



AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists will be able to:

- Identify four types of dementia, and describe their signs, symptoms, and overall impact
- Differentiate drugs and biologics approved for use in dementia by indication, appropriate administration, and effect on the retardation of cognitive decline
- Determine when patients are candidates for specific prescription drugs and/or referral to a specialist
- Describe appropriate counseling for patients, their family members, and caregivers to help them cope with neurologic disorders that result in the loss of cognitive functioning

After participating in this activity, pharmacy technicians will be able to:

- Identify four types of dementia, and describe their signs and symptoms
- Name drugs and biologics used to treat dementia
- Recognize new prescriptions for drugs used to treat dementia and refer patients and their caregivers to the pharmacist
- List sources of information for patients and their caregivers



The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this knowledge-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

ACPE#: 0009-0000-18-014-H01-P
ACPE#: 0009-0000-18-014-H01-T

Grant funding: None.

Activity Fee: \$7 for pharmacists, \$4 for pharmacy technicians

INITIAL RELEASE DATE: April 15, 2018
EXPIRATION DATE: April 14, 2020

To obtain CPE credit, visit the UConn Online CE Center <https://pharmacyce.uconn.edu/login.php>. Use your NABP E-profile ID and the session code

18YC14-PWX44 for pharmacists or
18YC14-SXT36 for pharmacy technicians

to access the online quiz and evaluation. First-time users must pre-register in the Online CE Center. Test results will be displayed immediately and your participation will be recorded with CPE Monitor within 72 hours of completing the requirements.

For questions concerning the online CPE activities, email joanne.nault@uconn.edu.

You Asked for It! CE



© Can Stock Photo / focalpoint

Differentiating Dementias, Delaying Decline: The Pharmacist's Role

ABSTRACT: Dementia is a broad term referring to myriad symptoms associated with changes in brain function. Irreversible, incurable symptoms include memory, personality, and behavior alterations. The four main types of dementia vary by symptoms, neurologic changes, and velocity of progression. Diagnosing dementia is a process of elimination. Diagnosticians must distinguish patients who are suffering from impairments that occur along a continuum or spectrum. Cognitive and/or behavioral (neuropsychiatric) symptoms interfere with the patient's ability to function, and may indicate the patient is declining. The Food and Drug Administration has approved two categories of pharmacologic management for dementia and related comorbidities. Choice of therapy depends on type of dementia and response to therapy.

FACULTY: Jeannette Y. Wick, R.Ph. MBA, is Assistant Director, Office of Pharmacy Professional Development, at the University of Connecticut School of Pharmacy. Kelsey Fontneau, B.S., is a 2018 Pharm. D. Candidate, at the University of Connecticut, School of Pharmacy.

FACULTY DISCLOSURE: Ms. Wick and Ms. Fontneau have no actual or potential conflicts of interest associated with this article.

DISCLOSURE OF DISCUSSIONS of OFF-LABEL and INVESTIGATIONAL DRUG USE: This activity may contain discussion of off label/unapproved use of drugs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of the University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

INTRODUCTION

Memory loss, regardless of who experiences it, is annoying. With age, many people experience some memory changes. Typically, older people retrieve memories more slowly than younger people. This is not memory loss, but rather, an age-related change. Eventually, the older individual will remember the information he or she is trying to retrieve and will retrieve it accurately. Patients who are on the road to a diagnosis of dementia, however, will experience more complex cognitive changes. Eventually, cognitive deficits will become clear to the patient him- or herself, and other people. A critical point for all clinicians to remember is that memory loss alone is not dementia, and people who have dementia have deficits in other cognitive domains, not just memory loss. Memory loss is not a terminal illness; dementia is.

TO REGISTER and PAY FOR THIS CE, go to: https://pharmacyce.uconn.edu/program_register.php



© Can Stock Photo / focalpoint

Dementia is a broad term referring to myriad symptoms associated with changes in brain function. Irreversible, incurable symptoms include memory, personality, and behavior alterations. Early detection and treatment may help alter the clinical course of specific types of dementia, and help maintain quality of life for as long as possible.¹

Dementia impacts the patient's entire family and social network. And, as dementia progresses, patients are forced to abdicate all decisions to caregivers. Clinicians will come to rely on a specific caregiver known as the "knowledgeable informant." This individual provides information and relates observations about the patient's day-to-day cognition and behavior. Most people do not slip into this role easily. Healthcare providers need to train informants about what to look for, and when to ask for help. They also need to train caregivers (people who help dementia patients with their personal hygiene and activities of daily living [ADLs]) who become decision-makers (people entrusted with the patient's medical, legal, and financial decisions) how to serve the patient's best interests. Unfortunately, it's difficult to find adequate support for patients who have dementia and many loved ones become informant, caregiver, and decision-maker. These individuals, who are emotionally, socially, and financially burdened, are at elevated risk for depression, isolation, stress-related illnesses, and poverty.²

The four main types of dementia—Alzheimer's dementia (AD), vascular dementia (VaD), frontotemporal dementia (FD) and dementia with Lewy bodies (DLB)—vary in three ways:

- Their symptoms differ significantly
- Diagnostic tests reflect different neurological changes
- They progress at different rates

Patients often display characteristics of multiple types of dementia (see **Table 1**), complicating diagnoses and treatment.^{1,3}

