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Stephanie Collier, MD, MPH
Editor-in-Chief

Volume 1, Issue 1
January/February/March 2022
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IN THIS ISSUE

Focus of the Month: **Dementia**

Learning Objectives

After reading these articles, you should be able to:

1. Determine best practices for interviewing and evaluating older patients for memory-related issues.
2. Identify and treat the common types of Alzheimer's disease and neurocognitive disorders.
3. Evaluate aducanumab as a treatment for patients with Alzheimer's disease.

How to Interview the Older Patient

Rehan Aziz, MD. Inpatient geriatric psychiatry, Hackensack-Meridian Health, Perth Amboy, NJ.

Dr. Aziz has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

The expanding population of older adults has created a need for all clinicians to participate in their care. Interviewing techniques require adaptation in older adults, such as accounting for hearing or vision impairment and speaking slowly and clearly. This article will cover additional factors to consider when evaluating older patients.

Functional assessment

Appraising a patient's functional status is critical. It's done by asking about activities of daily living (ADLs) and instrumental activities of daily living (IADLs). IADLs are advanced skills, the first activities impacted by dementia. I recommend asking about them in the presence of a caregiver because patients may minimize their own deficits. See the table on page 5 for the unfortunate mnemonics DEATH and SHAFT along with sample questions to assess ADLs and IADLs.

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Highlights From This Issue

Feature article

The safety assessment in older adults includes asking about suicidal thoughts, driving, wandering, and elder abuse.

Q&A

Although aducanumab removes plaques from the brain, data from two large trials are inconsistent about whether it slows the progression of cognitive impairment.

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Suspect rare causes of dementia when patients present with an early age of onset (<65 years), rapid progression of symptoms, or an abnormal neurological exam.

Q&A With the Expert

Aducanumab: What the FDA Approval Means for Clinicians
Andrew Budson, MD

Chief of Cognitive and Behavioral Neurology at the VA Boston Healthcare System; Associate Director and Leader of Education at Boston University Alzheimer's Disease Research Center; Lecturer at Harvard Medical School.

Dr. Budson discloses that his lab received research funding from Biogen, the manufacturer of aducanumab, in 2020. The funds were received by the Veterans Affairs Boston Health Care System and did not contribute to his salary. He also received funds for a one-day consultation meeting with Sage Pharmaceuticals (manufacturer of the antidepressant brexanolone) in February 2020. Dr. Carlat has reviewed the content of this interview and determined that there is no commercial bias as a result of these financial relationships.

CGPR: How does aducanumab work?

Dr. Budson: Aducanumab (Aduhelm), which is given intravenously once a month, is a monoclonal antibody directed against amyloid plaques that are associated with Alzheimer's disease. The idea is that aducanumab will stick to the plaques in the brain. Once there's an antibody on a plaque, the immune system signals the body's defense mechanisms to remove it.

CGPR: Does aducanumab slow the progression of Alzheimer's disease?

Dr. Budson: The studies clearly show that aducanumab removes plaques from the brain, but they have not consistently demonstrated whether aducanumab does anything to the progression of cognitive impairment. According to the publicly available data on the FDA's website, there are

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Expert Interview – Aducanumab: What the FDA Approval Means for Clinicians
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two large studies, each with about 1,000 participants. In one of the studies, aducanumab looked like it could slow down the disease by three months over an 18-month trial. In this study, high-dose aducanumab treatment was associated with a 22% slowing of decline on the primary outcome measure, the CDR-SB (a composite measure with cognitive and functional components), compared to placebo. But the other study showed the opposite—not only did aducanumab not work, but the patients in the placebo group outperformed the aducanumab group on cognitive tests by the equivalent of three months (www.tinyurl.com/yhszhmya). The effect size was about the same in both studies, one of them in the positive direction and the other in the negative direction.

CGPR: Which patients are eligible for aducanumab?

Dr. Budson: Individuals with mild cognitive impairment and individuals in the mild stage of Alzheimer's disease are eligible. In the original studies, patients had a Mini-Mental State Examination of 24 or above. But the FDA's ruling was for the mild stage, which is a little more lenient. A person in the mild stage of Alzheimer's disease might experience difficulty with instrumental activities of daily living, such as paying bills, managing medications, or grocery shopping. But they should not have difficulty with their basic activities of daily living, such as dressing, bathing, or maintaining their hygiene.

CGPR: What are the side effects of aducanumab?

Dr. Budson: Side effects included headaches, confusion, dizziness, and nausea. Microhemorrhages (bleeding in the brain) were seen 12% more often in those taking aducanumab compared to those taking placebo. Having many of these brain bleeds can impair a person's cognition.

CGPR: Any other side effects?

Dr. Budson: Aducanumab caused amyloid-related imaging abnormalities (ARIAs) in about 40% of people. Approximately 35% of people in the *Continued on page 3*

EDITORIAL INFORMATION

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This CME/CE activity is intended for psychiatrists, psychiatric nurses, psychologists, and other health care professionals with an interest in the diagnosis and treatment of psychiatric disorders.

The Carlat Geriatric Psychiatry Report

POSTMASTER: Send address changes to *The Carlat Psychiatry Report,* P.O. Box 626, Newburyport, MA 01950.

Introducing *The Carlat Geriatric Psychiatry Report*

Welcome to the inaugural issue of *The Carlat Geriatric Psychiatry Report*—our fifth CME newsletter. You've been asking for a source of unbiased reporting on geriatric psychiatry, and we've finally created one. We hope you'll find it useful.

Three years ago, I took a job as chief of psychiatry at MelroseWakefield Healthcare, and an important part of our mission is a 34-bed geriatric psychiatry unit, including a busy ECT service. Since I never did a geripsych fellowship, I had to get up to speed quickly—and I thank some of our excellent staff, including John Giragos, Jim Lech, and Mary Wilber, for allowing me to shadow them and learn how they help some of the most vulnerable and wonderful patients I've ever encountered.

