to be effective in delaying progression from MCI to AD and, thus, are chiefly recommended for use in patients who already have a diagnosis of dementia.

Three FDA-approved AChEIs are actively prescribed in the United States: **donepezil (Aricept), galantamine (Razadyne), and rivastigmine (Exelon)** (Table 59-7). While all three of these compounds are available as generic medications, some specific long-acting formulations and solutions of these drugs are still under patent (see Table 59-7) and, thus, are not yet available in generic form. In general, the most common adverse effects associated with AChEI use are nausea, anorexia, and diarrhea. Bradycardia, atrioventricular (AV) nodal block, and syncope and unintentional weight loss are additional potentially serious adverse side effects that would trigger deprescribing. It is recommended that patients are started on a low dose of the medication with dose increases approximately every 2 months until a therapeutic dose is achieved (see Table 59-7). Gastrointestinal side effects may be alleviated by taking the medications with food. Sleep disturbances are also common and may improve with altering the dosing schedule.

TABLE 59-7 ■ FDA-APPROVED MEDICATIONS FOR THE TREATMENT OF ALZHEIMER DISEASE[A]

MEDICATION	INDICATION	AVAILABLE FORMULATIONS	DOSE RANGE AND TITRATION	ADVERSE EFFECTS
ACETYLCHOLINESTERASE INHIBITORS				
Donepezil (available as generic donepezil or Aricept)	Mild-to-moderate AD	• 5- and 10-mg tablets • 5- and 10-mg oral disintegrating tablets	• 5–10 mg once daily at bedtime • May be taken with or without food • Oral disintegrating tablets should be dissolved on tongue and followed with water • Begin at 5 mg once daily for 4–6 weeks, then increase to 10 mg daily as tolerated • Effective dose: 5–10 mg daily	• Bradycardia or heart block, syncope, nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, anorexia
Donepezil (available as generic donepezil in 10-mg tablets or Aricept in 10- or 23-mg tablets)	Moderate-to-severe AD	• 10- and 23-mg tablets • 10-mg oral disintegrating tablets	• 10 mg once daily at bedtime • If the clinician thinks there is a strong indication for increased dosing, a patient who has been on 10 mg for 3 mo may increase to the 23-mg tablet daily • 23-mg tablets should not be split, crushed, or chewed • Effective dose: 10 or 23 mg daily	• Bradycardia or heart block, nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, anorexia
Galantamine (available as generic galantamine, galantamine ER, Razadyne, or Razadyne ER)	Mild-to-moderate AD	• 4-, 8-, and 12-mg immediate-release tablets • 4 mg/mL immediate-release oral solution • 8-, 16-, and 24-mg extended-release capsules	**Immediate-Release Tablets or Oral Solution:** • 4–12 mg twice daily • Should be taken with meals • Begin at 4 mg twice daily for at least 4 wk then increase to 8 mg twice daily for at least 4 wk then 12 mg twice daily as tolerated • For patients with moderate hepatic or renal impairment (creatinine clearance 9–59 mL/min), dose should not exceed 16 mg/d • Should not be used in patients with severe hepatic or renal impairment (creatinine clearance < 9 mL/min) **Extended-Release Capsules:** • 8–24 mg once daily • Should be taken in the morning with food • Begin at 8 mg once daily in the morning for at least 4 wk then increase to 16 mg once daily in the morning for at least 4 wk then 24 mg once daily as tolerated • Conversion from tablets (or oral solution) to extended release should occur at the same daily dosage with the last dose of the tablets (or oral solution) occurring in the evening and the extended-release formulation starting the next morning • Effective dose: 16–24 mg daily	• Nausea, vomiting, diarrhea, dizziness, headache, decreased appetite, weight loss

MEDICATION	INDICATION	AVAILABLE FORMULATIONS	DOSE RANGE AND TITRATION	ADVERSE EFFECTS
ACETYLCHOLINESTERASE INHIBITORS				
Rivastigmine (available as generic rivastigmine capsules or Exelon capsules, oral solution, or transdermal patch)	Mild-to-moderate AD	• 1.5-, 3-, 4.5-, and 6-mg capsules • 2 mg/mL oral solution • 4.6 mg/24 h and 9.5 mg/24 h patches	**Capsules or Oral Solution:** • 1.5–6 mg twice daily • Should be taken with meals • Oral solution may be taken directly or mixed with beverage • Begin at 1.5 mg twice daily for minimum of 2 wk then increase to 3 mg twice daily for minimum of 2 wk then 4.5 mg twice daily for minimum of 2 wk then 6 mg twice daily as tolerated • Patients with mild or moderate hepatic impairment or moderate-to-severe renal impairment may be able to only tolerate lower doses • Effective dose: 6–12 mg daily **Patch:** • Begin at 4.6 mg/24 h patch daily for 4–6 wk then increase to 9.5 mg/24 h patch daily as tolerated • Apply patch on intact skin for 24-h period; replace with a new patch every 24 h • Effective dose: 9.5 mg/24 h	• Nausea, vomiting, anorexia, dyspepsia, weakness
Rivastigmine patch (available as Exelon transdermal patch)	Mild, moderate, and severe AD	• 4.6 mg/24 h, 9.5 mg/24 h, and 13.3 mg/24 h patches	**Patch:** • Begin at 4.6 mg/24 h patch daily for a minimum of 4 weeks then increase to 9.5 mg/24 h patch daily as tolerated; may increase to maximum of 13.3 mg/24 h after minimum of 4 wk • Apply patch on intact skin for 24-h period; replace with a new patch every 24 h • Consider dose adjustments in mild-to-moderate hepatic impairment and low (< 50 kg) body weight • If switching to an Exelon patch from rivastigmine capsules (or oral solution), a patient on a total daily dose of < 6 mg of oral rivastigmine can be switched to the 4.6 mg/24 h patch while a patient on a total daily dose of 6–12 mg can be switched to the 9.5 mg/24 h patch • If switching, apply the first patch on the day following the last oral dose • Effective dose: 9.5 mg/24 h or 13.3 mg/24 h	• Nausea, vomiting, diarrhea
N-METHYL-D-ASPARTATE (NMDA) RECEPTOR ANTAGONIST				
Memantine (available as generic memantine tablets or Namenda tablets or oral solution)	Moderate-to-severe AD	• 5- and 10-mg tablets • 2 mg/mL oral solution	**Tablets or Oral Solution:** • 10 mg twice daily • May be taken with or without food • Begin at 5 mg once daily for 1 wk then increase to 5 mg twice daily for 1 wk then 10 mg in the morning and 5 mg in the evening for 1 wk then 10 mg twice daily as tolerated • In patients with severe renal impairment (creatinine clearance 5–29 mL/min) target dose is 5 mg twice daily • Effective dose: 20 mg daily	• Dizziness, headache, confusion, constipation
N-METHYL-D-ASPARTATE (NMDA) RECEPTOR ANTAGONIST (Cont.)				
Memantine extended release (available as Namenda XR)	Moderate-to-severe AD	• 7-, 14-, 21-, or 28-mg capsules	• Patients on memantine 10 mg twice daily may be switched to Namenda XR 28 mg daily the day following the last dose of 10-mg memantine • Patients with severe renal impairment (creatinine clearance of 5–29 mL/min) may be switched from memantine 5 mg twice daily to Namenda XR 14 mg once daily • May be taken with or without food • Capsules can be taken intact or may be opened and sprinkled on applesauce • Effective dose: 28 mg daily	• Headache, diarrhea, dizziness
COMBINATION THERAPY (ACETYLCHOLINESTERASE INHIBITORS AND NMDA RECEPTOR ANTAGONIST)				
Namzaric (memantine HCl ER and donepezil HCl) capsules	Moderate-to-severe AD	• 14-mg memantine HCl ER/10-mg donepezil HCl or 28-/10-mg capsules	• Once patient stabilized on a daily dose of memantine ER (10 mg twice daily or 28 mg ER once daily) and donepezil 10 mg daily may switch to Namzaric 28-/10-mg capsule once a day in the evening • Patients with severe renal impairment on memantine HCl (5 mg twice daily or 14 mg ER once daily) and donepezil HCl 10 mg daily may be switched to Namzaric 14-/10-mg capsule once a day in the evening • May be taken with or without food • Capsules can be taken intact or may be opened and sprinkled on applesauce • Capsules should not be divided, chewed, or crushed	• Headache, diarrhea, dizziness, anorexia, vomiting, nausea, ecchymosis
MONOCLONAL ANTIBODIES DIRECTED AGAINST AMYLOID				
Aducanumab (available as Aduhelm infusion)	MCI due to AD and mild AD	• Supplied in vials of 170 mg/1.7 mL or 300 mg/3 mL • Monthly IV infusion	• The first and second infusion doses are 1 mg/kg, the third and fourth infusion doses are 3 mg/kg, the fifth and sixth infusion doses are 6 mg/kg, the seventh infusion and beyond doses are 10 mg/kg	• Amyloid-related imaging abnormalities (ARIA) with brain effusion or hemorrhage • Headache, falls, and diarrhea

