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CME Activity

The Alzheimer's Disease Spectrum: A Clinically Focused Discussion Between Private Practice and Academic Neurologists and Psychiatrists

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The Alzheimer's Disease Spectrum: A Clinically Focused Discussion Between Private Practice and Academic Neurologists and Psychiatrists

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a roundtable discussion held in June 2017.

ACTIVITY DESCRIPTION

General practitioners and neurologists will be better able to discuss risk factors for AD progression and preventative strategies for maintaining cognitive function, to inform and provide disease information and resources to caregivers, patients and family, and to recognize and treat aggressive behavior, if needed.

TARGET AUDIENCE

This certified CME activity is designed for general practitioners, neurologists, psychologists and nurse practitioners with an interest in the diagnosis, treatment, and quality of life of patients with Alzheimer's Disease, their family and caregivers.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- Discuss current pathogenic mechanisms of Alzheimer's disease and rule out other causes of dementia.
- Assess the epidemiology and risk factors for developing dementia.
- Evaluate the diagnosis of people with mild cognitive impairment and dementia associated with Alzheimer's disease.
- Formulate treatment options for patients with Alzheimer's disease, including MCI and dementia.
- Formulate strategies to best prevent further cognitive decline.
- Discuss beneficial interventions for caregivers, AD patients and their families.

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The Alzheimer's Disease Spectrum: A Clinically Focused Discussion Between Private Practice and Academic Neurologists and Psychiatrists

Cognitive impairment and dementia, including Alzheimer's disease, are an increasing health issue that coincides with the silver tsunami—the large and aging population. Significant challenges in diagnosis and treatment of these patients and support for the families lie ahead as its prevalence and the societal burden of direct and indirect costs continues to grow worldwide. This roundtable discussion examines the importance and strategies of early diagnosis of Alzheimer's disease; risk factors; current theories on etiology and role of amyloid plaques and neurofibrillary (tau) tangles; monitoring and managing of the chronic disease; dealing with behavioral issues; and use of pharmaceutical therapies and non-pharmacological approaches to care in real-world scenarios.

NORMAL AGING AND EARLY WARNING SIGNS OF ALZHEIMER'S DISEASE

Ronald Devere, MD: Before we begin discussing Alzheimer's disease (AD), let's begin with our own opinion on what is normal and not in cognitive function as people age.

I usually include the five areas of cognition: memory, executive function, speech and language, personality, and visual perception. There may be others.[1]

Alireza Atri, MD, PhD: Some individuals are super-agers, and their cognitive performance in many domains, including recall memory, do not appear to substantially decline with age. On average, most individuals older than 65 years absorb and process information more slowly and less efficiently than young indivduals; thus, per unit time, their rate of learning, retrieving, analyzing, reacting and responding to information and actions is lower. Processing speed and therefore fluid intelligence on average tends to decline with age. However, semantic knowledge and crystallized intelligence, such as "skills," should be preserved, and can improve until old age. Older individuals may occasionally and temporarily have difficulty retrieving information, like a name, but should remember it later: i.e., the information is not lost and there is no true forgetting. Generally, aging should not significantly affect our daily functioning, behavior, personality, and mood.

A significant concern about changes in personality, mood or behaviors by the patient, a family member, a significant other, or the clinician can be a warning sign that should prompt an appropriate evaluation. Changes in cognition are not always the first signs.

The Alzheimer's disease clinical spectrum involves insidious and diverse cognitive behavioral syndromes. AD is a neurodegenerative disease which progresses slowly, over months to years, unless it is decompensated by a systemic condition (e.g., medical, toxic-metabolic). In making the diagnosis, the cognitive behavioral changes should not be due to a longstanding learning disabilities or normal aging exacerbated by a systemic condition; the diagnosis is not made during a course of delirium.

Gad A. Marshall, MD: Late life changes or a new onset of behavioral symptoms or neuropsychiatric symptoms is a concern, whereas if the behavioral pattern is present throughout most of life or in adulthood, it is less concerning.

For example, depression present in the 20s and throughout is not as clear a marker for neurodegenerative disease as late-onset depression in the 60s or 70s. A change is generally more concerning as a potential prodrome or risk factor for a neurodegenerative

TABLE 1. COMPARISON OF BEHAVIORS ASSOCIATED WITH NORMAL AGING AND EARLY ALZHEIMER'S DISEASE

	Normal Aging (occasional symptoms)	Early signs and Symptoms of Alzheimer's Disease (Lapses become more frequent)
Memory	Minor lapses and recalls later: Forgetting of appointment or names and remembering them later. Recall is slightly slower.	Memory loss, especially recently learned information; Important dates forgotten; Repetitive questioning for same answer in a short time frame; Need to rely on memory aids for tasks that they used to do themselves.
Planning or problem-solving	Develops a plan; follows recipes; occasional error when balancing checkbook, which person finds later.	Difficulty with developing a plan, Difficulty following a plan or using a familiar recipe. Difficulty working with numbers or paying bills Difficulty focusing on a project
Familiar task completion	Occasionally need help to record a television show.	Trouble using appliances. Trouble driving to a familiar location. Trouble remembering rules of a favorite game. Trouble managing a budget.
Recognition of time or place	Occasionally confused about day of week but remember it later.	Forget where they are or how they got there. Lose track of seasons, dates, or time. Trouble processing future events; mostly only aware of immediate events. Difficulty remembering the correct timeline of events.
Comprehension of visual images and spatial relationships	Vision changes related to cataracts, myopia, less acuity, driving at night and glare.	Vision problems such as difficulty reading, determining color or contrast, judging distance. May become disoriented—not knowing the location or how they arrived. Driving more difficult even in daylight due to lower ability to estimate distance and speed of oncoming traffic.
Recall of words during talking and writing	Occasional trouble finding word or phrase.	Difficulty joining and / or following a conversation. Struggle with vocabulary and may put words together to describe item. Forgetting meaning of some words
Ability to retrace steps	Able to retrace steps after misplacing item; finds item.	Frequently misplacing personal items; May leave things in odd places and be unable to retrace steps to find them. Occurs more frequently over time.
Judgment	An occasional bad decision	Decline in sound judgment, including with money, finances, personal interactions and actions – engaging in more risky, inappropriate or unusual behavior. More vulnerable to unscrupulous telemarketers.
Work or social activities	Usually like family and social events but sometimes need a break.	May avoid social interactions because they sense a change in their behavior. Attend less and have less interest in hobbies, projects, sports, and social activities. May not remember how to complete hobby project.
Mood and Personality	Prefer using a routine to do things.	May become anxious, depressed, less motivated, fearful, and suspicious. Can be easily upset when in out-of-comfort zone scenario. Often frustrated when cannot remember or do things.

Modification of "10 Early Signs and Symptoms of Alzheimer's Disease" from Alzheimer's Association[2]; and Schott.[1]

disease such as Alzheimer's disease. Conversely, a lifelong pattern is not as predictive.

I agree with Dr. Atri that even subjective complaints or concerns are important. We are noticing that self-reports of subjective decline usually predict objective decline for Alzheimer's disease. When you test an individual with subjective cognitive concerns with a sensitive objective cognitive assessment, that individual may still score in the normal range, but not optimally. Over time, that person's progressive decline becomes more easily detected on objective testing and noticed by others.

Reduced processing speed often occurs as one ages. Most cognitive tests have age-based and education-based norms. For example, an episodic memory test is controlled for age, as some parts of cognition will decline with age. Unfortunately, some of those normal values included people with mild cognitive impairment (i.e., impaired but not demented). Neuropsychological testing on an individual, that indicates, "normal for age," may need to be interpreted with a grain of salt.

The million-dollar question: Is this normal aging? Or should they be worried? A big red flag for an individual is a new problem that is persistent, is progressive, and affects daily functioning, especially if that individual was independent recently.

Pierre N. Tariot, MD: I give a different answer to my medical colleagues than I give to patients and family. I tell the patients and families, "Look, if you yourself are worried about your memory or

other thinking ability, or your family or your doctor is worried, that is cause for an evaluation. You don't need to be an expert. If there's worry, get an evaluation."

I tell my medical colleagues, "our processing speed diminishes, and our ability to maintain attention with multiple stimuli coming at us tends to decline as we age." I refer to my own need to shut off the radio when I'm on the entrance ramp merging on the highway, because I can't listen and merge at the same time anymore.

Recall of specific information, specific words and names, may be diminished due to age. If memory changes go much beyond that, then there is cause for concern and an evaluation.

Dr. Devere: Certainly the retrieval system becomes slower as we age. I'm 73 and have occasional word-finding lapses, an example of aging that often progresses. When the lapses become a prominent problem, or if family members are noticing the person's trouble with many basic memory issues, then it is likely beyond normal age changes.

Changes in speech and language, such as difficulty with joining or maintaining a conversation, is not part of normal aging. Although some vision problems, like myopia, cataracts, and poor night vision increase with age,[1] difficulties in visual perception and recognizing familiar locations are lapses beyond normal aging. Forgetting the location of the parked car or difficulty driving home from a frequently visited location raise concerns.

Reasoning, judgment, and executive function should not change much other than the slower processing during aging. A reasonable IQ does not change much until the people are in the 80s, assuming excellent health. Thus, reasoning, judgment, executive function should not change other than the slower processing. Table 1 compares the 10 common behaviors between older adults and those with early AD.

EPIDEMIOLOGY

Dr. Devere: Let's move on to epidemiology of Alzheimer's disease.

Dr. Marshall: As a brief review, the three most common dementias are AD, vascular dementia, and Dementia of Lewy bodies (DLB) or Parkinsonian dementia. After those three, other types of dementia are relatively rare.

Dr. Atri: AD prevalence is increasing worldwide because of the "silver tsunami" of people living to older ages. The major at-risk population in the US, elders of 65 to 84 years old, is projected to climb from 11.3% in 2012 to 17.8% in 2030.[3] Likewise, the percentage of 85+ aged US population is projected to increase from 1.8% in 2012, to 2.5% in 2030.[3] Some differences occur in different ethnicities and racial groups. Some aspects of the dementia syndrome may be delayed by, for example, maintaining cerebrovascular health and managing risk factors (e.g., blood pressure, metabolic syndrome, smoking).