The idea of starting a geripsych newsletter was a bit self-serving, since I felt a personal need to beef up my command of the topic. I reached out to Stephanie Collier, a colleague at McLean—only a few miles away from my own hospital. I was impressed by her infectious enthusiasm for education and her devotion to elderly patients. She dove into the task of recruiting authors and editing articles like a veteran, and I think you'll be pleased with the result.

Please drop either Dr. Collier or myself an email to let us know how you like the newsletter and what topics you'd like to see covered in future issues.

Sincerely, Daniel Carlat, MD
dcarlat@thecarlatreport.com

Welcoming Our New Editor-in-Chief

It's our pleasure to introduce Dr. Stephanie Collier, MD, MPH, as the editor-in-chief of *CGPR*. Dr. Collier is the director of education in the Division of Geriatric Psychiatry at McLean Hospital and an instructor in psychiatry at Harvard Medical School. Dr. Collier completed her psychiatry residency at Duke University Medical Center and her fellowship in consultation-liaison psychiatry at Brigham and Women's Hospital. She teaches and supervises medical students, residents, and fellows in geriatric psychiatry, and she works on projects training non-specialist clinicians in resource-limited settings.

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high-dose group had "ARIA-E" or amyloid-related vasogenic edema (www.tinyurl.com/yhszhmya). ARIA-E is not necessarily destructive, but it causes brain swelling. It's important to note that the study data excluded individuals with a history of heart attack, transient ischemic attack or stroke, or kidney disease, as well as people on blood thinners. Since many people meet these criteria, the reported rates of ARIAs are likely underestimates.

CGPR: How concerned should we be when we see ARIAs on imaging?

Dr. Budson: Most of the time this type of brain swelling resolves without any permanent damage, although sometimes it leads to a stroke if the tissue is too compressed or the swelling is too great. I'm always very cautious when I see ARIAs on a scan, and my rule of thumb is that a person with ARIAs is done from the study, and they don't get rechallenged.

CGPR: What's the cost of aducanumab, and will insurance cover it?

Dr. Budson: The cost is estimated to be around $28,000 a year, as aducanumab is titrated according to a patient's body weight. Thus far no insurance company covers it. The US Department of Veterans Affairs (VA) has chosen not to cover it and not to include it in the VA formulary. The Centers for Medicare and Medicaid Services (CMS) has issued a final decision to pay for aducanumab only in the setting of a clinical trial in order to obtain more information about risks and benefits.

CGPR: Do you think it's likely that CMS will pay for aducanumab outside of clinical trials in the near future?

Dr. Budson: I would hope they don't, based on everything I know about the data. CMS does not cover amyloid PET scans, which is the easiest way to determine if someone has Alzheimer's disease, and a sure diagnosis is necessary to administer this drug. Then there is the cost of repeated MRI scans, which cost $1,325 on average and would be necessary to monitor for microhemorrhages and swelling in the brain. MRIs are recommended prior to initiation and prior to the fifth, seventh, and 12th doses (or if symptoms suggestive of ARIAs occur). And even if CMS does cover the medication, patients are still responsible for 20% of the price tag.

> **"The studies clearly show that aducanumab removes plaques from the brain, but they have not consistently demonstrated whether aducanumab does anything to the progression of cognitive impairment."**
>
> Andrew Budson, MD

CGPR: People who are carriers of the APOE4 gene appear to be at higher risk for the development of ARIAs. Should we be screening patients for their carrier status to potentially administer a lower dose of aducanumab?

Dr. Budson: The benefit of aducanumab was only apparent when people received the highest dose; the low dose was not effective. In the negative trial, not enough individuals received the highest dose, even if they were APOE4 positive.

CGPR: Given the cost of the medication and the potential side effects, do you think that aducanumab will get much use?

Dr. Budson: I don't think so, at least not until there is proof that it works. If aducanumab is shown to be safe and effective (using clinically meaningful outcomes) in a diverse population with Alzheimer's disease, and its cost doesn't limit use to the wealthy, then I think a lot of people will use it, and I would be in favor of using it as well. There have now been a few deaths that were likely due to aducanumab, which changes the question of how we perceive the danger of ARIAs. Many patients may think, "Well, maybe it's not going to help me, but it can't hurt." When they hear that people have died, they'll be less likely to try it.

CGPR: Can you speak about the controversy associated with aducanumab's accelerated approval?

Dr. Budson: The FDA can approve medications based on a biomarker or other indication that the medication might work. It can approve a medication with the reasoning that it might help some people even though a definitive study has not been done. This FDA decision was controversial for two reasons: 1) One study was positive and the other was negative, so the obvious conclusion is that we need at least one more study to determine if the drug works; 2) The FDA's own advisory panel recommended that the drug not be approved. Every member of the FDA advisory panel either voted not to approve or abstained. The FDA's accelerated approval led to the resignation of three members of its advisory panel. The approval was so controversial that two congressional committees, plus the Health and Human Services Office of Inspector General, are conducting independent investigations to better understand the decision.

CGPR: Do you think aducanumab's approval is opening the floodgates for the approval of other amyloid-clearing therapies?

Dr. Budson: I hope not, unless there's more consistent evidence—in which case, we should definitely approve them. The amyloid hypothesis is controversial because it has repeatedly failed therapeutically; this is why meaningful outcomes are critically important. I hope the FDA realizes that they did not do the right thing. Whether they will retract their approval or not, I don't know. They already retracted one part of their initial ruling, which said that aducanumab was FDA approved for people at any stage of Alzheimer's; it now only includes people in the mild stage of disease (which makes sense since this was the population studied).

CGPR: If patients are interested in an aducanumab trial, where can they go?

Dr. Budson: People in the mild or very mild stages of Alzheimer's disease can sign up for a clinical trial at one of the 33 NIH-funded Alzheimer's disease research centers across the country. Patients can research trials at www.clinicaltrials.gov.

CGPR: Can centers administer aducanumab without a trial?