*Information obtained from prescribing information documents.

Memantine (Namenda) is an FDA-approved medication for use in moderate-to-severe AD. Memantine is an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. At high concentrations, memantine can inhibit mechanisms related to learning and memory, but at lower

concentrations, it can preserve or enhance memory in animal models of AD. Memantine can protect against the excitotoxic destruction of cholinergic neurons and may inhibit β-amyloid production. In persons with moderate-to-severe AD, memantine may slow the progression of cognitive decline. In addition, studies support that use of memantine was well tolerated and led to better outcomes on measures of cognition, activities of daily living, and behavior. Additional studies are needed before memantine can be recommended for earlier stages of AD. In patients with moderate-to-severe AD, combined treatment with a cholinesterase inhibitor and memantine has not been shown to be superior to treatment with either agent alone with regards to cognitive, functional, and behavioral outcomes. In patients who do not tolerate cholinesterase inhibitors due to gastrointestinal side effects or bradycardia, memantine may be used as first-line therapy. With use of either AChEIs or memantine, clinicians should educate families on what to expect with use of the medications, namely that they work to delay the progression of symptoms and not to significantly improve cognition. Consideration should be given to the modest expected benefit and monthly cost of both types of medications.

In June 2021, the US FDA approved **aducanumab** under accelerated approval based on the reduction in brain amyloid demonstrated in its clinical trials in patients with MCI and early stage AD. Aducanumab is a human monoclonal antibody targeting aggregated amyloid and amyloid oligomers. It is designed to enter the brain through the BBB, bind to amyloid plaques and oligomers, and stimulate microglia to clear the amyloid protein. In two clinical trials leading to the FDA approval, aducanumab was shown to significantly lower amyloid burden in the brain assessed by amyloid PET scans, in some study participants to near normal levels. In one of the two trials, treatment resulted in a 22% reduced rate of cognitive decline in the primary outcome measure (the Clinical Dementia Rating—Sum of Boxes) over an 18-month period; however, no statistically significant benefit was seen in the other study. Importantly, the aducanumab studies were initially halted based on futility analyses; however, reanalysis of datasets including newly collected data revealed statistically significant reduction in the rate of cognitive decline in only the high-dose group. Importantly, administration of aducanumab was associated with adverse effects on MRI imaging. These side effects called amyloid-related imaging abnormalities-effusion (ARIA-E) and -hemorrhage (ARIA-H) were seen in 34% to 36% of participants

receiving the high dose. Approximately 80% of those with ARIA did not have symptoms; however, those with symptoms experienced headache, dizziness, visual disturbances, and nausea.

Controversy has arisen over how the study data were analyzed, the true clinical benefit to an individual as measured by the study outcomes, and the social and political pressure on the FDA approval process. Despite these concerns, the FDA approval of aducanumab has ushered in a new research-clinical paradigm that, for the first time, utilized amyloid clearance as a surrogate measure in the approval of a disease-modifying therapy. It is projected that approval of aducanumab will lead to the discovery of newer analogues of antiamyloid monoclonal antibodies with more favorable adverse effect profiles and demonstration of clinical efficacy.

Additionally, there are no clear guidelines on several issues directly relevant to aducanumab treatment, including patient selection, inclusion/exclusion criteria, payment for amyloid PET scan and MRIs necessary to monitor presence and progression of ARIA, and duration of treatment.

In addition to targeting β-amyloid pathways, novel research is focusing on the effects of inhibitors of tau phosphorylation and aggregation and the stabilization of microtubules. Other potential therapeutic agents are directed toward inflammation and oxidation, insulin signaling, mitochondrial function, and nerve growth factor signaling.

Clinical trials have not conclusively shown that treating vascular risk factors delays the development or progression of AD. However, aggressive treatment of vascular risk factors in many patients with memory complaints, including those associated with AD, may be warranted. Vascular risk factor modification has known cardiovascular benefits that may lead to reduction in cerebrovascular disease, stroke, myocardial infarction, and coronary artery bypass grafting—factors strongly linked to cognitive decline. Trials are under way to clarify if vascular risk factor reduction and improved cerebral perfusion modify the course of AD. Until the completion of such trials, clinicians should follow established cardiovascular prevention guidelines for patients presenting with memory complaints, taking into account the patient's comorbid illnesses, quality of life, treatment costs, and life expectancy.

