to those with cognitive impairment should increase the diagnostic accuracy of AD or non-AD dementia in patient evaluations and might provide helpful information on predicting the likelihood of future decline in those with very mild symptoms.[74] However, the true application of these new research-based criteria needs validation and is likely to undergo further revisions.[75]

Positron Emission Tomography–based Biomarkers

Currently four tracers for Aβ plaques and neurofibrillary tau have been approved by the US Food and Drug Administration (FDA). For both Aβ and tau pathologies, postmortem studies have demonstrated a strong regional correlation between premortem PET scans and postmortem pathology. Subsequently, both are considered valid markers for AD-related Aβ plaque and neurofibrillary tau changes in those with symptoms of dementia. Additionally, preliminary studies suggest that regional tau PET tracer retention correlates broadly with different clinical phenotypes of AD (FIGURE 1-7).[76] However, it should be noted that current tau PET tracers do not accurately identify non-AD–related tau aggregates, suggesting that currently approved tau PET tracers are more specific to AD-related tau pathology. However, currently AD-specific PET scans (Aβ plaque and tau PET) are not reimbursed by Medicare or private insurers in

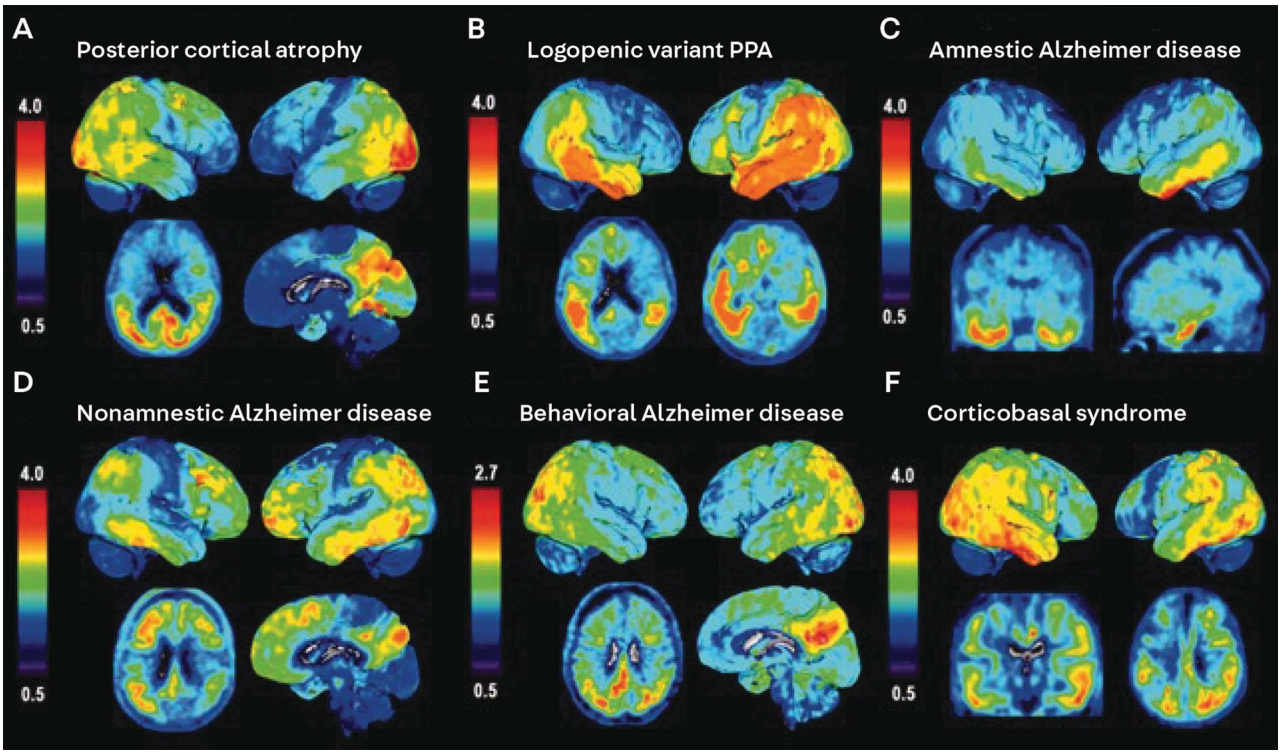

FIGURE 1-7

Regional tau positron emission tomography (PET) correlates with Alzheimer disease clinical phenotypes.Tau PET binding in Alzheimer disease highlights the differences in the pattern of neurofibrillary tau burden that reflects differences between amnestic and nonamnestic-predominant phenotypes. Color scale represents standardized uptake value ratio (SUVR), with *yellow-red* representing regions of higher retention of tau PET tracer.