Dr. Budson: Yes, centers and individual neurologists and other providers are free to prescribe aducanumab if a patient can pay out of pocket.

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CGPR: What else do you recommend to patients with Alzheimer's disease?
Dr. Budson: I recommend the standard treatments to help memory for Alzheimer's disease, including the cholinesterase inhibitors. Those have been shown to turn the clock back on cognitive decline by six to 12 months (Cummings JL, *Am J Geriatr Psychiatry* 2003;11(2):131–145). These medications can't stop the clock from ticking down, and they can't change the rate at which the clock ticks down, but turning the clock back six to 12 months is still pretty good. To put this in perspective, it's actually better than the positive subgroup analysis of aducanumab that may turn the clock back three months.
CGPR: What do you mean by "turning the clock back six to 12 months"?
Dr. Budson: This is extrapolated from a *JAMA* article in which the researchers looked at changes in the scores of tests like the ADAS-COG: the Alzheimer's Disease Assessment Scale—Cognitive Subscale (Cummings, 2003). They compared people who took cholinesterase inhibitors and placebos to the expected decline on the test every year due to progression of the illness. The researchers found that people taking cholinesterase inhibitors improved by an amount equivalent to raising their score to where they were cognitively six months ago, or for some people to where they were a year ago.
CGPR: And what would that look like—a drug-placebo difference of two or three points on the 70-point ADAS-COG?
Dr. Budson: Right, a very tiny difference. We don't have a good understanding of how this translates to daily functioning.
CGPR: Do you have additional recommendations for people with Alzheimer's disease?
Dr. Budson: I recommend engaging in aerobic exercise for at least 30 minutes a day five days a week. I also recommend a Mediterranean menu of foods such as fish, olive oil, fruits and vegetables, nuts and beans, whole grains, and chicken. Everyone can also benefit from engaging in social activities, along with doing something novel with their brain. And finally, having a positive mental attitude toward aging and life in general has been shown to be important (Levy BR and Myers LM, *Prev Med* 2004;39(3):625–629). People with a positive attitude are more likely to be outgoing, to participate in social activities, and to take care of themselves by eating right and engaging in physical activity.
CGPR: How do these recommendations fare in terms of patient outcomes as compared to medications?
Dr. Budson: I don't know of any study that has compared these recommendations, but the effects of diet, exercise, and social activities are very powerful. In studies that looked at a combination of lifestyle changes, when people made healthy lifestyle changes in middle age, even if they later developed dementia, they did so at a later age compared to those who did not engage in healthy activities (Rosenberg A et al, *J Prev Alzheimers Dis* 2020;7(1):29–36).
CGPR: Thank you for your time, Dr. Budson.

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How to Interview the Older Patient
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For both ADLs and IADLs, I determine whether patients are independent, require assistance, or are fully dependent on others. To assess the presence of caregiver support, I ask patients, "During the past four weeks, was someone available to assist you if you wanted help?"

Mental status assessment
Evaluation of mental status is similar to younger patients, but involves a few additional observations, which we detail below.

Appearance
Patients who experience depression or apathy might neglect hygiene. Those with cognitive disorders might be dressed inappropriately, such as wearing several layers on a warm day. Appearance can also provide a clue regarding the adequacy of the patient's supports. Overwhelmed caregivers may have less time or energy to help a compromised patient.

Psychomotor activity
Older adults with depression, dementia, or altered mental status may have slowed movements. Patients with advanced dementia might appear disengaged from the interview. Patients with moderate dementia may pace. Patients with anxiety might fidget or wring their hands.

Affect
Older adults may demonstrate reduced emotions even in the absence of mental illness—in other words, a constricted affect doesn't mean a patient is depressed. Depressed elders might present as withdrawn, irritable, weary, or apathetic.

Paranoia, delusions, hallucinations
Hearing or vision deficits can sometimes trigger hallucinations (fixable by correcting the deficits). Patients with Parkinson's disease or dementia with Lewy bodies often experience complex visual hallucinations of people, animals, or shadows. Second-person auditory hallucinations are common in older adults with dementia. Severely depressed older patients may have auditory hallucinations that condemn them or encourage self-destructive behavior.

Elders with moderate dementia often suffer from delusions. They can take various forms, such as delusions of infidelity or paranoia. Delusions may be triggered by short-term memory loss (eg, misplacing household items, then accusing a family member of theft). Delusional depression is more prevalent in older patients than in middle-aged adults (Blazer DG, *FOCUS Spring* 2004;11(2):224–235). The most common delusions are somatic or feature negative content, eg, "I'm losing my mind" (Gournellis R et al, *Int J Geriatr Psychiatry* 2001;16(11):1085–1091).

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Cognition

A cognitive evaluation should be part of every initial assessment and then administered periodically. The most commonly used in-office standardized scales are the proprietary Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). Scales in the public domain include the Saint Louis University Mental Status exam (SLUMS) and the Mini-Cog (www.mini-cog.com). The single best assessment is the clock-drawing test: Ask the patient to draw the numbers on the face of a clock with the hands pointing to a specific time (often 10 minutes past 11 o'clock).

Safety assessment

Suicidal thoughts

I start by asking every patient if they have thought that life is not worth living. Keep in mind that older adults may have thoughts about death and dying even if they are not suicidal, which is starkly different from younger individuals. If a patient has had suicidal thoughts, I ask how they would attempt suicide and whether they have the means to do so. Contrary to popular belief, most older patients are not offended by these questions. Intervention is necessary when a patient has seriously considered suicide and has the tools available to carry it out, such as firearms (Blazer, 2004). Because men drive suicide rates in the older adult population, pay close attention to ensure protective factors are in place for these patients.