On a positive note, more people are taking better care of their cerebrovascular risk factors, and have higher education levels which provide more cognitive reserve. However, so many people are coming into the age of risk that the number of AD cases is still increasing.

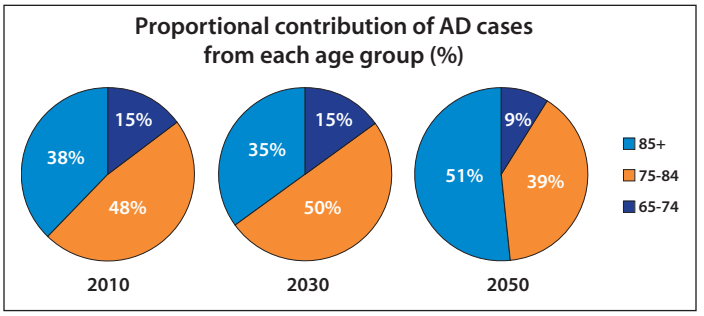

Figure 1. Trends in Alzheimer's disease. Data adapted from Hebert LE, et al.[79]

Dr. Devere: What factors contribute to the decrease in AD prevalence in people over 90 years old versus the prevalence in 65 to 80 year-olds?

Dr. Atri: As we get older, mixed pathology in dementia is more common. Older individuals with dementia may have Alzheimer's pathology, and a second or third type of brain pathology, most commonly vascular-ischemic pathological changes.[4] These pathologies add, and may even synergize, to cause synaptic disruption and neurodegeneration through several mechanisms including inflammation, energy failure, and apoptosis, ultimately causing cognitive behavioral network dysfunction and clinical manifestations. Each additional pathology, in a sense, lowers one's threshold for succumbing and showing dementia symptoms.

Dr. Marshall: Many dementia cases are due to mixed pathology, which mimics Alzheimer's disease clinically. It can occur at any age but certainly occurs more in older folks. The incidence and prevalence of AD in the ≥90 year-old adults relies on a few studies, some of very specific subgroups of the population. For example, the 90+ study in Southern California by Kawas' group5,6 provides a wonderful wealth of information about those individuals in that age group.[5,6] However, this aging population living in a well-to-do retirement community which provides free access to golf, pool, and many social and physical activities, may not be representative of the larger 90+ adult population nation or worldwide.

That said, our data on the 90+ adult US population is improving because people are living longer, and researchers seek more diverse samplings of the population.

A little over five million individuals in the US are currently diagnosed with Alzheimer's disease at the stage of dementia. That number is expected to reach 7.1 million in the US by 2025 and about 13-16 million by 2050.7 People over 65 years have at least a 10% prevalence of AD dementia.

Dr. Tariot: In the US, at least half of all people with dementia die

without ever having a conversation with their doctor about that syndrome. Identification and diagnosis, possibly in collaboration with a specialist, can lead to specific treatment, prognostic advice, and support for family and caregivers. Thus, we encourage our primary care colleagues to pay more attention to people with possible dementia and begin the conversation so the patients and families can receive the needed support.

Dr. Marshall: The economic, financial, and psychosocial burdens coupled with lost income from both patients and caregivers are huge. Treatments, hospitalizations, and supportive care, such as nursing homes or assisted living facilities are major costs.

Dr. Tariot: Furthermore, up to 50% of care partners or caregivers will experience a major depression and/or a major medical illness that they would not have otherwise. In 2016, the aggregate cost of care for AD was $216 billion in the US.[7] It is estimated to reach as much as 1.2 trillion dollars annually in direct and indirect costs by 2050.[7]

Dr. Marshall: Alzheimer's disease is the fifth-leading cause of death in 65+ year-olds and the sixth-leading cause of death overall in the US.[7] Moreover, AD is the only cause of death that is still rising in the US whereas other common causes of death, such as cancer and cardiovascular disease, are declining.

Dr. Devere: I have seen so many death certificates for somebody who died of a cardiac problem or a pneumonia and the diagnosis of Alzheimer's is put number one as the cause of death. That bothers me. Do you believe the data on the deaths from AD as a primary cause is totally valid?

Dr. Tariot: The sharp rise in AD as a cause of death reflects both the increasing prevalence, and a change in reporting. More physicians and families are drawing the correct conclusion, that the reason Dad developed a fatal pneumonia was because he was mute, contracted, and bedbound from advanced AD.

Dr. Atri: I agree. AD as cause of death is up 70% from 2002 to 2012.[8] When someone with end-stage AD is on hospice—is aspirating, has suffered repeated infections, and has been taken off the other medications—I think AD as the cause of death is appropriate; the pneumonia is secondary. For decades, AD as a cause of death has been under-reported.

Dr. Devere: For patients on hospice—I agree. But I have many patients who die with mild to moderate AD, and many of these people have been labeled with AD as the cause of death. I think at least some of them are getting misclassified.

Dr. Marshall: I think that it is much harder to pin the cause of death on AD if the AD patients were not very impaired. Conversely, the early-onset (e.g. 50 year-old) AD patients who die 10 years later had died of complications of AD. These complications arose because the patients had early-onset AD and an AD cause of death is appropriate. I think AD curtails the lifespan, and in general, these numbers are likely correct. If AD patients live long enough, they will die from its complications.

RISK FACTORS

Dr. Devere: What are the frequent risk factors in triggering the progression of AD? We also need to address the role of stress in the development of mild cognitive impairment (MCI), AD, and dementia. Although midlife work-related stress was initially associated with development of MCI, and dementia by initial self-reports, the stress during midlife did not remain associated in later follow-ups.[9]

Dr. Tariot: I separate the risks for early-onset AD and late-onset AD. Early-onset refers to onset of frank dementia before the age of 65, and usually well before that. This important minority accounts for <1% of all people with Alzheimer's disease.[7] The risks include causative mutations in three genes, presenilin 1, presenilin 2, and the amyloid precursor protein. Individuals with Down syndrome are at very high risk for developing the pathology of AD early in life. These genetic mutations or the full or partial trisomy of chromosome 21 in Down syndrome, are associated with abnormal amyloid protein processing, which is an important clue to the pathobiology of the disease.

A major risk factor for the more common late-onset AD is age. Those of us younger than 65 are in 4% prevalence range, from 65 to 74 are in the 15% prevalence range, but 75 to 84 year-olds have a 44% prevalence, and beyond 85, the prevalence of dementia, which is often a mixed type, is higher.[10] So age is a huge risk factor for late-onset AD.

Genetics also affects prevalence in opposing ways. The apolipoprotein protein E (APOE) has three alleles, 2, 3, and 4. One or two copies of APOE4 allele leads to a higher risk of late-onset Alzheimer's disease (three-fold and eight-fold, respectively) and usually an earlier onset. Although about half of AD patients have 1 or 2 copies of APOE4, many people with APOE4 do not develop AD.[11] In contrast, APOE2 allele is protective. A rare coding mutation in the amyloid precursor protein (APP) gene protects against Alzheimer's disease; the mutation is adjacent to the BACE site in APP and is associated with a roughly 40% reduction in the formation of amyloidogenic peptides.[12] This finding[12] lends strong genetic evidence for the so-called amyloid hypothesis.

Interplay occurs between age and genetic vulnerability or protection, and possibly protective lifestyle variables. A brain healthy lifestyle is a heart-healthy lifestyle. We may be able to modulate risk by how we treat ourselves, especially in midlife.

Dr. Marshall: Cardiovascular risk factors generally apply to dementia. They affect risk not only for vascular dementia, but also for AD. The pathophysiological connection seems more logical for

vascular dementia. Autopsy-proven data shows that having elevated blood pressure, cholesterol, and/or diabetes increases the risk of developing AD.

Prevention studies that target several vascular risk factors at once, not usually only one, and maybe other lifestyle modifications, have been at least modestly effective in preventing Alzheimer's disease. Lifestyle elements for prevention include certain diets and aerobic exercise. There are modifiable factors.

Dr. Atri: In addition to age, females also have a slightly higher risk. Women who are 71 years or older have a 16% chance of having AD or other dementias whereas men of the same ages have an 11% chance.[7] Another risk factor is head trauma. Possible mechanisms include an inciting event, reduction of brain's reserve, or inflammatory processes. An additional 20 other AD risk genes have been identified in late-onset AD; but APOE4 has by far the most influence on susceptibility. Excessive production of the toxic Amyloid beta-42 protein (Aβ42) plays a more central role in early-onset AD. While, in late-onset AD a multitude of factors probably co-mingle in a dynamic way to cause low clearance and thus abnormal accumulation of Aβ42—vascular, inflammatory, metabolic, mitochondrial—and to neurofibrillary tau tangle formation. In both conditions, it is the neurofibrillary tangles that spatiotemporally best correlate with neurodegeneration and symptoms.

Dr. Devere: I think the presence of multiple periventricular white matter lesions can indicate compromised brain regions and functions. However, the American Academy of Radiology, including neuroradiology, interpret multiple periventricular white matter lesions in the brain as nonspecific and age-related. Unfortunately, neurologists and the family practice doctors usually miss the significance of them. After reviewing much literature on diffusion tensor imaging,[13,14] I conclude that these lesions are not silent, particularly in somebody who has cognitive symptoms.

Furthermore, a reason many stroke patients do not stabilize despite treatment, is the "tons" of amyloid deposits in their brain[15] which was confirmed by autopsy. Thus, those periventricular white matter lesions are not silent.

Dr. Marshall: I agree; There is definitely a disconnect. Even neuroradiologists, not just general radiologists, often would read atrophy or call lesions as age appropriate. I agree that these changes seen best on MRI are not due to normal aging.