Diagnosing dementia is a process of elimination. Primary care providers, often the first clinicians to detect/diagnose dementia, must rely on symptomatology and narratives from patients and family members. They must distinguish patients who are suffering from impairments that occur along a continuum or spectrum. For example, age-associated cognitive impairment (AACI) is benign memory impairment, or cognitive changes consistent with age-defined norms. Patients with AACI have no interference or compromise of ADL. A more impairing condition that represents a step along the continuum, mild cognitive impairment (MCI), is cognitive decline that exceeds age-related norms and limits the patient's independence and ability to perform ADLs. About 50% of patients with MCI develop dementia within 5 years. Management is nonspecific, focused on minimizing risk factors for disease progression (reducing vascular risk factors, reducing anticholinergic drug exposure, treating cognition-depleting comorbidities [i.e. depression]).^{1,3,4}

Table 1. Four Main Types of Dementia

	AD	VaD	FD	DLB
Progression	Gradual	Marked by cerebral and CVEs	Insidious	Fluctuates
Signs/Symptoms	Memory loss Learning impairment Psychotic features Wandering Dysphagia Gait disturbance Language loss	Confusion Disorientation Trouble speaking Trouble understanding speech Vision loss	Behavioral changes Language changes Hyperorality	Memory loss Hallucinations Parkinsonian
Brain	Aβ plaques	Infarcts	Frontal lobe Temporal lobe	Cortex
Treatment	ChEI NMDA antagonists	ChEI NMDA antagonists	Palliative	ChEI NMDA antagonists No atipsychotics

Abbreviations: ChEI = cholinesterase inhibitor ; CVEs = cardiovascular events; NMDA = N-methyl-D-aspartate

References: 1, 3- 11

Alzheimer's Dementia

As the 6th leading cause of death in the United States, AD causes almost 75,000 deaths each year.¹² Up to 85% of patients with dementia have AD, making it the most common type of dementia.¹ Risk increases over the age of 65; one in 10 Americans over 65 years old has AD and its prevalence increases to 32% after age 85.^{13,14} Patients, their families, and acquaintances may not notice or report early/mild symptoms (short-term memory and learning impairment), as they are often indistinguishable from normal AACI. In AD, progression is associated with gradual loss of abstract thinking, reasoning, and other executive function losses.^{1,4} Continual decline impairs daily functioning without plateaus or functional improvements.^{1,5} AD eventually leads to complete incapacitation and death.

In early stages, patients may develop depression and apathy, both of which are concerning. With progression to moderate-severe stage disease, more pronounced symptoms occur: psychotic features (agitation, irritability, combativeness), wandering, dysphagia (difficulty swallowing), incontinence, myoclonus (spasmodic jerky muscle group contraction), and seizures. Patients with late stage AD are often mute, bedbound, and burdened by gait disturbances and language and motor impairment.^{4,5}

Amyloid-beta (A β) plaques and tau tangles are AD's hallmark neurological findings. A β plaques accumulate outside neurons while abnormal tau protein accumulates within neurons. A β plaques impair neuron-to-neuron communication and tau tangles block nutrient/molecule transport into neurons, contributing to inflammation and cell death. Brain scans reveal shrinkage from cell loss and dead/dying neurons.¹⁴

Post-diagnosis, patients have an average lifespan of four to eight years.¹⁵ Practitioners use cholinesterase inhibitors (ChEI) and N-methyl-D-aspartate (NMDA) receptor antagonists as treatment staples.^{6,7}

Vascular Dementia

VaD, the second most common type of dementia, appears abruptly following a vascular comorbidity or complication. Blocked blood flow or cerebral blood vessel injury causes damage to brain cells and tissues. Imaging reveals white hyperintensities (areas showing increased density) and infarcts (area showing decreased density).^{3,4} Vascular risk factors include hypertension, diabetes, smoking, obesity, hypercholesterolemia, atrial fibrillation, atherosclerosis, and arteriosclerosis.⁴ VaD typically progresses unpredictably and slowly with a step-wise decline after another cerebral or cardiovascular event (CVE).¹

Patients may struggle to communicate, having difficulty speaking coherently or understanding others resulting in confusion and frustration. Other symptoms include impaired ability to plan, follow direction, or complete ADLs; disorientation; and impaired/blurred vision.⁵ Memory loss is usually secondary to

Pause and Ponder:

What types of questions would be best answered by a knowledgeable informant?



© Can Stock Photo / Nevenova

executive function loss and cognitive impairment after a CVE. Patients are often very aware of their deficits, and develop depression, apathy, and mood, personality, and behavior changes.^{1,4} The drugs approved for AD have modest effects in VaD patients.⁸ VaD very commonly occurs concurrently with AD and/or DLB.

