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Current and Emerging Solutions to Challenges in the Management of Alzheimer's Disease

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This ACADEMIC HIGHLIGHTS section of *The Journal of Clinical Psychiatry* presents the highlights of the series "A Multidisciplinary Approach for Addressing Challenges in Alzheimer's Disease," which consisted of teleconferences and meetings held between September 2018 and April 2019. In conjunction with the activity Chair and faculty, this report was prepared and independently developed by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by educational grants from ACADIA Pharmaceuticals Inc.; Allergan; Avanir Pharmaceuticals, Inc.; and Biogen MA, Inc.

The program was chaired by **Alireza Atri, MD, PhD**, from Banner Sun Health Research Institute, Sun City, Arizona; and Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts. The faculty were **Danielle Goldfarb, MD**, from Banner Alzheimer's Institute, Banner Sun Health Research Institute, and University of Arizona College of Medicine, Phoenix, Arizona; **Simon Sheard, DO**, from Banner Health Center, Maricopa, Arizona; and **Lynn Shaughnessy, PsyD**, from Beth Israel-Deaconess Hospital and Harvard Medical School, Boston, Massachusetts.

CME Objective

After studying this article, you should be able to:

- Provide pharmacologic and nonpharmacologic treatment options to diminish cognitive, behavioral, and psychological symptoms of Alzheimer's disease in conjunction with other health care providers

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Alzheimer's disease (AD) is a clinically heterogeneous, progressive, and ultimately fatal condition in which neurodegenerative processes cause a vicious cycle of inflammatory, microvascular, and neurochemical dysfunction and damage that leads to progressive cognitive, behavioral, and functional changes. These changes manifest insidiously over years through a wide range of symptoms that can include forgetfulness; word-finding or speaking difficulties; poor decision-making, judgment, planning, organization, and task completion; trouble with calculations or navigation; sleep problems; apathy, withdrawal, irritability, anxiety, and low mood; and changes in personality, and comportment.

Clinicians must first appropriately detect impairments, evaluate the nature and cause(s) and contributing factors, and disclose the diagnosis in a timely and compassionate fashion that involves both the person with the illness and a care partner (often a spouse or family member). Then, they will use a combination of nonpharmacologic, behavioral, and pharmacologic treatments to ease the burden of this disorder on patients and care partners. In this Academic Highlights, Drs Atri, Goldfarb, Sheard, and Shaughnessy discuss best practices for addressing the symptoms and impairments experienced by patients with AD, as well as the importance of working with and assessing the needs of the care partner.

BUILDING A THERAPEUTIC ALLIANCE AND DEVELOPING A CARE PLAN

According to Dr Atri, after an appropriate diagnosis and disclosure process, effective management of AD should include 3 essential patient-centered and personalized elements: (1) nonpharmacologic and behavioral psychoeducation and interventions; (2) pharmacologic management; and (3) establishment and maintenance of a triadic therapeutic alliance with the patient-care partner dyad for care planning, implementation, and monitoring.¹ The extent to which a clinician

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Financial Disclosure

Dr Atri has no equity, shares, or salary from any pharmaceutical or biotechnology company and is not a member of any pharmaceutical company's speakers' bureau. In the last 12 months, Dr Atri has received, or may receive, honoraria for consulting, educational lectures/programs/materials, or medical/scientific advisory/data safety monitoring boards from AbbVie, Alzheimer's Association, Biogen, Eisai, Grifols, Harvard Medical School Graduate Continuing Education, Novo Nordisk, Roche/Genentech, Suven, and Synexus. Dr Atri's institution (Banner Health) has received, related to Dr Atri's activities, observational study/clinical trial study-, infrastructure development- and/or outreach and awareness-related funding from Arizona Alzheimer's Research Consortium, National Institutes of Health/NIA, Novartis, Alzheimer's Clinical Trial Consortium (ACTC), Alzheimer's Therapeutic Research Institute (ATRI), University of Indiana School of Medicine, and Global Alzheimer's Platform (GAP). Dr Atri has received book royalties from Oxford University Press. **Drs Sheard, Goldfarb, and Shaughnessy** have no personal affiliations or financial relationships with any commercial interest to disclose relative to the activity.

Review Process

The faculty member(s) agreed to provide a balanced and evidence-based presentation and discussed the topic(s) and CME objective(s) during the planning sessions. The faculty's submitted content was validated by CME Institute staff, and the activity was evaluated for accuracy, use of evidence, and fair balance by the Chair and a peer reviewer who is without conflict of interest.