Another example: The white matter hyperintensities can suggest underlying small vessel ischemic disease, consistent with vascular dementia. The multi-infarct model is not that common. Abundant small vessel disease is the most common driver of vascular dementia. The interplay is complex between abundant small vessel disease, amyloid pathology, and other more accepted AD pathologies. More cumulative damage in the brain reduces brain reserve opening the door for clinical deficits to emerge.

Dr. Marshall: Gradual accumulation of small vessel ischemic disease can manifest with memory impairment, which appears clinically similar to AD. Some nuances and differences can appear in the assessment. But I usually view small vessel ischemic disease as yet another pathology in the brain on top of Alzheimer's disease. For example, one lacunar stroke on top of a typical AD syndrome makes the person worse cognitively.

Dr. Marshall: Another risk factor is a developmental learning disability at a young age, probably due to less brain reserve. It lowers the chances of withstanding more pathology at a later date. Many people can harbor a pathology and compensate for it, but many cannot. Many people have amyloid in their brain when they are normal cognitively or clinically. Often as they age, they no longer remain normal cognitively because it is harder for them to compensate for the accruing pathology.

Dr. Devere: Multiple head injuries, including mild traumatic brain injuries, are a risk factor for AD.[16]

Dr. Marshall: People with mild traumatic brain injuries and especially people with multiple injuries, have a higher risk for development of AD and other dementia.

As a panel, we agree that clinicians should not ignore leukoaraiosis—white matter hyperintensities—and small white matter lesions observed on brain MRI. They need to consider that these lesions, whether periventricular or in other subcortical regions as possibly playing a role in patients with cognitive impairment, and to consider mitigating the risk factors and treating co-morbid conditions related to them.[17,18]

Dr. Atri: Vascular cognitive impairment (VCI) while common, particularly in those above 80; as a subset, multi-infarct dementia is much less common.[18] Atrophy and synaptic loss and white matter lesions are early manifestations of cerebrovascular brain injury, and a large risk factor for both VCI, as well an additional risk factor for AD and dementia.[17,18]

Schneider's review paper from the Memory and Aging Project, and the Religious Orders Study updates the threshold model of multiple brain pathologies contributing to dementia.[4,19,20] The threshold for dementia decreases with multiple pathologies, and having a single pathology is very uncommon in older individuals.[4] Pure AD occurs for the most part in younger, 40 to 60 year-olds who have early-onset, and often atypical and aggressive forms of AD.

MODIFIABLE PROTECTIVE FACTORS

Dr. Atri: Dr. Deborah Barnes and Dr. Kristine Yaffe provide compelling support that reduction of seven modifiable risk factors of cognitive inactivity, depression, diabetes, lower educational attainment, midlife hypertension, midlife obesity, physical inactivity, or smoking may substantially decrease the risk of developing

dementia.[21] In addition, the brain healthy habits that Dr. Tariot was describing: taking care of your blood vessels, higher education, continued learning, engagement, exercise, and diet may also help reduce the risk of developing dementia.[21]

Regarding diet, the Mediterranean-DASH Intervention for neurodegenerative Delay (MIND) Diet, developed by Dr. Martha Morris and colleagues at Rush University Medical Center which combines elements of the Mediterranean (MedDiet) diet and DASH diet (to reduce blood pressure) provides the best evidence base for cognitive protection.[22] The MIND diet involves ten brain-healthy components to eat; and five brain unhealthy components to avoid/limit—for example, emphasizing a higher frequency of vegetables, nuts, berries, poultry, and use of olive oil; and avoiding red meats, sweets, and fast/fried foods. Initial data, gathered in over 900 individuals aged between 58-92 years of age, studied on average for 4.5 years, suggested that the MIND diet may lower risk of developing AD dementia by about 35 percent for individuals who followed the diet moderately well and up to 53 percent for those who adhered to it.[22] There are now several, ongoing, large, longitudinal studies of multifactorial lifestyle interventional approaches to reduce the risk of cognitive decline and dementia, most notably the FINGER study by Dr. Miia Kivipelto and colleagues.[23]

MECHANISMS OF AD

Dr. Devere: Let's move on to discuss the underlying mechanisms of Alzheimer's disease.

Dr. Tariot: Here are five key points. First, a variety of genetic factors confer increased or decreased risk. Second, environmental factors can increase risk, such as head injury, maybe toxins. Third, endogenous factors can increase or decrease risk such as diet, cardiovascular risks, smoking, head injury, and age. Fourth, some exogenous factors could be protective, but evidence is mixed for estrogen replacement in women, anti-inflammatory drugs, or even antihypertensives. Fifth, we each have an individual pattern of increased or decreased susceptibility. People who got Alzheimer's disease reached a particular tipping point, and unleashed molecular cascades.[24]

These initial stressors are not fully understood, but certainly amyloid dysregulation appears to be sufficient to trigger AD in some but not all cases. Proximal apoptosis, impaired neurotrophic function, excessive oxidative stress, and / or excitotoxity can contribute. The initial dysfunction occurs and stress responses presumably try to normalize it but fail. A cascade that can include cell cycle dysregulation, kinase and phosphatase dysfunction, protein misfolding, and/or altered DNA repair likely ensues. Maybe vascular and membrane dysfunction also occurs. The repair responses fail. Downstream molecular pathology, inflammation, cytoskeletal deterioration, synaptic dysfunction, mitochondrial damage, and eventually apoptosis occurs. Cell death follows.

The neuropathology becomes measureable fairly late in the process. At the time of cell injury, we can detect evidence of neurofibrillary (tau) tangles and amyloid plaques. Symptoms emerge sometime later. This story explains how a fairly uniform clinical neuropathological and molecular phenotype can arise from a whole variety of different starting points.

FDA approved medications for the treatment of Alzheimer's disease suggest dysfunction occurs in at least these two neurotransmitter receptor signaling pathways: nicotinic and muscarinic acetylcholine receptors and the N-methyl-D-aspartate (NMDA) receptors of the glutamate neurotransmitter. Low levels of synaptic acetylcholine (ACh) are associated with AD, and the three commercially available inhibitors of acetylcholinesterase (AChE) may help slow progression of AD symptoms in many patients.[25] AChE inhibitors in their current formulations have not been shown to reverse the AD disease process.[25]

Hippocampal loss of glutamate NMDA receptors is associated with progression of AD dementia, as assessed by postmortem Braak staging.[26] Interestingly, beta-amyloid affects the signaling of the NMDA receptors via modulation of metabotropic glutamate receptor 7 (mGluR7).[27] NMDA receptors are also involved in redox homeostasis, which plays a role in memory maintenance in the elderly.[28] NMDA receptors also play a role in excitotoxicity, which can lead to neuronal death.[29] Dysfunction of NMDA receptor signaling is observed in mild cognitive impairment stage of AD, which suggests its potential role in AD pathobiology.[30] The NMDA antagonist, memantine, is an FDA approved treatment for moderate to severe AD, alone or in combination with a cholinesterase inhibitor. While the basis for its clinical efficacy is unknown, it is possible that some of the mechanisms described above are relevant.

The efficacy of combined therapy (memantine and an AChE inhibitor) in some patients with AD suggests that symptoms of AD may result from multifactorial pathogenic mechanisms.[31] Cerebral glucose metabolism is lower in many neurodegenerative diseases, including AD.[32] Imaging studies showed that patients with mild cognitive impairment or AD dementia had significantly lower metabolism in the parietal and temporal lobes than healthy controls.[33] Altered mitochondrial function is also associated with AD and neurodegenerative disease.[34] Insulin resistance in the hippocampal region also may be involved in cognitive decline in AD.[35]

Dr. Devere: Let's look at the old story that too much amyloid β42 from gamma-secretase causes AD and prevention of tau phosphorylation maybe can save the cells. I realize different mechanisms can do that.

Dr. Tariot: Much new information focuses on amyloid and tau dysregulation. Longitudinal studies indicate that most of us walk around with many tau tangles in our heads. We can develop some amyloid deposits. AD pathobiology seems to develop after amyloid deposits start flaring. After one to three years, the flaring amyloid

plaques seem to trigger the flowering of tau and tangle dysregulation. My point is that dysregulation of other more fundamental cellular processes precede the formation of amyloid deposits and tau tangles.

Dr. Marshall: Many of our treatments and emerging candidates focus on amyloid and more recently on tau. We have not had any fully successful Phase 3 trials for treating patients with dementia, or more recently, patients with MCI with these targeted therapies. So we have not clearly shown that amyloid deposits are causative in a randomized clinical trial, which is the ultimate proof.

However, the autosomal dominant mutations all relate to amyloid production, where it can be a causative agent. Under the microscope, the autopsied brains from these young individuals with autosomal dominant mutations appear similar to brains from the more common late-onset Alzheimer's disease population. Although they are similar, they are not exactly the same.

It's tempting to say, "These rare mutations, which are the basis for most animal models, support the hypothesis that amyloid is causative of AD." But other pathologies can contribute, and dysregulation of many pathways can converge leading to AD symptoms. The new exciting data about tau pathology propagating in a prion-like fashion has been replicated in a couple of very good labs,[36-41] but not yet extensively. They showed that tau in a lab setting can propagate from one synapse to another.[36-39] This new finding hopefully will make a difference in terms of treatment targets.

However, we cannot explain the broad detectable pathology in people who are asymptomatic. Although these individuals over time have a higher risk of developing symptoms, progression to AD dementia is not 100%. The causes of the clinical presentation of AD, especially in individual patients with late-onset AD, remain varied; and diagnosis of individual patients needs elucidation of contributing and non-contributing factors.

WHY DIAGNOSE?

