Article Archive

Differentiating Dementias: Alzheimer's Disease and Its Management — Part One in a Two-Part Series
By Susan Scanland, MSN, CRNP, GNP-BC, CDP, CSP, and Tyler Bielinski
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The incidence of dementia, which occurs in several forms, continues to increase as the elder population expands. Properly identifying the type of dementia and promptly initiating appropriate treatment are essential to proper management.

One of society's most pressing issues is the current dementia epidemic. Dementia affects nearly 10% of persons aged 65 and older.1 As the geriatric population continues to grow to an estimated 74 million people by 2030,2 the need for accurate dementia diagnosis becomes more urgent. Alzheimer's disease (AD), only one type of dementia, is expected to increase from approximately 5.4 million Americans currently to 13.8 million by 2050. In 2015, 15 million families and unpaid caregivers provided approximately 18.1 billion hours of care to persons with AD and other dementias.1

Dementia is an umbrella term for numerous neurocognitive disorders such as AD, vascular dementia, Lewy body dementia, Parkinson's dementia, and frontotemporal dementia. Similarities exist between various dementia types. This leaves clinicians the challenging task of differentiating the type of dementia for accurate diagnosis and treatment. The diagnostic category of "dementia not otherwise specified" was used in 92.9% of a national sample of 21.6 million fee-for-service Medicare beneficiaries between 2011 and 2013.3

Alzheimer's Disease

AD is the most prevalent type of dementia, affecting one in nine persons in the United States over the age of 65.1 Alzheimer's pathology is defined by the presence of beta-amyloid proteins, neurofibrillary tangles, and oxidative stress.4 Beta-amyloid proteins destroy synapses and form plaques that disrupt neurons.5 Neurofibrillary tangles are made up of abnormal tau proteins found in neurons that impede nutrient transport and lead to cell death.4,6-8 Oxidative stress is caused by the production of free radical oxygen. In AD, mitochondrial dysfunction and accumulation of beta-amyloid and tau proteins result in oxidative stress in the brain. In addition, oxidative stress promotes the formation of more beta-amyloid plaques and phosphorylation and polymerization of tau, forming a vicious feedback loop that promotes the worsening of AD.5,9

AD has two different genetically based presentations: early-onset Alzheimer's, with onset occurring prior to the age of 65, and late-onset Alzheimer's, in which symptoms begin at or after the age of 65. The early-onset type is inherited with mutations in three genes: amyloid precursor protein, presenilin 1, and presenilin 2.

The genetics of late-onset "sporadic" AD involves the gene encoding the apolipoprotein (APOE-e4) gene.10 Genetic testing should be offered to families with early-onset Alzheimer's but is not predictive or useful in late-onset AD.

AD is diagnosed through a detailed history of declines in cognition, function, mood, and behaviors. A patient's past psychiatric history and family history of dementia or other psychiatric illnesses, particularly psychotic depression, are relevant. Also essential is a detailed medication history, including straight and as-needed use and the degree of effectiveness of previous trials with antidepressants, hypnotics, and benzodiazepines. A full physical exam with emphasis on the neurological and gait evaluation is key. Cognitive testing, laboratory tests, and neuroimaging play an important role in the dementia workup.

The typical history in AD involves a gradual onset with an inability to pinpoint when memory or function began to decline. Initial presentation usually involves financial difficulties and executive function impairment (the ability to sequence activities to complete a task). These manifest in disorganization of the steps involved in completing the instrumental activities of daily living (IADL) such as household management, meal preparation, taking medications, transportation, keeping appointments, and attending social events.

AD also manifests in difficulty with verbalizing thoughts and recognizing familiar people, places, and items. An excellent function-based questionnaire to assess the impact of cognitive loss on function is the Everyday Cognition Scale.11 Retrospective functional questions can pinpoint when the cognitive decline began. Additionally, mood changes such as apathy, irritability, or anxiety may occur in the early stage of AD, along with personality changes and decreased awareness of others' needs.

As AD progresses into the moderate and late stages, an individual becomes more dependent on others for dressing, grooming, bathing, toileting, and ambulating. Wandering, pacing, restlessness, and shadowing family members may occur when anxiety increases. The majority of those with AD develop dementia-related behaviors or agitation in the moderate and later stages of the disease. Paranoid delusions and hallucinations often occur, and during the moderate and later stages in Alzheimer's, a patient may truly believe and act out scenarios from earlier in life.