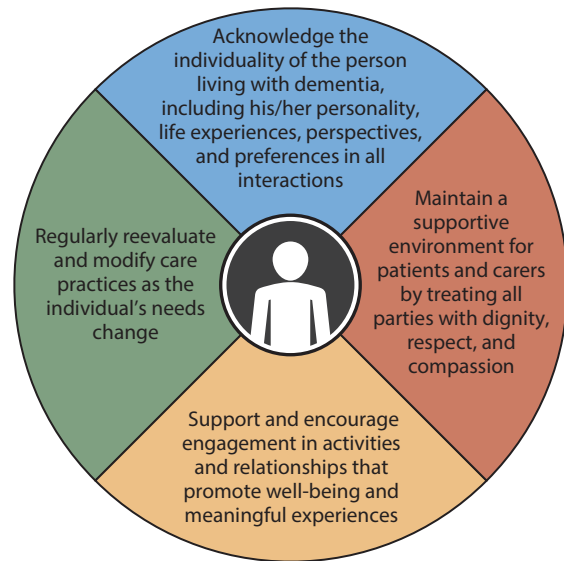
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is successful in achieving the third element will largely determine the success of the other two elements.

Current guidelines^{2,3} for the management of patients with AD and related dementias (ADRD) emphasize that care must be person-centered. Person-centered care is based on several principles that revolve around the idea that people living with dementia are individuals with unique experiences and personalities, and their perspectives, goals, and lives have value (Figure 1).

As part of practicing person-centered care, Dr Atri communicates to all of his patients and their care partners that he is their "advisor"; they are "the boss"; and that he will always be their advocate and honestly share his assessment and recommendations with them truthfully and compassionately. Dr Sheard added that clinicians must be clear about uncertainties regarding a patient's prognosis

Figure 1. Principles of Person-Centered Care^a



^aBased on Fazio et al² and National Institute for Health and Care Excellence.³

because dementia manifests, progresses, and responds to treatment differently in every person. There should also be a focus on making the best of the present, rather than becoming trapped by fear regarding what the future may hold. Dr Goldfarb stated that clinicians must be mindful of the new reality confronting the patient and care partner because their identities and sense of self are changing, as is their relationship with each other.⁴ Dr Shaughnessy emphasized that it is important to consider cultural, social, educational, and resilience factors; environmental supports; and vulnerabilities when characterizing the person with dementia's profile with regard to cognitive and functional strengths and weaknesses. She stated the critical importance of these considerations both during the assessment and when providing personalized recommendations that leverage strengths and shore up support systems to pragmatically implement interventions and care plans that benefit both patients and care partners.

An individual living with AD described his concerns:



Patient Perspectives

"I'm scared of the unknown. I don't know if I have 6 months to communicate or 6 years. I worry about going to bed at night and whether I'm going to be as bad tomorrow. This disease is with you 24/7. It's in my brain and I can't get away from it—it is a scary thing."⁵

Clinicians should begin and interweave conversations about long-term life and care planning during the diagnostic disclosure process.⁶ Drs Atri, Goldfarb, Sheard, and Shaughnessy underscored the importance of addressing key topics, such as the patient's preferences for care, advance directives, potential safety issues, and

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financial planning, as soon as possible to maximize the potential that the patient is able to participate in decision-making and to minimize the potential for harm to the patient, care partner(s), and others. As Dr Goldfarb explained, the goals of life and care planning are to keep the patient safe and autonomous as long as possible, to help and care for her/his care partner(s), and to minimize the risk of crisis and potentially avoidable poor life and health outcomes (eg, falls, accidents, financial ruin).

Dr Shaughnessy identified critical topics to address, including medication management, driving, and finances, because these are areas in which difficulties are likely to arise as the patient's disease progresses. Therefore, it is important to initiate and have continuing conversations, often over several visits and with the aid of assessment, psychoeducation, and counseling by colleagues and community resources (eg, neuropsychology, social work, occupational therapy, Alzheimer's Association care consultation) to agree on and implement concrete plans for ongoing assessment, monitoring, and appropriate support at home and in the community.

Dr Atri stated that having plans in place as early as possible, which are periodically evaluated, can identify when the patient is no longer able to safely complete these tasks and other activities of daily living independently, increase patient autonomy in decision-making, identify when the patient no longer has decision-making capacity (triggering predetermined proxy decision-making), minimize catastrophic outcomes, and avoid crisis situations. It can also facilitate triggering action regarding the need for additional support at home or transition in living and care environment, such as moving into continuing residential care, assisted living, or a memory care/dementia unit.

