Late-Onset Alzheimer Disease

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KEYWORDS

• Late-onset • Alzheimer disease • Dementia • Oldest-old • Pathology

KEY POINTS

- There is an urgent societal need for interventions to delay or treat Alzheimer disease (AD), particularly in the oldest-old, which represent the fastest growing segment of society.
- Rates of dementia continue to increase as people age into their 9th and 10th decades.
- Dementia in the oldest-old is often due to mixed pathologies, including amyloid plaques and neurofibrillary tangles of AD, as well as microinfarcts, hippocampal sclerosis, and more rarely Lewy Bodies.
- The typical presentation of AD in the oldest-old is short-term memory impairment gradually progressing to involve other domains of cognition (language, visuospatial, and executive dysfunction) and leading to functional impairment.
- It is challenging to diagnose dementia in the oldest-old due to reduced societal and familial expectations of function, medical comorbidities, and difficulty performing cognitive testing due to visual or hearing impairment, fatigue, and physical disability.

OVERVIEW

The oldest-old, people 85 years and older, are the fastest growing segment of society, and neurologists must be prepared to diagnose and treat dementia in this age group. The prevalence and risk of dementia in this group is high and continues to rise with advancing age. Increasingly, we have come to recognize that the oldest-old are a

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unique population with unique risk factors for Alzheimer disease (AD) and dementia. AD remains the most common cause of dementia in the oldest-old, but mixed pathologies are often present and contribute to cognitive impairment. The typical presentation of clinical AD in the oldest-old often begins with the gradual onset of short-term memory impairment, then progresses to involve other domains of cognition, such as language, visuospatial, and executive function, ultimately leading to functional impairment. It can be challenging to diagnose dementia in the oldest-old due to lack of an informant for the many oldest-old who live alone, reduced functional expectations, difficulty performing and interpreting cognitive testing in this age group, and presence of positive amyloid biomarkers in many cognitively healthy elderly persons. Treatment of AD dementia in the oldest-old is extrapolated from younger elderly persons, because the oldest-old have generally been excluded from treatment trials. There is no treatment that can slow or reverse the progression of AD dementia, although acetylcholinesterase inhibitors and memantine can provide modest cognitive and functional benefits. Treating medical and psychiatric comorbidities and ensuring adequate home care and social support are critical. There is an urgent need for interventions to prevent or delay AD dementia in the oldest-old, for the benefit of individuals at risk, their families, and society.

EPIDEMIOLOGY

Our oldest citizens are the fastest growing segment of societies worldwide. In 2010, there were approximately 5.6 million people age 85 and older in the United States. This number is projected to quadruple by midcentury.[1] However, living long does not necessarily mean living well, as the oldest-old have the highest rates of incident and prevalent dementia and AD in the population.[2]

Fig. 1 shows the estimated total number of people age 85 and older[1] and the projected number of oldest-old with prevalent AD dementia[3] in the United States from
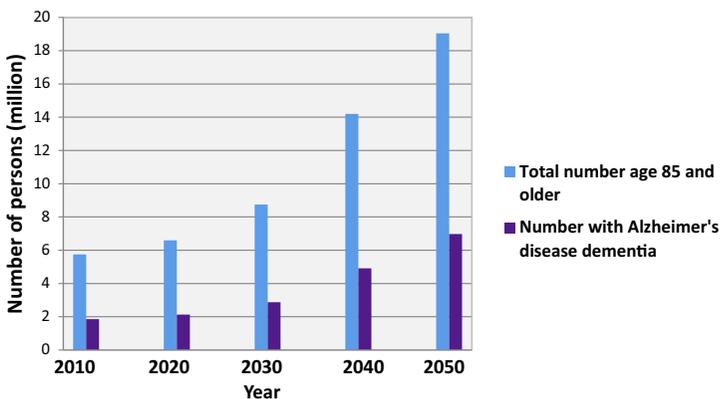
Fig. 1. Predicted number of oldest-old total and with dementia in the United States. The predicted total number of oldest-old and the predicted number of oldest-old with AD dementia in the United States 2010 to 2050 based on the national population projections data by the US Census Bureau and AD prevalence estimates by Hebert and colleagues. (*Data from* National Population Projections (Based on Census 2000). Table 12. Projections of the population by age and sex for the United States: 2010 to 2050 2008. Available at: http://www.census.gov/population/www/projections/summarytables.html. Accessed February 29, 2012; and Hebert LE, Weuve J, Scherr PA, et al. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. Neurology 2013;80:1778–83.)

