ALZHEIMER DISEASE

Alzheimer disease (AD) is characterized by progressive cognitive decline including memory loss, disorientation, and impaired judgment and learning. AD is the most common type of dementia. Various classifications of dementia include dementia of the Alzheimer type, vascular dementia, and dementia due to human immunodeficiency virus (HIV) disease, head trauma, Parkinson disease, Huntington disease, Pick disease, or Creutzfeldt-Jakob disease.

The severity of AD correlates with increasing age and is classified as mild, moderate, or severe. Other risk factors for AD include family history, female gender, and vascular risk factors such as diabetes, hypertension, heart disease, and current smoking.

The etiology of AD is unknown; however, genetic and environmental factors may contribute to errors in protein synthesis resulting in the formation of abnormal proteins involved in pathogenesis.

❖ PATHOPHYSIOLOGY

The exact pathophysiologic mechanism underlying AD is not entirely known. *Pathologic hallmarks of the disease in the brain include neurofibrillary tangles and neuritic plaques (senile plaques) made up of various proteins that result in a shortage of the neurotransmitter acetylcholine (Ach)*. These are primarily located in brain regions involved in learning, memory, and emotional behaviors such as the cerebral cortex, hippocampus, basal forebrain, and amygdala.

-In AD, the plaques and tangles damage Ach pathways, leading to a shortage of Ach, resulting in learning and memory impairment. The loss of Ach activity correlates with the severity of AD. The basis of pharmacologic treatment of AD has been to improve cholinergic neurotransmission in the brain. Blocking acetylcholinesterase, the enzyme that degrades Ach in the synaptic cleft, leads to an increased level of Ach with a goal of stabilizing neurotransmission.

-Glutamate is the primary excitatory neurotransmitter in the central nervous system; it is involved in memory, learning, and neuronal plasticity. In AD, one type of glutamate receptor, *N*-methyl-d-aspartate (NMDA), is less prevalent than normal.

There also appears to be overactivation of unregulated glutamate signaling which leads to neuronal death and an increased production of amyloid precursor protein that is associated with higher rates of plaque development.

-Increased cholesterol concentrations have been associated with AD. The cholesterol increases β-amyloid protein synthesis, which can lead to plaque formation.

-Estrogen appears to have properties that protect against memory loss associated with normal aging. Despite this, a study reported that hormone replacement therapy with either estrogen alone or estrogen plus medroxyprogesterone resulted in negative effects on memory.

❖ CLINICAL PRESENTATION AND DIAGNOSIS

AD is primarily diagnosed by exclusion of other potential causes for dementias. There is no single symptom unique to AD; therefore, diagnosis relies on a thorough patient history and physical examination.

⇨ Signs and Symptoms

•• *Cognitive*: memory loss, problems with language, disorientation to time and place, poor or decreased judgment, problems with learning and abstract thinking, misplacing things

•• *Noncognitive*: Changes in mood or behavior, changes in personality, or loss of initiative

•• *Functional*: Difficulty performing familiar tasks

⇨ Laboratory Tests

•• *MRI or CT* to measure changes in brain size and volume and rule out stroke, brain tumor, or cerebral edema.

•• *Tests to exclude possible causes of dementia*: depression screen, vitamin B12 levels, thyroid function tests (thyroid stimulating hormone and free triiodothyronine and thyroxine), complete blood count, and chemistry panel.

•• Other diagnostic tests to consider for differential diagnosis: erythrocyte sedimentation rate, urinalysis, toxicology, chest x-ray, heavy metal screen, HIV testing, CSF examination, electroencephalography, and neuropsychological tests such as the Folstein Mini Mental State Examination (MMSE) (a 30-point questionnaire used extensively in clinical and research settings to measure cognitive impairment).

❖ TREATMENT

⇨ Desired Outcomes

Treatment is focused on delaying disease progression and preservation of functioning as long as possible. Secondary goals include treating psychiatric and behavioral symptoms that may occur during the course of the disease.

There is no cure for AD; however, drug treatment can slow symptom progression.

There are four agents approved for the treatment of AD, but none are curative or known to directly reverse the disease process.

⇨ General Approach to Treatment

The current gold standard of treatment for cognitive symptoms includes pharmacologic management with a cholinesterase (ChE) inhibitor and/or an NMDA antagonist**.** Donepezil, rivastigmine, and galantamine are three ChEs used for cognitive symptoms. The only NMDA antagonist is memantine. Psychiatric and behavioral symptoms that occur during the course of the disease should be treated as they occur.