PSYCHOEDUCATION AND NONPHARMACOLOGIC INTERVENTIONS

Psychoeducation and nonpharmacologic or behavioral interventions are the first foundational element of care employed in the management of AD; they involve both the patient and care partner and should continue throughout the disease course.² Patients and care partners should receive education about AD in general, possible symptoms, prognosis, treatment options, safety issues, and support and care resources.⁷ This information should be conveyed in a way that is understandable to patients and care partners and relevant to the patient's unique circumstances.³

Dr Goldfarb pointed out that the results of neuropsychological testing done for diagnostic purposes can also reveal important areas of deficit that can be addressed with adaptive or compensatory strategies.⁸ Dr Shaughnessy explained that, even in individuals with very mild changes or cognitive impairment, lower performance in particular cognitive domains is highly predictive of progressive decline and later

Table 1. Cognitive Domains Associated With Development of Functional Disability^a

Domain of Impairment	Examples of Effects on Daily Life/Functioning
Executive functioning	Impaired judgment and impulsivity can lead to financial victimization or motor vehicle accidents. Impaired problem solving can jeopardize effective decision-making, particularly in emergency situations. Difficulties with planning and organization can interfere with activities ranging from meal planning to medication management.
Visuospatial abilities	Patients may have difficulty navigating, may get lost, or have more accidents (eg, trips and falls, motor vehicle).
Memory	Patients may forget medications, medical appointments, paying bills, important conversations, and responsibilities.

^aBased on Lau et al⁹

functional disability.⁹ Changes in these domains are important for planning considerations and as targets for psychoeducation, compensatory strategies, and nonpharmacologic interventions. Older adults with normal cognition or with mild cognitive impairment at baseline who reported more severe baseline cognitively based functional limitations on cognitive assessments were 4 times more likely to later develop functional disability in instrumental activities of daily living.⁹ The cognitively based functional domains associated with the greatest risk of later functional disability were everyday planning (associated with the cognitive domain of executive function), everyday memory, and everyday visuospatial abilities (Table 1).

Lifestyle Interventions

Clinicians should take a holistic approach when treating patients with AD.² Lifestyle interventions can be used to promote the individual's physical, emotional, and cognitive functioning. Health-related issues such as hypertension, obesity, diabetes, depression, hearing loss, smoking, and physical inactivity are all risk factors for dementia,¹⁰ and interventions that promote a brain-healthy lifestyle may help support the patient and mitigate clinical decline.^{10,11} Following a brain-healthy diet and engaging in frequent physical and cognitive activity have been found to be associated with a reduced incidence of AD.¹² Dr Sheard recommended that patients with AD follow the same type of diet as patients with cardiovascular conditions and engage in regular physical and social activities. Physical activity does not have to be strenuous—especially if the patient has been fairly inactive—but it does have to be routine. Activities need to be targeted to the patient's needs, preferences, abilities, and level of functioning.

An individual with AD shared how exercise has helped in maintaining a positive attitude toward his diagnosis:



Patient Perspectives

"When I was diagnosed, I took a positive approach and said, 'Okay, this is who I am; it's part of my life.' I decided to maximize what I've got rather than be depressed about it. I also chose to be physically active because early in life I learned that physical activity raises my spirits. I got back on my bike, and I even ride in the winter—it's exhilarating! I can honestly say that giving up my driver's license enriched my life."¹³

Drs Atri and Goldfarb discussed the importance of sleep for patients with AD. Sleep problems, including short sleep duration, sleep fragmentation, altered circadian rhythms, and sleep disordered breathing and sleep apnea, occur in up to 45% of patients with AD.¹⁴ The pathogenesis of AD involves accumulation and aggregation of toxic β -amyloid₄₂ protein ($A\beta_{42}$) species, and the sleep-wake cycle is involved in regulating $A\beta_{42}$ clearance.¹⁵ Therefore, disruptions to the sleep-wake cycle may lead to increasing AD-related toxicity and pathology.