Dr. Atri: The first tenet of care is appropriate early and accurate diagnosis and compassionate disclosure. Early detection and an accurate diagnosis of cognitive impairment/dementia can help avoid years of inappropriate and inefficient care and higher costs; and prevent safety and financial catastrophes. Undiagnosed affected individuals can suffer from symptoms efficiently manage their own medications, which can lead to multiple hospitalizations. Early diagnosis allows greater autonomy, justice, and benefit in being able to

TABLE 2. THE 2011 NIA-ALZHEIMER'S ASSOCIATION (AA) CLINICAL CRITERIA FOR DEMENTIA OF ALL-CAUSES

Dementia is diagnosed when there are behavioral (neuropsychiatric) or cognitive symptoms that:		
1.	Interfere with the ability to function at work or usual activities, and	
2.	Represent a decline from previous levels of performing and functioning, and	
3.	Are not explained by delirium or major psychiatric disorder;	
4.	Cognitive impairment Is detected or diagnosed through a combination of:	
a.	History-taking from the patient and a knowledgeable informant	
b.	Objective cognitive assessment by: i . Bedside mental status examination or	
	ii. Neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.	
5.	Cognitive or behavioral impairment involves a minimum of two of the following five domains:	Symptoms
a.	Impaired ability to acquire and remember new information	Forgetting events or appointments; Getting lost on a familiar route; Misplacing personal belongings; Repetitive questions or conversations.
b.	Impaired reasoning and handling of complex tasks, poor judgment	Inability to manage finances; Poor understanding of safety risks; Poor decision-making ability; Inability to plan complex or sequential events.
c.	Impaired visuospatial abilities	Inability to recognize faces or common objects, even if in direct view; Inability to orient clothing to body or operate simple implements.
d.	Impaired language function (reading, speaking, writing)	Difficulty thinking of common words while speaking, hesitations; increased frequency of errors in speech, spelling, and writing.
e.	Changes in personality, behavior, comportment	Uncharacteristic mood fluctuations such as agitation, apathy, compulsive or obsessive behaviors, decreased interest in previous activities, impaired motivation or initiative, loss of empathy, loss of drive, socially unacceptable behaviors.
Adapted from McKhann, et al.[43]		

support the patient and caregivers, and to monitor and manage the disease course while individuals have greater capacity, and before substantial abilities are lost. Secondly, we try to have some specificity regarding the cause or causes for the patient's disease management. An accurate diagnosis affects counseling; medications and non-pharmacological and environmental interventions; strategic care and financial planning; opportunities for clinical trial participation, and prognosis.

Dr. Devere: What are the clinical differences between all these different dementias? Let's compare how we make a diagnosis between different dementias in the office. They have dementia by the 2011 NIA-Alzheimer's Association (AA) criteria for dementia from all-causes (Table 2).[43]

They have dementia by the criteria of progressive disease with two out of five areas of cognitive or behavioral impairment. The core criteria for AD dementia are listed in Table 3.

Any tips that can distinguish between AD symptoms and other underlying causes including vascular dementia, dementia with Lewy bodies (DLB) or Parkinson's Disease with dementia (PDD), certain vitamin deficiencies, and medications?

Dr. Atri: My first approach is to assess whether their symptoms (or concerns by them or someone who knows them well), in the context of an estimate of their past level of cognitive performance, function and achievements (e.g., education, work/life achievements/positions), are consistent with the normal cognitive aging. The vast majority of middle-aged and older individuals experience a drop off in "fluid intelligence" and executive functions due to slower information processing with progressive aging. Thus, learning per unit time, psychomotor processing, information-response input, manipulation, assessment, multi-tasking, retrieval, and responses are slower (see Salthouse 2006 for a review).[44] For example, information that is stored shouldn't be "lost." If their presentation includes symptoms beyond normal aging, I request more information from the individual, and importantly, from another reliable source (e.g., family member) regarding previous level and trajectory (changes and time course) of functioning, behavior, and personality. I also assess their risk factors for cognitive impairment/dementia (e.g., family history, cerebrovascular risk factors). Then I formally assess, using standardized and validated instruments, their cognitive performance, neuropsychiatric symptoms, and activities of daily living (ADL).[45,46] By doing this, I get a better sense of their clinical cognitive behavioral syndrome. If I'm still concerned,

TABLE 3. 2011 NIA-ALZHEIMER'S ASSOCIATION (AA) CORE CLINICAL CRITERIA FOR PROBABLE AD DEMENTIA

Probable AD dementia is diagnosed when the patient		
1.	Meets criteria of all-cause dementia presented in Table 2.	
2.	Has the following characteristics:	
a.	Insidious onset, such as gradual onset over months to years, not sudden over hours or days.	
b.	Clear-cut history of worsening of cognition by report or observation	
c.	Initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:	Symptoms
	i. Amnestic presentation	AD's most common presentation; Impairment in learning and recall of recently learned information. Evidence of cognitive dysfunction also in reasoning, judgment, visuospatial recognition, language functions, or behavior and personality changes.
	ii. Nonamnestic presentation	Deficits in other cognitive domains should be present.
	Language presentation	Prominent deficits in word-finding, conversation.
	Visuospatial presentation	Spatial cognition such as object agnosia, impaired face recognition, simultanagnosia, and alexia.
	Executive dysfunction	Impaired reasoning, judgment, and problem-solving.
d.	Diagnosis of probable AD dementia should NOT be applied when there is evidence of:	
	i. Substantial concomitant cerebrovascular disease, such as history of stroke temporally related to the onset or worsening of cognitive impairment; Presence of multiple or extensive infarcts; Severe white matter hyperintensity burden	
	ii. Core features of Dementia with Lewy bodies other than dementia itself	
	iii. Prominent features of behavioral variant frontotemporal dementia	
	iv. Prominent features of semantic variant primary progressive aphasia or nonfluent/ agrammatic variant primary progressive aphasia.	
	v. Another concurrent, active neurological disease.	
	vi. Non-neurological medical comorbidity.	
	vii. Use of medication that could have a substantial effect on cognition.	
Adapted from McKhann, et al.[43]		

I begin the process of confirming the cognitive behavioral syndrome and investigating the specific etiology or etiologies using a combination of screening laboratory tests, more expanded cognitive/neuropsychological testing (and in many cases formal neuropsychological evaluation), and structural brain with MRI (unless there's a contraindication).

Some potential causes or exacerbating conditions can be found during the medical history, including medications, such as anticholinergics, sedative-hypnotics, barbiturates, and benzodiazepines. We also assess motor symptoms, neuropsychiatric features, excessive use of alcohol or drugs, and sleep apnea.

Oftentimes it could be multiple causes, and some may exacerbate a potential underlying neurodegenerative dementing process. For example, functional thyroid insufficiency can exacerbate cognitive dysfunction in an individual with early subclinical/minimally clinical Alzheimer's disease, so treating the thyroid can improve cognitive function. So we check for adequate vitamin B_{12}, and thyroid deficiency (TSH), because it's so prevalent, cheap, and a simple fix. While these underlying conditions ~~–~~medicines, dehydration, urinary tract infection, B_{12} deficiency, and thyroid deficiency~~–~~contribute to the clinical syndrome, they are rarely the primary or sole cause; these are potentially more "reversible" in people with recently developed, very mild symptoms. Use of multiple cognitively deleterious medicines (polypharmacy), excessive alcohol and drug use, anxiety and mood disorders, and sleep disorders/apnea, or often a combination of these factors, are also not only warning signs but can be primarily causative in a some individuals.

Dr. Marshall: That's a very good general approach. The three most prevalent types of dementia—AD, vascular dementia, and DLB or PDD—have many variations on presentation, especially AD.

AD has the typical amnestic presentation, but several other presentations are not that rare at our tertiary referral center. A visual variant with posterior cortical atrophy is often due to underlying Alzheimer's disease pathology. A dysexecutive variant which presents with primarily executive dysfunction and not as much behavioral issues is in fact usually AD rather than frontotemporal dementia (FTD). Two other AD variants include a behavioral variant AD, which resembles behavioral variant FTD, and logopenic primary progressive aphasia. These AD variants are usually more common than the other rare types/causes of dementia, and their symptoms can mimic the rare types of dementia. We have approximately 80% accuracy clinically in differentiating between these underlying causes. The causes are mixed. We consider contributing factors and multiple etiologies. We don't say that only one thing is causing these problems.

Dr. Devere: Most people with pure Parkinson's disease develop dementia later in the disease process versus those with DLB who generally start with cognitive impairment. PDD may be more obvious because motor symptoms arise before the dementia. However, cases are being reported now with both Alzheimer's and Parkinson's. It is not all alpha-synuclein dysregulation.

Dr. Marshall: Statistically, co-occurring pathologies of AD and Parkinson disease (PD) are common. Parkinson disease patients with dementia have more amyloid uptake in their brain than PD patients with mild cognitive impairment.[47] The brains of DLB patients rarely have no amyloid. To have only alpha-synuclein anomalies in PD is actually quite rare. Usually some amyloid plaque is detected in PD patients.

CURRENT AD DIAGNOSIS

Dr. Devere: In addition to the listed guidelines, how would you evaluate people you suspect with AD or mild cognitive disorder?

We consider the caregiver as the most important source of information. I send the caregiver out into the waiting room to complete several Activity of Daily Living (ADL) sheets with 60 questions. Concurrently, I do my cognitive testing with the patient in the office. A very detailed medical history is imperative. I review the caregiver's information later. Let's review the cognitive testing done in your office as part of your evaluation to diagnose MCI, dementia, or AD.

Dr. Marshall: I'll start with non-dementia specialists. If somebody may have mild cognitive impairment or mild dementia, one of the more useful available tests is the Montreal Cognitive Assessment or the MoCA.[48] It targets the range of impairment in MCI to mild dementia very well. It takes about 10 to 15 minutes, and I recommend it highly. MoCA picks up much more than the MMSE (Mini-Mental State Examination).

The MMSE is a good test for moderate dementia and is very heavy on memory and language competency. The MMSE is very light on executive function, visuospatial function, and the various components of memory. It does not have much nuance in terms of the encoding and retrieval components and does not assess storage at all even though a storage deficit is the hallmark of AD. Thus, the MMSE is not so great for mild dementia and terrible for assessing MCI—you can score perfectly on the MMSE and still have MCI.

Dr. Devere: I like the short test mental status (38 points) from the Mayo Clinic.