Driving

Older adults are at higher risk for motor vehicle accidents (Cicchino JB, *Accid Anal Prev* 2015;83:67–73) due to decreased reaction times, impaired vision and hearing, and difficulty managing complex road situations. If I suspect cognitive impairment, I usually interview a family member. I ask whether the patient has gotten lost driving in familiar neighborhoods or whether they have missed traffic signs in the past few months. I also ask about recent tickets. I may perform a Trail Making Test Part B in the office, as there is good evidence that it correlates with driving ability. If I suspect a patient is unsafe driving, I request a driving evaluation or a retest. In the case of dangerous driving, clinicians may be obligated to alert the DMV.

DEATH and SHAFT Mnemonics With Sample Questions

ADLs[1]	IADLs[1]
Dressing • Have you needed help getting dressed?	**Shopping** • How do you go about shopping for groceries and personal items? • Have you had trouble handling money or credit cards?
Eating • Do you need assistance with consuming your meals?	**Housekeeping** • Are you having trouble keeping your living area clean? • Do you experience any difficulty with operating the dishwasher or doing the laundry?
Ambulating • Do you experience trouble getting out of bed or a chair? • How many falls have you had in the past few months?	**Accounting** • How do you keep up with finances and bills?
Toileting • Do you have difficulty getting to the bathroom in time? Have you had accidents?	**Food Preparation** • How do you manage your meals? Do you cook yourself? • Have you burned food or left the stove/oven running?
Hygiene • Do you need assistance bathing? • Do you need help combing your hair or brushing your teeth?	**Transportation** • Have you gotten lost while driving? • Have you been in any accidents in the last year?

[1]*Source: Bickley LS.* Bates' Guide to Physical Examination and History Taking. *12th ed. Alphen aan den Rijn, The Netherlands: Wolters Kluwer; 2017.*

Wandering

Wandering becomes an issue in moderate and severe dementia. Patients may become disoriented and unable to retrace their steps home. In some instances, patients wander outside in cold weather or onto highways. If a patient or caregiver reports concern about wandering, I suggest a few interventions. The patient can wear a medical ID bracelet or carry an item with embedded GPS tracking, such as a necklace, bracelet, or phone. I also recommend installing deadbolts, doorway alarms, or even cameras, and alerting neighbors and the local police of a patient's wandering risk.

Elder abuse

Elder abuse can take many forms: physical, financial, sexual, abandonment, and neglect. Clinicians are mandated reporters of suspected abuse. Generally, I will interview the patient alone about how they feel at home, or how they feel with their family members or caregivers. I ask how they are managing financially. I review the patient's advance directives and pay attention to who has permission to communicate with the patient's clinicians. I observe weight loss, the patient's hygiene, and whether the patient has bruises or cuts (keeping in mind that older adults may bruise from blood thinners or medical illnesses). Depending on the circumstances, I may call the local adult protective services agency. Many local, state, and national social service agencies can also help with emotional, legal, and financial abuse. If I suspect the patient is in immediate danger, I call 911 or the local police immediately.

CARLAT VERDICT

Older adults require an expanded assessment, taking into account functional capacity, social support, cognition, and safety.

How to Distinguish the Dementias

Jose Ribas Roca, MD. Assistant Professor, Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX.

Dr. Roca has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

There are several types of dementia, and each has a different prognosis and treatment course. In this article I'll outline my approach for distinguishing between the most common varieties—Alzheimer's, vascular, Lewy body, and frontotemporal. In addition, I'll cover how to differentiate between mild and major neurocognitive disorder (NCD). (See "Differentiating Among the Most Common Types of Dementia" on page 7 for a quick-reference table.)

Alzheimer's disease

The most common dementia is Alzheimer's disease (AD), which accounts for 60%–70% of dementia cases (www.tinyurl.com/5a9uubva). Symptoms usually start after age 65 and progress slowly. If a patient's symptoms begin before age 65, this is considered early-onset AD.

The cornerstone symptom of AD is short-term memory loss, which leads to the repetition of questions and stories. AD also impacts executive functioning. Language and social cognition are relatively preserved until later in the illness. Neuropsychiatric symptoms such as agitation, delusions, hallucinations, and apathy tend to occur in the moderate to severe stages, although anxiety and depression may appear earlier. AD usually progresses gradually, without plateaus.

Although AD is the most common dementia, it's important to think through alternative explanations prior to making the diagnosis (see the "Non-Alzheimer's Causes of Cognitive Impairment" table on page 7).

Vascular dementia

Vascular dementia (VD) is the second most common dementia, accounting for 15%–20% of dementia cases. Like AD, it becomes more prevalent as people age. VD is caused by damage to the brain's blood vessels. I suspect VD when patients have vascular risk factors such as hypertension, diabetes, or high cholesterol, especially if there has been end-organ damage. The clinical symptoms of VD vary depending on the location and size of damaged brain tissue. VD can progress in a stepwise pattern, such as following strokes, or it may be gradual, such as in progressive microvascular deterioration. Executive function is commonly affected.

Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) usually progresses gradually after the age of 60. I suspect DLB when a patient presents with core symptoms of Parkinsonism, recurrent visual hallucinations, or fluctuating cognition. In DLB, cognitive impairment occurs before motor symptoms, whereas in Parkinson's disease, cognitive impairment occurs in the context of established motor symptoms. REM sleep behavior disorder and neuroleptic sensitivity are often present in DLB. I always ask about whether the patient is experiencing well-defined visual hallucinations and acting out their dreams. I assess gait for instability and bradykinesia, and I look for abnormal movements such as a "pill rolling" tremor. Any of these signs would warn me against a trial of antipsychotics, since patients with DLB often have severe neuroleptic sensitivity. If an antipsychotic is necessary, I consider low-dose quetiapine first, followed by pimavanserin or clozapine.

Frontotemporal dementia

Frontotemporal dementia (FTD) is divided into two variants: behavioral variant FTD (bvFTD) and the language variant, also known as primary progressive aphasia (PPA). Family members may be puzzled and concerned by bvFTD, especially when a patient's personality changes include behavioral disinhibition and socially inappropriate behavior. Apathy, loss of empathy, and perseverative or compulsive behavior are often present.