⇨ Nonpharmacologic Therapy

••Using a gentle, calm approach to the patient
••Giving reassurance when needed
••Empathizing with the patient's concerns
••Using distraction and redirection
••Maintaining daily routines
••Providing a safe environment
••Providing daytime activities
••Avoiding overstimulation
••Using familiar decorative items in the living area
••Bringing abrupt declines in function and the appearance of new symptoms to professional attention

⇨ Treatment Algorithm for Cognitive Symptoms of AD

1. Patient diagnosed with AD
2. Assess all comorbid medical disorders and drug therapies that may affect cognition
3. Rule out comorbid depression
4. Evaluate for pharmacotherapy based on illness stage

a) Mild AD: Cholinesterase inhibitor

b) Moderate to severe AD: Cholinesterase inhibitor, memantine, or combination cholinesterase inhibitor and memantine

3. Deteriorating MMSE score > 2–4 points after 1 year: Change to a different cholinesterase inhibitor
4. Stable MMSE: Continue regimen

⇨ Pharmacologic Therapy

»» ***Conventional Pharmacologic Treatment for Cognitive Symptoms***

ChE Inhibitors (Donepezil, Rivastigmine, and Galantamine)

The ChE inhibitors are FDA approved for the treatment of AD. Guidelines recommend the use of ChE inhibitors as a valuable treatment for AD and the use of memantine for moderate to severe AD. Treatment should begin as early as possible after diagnosis.

Patients should be switched to another ChE inhibitor from their initial ChE inhibitor if they show an initial lack of efficacy, initially respond but then lose clinical benefit, or experience safety/tolerability issues. This switch should not be attempted until the patient has been on a maximally tolerated dose for 3 to 6 months.
ChE inhibitor therapy should be discontinued in patients who experience poor tolerance or adherence, who do not improve after 6 months at optimal dosing, who fail attempts at monotherapy with at least two agents or combination therapy, who continue to deteriorate at the pretreatment rate, who have dramatic clinical deterioration following initiation of treatment, or who deteriorate to the point where there is no significant effect on quality of life. Patients with a MMSE score less than 10 may also benefit from discontinuation of medication.

Donepezil
Donepezil is a piperidine ChE inhibitor that reversibly and noncompetitively inhibits centrally active acetylcholinesterase. A dose of 10 mg/day has demonstrated efficacy in patients with either mild to moderate or moderate to severe forms of AD.
The most frequent adverse effects are mild to moderate gastrointestinal symptoms.

Rivastigmine
Rivastigmine, approved for the treatment of mild to moderate AD, has central activity for both acetylcholinesterase and butyrylcholinesterase. The dual inhibition of acetylcholinesterase and butyrylcholinesterase may lead to broader efficacy.
Rivastigmine is available as an oral formulation and as a patch. When switching from the oral formulation to the patch, if the patient is taking less than 6 mg/day orally, the 4.6 mg/24 hour patch is recommended. The first patch should be applied on the day following the last oral dose.
Cholinergic side effects are common, but they are usually well tolerated if the recommended dosing schedule is followed.

Galantamine
Galantamine, approved for the treatment of mild to moderate AD, is a ChE inhibitor, which elevates Ach in the cerebral cortex. It also modulates the nicotinic Ach receptors to increase Ach release from surviving presynaptic nerve terminals. It may also increase glutamate and serotonin levels, but whether this brings additional benefit is unknown.

NMDA Receptor Antagonist
Memantine is a noncompetitive antagonist of the NMDA type of glutamate receptors, which are located throughout the brain. It regulates activity throughout the brain by

controlling the amount of calcium that enters the nerve cell, a process essential for establishing an environment required for information storage.

Overstimulation of the NMDA receptor by excessive glutamate allows too much calcium into the cell, disrupting information processing. Blocking NMDA receptors with memantine may protect neurons from the effects of excessive glutamate without disrupting normal neurotransmission.

Memantine is approved to treat moderate to severe AD. It can be given as monotherapy or in combination with ChE inhibitors. Traditional maximum dose is 20 mg/day.

Adverse reactions associated with memantine include constipation, confusion, dizziness, headache, coughing, and hypertension. Closer monitoring should be done if memantine is given concurrently with a ChE inhibitor.

⇨ Treatment of Behavioral Symptoms

Treatment of behavioral symptoms should begin with nonpharmacologic treatments but may also include antipsychotic agents and/or antidepressants. Nonpharmacologic recommendations for treatment include:

•• Music
•• Videotapes of family members
•• Audiotapes of the voices of caregivers
•• Walking and light exercise
•• Sensory stimulation and relaxation

Antipsychotics are frequently used for neuropsychiatric symptoms associated with AD. It is important to individually assess and balance the risk versus benefit of antipsychotic use in this population.

The selective serotonin reuptake inhibitors (SSRIs) are most commonly used based on their side-effect profile and evidence of efficacy. Indications for the use of antidepressants include depression characterized by poor appetite, insomnia, hopelessness, anhedonia, withdrawal, suicidal thoughts, and agitation.

Other miscellaneous therapies for AD include benzodiazepines for anxiety, agitation, and aggression. However, their routine use is not advised. Additionally, benzodiazepines are associated with an increase in falls leading to the potential for hip fractures in the elderly. Mood stabilizer anticonvulsants, carbamazepine, valproic acid, or gabapentin may be used as alternatives, but the current evidence is conflicting. Buspirone has shown benefit in treating agitation and aggression in a limited number of patients with minimal adverse effects. In open-label and controlled studies, selegiline decreased anxiety, depression, and agitation. Finally, trazodone has been shown to decrease insomnia, agitation, and dysphoria, and it has been used to treat sundowning in AD patients.