2010 to 2050. In 2010, approximately 32% of the oldest-old had AD dementia, affecting approximately 1.8 million people. This number is predicted to increase to approximately 7 million (36.6%) oldest-old individuals with AD dementia by 2050. Based on the growth of the Baby Boomer generation, by midcentury 50% of all AD dementia cases will be in the oldest-old.[3]

The incidence of AD is also the highest among the oldest-old. In 2016, the estimated annual incidence of AD in people age 85 and older was approximately 37 new cases per 1000 persons, which is almost triple the incidence rate of 13 new cases per 1000 persons among people age 75 to 84. The higher incidence rate of all-cause dementia, including AD dementia, in the oldest-old has also been demonstrated by a number of different epidemiologic studies from around the globe, as shown in Fig. 2. Similarly, the mortality rate from AD is also highest among the oldest-old. Although the AD attributable death rate is estimated at 172 per 100,000 persons in people aged 75 to 84 years, this rate jumps to 930 per 100,000 persons in people aged 85 and older in the United States.[4]

RISK FACTORS

Studying risk and protective factors for AD in the oldest-old is particularly challenging, as the proportion of underlying mixed pathologies increases with age.[2] Subsequently,
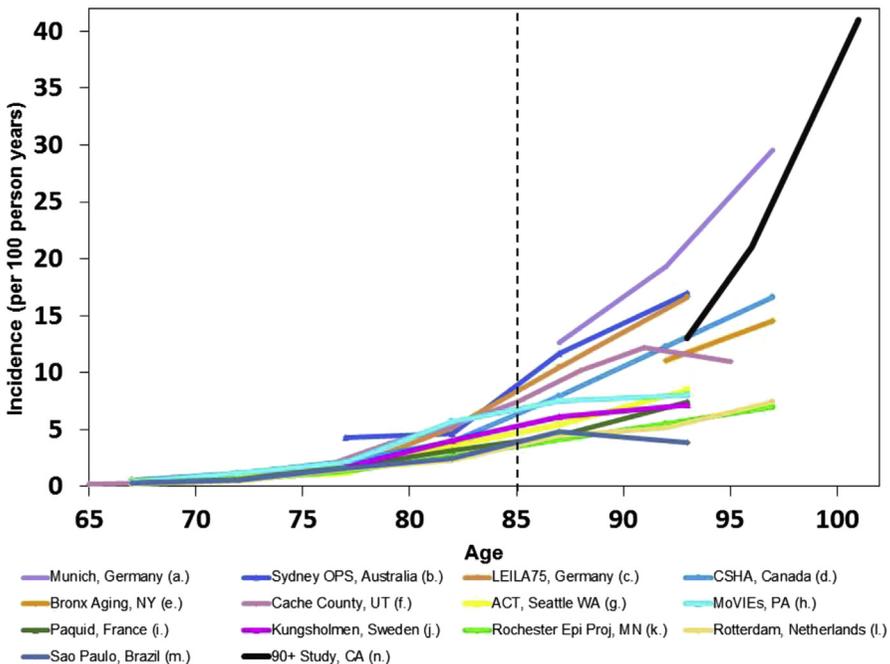
Fig. 2. Age-specific incidence of dementia in studies with oldest-old subjects. [a] Fichter MM, Eur Arch Psychiatry Clin Neurosci, 1996; [b] Waite LM, Int J Geriatr Psychiatry, 2001; [c] Riedel-Heller SG, Br J Psychiatry, 2001; [d] Canadian Study of Health and Aging, Neurology, 2000; [e] Hall CB, Neurology, 2005; [f] Miech RA, Neurology, 2002; [g] Kukull WA, Arch Neurol, 2002; [h] Ganguli M, Neurology, 2000; [i] Letenneur L, Int J Epidemiol, 1994; [j] Fratiglioni L, Neurology, 1997; [k] Edland SD, Arch Neurol, 2002; [l] Ruitenberg A, Neurobiol Aging, 2001; [m] Nitrini R, Alzheimer Dis Assoc Disord, 2004; and [n] Corrada MM, Ann Neurol, 2010. (*Courtesy of* Dr Maria M. Corrada.)

