Chapter 53: Alzheimer Disease

INTRODUCTION

- *Alzheimer disease* (AD) affects ~7.5 million Americans of all ages and is a progressive illness of unknown cause characterized by loss of cognitive and physical functioning, commonly with behavior symptoms.

PATHOPHYSIOLOGY

- Dominantly inherited forms of AD are fewer than 1% of cases. More than half of young-onset, dominantly inherited cases are attributed to chromosomal alterations that affect processing of the amyloid precursor protein. Genetic susceptibility to late-onset AD is primarily linked to the apolipoprotein E (*APOE*) genotype, but an interaction of multiple genes with the environment may be at play.
- AD risk factors include age, decreased reserve capacity of the brain, head injury, Down syndrome, depression, mild cognitive impairment, and risk factors for vascular disease, including hypertension, elevated homocysteine, elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, obesity, metabolic syndrome, and diabetes.
- Signature findings include intracellular neurofibrillary tangles (NFTs), extracellular amyloid plaques in the cortex and medial temporal lobe, degeneration of neurons and synapses, and cortical atrophy. AD-affected individuals appear to have a higher burden of plaques and NFTs in their younger years compared to age-matched controls.
- Proposed mechanisms for these changes include: (1) β-amyloid protein aggregation, leading to formation of plaques; (2) hyperphosphorylation of tau protein, leading to NFTs; (3) synaptic failure and depletion of neurotrophin and neurotransmitters; (4) mitochondrial dysfunction; and (5) oxidative stress. The amyloid cascade hypothesis states that there is an imbalance between production and clearance of β-amyloid, with aggregation and accumulation of β-amyloid leading to AD. Whether this is the primary pathology in most forms of AD remains to be shown.
- Of neurotransmitter deficits, loss of cholinergic activity is most prominent, and it correlates with AD severity. Cholinergic cell loss seems to be a consequence of AD pathology, not the cause of it.
- Other neurotransmitter considerations include: (1) serotonergic neurons of the raphe nuclei and noradrenergic cells of the locus ceruleus are lost; (2) monoamine oxidase type B activity is increased; (3) glutamate pathways of the cortex and limbic structures are abnormal; and (4) excitatory neurotransmitters, including glutamate, may be neurotoxic.

CLINICAL PRESENTATION

- Cognitive decline is gradual and includes memory loss, aphasia, apraxia, agnosia, disorientation, and impaired executive function. Other non-cognitive symptoms include depression, psychotic symptoms, aggression, motor hyperactivity, uncooperativeness, wandering, and combativeness. Patients become increasingly unable to care for themselves. **Table 53-1** shows the stages of AD.

TABLE 53-1

Stages of Alzheimer Disease

Mild (MMSE score 26–21)	Patient has difficulty remembering recent events. Ability to manage finances, prepare food, and carry out other household activities declines. May get lost while driving. Begins to withdraw from difficult tasks and to give up hobbies. May deny memory problems.
Moderate (MMSE score 20–10)	Patient requires assistance with activities of daily living. Frequently disoriented with regard to time (date, year, and season). Recall of recent events is severely impaired. May forget some details of past life events and names of family and friends. Functioning may fluctuate from day to day. Patient generally denies problems. May become suspicious or tearful. Loses ability to drive safely. Agitation, paranoia, and delusions are common.
Severe (MMSE score 9–0)	Patient loses ability to speak, walk, and feed self. Incontinent of urine and feces. Requires care 24 hours a day, 7 days a week.

MMSE, Mini-Mental State Examination.