Evidence also supports that encouraging AD patients to engage in nonpharmacologic interventions, including physical activity and exercise,

mentally stimulating activities, and social activities, may lead to cognitive benefits. Depending on an individual's physical abilities, comorbid illness, social situation, and interests, clinicians should encourage AD patients and persons with cognitive impairment to seek out opportunities for exercise and activities that promote use of their intact areas of cognitive function. For example, an AD patient with prominent language deficits but intact visuospatial skills may find crosswords or word search puzzles very frustrating, but may enjoy playing checkers or painting birdhouses. Such activities may need to be adjusted over time to account for progressive cognitive changes.

Behavioral Management

Noncognitive neuropsychiatric symptoms of dementia include aggression, agitation, depression, anxiety, delusions, hallucinations, apathy, and disinhibition. Such behaviors may be more distressing to family and caregivers than the actual memory decline. Neuropsychiatric symptoms may be managed by nonpharmacologic as well as pharmacologic interventions. Nonpharmacologic therapies should in general be explored prior to using pharmacologic therapy, unless the person's agitation threatens his or her safety or living situation. Chapter 60 includes detailed information on pharmacological and nonpharmacological management of behavioral symptoms of dementia.

Safety Management

Reviewing common safety concerns in persons with dementia may help identify significant risks and provide an opportunity for educating family members and caregivers on what areas to monitor closely and what safeguards to take to protect the person with AD. Some patients may require further evaluation to assess driving safety, which can be done through some occupational therapy departments, local driving schools, state Department of Motor Vehicles, or other similar agencies. Pill boxes, electronic reminders, or other similar medication planners may facilitate correct administration of medications and allow family or caregivers to help in setting up the medications properly. Other safety concerns, such as proper use of the stove, woodworking equipment, and access to firearms, should be discussed and appropriate supervision and/or limitations be arranged.

Caregiver Support

There is convincing evidence that the effects of AD are felt not only by the patient but also by the caregivers. Caregivers have increased depression, work absence, and health problems compared to those not caring for a family member with dementia. Clinicians and health care team members should direct caregivers toward educational resources on the disease, practical tips on helping someone with AD optimize their function, effective communication strategies, legal and financial planning, and the importance of caregiver health and social support. Use of respite services from family, friends, neighbors, home health agencies, and local adult day centers may allow for caregivers to take the appropriate time needed to maintain their own health and social connections. Local support groups allow for caregivers to share ideas and experiences. Other initiatives such as memory cafés, dementia-friendly communities, and online resources may provide caregivers important support and interaction.

PREVENTION

The Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension (SPRINT-MIND) randomized trial has shown that targeting a systolic blood pressure goal of 120 mm Hg relative to what was at the time standard, 140 mm Hg, led to a statistically significant, 19% reduction in the incidence of MCI (see Chapter 79 for details). Currently, there are no established preventive therapies for AD and no approved medications to treat MCI. Evidence supports that therapies that either delay or prevent the onset of AD may need to be started in midlife in high-risk populations in order to significantly influence the onset and course of the disease. As the underlying pathologic changes that eventually lead to clinical AD begin decades before the onset of symptoms, primary prevention trials with conversion to AD as their primary outcome will be costly and time consuming. Integrating biomarkers with strong relationships to clinically relevant outcomes into such primary prevention trials may allow for earlier identification of disease-modifying effects of potential preventive therapies. Given the multifactorial nature of AD, future preventive strategies will most likely target a variety of mechanisms related to disease progression, similar to those used in cardiovascular disease prevention. Some potential prevention therapies currently under investigation include antiamyloid

therapies, vascular risk factor modification, anti-inflammatory medications, antioxidants, and lifestyle interventions such as exercise, social engagement, and cognitive stimulation.

SPECIAL ISSUES

Comorbidity

Managing comorbid illnesses in a person with AD can be challenging. Patients may forget to take important medications for comorbid conditions which, in turn, may exacerbate confusion. Persons with AD may not be able to remember symptoms related to other comorbid illnesses, such as recent episodes of chest pain, shortness of breath, or localization of arthritis pain. Thus, it is important to educate families and caregivers on how they can best assist their loved one in managing their comorbid illnesses. For example, a caregiver of an AD patient with diabetes may need to directly observe insulin administration and meal intake to maintain good glucose control. An AD patient with significant chronic pain may need their caregiver to write down the time of day that they become more agitated with the goal of optimizing the timing of their pain medications. Each management plan will need to be tailored to the AD patient's comorbid illnesses and social situation, utilizing community resources as available.

Persons with dementia are more likely to experience delirium in response to medical illness or surgery. Thus, educating families that acute episodes of confusion may suggest a harboring infection or other illness may help families seek out appropriate medical care when watching for behavioral changes. Caregivers should be forewarned that an AD patient is at increased risk for delirium following surgical procedures and that interventions such as avoiding anticholinergic and sedative hypnotic medications, maintaining good sleep-wake cycles, optimizing pain control, using hearing aids and glasses as appropriate, and establishing daytime activities may help reduce risk of escalating postoperative delirium (see also Chapter 58).

Care Settings

Ensuring a safe living environment is a high priority for patients with any form of dementia including AD. Patients living in their own house or independent apartment may need additional safety measures implemented around their home, such as by posting emergency numbers on the wall, using

timers to remind them to turn the stove off, using medical alert systems, and optimizing use of home care services to assist with tasks such as bathing, cleaning, meal preparation, transportation, and medication administration. Once patients can no longer identify what to do in an emergency situation, then 24-hour supervision is recommended. Through partnering with family and friends and use of community resources, some individuals with AD are able to stay in their own home their entire lives. However, a variety of social circumstances, medical or behavioral issues, or economic limitations may necessitate that a person with AD move to a more structured, supervised setting. The choice of setting (eg, assisted living facility, skilled nursing facility, or locked dementia unit) varies from patient to patient and depends on the degree of cognitive impairment, cultural preferences, comorbid illnesses, economic resources, and behavioral and safety concerns.

Palliative and End-of-Life Care

Upon diagnosis of AD, many patients and families have questions as to what to expect in the years ahead. Since the course of AD progression may depend not only on genetic and environmental factors but also comorbid medical conditions, the rate of decline is difficult to predict. Once an AD patient is medically treated and after all potentially reversible contributing factors have been addressed, obtaining repeat cognitive testing may give the clinician an idea of the trajectory of the individual's decline and help inform the family on what to expect in the years ahead. Providing information to family and caregivers early in the disease course on end-of-life planning may help smooth this difficult transition later in the illness. Use of respite services, home health aides or family members, or palliative care may help the person with AD stay in the home longer. If their social network cannot support the patient as care needs increase, then nursing home placement or hospice care may be necessary. Caregivers of AD patients may go through feelings of guilt when a loved one is moved from home to a facility, so appropriate support should be provided. Capacity for decision making should be assessed regularly throughout the course of the illness with appropriate activation of advanced care planning when the patient is no longer able to make their own health care decisions.