many studies have focused on identifying risk and protective factors for all-cause dementia in this age group. Nevertheless, it is evident that the constellation of risk and protective factors for all-cause dementia and AD change in the oldest-old. Among all risk factors, age remains the strongest risk factor for dementia and AD in the oldest-old.[5] Low levels of education, low levels of physical activity, and poor physical performance have also been associated with an increased risk of late-age dementia.[2,6] However, many of the traditional risk factors lose their effect or have the opposite effect on the risk of developing AD. In particular, Apolipoprotein E ε4 allele (APOE*E4), a strong genetic risk factor for AD dementia in younger elderly,[7] has been shown to have little effect on the risk of dementia in the oldest-old.[2,5,7] On the other hand, although the presence of elevated blood pressure increases the risk of dementia and AD in younger elderly, its effect after age 85 appears to be protective for dementia.[5,8] The mechanism of the observed protective effect of hypertension in the oldest-old is still under investigation, although one hypothesis is that it is related to protection from cerebral hypoperfusion that develops as an aging-associated phenomenon.[2,5] Moreover, data from the Oregon Brain Aging Study showed that good or optimal health (ie, having had no history of major medical, neurologic, or psychiatric illnesses; vitamin deficiencies; major surgeries; head trauma; or substance abuse) at age 85 and older was associated with delayed onset of AD, although the lifetime risk of the disease remained the same as in the general population.[9]
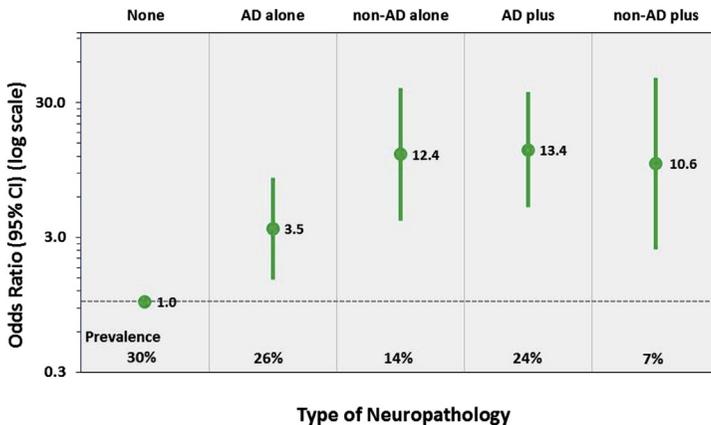
PATHOLOGY

The neuropathological signature of AD dementia is the presence of amyloid plaques and neurofibrillary tangles. The prevalence of AD plaques and tangles in the brain increases with advancing age, and 60% to 70% of the oldest-old with clinical dementia have intermediate and high levels of AD pathology, defined by the National Institute of Aging (NIA)-Reagan criteria.[10] Although AD is the most frequently detected pathology, the hallmark of the neuropathology underlying dementia in the oldest-old is the presence of multiple pathologies. Most individuals with dementia have 2 or more pathologies at autopsy, including many forms of vascular disease (small and large cerebral infarctions, microinfarcts, cerebral amyloid angiopathy, atherosclerosis), hippocampal sclerosis, and to a lesser extent, Lewy bodies and changes of frontotemporal lobar degeneration. The frequency of multiple pathologies complicates making the etiologic diagnosis of the dementia in these patients. Further confounding the diagnostic process is the high frequency of AD pathology in individuals without dementia in this age range. In *The 90+ Study,* a population-based cohort study of aging and dementia in people aged 90 years and older, approximately 40% of individuals without dementia had intermediate and high levels of AD pathology. It is not known if this represents preclinical disease or resilience.