Frontotemporal Dementia

FD is associated with behavioral and language abnormalities rather than memory disorders. FD follows nerve cell damage in the brain's frontal and temporal lobes. MRIs can detect brain atrophy in areas associated with behavior and language.^{3,4} FD makes up approximately 10% to 15% of dementia cases, but occurs the earliest in life; patients tend to be diagnosed between age 35 and 75.^{1,9} Onset is insidious and steadily progressive; patients may experience severe symptoms in as few as two years.^{1,5} Behavior changes are so prominent with this type of dementia, clinicians may initially misdiagnose patients with mental disorders.^{4,9}

Common behavioral symptoms include impaired social cognition/appropriateness, lack of insight, disinhibition, apathy, and hyperorality (the propensity to place inappropriate objects in the mouth). The language component includes a prominent decline in language ability, word finding, object naming, grammar, word comprehension, and speech production.^{4,5} Patients may present with language and/or behavioral components.⁴ Learning, memory, and perceptual-motor function is typically unaltered.⁵ There is no cure; treatment is palliative in nature to ease symptoms. Average survival time after diagnosis is six to eight years, with patients in late stages requiring 24-hour care.⁹

Lewy Body Dementia

DLB may be the most misdiagnosed of dementias.^{1,3} Ten percent to 25% of patients with dementia have DLB, experiencing symptoms similar to AD and Parkinson's disease (PD). Three core features include

- fluctuating cognition with pronounced variations in attention and alertness (may fluctuate hourly/daily)
- visual hallucinations
- spontaneous parkinsonian features (tremor, bradykinesia, rigid muscles, loss of automatic movements, speech changes, writing changes, impaired posture and balance).^{1,3,10,11}

Other features include rapid eye movement sleep-behavior disturbances, low dopamine in the brain, and neuroleptic sensitivity.¹ DLB's cognitive symptoms start shortly before or concurrently with motor symptoms.

Genetic risk factors have been identified, but most patients have no family history. DLB is due to the formation of Lewy bodies (abnormal deposits of alpha-synuclein protein) inside nerve cells in the brain's cortex.¹⁶ The subsequent formation of β -amyloid and senile plaques are associated with dopaminergic metabolism changes, extrapyramidal symptoms, and acetylcholinergic deficits.^{1,3} In patients who have DLB, the brain's medial temporal lobe is preserved, with hypoperfusion and hypometabolism of posterior parietal and occipital areas.¹⁴ Neuropsychological testing, EEG, MRI, PET, and polysomnography may help diagnose DLB.¹

DLB progresses with development of additional symptoms including impaired problem-solving, auditory hallucinations, transient loss of consciousness, falls, and autonomic dysfunction.^{4,3} Patients typically live for five to seven years after diagnosis.¹⁷ Patients with DLB rarely respond to dopaminergic drugs, however ChEI may help delay disease progression.¹ The pharmacy team needs to recognize a critical issue: antipsychotic medications, "neuroleptics," cause severe side effects in up to 50% of patients with DLB, including worsening condition, sedation, increased parkinsonism, and neuroleptic malignant syndrome (a possibly fatal condition with fevers, muscle rigidity and breakdown, and kidney failure).¹⁷

DIAGNOSIS AND TREATMENT

Diagnostic guidelines were published by the National Institute on Aging and the Alzheimer's Association in 2011^{18,19} and by the British Association for Psychopharmacology in 2017.¹⁴ Both guidelines describe a diagnosis of "dementia" as a general term encompassing all patients within the spectrum. The extent of impairment and symptoms varies widely between mild and severe patients, affecting patients' ability to live. Guidelines are separated by specific diagnosis, so appropriate diagnosis is essential for proper treatment and maintenance of quality of life.^{14,18,19}

Pause and Ponder:

What specific symptoms would you anticipate to be different in a patient who had AD and a patient who has LBD?

Cognitive and/or behavioral (neuropsychiatric) symptoms are particularly troublesome. They interfere with the patient's ability to function in usual activities and perform ADLs. They also can signal decline from previous levels of function, and are not otherwise explained by delirium or major psychiatric disorder (see sidebar).^{14,18,19}

Differential Diagnosis: Delirium and Psychiatric Disorders

Several disorders affect cognitive function, and patients who are diagnosed with dementia may have concurrent delirium or psychiatric diagnoses. Pharmacists and pharmacy technicians should keep the following points in mind:

- **Comorbid depression or delirium and dementia are common.** Delirium tends to start abruptly and is associated with periods of waxing and waning alertness. Dementia is a slow, progressive process and is associated with consistent levels of alertness. Generally, delirium has an underlying (potentially correctable) cause such as
 - o Alcohol intake
 - o Dehydration
 - o Electrolyte imbalance
 - o Medication adverse event or abrupt cessation of certain drugs
 - o Urinary tract infection, infection, or influenza
 - o Stroke or head injury
- **Depression is often associated with an antecedent event** (e.g., the death of a spouse or a new diagnosis with the significant or life-threatening disease). Patients who have depression typically report levels of cognitive impairment that far exceed that indicated by cognitive testing.
- **Patients who have psychiatric illnesses characterized by delusions have thoughts that are unrelated to reality but have intact cognitive function.** For example, they may believe they are God but are perfectly able to balance their checkbook. In the patient with dementia, delusions generally don't occur until the middle or late stages of the disease. These patients will have a variety of delusions and also have difficulty doing even simple math, expressing cohesive thoughts, or remembering.