Advanced dementia is associated with poor nutritional intake, urinary incontinence, skin breakdown, and infections such as pneumonia. Palliative and end-of-life care services are increasingly being used for patients with

end stages of AD and other forms of dementia. As the disease progresses, patients may reach a point when they are no longer able to express their needs. When patients are at a stage of disease where they no longer are able to engage meaningfully in social interactions or participate in self-care, then consideration should be given to discontinuing cholinesterase inhibitors and/or memantine therapy. At that point, medication regimens may be simplified to focus on therapies that optimize patient comfort. As swallowing difficulties develop, modified diets and one-on-one feeding may be needed to maintain a patient's nutritional status. Feeding tubes are not recommended in end-of-life for patients with advanced AD as they do not prolong survival or increase comfort and have not been shown to reduce the risk of pressure sores, infection, or aspiration.

Hospice care can help with symptom management late in the course of the illness. Caregiver involvement in Alzheimer support groups can provide comfort during the unique grieving process related to dementia, as family and caregivers watch the cognitive and personality transformations in their family member with AD.

SUMMARY

AD is the leading cause of dementia with 44 million individuals currently affected worldwide. Unless effective preventive strategies are identified, it is anticipated that the prevalence of AD will double every 20 years. Given the widespread prevalence of AD and its impact on the well-being and quality of life of patients and their caregivers, it is critical for clinicians to be well-trained in identifying early cognitive changes, differentiating AD from other common medical and psychiatric conditions, diagnosing the disorder, and developing an effective management plan with their patients and families. Knowledge and use of educational and community resources can provide additional culturally tailored support to AD patients and their caregivers. In most situations, AD can be effectively diagnosed and managed within a primary care setting, through careful history-taking, a physical examination, and brief cognitive testing. Ancillary laboratory tests and neuroimaging can help differentiate between various causes of memory loss and different types of dementia. AD treatment involves not only pharmacologic therapy—with cholinesterase inhibitors, NMDA receptor antagonists, and soon aducanumab and potentially other monoclonal antibodies directed against amyloid—but also careful assessment of safety,

behavioral concerns, and education for the patient, family, and other caregivers. While preventive therapies have not yet been established, novel therapies are under investigation to delay or preferably arrest the development and progression of AD. Clinicians are encouraged to be active champions of educational and research efforts to improve early diagnosis, treatment, and prevention of AD by promoting clinical research participation among willing patients and families. Annual updates on large-scale initiatives such as the United States National Alzheimer's Project Act (NAPA), Alzheimer's Disease International's World Alzheimer Report, the Alzheimer's Association's Facts and Figures, and other international collaborations and publications will keep clinicians informed on global efforts to optimize early diagnosis and effective care of patients at risk for AD and related dementias.

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Chapter 60

Behavioral Symptoms of Dementia and Psychoactive Drug Therapy

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EPIDEMIOLOGY

It is estimated that 5.3 million Americans live with Alzheimer disease (AD), the most common cause of dementia, and that 13.8 million people older than 65 years will be diagnosed in the United States by 2050. In the United States, annual health care costs for persons with AD are more than $172 billion, including $123 billion in costs to Medicaid and Medicare alone.

Neuropsychiatric symptoms (NPS) affect almost all persons with dementia over the course of illness. Although cognitive deficits are the hallmark of dementia, almost 98% of patients with AD experience depression, agitation, anxiety, psychosis, hallucinations, apathy, eating disorders, disinhibition, and/or sleep disturbances. Depression, apathy, and anxiety are the most common NPS in dementia. NPS are also present in the prodromal or mild cognitive impairment (MCI) stages of dementia. Depression and irritability are common even prior to the onset of MCI and dementia and appear to be the first symptoms of well over half of people who later develop dementia. Late-life onset of NPS of any severity in individuals without dementia, lasting for over 6 months, that are not attributable to another concurrent psychiatric disorder (such as major depressive disorder) are now referred to as mild behavioral impairment (MBI). While NPS are seen at all stages of dementia, including prior to cognitive decline, the severity of NPS increases with progressive cognitive decline both in community and nursing home populations.

The impacts of NPS on both patients and caregivers are significant: They are associated with worse quality of life, increased mortality, accelerated disease progression, and increased cost of care and caregiver burden/stress. Difficult behaviors and psychotic symptoms are among the highest determinants of institutionalization.

NPS are broadly categorized into four groups: (1) affective and motivational symptoms, such as depression; (2) psychotic symptoms, such as delusions or perceptual disturbances; (3) disturbances of basic drives, including feeding and sleeping; and (4) disinhibited and other socially inappropriate behaviors. Examples of symptoms in each category of NPS are in **Table 60-1**.

TABLE 60-1 ■ NEUROPSYCHIATRIC SYMPTOMS

DOMAIN	EXAMPLES OF SYMPTOMS
Depression/dysphoria	Low mood Tearfulness Changes in sleep, appetite, energy Negative thoughts about him/herself (eg, putting him/herself down, feeling like a failure, feeling like he/she deserves to be punished, feeling like the family would be better off without him/her)
Anxiety	Frequently asking for reassurance Easily becoming upset when separated from caregiver Worry about planned events Periods of feeling shaky, unable to relax, feeling excessively tense Avoidance of certain places or situations that cause nervousness
Apathy/indifference	Indifference Disinterest in activities Poor motivation Less spontaneous (eg, less likely to initiate conversation)
Irritability/lability	Easily upset or frustrated Rapid changes in mood (eg, sudden flashes of anger over small things) Impatience (eg, having difficulty coping with small delays)
Agitation/aggression	Arguing Pacing Disruptive vocalizations Physical aggression (eg, throwing things, attempting to hit others) Rejection of care (eg, bathing, changing clothes) Repetitive questions
Disinhibition	Making socially inappropriate comments Talking openly about very personal or private matters Overfamiliarity with strangers Impulsive behaviors Overeating Overspending
Nighttime behaviors	Difficulty falling asleep Early awakening Excessive nighttime awakening (more than getting up once or twice to use the bathroom and falling back asleep immediately) Excessive napping during the day
Appetite/eating	Weight changes Loss of appetite or increase in appetite Change in types of food he/she likes (eg, eating too many sweets)
Motor disturbance	Wandering Rummaging Pacing Doing things repeatedly (eg, picking at things) Excessive fidgetting
Hallucinations	Hallucinations can occur in any sensory modality, but visual and auditory hallucinations (ie, seeing or hearing things that are not present) are most common
Delusions	False beliefs (eg, that others are stealing from him/her or planning to harm him/her, that their spouse is having an affair, that family members plan on abandoning them)
Elation/euphoria	Appearing excessively happy Laughing inappropriately Childish sense of humor Inflated sense of self (eg, claiming to have more abilities or wealth than is true)

LEARNING OBJECTIVES

- Learn the presentation, epidemiology, and pathophysiology of common neuropsychiatric symptoms (NPS), including behavioral disturbances, seen in patients with dementia.
- Understand the best approach to evaluate NPS in patients with dementia and effective strategies to manage such symptoms.
- Learn about the significance and efficacy of nonpharmacologic interventions.
- Understand the appropriate indications, limitations, and adverse effects of pharmacologic interventions.