Dr Atri pointed out that, in persons with AD, poor sleep and reversal of wake-sleep cycle often contribute to irritability, anxiety, low mood, agitation, or even aggression and are a large source of stress and burden for caregivers. He stated that clinicians must be proactive to assess for sleep problems and other potential triggers and contributors to behavioral issues, such as anxiety, fear, loneliness, depression, dehydration, hunger, constipation, chronic pain (eg, arthritis), metabolic or electrolyte derangements, and infections/medical illness (eg, urinary tract infection). Promoting a consistent and supporting routine; "just right" activities, exercise, and social engagement; hydration; a healthy diet; and good sleep hygiene is important for overall health and could have a therapeutic impact in reducing stress and anxiety, mitigating AD symptoms, and preventing crisis.¹

Behavioral/Environmental Interventions

Integrating nonpharmacologic strategies for managing behavioral symptoms of patients with AD is key (Table 2).¹⁶ Dr Sheard emphasized the importance of tailoring these types of interventions to each patient.⁶ For instance, if a patient has gait imbalance and is at risk for falls, environmental modifications such as removing rugs and adding a bar in the shower, and also making a referral for evaluation of balance and gait, are helpful. He suggested that referral to physical therapy and occupational therapy home safety evaluations or a visit from a home health nurse can assist care partners in finding and addressing these issues.

Dr Atri recommended that care partners try to remain calm, positive, and reassuring in interactions and try to simplify the environment and make it calm, predictable, and comforting. To avoid or diffuse agitation or aggression in individuals with AD, he recommended that care partners use a soothing tone of voice or gentle touch; avoid confrontation, correction, or convincing; and not say "no" and allow the moment to pass unless there is a

Table 2. General Nonpharmacologic Strategies for Managing Behavioral Symptoms of Dementia^a

Symptom Domain	Key Strategies
Activities	<ul style="list-style-type: none"> Introduce activities that tap into preserved capabilities and previous interests Suggest activities that are "just right," engaging, and pleasurable Help patients initiate participation
Care partner education and support	<ul style="list-style-type: none"> Understand that behaviors are not intentional Relax the rules (unless immediate safety is involved) Consider that the patient may need task guidance and cueing Take care of self Seek and draw upon a support network
Communication	<ul style="list-style-type: none"> Allow patient sufficient time to respond to a question Provide simple verbal commands Use a calm tone and avoid negative words Identify self and others if patient doesn't remember names Help patient communicate as needed
Simplify environment	<ul style="list-style-type: none"> Remove clutter Use labeling or other visual cues Eliminate noise and distractions when communicating or when patient is engaging in an activity Use simple reminders (eg, arrows pointing to bathroom)
Simplify tasks	<ul style="list-style-type: none"> Break tasks into simple steps Use verbal or tactile prompt for each step Provide structured, predictable daily routines

^aBased on Gitlin et al¹⁶

dire need to address an immediate issue of safety. Because individuals with AD often have difficulty with processing speed, working memory, and multistep commands, care partners should talk slowly and deliberately and should simplify and condense instructions.

Dr Atri emphasized that as dementia progresses, care partners will need to learn "a new way and language" to communicate. This involves being mindful and selective about what, how, and when to provide information, to sometimes compassionately withhold information that may upset the person with dementia, and to use distraction or redirection to avoid topics that the patient may find disturbing. For example, when a person with dementia forgets that her/his spouse, sibling, or other loved one has died and repeatedly asks about them, it may be better not to continue to remind them that the loved one died; the person with dementia would continue to forget, yet each time may experience intense grief, and the feelings of sadness and anxiety often remain with them for hours or days, long after they forget the information. He emphasized that care partners need ongoing psychoeducation and emotional and psychological support to be able to implement and maintain these strategies, since they are under chronic stress and what they do is challenging mentally, emotionally, and physically.

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A care partner shared her thoughts on withholding distressing information from her mother:



Care Partner Perspectives

"There are times when honesty is painful for everyone when a loved one has dementia. When my mom wondered when Dad was coming home from the hospital, I initially walked her through his death and how we were all surrounding him. I still puddle at the memory of these conversations and it's been more than 5 years since I had them with Mom. She relived the pain as did I. Why didn't I just say that he would be home in a few days? I had a fixed belief that honesty was the best policy . . . but there were many times when it didn't serve my mom."¹⁷

Care Partner–Directed Interventions

Dr Sheard stated that he considers the care partners of his patients with AD to be his second patients, and he screens them for issues such as fatigue, stressors, anxiety, depression, and need for respite. Dr Goldfarb added that, ideally, care partners should use the time they get from respite care to do something they find enjoyable, rather than always running errands. Dr Goldfarb also stated that care partners feel validated and comforted when health care providers simply acknowledge their importance and show concern for their needs.