Dr. Atri: The GPCOG, MIS, and the Mini-Cog have been recommended for primary care physicians.[46] I would recommend taking the additional few minutes, and using the MoCA as a first step screening instrument for cognitive impairment in most individuals. The MoCA is free, has multiple English versions, and has many non-English versions. However, when interpreting results, one caveat is that it can be quite difficult for individuals with very low education or low estimated pre-morbid IQ.

Several commonly used scales to assess the patient's ability to perform activities of daily living (ADL) are listed in Table 4.[45]

TABLE 4. COMMONLY USED SCALES FOR ASSESSING PATIENT'S ABILITY TO PERFORM ACTIVITIES OF DAILY LIVING (ADL)

Activities of Daily living Scales	Elderly,	MCI	Mild dementia	Moderate dementia	Severe dementia	Reference
Lawton and Brody Scales;			Informant-based	Informant-based		Lawton and Brody[49]
Functional Activities Questionaire (FAQ)	Self-report	Informant-based	Informant-based			Pfeffer et al.[50]
Alzheimer's Disease Cooperative Study (ADCS)			Informant-based	Informant-based		Galasko et al.[51]
Clinical Dementia Rating Scale	ADL items are Informant-based	ADL items are Informant-based	ADL items are Informant-based	ADL items are Informant-based	ADL items are Informant-based	Morris[52]
Everyday cognition (Ecog)	Self-report, Informant-based	Self-report, Informant-based	Self-report, Informant-based			Farias et al.[53]
Adapted from Marshall et al.[45]						

Dr. Devere: What about neuropsych testing? Where does that play a role in the diagnosis of dementia, even MCI, after you get your clinical information and you do your office cognitive test, to make a diagnosis? And then what other tests would you run to evaluate that patient to come up with a diagnosis of MCI or come up with a diagnosis of dementia and AD?

Dr. Atri: Figure 2 depicts the progression from normal elders to severe AD dementia as a continuum. Depending on etiology, some individuals with mild cognitive impairment (MCI) will progress to mild dementia and beyond. However, not every individual with MCI progresses to mild dementia. Syndromic criteria such as MCI/dementia and minor/major neurocognitive disorder label the syndrome based on severity of cognitive function and impact on function and behavior, but they don't elucidate the cause(s)/etiology. Biomarkers can be helpful to inform specific etiology of the syndrome and predictive utility regarding probability and estimated time course of progression.

Dr. Atri: Biomarker use during diagnosis can increase the clinical probability of correct diagnosis of the AD clinical syndrome, according to the International Working Group or the National Institute on Aging (NIA)-AA criteria.[43,54,55] After the clinical syndrome meets criteria for MCI/dementia but a specific diagnosis is uncertain, a specialist can increase her/his probability of identifying the etiology of the clinical syndrome by assessing biomarkers which may include brain MRI; cerebrospinal fluid (CSF) fluid analysis of amyloid and tau abnormalities; FDG-PET scan for metabolic activity pattern (can aid to distinguish FTD and AD), or amyloid PET imaging.[56]

If after the routine first/second tier assessments and studies have been completed, a primary care clinician requires higher diagnostic certainty, she/he may consider referring the appropriate patient to a specialist. Then, as needed, these tests can be done in conjunction with a specialist who can help interpret the findings. More trained eyes of dementia specialists can in many instances discern specific more subtle patterns of atrophy on brain MRI or hypometabolism on FDG-PET scans that may not have been commented on by the clinical read or simply classified as "age-related."

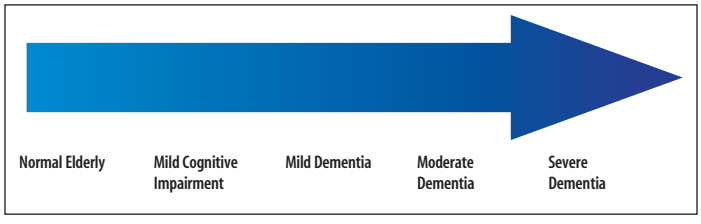

Figure 2. A continuum of progressive symptoms connect MCI and the different stages of AD dementia.

Dr. Devere: In private practice, an amyloid PET scan has too high of an out-of-pocket cost: $10,000 for routine use. Second, FDG-PET is only covered by Medicare if you have pure Medicare, and patient does not have managed care. So if an FDG-PET scan diagnosis is ordered to differentiate between FTD versus Alzheimer's, Aetna or United Healthcare will not cover it; which limits the test results I can obtain. Although very unpopular among neurologists, I perform a lumbar puncture followed by an analysis of phosphorylated tau and amyloid beta 42 in the cerebrospinal fluid (CSF). It's less expensive and most is covered by insurance or Medicare.

Dr. Marshall: Phosphorylated tau and amyloid beta 42 markers are markers of pathology versus more general markers that are nonspecific. The presence of amyloid and tau pathology suggests that the patient has AD as the main cause. CSF analysis costs about $1,000 as opposed to about $6,000 for an amyloid PET.

Currently, amyloid assessment in CSF or by imaging are FDA approved tests. Tau imaging will probably soon be FDA approved.

Other proteinopathies like alpha-synuclein or TDP-43 are very common, and tests are in development. A structural MRI with FDG-PET can be suggestive of the underlying pathology, but in fact it could just mirror the clinical syndrome and not reveal the underlying pathology.

Physicians who are non-dementia experts should be encouraged to order a structural scan, an MRI or a CT scan, because it reveals the extent of vascular burden and focal atrophy. It also can detect a slowly growing benign tumor like a meningioma rarely mimicking a neurodegenerative disease. I've had good examples of typical amnestic MCI and logopenic PPA due to meningiomas growing for years in the right location. A single MRI detected the meningioma.

Dr. Tariot: First, a thorough medical history is "everything," providing a foundation. Appropriate physical and neurological examinations, cognitive testing, and MRI workup has been the gold standard for some time now. With this workup, experienced clinicians saying, "I think this is probably Alzheimer's disease," are right about 80% of the time, according to studies of autopsies of patients diagnosed with AD.

However, we do not have evidence to define best practice yet for analysis of CSF for amyloid beta and tau. I think we can agree that FDG-PET imaging has a specific role, but it is not necessary for all patients.

Dr. Marshall: I agree that we require more guidelines for use of these "biomarkers of underlying pathology." The proposed guidelines for use of amyloid PET imaging are being tested currently, mostly through research. Even with better insurance coverage, many people do not opt for analysis of the CSF because of the invasive sampling (lumbar puncture).

The sensitivity of FDG-PET is about 80%, with some studies showing higher and others slightly lower.[57] Combining FDG-PET with amyloid PET increased the predictive ability to greater than 90%.[57]

Analysis of large data sets like the Alzheimer's Disease

TABLE 5. MEDICATIONS TO AVOID IN DEMENTIA PATIENTS FROM AMERICAN GERIATRICS SOCIETY 2012 UPDATED BEERS CRITERIA

Anticholinergic Agents		
Antidepressants	**Antihistamines**	**Antimuscarinics (urinary incontinence)**
Amitriptyline	Brompheniramine	Darifenacin
Amoxapine	Carbinoxamine	Fesoterodine
Clomipramine	Chlorpheniramine	Flavoxate
Desipramine	Clemastine	Oxybutynin
Doxepin	Cyproheptadine	Solifenacin
Imipramine	Dimenhydrinate	Tolterodine
Nortriptyline	Diphenhydramine	Trospium
Paroxetine	Hydroxyzine	
Protriptyline	Loratadine	
Trimipramine	Meclizine	
Antiparkinson agents	**Antipsychotics**	**Antispasmodics**
Benztropine	Chlorpromazine	Atropine products
Trihexyphenidyl	Clozapine	Belladonna alkaloids
	Fluphenazine	Dicyclomine
Skeletal muscle relaxants	Loxapine	Homatropine
Carisoprodol	Olanzapine	Hyoscyamine products
Cyclobenzaprine	Perphenazine	Propantheline
Orphenadrine	Pimozide	Scopolamine
Tizanidine	Prochlorperazine	
	Promethazine	
	Thioridazine	
	Thiothixene	
	Trifluoperazine	
Other Mechanisms of Actions		
Barbiturates	**Benzodiazepines**	
Amobarbital	*Short and intermediate-acting*	*Long-acting*
Butabarbital	Alprazolam	Chlorazepate
Butalbital	Estaazolam	Chlordiazepoxide
Mephobarbital	Lorazepam	Chlordiazepoxide-amitriphyte
Pentobarbital	Oxazepam	Clidium-chlordiazepoxide
Phenobarbital	Temazepam	Clonazepam
Secobarbital	Triazolam	Diazepam
		Flurazepam
Nonbenzodiazepines hypnotics	**Others**	Ouazepam
Eszopiclone	Chloral hydrate	
Zolpidem	Meprobamate	
Zaleplon		

Adapted from the American Geriatric Society.[62]

Neuroimaging Initiative can show some added value for looking at Aβ42 and tau in CSF over typical hippocampal atrophy or typical hypometabolism on FDG-PET that is suggestive of Alzheimer's disease.[58] Conversely, because hippocampal atrophy or FDG hypometabolism results capture some non-AD-specific changes, their value on top of amyloid beta[42] and tau results is not as strong. Thus, more data are needed for firm recommendation.

Dr. Altri: Most people with dementia with Lewy bodies (70 to 80%) and 30% of Parkinson's disease patients have cortical amyloid deposits. These specialized studies should only be considered as a level three or a level four consideration in individuals with early-onset AD or less usual dementia syndromes with an equivocal diagnosis after an appropriate workup.[59] As yet, initial diagnosis should not require these specialized assays unless there is something quite unusual in the clinical profile, or high diagnostic certainty is important. For example, it would not be appropriate for the "average" 78-year-old with a very classic syndrome of the AD type where our clinical certainty for AD is quite high, or for a 40-45 year-old with anxiety, depression, sleep apnea, and use of multiple neuropsychoactive medications and excessive alcohol. The primary underlying pathology in such an "average" 78 year-old with classic AD may actually not be due to AD in about 10% of individuals (higher if APOE4 non-carrier, and lower if a carrier), but at this time, unless that individual is going into a clinical trial that specifically targets underlying pathology (e.g., abnormal amyloid or tau), she/he would not require an assay.[59]

Dr. Devere: An 80% accuracy for AD diagnosis is common among various studies.[60] In a large NIA study, 39% of patients (88 of 526) diagnosed with an alternate type of dementia (non-AD, tangle-only dementia, cerebrovascular disease, FTD, DLB, hippocampal sclerosis) showed sufficient Aβ and tau histopathology of AD to meet or exceed the threshold for AD.[60] The 438 of 526 subjects diagnosed clinically with AD also showed neuropathological AD (i.e, 83%).