PPA may present with a loss of word comprehension but intact verbal fluency, making the meaning of a patient's speech incomprehensible. Alternatively, patients may experience early speech impairments including the loss of fluency, difficulty naming (anomia), and difficulty constructing sentences while preserving individual words (agrammatism).

Mixed dementia

The exact prevalence of mixed dementia is not known. According to pathology reports, mixed dementia is the most common form of dementia and found in 46% of persons with clinically diagnosed AD (Arvanitakis Z et al, *JAMA* 2019;322(16):1589–1599). It is more common in older adults, and the most common combination is AD + VD.

Distinguishing between mild and major NCD

When a patient reports memory concerns, I set out to identify whether the memory issues are due to depression, aging, mild cognitive impairment, or dementia. Depression in late life is often the harbinger for dementia. I first identify which neurocognitive domains are affected (complex attention, executive function, learning and memory, language, perceptual-motor, and social cognition), as well as the order by which each domain is impacted. Most patients present with memory impairment plus impairment in at least one additional domain. I verify that the deficit is a significant decline from a previous level of functioning.

Identifying whether a patient's symptoms are due to mild NCD ("mild cognitive impairment") or major NCD ("dementia") holds important prognostic implications. To make this differentiation, I go over a patient's ability to perform activities of daily living (ADLs) and instrumental activities of daily living (IADLs). (See page 4 for a table of ADLs and IADLs.) The diagnosis of major NCD requires interference with ADLs, such as bathing or dressing, whereas the diagnosis of mild

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NCD requires impairment in IADLs, such as managing finances and preparing meals. People with mild NCD require greater effort, compensatory strategies (such as lists), or accommodations, but they should still be able to perform their ADLs independently. Mild NCD does not necessarily progress to dementia. Annual conversion rates are often 10%–15% in clinic samples and 3.8%–6.3% per year in community-based studies (Farias ST et al, *Arch Neurol* 2009;66(9):1151–1157).

Meds, labs, and imaging

When determining potential causes of cognitive impairment, I begin by reviewing a patient's medication list to identify culprits (anticholinergics, antihistamines, benzodiazepines, and opioids are top offenders). I order laboratory tests to rule out metabolic and infectious processes that can mimic dementia. Screening labs include a complete blood count, electrolytes, glucose, liver function, renal function, and thyroid profile. Urinalysis is particularly important, because changes in cognition are often the first sign of a urinary tract infection in the elderly. I often order a fasting lipid profile and hemoglobin A1c in patients with risk factors for VD. For many patients, I will consider vitamin B12 and folate levels. In patients with a history of high-risk behavior, I order HIV antibodies and syphilis tests.

Structural brain imaging can help differentiate among dementias. A brain CT can show areas of cortical atrophy. Patients with AD may exhibit atrophy in the hippocampus and temporoparietal cortex, while patients with FTD may exhibit atrophy in the frontal and temporal lobes. Ventricular enlargement from normal pressure hydrocephalus will be evident on a CT scan. For VD, MRI is favorable, as it provides greater detail about prior strokes, small vessel disease, or subcortical ischemic changes.

Additional imaging is usually reserved for complex cases with atypical presentation. FDG-PET differentiates AD from FTD, amyloid-PET provides supportive evidence for AD, and a DaTscan differentiates between AD and DLB (although it does not distinguish DLB from other Parkinsonian disorders). Memory disorder clinics may offer these tests as part of research protocols.

If I suspect rare causes of dementia, I will refer the patient to neurology (for more on rare causes of dementia: www.thecarlatreport.com/raredementias). Warning signs include an early age of onset (age <65 years), rapid progression of symptoms, or the presence of an abnormal neurologic exam (Arvanitakis et al, 2019). The neurologist may consider further workup, such as an EEG and spinal fluid exams to look for periodic sharp wave complexes and 14-3-3 proteins in Creutzfeldt-Jakob disease. A sleep study is indicated when there is suspicion of sleep apnea or REM sleep behavior disorder; the latter is common in people with Parkinson's disease and DLB.

Cognitive screening tools

I find standardized screening tools to be helpful in

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Differentiating Among the Most Common Types of Dementia

	Symptoms (most characteristic symptoms in bold)	Neuropathology
Alzheimer's dementia	**Short-term memory loss** Difficulty learning new information Impaired executive function	Amyloid plaques and neurofibrillary tangles
Dementia with Lewy bodies	**Visual hallucinations** Fluctuation in cognition REM sleep behavior disorder Neuroleptic sensitivity Parkinsonism	Intracellular deposits of misfolded alpha-synuclein (Lewy bodies)
Frontotemporal dementia	**Disinhibition, apathy, compulsive behavior** (behavioral variant) **Gradual language dysfunction** (primary progressive aphasia)	Atrophy of frontal and temporal regions of the brain Hyperphosphorylated tau protein
Vascular dementia	**Impaired executive function and complex attention** Symptoms vary depending on location	Large and small vessel disease Chronic progressive white matter disease Prior infarcts

Non-Alzheimer's Causes of Cognitive Impairment

Risk Factor	Potential Condition
Age <65 years	Autoimmune diseases Drug or alcohol use disorders Infections of the central nervous system Metabolic abnormalities Traumatic brain injuries
Changes in motor function (tremor, bradykinesia)	Dementia with Lewy bodies Parkinson's disease dementia
Focal neurological signs	Neoplasia Vascular dementia
Gait impairment	HIV-associated dementia Normal pressure hydrocephalus Vascular dementia
Motor symptoms +/- hallucinations	Creutzfeldt-Jakob disease Huntington's disease Parkinson's disease
Myoclonus	Creutzfeldt-Jakob disease Paraneoplastic encephalitis
Rapid onset (<1 year)	Creutzfeldt-Jakob disease Frontotemporal dementia HIV-associated dementia Paraneoplastic limbic encephalitis
Severe disinhibition	Frontotemporal dementia
Waxing and waning consciousness	Delirium Dementia with Lewy bodies

Q&A With the Expert

Treating Dementia: An Approach From the United Kingdom

Elizabeta B. Mukaetova-Ladinska, MD, PhD

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Dr. Mukaetova-Ladinska has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

CGPR: Clinicians often struggle with initiating medications for memory impairment in people with dementia. Can you describe your approach to treatment?