PPA = primary progressive aphasia.

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the United States, thereby significantly limiting the utility of this diagnostic modality in clinical practice.

Fluid-based Biomarkers

The most well-established fluid biomarkers of AD pathophysiologic changes are from the CSF: Aβ42 and Aβ40 peptides, total tau, and p-tau.[77] The typical pattern of AD is low Aβ42 levels (which are proposed to occur as soluble Aβ42 is sequestered into Aβ plaques) and elevated p-tau and total tau (which are proposed to represent the changes in tau metabolism and release from neurons in response to Aβ plaques). However, major advances have recently been made in the development of validated blood-based biomarkers of both Aβ and AD-related tau changes.[78] One blood-based biomarker has received a Breakthrough Device designation from the FDA and is now available in the United States.[79,80] (Readers should note that the blood-based amyloid-β test is licensed by C2N, which was cofounded by colleagues of Dr McDade. Washington University will receive royalties from the use of this test, but Dr McDade will not receive personal compensation.) The blood-based biomarkers may become an important tool for diagnosing AD should current findings from the research cohort translate to clinic- and community-based populations. Additional blood-based biomarkers specific to AD-related changes of tau[71] and nonspecific markers of neurodegeneration (eg, neurofilament light chains [Nfl]) and central nervous system immune function (glial fibrillary acidic protein [GFAP])[81] are likely to improve the diagnostic and prognostic capabilities of neurologists in the near future as well.

TABLE 1-2 **Comorbid Conditions and Associated Treatments as Part of a Comprehensive Approach to Treating Alzheimer Disease**[a]

Comorbidity	Treatment approach
Elevated homocysteine/low folic acid and cyanocobalamin	Folic acid supplementation, vitamin B_{12} supplementation, review diet for any major deficiencies
Hypertension	Antihypertensives, diet, exercise
Orthostatic hypotension	Adequate hydration, supportive stockings, pharmacologic therapy for refractory cases
Sedentary lifestyle; social isolation	Structured activity programs (memory care day programs), in-home services (social support), scheduled activities outside of the home (with opportunity for respite care for primary caretakers)
Alcohol or other substance abuse	Remove access, educate family/caregivers on need for removal
Use of central acting anticholinergic/ antihistaminergic drug	Discontinue and identify alternative therapies to treat symptoms being targeted (insomnia, incontinence, seasonal allergies)
Obstructive sleep apnea	Weight loss, continuous positive airway pressure (CPAP), oral device, avoidance of central-acting sedatives
Insomnia	Increase daytime activities, limit caffeine, address medications potentially contributing (selective serotonin reuptake inhibitors [SSRIs], antihypertensives), alcohol use, melatonin and judicious use of nonbenzodiazepine sedatives

[a] Well-controlled clinical trials may not have been performed for each comorbidity to provide a specific class of recommendation.

TREATMENT OF ALZHEIMER DISEASE

The therapeutic approach to AD is broad and covers pharmacologic and nonpharmacologic considerations that are highlighted below. Additionally, the stress associated with caregiving of individuals with AD requires consideration of care plans that extend to both the patient and their support network.

General Approach

The treatment of AD requires a comprehensive pharmacologic and nonpharmacologic approach that evolves with disease progression and targets both the cognitive and noncognitive symptoms (TABLE 1-2). With the decline in functional abilities (day-to-day activities), the alterations of circadian rhythm, and the frequent neuropsychiatric symptoms that occur in individuals with AD, a tremendous caregiver burden often occurs; addressing these issues is part of the overall treatment plan. Although the underlying neurodegenerative process is the cause of the progressive symptoms of AD, other medical comorbidities likely exacerbate some of the symptoms and may accelerate the progression of the disease and thus should addressed.

Cognitive Impairment

No disease-modifying therapies for AD or new therapies had been approved by US regulatory agencies since 2003 until the Accelerated Approval indication granted by the FDA for aducanumab in June 2021. Aducanumab is an anti-Aβ immunotherapy that has demonstrated a strong effect on Aβ plaque reduction (as measured by amyloid PET).[82] However, the clinical benefit of aducanumab in mild AD remains controversial as the approval was, in fact, based primarily on the ability of the drug to reduce Aβ pathology and an assumption that the reduction of Aβ pathology would result in a slowing of cognitive decline.[83] Additional recent phase 2/3 studies of other anti-Aβ immunotherapies have suggested therapeutic benefit,[84] and trials are under way to better test the potential benefit of removing Aβ plaques in symptomatic AD.