When florbetapir (amyloid) PET scans from Avid and Lilly were only $500 (with vouchers), I checked all my patients. About 20% of my patients had frontotemporal dementia (FTD) as they had no amyloid plaques, etc. The wrong diagnosis can prompt the wrong treatment. Thus, it is important to make as accurate a diagnosis as possible for both disease management and cost effectiveness.

Dr. Marshall: Although lack of amyloid does not necessarily mean a diagnosis of FTD and many cases will have vascular dementia, the final diagnosis of individual patients also depends on additional clinical symptoms.

Dr. Atri: I agree with Dr. Tariot. Many different pathways can contribute to the late development of neurotransmitter abnormalities in AD and other neurodegenerative disorders. Usually the issue is under-diagnosis. At least 20% of demented individuals residing in nursing homes have no AD or specific dementia diagnosis coded. An early and appropriate dementia diagnosis, and institution of early management, can produce meaningful benefits for the patient, family, and caregivers.[42]

Dr. Marshall: The three most common causes of dementia ~~AD~~, vascular, and parkinsonian dementia (primarily DLB) ~~can~~ all benefit from a cholinergic agent. DLB patients usually have a greater cholinergic deficit than AD patients. Three out of the four AD agents available on the market are cholerinergic agents (cholinesterase inhibitors): donepezil, rivastigmine, and galantamine.[61] Memantine is not a cholinergic drug and has not been shown to be effective for vascular dementia or parkinsonian dementia. None of these AD medications are appropriate for FTD.

Until we have approved treatments that target underlying pathology, like the commonly tested amyloid modifying drugs in current clinical trials, knowing the exact underlying pathology will help with many aspects of patient management but not dictate the medication choice.

TREATMENT

Dr. Devere: Let's move into treatment.

Dr. Atri: The first steps after a reliable diagnosis, are teaching the family and patients these non-pharmacological behavioral strategies.

- Educating them about the nature and course of the illness; that it is a disease and is not their "fault."
- Shoring up their support systems.
- Providing strategies to monitor home health and safety.
- Ensuring medication administration, supervision and monitoring – the vast majority of patients should not be "in charge" of their medication management. They are too vulnerable to risk it, and many "side effects" and adverse events can be avoided by ensuring strict medication supervision.
- Caring for the caregivers and teaching them a new language of how to communicate and support the patient; teaching caregivers behavioral strategies, how to be proactive in management, and how to avoid behavioral and environmental triggers.

From a pharmacological side, the very first task that most of us do is to review and simplify the big medication list. We remove the benzodiazepines, and anticholinergic medications, often taken for sleeplessness, urinary incontinence, allergies, or anxiety (Table 5).

Dr. Marshall: One more plug in terms of medication cleanup. As dementia progresses and life expectancy declines (e.g. to five years), some medications that we use for medical conditions, like for preventing heart disease or stroke, are not appropriate anymore because their effects may not be realized for 10 or so years. Geriatricians focus on reducing the medication load to those providing short term benefit. There are a lot of offensive medications out there.

TABLE 6. RESOURCES FOR FAMILIES AND CAREGIVERS

Resources for	Organization	URL
Caregivers	Alzheimer's Disease	http://www.alz.org/care/alzheimers-dementia-daily-plan.asp
	Mayo Clinic	http://www.mayoclinic.org/healthy-lifestyle/caregivers/in-depth/alzheimers-caregiver/art-20047577
	AARP	http://www.aarp.org/home-family/caregiving/care-guides/dementia-caregiving/
Family	Alzheimer's Disease, Disease basics	http://www.alz.org/ and http://www.alz.org/what-is-dementia.asp http://www.alz.org/living_with_alzheimers_4521.asp

Dr. Atri: Putting them on a cholinesterase inhibitor with a low dose is often the first AD medication. The patient and caregiver/family member need specific counseling about helping the patient take it during the day after a full meal and monitoring it. Family members and caregivers need to have realistic expectations for the medications (improvement in 15-25% of AD patients, particularly on cognition; stabilization in about 50-60%) in the short term, six to12 months. The medications appear to slow the clinical decline (not return them to normal).[63,64] We do not know their specific effects on Alzheimer's pathology in the brain.

Dr. Tariot: For treatment, everybody with Alzheimer's disease deserves the option of enrolling in a trial on a cholinesterase inhibitor. Everybody who either progresses rapidly or progresses to moderate stages should consider a trial of co-administered memantine.

Although this comment is not FDA approved, the AD patients should be evaluated for the presence of neuropsychiatric signs and symptoms. If clinically indicated, appropriate, and family approved, psychotropics should be considered. I'm going to emphasize that is an off-label use remark, but I think there is a difference between regulatory indication and clinical indication.

I agree with Dr. Atri: Our patients' families need "non-medical" support, information, and strategies. They need to learn about the illness: What is this, why does it happen, what lies ahead, what are the genetic implications? Plus many management issues around daily living: Optimizing safety, independence, dignity, quality of life while living with this new chronic illness. What do we tell our family and friends? When do I stop work and how? When is it no longer okay for me to manage my legal and financial affairs? What about driving? What about planning ahead? What about changes in communication and behavior? Sleep, nutrition? Eventually changes in daily bodily functions? What about advanced dementia, grief, hospice, death. Doctors are rarely trained or have time to coach the families on these issues. Table 6 lists a few resources.

Dr. Devere: Very good. Any pharmacological suggestions that people are using for behavioral issues? Anything that relates to the dementia and caregiving?

Dr. Atri: Dr. Tariot's point on FDA label indications also applies for initiating the AD-specific medications, whether cholinesterase inhibitors or memantine in clinical practice. Some clinicians may be starting treatment with a cholinesterase inhibitor in the MCI stage if there is strong support that the MCI syndrome is due to AD, however, this is an off-label use. Contraindications for cholinesterase inhibitors include unstable peptic ulcer disease, arrhythmias, seizure disorder, syncope; for memantine, it is poor renal function (the dose is halved in individuals with CrCl <30).

Potential side effects of these medications can be mitigated by ensuring appropriate administration (including supervision), starting low and going slow, and counseling.[61] For example, oral cholinesterase inhibitors taken on an empty stomach, may cause some individuals nausea, loose stools, flatulence, and increased GI secretions; some individuals taking these at night may have very vivid dreams. Memantine is usually pretty well-tolerated, but some individuals can be "more confused" during the period of initial titration to maximum dose. In all cases a thorough review of symptoms, the patient's condition (e.g., are they dehydrated, are they confused because they are partially more aware and active?) and how/when the medication is administered and monitored is indicated, dropping to a lower dose and trying a slower titration in the future can often mitigate issues. Once individuals are in the moderate dementia stages and beyond, combination treatment with memantine added to cholinesterase inhibitor is beneficial and recommended (for example, see the European Guidelines[65]).

Anxiety and depression should also be formally assessed, and if observed, treated.

Dr. Marshall: We also consider treating patients with normal heart conduction (QTc) with citalopram (Celexa) for agitation because there's nice evidence from a clinical trial showing its benefit.[66] Starting at a dose of 10mg and gradually escalating up to a dose of 30mg/daily. However, it is an off-label use of citalopram. None of the antipsychotics have really shown benefit in clinical trials for treatment of agitation in the absence of psychotic symptoms, and they would also be off-label.

Dr. Atri: Many older patients also have a vascular contribution. If

they do not have microhemorrhages, severe cardiovascular disease, history of bleeding, or use blood thinners, I recommend 1000 IU vitamin E (alpha tocopherol) twice a day, based on two large studies, Sano et al.,67 and Dysken et al, 2014.68 that indicate about a 20% lowering of decline in function (ADL). Assuming no microhemorrhages, bleeding diathesis or other contraindications (or relative contraindications, such has already being on a blood thinner or antiplatelet agent), I also may consider putting some individuals with higher cerebrovascular risk or leukoariosis burden on a baby aspirin two to three times a week. This is my own "evidence-based opinion" and is not purely evidence-driven.

Lifestyle changes include reducing stress, reducing alcohol intake, ensuring adequate sleep, remaining physically active during the day, exercising, and resisting benzodiazepines. The DICE approach for problem behaviors can be helpful to mitigate behavioral issues and to avoid the need for an antipsychotic.[69] However, an antipsychotic may be used, off-label, if there's an immediate danger to safety because of severe psychosis, agitation, and/or aggression. In Europe, risperidone is approved for short term use in such cases; in the US there is a boxed warning for use of all antipsychotics in dementia. Otherwise we make a very deliberate and concerted effort not to use antipsychotics.

Dr. Marshall: Interventions for behavior modification of behavioral issues are very important, especially for institutionalized patients. Their caregivers can share the triggers that make the AD patient misbehave. Just listening to the caregiver and then educating the staff goes a long way sometimes. If staff can do it slowly and patiently, staff may avoid a big mess in terms of bad behavior that escalates. If medications are used, then side effects often occur, and it triggers a big cycle. Behavior modification is really important.

In earlier and later stages, strategies include not engaging the individual in certain situations, distracting them, redirecting them, while ensuring their safety. Let the disease help the staff: if the patient is going to forget what happened five minutes later, that can be a good thing because that will include forgetting the cause for agitation. Training staff on effective methods to modify behaviors of AD patients is very important.