Fig. 3 shows the distribution of primary and secondary pathologies in individuals aged 90 and older with and without dementia. One of the most frequent "other pathologies" is hippocampal sclerosis. The prevalence of hippocampal sclerosis is strongly age-related and occurs in 20% to 30% of individuals with dementia who die when older than 85. However, we have no validated clinical criteria for the diagnosis of this disorder, and most of these patients are clinically diagnosed as AD, which they frequently also have at autopsy. Similarly, the presence of microinfarcts increases with age. Several investigators have noted a relationship between microinfarcts and dementia that is independent and as strong as the relationship of AD neurofibrillary tangles to dementia.[11,12] The greater the number of pathologies detected at autopsy, the greater the risk and the severity of dementia.[13] Although
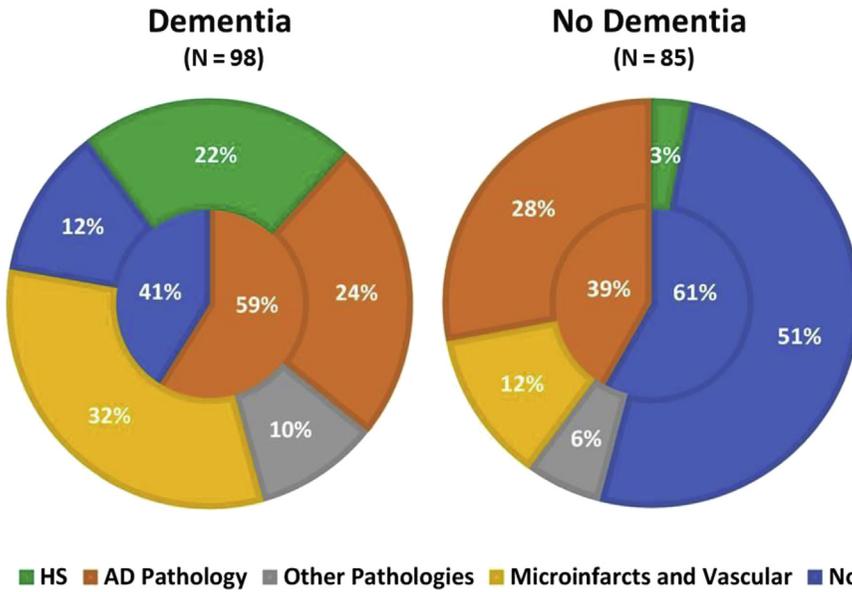
Fig. 3. Distribution of pathologic findings in participants aged 90 and older with and without dementia from *The 90+ Study*. The inner circles show the distribution of the primary pathology (AD or none). The outer circles depict the distribution of the secondary pathologies in relationship to the primary pathologies. AD: Intermediate/High level pathology by NIA-Reagan criteria; Vascular: Lacunar infarcts, large-vessel infarcts, white matter gliosis; Other: Lewy bodies, cerebral amyloid angiopathy, glioblastoma, cortical basal degeneration. (*Courtesy of* Mr Thomas Trieu.)

the number of neuropathologies at autopsy is related to risk and severity of dementia, not all pathologies are equal. **Fig. 4** shows the odds of having dementia in *The 90+ Study* in the presence of AD pathology alone, other types of pathology alone, and each in combination with one or more additional pathologies. Participants with

Fig. 4. Odds of dementia by type of neuropathology in *The 90+ Autopsy Study*. Analyses were done using logistic regression adjusting for age at death and sex (N = 183). CI, confidence interval. (*Data from* Kawas CH, Kim RC, Sonnen JA, et al. Multiple pathologies are common and related to dementia in the oldest-old: The 90+ Study. Neurology 2015;85:535–42.)

intermediate/high AD pathology alone were 3 times more likely to have dementia (odds ratio = 3.5), but those with single non-AD pathologies (mostly hippocampal sclerosis and microvascular ischemic disease) were 12 times more likely to have dementia (odds ratio = 12.4). When a second pathology was present, the likelihood of dementia increased fourfold in those with intermediate/high AD pathology but did not change in those with non-AD pathologies, suggesting that pathologies may interrelate in different ways.