DIAGNOSIS

- The National Institute on Aging and the Alzheimer's Association view AD as a spectrum beginning with an asymptomatic preclinical phase progressing to the symptomatic preclinical phase and then to the dementia phase. AD is a clinical diagnosis, based largely on identified symptoms and difficulty with activities of daily living revealed by patient and caregiver interviews.
- Patients with suspected AD should have a history and physical examination with appropriate laboratory tests (serum B_{12}, folate, thyroid panel, blood cell counts, serum electrolytes, and liver function tests), and computed tomography (CT) or magnetic resonance imaging (MRI) may aid diagnosis.
- International guidelines recommend structural imaging (ie, noncontrast enhanced CT or MRI) be performed when evaluating people with suspected dementia to identify structural abnormalities consistent with AD or other pathology, such as brain atrophy, vascular damage, or tumors. To exclude other diagnoses, cerebrospinal fluid analysis or an electroencephalogram can occasionally be justified.
- Obtain information on medication use; alcohol or other substance use; family medical history; and history of trauma, depression, or head injury. Rule out medication use (eg, anticholinergics, sedatives, hypnotics, opioids, antipsychotics, and anticonvulsants) as contributors to dementia symptoms. Rule out medications that could contribute to delirium (eg, digoxin, nonsteroidal anti-inflammatory drugs [NSAIDs], histamine-2 [H_2] receptor antagonists, amiodarone, antihypertensives, and corticosteroids).
- The Folstein Mini-Mental State Examination (MMSE) can help establish a history of deficits in two or more areas of cognition at baseline against which to evaluate change in severity over time. The average expected decline in an untreated patient is 2–4 points per year (**Table 53-1**). Other scales for assessment are also available.
- In the future, improved brain imaging and validated biomarkers of disease will enable a more sophisticated diagnosis with identified cognitive strengths and weaknesses and neuroanatomic localization of deficits.

TREATMENT

- Goals of Treatment: The goal of treatment in AD is to maintain cognitive functioning and activities of daily living as long as possible, with a

secondary goal to treat the psychiatric and behavioral symptoms.

Nonpharmacologic Therapy

- The general approach to nonpharmacologic strategies for cognitive and non-cognitive symptoms of AD is to identify the symptom and causative factors, and adapt the caregiving environment to remedy the situation.
- Sleep disturbances, wandering, urinary incontinence, agitation, and aggression should be managed with behavioral and environmental interventions whenever possible, for example, redirecting the patient's attention and removing stressors and triggers.
- On initial diagnosis, the patient and caregiver should be educated on the course of illness, available treatments, legal decisions, changes in lifestyle that will become necessary, and other quality-of-life issues.
- Primary prevention of AD may include smoking cessation, increasing physical activity, and reducing midlife obesity, hypertension, and diabetes. Also adherence to the Mediterranean Diet or Dietary Approaches to Stop Hypertension (DASH) Diet may reduce the risk of cognitive impairment or decline.

Pharmacologic Therapy of Cognitive Symptoms

- Cholinesterase inhibitors and NMDA-receptor antagonists are indicated for treatment of AD. Current guidelines do not have a specific preference for cholinesterase inhibitor initiation.
- Reasonable expectations of treatment may be a slowed decline in abilities and delayed long-term care placement.
- Dosing regimens should be simplified and patient and caregiver preferences considered in an effort to improve medication adherence and persistence.
- Gaps in treatment may be associated with a loss of benefits when medication is stopped but this is controversial.

Cholinesterase Inhibitors

- **Table 53-2** summarizes dosing of the cholinesterase inhibitors and memantine.
- No comparative trials have assessed the effectiveness of one agent over another. **Donepezil**, **rivastigmine**, and **galantamine** are indicated in mild-to-moderate AD; donepezil is also indicated for severe AD.
- MMSE is practical to use in the clinical setting to measure changes in cognitive function. Successful treatment would show a decline in MMSE sco re of less than 2 points per year.
- The three cholinesterase inhibitors have similar efficacy in mild-to-moderate AD, and duration of benefit lasts 3–24 months. Because of their short half-lives, if rivastigmine or galantamine treatment is interrupted for several days or longer, retitrate starting at the lowest dose. Gradual dose titration over several months improves tolerability. When switching from one agent to another, a washout period is recommended.
- **Table 53-3** lists common side effects and monitoring parameters for the cholinesterase inhibitors. Abrupt discontinuation can cause worsening of cognition and behavior in some patients.