Current AD practice guidelines^{2,3,18} provide recommendations for assessing and supporting the needs of care partners throughout the stages of AD. Interventions for care partners can include psychoeducation and skills training designed to instruct them in the best methods for dealing with dementia-related difficulties and practical aspects for providing care.^{3,18} Care partners may find this challenging if they have been in a long-term relationship with the patient because, as Drs Atri and Goldfarb explained, they have established ways of interacting with each other.⁶ When the patient says something that is incorrect or does something disagreeable, the care partner's impulse may be to correct or argue with the patient. Dr Goldfarb pointed out that care partners may need to be reminded that they are not going to win an argument with a person with AD. Dr Sheard agreed and stated that when conflicts arise, rather than arguing with or contradicting the person with AD, care partners should try to diffuse the situation by distracting or redirecting the individual. Dr Atri provided some strategies that care partners can use in situations in which their loved one with AD may become agitated or aggressive, such as redirecting them to engage in an activity that is calming and enjoyable, which could be anything from folding towels to retelling a favorite story. Dr Atri reiterated that he often tells his care partners that, unless safety is at risk, they should avoid reactively saying "No" to the patient. Instead, they should calmly redirect, remove the trigger for potential confrontation or agitation, and use forgetfulness as an ally "to allow the moment to pass." Dr Atri recommended the DICE (Describe, Investigate, Create, Evaluate) approach to assessing and managing the behavioral and psychological symptoms of AD and dementia.¹⁹



Case Practice Question

Discussion of the best response can be found at the end of the activity.

Case 1. Carlos is a 78-year-old man with moderate to severe AD dementia. His wife was his primary care partner until her death a year ago. Carlos moved in with his daughter, Maria, and her husband, who have 3 children—one married, one away at college, and one in high school. Maria put Carlos in her oldest child's room, which is still full of her belongings. At first, Carlos enjoyed walking the dog daily with his grandson, playing his violin, and working jigsaw puzzles with Maria. However, when the school year ended, Maria's 2 sons were both at home, often watching television or playing video games, and Carlos' condition deteriorated. He has stopped activities he previously enjoyed, is no longer going on his daily walk, now frequently asks for his wife, and often becomes agitated when he can't find his keys because he thinks he needs to leave for work, although he is retired and has stopped driving. He is increasingly hostile in his interactions with Maria and his grandsons. Which of the following strategies is the *least* likely to aid Carlos, Maria, and her family?

- To avoid conflict, encourage Maria to restrict Carlos more to his room so as not to get overstimulated by his grandsons; provide a rocking chair to replace walks outside; and provide his own listening music to drown out the noise from the television and video games.
- Instruct the family to remain calm in their interactions, help Carlos by not reminding him that his wife died or that he retired, and redirect his attention when he is agitated.
- Advise Maria to declutter Carlos' room to provide a calming environment, and suggest her sons wear headphones for video games and use subtitles on the television so that the volume can be lowered.
- Suggest that Maria or her son resume daily walks with Carlos, and also consider sending him to a day-care facility for people with AD to help him participate in suitable activities and to provide a break for Maria and her family.

PHARMACOLOGIC TREATMENT

The goals of pharmacologic treatment of AD are to manage symptoms and slow decline.¹³ However, Drs Sheard and Atri emphasized that before clinicians consider adding pharmacotherapy, they should review the patient's current treatment regimen to determine if any medications can be eliminated. Dr Atri said that patients diagnosed with dementia often exhibit "medication drift," which is a phenomenon in which, over time, patients are prescribed more and more medications to treat various symptoms or side effects. Many of the medications act in opposition, are relatively contraindicated, and create additional symptoms that lead to additional medication prescriptions. Dr Goldfarb added that polypharmacy is frequently an issue with psychiatric medications and pointed out that any changes in a patient's medication regimen should involve the primary care doctor and any specialists.

According to Dr Atri, the American Geriatrics Society's Beers Criteria for Potentially Inappropriate Medication

Table 3. Medications to Avoid in Alzheimer's Disease Treatment Plans^a

Anticholinergics
Benzodiazepines
Nonbenzodiazepine hypnotics
Antipsychotics

^aBased on American Geriatrics Society.²⁰

Use in Older Adults²⁰ is a useful resource for determining which medications should be removed or avoided in patients with AD (Table 3).