Dr. Mukaetova-Ladinska: Although breaking the news to a patient or relative is challenging, discussing dementia often comes as a relief. A diagnosis helps explain why a patient is experiencing symptoms, and it opens the door to discuss expectations and management. We use a "person-centered approach" that focuses on a patient's abilities, not their condition. In introducing and adjusting medications, I inform patients about their medication options, including formulations (tablet, liquid, or patch) and their benefits and limitations.

CGPR: In patients with Alzheimer's disease, when do you start a cholinesterase inhibitor or memantine?

Dr. Mukaetova-Ladinska: The National Institute for Health and Care Excellence (NICE) guideline for 2018 recommends all three acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine) as options for managing mild to moderate Alzheimer's disease. They are not approved for mild cognitive impairment. Memantine is recommended for people with moderate or severe Alzheimer's disease, either alone or as an adjuvant therapy for people already taking a cholinesterase inhibitor. The cumulative evidence shows that the effects of anti-dementia medications on cognition are relevant for at least two years (Farlow MR, *Int J Clin Pract Suppl* 2002;(127):37–44). A recent study confirmed that all cholinesterase inhibitors decrease long-term cognitive decline and risk of death in people with Alzheimer's disease, but galantamine was the only anti-dementia medication associated with a significant reduction in the risk of developing severe dementia (Xu H et al, *Neurology* 2021;96(17):e2220–e2230). Increasing evidence suggests that both cholinesterase inhibitors and memantine may help in the management of behavioral and psychological symptoms of dementia (BPSD).

"Only try an antipsychotic for agitation in people with dementia if they are at risk of harming themselves or others, or if they are experiencing agitation, hallucinations, or delusions causing severe distress."

Elizabeta B. Mukaetova-Ladinska, MD, PhD

CGPR: When do you consider the use of cholinesterase inhibitors in non-Alzheimer's dementia?

Dr. Mukaetova-Ladinska: There is good evidence that cholinesterase inhibitors are effective and safe in people with Lewy body dementia or dementia due to Parkinson's disease. The NICE guideline recommends the use of cholinesterase inhibitors for the treatment of mixed dementia, but not for vascular dementia alone, nor for frontotemporal dementia, as they may worsen symptoms in the latter.

CGPR: What side effects do clinicians need to be aware of when initiating these medications?

Dr. Mukaetova-Ladinska: The most frequent side effects of cholinesterase inhibitors are nausea and vomiting, diarrhea, muscle cramps, headaches, dizziness, appetite loss, vivid dreams, nightmares, and skin reddening. With memantine, they are dizziness, drowsiness, constipation, and headaches. Some patients may develop delirium. We can minimize these side effects by initiating at low doses and slowly titrating to the therapeutic dose. Some side effects, like nausea, can be managed by changing the timing or by switching to a transdermal formulation. There are a few serious side effects with anti-dementia medications, including bradycardia, syncope, hypotension, and significant weight loss.

CGPR: There's controversy in the field over when it's appropriate to discontinue dementia medications. What are your thoughts?

Dr. Mukaetova-Ladinska: I would approach the discussion of discontinuation if a patient experiences serious side effects or is in the end stages of dementia. However, we should not stop anti-dementia drugs in patients with moderate dementia simply because the disease appears to be gradually worsening. Discontinuation feels risky, especially in people who are still functioning fairly well and who have been relatively stable. Stopping the medication may worsen a patient's psychological well-being and physiological state, and it contributes to caregiver stress. There are a range of problems associated with medication discontinuation, including behavioral problems and a higher rate of requiring 24-hour care.

CGPR: How do you decide which nonpharmacological treatments to start first in the treatment of BPSD?

Dr. Mukaetova-Ladinska: To treat BPSD nonpharmacologically, you have to know the patient with dementia well. Their personality and life experiences will influence their response to treatment.

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CGPR: Which interventions have evidence behind them?

Dr. Mukaetova-Ladinska: The use of lifelike dolls or soft toy animals has been shown to benefit patients with dementia, particularly those with behavioral problems living in residential care. They may care for the "baby" or watch sports with their "grandson" sitting on their lap. Dolls or soft toys promote feelings of relaxation, pleasure, belonging, and responsibility. Sensory stimulation interventions can positively affect behavior, and patients with dementia benefit most when they are provided stimulation on a one-to-one basis. These interventions include music, light therapy, acupressure/reflexology, massage, Snoezelen therapy (a toolbox of equipment to meet different sensory needs), aromatherapy, and gustatory and tactile stimulation. They should be incorporated into daily programs and should not be used on an ad hoc basis, as the cessation of sensory stimulation sessions can have negative withdrawal effects.

CGPR: What about music and art therapy?

Dr. Mukaetova-Ladinska: "Singing for the brain," an intervention based on group singing activities, was developed by The Alzheimer's Society for patients with dementia and their caregivers. Virtual singing services are available for a fee via the internet or over the telephone (for an example, see Ring and Sing: www.store.listenlearnmusic.com/product/ring-and-sing/). This type of musical activity has been found to improve relationships, memory, and mood, as well as acceptance of and coping with a dementia diagnosis. There is also evidence behind art therapy. In a recent systematic review by our group, we identified four outcome domains when using creative art therapies: well-being, quality of life, BPSD, and cognitive function. These interventions incorporate elements of being "in the moment," and they increase opportunities for communication between patients and their caregivers (Emblad SYM and Mukaetova-Ladinska EB, *J Alzheimers Dis Rep* 2021;5(1):353–364).