Table 2. Diagnosis Points: Mild Cognitive Impairment and Alzheimer's Disease

Guidelines for MCI diagnosis	Guidelines for AD diagnosis
Identify four core clinical criteria: <ul style="list-style-type: none">• The patient, an informant who knows the patient well, or a clinician must show concern regarding a change in the patient's cognitive function• Impairment in at least one cognitive domain that does not improve over time but continues to decline, established through objective cognitive testing and/or histories from patient or knowledgeable informant• Patients perform usual tasks independently, but may experience more difficulty/make more errors• Patients are not demented in that cognitive changes are mild enough to not interfere significantly with social or occupational functioning	Impairment must include at least two of five major domains: <ul style="list-style-type: none">• Impaired ability to learn and retain new information• Impaired reasoning and handling of complex tasks, poor judgment• Impaired visuospatial abilities (inability to recognize faces/common objects, inability to find objects in direct view, inability to operate simple instruments, inability to orient clothing to body)• Impaired language functions• Changes in personality or behavior

Source: References 14, 18, and 19

Clinicians detect and diagnosis cognitive impairment using a combination of objective testing and narratives from patients and knowledgeable informants. Differentiation from MCI depends on interference with ADLs; AD interferes with daily activities, while MCI does not (see [Table 2](#)).¹⁸ Clinicians must rule out cognitive decline caused by other systemic or brain diseases.¹⁹

Current evidence suggests that AD's pathophysiological process is a continuum that begins years before the diagnosis of clinical dementia. Patients with "preclinical AD" have biomarker evidence of AD, but no clinical symptoms. Preclinical characteristics do not mean that patients will necessarily progress to either MCI or AD but that they are asymptomatic and at risk for AD dementia. If it could be identified reliably, the preclinical phase would be a critical window to begin therapeutic intervention to avoid or stall progression to MCI or dementia before clinical symptoms.²⁰

The patient's dementia stage dictates treatment. Clinicians must work closely with patients/caregivers to develop and implement an ongoing treatment plan with specific goals. Current treatment recommendations include therapies to treat cognitive decline, treatment of behavioral symptoms and mood disorders, non-pharmacologic approaches (i.e. environment modifications, task-simplification), and treatment of comorbid conditions.²¹



© Can Stock Photo / focalpoint

Evidence-based Therapies

The Food and Drug Administration (FDA) has approved two major categories of pharmacologic management for dementia and related comorbidities:

- Drugs that may improve cognitive management and delay disease progression
- Drugs that manage behavioral and psychological symptoms.

Choice of therapy depends on type of dementia and response to therapy. Currently, a handful of drugs are available to treat dementia, and several promising drugs and biologics are in clinical trials.

Cholinesterase inhibitors

ChEI were developed to promote higher acetylcholine (ACh) levels and improve the brain's cholinergic function. ACh plays a crucial role in mediating learning and memory. A β peptide accumulation is a hallmark pathophysiologic finding in AD. Investigators suggest that direct interactions exist between A β and cholinergic systems. Alterations in the negative feedback loop controlling peptide production produces abnormal A β accumulation, reducing cholinergic transmission. In other words, cells don't have the peptides they need, so proteins accumulate, and consequently, patients lose one mechanism that is critical for them to learn and remember.²⁰

ChEI (donepezil, rivastigmine, and galantamine) inhibit the enzyme responsible for degrading ACh, acetylcholinesterase, to promote higher ACh levels and improve the brain's cholinergic function.^{6,7} All three FDA-approved medications are equally effective, and more effective than placebo on the Alzheimer Disease Assessment Scale–Cognitive Subscale. Mild-modest

functional improvements tend to last for six months to a year, improving quality of life and briefly allowing continued independence. Most medications in this class are well-tolerated, with dose-related adverse effects (nausea, vomiting, diarrhea, anorexia, weight loss).⁷

Donepezil, a long-acting reversible ChEI, is indicated for mild, moderate, and severe AD. Donepezil is available as immediate release tablets in 5 mg, 10 mg, and 23 mg, and orally-disintegrating tablets (ODTs) in 5 mg and 10 mg. The labeling recommends 5 mg to 10 mg once daily dosages for patients with mild-moderate AD; patients with moderate-severe AD may need 10 mg or 23 mg once daily. All patients should start treatment with 5 mg daily and titrate upward. In addition to the common adverse effects associated with all ChEI, donepezil is associated with muscle cramping.^{7,22}

Galantamine (Razadyne), a reversible competitive ChEI, is indicated only for mild to moderate AD. Oral immediate release formulations are available as 4 mg, 8 mg, and 12 mg tablets, and 4 mg/mL oral solution. Oral extended release formulations are available as 8 mg, 16 mg, and 24 mg capsules. Immediate release galantamine is recommended to be dosed twice daily with morning and evening meals; extended release galantamine should be administered with the morning meal. Patients generally start with 4 mg twice a day, which may be titrated up as needed by 4 mg twice per day after a minimum of four weeks. The recommended starting dose of extended release galantamine is 8 mg daily. Clinicians may titrate the dose by 8 mg once daily after a minimum of four weeks. If therapy is interrupted for more than 3 days the patient should be restarted at the recommended starting dose and re-titrated up.²³

Rivastigmine (Exelon) is a pseudoreversible ChEI indicated for mild to moderate AD and mild to moderate dementia associated with Parkinson's disease. Rivastigmine's effects tend to diminish as the disease process advances and fewer cholinergic neurons remain functionally intact. Orally available formulations (1.5 mg, 3 mg, 4.5 mg, 6 mg capsules; 2 mg/mL oral solution) should be taken with morning and evening meals in divided doses. Rivastigmine is available as a transdermal patch (4.6 mg, 9.5 mg, 13.3 mg) that should be replaced every 24 hours.^{24,25}