Key Clinical Points

1. **NPS are seen in up to 98% of patients with dementia and are the result of high-order loss of behavioral control due to disease involvement of major brain networks and neurotransmitters.**
2. **Patients with NPS have higher mortality and progress more rapidly from mild to severe dementia.**
3. **Careful history-taking is essential and exclusion of delirium is paramount for proper diagnosis and management of NPS associated with dementia.**
4. **Onset of new NPS in patients with dementia, especially systematized delusions, can be mistaken for another psychiatric disorder, such as a major depressive disorder with psychotic features or schizophrenia.**
5. **Nonpharmacologic interventions should be the first-line treatment and antipsychotics should be avoided as much as possible, given their lack of efficacy in randomized trials and higher incidence of adverse treatment effects.**
6. **Appropriate indications for medications include failure of nonpharmacologic therapies and presence of NPS severe enough to interfere with the patient's overall quality of life and function.**
7. **If medications are started, use slow titration, use the lowest effective dose, and reassess its risk/benefit ratio on a regular**

basis.

PATHOPHYSIOLOGY OF NEUROPSYCHIATRIC SYMPTOMS

The underlying cause of NPS is multifactorial. Causal contributors include a combination of underlying brain circuitry disruptions, preexisting risk factors, and precipitating stressors. Disruptions in white matter and its associated cortices in sensory and limbic brain areas are thought to be involved in NPS in the context of dementia. In particular, disruptions to the corticocortical and frontal-subcortical circuits, key to regulating emotions and behaviors, have been implicated in the pathogenesis of NPS. AD pathologies, such as neuronal loss and neurofibrillary tangles, are abundant in the limbic system, which include the amygdala, basal forebrain, brainstem, and hypothalamus. The hypothalamus, among other things, is important for the regulation of appetite, circadian rhythms, and regulating emotional responses. Though these areas have been implicated in NPS, the degree to which pathologic involvement of these structures correlate with specific NPS has not been well studied.

Dysfunction in the projections of excitatory and inhibitory neurons from the brain stem to cortical regions modulating monoamines (dopamine, serotonin, and norepinephrine), glutamate, and acetylcholine, may also contribute to NPS. For instance, agitation and aggression have been associated with cortical dysfunction in the insula, amygdala, anterior cingulate gyrus, hippocampus, middle frontal gyrus, lateral frontal gyrus, and lateral temporal gyrus; these behaviors may be related to deficits in acetylcholine neurotransmission. Similarly, prominent aggressive behavior in patients with AD has been associated with loss of serotonin in the inferior frontal cortex. Psychosis is most prominently associated with functional deficits in the anterior cingulate cortex and frontal cortex, both of which receive dopaminergic innervation. Depressive symptoms have been related in part to disturbances in serotonin, norepinephrine, and dopamine, and have been associated with loss of serotonergic receptors in the hippocampus, noradrenergic neurons in the locus coeruleus, and serotonergic neurons in the raphe nucleus. The resulting imbalances of dopamine, noradrenaline, and

serotonin neurotransmitters lead to NPS. Apathy is associated with dopamine and noradrenaline; depression is associated with serotonin and noradrenaline, psychosis is associated with dopamine, while agitation and aggression are associated with dopamine, noradrenaline, and serotonin.

These neurological disruptions, in combination with other underlying risk factors (such as personality factors, resilience, and psychiatric comorbidities), increase an individual's vulnerability to stressors or "triggers." Categories of stressors include patient factors (eg, physical discomfort, unmet needs, medical illness), environmental changes (eg, overstimulation or understimulation), and interpersonal stressors (eg, unrealistic caregiver expectations, negative communications). Thus, responses to these stressors in individuals with disruptions in brain circuitry due dementia may manifest as NPS.

DIAGNOSTIC APPROACH

History Taking

Due to the nature of cognitive impairment, a patient with dementia may not be able to provide an accurate history because of lack of insight, memory loss, and/or language problems. It is therefore critical to involve a reliable and knowledgeable informant during history taking. This helps elucidate a clear timeline of symptoms—whether the onset was insidious versus abrupt, the frequency if symptoms are episodic, and whether there have been precipitating events. Common stressors or "triggers" associated with NPS are in **Table 60-2** and should be considered during the history taking process. The severity of symptoms and associated distress (of both the patient and their caregiver) should be assessed. A thorough psychiatric and medical history is essential in considering differential diagnoses, which is discussed in greater detail below. An important part of history taking is asking caregivers how the behaviors are currently being managed and how the patient is responding to these interventions. Lastly, a careful history of physical symptoms should also be taken to determine whether medical causes and delirium may be contributing to the behavioral disturbance.

TABLE 60-2 ■ COMMON CONTRIBUTING CAUSES OF NEUROPSYCHIATRIC SYMPTOMS

- A biological stress or delirium due to a recurrent or new medical condition
- A psychiatric syndrome that is either recurrent or associated with the dementia
- Reaction to cognitive disturbance (eg, reaction due to inability to express oneself)
- An environmental stressor (eg, excessive stimulation, unfamiliar surroundings)
- Unmet needs (eg, hunger, thirst, pain, constipation)
- Sensory deficit (eg, unable to see or hear properly without the use of eyeglasses or hearing aids)
- Unsophisticated caregiving (eg, poor communication, rushing patient)
- Medication side effects

Physical Examination

Physical and neurological examination should be completed as part of the assessment to identify factors that may contribute to or worsen NPS, such as physical discomfort or delirium. Physical findings such as signs of infection, shortness of breath, pain, fluid overload or new neurological deficits may point to delirium due to an acute medical condition.

Clinical Measurements

The Neuropsychiatric Inventory (NPI) and its variations can be a useful tool in quantifying NPS. The NPI is the most widely used instrument for measuring NPS in clinical research. It includes questions pertaining to changes in the patient's behavior with screening for the presence of NPS, in addition to ratings of their frequency and severity. The Neuropsychiatric Inventory-Questionnaire (NPI-Q) is a brief version suitable for use in clinical settings. It is a self-administered informant-based instrument that measures the presence and severity of 12 NPS, as well as informant distress. The Neuropsychiatric Inventory-Clinician Rating (NPI-C) is a clinician version that includes expanded domains and items.