CGPR: Are there any additional interventions that can supplement these therapies?

Dr. Mukaetova-Ladinska: Mobile applications can assist patients with brain training and improve their working memory (Klimova B and Valis M, *Front Aging Neurosci* 2018;9:436). In instances when technological devices are not applicable, engaging in creative therapies such as knitting, painting, pottery, or basket weaving can structure the day and combat boredom and apathy. I've also learned about how to incorporate oxygen therapy, yoga, meditation, Ayurveda, physical activities, and diet into treatment.

CGPR: When should we choose antipsychotics to treat agitation in patients with dementia?

Dr. Mukaetova-Ladinska: Before starting nonpharmacological or pharmacological treatment, we need to explore the possible reasons for a patient's distress. A patient should only try an antipsychotic if they are at risk of harming themselves or others, or if they are experiencing agitation, hallucinations, or delusions causing severe distress. Antipsychotics should be used at the lowest effective dose and for the shortest period of time. The patient should be assessed at least every six weeks, and the antipsychotic should be discontinued if it is unhelpful or no longer needed. I speak with patients about adverse effects including sedation, Parkinsonism, an increased risk of infections and falls, and an increased risk of cardiovascular adverse events and death.

CGPR: What is the evidence for using antidepressants such as SSRIs, mirtazapine, and trazodone to treat agitation in dementia?

Dr. Mukaetova-Ladinska: Among these medication classes, SSRIs have the best evidence. In a 2011 Cochrane review, sertraline and citalopram were associated with a reduction in symptoms of agitation when compared to placebo in two studies (Seitz DP et al, *Cochrane Database Syst Rev* 2011;(2):CD008191). Mirtazapine is a commonly used alternative, especially in lower doses. However, in the recent SYMBAD study, mirtazapine failed to show benefit as a treatment for agitation in dementia (Banerjee S et al, *Lancet* 2021;398(10310):1487–1497). Trazodone is sedating and has a low rate of adverse effects. It may improve agitation, aggressiveness, and compliance with care acceptance, but it has not been associated with a statistically significant benefit for BPSD. It is also cardiotoxic and should be used with caution in older adults with heart arrhythmias or cardiovascular disease.

CGPR: What about anticonvulsants for agitation?

Dr. Mukaetova-Ladinska: Although anticonvulsants, especially valproate, are still commonly used to treat agitation, the evidence suggests that they are not effective in treating BPSD. A randomized controlled trial and meta-analysis of valproate did not support its use in treating agitation in dementia (Gallagher D and Herrmann N, *Drugs* 2014;74(15):1747–1755). Furthermore, valproate can aggravate BPSD and can cause confusion and memory impairment.

CGPR: Is melatonin helpful in patients with BPSD?

Dr. Mukaetova-Ladinska: Altered circadian rhythm can aggravate BPSD in patients with dementia. Melatonin on its own or in combination with light therapy at bedtime may be useful in treating altered night sleep, "sundowning," or daytime sleepiness. In several randomized controlled studies, melatonin has also been shown to be effective for the treatment of dementia-related behavior disturbances, but not for the treatment of cognitive impairment.

CGPR: What are your thoughts about scheduled pain protocols in the management of agitation?

Dr. Mukaetova-Ladinska: Pain is one of the major contributors to agitation (Achterberg WP et al, *Clin Interv Aging* 2013;8:1471–1482). One study showed that agitation, as well as the overall severity of neuropsychiatric symptoms in patients with moderate to severe dementia, improved with paracetamol (acetaminophen)

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(Husebo BS et al, *BMJ* 2011;343:d4065). I don't think that paracetamol is a "cure" for agitation per se; it could be that regulating the pain in study participants contributed to improvement in cognitive performance and BPSD.

CGPR: Apathy is often mistaken for depression. How do you distinguish between the two?

Dr. Mukaetova-Ladinska: Apathy is present in nearly half of patients with dementia and becomes more prominent in the later stages. Whereas depression is characterized by the presence of low mood, guilt, early morning awakenings, and so on, people with apathy lack motivation and interest. They may rely on others to suggest and organize activities, or seem detached from events.

CGPR: How do you approach the management of apathy? Do you trial antidepressants?

Dr. Mukaetova-Ladinska: I prefer nonpharmacological approaches such as arts, reminiscence (revisiting moments of a patient's past), and cognitive stimulation. People with apathy may benefit from establishing a daily routine consisting of enjoyable and meaningful tasks and activities. Antidepressants do not provide benefits in treating apathy, and in some instances they may worsen it. Emotional blunting is one of the major adverse effects of antidepressants.

CGPR: What about using memantine or stimulants for apathy?

Dr. Mukaetova-Ladinska: Dopaminergic dysfunction in certain brain areas is an important correlate of apathy in Alzheimer's disease. Memantine may help with motivation in moderate or severe dementia by stimulating the dopamine receptor, causing a dose-dependent increase in dopamine. However, in mild Alzheimer's disease, memantine is probably no better than placebo (McShane R et al, *Cochrane Database Syst Rev* 2019;3(3):CD003154). The NICE guideline does not recommend using stimulants to treat apathy. However, a recent trial suggested that methylphenidate may decrease apathy, although it did not improve quality of life (Mintzer J et al, *JAMA* 2021;78(11):1324–1332).

CGPR: Antidepressants haven't performed very well in clinical trials for depression in patients with dementia. What are your thoughts about this?

Dr. Mukaetova-Ladinska: The 2018 NICE guideline recommends psychological treatments for patients with dementia and mild to moderate depression and/or anxiety. We should not routinely offer antidepressants unless they are indicated for a preexisting severe mental health problem. Antidepressants can be considered in severe depression, or in depression not managed through nonpharmacological means alone. Many antidepressants also have "added benefits," such as stimulating appetite. Mirtazapine, in particular, seems to be a useful approach to counteract weight loss in Alzheimer's disease. In advanced dementia, greater neurotransmitter loss may be reflected in serotonergic dysfunction in the gastrointestinal tract, and SSRIs can be helpful in managing symptoms such as constipation. This is important, as constipation is a risk factor for delirium and can worsen cognition in patients with dementia.