CLINICAL FEATURES

The most typical clinical features of late-onset AD include the gradual onset of short-term memory impairment, which over the course of several years progresses to involve other aspects of cognition, including language impairment, executive dysfunction, and visuospatial impairment, and ultimately impacts the ability to perform activities of daily living.

Typical early symptoms of late-onset AD include forgetfulness, such as forgetting conversations, repeating statements and questions, and misplacing personal items. Long-term memory remains relatively preserved. In the early stages of AD, a patient may be aware of his or her short-term memory impairment and have preserved insight. Later symptoms may include word-finding difficulty, trouble with calculations, trouble with decision-making, and getting lost in familiar surroundings.

Often the earliest stage of symptoms may be subjective cognitive impairment, wherein patients may notice declines in memory, yet they are still testing normally on bedside cognitive testing and neuropsychological testing, and they remain able to perform all of their activities of daily living. The next stage may be mild cognitive impairment (MCI), wherein a patient or informant has a cognitive complaint, which is detectable on testing, yet he or she is still able to compensate and perform daily activities. MCI may be classified as amnestic or nonamnestic (signifying if memory impairment is present) and single domain or multiple domain. The most typical presentation of AD begins with subjective cognitive impairment, then amnestic single-domain MCI, then amnestic multiple-domain MCI, then mild dementia. However, it is important to note that many patients may not pass through these stages in a stereotypical fashion. In a study of the oldest-old, incidence of dementia was 31.4% per year in persons with amnestic MCI compared with 8.4% per year in persons with normal cognition.[14] The transition from MCI to mild dementia involves a loss of independence in functional abilities, for example, inability to manage medications, appointments, transportation, or finances.

As patients progress through stages of AD dementia, initially they may only require assistance with instrumental activities of daily living (medication management, finances, transportation); however, as they progress to a moderate stage of dementia, they will require assistance with more basic activities of daily living, such as dressing, bathing, and grooming. As they progress to a severe stage of AD dementia, they will need to be fed and will eventually become incontinent. Finally, in the end-stage, patients may progress to become nonverbal, unable to swallow, and bedridden.

The psychiatric symptoms associated with AD are varied and can be distressing to the patient and caregiver. Early psychiatric symptoms, most typical in the MCI stage, may include apathy, depression, and anxiety. Later psychiatric symptoms may include paranoid delusions, disinhibition (childlike behavior), and agitation. Sleep disorders are also common in late-onset AD, including insomnia, hypersomnia, disrupted sleep, and Circadian rhythm dysregulation.

DIAGNOSIS

The diagnostic evaluation for AD in the oldest-old can be challenging due to the many factors that may influence a person's cognitive or functional abilities that are not due to underlying neuropathology. These may include sensory impairments (visual or hearing), physical disability, and reduced family and societal expectations for functional independence.

Of note, the prior set of guidelines for the diagnosis of AD, the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Criteria from 1984[15] specified that the onset of deficits begins between the ages of 40 and 90. However, the current set of guidelines for the diagnosis of dementia due to AD from the NIA–Alzheimer's Association (NIA-AA) workgroup does not set an upper age bound for the onset of symptoms.[16] Core clinical criteria for probable AD dementia (NIA-AA) include (1) dementia, (2) insidious onset, (3) cognitive deficits by history and examination with amnestic or nonamnestic (language, visuospatial, or executive) presentation, and (4) exclusion of other neurodegenerative, neurologic, medical, or medication comorbidities.[16]

The diagnostic evaluation for late-onset AD begins with a careful history. In many cases, patients in the early stages of AD (subjective cognitive impairment or early MCI) may have preserved insight and notice concerning changes in their own memory; however, it is typical in the later stages of MCI or dementia for patients to lose their insight and awareness of their memory impairment. Thus, it is optimal to obtain history from both the patient and an informant, who is aware of the patient's cognitive performance and functional abilities. The informant is often someone living with the patient (a spouse, adult child, or other family member), or it may be a staff member in the patient's living facility. However, many older adults are now living alone: in the United States in 2010, 48% of adults older than 85 lived alone.[17] In this case, the informant may be an adult child, other family member, or friend who does not have detailed knowledge of the patient, which may limit the accuracy of the clinical history.