Dr. Atri: I completely agree with Dr. Marshall about the use of behavioral strategies, and when possible avoiding antipsychotic medications. I recently reviewed short term effect sizes for different medications/classes: generally, for cholinesterase inhibitors they range from 0.2 - 0.4 over six months (depending on dose and outcome: cognition, function, behavior or global severity); for memantine they were about 0.2-0.3, mostly in combination to a cholinesterase inhibitor. The effect sizes for antipsychotics (risperidone, aripiprazole, olanzapine) for different behaviors/neurpsychiatric symptoms ranged from 0.12 to 0.2. For agitation, four trials for olanzapine and six for risperidone were performed, and their effect sizes are between 0.19 and 0.22.

Antipsychotics can bring three additional problems: reduced cognition, functional capacity and movement (e.g., extrapyramidal side effects), increased risk of oversedation, falls, aspiration, stroke and death, and extra cost. Relative risk for mortality could be anywhere from 1.5 to 1.7 in the short term and 3.0 to 3.4 in the long term.[70] In the CitiAD study Dr. Marshall referenced,[66] while there were small short term (nine weeks) treatment benefits in favor of citalopram 30mg daily; there was also suggestion of a decrease in the MMSE scores by about 1.5 points, and a prolongation in QTc.[70]

Of note, a cluster randomized trial showed that pain management, including by paracetamol (Tylenol), in 352 nursing home residents significantly decreased behavioral issues (verbally agitated behaviors, physically non-aggressive behaviors, and aggressive behaviors).[71] It is actually a very reasonable approach since many elderly may have pain, for example from arthritis, which they may not be able to properly verbalize and which may escalate a vicious cycle of pain, sleeplessness, anxiety, agitation, etc.

Also, Nuedexta was studied in a 10-week trial, there was suggestion of modest efficacy but also a signal for more falls.

On the behavioral approaches, I completely agree with Dr. Marshall, including:

- Simplifying environments, establishing routines, providing stimulating or relatable activities.
- Making the environment safe, and calm.
- Using positive redirection and reassurance.
- Providing bite-sized information, that is simple to understand.
- Not saying no, use the memory disorder to help you allow the moment to pass. Do not confront, correct, or try to convince. Unless it is an acute safety issue, just let it go, let it pass.
- Be aware that an underlying condition may be causing the behavioral issues, and deal with it: Are they dehydrated, have sleep problems, have pain, are constipated, fighting an infection, or are feeling fearful, anxious or depressed?

Other issues to address include identifying and monitoring risks such as weapons in the home, stove use, driving, and financial and asset management. Also some individuals may benefit from physical therapy, occupational therapy, and/or speech and language pathology therapy. Other patients and families may be appropriate for genetic counseling. Finally, it's of utmost importance to provide referral for counseling and support groups, and also to "care for the caregivers" during this process.

Dr. Devere: Since I started taking patients' history on their emotional incontinence for six months, I can't believe how many people have that. I started treating with Nuedexta about six months ago and I've had terrific results. I know it can cause first degree atrioventricular heart block so heart disease is a contraindication. The company is pursuing approval for anxiety and agitation. I find it very helpful in many patients.

Secondly, I just reviewed more than 30 articles on music and dementia.[72,73] I now suggest that caregivers play music that is loved/enjoyed by their patients. While it is more complex in assisted living

facilities, the caregiver at home can play the music that their loved one likes. A scale can monitor the patient's emotions: Does he talk when the music is on? Does he raise his arm? Does he smile?

These approaches that everybody's mentioned on other non-pharmacologic treatments, and plus music therapy can greatly reduce the need for antipsychotic medications. I pretty well stopped using antipsychotics in my practice.

Dr. Tariot: I think the big picture is that behavioral changes are common, they're morbid. We really need to understand each individual on a case by case basis, an impossible task in a few minutes.

Dr. Atri: That is a huge point that Dr. Tariot brought up. Although we read studies that provide data regarding averages, we don't treat an "average patient." We treat individual dyads of patients and caregivers. Supporting the dyad is very complex, both in the diagnostic and in the care end, and needs more emphasis.

These behavioral interventions are very time intensive and resource intensive, but we can teach caregivers these strategies. Effect sizes range from 0.2 to 0.5, so using these interventions can actually make meaningful differences in people's lives.

MONITORING

Dr. Devere: How do you monitor your patients? How often do you see them and how do you evaluate them in a follow up visit?

Dr. Marshall: During the first several visits for a diagnosis, I try to see my patients more frequently, every two to three months for a period of about nine months. I may start them on medication. After an established relationship and intermittent phone calls, I see them about every six months for somebody with mild cognitive impairment or mild dementia.

If a patient is very stable for a couple of years, visits may even spread out to once a year, but it's not common. After six months, the patient with mild dementia will progress. New issues arise, and the patient and family members or loved ones need further education.

We monitor and reassess their health by using the short evaluation batteries focused on cognition, activities of daily living and neuropsychiatric symptoms at least every six months. After the patient and family are comfortable with the care, which may take several visits, I bring up issues on advanced care planning while everybody can still make decisions about their desires for the future. The family may need this conversation several times.

As things change, the assessments change. As patients decline, often we do very limited assessment of them directly and really focus on the caregiver's reports. It is a tough situation: we still want to be respectful of the patient, and we want to get the valuable forgotten information from their caregiver. We certainly transition into getting more of the information from the caregiver as things progress.

Dr. Tariot: Here is a golden rule for everybody to keep front and center: If a sudden change occurs in a person's status ~~if~~ they get confused suddenly—ask caregivers to run, not walk, to the doctor. It is delirium until proven otherwise. This fundamental management principle applies throughout the course of illness.

MCI PATIENTS

Dr. Devere: Do you treat MCI patients pharmacologically in any way, and how often do you follow them?

Dr. Marshall: I follow up the MCI patients every six months. If they are really stable, then every year. Dr. Atri and I have discussed pharmacological treatment many times. Much variability exists: actual clinical use can follow FDA label but also commonly involves off-label use. Many doctors and experts in the field will use these medications in patients at earlier disease stages than the FDA label indicates. Although off-label at the MCI stage, some experts will argue that at least donepezil with a three-year trial had some signal in the right direction, especially for people at greater risk who were APOE4 carriers. Some non-clinical trial data obtained by Dr. Atri from the Memory Disorders Clinic setting in real-world scenarios have provided a benefit at that stage.[64]

Dr. Tariot: I present the evidence about cholinesterase inhibitors and donepezil specifically to my patients with MCI: the glass is half full. Then, I tell them about clinical trials that they may be eligible for. With that approach, approximately 50% choose to go on a cholinesterase inhibitor, and many opt for clinical trial referral as well.

Dr. Devere: What do you tell your patients about the prognosis of MCI?

Dr. Tariot: I tell them I don't have a crystal ball. Some people who meet MCI criteria actually revert to normal. Some people do not change much over time. The majority do progress over time, and prediction of who is going to progress and who is not can be troublesome.

I just want to caution against over valuing the APOE4 data in the Petersen New England Journal paper.[74] The error around the association of APOE4 and progression to frank dementia in people with MCI was so great that it is not conclusive at all.

Dr. Atri: I think that the APOE4 carriers benefited in the Petersen study,[74] because they were probably a sample of people more likely to have AD pathology and thus to progress to the dementia stage in the three-year time frame of the study. In contrast, the APOE4 non-carriers were more likely not to have AD pathology and many did not progress. The APOE4 non-carrier data acted as dead weight in the clinical trial and diluted the potential efficacy signal for donepezil.

In the US, data show that many patients with MCI who see specialists are going to be started, off-label, on a cholinesterase

inhibitor. The risk/benefit ratio appears pretty low; and the cost of donepezil is also quite low; it is generically available. The three-year study by Petersen, et al. in the *New England Journal of Medicine* in 2005,[74] did not detect a significant decline in MCI progression to AD dementia by either vitamin E (initial 1000 - 2000 IU) or donepezil (5mg to 10mg) at three years, but significant differences in the favor of donepezil treatment was observed at earlier time points. The authors' conclusions verbatim[74] are:

> "Observed relative reduction in the risks of progression to Alzheimer's disease [of course they mean the dementia stage] of 58% at one year, and 36% at two years in the entire cohort is likely to be clinically significant. Although the findings do not provide support for a clear recommendation for the use of donepezil in persons with MCI, they could prompt a discussion between the clinician and the patient about this possibility."

I have yet to meet any neurologist or psychiatrist or dement-ologist who will answer in the negative when I say "Will you try your mom or dad on it [donepezil] at the MCI stage if you are convinced that your parent has AD?"

Dr. Marshall: I don't counsel my patients based on that question, and I care about my patients and want to do the best for them. I tell them what the evidence for cholinesterase inhibitor use in MCI is. Its effects were in the right direction, but did not meet strict gold standards for efficacy.

Unfortunately for supplements, we have limited data for many supplements, and we have good data showing that some supplements are not effective (e.g., ginkgo biloba). Vitamin E was effective at the stage of dementia as discussed earlier. However, vitamin E administered at the stage of MCI in the Petersen study[74] was completely useless, but safe.

Dr. Devere: Any experience with Vayacog? The Vayacog (PS-DHA) literature on subjective memory complaints and MCI was a randomized, double-blind, placebo controlled trial with a 15 week duration at a single center in Israel followed by an open-label extension.[75,76] Safety profile was good. They used the Hebrew version of the Rey Auditory Verbal learning Test, Rey Complex Learning Test, Clinical Global Impression of Change, and NexAde to assess baseline and cognitive abilities. The treated group (n=60) showed significantly greater immediate recall in 15 weeks than the placebo controls (n=61).

Dr. Atri: Unfortunately, I think that the evidence for efficacy of medical foods and supplements is very limited in the dementia stage of AD. I would love to think that they could provide benefits, but the clinical trial data produced so far is not sufficient for me to recommend them. Whether it is curcumin, ginkgo biloba, DHA/EHA, vitamin B_{12}/B_6/folic acid combinations, resveratol, Cerefolin, Axona, Souvenaid, or a dozen others, we either don't have the dose right, the right preparation, the right stage/timing, or the right narrow population who would benefit; or they don't work, period. In any case, many of us have been involved in these clinical trials, but they have not panned out.