Recommended initial oral dosing of rivastigmine for AD is 1.5 mg twice daily, increased by 1.5 mg per dose no sooner than every two weeks. The maximum oral dose is 12 mg daily. When using the patch, patients should start with one 4.6 mg patch/24 hours. Clinicians may increase the dose to 9.5 mg after a minimum of four weeks if necessary, followed by titration to 13.3 mg after a minimum of four weeks. If dosing is interrupted for more than three days, treatment must be restarted at the lowest patch dose and re-titrated up.^{24,25}

NMDA antagonists

Glutamate, an excitatory neurotransmitter, may sometimes act as an endogenous neurotoxin. Evidence indicates that the glutamatergic system is involved in dementia's pathophysiology. Glutamatergic overstimulation causes calcium overload, mitochondrial dysfunction, and increased nitric oxide production. These changes produce high levels of oxidants and cause neuronal apoptosis (cell death). NMDA receptor antagonists block overstimulation of glutamate-mediated excitotoxicity.

The FDA approved memantine (Namenda) in 2003 to be used alone or with ChEI for moderate to severe AD.^{6,7} Memantine's proposed mechanism of action is to bind preferentially to the NMDA receptor-operated cation channels. No evidence that memantine prevents or slows neurodegeneration in patients with AD exists, but clinically, some patients' symptoms improve temporarily.²⁶ Memantine is orally available as an immediate release tablet of 5 mg or 10 mg, an immediate release 2 mg/mL oral solution, and as an extended release capsule of 7 mg, 14 mg, 21 mg, or 28 mg. The recommended starting dose of immediate release formulations is 5 mg daily, increased in 5 mg increments no sooner than weekly. The recommended effective dose is 20 mg. The oral solution should not be mixed with any other oral liquid and should only be administered with the device provided by the manufacturer. Patients stable on immediate release memantine can be transitioned to extended release capsules. Caregivers can open capsules and sprinkle the contents on food to ease administration. Major side effects include dizziness, headache, confusion, and constipation.^{26,27}

Combination therapy

In practice, memantine is either prescribed alone or added to a ChEI. Memantine and donepezil are available as a combination product (Namzaric) indicated for treatment of moderate to severe AD with 10 mg of donepezil and 7 mg, 14 mg, 21 mg or 28 mg of memantine. Here too, caregivers can sprinkle the capsule's contents on applesauce to ease administration. The recommended starting dose is one 10 mg/7 mg capsule taken every evening. Clinicians should titrate the dose upward by 7 mg memantine at a time after a minimum of 7 days until the patient reaches the target maintenance dose of 10 mg/28 mg. However, patients who were already taking memantine before switching to the combination product may begin at the maintenance dose. The most common adverse events are diarrhea, vomiting, nausea, anorexia, and ecchymosis (bruising).²⁸

Pause and Ponder:

How would you answer the question, "Is combination therapy superior to single drug therapy in dementia?"



IMPLICATIONS IN THE PHARMACY

Researchers estimate that a new patient is diagnosed with AD every 68 seconds in the U.S. As life expectancy increases and the Baby Boomer generation ages, the number of patients at risk for AD increases.^{14,36} Pharmacy employees will see many more patients with dementia in the future.

Identifying Appropriate Patients for Treatment

Although pharmacists don't diagnose, knowing the patient's specific diagnosis and stage (mild, moderate, and severe) is essential.

- Based upon guidelines published by the National Institute on Aging-Alzheimer's Association, MCI does not need pharmacologic treatment.^{19,20}
- Guidelines recommend ChEI for mild to moderate dementia.
- Donepezil is the only ChEI that is specifically labeled for treatment of severe dementia.
- NDMA antagonists are recommended for treatment of mild to moderate dementia.^{6,7,22}

Once patients begin taking medication for dementia, clinicians need to assess whether the medication is working. This is particularly complex with dementia patients because they lack the insight and judgment to assess their own symptoms. Ideally, they should assess these patients every three months or more often. Treatment's goal is to maximize quality of life and function, so caregiver/informants will need to work with clinicians to identify key concerns and develop monitoring plans. Often, the patient's demeanor and anxiety are measurable symptoms. Caregivers/informants may report that after medication starts, the patient is calmer and less anxious or less angry, or is able to nap during the day.

One area where many prescribers and families experience difficulty is deciding when to stop pharmacologic treatment. Unfortunately, we have little clinical trial data to rely on when we need to make these decisions. Various professional guidelines, textbooks, and disciplines have interpreted the limited findings in entirely different ways.³⁷ A recent randomized controlled trial in institutionalized patients with moderate-to-severe AD—the only double-blind randomized controlled trial to date on this topic—found no convincing differences between patients who continued or discontinued ChEI treatment.³⁸

Lacking direction from reliable sources, clinicians use various methods to decide if treatment should continue. With no formula to make these decisions, each decision must reflect the individual patient. Tools include mental status assessments, patient self-report, and caregivers' observations. Most clinicians, recognizing that ChEI may provide benefit for six months to a year, continue the drugs if the patient seems to tolerate the medication well and can afford it, and is deriving benefit. If

Amyloid-directed Immunotherapy

The FDA has not approved any new drugs for AD treatment since 2013. Currently available therapies are only symptomatic treatments, with no effects on neuropathological disease process. Researchers are now actively pursuing etiology-based treatments to stop or delay dementia progression. Major categories in drug development target secretase modulation, amyloid binding, and hyperphosphorylation of tau protein.^{6,29,30}