Aducanumab has been approved for the treatment of MCI due to AD and mild AD dementia (MMSE score >23 or Clinical Dementia Rating [CDR] of 0.5 ,which indicates very mild dementia) and, although not explicitly listed in the drug's label, requires the presence of molecular biomarkers of AD (specifically Aβ) as this is the target of the drug.[85]

Additionally, approximately 40% of participants on active treatment in the phase 3 studies had evidence of amyloid-related imaging abnormalities (ARIA) (ie, brain edema or microhemorrhages) on MRI, with approximately 7% discontinuing the study because of ARIA-related issues. The highest risk factors for ARIA were the presence of an *APOE* ε4 allele (approximately 40% risk of ARIA for *APOE* ε4 carriers compared to approximately 20% for those without) and/or the presence of microhemorrhage on the MRI used for trial entry. Subsequently, it is recommended that an MRI be performed within 1 year of starting aducanumab, before the start of the highest dose (typically 6 months after starting), and before the 12th dose (approximately 1 year after starting). Although controversy remains as to clinical effect from the phase 3 studies of aducanumab, it is clear that the risk-benefit profile for this and related drugs does not support the use beyond mild AD. Therefore, clinicians considering the use of aducanumab will need to ensure access to appropriate MRI sequences to detect cerebral microbleeds before starting the drug and regularly follow patients for

KEY POINTS

- A decrease in CSF Aβ42 and an increase in CSF phosphorylated tau and total tau is the pattern specific for AD.
- Current tau positron emission tomography tracers are specific to AD-related tau conformational changes and not to non-AD tauopathies.
- Currently three amyloid positron emission tomography (PET) tracers, one tau PET tracer, and a Breakthrough Device Designation for one blood-based biomarker of amyloid pathology have been approved by the US Food and Drug Administration.

ARIA and follow a reliable clinical diagnostic process to ensure an appropriate clinical stage of AD. For more information in ARIA, refer to the article "The Value of Neuroimaging in Dementia Diagnosis" by Cyrus A. Raji, MD, PhD, and Tammie L. S. Benzinger, MD, PhD,[38] in this issue of *Continuum*. Appropriate use criteria have been published for guidance,[86] or clinicians may choose to refer to specialty clinics. Based on the uncertainty of the magnitude and consistency of the clinical benefit of aducanumab, the Centers for Medicare & Medicaid Services (CMS) recently proposed to provide financial coverage of aducanumab and any "FDA approved monoclonal antibodies directed against amyloid for the

TABLE 1-3 **US Food and Drug Administration-Approved Cognitive-Enhancing Therapies for Alzheimer Disease**

Therapy	Mechanism of action[a,b]	Stage of disease to start	Titration and target dose	Common side effects[c]
Donepezil	Acetylcholinesterase inhibitor	All	Begin 5 mg/d once daily; may increase to 10 mg/d once daily (standard dose) after 4-6 weeks; maximum dose 23 mg/d once daily	Nausea, vomiting, diarrhea, dizziness, muscle cramps, vivid dreams, bradycardia
Galantamine	Acetylcholinesterase inhibitor	Mild to moderate	Begin 8 mg/d given in two divided doses for immediate release or a single daily dose for extended release; maximum 16-24 mg/d given in two divided doses for immediate release or a single daily dose for extended release	Nausea, vomiting, diarrhea, dizziness, headache
Rivastigmine	Acetylcholinesterase inhibitor	Mild to moderate	Oral: 3 mg/d given in two divided doses; maximum 12 mg/d given in two divided doses Transdermal: 4.6 mg/d applied daily; maximum 13.3 mg/24 hours for moderate to severe Alzheimer disease, 9.5 mg/24 hours for mild to moderate Alzheimer disease	Nausea, vomiting, diarrhea, dizziness, drowsiness, headache
Memantine	*N*-methyl-D-aspartate (NMDA) receptor antagonist	Moderate to late	Begin 5 mg/d once daily; maximum 20 mg/d (given in two divided doses); extended release: 7 mg/d once daily, titrated to 14 mg/d once daily, then 28 mg/d once daily maximum every 1-2 weeks; 14 mg/d maximum for significant renal insufficiency for extended release and 10 mg/day for immediate release	Constipation, dizziness, headache, nonspecific pain, flulike symptoms