Dementia Screening and Workup

Screening for cognitive decline is not complicated for primary care physicians, specialists, nurse practitioners, or physician assistants. Sensitive instruments can be used even during a brief visit. These include the clock-drawing test, which asks a patient to complete a clock face on a predrawn circle and assesses the placement of the numbers and hands to a designated time.12 The time and change test evaluates the ability to make change and tell time.13 The St. Louis University Mental Status examination combines recall and clock drawing to screen for mild cognitive impairment, which usually occurs prior to the onset of functional and more observable emotional and cognitive deficits in various dementias.14 The Mini-Cog is an excellent tool to screen for dementia in a primary care setting.15 These tests are extremely useful, valid, and reliable for screening, but a full dementia workup is necessary for a clinical diagnosis.

If the above screening instruments indicate positive results, use a dementia workup to rule out reversible causes of confusion. Diagnostic testing should include structural neuroimaging such as a brain CT or MRI, full chem profile, complete blood count, vitamin B12, folate, thyroid-stimulating hormone test, vitamin D, electrocardiogram, and urinalysis. If there is a history of significant outdoor exposure to ticks, it's essential to rule out Lyme neuroborreliosis16 or Bartonella neural infections presenting as dementia or cognitive/mood impairment. Diagnostic challenges with high rates of false negative Lyme serology should steer a clinician toward a discussion with clients/families regarding consideration of investing in testing from a laboratory specializing in tick-borne illnesses such as IGeneX17 or in Bartonella.18 Persons with a history of high-risk sexual behaviors should have syphilis and HIV testing added to the diagnostic workup.

Individuals under the age of 65 need referral to a specialty memory clinic, ideally one with genetic counseling and testing.19 It is essential to differentiate early-onset AD from frontotemporal dementia, which frequently has an onset before the age of 65, and from vascular dementia, which may occur at a younger age due to multiple cerebrovascular risk factors.

Safety Issues

Navigational ability becomes impaired early in AD, along with self-orientation and scene localization.20 A patient leaving his or her environment alone can present hazards in numerous situations. Safety issues, such as the ability to drive, should be assessed as early as possible by an occupational therapist. It may become necessary to take car keys from an AD patient's possession. Primary care providers must be aware of state reporting laws with respect to impaired driving in older adults.21 Individuals with mild dementia are more likely than nondemented elders to make unsafe decisions to cross a street in traffic, which could lead to pedestrian/car collisions.22 The home environment must be cleared of all firearms23 and other hazards that can result in injury or death; limit risks with stove use and heating units and assess items/areas that create fall hazards.

Financial safety and legal matters, such as designating power of attorney for health care and financial matters, and executing a will must be addressed as soon as a diagnosis is made. Providers can recommend engaging a trusted lawyer or certified elder law attorney and trusted financial advisors.

Caregiving is a significant issue; family and/or significant others should be referred to local Alzheimer's or dementia support groups.24 Compassion from providers is especially important for all families affected by dementia, and support is necessary for issues unique to early-onset AD. Caregivers of parents often are concurrently parenting teens and younger children with the associated physical, emotional, and financial responsibilities.25 If there are indications of wandering, a registration/identification/location system should be arranged, such as the Alzheimer's Association Safe Return or MedicAlert 24-hour national emergency response system.26

Geriatric care managers can provide a lifeline, especially when there is disagreement among family members about options or if families are providing caring from a distance.

FDA-Approved AD Medications

There are two totally different mechanisms with the two different categories of FDA-approved medications for AD: cholinergic and glutamatergic. Acetylcholinesterase inhibitors (AChEIs) increase the pathologically lowered levels of the neurotransmitter acetylcholine by preventing acetylcholine breakdown by acetylcholinesterase. Memantine does not work on cholinergic pathways but rather prevents the excessive glutamatergic stimulation that results in neurotoxicity.27