CGPR: Thank you for your time, Dr. Mukaetova-Ladinska.

How to Distinguish the Dementias
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patients of advanced age. The National Institute on Aging has a website that includes cognitive screening tests and tools for diagnosis (www.nia.nih.gov/health/alzheimers-dementia-resources-for-professionals). Keep in mind that screening tools tend to overestimate cognitive impairment in the elderly, individuals with less than eight years of school, and ethnic minorities. They may also fail to detect cognitive impairment in highly educated individuals. They do not distinguish between dementia types or cognitive issues due to depression.

The Mini-Mental State Examination (MMSE; www.tinyurl.com/y59tcxhk) is considered the gold standard of dementia screening. However, it is slowly starting to fall out of favor, as shorter tests have similar sensitivity and specificity. I prefer the Mini-Cog (www.mini-cog.com), which takes less than five minutes and entails a three-word recall and clock-drawing exercise. The Mini-Cog is more sensitive and is less affected by education level than the MMSE, but it has similar specificity (Milian M et al, *Int Psychogeriatr* 2012:24(5):766–774). I also use the Saint Louis University Mental Status exam (SLUMS; www.slu.edu/medicine/internal-medicine/geriatric-medicine/aging-successfully/pdfs/slums_form.pdf), which is in the public domain.

When I feel the need to test more cognitive areas, such as attention, language, and executive function, the Montreal Cognitive Assessment (MoCA; www.mocatest.org) screening test covers all major domains. Finally, if I suspect FTD, the Frontal Assessment Battery (FAB; www.tinyurl.com/yw99h8pw) is very useful to differentiate FTD from AD. To stage dementia, I use the Clinical Dementia Rating scale (CDR; www.tinyurl.com/smw2fr6y).

CARLAT VERDICT

Taking the time and effort to differentiate among the types of dementia helps the clinician look for symptoms that may otherwise go unreported. As a result, the clinician will be better suited to advise patients and families on optimal management and to avoid side effects from unnecessary medications.

CME Post-Test

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1. In older adults, when is intervention for suicidal thoughts necessary (LO #1)?
   - [ ] a. When the patient has seriously considered suicide and has the tools to carry it out
   - [ ] b. When thoughts of death occur
   - [ ] c. If the patient had suicidal thoughts or attempts when they were younger
   - [ ] d. When the tools to act on suicidal thoughts are available

2. Which of the following is the most common type of dementia (LO #2)?
   - [ ] a. Frontotemporal dementia
   - [ ] b. Vascular dementia
   - [ ] c. Alzheimer's disease
   - [ ] d. Dementia with Lewy bodies

3. Compared to placebo, what was concluded from the two large trials of aducanumab for Alzheimer's disease (LO #3)?
   - [ ] a. High-dose aducanumab significantly slowed the progression of dementia in both trials
   - [ ] b. Low-dose aducanumab significantly slowed the progression of dementia in both trials
   - [ ] c. Placebo significantly outperformed high-dose aducanumab in both trials
   - [ ] d. High-dose aducanumab had a positive effect size in one trial but a negative effect size of almost equal magnitude in the other trial

4. Which of the following is considered an instrumental activity of daily living (LO #1)?
   - [ ] a. Hygiene
   - [ ] b. Food preparation
   - [ ] c. Dressing
   - [ ] d. Eating

5. Which acetylcholinesterase inhibitor was found to significantly reduce the risk of developing severe dementia in patients with mild to moderate Alzheimer's disease (LO #2)?
   - [ ] a. Galantamine
   - [ ] b. Donepezil
   - [ ] c. Rivastigmine
   - [ ] d. No acetylcholinesterase inhibitor was found to reduce the risk of developing severe dementia

6. According to Dr. Budson, studies show that healthy lifestyle changes adopted in middle age delayed the development of dementia compared to those who did not perform healthy activities (LO #3).
   - [ ] a. True
   - [ ] b. False

7. What is the most common type of delusion experienced by elders (LO #1)?
   - [ ] a. Persecutory delusions
   - [ ] b. Erotomanic delusions
   - [ ] c. Grandiose delusions
   - [ ] d. Somatic delusions

8. According to Dr. Mukaetova-Ladinska, which medication or medication class significantly improves agitation in elderly patients with dementia (LO #2)?
   - [ ] a. Valproate
   - [ ] b. SSRIs
   - [ ] c. Trazodone
   - [ ] d. Mirtazapine

THE CARLAT REPORT
GERIATRIC PSYCHIATRY
P.O. Box 626
Newburyport, MA 01950

This Issue:
Dementia
January/February/
March 2022

Next Issue:
Anxiety in Older Adults
April/May/June 2022

News of Note

Adlarity: A Second Cholinesterase Inhibitor Patch Is Approved

On March 14, 2022, Adlarity (donepezil hydrochloride) received FDA approval for the treatment of patients with mild, moderate, or severe Alzheimer's dementia. Adlarity is as effective as other cholinesterase inhibitors. It delivers donepezil through a once-weekly transdermal patch (versus the daily rivastigmine [Exelon] patch). Advantages include its ability to treat swallowing-compromised patients, fewer GI side effects, and convenience for caregivers. The Adlarity patch is applied to a patient's back, upper buttock, or outer thigh once a week and is available in doses that deliver 5 mg/day or 10 mg/day of donepezil over seven days.

Adlarity is expected to be available in fall 2022. While its cost has not yet been announced, we expect it to be much higher than its generic competitors, including the rivastigmine daily patch. Another disadvantage is that doses >10 mg/day have not been evaluated. For now, patients are recommended to wear only one patch at a time.

—Stephanie Collier, MD, MPH, and Talia Puzantian, PharmD. Dr. Collier and Dr. Puzantian have disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

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