A careful review of the past medical history and current medications may assist in identifying causes of dementia other than AD. Polypharmacy is common in older adults, and many commonly prescribed medications, such as benzodiazepines, anticholinergics, and antihistamines, can cause cognitive impairment. Also, alcohol use and depression are often-overlooked contributors to cognitive impairment in the elderly.

A detailed physical and neurologic examination often will be normal if the dementia is due to AD, thus abnormal findings may point toward other causes or contributors to the dementia. For example, subtle focal neurologic findings, such as pronator drift or subtle unilateral weakness, spasticity, or hyperreflexia, may indicate prior silent stroke and thus a vascular contribution to cognitive impairment. Parkinsonian features, such as bradykinesia, shuffling gait, and rigidity, may indicate a Lewy body spectrum disorder.

Cognitive testing should be performed next, which may be bedside cognitive testing, such as the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), or other tests. If cognitive impairment is not identified on bedside cognitive testing, but the clinician has a high suspicion for cognitive impairment, neuropsychological testing may be appropriate. It is important to note that both bedside cognitive tests and neuropsychological tests have age-adjusted norms, and the cutoffs used in younger populations may be too strict when applied in the oldest-old. For example, in *The 90+ Study*, the mean MMSE score in adults older than 90 years without dementia was 26.1, with the 10th percentile score being 23.[18]

In addition, sensory and physical limitations, such as visual impairment, hearing impairment, fatigue, or pain, may impact performance on cognitive testing in the oldest-old.

Laboratory assessment is critical and should include complete blood count and comprehensive metabolic panel to evaluate for infection, anemia, electrolyte abnormalities, liver, or kidney dysfunction that may contribute to cognitive dysfunction. Hormone abnormalities and vitamin deficiencies also may contribute to cognitive dysfunction, thus it is recommended to check thyroid function tests and vitamin levels (B12, folic acid, B1, and D) because deficiencies are commonly found in this age group.

Brain imaging is important in the assessment, and MRI is the preferred measure. Common findings that may not aid in differential diagnosis may include cerebral atrophy and periventricular and subcortical white matter hyperintensities, both of which are age-associated and frequently present to a mild or moderate degree in elderly individuals with and without dementia. The underlying pathologic substrates of white matter hyperintensities are not yet completely defined, but may represent microvascular ischemic change or gliosis. In AD, common findings may include biparietal and bitemporal atrophy, particularly involving the hippocampus; however, the wide range of normal age-related atrophy overlaps with findings in AD.

The NIA-AA guidelines for the diagnosis of dementia due to AD do not advocate the use of biomarkers for routine diagnostic purposes[16]; however, the guidelines give leeway to clinicians for use when deemed appropriate, such as in complex cases or when more certain diagnosis would change management. These specific AD biomarkers may include cerebrospinal fluid amyloid-beta42, phosphorylated-tau, and total tau. Also available is brain PET imaging for amyloid plaques using tracers such as florbetapir, flutemetamol, and florbetaben. However, it is important to note that many of the oldest-old with normal cognition may have positive biomarkers for AD. The overall prevalence of "amyloid positivity" among the cognitively normal oldest-old population has been estimated to be more than 50%.[19] For very old individuals, the significance of amyloid biomarkers is uncertain. For example, it is not known if they will ultimately develop AD dementia with the passage of time, or if perhaps they are somewhat "resistant" to these pathologies. In any case, testing for these biomarkers in an elderly adult with normal cognition is not recommended. Even in an oldest-old patient with clinical AD, the tests may not be helpful, as the dementia may be due to a different or multiple pathologies, and the Alzheimer pathology may be a bystander. Thus, testing for AD biomarkers may be most helpful when results are negative, providing information that it is highly unlikely that dementia is due to underlying AD.

TREATMENT

Bearing in mind the complexity of contributing factors to clinical AD in the oldest-old, an important first step is addressing medical contributors to dementia if possible, such as the removal of offending medications (eg, benzodiazepines, anticholinergics, antihistamines), and adequate treatment of depression, anxiety, and sleep disorders.