Currently there are four FDA-approved medications to treat AD; three are AChEIs. Patients, upon initial diagnosis and in the mild stage of AD should immediately be started on one of the three AchEIs: donepezil (Aricept),28 rivastigmine (Exelon),29,30 or galantamine (Razadyne),31 all of which are approved for the early stage of AD.28-31 Donepezil (Aricept)28 and rivastigmine transdermal system (Exelon patch)30 also have FDA approval for the moderate and severe stages of AD. Rivastigmine capsules and solution (Exelon) are approved for mild to moderate AD.29

Donepezil (Aricept) is available in 5 mg, 10 mg and 23 mg tablets, with orally disintegrating tablets available in both 5 mg and 10 mg.28 The 5 mg and 10 mg doses are for mild to moderate AD while the 10 mg and 23 mg doses are indicated for moderate to severe AD.

Rivastigmine (Exelon) is available via capsule or oral solution. The initial dose is 1.5 mg twice daily with titrations at least two weeks apart; subsequent dose titrations are 3 mg bid, 4.5 mg bid, and finally 6 mg bid.29 Initial dosing with the rivastigmine transdermal system (Exelon patch) is 4.6 mg/24 hours once daily (replacing with a new patch every 24 hours) for four weeks. Since the minimum effective dose is 9.5 mg daily/24 hours, that is the dose for the fifth week. Four weeks after the 9.5 mg/24 hours dose is started, the dose can be increased to 13.3 mg patch/24 hours. The 13.3 mg patch is indicated for all stages of AD, but especially for the severe stage.30

Galantamine (Razadyne and Razadyne ER) is approved for mild to moderate—but not severe—AD. The extended release is administered once daily in the morning with food. Razadyne ER's starting dose is 8 mg per day with the next dose titration to 16 mg daily after completing four weeks of the 8 mg dose. The next increase to 24 mg per day should be attempted after four weeks at 16 mg per day. Razadyne tablets and oral solution dosing begins at 4 mg twice daily for four weeks, then to 8 mg twice daily for four weeks. The final titration to 12 mg twice daily is made after four weeks at an 8 mg twice-daily dosage.31

Cholinesterase inhibitor precautions and warnings include bradycardia, heart block, asthma, COPD, seizures, gastrointestinal bleeding, and bladder outflow obstruction. AChEIs are likely to exaggerate succinylcholine-type muscle relaxation during anesthesia. Potential drug interactions may occur with metoclopramide, beta blockers, cholinomimetics, and anticholinergic agents. The most common side effects are gastrointestinal, such as nausea, vomiting, diarrhea, or anorexia.28-31 If weight loss occurs, providers should decrease to the previous titrated dose rather than discontinuing the medication. If gastrointestinal symptoms continue to occur, the prescriber should attempt a switch to another AChEI to continue the advantages of decelerating the disease decline related to cholinergic loss.

One study revealed that switching from other cholinesterase inhibitors to the rivastigmine patch following a patient's decreased response/tolerability to the initial AChEI may reduce the progression of global cognitive impairment, especially in mild AD. Additionally, stabilization of clinically relevant depression and apathy phenomena could result from switching cholinesterase inhibitors.32

Dual neurotransmitter activity in the Alzheimer's brain indicates that memantine (Namenda), which is FDA approved for moderate to severe AD, should be added to the existing cholinesterase inhibitor as soon as a patient reaches the moderate stage of AD. Combination therapy, AChEI plus memantine, is essential to minimize rapid declines in cognition, function, and behaviors. Moderate stage AD can be identified by a shift from loss of IADL to a loss of activities of daily living and a score of lower than 20 on the Mini-Mental State Examination.33

This is the optimal time to initiate memantine, given as Namenda tablets/solution or Namenda XR or Namzaric (memantine/donepezil). Memantine's (Namenda) initial dose is 5 mg once daily for one week, then 5 mg twice daily for the second week, then 5 mg and 10 mg separate doses during the day (total 15 mg/day) for the third week. The final titration of 10 mg twice daily (total 20 mg) is the final and ongoing maintenance dose. Drugs, diseases, or foods that make the urine more alkaline may decrease the clearance of memantine by approximately 80%.34 Namenda XR's starting dose is 7 mg once daily, titrated at a minimum of weekly intervals by 7 mg to the recommended maintenance dose of 28 mg once daily (14 mg maximum dose if severe renal impairment exists).35 Namenda's side effects, which occur in 5% to 10% of patients, include dizziness, headache, confusion, and constipation. Memantine requires dosage reduction in severe renal or hepatic impairment.34