Stepwise Approach to the Pharmacologic Treatment of Cognitive Symptoms of AD

Currently, no treatment can modify the Alzheimer's disease process, but a number of pharmacotherapies have a beneficial effect on cognitive and neuropsychiatric symptoms of dementia and help to mitigate clinical decline in cognition, daily function, and behavior.²¹ Medications approved by the US Food and Drug Administration include the cholinesterase inhibitors (ChEIs) donepezil, rivastigmine, and galantamine and the *N*-methyl-*D*-aspartate (NMDA) antagonist memantine. The selection of pharmacotherapy should be dictated by the stage, severity, and particular circumstances of the patient. After appropriate evaluation and counseling, in patients for whom adequate supervision and monitoring are available, treatment with AD medications is recommended: starting a ChEI in mild stages, adjusting dose (gradually up to intermediate range),⁷ and then implementing add-on combination therapy (memantine added to background ChEI) as dementia stages progress.^{18,22}

Dr Atri stated that he uses donepezil as first-line treatment for AD. Donepezil is a generic oral medication approved for treating all stages of AD. There is a central cholinergic deficit from the loss of cholinergic brain neurons in individuals with AD. Like the other ChEIs, donepezil derives its therapeutic effect from inhibiting acetylcholinesterase, increasing the availability of acetylcholine in the synaptic cleft, and thus facilitating cholinergic signal transduction.^{23,24}

The benefits of treatment by all 3 ChEIs, as well as memantine, in AD have been reviewed in systematic reviews and meta-analyses that include 30–142 studies and tens of thousands of participants.^{24–27} Randomized placebo-controlled trials lasting 24 to 52 weeks have demonstrated small to medium effect size treatment benefits of ChEIs at the group level for improving, stabilizing, or delaying decline in cognition, activities of daily living, and global status and for ameliorating behavioral and psychiatric symptoms and caregiver burden.^{1,7} For example, a Cochrane Database review²⁴ of 30 studies found that donepezil treatment was associated with benefits in cognitive function, activities of daily living, and clinician-rated global clinical state in patients in all stages of AD.

Similar reviews of rivastigmine²⁸ and galantamine²⁹ have also been conducted. All show modest but significant treatment benefits.^{26,27}

Dr Atri uses memantine as second-line add-on combination treatment for AD as the clinical stage progresses. Memantine, which is approved for the treatment of moderate-to-severe AD, either alone or in combination with donepezil, is a low-to-moderate-affinity antagonist of NMDA glutamate receptors.^{7,30} Early pathological changes in AD affect brain regions with high concentrations of NMDA glutamate receptors such as the hippocampus, a critical area for binding of new information, learning, and encoding of episodic memory. Memantine is a low-to-moderate affinity NMDA glutamate receptor channel blocker with rapid kinetics. It is postulated to exert its effects in the AD brain by improving neurochemical signal transduction signal-to-noise characteristics and mitigating potential calcium-induced glutamate/NMDA-receptor-mediated neurotoxicity, working in a complementary fashion with ChEIs.^{30–32}

In randomized controlled trials, systematic reviews, and meta-analyses of trials in persons in the moderate or severe stages of AD dementia, memantine monotherapy and memantine add-on combination therapy to background ChEI have been found to produce significant benefits on cognition, behavioral disturbances, activities of daily living, and global functioning and be well-tolerated.^{25–27,33}

Current international guidelines support use of ChEIs and memantine in the pharmacologic treatment of AD dementia^{18,22,34} and recommend using a combination of ChEIs and memantine in patients with moderate-to-severe AD.²²

Short-term responses to AD medications vary between individuals. Aggregate data support that during the initial 6–12 months of treatment, cognition, activities of daily living, behavioral symptoms, or global clinical impression of change may improve in a minority (10%–20%), plateau in nearly half (30%–50%), and continue to deteriorate in about a third (20%–40%) of treated patients.^{1,7} Discontinuation of ChEI treatment is, on aggregate, harmful.^{1,7} On average, patients taken off, or those inconsistently taking, AD medications progress more rapidly than those who continue treatments, particularly ChEIs. Discontinuation trials of ChEIs to see if there is worsening should be avoided, as even temporary discontinuation is associated with irreversible decline and greater risk of nursing home placement.^{35–38}

Sustained treatments provide a modest expectation of short-term stabilization or improvement and longer-term slowing of clinical decline. As the disease progresses over several months to years, patients who may initially show improvement or stability will eventually decline. Dr Atri stressed that clinicians should communicate about practical issues associated with pharmacologic treatment, including rationale, need for monitoring, and expectations.

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Dr Atri noted that AD medications can be continued in late stages of dementia to support basic psychomotor processes and behavioral responses that assist caregivers to deliver basic care by maintaining praxis, functional communication, and the elementary processes of movement and eating. The benefits of maintaining treatment may also extend to reducing emergence or increasing severity of behavioral issues and need for antipsychotic use.