Medication Review

A careful review of medications, including the time course of symptoms in relation to recent medication changes, is needed. Certain classes and combinations of medications may contribute to NPS. Classes of medications most likely to be associated with delirium, largely due to anticholinergic effects, include opiates, anticholinergics, benzodiazepines, antihistamines, tricyclic antidepressants (TCAs), muscle relaxants, and antiepileptic medications. Common examples of anticholinergic medications are in **Table 60-3**. Behavioral changes associated with these medications may include sedation, changes in sleep-wake cycle, and worse confusion or agitation. Medications used to treat Parkinson disease, such as dopaminergic agents, can precipitate impulsive behaviors. Anticholinergics, amantadine, dopaminergic agents, and catechol-O-methyl transferase (COMT) inhibitors, often used in Parkinson disease, can exacerbate psychotic symptoms, such as hallucinations and delusions.

TABLE 60-3 ■ MEDICATIONS WITH ANTICHOLINERGIC ACTIVITY, WHICH HAVE INCREASED RISK OF CAUSING DELIRIUM

Amantadine (Symadine)
Benztropine (Cogentin)
Cyproheptadine (Periactin)
Digoxin (Lanoxin)
Diphenhydramine (Benadryl)
Dipyridamole (Persantine)
Doxylamine (Aldex, Doxytex, Nitetime Sleep-Aid, Sleep Aid, Unisom)
Furosemide (Lasix)
Hydroxyzine (Vistaril, Atarax)
Low-potency antipsychotics
Meclizine (Dramamine)
Metoclopramide (Reglan)
Oxybutynin (Ditropan)
Prochlorperazine (Compazine)
Promethazine (Phenergan)
Ranitidine (Zantac)
Scopolamine (Transderm-V)
Theophylline (Aerolate)
Tricyclic antidepressants

Diagnostic Testing

For acute, new-onset NPS in dementia, work-up with a physical examination and laboratory studies is needed in many cases to evaluate for an underlying general medical cause. Laboratory testing typically consists of complete blood count, metabolic panel, liver function tests, and urinalysis/urine culture. Thyroid function tests, folate, vitamin B_{12}, levels, toxicology, and electrocardiogram may be considered as additional tests if indicated based on history and physical examination. If there are signs and symptoms of a respiratory infection, chest radiography is indicated. Brain imaging, such as

computed tomography (CT) or magnetic resonance imaging (MRI) may be indicated particularly if focal neurologic findings are present. Electroencephalogram (EEG) is indicated if seizures are suspected. Cerebrospinal fluid analysis is rarely needed but indicated if meningitis or encephalitis is suspected.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis for NPS includes: medical conditions, delirium and primary psychiatric disorders such as major depression, bipolar disorder schizophrenia, etc. Presentation with acute changes in cognition and behavior should raise suspicion for delirium, and the underlying medical cause for delirium should be investigated accordingly.

In formulating a differential diagnosis, one should keep in mind that there may be more than one cause. Older individuals with primary psychiatric disorders such as major depressive disorder, bipolar disorder, anxiety disorders, and schizophrenia can develop dementia or delirium superimposed on their psychiatric illnesses. There are also late-onset forms of these disorders. Late-onset depression and anxiety are common among older adults (and among individuals with dementia), while late-onset bipolar disorder and schizophrenia are rare. However, if new psychiatric symptoms emerge in the setting of dementia, the underlying etiology is likely dementia as opposed to a separate, concurrent psychiatric disorder.

Delirium

If a patient exhibits a sudden drop or fluctuation of cognition, delirium should be considered in the differential diagnosis. Delirium is characterized by acute onset over hours or days with a fluctuating course. Cognitive deficits in delirium typically include inattention, disorganized thinking, or an altered level of consciousness. Delirium has a wide range of presentations, including hyperactive (eg, psychosis and agitation), hypoactive (eg, severe apathy, lethargy, and withdrawal), and mixed presentations where features of both hyperactive and hypoactive delirium are present. It is a syndrome with multiple potential etiologies. Providers should rule out delirium first in the setting of any acute change in cognition and/or consciousness, and assess for potential etiologies such as medication withdrawal, metabolic imbalance, infection, and intoxication.

Once the underlying cause is corrected, a patients' mental status and behavior should improve, though it commonly persists well beyond correction of the underlying cause—in some cases weeks to months. Some patients take a "cognitive hit" and may not fully return to their prior baseline. Short-term, low-dose use of oral or intravenous haloperidol or atypical antipsychotics can be considered for management of significant agitation in the context of delirium. Commonly used medications and starting doses include the following:

- Haloperidol (0.25–0.5 mg oral or intravenous every 6 hours as needed for agitation)
- Quetiapine (12.5–25 mg oral every 6 hours as needed for agitation)
- Olanzapine (2.5 mg oral or 1.25–2.5 mg intramuscular every 6 hours as needed for agitation)
- Risperidone (0.25–0.5 mg oral or intravenous every 6 hours as needed for agitation)

Depressive Symptoms

Major depressive disorder is a heterogeneous syndrome with a wide severity range. Symptoms include sleep disturbance, reduced energy, anhedonia, guilt, and suicidal ideation. It may include psychotic symptoms such as delusions and hallucinations. In individuals with dementia who experience new symptoms of depression, it can generally be presumed that the depressive symptoms are due to underlying neurodegeneration. Depressive symptoms of poor concentration, memory deficits, and anhedonia may be confused for cognitive deficits and apathy that are common to dementia.

Up to 50% of individuals with dementia will suffer from depression over the course of their illness, and it is one of the most common psychiatric symptoms in early dementia. Depression in dementia is associated with increased health care utilization, greater severity and acceleration of cognitive impairment, decreased quality of life for the affected individual and caregiver, and increased risk of suicide.

Among individuals with AD, risk factors for depression include older age, female gender, personal history of depression, and less education. Depression in individuals with dementia may go undetected because the symptoms they experience as part of a major depressive disorder can differ considerably from older individuals with normal cognition. For example,

depression in dementia is more likely to present with agitation, irritability, and anxiety. Validated scales such as the Cornell Scale for Depression in Dementia and Geriatric Depression Scale (GDS) may be helpful as measures of depression.

Anxiety Symptoms

Symptoms of anxiety are relatively common in older adults and may be accompanied by agitation. They are often associated with comorbid depression and tend to go unrecognized. Similar to depression in dementia, new anxiety syndromes observed in dementia are most likely related to the underlying dementia as opposed to a separate anxiety disorder. The most common anxiety syndromes include generalized anxiety disorder, panic disorder, and phobias. Patients with posttraumatic stress disorder may become agitated when reexperiencing traumatic and painful memories ("flashbacks"). These episodes may become difficult for patients with dementia to distinguish from reality due to cognitive impairment (eg, short-term memory loss and disorientation) and because remote memory tends to be preserved until late in the course of many dementias. Clinicians should routinely inquire about a history of trauma when evaluating patients with dementia who are agitated.

