Alzheimer’s disease (AD)

By

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- Alzheimer's disease (AD) is a progressive dementia affecting cognition, behavior, and functional status with no known cause or cure.

- Patients eventually lose cognitive, analytical, and physical functioning, and the disease is ultimately fatal.

Pathophysiology:

✓The signature findings are intracellular neurofibrillary tangles (NFTs), extracellular neuritic plaques, degeneration of neurons and synapses, and cortical atrophy.

Mechanisms proposed for these changes are:

✓β-Amyloid protein aggregation, leading to formation of plaques.

✓Hyperphosphorylation of tau protein, leading to intracellular NFT development and collapse of microtubules.

✓Inflammatory processes—levels of multiple cytokines and chemokines are elevated in AD brains.

✓ Neurovasculature dysfunction.

✓ Oxidative stress.

✓ Mitochondrial dysfunction.

- Neuritic plaques are lesions found in brain and cerebral vasculature.
- Whether genetic variations promote a primary β-amyloidosis in the majority of AD patients is unresolved.
- Density of NFTs correlates with severity of dementia.

- While there is a variety of neurotransmitter deficits, loss of cholinergic activity is most prominent and correlates with AD severity.

• It is clear that replacement of acetylcholine activity cannot compensate for all the changes that take place in AD.

• Deficits that exist in other pathways are:

✓ Serotonergic neurons of the raphe nuclei and noradrenergic cells of the locus ceruleus are lost.

✓ Monoamine oxidase type B activity is increased.

✓ Glutamate pathways of the cortex and limbic structures are abnormal.

• Excitatory neurotransmitters, including glutamate, have been implicated as potential neurotoxins in AD.

• Risk factors for AD are hypertension, elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, and diabetes.

Stages of Alzheimer's Disease

Mild (MMSE score 26–18)	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 17–10)	Patient requires assistance with activities of daily living. Frequently disoriented with regard to time (date, year, season). Recall for recent events is severely impaired. May forget some details of past life 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.

Clinical Presentation of Alzheimer's Disease

General

The patient may have vague memory complaints initially, or the patient's significant other may report that the patient is "forgetful." Cognitive decline is gradual over the course of illness. Behavioral disturbances may be present in moderate stages. Loss of daily function is common in advanced stages.

Symptoms

Cognitive

- Memory loss (poor recall and losing items)
- Aphasia (circumlocution and anomia)
- Apraxia
- Agnosia
- Disorientation (impaired perception of time and unable to recognize familiar people)
- Impaired executive function

Noncognitive

- Depression, psychotic symptoms (hallucinations and delusions)
- Behavioral disturbances (physical and verbal aggression, motor hyperactivity, uncooperativeness, wandering, repetitive mannerisms and activities, and combativeness)

Functional

- Inability to care for self (dressing, bathing, toileting, and eating)

Laboratory tests

- Rule out vitamin B_{12} and folate deficiency
- Rule out hypothyroidism with thyroid function tests
- Blood cell counts, serum electrolytes, liver function tests

Other diagnostic tests

- CT or MRI scans may aid diagnosis

DIAGNOSIS:

Patients with suspected AD should have a history and physical examination with appropriate laboratory and other diagnostic tests, neurologic and psychiatric examinations, standardized rating assessments, functional evaluation, and a caregiver interview.

• Information about prescription drug use; alcohol or other substance use; family medical history; and history of trauma, depression, or head injury should be obtained. It is important to rule out medication use as a contributor or cause of symptoms (e.g., anticholinergics, sedatives, hypnotics, opioids, antipsychotics, and anticonvulsants) as contributors to dementia symptoms. Other medications may contribute to delirium, e.g., digoxin, nonsteroidal anti-inflammatory drugs, histamine receptor antagonists, amiodarone, antihypertensive, and corticosteroids.

• The Folstein Mini-Mental State Examination (MMSE) can help to establish a history of deficits in two or more areas of cognition and establish a baseline against which to evaluate change in severity. The average expected decline in an untreated patient is 2 to 4 points per year.

DESIRED OUTCOME

- The primary goal of treatment in AD is to maintain patient functioning as long as possible.