[a] Head-to-head comparisons of the acetylcholinesterase inhibitors have not been published, so no evidence of superiority exists for any compounds in this class.
[b] Differences in the specific cholinergic receptors might result in some differences in the benefits on an individual level, so some Alzheimer disease experts will consider switching therapies once.
[c] Additional categories of adverse events identified following the approval of the acetylcholinesterase inhibitors include syncope/loss of consciousness,[89] seizures, and rhabdomyolysis (donepezil).[90]
[d] Evidence for clinical benefit of 23 mg/d has been debated[91,92]; adverse events are clearly greater in 23 mg/d dose compared to 10 mg/d dose, so the author typically reserves 23 mg dose for those with a clear benefit and minimal side effects at lower doses.

treatment of Alzheimer's disease (AD)" under the coverage with evidence development (CED) in CMS-approved randomized controlled trials. This coverage decision means that CMS will only cover the cost of drugs such as aducanumab when they are used in National Institutes of Health–sponsored clinical trials and not in clinical practice. As of January 2022, aducanumab currently is the only FDA-approved Aβ monoclonal antibody, but it is possible that others will be approved in the near future. If so, it is uncertain whether the CED coverage by the CMS will apply to others as well.

For a comprehensive review of the current AD therapeutic landscape, the reader is referred to recent publications.[87,88]

The other approved therapies for the treatment of the cognitive impairment of AD are the acetylcholinesterase inhibitors (which increase synaptic acetylcholine levels) and an *N*-methyl-D-aspartate (NMDA) receptor antagonist (which reduces neuronal hyperexcitability) (**TABLE 1-3**[89-92]). In all cases, these therapies have demonstrated a modest symptomatic benefit.

No evidence has shown that any of the currently approved symptomatic therapies for AD are beneficial in preventing the progression from mild impairment to more severe stages of AD dementia. Therefore, it is not recommended that these therapies be prescribed for MCI. Although claims have been made that patients with very early AD/MCI who carry an *APOE* ε4 allele may have a slower progression to later stages of AD when treated with an acetylcholinesterase inhibitor, no clear evidence for this exists,[93,94] and therefore, no clear evidence has been shown to support the use of this class of therapies at the very earliest detectable stages of symptomatic AD. In a study of patients with late-life depression, patients with MCI treated with donepezil and antidepressants were found to have a greater frequency of recurrent major depression over the 2-year study compared to those treated with placebo and antidepressants,[95] suggesting a potential risk of harm in patients with MCI with comorbid depression.

When to discontinue the cognitive-enhancing therapies remains uncertain. However, as the goal of treatment is to provide symptomatic benefit and prolong independence, the general consensus is that if an individual is moved to a skilled nursing facility for full-time care, it is reasonable to discontinue cognitive-enhancing therapies and monitor for any abrupt worsening.

The use of vitamins and related supplements (eg, micronutrients) is common in patients with AD and related dementias. However, clear support of the benefit of clinical-cognitive outcomes in AD is lacking for any particular intervention/vitamin supplements. Although folic acid supplementation reduces elevated serum homocysteine levels and possibly decreases brain atrophy, no clear evidence of benefit has been shown for slowing cognitive decline in AD. Therefore, in the absence of targeting elevated homocysteine levels, no clear benefit exists for folic acid supplementation. Some support exists for the use of high-dose vitamin E (2000 IU/d) to slow down the decline of measures of functional status but not cognitive decline.[96] Although concerns exist of potential side effects from high-dose vitamin E, no significantly elevated adverse events were identified in trials of vitamin E relative to the placebo group, suggesting this as a reasonable option for treatment of patients with moderate AD.

Nutraceuticals are frequently used by patients, but the evidence for any particular nutraceutical, despite many having reasonable preclinical foundations, is lacking. Unfortunately, despite the lack of benefit, their use has continued to increase.[97,98] Of note, one prescription-based option, a medium-chain

KEY POINT

- **No evidence has shown that any of the currently approved symptomatic therapies for AD are beneficial in preventing the progression from mild impairment to more severe stages of AD dementia.**

triglyceride-based supplement, is purported to address impairments of the glycolytic pathway in AD. However, the initial modest benefit demonstrated in a phase 2 study was not confirmed in a larger phase 3 study. Although ketosis may be an effective approach for AD, the necessary confirmatory studies have not yet been reported.