Namzaric, which is a combination of donepezil and memantine, is indicated for moderate to severe AD. If a patient is not on either medication, he or she needs to start on donepezil first, increasing to donepezil 10 mg daily prior to switching to the combination medication memantine/donepezil (Namzaric). Patients on other cholinesterase inhibitors desiring combination treatment need to switch first to donepezil 10 mg prior to initiating Namzaric.36 Patients already taking donepezil 10 mg will discontinue the donepezil-only medication, and start the next day on Namzaric 7 mg/10 mg (namenda 7 mg/donepezil 10 mg) once daily in the evening. The dosage should be increased by 7 mg to the recommended maintenance dose of 28 mg/10 mg. The minimum recommended time interval between dose increases is one week. Patients on memantine only (10 mg twice daily or 28 mg extended release once daily) and donepezil hydrochloride 10 mg once daily can be switched to Namzaric 28 mg/10 mg, taken once daily in the evening. If severe renal impairment exists, the recommended maintenance dose for Namzaric is 14 mg/10 mg once daily in the evening.36

Clinical benefits of combination therapy (cholinesterase inhibitors plus memanine) vs monotherapy (cholinesterase inhibitors alone) have been revealed in both a meta-analysis of seven studies (n=2,182)37 and an analysis of four randomized trials (n=1,408)38 for moderate and severe AD. Improved behaviors, function, and global impressions using cholinesterase inhibitors and memantine simultaneously during the middle and late stages should convince clinicians who are skeptical or apathetic about the use of combination therapy throughout the moderate and late stages of AD.

Clinicians often ask when, over the course of disease progression, treatment should be stopped. Combination therapy should be used in the severe stage of AD. Discontinuation of cholinesterase inhibitors in nursing home residents with dementia was associated with adverse behavioral changes and decreased time spent in leisure activities.39 It was discovered that the longer patients continue treatment, the better they perform cognitively, globally, and functionally. Findings also suggested that antidementia drugs may benefit patients even when given in advanced or profound stages of AD.40

The Functional Assessment Staging Test, a functional measure of the various stages of AD,41 categorizes stages of the disease; this is extremely helpful in educating families who may disagree with or be in denial about the diagnosis. It also guides families on what to expect at each stage of AD and helps in planning for the safest living environment (eg, home care, memory care assisted living, or long term care dementia unit). It can be used to guide professional staff on situations such as family discussions preparing for end-of-life issues (eg, avoidance of tube feeding) or adjustment of advance directives to avoid futile treatment. Hospice staff experienced with dementia can be brought into continuing care communities, home care, or long term care settings to guide families during this care

transition. Families with high levels of stress, tension, or guilt at the end of life can be encouraged to seek spiritual advice or professional guidance from hospice or counseling staff.

Differentiating AD from other dementias (detailed in Part Two of this article in the May/June issue) is essential for primary care or specialty physicians, nurse practitioners, and physician assistants. Differences exist in the presentation, symptoms, safety issues, medications, and family support.

Evidence-based research reveals that combining memantine and cholinesterase inhibitors improves behaviors, activities of daily living, and global function in the moderate and severe stages of AD. Such gains would translate across both home and clinical settings, offering improved quality of life for individuals with AD and decreased caregiver burden for families, home care aides, long term care nursing assistants, and professional staff.

— Susan Scanland, MSN, CRNP, GNP-BC, CDP, CSP, a certified speaking professional and practicing geriatric nurse practitioner, specializes in behaviors and optimal dementia pharmacotherapy. Through her firm, Dementia Connection, she's presented extensively on dementia in the United States, Canada, and Europe. She has served as an advisor or speaker for Alzheimer's pharmaceutical corporations and is a nursing faculty specialist at the University of Scranton in Pennsylvania.

— Tyler Bielinski is a junior premed neuroscience major with a minor in biochemistry at the University of Scranton. He is a telehealth technician and student supervisor for the Telehealth Intervention Program for Seniors, which provides daily vital sign monitoring through the use of wireless technology for approximately 200 older adults throughout northeastern Pennsylvania.

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