Psychotic Symptoms

Psychotic symptoms, such as delusions and hallucinations, occur in 20% to 30% of patients with AD and in over 50% of patients with dementia with Lewy bodies (DLB) or Parkinson disease dementia. They may cause distress for the patient (and caregiver), and often contribute to the development of agitation.

Delusions are more common than hallucinations in dementia and can stem from cognitive impairment. For example, memory deficits may lead to the fixed and false belief that a misplaced item was stolen. Individuals with agnosia may misidentify formerly familiar individuals or objects. Less common delusions include delusions that they are being poisoned or that their partner has been unfaithful.

In AD, hallucinations are more likely to be visual than auditory, and tend to occur in the moderate to severe stages of dementia. In many circumstances, auditory hallucinations do not cause distress to the patient and as such, do not need to be treated pharmacologically. Visual hallucinations are more

common in DLB than AD and may be the most clinically useful feature to distinguish DLB from AD. In DLB, hallucinations tend to be well-formed images of people, animals, or objects, but can also appear as simple shapes in the corner of one's eyes. Hallucinations are typically not distressing in DLB unless they are accompanied by delusions or occur in severely demented individuals.

Of note, many medications used to treat Parkinson disease, such as anticholinergic agents, amantadine, dopaminergic agents, and COMT inhibitors, can exacerbate visual hallucinations and delusions.

GENERAL MANAGEMENT

Dementia Care Models

The "DICE" (Describe, Investigate, Create, and Evaluate) approach (**Table 60-4**) provides a useful mnemonic for a methodic approach to the management of NPS. The "describe" phase involves characterization of the NPS, enabling the provider to identify underlying patterns or contributory factors to the behavior and establish treatment goals. In the "investigate" phase, the provider examines the patient and identifies potential underlying and modifiable causes. Behavioral disturbances are often multifactorial. As described in the previous section, common contributing factors may include delirium, pain, undiagnosed medical conditions (eg, dehydration, infection, constipation), medication side effects, underlying psychiatric comorbidity, sensory impairment, and environmental factors. In the "create" phase, the patient, caregiver, and treatment team collaborates to design and implement a treatment plan. This may involve both pharmacologic and nonpharmacologic interventions. The final step of the "DICE" approach is for the provider to "evaluate" whether recommended strategies were attempted and effective. If the caregiver did not implement the intervention, the provider should attempt to understand the barriers and brainstorm solutions with the caregiver. If interventions include a psychotropic medication, the provider and caregiver should monitor for changes in behaviors and potential side effects and evaluate the need for continued medication use on an ongoing basis.

TABLE 60-4 ■ DESCRIBE, INVESTIGATE, CREATE, AND EVALUATE (DICE) APPROACH

Describe	Caregiver describes problematic behavior

	Context of behavior Social and physical environment Patient perspective Degree of distress to patient and caregiver
Investigate	Provider investigates possible causes of problem behavior Undiagnosed medical conditions Underlying psychiatric comorbidity Limitations in functional ability Poor sleep hygiene Boredom, fear, sense of loss of control Medication side effects Sensory impairment Environmental factors Unmet needs
Create	Provider, caregiver, and team collaborate to create and implement treatment plan Respond to medical problems Strategize behavioral interventions Provide caregiver education and support Create meaningful activities for the patient Simplifying tasks Ensuring the environment is safe Enhancing communication with the patient Increasing or decreasing stimulation in the environment
Evaluate	Provider evaluates whether the interventions have been implemented by caregiver and whether they are effective

Data from Kales HC, Gitlin LN, Lyketsos CG, et al. Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel. J Am Geriatr Soc. 2014;62(4):762–769.

Support for Patients and Caregivers

The Alzheimer's Association estimates that 60% to 70% of older adults with AD and other dementias live in the community and are cared for by family and friends. Nearly all have unmet needs regarding care, services, and support. The Maximizing Independence at Home (MIND at Home) Study found that 99% of patients had unmet needs. The most common domains with unmet needs included: safety (personal and home), general health and medical care, meaningful activities, legal issues, and advanced care planning. Higher unmet needs were reported in individuals who were minorities, had lower income, had fewer impairments in activities of daily living (ADLs), and more symptoms of depression. Caregivers, too, reported unmet needs. Ninety-seven percent reported having one or more unmet needs, with the most common domains being resource referrals, caregiver dementia education, mental health care, and general medical health care.

These findings highlight some of the areas that a dementia care team should address for every patient (**Table 60-5**). The care team should work with the patient and caregiver to maintain the patient's optimal physical and mental health, provide a safe environment that maximizes the patient's physical and cognitive abilities, and preserve the patient's dignity. Ideally, such an environment would allow patients to receive support for their ADLs and instrumental activities of daily living (IADLs), be well-nourished, maintain good sleep hygiene, and engage in activities and socialization. In-home activities tailored to the interests and capabilities of patients with dementia have been demonstrated to significantly increase the patient's engagement, reduce NPS, and reduce caregiver burden. In-home occupational therapy assessments, using a functional assessment method such as the Assessment of Motor and Process Skills (AMPS), can provide useful data about a patient's care needs as well as assess the safety of the home environment. For more information about providing supportive care for patients, we refer you to the book *The 36-Hour Day* by Mace and Rabins (2017) and the Alzheimer's Association website (www.alz.org).

TABLE 60-5 ■ SUPPORTIVE CARE FOR THE PATIENT WITH DEMENTIA

- Carefully evaluate the patient's dementia-related needs.
- Provide education about the diagnosis and trajectory of dementia to the patient (if appropriate) and caregiver.
- Manage medical comorbidities: Encourage routine follow-up with primary care, dental, vision, and hearing specialists. Assist with medical decision making.
- Address safety needs, particularly regarding falls, wandering, driving, ability to live alone, environmental hazards (eg, access to weapons, removing items patients may stumble upon), and medication management. Consider obtaining a home safety evaluation and driving evaluation. Encourage the use of monitoring devices.
- Provide comfort and emotional support.
- Provide meaningful activities, stimulation, and socialization. This may be achieved through adult day care, senior centers, and in-home activities.
- Maintain and document wishes for end-of-life care and distribution of finances after death. These should be addressed while individuals still have decision-making capacity.
- Provide quality nursing care in advanced stages.