Aducanumab, an amyloid binder, works using microglia-mediated clearance. Phase 3 clinical trials are examining passive immunotherapy against A β peptides. Aducanumab selectively targets aggregated A β . Study results show that intravenous aducanumab infusions to patients with preclinical or mild AD reduced brain A β in a dose- and time-dependent manner and slowed clinical decline.^{31,32}

Several anti-A β drugs recently failed clinical trials in late-stage disease, suggesting that earlier intervention in the disease course would be more successful.³⁰ Anti-A β monoclonal antibodies are now being tested in preclinical AD to evaluate delay of disease progression. Solanezumab failed to produce clinically significant slowing of cognitive decline in AD patients in phase 3 trials. Further studies are currently in progress evaluating this biologic in patients with preclinical AD.³³

A β binds within a signaling cascade to cellular prion protein on the neuronal cell surface, activating intracellular Fyn kinase to mediate synaptotoxicity. Both *in vitro* and human studies have shown the relationship of Fyn kinase in the pathophysiology of AD. Researchers are studying saracatinib, a Fyn kinase inhibitor, for mild to moderate AD.^{34,35}

The preclinical patient population, patients at risk for AD development, may benefit most from etiology-based therapies.³¹

caregivers report that patients are developing hallucinations, asking questions repetitively, wandering or getting lost, are increasingly delusional or agitated, it's likely that the medication is no longer working.^{7,22} If the patient's symptoms become noticeably more pronounced as the medication is tapered, the medication may still be working, and some experts recommend restarting the medication. Sometimes, clinicians and family members do not stop these medications until a patient enters palliative care. Good advice comes from a recent systematic review of various recommendation: "None of this would be a substitute for eliciting patient and family values and preferences for care, or for having a thoughtful discussion about the risks of and realistic expectations for treatment."³⁹ Regardless, all of these medications should be discontinued gradually and one at a time.

Other factors are also important and can be identified and addressed at the pharmacy. For example, pharmacists can urge prescribers to consider patients' pill burden and discontinue medication if they experience no benefit. Many patients who have dementia develop dysphagia (swallowing difficulties) or become combative at medication administration times. For these patients, alternative dosage routes including patches and liquids can be extremely helpful.^{4,5} Pharmacy staff should also recommend local and national Patient Access Programs if cost is a problem.

PATIENT COUNSELING

Counseling any patient about any condition can be challenging, and pharmacy staff need to assess the patient's ability to understand and the best way to provide information quickly. A diagnosis of dementia introduces a different dynamic for counseling. Families/caregivers are often troubled and overwhelmed, and patients' ability to understand is a moving target. Here too, knowing the patient's dementia stage is helpful. Pharmacists must adapt with their patients. Recognizing increasing cognitive changes and making adjustments during counseling sessions will allow patients to voice their concerns and receive answers.^{40,41}

Patients in the early stages of dementia are usually able to make medical and clinical decisions and need to be included as active partners in their care. Patients with more advanced stages of disease may have designated decision-makers/caregivers with whom discussions should be held.

The sidebar provides counseling tips for dealing with patients who have dementia.

Communicating with Dementia Patients

Many patients will have trouble with word-finding.

- Notice patients' unique words and gestures; patients who have dementia (especially of the AD type) often make up words or rely on gestures to convey their points.
- Family members and caregivers may be valuable resources as they have more experience communicating with and interpreting the patient.

Make it a point to attract and keep the patient's attention.

- Reduce background noise and distracters so that patients can focus on the interaction.
- Approach patients from the front, identify all people present, and address patients respectfully by their name.
- Using a patient's name often will help him or her focus and concentrate.
- Maintain eye contact with patients to monitor facial expressions and body language.

Dementia patients may be overcome with bouts of unpredictable anger, frustration, agitation, or lack of concentration.

- Actively monitor patients for behavioral change and redirect their attention if necessary.
- Give patients ample time to concentrate, comprehend, and respond. Use pauses of four to five seconds for processing and up to a minute for patients to produce a response.
- Do not make patients feel rushed, and let them know that they should take their time.

Speak naturally, avoid speaking very loudly or too quickly.

- Use simple words and positive language. For example, instead of saying, "Let's not discuss your medication regimen here by the register. It's too loud." Say, "Let's step into the counseling room where it's quieter."
- Ask one question at a time and use one-step directions. For example, instead of saying, "How are you doing on this medication? Have you had any side effects?" say, "Tell me about your medicine."
- Redirect patients positively, rather than using negative language. For example, saying "No, you should not take your medication at bedtime," say, "It would be better to take your medication in the morning."
- Rephrase rather than repeat when a patient has misunderstood or is confused. For example, if the patient seems not to understand when you say "It would be better to take your medication in the morning," rephrase it and say, "What I'm saying is, try taking this medication in the morning when you take your other medicine."

Consider rescheduling discussion and have family members or caregivers join in the decision making if necessary.⁴¹

Many primary care providers have little training related to diagnosis and management of dementia, yet most patients who are developing dementia seek care from their primary care providers. Lack of knowledge about AD is associated with missed or delayed diagnoses and treatment. And, patients/caregivers may not be given much information at diagnosis and may not know what questions they should ask. As the reality of the diagnosis sets in, many patients turn to the Internet for answers. However, the sheer amount of information available online can be overwhelming, and some of it is incorrect. Pharmacists and pharmacy technicians in all settings can answer questions and help patients and their caregivers find information that is easier to process. A list of reliable Internet sources of information appears to the right.