In the oldest-old, there is frequently a vascular contribution to AD dementia, so treatment of vascular risk factors is important; however, it is unclear how aggressively to treat hypertension, diabetes, and hypercholesterolemia in the oldest-old. It is possible that maintaining cerebral perfusion is critical to cognitive performance, so blood pressure targets may be somewhat liberalized in late life. Additionally, the side effects of medications to treat vascular risk factors may be problematic in the

oldest-old. These may include orthostatic hypotension and renal insufficiency among the blood pressure medications, hypoglycemia among the diabetic medications in frail elderly patients with inadequate caloric intake, muscle cramps and weakness among the statins, and risk of cerebral hemorrhage in elderly individuals on anticoagulants, a higher prevalence of cerebral amyloid angiopathy, and with high fall risk. Each patient is an individual, and management of vascular risk factors as prevention and treatment of dementia should be undertaken in partnership between the primary care physician (who may be a family physician, internist, or geriatrician) and the neurologist.

The medications that are approved by the Food and Drug Administration for the treatment of AD dementia include acetylcholinesterase inhibitors: donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl); and memantine (Namenda.) These medications improve cognitive and functional performance but do not reduce the risk of progression from MCI to dementia nor do they slow progression of dementia. Acetylcholinesterase inhibitors are approved for use in all stages of AD dementia, and memantine is approved for moderate and severe-stage AD dementia. The clinical trials that demonstrated efficacy of these medications enrolled patients with a mean age between 72 and 76 years.[20–23] In some of the studies, patients older than 85 were excluded. Thus, the use of these medications in the oldest-old is an extrapolation from younger populations. It is appropriate to use these AD medications in the oldest-old population with the realization that the oldest-old may be more susceptible to the expected side effects, such as nausea, vomiting, diarrhea, and bradycardia, due to expected changes in pharmacokinetics and pharmacodynamics associated with aging.[24] The familiar adage for medication use in the elderly applies to the use of AD medications: "*Start low and go slow*."

As with patients of any age with AD, it is the neurologist's responsibility to assess safety, including ensuring the patient has adequate supervision and is not suffering from abuse or neglect. Significant safety issues to address include wandering and driving. Several states in the United States mandate that physicians report patients with AD or dementia to the Department of Public Health or Department of Motor Vehicles. Even in states that do not mandate physician reporting, it is important to discuss driving with patients and their families, including the fact that patients with AD are at high risk of car accidents. It is helpful to refer patients and their families to social services agencies, including the local chapter of the Alzheimer's Association or other advocacy groups for family support and future care planning. It is also important to involve and document the patients' wishes about future care (including cardio-pulmonary resuscitation, invasive medical care, and feeding tube placement) while they are still able to participate in such discussions. Wishes should be recorded in an Advanced Directive, and 42 states have POLST (Physician Orders for Life-Sustaining Treatment) laws in place that allow physicians to document patients' end-of-life decisions in a portable medical order. Finally, as a patient reaches the end of life and develops difficulty with ambulation or feeding, it is appropriate to involve palliative care and hospice.

SUMMARY

AD dementia in the oldest-old is challenging to study, diagnose, and treat, relating to the complexities of mixed pathologies, medical comorbidities, and the expected changes of normal aging in cognition, physical performance, and functional status. Diagnosis relies on identifying progressive cognitive impairment, typically amnestic, leading to functional impairment, and excluding other causes through history, medication list, laboratory studies, and often neuroimaging. Symptomatic medical treatment

with acetylcholinesterase inhibitors and memantine and supportive care are the main-stays of treatment. Identifying an intervention that can prevent or slow AD progression regardless of age is of critical importance; however, there is a particular urgency for the oldest-old, who represent the fastest growing segment of our society, and are at highest risk of developing AD dementia. Due to the differences in risk factors and pathology of dementia in the oldest-old compared with the younger elderly population, it is possible that successful treatment paradigms may ultimately differ based on age. Future clinical trial designs should include the oldest-old, as efficacy and tolerability need to be defined in this group in which the medications will be used.

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