No convincing evidence exists of a particular dietary program improving cognitive impairment at the symptomatic stages of disease; however, the Mediterranean diet (whole grains, fruit, vegetables, low animal-based saturated fats, and modest amounts of lean meats, particularly fish) has the best evidence for lowering dementia risk.[99] Recent studies suggested that the Mediterranean diet impacted AD-related biomarkers and preserved hippocampal volumes in an older-adult Western European cohort.[100]

Behavioral and Psychological Symptoms of Dementia

The most challenging symptoms of Alzheimer disease are the behavioral and psychiatric manifestations of the disease. Beyond the importance of identifying psychiatric symptoms for treatment, evidence also exists that pervasive psychiatric symptoms (delusions, agitation, hallucinations) are an important prognostic factor associated with a more rapid progression.[101] Unfortunately, these symptoms are often difficult to treat, but it is important to note that a substantial number of patients with behavioral and psychiatric symptoms improve within 3 months without any intervention.[102] Therefore, the approach to treatment should always be to (1) ensure that no secondary cause is present (eg, undiagnosed infection/pain, significant change in environment, side effect of a medication) and address if any source is identified, (2) counsel caregivers on how to deal with patients experiencing these symptoms, and (3) work with caregivers to establish an environment that minimizes stressors and enhances opportunities for relieving stress (eg, exercise, background music, creative outlets), which often requires referrals to support services.

If behavioral/environmental approaches are not fully effective in treating behavioral/psychiatric symptoms, pharmacotherapies can be considered with the goal of controlling behaviors that are resulting in significant stress for patients or safety concerns for patients and caregivers.[103] Both acetylcholinesterase inhibitors, primarily donepezil, and NMDA receptor antagonist have modest evidence for improving behavioral and psychological symptoms of dementia in mild to moderate AD[101,104] and should be considered first-line therapies. The next class of therapies to consider are selective serotonin reuptake inhibitors (SSRIs) and related compounds. Although a large number of SSRIs and related therapies are available to choose from, the best evidence from randomized trials is for citalopram (up to 30 mg/d) for the reduction of agitation in AD.[105] Citalopram at a dose of 40 mg/d has been associated with an increase in ECG abnormalities, so if symptoms have not responded at 30 mg, it is not recommended to increase the dosage further. The response to this class of therapies varies by individuals, which may result in the need to try a different SSRI, and consideration of other symptoms that the patients may be experiencing can help to tailor drug selection (eg, using trazodone in patients with both insomnia and behavioral and psychologic symptoms of dementia).

The last class of therapies to be considered for the treatment of behavioral and psychological symptoms of dementia is the antipsychotics. In general, this class of therapies should be used as a last resort, at the lowest effective doses possible, and with frequent reassessments so that treatment can be discontinued if the

targeted symptom has improved or is not responding. The antipsychotics have been associated with an increased risk of sudden death and stroke and include an FDA boxed warning related to these potential side effects. Therefore, caregivers should be informed of these unlikely but potential risks. Additionally, extrapyramidal symptoms, sedation, falls, cerebrovascular events, pneumonia, and an increased risk of hospitalization are associated with these therapies and the benefits are typically modest, so the risk-benefit profile should be considered. The strongest evidence for efficacy in treating the behavioral and psychological symptoms of dementia is for risperidone (maximum of 1 mg/d),[103] with some support for aripiprazole (5 mg/d to 10 mg/d),[106] with insufficient evidence for other atypical antipsychotics. Recently, the more selective 5-hydryoxytryptamine 2A (5-HT_{2A}) receptor inverse agonist/antagonist pimavanserin has demonstrated benefit in a phase 2 study of behavioral and psychological symptoms of dementia in AD, but a phase 3 confirmatory study has yet to be completed.[102] The overall safety profile from the phase 2 study appears to be superior to other atypical antipsychotics, but larger studies in this population are required to confirm these findings.

KEY POINTS

- **Antipsychotics should be used as a last resort, at the lowest effective doses possible, and with frequent reassessments so that treatment can be discontinued if the targeted symptom has improved or is not responding.**
- **The antipsychotics have been associated with an increased risk of sudden death and stroke and include an FDA boxed warning related to these potential side effects. Therefore, caregivers should be informed of these unlikely but potential risks.**

CONCLUSION

In the absence of effective disease-modifying therapies, AD will remain a major problem in older adults. Although the clinical manifestations of the disease can be variable with age of onset likely contributing to a higher likelihood of nonamnestic patterns, episodic memory problems remain the core symptom in the majority of patients, highlighting the importance of identifying a consistent pattern of memory decline in the diagnosis of AD. Advances in diagnostic biomarkers will lead to changes in the approach to diagnosing AD, particularly in the very early stages, yet the true impact of these changes in the absence of more effective treatments remains to be seen. Until breakthroughs in treatments are discovered, the focus of the neurologist will remain on accurately diagnosing patients and developing an individual treatment plan that optimizes cognitive health in the setting of a progressive neurodegenerative disorder.

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