Pharmacists can provide recommendations for creating safe environments and suggest techniques for management of progressive dementia (such as memory aids, written instructions for performing tasks, creating reminders), improving quality of life. The Alzheimer's Association offers excellent resources that describe safety measures.⁴²

Patients who have dementias are at elevated risk of adverse drug reactions (ADRs) for several reasons. Most of them are elderly and may have comorbidities that result in polypharmacy or polymedicine (the rational use of two or more medications for the same diagnosis). In addition, they experience age-related pharmacokinetic and pharmacodynamic changes. Although poor adherence is a concern in many older patients, in patients who have dementia, cognitive impairment and behavioral

changes compound the risk.⁴³ Patients who have dementia may also see several practitioners and specialists; pharmacists must monitor drug regimens, identify drug-drug interactions (DDIs; see **Table 3**) and contraindications.

CONCLUSION

Pharmacists and pharmacy technicians should stay up to date about developments in treatment/management and clinical trials for dementia, and encourage appropriate patients to enroll in clinical trials.⁴⁴

ADDITIONAL RESOURCES

Alzheimer's Association

www.alz.org

- Provides detailed education and awareness information, coping tips, and latest news and research

Alzheimer's Disease Education and Referral Center

www.nia.nih.gov/alzheimers

- Run by the National Institutes of Health, this site provides the latest AD research and news

Alzheimer's Foundation of America

www.alzfdn.org

- Has a toll-free hotline to answer questions and provide information on social services, advocacy, and grants

Alzheimer's Association

TrialMatch

https://www.alz.org/research/clinical_trials/find_clinical_trials_trialmatch.asp

Table 3. Drug-drug Interactions of Concern in the Dementia Patient

Drug or drug class	Notes for Pharmacy Staff
Acetylcholinesterase inhibitors	<ul style="list-style-type: none"> ● Donepezil and galantamine are metabolized using CYP2D6 and CYP3A4; metabolism may be affected by specific substrates, inhibitors, or enhancers ● Studies of drug interactions with AChI produced mixed results; clinicians should monitor patients closely, especially if the patient has renal or hepatic impairment ● May decrease the effectiveness of drugs having anticholinergic action such as antipsychotics, antidepressants, antihistamines, bronchodilators, and drugs for urinary incontinence
Memantine	<ul style="list-style-type: none"> ● Memantine is a weak base; dietary habits that alter urine pH may increase or decrease excretion ● Reduced renal function may increase memantine levels ● Coadministration with drugs using the same transport system (cimetidine, ranitidine, procainamide, quinidine, quinine, and nicotine) may increase memantine levels ● Coadministration may reduce serum hydrochlorothiazide levels ● Monitor patients taking warfarin for possible increases in international normalized ratio or prothrombin time ● Concurrent administration with amantadine, ketamine or dextromethorphan may cause pharmacotoxic psychosis