For caregivers, providing education about the disease and skills training in communication for dementia can significantly improve the quality of life for patients and increase positive interactions. A recent meta-analysis examining different caregiver interventions found that the most beneficial interventions address caregiving competency initially, then gradually addressing the care needs of the patient. In the United States, about 25% of people with dementia receive care from nonfamily caregivers, such as home health aids or nursing assistants hired directly by the family to care for a patient in the home setting. These caregivers may not always receive the necessary training to provide dementia care and face a challenging work environment. For nonfamily caregivers, interventions focused on facility staff training programs have been associated with reduction of NPS in patients and staff wellbeing. Some caregivers may benefit from encouragement to attend to their own emotional and personal needs. They should be

encouraged to maintain their own medical appointments, hobbies, and social network. Utilization of respite from caregiving as needed, which can provide temporary relief for caregivers through provision of substitute care, should also be encouraged. Support groups can provide caregivers with the opportunity to share concerns, personal feelings, and seek support from peers. Psychological interventions, such as counseling and supportive therapy, have also been associated with positive impacts on psychosocial outcomes between patients and their informal caregivers.

NONPHARMACOLOGIC MANAGEMENT

Nonpharmacologic interventions are first-line in the management of NPS in dementia patients to avoid the risks and side effects associated with medications. An exception is emergency situations in which the safety of the patient or others is compromised, for example due to severe agitation.

Multiple small studies report modest improvement in quality of life and NPS with reminiscence therapy, music therapy, bright light therapy, aromatherapy, pet therapy, physical therapy, occupational therapy, exercise training, speech therapy, and multisensory stimulation. However, most studies of nonpharmacologic interventions included patients with mild to moderate NPS and few controlled data suggest that these nonpharmacologic interventions provide longer-term benefits, outside of the treatment session. Psychotherapy can be useful, particularly for patients in the early stages of dementia who are demoralized, depressed, or anxious.

Nonpharmacologic interventions that can be implemented by caregivers for common NPS are summarized in **Table 60-6**. Unfortunately, some of these can be difficult to implement in real-world settings or may not provide sufficient control of disruptive NPS. There is preliminary evidence that family caregiver interventions, such as promoting helpful coping, effective communication and scheduling of pleasant activities, and tailored activities for persons with dementia and their caregivers may improve quality of life in people with dementia living in the community.

TABLE 60-6 ■ GENERAL BEHAVIORAL STRATEGIES FOR COMMON NEUROPSYCHIATRIC SYMPTOMS

BEHAVIORS/SYMPTOMS	KEY STRATEGIES
Disorientation or confusion with person/object recognition	Provide reminders, cues, or prompts Identify individuals if patient does not remember names or has aphasia Use environmental cues (eg, calendars, keeping blinds raised during the day, keeping lights off at night) Keep objects for individual tasks in separate, labeled containers Use simple visual reminders (eg, pictures, arrows pointing to the bathroom)
Confusion/overwhelmed with tasks and environment	Eliminate noise and distractions while patient is engaged in an activity Break each task into very simple steps Offer simple choices (no more than two at a time) Provide simple verbal commands, using only one or two steps at a time Remove unnecessary items from the room while patients is engaged in a task Provide daily, structured, and predictable routines
Wandering or inability to respond appropriately to an emergency	Provide 24-hour supervision for the patient Place locks on all exits Develop an emergency plan. Inform neighbors, fire department, and police of the patient's condition Provide patient with medical alert and safe return ID bracelets
Nighttime wakefulness	Encourage good sleep hygiene (avoid stimulating activity, reduce caffeinated and alcoholic beverages that may affect sleep, limit daytime napping) Create a quiet routine for bedtime Evaluate environment for modifiable elements, such as temperature, noise level, light, shadows, and bed comfort
Anxiety, irritability, repetitive questioning, frustration	Use a relaxed and reassuring voice and light touch to help calm or redirect Avoid negative words and tone Allow patient sufficient time to respond to questions Help patient with aphasia find the words to express him/herself Allow extra time for tasks and activities Distract the patient as necessary Understand that behaviors are not always intentional
Boredom and restlessness	Create a structured, daily schedule that includes entertainment and exercise Provide meaningful activities that draw on preserved capabilities and interests Engage patients in activities involving repetitive motion (eg, folding towels, putting items in containers)
Delusions and hallucinations	Go along with patient's point of view of what is true. Avoid arguing or trying to reason as this can make the situation worse Ignore symptoms that are not distressing the person Distract the patient as necessary
Apathy	Give the patient a job at home, such as folding laundry Focus on the process of doing things rather than the results
Disinhibition	Distract from an inappropriate topic by calmly and firmly changing the subject Avoid television shows with violence or sexual content

PHARMACOLOGIC MANAGEMENT

Some patients who do not respond to nonpharmacologic approaches may require targeted medication therapy. It should be noted that while psychotropics are frequently prescribed for NPS in dementia, there are currently no pharmacotherapies with US Food and Drug Administration (FDA) approval for this purpose. Several classes of "psychiatric" medications have been studied specifically for NPS in dementia, but treatment response has been disappointing, with few randomized clinical

trials (RCTs) showing clear efficacy of antipsychotics, antidepressants, or anticonvulsants. Risks and benefits of each class of medication are discussed in detail below.

Due to the inherent risks of using medications to treat NPS in dementia, nonpharmacologic approaches should be first-line therapy. Psychotropics should be used only after other efforts have been made to mitigate NPS, with three exceptions: (1) clear-cut major depression; (2) psychosis causing harm or with significant potential of harm to self or others; and (3) aggression causing harm or risk of harm to self or other.

Clinicians should obtain informed consent for medication use from the patient or their legal representatives after discussing potential risks (including so-called "black box warnings" of mortality in the case of antipsychotics) and benefits. Medications should be slowly titrated using starting doses appropriate for older individuals. Although a slow titration schedule is recommended for older adults, medications should still be increased as tolerated to produce an improvement in target symptoms. Behavior logs kept by the caregiver, documenting the timing and pattern of behaviors, may help identify optimal times for medication administration (eg, timing doses of medication to target difficult behaviors such as prior to bathing or dressing).

Clinicians should pay close attention to side effects and educate the caregiver about what to look out for. It is important to keep in mind that older individuals are at higher risk of adverse effects to medications due to (1) decreased renal clearance and slowed hepatic metabolism, (2) medical comorbidities, (3) potential for drug–drug interactions due to being on multiple medications, (4) increased risk of orthostatic hypotension and falls due to decreased autonomic regulation, and (5) elevated risk of delirium. The American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults provides an overview of medications and guidelines on when they should potentially be avoided older adults.

In prescribing psychotropic medications for NPS, clinicians should keep potential pitfalls in mind. Though there are no FDA-approved medications for NPS in dementia, clinicians routinely prescribe psychotropics despite safety and efficacy concerns. In a study of newly admitted nursing home residents, only 12% received nonpharmacologic interventions within the first 3 months of admission, while 71% received at least one psychotropic medication. Moreover, more than 15% were taking four or more