He said that in the long run, current pharmacologic treatments for AD mitigate decline but do not prevent it, so as the disease progresses to very severe or end-stage dementia, clinicians must, on a case-by-case basis and in a patient-centered collaboration with family and care partners, weigh and discuss the calculus regarding discontinuation of AD medications and turning the focus to palliation, hospice, and comfort care.^{1,7,39}

systems that regulate mood and behavior. Interpersonal and environmental triggers may also cause or contribute to BPSs. These symptoms increase care partner burden and the likelihood of nursing home placement, reduce quality of life, and accelerate disease progression and functional decline.¹⁶ A care partner described his experience with his mother wandering out of the house at night:



Care Partner Perspectives

*"Right before the tipping point, she started staying awake really odd hours. She would not sleep for 48–72 hours straight, then sleep all day. When she was awake and I [was] asleep, she would knock on my bedroom door in the middle of the night to make sure I was still here. As hard as that was, it was nothing compared to the call from our local police when they found her a good distance from our home, not aware of where she was or even who she was. Luckily for me, the police were aware of the situation and knew who she was and where she lived. But it made me realize that if she had wandered into the street and a car had hit her, I would have to live with the knowledge that I would have indirectly caused the situation by not taking action. I could not imagine how a person would feel had they accidentally hit my mother, and I never wanted to feel that way. So for me, that was the moment when I realized I could no longer take care of her at home and that I needed to find a different solution, as hard as that 'different solution' was (and believe me, it was HARD)."*⁴⁰

Although nonpharmacologic interventions should be the preferred treatment for behavioral symptoms, practice guidelines acknowledge that some patients may warrant pharmacologic treatment if they are a safety risk to themselves or others or if their psychological symptoms are causing severe distress.^{2,3} Dr Atri stated that some of the medications used to treat the cognitive symptoms of AD may also have a therapeutic effect on symptoms such as mood, apathy, aggression, and irritability.⁷ Dr Goldfarb mentioned that antidepressants, namely selective serotonin reuptake inhibitors (SSRIs), can be helpful for mood symptoms. The SSRIs sertraline, citalopram, and escitalopram have been found to have efficacy for reducing agitation and irritability.⁴¹

Antipsychotics have been investigated for treating BPSs, but these agents have been found to confer limited benefits while carrying considerable morbidity risks, including increasing mortality.¹⁹ Antipsychotics should be considered a last resort and only used for patients with severe behavioral disturbances that have not responded to other treatments or for patients who pose an immediate safety risk to themselves or others.^{7,19,42} After discussing the risks with the patient's family and care partners, if the decision is made to start antipsychotic treatment, the lowest possible dose should be used, the patient must be closely monitored, and the medication should be discontinued as soon as possible. Dr Sheard stated that he has had some success using quetiapine in patients with severe hallucinations. Risperidone, which is approved for the treatment of BPSs in Europe but not in the United States, may also be considered.¹⁹

Case Practice Question

Discussion of the best responses can be found at the end of the activity.

Case 2. Glenda is a 62-year-old woman who just moved to the area to live with her daughter, and this is her first visit at your primary care clinic. Glenda has been treated for depression on and off since her early forties. About 1.5 years ago, shortly after the death of her husband, she began to experience insomnia, irritability, and forgetfulness, which she ascribed to depression. She was not taking an antidepressant at the time; therefore, her previous primary care doctor started her on 10 mg of escitalopram each morning. Her mood symptoms improved, but her sleep issues and forgetfulness worsened. She was diagnosed with early-stage AD and started on a ChEI taken in the evening. Her cognitive status stabilized, but her sleep difficulties worsened, and 4 months ago she started using over-the-counter (OTC) diphenhydramine for her insomnia. Her daughter reports that she has been much more confused in the last few months. Considering Glenda's diagnosis of AD, which of the following is the best next step?

- Discontinue escitalopram and her ChEI.
- Advise her to discontinue OTC sleep aids, move dosing of her ChEI to after breakfast, and move her escitalopram dose to bedtime.
- Advise her to switch from OTC sleep aids to a prescription sleep aid such as eszopiclone or zolpidem.
- Refer Glenda to a specialist.

PHARMACOTHERAPIES FOR BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS

Behavioral and psychiatric symptoms (BPSs) in persons with AD can be very distressing and challenging to treat.¹⁶ These symptoms include mood disturbance, anxiety, sleep disturbance, wandering, repetitive questioning, agitation, aggression, and psychosis. Nearly all individuals with AD will experience at least one BPS, with depression, apathy, and anxiety being the most common.¹⁹ These symptoms are thought to stem from neurodegeneration in brain



Case Practice Question

Discussion of the best response can be found at the end of the activity.