Source: Reference 43

REFERENCES

1. Wick JY, Zanni GR. Differentiating dementias in long-term care patients. *Consult Pharm*. 2007;22(1):14-28.
2. Cotter VT, Karlawish JHT, Clar CM. Dementia. In: Forciea MA, Schwab EP, Raziano DB, Lavizzo-Mourey R, eds. *Geriatric Secrets*, 3rd ed. Philadelphia, PA: Hanley & Belfus; 2004:47-54.
3. De Lane AP. Sponsored post: If it's not Alzheimer's, what type of dementia is it? 5 common types of dementia. *Orlando Sentinel*. May 5, 2017.
<http://proquest.com.library.access.arlingtonva.us/docview/1901730047?accountid=46215>. Accessed January 11, 2018.
4. Differentiating dementias. In *Brief for Clinical Professionals*.
7. https://www.alz.org/health-care-professionals/documents/InBrief_Issue7_Final.pdf. Accessed January 11, 2018.
5. Kendler KS, Freedman R, Blazer DG, et al. *Diagnostic and statistical manual of mental disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
6. Mendiola-Precoma J, Berumen LC, Padilla K, Garcia-Alcocer G. Therapies for prevention and treatment of Alzheimer's disease. *Biomed Res Int*. 2016;2016:2589276.
7. Schneider LS. Alzheimer disease pharmacologic treatment and treatment research. *Continuum*. 2013;9(2):339-357.
8. Alzheimer's Association. Vascular dementia. Available at <https://www.alz.org/dementia/vascular-dementia-symptoms.asp>. Accessed January 15, 2018.
9. Alzheimers.net website. What is frontal lobe dementia? Available at <https://www.alzheimers.net/frontal-lobe-dementia/>. Updated 2017. Accessed January 16, 2018.
10. The Mayo Clinic. Parkinson's disease [July 7, 2015. Available at https://www.mayoclinic.org/diseases-conditions/parkinsons-disease/symptoms-causes/syc-20376055](https://www.mayoclinic.org/diseases-conditions/parkinsons-disease/symptoms-causes/syc-20376055). Accessed January 16, 2018.
11. Alzheimer's Association. Dementia with Lewy Bodies. Available at <https://www.alz.org/dementia/dementia-with-lewy-bodies-symptoms.asp>. Accessed January 16, 2018.
12. National Center for Health Statistics: Alzheimer's Disease. Centers for Disease Control and Prevention website. Available at <https://www.cdc.gov/nchs/fastats/alzheimers.htm>. Updated October 6, 2016. Accessed January 12, 2018.
13. Alzheimer's Association. 2017 Alzheimer's Disease Facts and Figures. Available at <https://www.alz.org/facts/overview.asp>. Updated 2018. Accessed February 6, 2018.
14. O'Brien JT, Holmes C, Jones M, et al. Clinical practice with anti-dementia drugs: A revised (third) consensus statement from the British Association for Psychopharmacology. *J Psychopharmacol*. 2017;31(2):147-168.
15. Alzheimer's Association. Stages of Alzheimer's. Available at https://www.alz.org/alzheimers_disease_stages_of_alzheimers.asp. Accessed January 15, 2018.
16. The National Institute on Aging. What is Lewy Body Dementia? Available at <https://www.nia.nih.gov/health/what-lewy-body-dementia>. Accessed February 6, 2018.
17. Lewy Body Dementia Association. Treatment. Available at <https://www.lbda.org/content/treatment-options>. Accessed February 6, 2018.
18. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*. 2011;7:263-269.
19. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*. 2011; 7: 270-279.
20. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*. 2011; 7: 280-292.
21. Cherry D, Jones R, Williams B, et al. Alzheimer's Disease Management Guideline: Update 2008. *Alzheimer's & Dementia*. 2011; 7(3): e51-e59.
22. Aricept [package insert]. Woodcliff Lake, NJ: Eisai Co., Ltd; 2012.
23. Razadyne ER and Razadyne [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2013.
24. Exelon [package insert]. East Hanover, NJ: Novartis; 2016.
25. Exelon patch [package insert]. East Hanover, NJ: Novartis; 2016.
26. Namenda [package insert]. Irvine, CA: Allergan; 2016.
27. Namenda XR [package insert]. Irvine, CA: Allergan; 2010.
28. Namzaric [package insert]. Irvine, CA: Allergan; 2016.
29. Folch J, Petrov D, Ettcheto M, et al. Current research therapeutic strategies for Alzheimer's Disease treatment. *Neural Plast*. 2016;2016: 501693.
30. Panza F, Seripa D, Lozupone M, et al. The potential of solanezumab and gantenerumab to prevent Alzheimer's disease in people with inherited mutations that cause its early onset. *Expert Opinion on Biological Therapy*. 2018;18(1): 25-35.
31. Sevignyl J, Chialo P, Bussiere T, et al. The antibody aducanumab reduces A β plaques in Alzheimer's disease. *Nature*. 2016; 537: 50-58.
32. Hung S, Fu W. Drug candidates in clinical trials for Alzheimer's disease. *Journal of Biomedical Engineering*. 2017;24(47).
33. Sullivan MG. Antimyloid solanezumab fails to slow decline in mild AD. *Family Practice News*. 2016; 40(20): 3-4.

34. Folch J, Petrov D, Ettcheto M, et al. Current research therapeutic strategies for Alzheimer's disease treatment. *Neural Plasticity*. 2016; 2016(8501693).
35. Nygaard et al. A phase Ib multiple ascending dose study of the safety, tolerability, and central nervous system availability of AZD0530 (saracatinib) in Alzheimer's disease. *Alzheimer's Research & Therapy*. 2015; 7(35).
36. CNN. American generation fast facts. Available at <https://www.cnn.com/2013/11/06/us/baby-boomer-generation-fast-facts/index.html>. Accessed January 29, 2017.
37. Renn BN, Asghar-Ali AA, Thielke S, et al. A systematic review of practice guidelines and recommendations for discontinuation of cholinesterase inhibitors in dementia. *Am J Geriatr Psychiatry*. 2018;26(2):134-147.
38. Herrmann N, O'Regan J, Ruthirakuhan M, et al: A randomized placebo-controlled discontinuation study of cholinesterase inhibitors in institutionalized patients with moderate to severe Alzheimer disease. *J Am Med Dir Assoc*. 2016;17:142-147.
39. Renn BN, Asghar-Ali AA, Thielke S, et al. A systematic review of practice guidelines and recommendations for discontinuation of cholinesterase inhibitors in dementia. *Am J Geriatr Psychiatry*. 2018 Feb;26(2):134-147.
40. Terrie YC. The pharmacist's role in the management of Alzheimer's disease. Pharmacy Times website. <http://www.pharmacytimes.com/publications/issue/2007/2007-01/2007-01-6235>. Published January 1, 2007. Accessed January 23, 2018.
41. Wick JY. How to communicate effectively with dementia patients. Available at http://contemporaryclinic.pharmacytimes.com/chronic-care/how-to-communicate-effectively-with-dementia-patients_ Published August 29, 2016. Accessed January 23, 2018.
42. Alzheimer's Association. Home safety and Alzheimer's. Available at <https://www.alz.org/care/alzheimers-dementia-home-safety.asp>. Accessed January 24, 2018.
43. Pasqualetti G, Tognini S, Calsolaro V, Polini A, Monzani F. Potential drug-drug interactions in Alzheimer patients with behavioral symptoms. *Clin Interv Aging*. 2015;10:1457-466.
44. Alzheimer's Association. Alzheimer's Association Trial Match. Available at https://www.alz.org/research/clinical_trials/find_clinical_trials_trialmatch.asp. Accessed January 23, 2018.