TABLE 53-2

Dosing of Drugs Used for Cognitive Symptoms

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Cholinesterase inhibitors					

Donepezil	Aricept, Aricept ODT	5 mg daily in the evening	5–10 mg daily in mild to moderate AD 10–23 mg daily in moderate to severe AD	No dosage adjustments recommended	Available as: tablet, ODT, oral solution Can be taken with or without food Weight loss associated with 23 mg daily dose
Rivastigmine	Exelon	1.5 mg twice daily (capsule, oral solution) 4.6 mg/day (transdermal patch)	3–6 mg twice a day (capsule, oral solution) 9.5–13.3 mg/day (transdermal patch)	Capsule/oral solution: renal impairment, hepatic impairment, or low body weight (<50 kg [<110 lb]): patients may be able to only tolerate lower doses Transdermal patch: mild to moderate hepatic impairment or low body weight: consider maximum daily dose of 4.6 mg every 24 hours	Available as: capsule, oral solution, transdermal patch Take with meals Also indicated for Parkinson disease dementia Application of multiple transdermal patches at same time associated with hospitalization and death
Galantamine	Razadyne, Razadyne ER	4 mg twice daily (tablet, oral solution) 8 mg daily in the morning (extended-release capsule)	8–12 mg twice a day (tablet, oral solution) 16–24 mg (extended-release capsule)	Moderate renal or hepatic impairment: maximum daily dose of 16 mg Severe renal or hepatic impairment: not recommended	Available as: tablet, oral solution, extended-release capsule Take with meals
***N*-methyl-D-aspartate (NMDA) receptor antagonist**					
Memantine	Namenda, Namenda XR	5 mg daily (tablet, oral solution) 7 mg daily (extended-release capsule)	10 mg twice daily 28 mg daily (extended-release capsule)	Severe renal impairment: recommended maintenance dose of 5 mg twice daily (tablet, oral solution) or 14 mg daily (extended-release capsule) Severe hepatic impairment: administer with caution	Available as: tablet, oral solution, extended-release capsule Can be taken with or without food Can open capsule and sprinkle contents on applesauce for ease of administration
Cholinesterase inhibitor + NMDA receptor antagonist					

Memantine + donepezil	Namzaric	7 mg/10 mg (if patient is stabilized on donepezil and not currently on memantine) 28 mg/10 mg (if patient is stabilized on memantine and donepezil)	28 mg/10 mg daily	Severe renal impairment: 14 mg/10 mg daily	Available as: memantine extended-release and donepezil capsule Can be taken with or without food Can open capsule and sprinkle contents on applesauce for ease of administration

ODT, orally disintegrating tablet.

TABLE 53-3

Monitoring Drug Therapy for Cognitive Symptoms

Drug	Adverse Drug Reaction	Monitoring Parameters	Comments
Galantamine	Serious skin reactions (Stevens–Johnson syndrome and acute generalized exanthematous pustulosis)	Appearance of skin rash	Discontinue galantamine at first sign of skin rash, unless clearly not drug related If signs/symptoms are suggestive of a serious reaction, consider alternative treatment and do not rechallenge
Rivastigmine	Allergic dermatitis	Application site reaction spread beyond patch size, evidence of a more intense local reaction (increasing erythema, edema, papules, vesicles), and persistence of symptoms for more than 48 hours after patch removal	Discontinue rivastigmine if evidence of disseminated allergic dermatitis appears Patients sensitized by exposure to the transdermal patch may not be able to take rivastigmine by mouth either; allergy testing and close medical supervision recommended
Cholinesterase inhibitors	Dizziness, syncope, bradycardia, atrial arrhythmias, sinoatrial and atrioventricular block, myocardial infarction	Report of dizziness or falls, pulse, blood pressure, and postural blood pressure change	Dizziness is usually mild, transient, and not related to cardiovascular problems Routine pulse checks at baseline, monthly during titration, and every 6 months thereafter
	Nausea, vomiting, diarrhea, anorexia, weight loss	Weight and GI complaints	Take with food to decrease GI upset Usually transient, dose-related GI adverse effects seen with drug initiation, dosage titration, or drug switch Debilitated patients or those weighing <55 kg (<121 lb) may be more likely to experience GI adverse effects and significant weight loss, particularly when rivastigmine is prescribed or

			when titrating to donepezil 23 mg GI adverse effects less prominent with transdermal versus oral rivastigmine
	Peptic ulcer disease, GI bleeding	Signs or symptoms of active or occult GI bleeding	Of particular concern for patients at increased risk of developing ulcers, such as those with a history of ulcer disease or concurrently taking NSAIDs
	Insomnia, vivid/abnormal dreams, nightmares	Complaints of sleep disturbances, daytime drowsiness	Donepezil can be taken in the morning to decrease risk of sleep disturbances
Memantine	Headache, confusion, dizziness, hallucinations	Report of dizziness or falls, hallucinations	Confusion may be observed during dose titration and is usually transient
	Constipation	GI complaints	Memantine may mitigate GI adverse effects associated with cholinesterase inhibitor therapy

GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.