Case 3. Russell, a retired law enforcement officer, and Jeannette, a retired school teacher, have been married for over 50 years. Jeanette has been diagnosed with AD, which is now of moderate severity. Russell has been caring for her at home with help from their grown children and home health nurses. A safety assessment of their home determined that Russell owns several firearms, but because these are in a locked safe, the care team determined that they did not pose a risk. As Jeanette's AD progressed, she would get up and wander at night and often mistake Russell for an intruder. Recently, Jeannette confronted Russell with one of his guns because she thought he was a burglar. The gun was not loaded, and Russell was able to calm Jeanette and obtain the gun. Russell is unsure if Jeanette found the key to open the safe or if he had accidentally left it unlocked. Would an antipsychotic be an appropriate treatment for Jeanette's symptoms?

- Yes
- No



Discussion of Case Practice Questions

Case 1: Preferred response is *a*. To avoid conflict, encourage Maria to restrict Carlos more to his room so as not to get overstimulated by his grandsons; provide a rocking chair to replace walks outside; and provide his own listening music to drown out the noise from the television and video games.

Stopping physical activity, increasing isolation, and allowing noisy environments are not recommended for patients with AD. Carlos' problems seemed to arise when his routine and environment were disrupted and became too noisy, while his physical activity (daily walks) and engagement diminished. Adjusting his environment, having him resume his daily walks, and providing his family some relief in the form of day care would be advisable.

Case 2: Preferred response is *b*. Advise her to discontinue OTC sleep aids, move dosing of her ChEI to after breakfast, and move her escitalopram dose to bedtime.

First-generation antihistamine sleep aids and prescription sleep aids are included in the Beers Criteria of medications to avoid in patients with dementia or cognitive impairment—they are anticholinergic, counteracting the cholinergic benefits of ChEI and suppressing cognitive functions. ChEIs can increase alertness and cause vivid dreams and disrupt sleep if given at night. Moving the ChEI dose to the morning, to be given after food (if taken orally) to mitigate potential cholinergic side effects on an empty stomach (eg, nausea, flatulence, loose stools), can be beneficial to mitigate sleep problems. Because Glenda did experience some improvement in mood symptoms following initiation of escitalopram, this treatment should be continued, and because sedation is a common side effect of this agent, moving her dose to bedtime may ease her insomnia.

Case 3: Preferred response is *b*. No.

Because of the risks of antipsychotic treatment, they should be used only if the patient is an imminent threat to herself or others. Although Jeanette confronted her husband with a gun, she was amenable to Russell's calming techniques. The best option would be to eliminate the firearms from the household. Furthermore, Jeanette should have a comprehensive evaluation (eg, the DICE approach¹⁹) to assess triggers and any physical, medical, and other causes of her psychological symptoms.

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Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, sertraline, citalopram, escitalopram, quetiapine, and risperidone are not approved by the US Food and Drug Administration for the treatment of Alzheimer's disease, but their potential use in selective clinical situations for mood, anxiety, irritability, agitation, aggression, and psychosis symptoms in patients with Alzheimer's disease was discussed.



Clinical Points

- Practice person-centered communication and care when evaluating and managing persons with Alzheimer's disease.
- Strive to develop and maintain a strong triadic therapeutic relationship that involves both the patient and care partner(s) and to provide ongoing psychoeducation and support regarding the condition, care considerations, and resources.
- Begin discussions about safety and care planning early in the process to maximize the potential for the patient to be involved in current and future decision-making.
- Provide counseling regarding expectations of treatment, which are to mitigate long-term clinical, functional, and behavioral decline as the disease progresses.
- Advise patients and care partners how to take and monitor medications (to ensure proper adherence).
- Implement, monitor, and slowly adjust/titrate stage-dependent cholinesterase inhibitors and/or memantine monotherapy or combination therapy.
- Always provide psychoeducation and implement nonpharmacologic interventions before considering pharmacotherapy for behavioral and psychiatric symptoms (BPSs).
- Use antipsychotics sparingly and only under specific conditions in some individuals with severe refractory BPSs, which should always be done with thoughtful risk-benefit calculus and with extreme caution as a last resort for severe and refractory BPSs or when risk to safety of self or others is involved.
- Support patients, families, and care partners by advocating pragmatic care plans and activities that promote general health, safety, and well-being for the patient and the care partner(s).

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