Dr. Devere: Does anybody else use Vayacog in MCI? I have been using it in my MCI patients.

Dr. Atri: Adding to Dr. Tariot's comments for MCI diagnosis, various factors increase the risk of MCI being due to AD pathology, and thus of progression from MCI to dementia stages. Hippocampal, medial and lateral temporal, and parietal atrophy are associated with AD pathology. Abnormal CSF AD-profile and positive amyloid scans support that underlying AD pathology. Hansson, et al. shows that patients with MCI syndrome and positive for tau and amyloid beta 42 in the CSF have a 17-fold higher probability of progressing over the next four to five years to the dementia stage of Alzheimer's disease.[77] According to the Australian Imaging Biomarkers and Lifestyle Research Group, people with higher cerebral amyloid 42 burden had a higher risk for progression to AD in 18 months than people with lower Aβ42 burden.[78] The cerebral amyloid burden was a greater risk factor than APOE4 genotype.[78] No interaction between these two factors was detected.[78]

Dr. Devere: Although several of you have mentioned a six month to 1 year follow up of MCI patients, it is too long for most of my early patients. If their treatment is minimal for more than six months or even four months, they forget or are too busy to come back. Thus, I have shorter follow up of three months usually. Have you noticed that in practice?

In summary, the silver tsunami—the aging population—is increasing the global healthcare burden of cognitive decline and dementia, due to Alzheimer's disease, vascular dementia, and DLB. Whereas the etiology of early-onset AD involves mutations mainly in three genes, the etiology of the most common late-onset Alzheimer's dementia is multifactorial and involves interaction between individual genetic susceptibilities or protective factors, exogenous and environmental factors (head injury, cardiovascular health, diet, smoking, toxins) and age. We discuss how mild cognitive impairment and dementia involve cognitive decline beyond normal aging. Family members and caregivers can be helpful in relating recent changes in function and behavior. Several tests such as the MoCA and MMSE can aid in diagnosis of people with mild cognitive impairment and moderate dementia, respectively. Some people can harbor amyloid deposits and tau tangles without symptoms, although many progress to dementia. Current FDA approved treatments include three cholinesterase inhibitors and a NMDA modulator, memanatine, suggesting abnormal signaling in the acetylcholine and NMDA pathways in AD development and its progression. Discussions on combination therapy are recommended. We also presented numerous non-pharmaceutical strategies such as reducing

the medication load of the patient; the MIND diet; habits which also support brain health; music therapy; behavioral modifications; and resources for caregivers and families for use in real-world scenarios.

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THE ALZHEIMER'S DISEASE SPECTRUM: A CLINICALLY FOCUSED DISCUSSION BETWEEN PRIVATE PRACTICE AND ACADEMIC NEUROLOGISTS AND PSYCHIATRISTS POST TEST QUESTIONS/ACTIVITY EVALUATION

1 *AMA PRA Category 1 Credit™* Expires September 2018

1. A 69-yr-old male who has recently retired occasionally forgets the day of the week. He no longer makes his breakfast and is having challenges in paying bills on time. He is less interested in his hobby of fly fishing and making "fly lures". He is hesitant to drive at night due to lower acuity at night. He may be getting a cataract. He occasionally has trouble remembering the correct word but enjoys visiting and talking with family and friends. Which of the observations may indicate a risk for MCI or early AD/dementia?

A. Occasionally forgets the day and has trouble remembering a word, but remembers them later.
B. No longer makes his breakfast, less interested in his hobby, and having challenges paying bills routinely.
C. Hesitant to drive at night due to lower acuity and may be developing a cataract.
D. All of the above.

2. A 76-year old female has some memory issues and is accompanied by a family member. The clinician takes the medical history and the family member provides information on her Activities of Daily Living and symptoms that indicate changes in her behavior and cognitive abilities. The presence of periventricular white matter lesions in the brain on MRI is interpreted by the radiologist as non-specific and age-related. Which interpretation should the neurologist NOT assume for these lesions?

A. Silent, age-related, and non-specific lesions.
B. A reduced brain reserve.
C. White matter hyperintensities may suggest underlying small vessel ischemic disease, consistent with vascular dementia or cognitive impairment.
D. Lesions associated with a decline in cognitive ability or with cerebrovascular risk factors.

3. 65-year-old male geologist came for evaluation because he was concerned that his father had died of Alzheimer's disease in his 60's. He and his wife are not aware of any cognitive decline yet, and they are interested in the pathogenic mechanisms of AD and strategies that may derail the process. What would you explain?

A. A major risk factor for late-onset AD is being a male, with the highest prevalence (15%) in the 65 to 74 year-olds.
B. Lifestyle modifications that improve cardio/cerebrovascular health, including the MIND diet, physical exercise, cognitively stimulating activities, and continued learning of new tasks or knowledge may help increase brain reserve; these may help to prevent or delay the onset of Alzheimer's disease symptoms.
C. Autosomal dominant familial AD is not uncommon (about 10 - 15% of all cases), is often caused by a mutation in the tau precursor protein; and usually strikes adults in their 60's.
D. Major head trauma, cerebrovascular risk factors, and environmental toxins have no association with the development of AD.

4. The pathogenic mechanisms of late-onset AD dementia are multi-factorial and not fully elucidated. The brain pathology probably develops over years to decades. Both protective and susceptible genetic factors interact with environmental factors, lifestyle choices (diet, exercise routine, cardiovascular risks), head injury, and age to form each individual's risk of AD. Which neurotransmitter receptors are involved in redox homeostasis, excitotoxicity, memory mechanisms, and are targeted by the FDA approved medication, memantine?

A. GABA receptors
B. Acetylcholine receptors
C. NMDA receptors for glutamate.
D. Serotonin receptors

5. A 72-year old female and a family member are concerned about her recent memory lapses which are becoming more frequent. You would like to assess whether her occasional memory lapses may indicate a diagnosis of mild cognitive impairment or mild dementia. Which test would you use to assess cognitive ability for people with possible MCI?

A. MoCA
B. MMSE
C. Lawton and Brody scales
D. Alzheimer's disease Cooperative Study (ADCS)

6. You are evaluating a 79-year-old male with cognitive decline and have been informed by his family member about recent changes in behaviors and activities of daily living. After an initial assessment, you strongly suspect that the 79-year-old has mild cognitive decline, and you are interested in checking for any potential exacerbating factors. What would you NOT check for immediately?

A. Any medications that are anticholinergic agents, benzodiazepines, and barbiturates in his prescription list.
B. Vitamin B12 levels and thyroid (TSH) levels.
C. Glucose metabolism in brain with a FDG-PET scan.
D. A structural neuroimaging scan—MRI (or head CT)

7. A 71-year old female has progressed to moderate AD dementia has been taking the FDA-approved cholinesterase inhibitor donepezil (10mg daily), one of three acetylcholinesterase inhibitors. What treatment regimen would you recommend and why?

A. Consider switching the medication to galantamine in case this anticholinesterase works better in her.
B. Consider switching the medication to rivastigmine in case this anticholinesterase works better in her.
C. Consider adding another cholinesterase inhibitor (galantamine or rivastigmine) to her current donepezil.
D. Consider combination therapy of the FDA-approved medications, any acetylcholinesterase inhibitor and memantine, because clinical trial data and a recent meta-analysis of seven studies support significant benefits in moderate and severe AD dementia.

8. Behavioral issues in AD patients are relatively common. A 74-year old male with moderate AD dementia has been exhbiting behavioral issues, rendering his care more challenging. Your staff has helped educate the caregiver about the course of the illness, provided strategies for administering medication and monitoring home health and safety, and suggested music therapy with the AD patient's favorite music. Behavioral issues have diminished, but the caregiver still needs further help. What would you NOT recommend?

A. Distracting the patient, redirecting the patient, while ensuring their safety.
B. Identifying potential underlying causes for behavioral issues such as dehydration, sleep problems, constipation, an infection, and resolving the issue(s).
C. If there is no contraindication, trying a trial of acetaminophen/paracetamol in case he is having pain.
D. Prescribing a trial of antipsychotics for a patient with mild behavioral issues.

ACTIVITY EVALUATION

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Discuss current pathogenic mechanisms of Alzheimer's disease and rule out other causes of dementia.	_____	_____	_____
Assess the epidemiology and risk factors for developing dementia.	_____	_____	_____
Evaluate the diagnosis of people with mild cognitive impairment and dementia associated with Alzheimer's disease.	_____	_____	_____
Formulate treatment options for patients with Alzheimer's disease, including MCI and dementia.	_____	_____	_____
Formulate strategies to best prevent further cognitive decline.	_____	_____	_____
Discuss beneficial interventions for caregivers, AD patients and their families.	_____	_____	_____

Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity as required by the Accreditation Council for Continuing Medical Education (ACCME).

Name and email: _____

Do you feel the program was educationally sound and commercially balanced? ❒ Yes ❒ No

Comments regarding commercial bias:

_____

_____

Rate your knowledge/skill level prior to participating in this course: **5 = High, 1 = Low** _____

Rate your knowledge/skill level after participating in this course: **5 = High, 1 = Low** _____

Would you recommend this program to a colleague? ❒ Yes ❒ No

Do you feel the information presented will change your patient care? ❒ Yes ❒ No

Please identify how you will improve/change: _____

Change the management and/or treatment of patients. Please specify:

_____

_____

Create/revise protocols, policies, and/or procedures. Please specify:

_____

_____

Please identify the barriers to change.

_____ Cost ___ Lack of consensus or professional guidelines _____ Lack of administrative support _____ Lack of experience

_____ Lack of time to assess/counsel patients _____ Lack of opportunity (patients) _____ Reimbursement/insurance issues

_____ Lack of resources (equipment) _____ Patient compliance issues _____ No barriers _____ Other

Please specify: _____

This information will help evaluate this CME activity, we may contact you by e-mail in 1-2 months to see if you have made this change? If so, please provide your e-mail address below.

_____

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