N-Methyl-D-Aspartate (NMDA) Receptor Antagonist

- **Memantine** (Namenda) blocks glutamatergic neurotransmission by antagonizing NMDA receptors, which may prevent excitotoxic reactions. It is used as monotherapy and in combination with a cholinesterase inhibitor. It is indicated for treatment of moderate to severe AD, but not for mild AD. It is not metabolized by the liver and is primarily excreted unchanged in the urine. Dosing must be adjusted in patients with renal impairment. It is usually well tolerated; side effects include constipation, confusion, dizziness, and headache (**Table 53-3**).
- Combination therapy with cholinesterase inhibitors and memantine, individually or as **Namzaric**, is generally prescribed for people with moderate-to-severe AD and has been shown to slow cognitive and functional decline to a statistically significant degree compared to cholinesterase inhibitor monotherapy or no treatment. Memantine may help mitigate some of the GI adverse effects seen with cholinesterase inhibitors.

Other Drugs

- Use of estrogen, NSAIDS, prednisone, statins, or ginkgo biloba is not recommended to prevent or treat dementia.
- Vitamin E is under investigation for prevention of AD and is not recommended for treatment of AD.
- Do not use ginkgo biloba in individuals taking anticoagulants or antiplatelet drugs, and use cautiously in those taking NSAIDs.
- There is currently insufficient evidence to recommend medical foods such as Axona, Souvenaid, and Cerefolin NAC for treatment of AD.

Pharmacologic Therapy of Noncognitive Symptoms

- No drug is FDA approved for the treatment of AD behavioral and psychological symptoms such as psychotic symptoms, inappropriate or disruptive behavior, and depression.

- General guidelines include: (1) starting with reduced doses and titrating slowly; (2) monitoring closely; (3) periodically attempting to taper and discontinue medication; and (4) careful documentation.
- Some evidence supports that cholinesterase inhibitors and memantine may be beneficial in treating non-cognitive symptoms, but they do not reduce acute agitation. Avoid anticholinergic psychotropic medications as they may worsen cognition.

Antidepressants

- Depression and dementia share many symptoms, and the diagnosis of depression can be difficult, especially later in the course of AD.
- A **selective serotonin reuptake inhibitor** (SSRI) is usually given to depressed patients with AD, and the best evidence is for **sertraline** and **citalopram**. **Tricyclic antidepressants** are usually avoided.

  ✔ Common side effects seen with SSRIs can be found in Chapter 68.

Antipsychotics

- Antipsychotic medications have traditionally been used for disruptive behaviors and neuropsychiatric symptoms, but the risks and benefits must be carefully weighed.
- Atypical antipsychotics (ie, **aripiprazole**, **risperidone**, **olanzapine**, and **quetiapine**) have been shown to be more effective compared to placebo; however, the higher risk of adverse effects and mortality offset this benefit. Antipsychotics in AD should be restricted to patients with severe symptoms that have not responded to other measures, and treatment should be tapered as early as possible and rarely used beyond 12 weeks.

  ✔ Common adverse events include somnolence, extrapyramidal symptoms, abnormal gait, worsening cognition, cerebrovascular events, and increased risk of death (see black-box warning). See Chapter 70 for more information.

Miscellaneous Therapies

- Evidence for benzodiazepine use is lacking and not advised due to significant adverse effects.
- Use of antiepileptic medication (ie, carbamazepine and gabapentin) may be alternatives for agitation, but evidence is conflicting. Use of valproic acid is no longer recommended due to severe adverse effects.

EVALUATION OF THERAPEUTIC OUTCOMES

- At baseline interview both patient and caregiver to identify target symptoms; define therapeutic goals; and document cognitive status, physical status, functional performance, mood, thought processes, and behavior.
- Use the MMSE for cognition, Bristol Activities of Daily Living Scale for activities of daily living, and Neuropsychiatric Inventory Questionnaire for assessment of behavioral disturbances to quantify changes in symptoms and functioning.
- Observe the patient carefully for potential side effects. The specific side effects to be monitored and the method and frequency of monitoring should be documented.
- Assess for drug effectiveness, side effects, adherence to regimen, and need for dosage adjustment or change in treatment at 2–4 weeks, and 8–12 weeks after initiation, followed by every 3–6 months thereafter. Several months to 1 year of treatment may be required to determine whether medications for cognition are beneficial.
- Drug deprescribing for people with AD is aided by the availability of deprescribing guidelines. When to stop treatment due to lack of efficacy, if ever, is controversial.

See Chapter 71, Alzheimer Disease, authored by Emily P. Peron, Kristin M. Zimmerman, Ericka L Crouse, Patricia W. Slattum, and Sarah E. Hobgood, for

a more detailed discussion of this topic.