Secondary goals are to treat the psychiatric and behavioral sequelae.

TREATMENT:

NONPHARMACOLOGIC THERAPY:

- Sleep disturbances, wandering, urinary incontinence, agitation, and aggression should be managed with behavioral interventions whenever possible.

- On initial diagnosis, the patient and caregiver should be educated on the course of illness, available treatments, legal decisions, changes in lifestyle that will be necessary with disease progression, and other quality of life issues.

The Alzheimer's Association recommends staying physically, mentally, and socially active, adopting a low-fat/low-cholesterol diet rich in dark vegetables and fruit, and managing body weight.

PHARMACOTHERAPY OF COGNITIVE SYMPTOMS:

- Managing blood pressure, cholesterol, and blood sugar may reduce the risk of developing AD and may prevent the worsening of dementia in patients with AD.

- Successful treatment reflects a decline of less than 2 points each year on the MMSE score.

- **Cholinesterase Inhibitors:** No direct comparative trials have assessed the effectiveness of one agent over another. Donepezil, rivastigmine, and galantamine are indicated in mild to moderate AD, while donepezil is also indicated in severe AD.

- If the decline in MMSE score is more than 2 to 4 points after treatment for 1 year with the initial agent, it is reasonable to change to a different cholinesterase inhibitor. Otherwise, treatment should be continued with the initial medication throughout the course of the illness.

- **Donepezil (Aricept)** is a piperidine derivative with specificity for inhibition of acetylcholinesterase rather than butyrylcholinesterase.

- **Rivastigmine** has central activity at acetylcholinesterase and butyrylcholinesterase sites, but low activity at these sites in the periphery.

- **Galantamine** is a cholinesterase inhibitor that also has activity as a nicotinic receptor agonist.

- **Tacrine** was the first cholinesterase inhibitor approved for the treatment of AD, but it has been replaced by safer drugs which are better tolerated.

Clinical Pharmacology of the Cholinesterase Inhibitors

	Donepezil	**Rivastigmine**	**Galantamine**
Brand name	Aricept	Exelon	Razadyne
Dosage forms	Tablet Orally disintegrating tablet	Capsule Oral solution Patch	Tablet Oral solution Extended-release (ER) capsule
Starting dose	5 mg daily at bedtime	1.5 mg twice a day 4.6 mg/day (patch)	4 mg twice a day (8 mg daily for ER)
Maintenance dose	5–10 mg daily	3–6 mg twice a day 9.5 mg/day (patch)	8–12 mg twice a day (16–24 mg daily for ER)
Meals	No effect of food	Take with food	Take with food
Half-life	70 hours	1.5 hours	7 hours
Protein binding	96%	40%	18%
Metabolism	Substrate (minor) of CYP2D6 and 3A4 Glucuronidation	Cholinesterase-mediated hydrolysis –	Substrate (minor) of CYP2D6 and 3A4 Glucuronidation
Renal elimination	Yes	Major pathway	Yes

Other Drugs:

Memantine (Namenda) blocks glutamatergic neurotransmission by antagonizing N -methyl- D -aspartate receptors, which may prevent excitotoxic reactions.

- It is used as monotherapy, and data suggest that when it is combined with a cholinesterase inhibitor, there is improvement in cognition and activities of daily living.

✓It is indicated for treatment of moderate to severe AD.

✓It is not metabolized by the liver, but is primarily excreted unchanged in the urine (half-life of elimination = 60 to 80 hours).

✓It is usually well tolerated, and side effects include constipation, confusion, dizziness, hallucinations, headache, cough, and hypertension.

✓It is initiated at 5 mg/day and increased weekly by 5 mg/day to the effective dose of 10 mg twice daily. Dosing must be adjusted in patients with renal impairment.

❑ Because of a significant incidence of side effects and a lack of compelling evidence, Nonsteroidal anti-inflammatory drugs are not recommended for treatment or prevention of AD.

• There is interest in the use of lipid-lowering agents, especially the 3- hydroxy-3-methylglutaryl coenzyme A–reductase inhibitors, to prevent AD. Pravastatin and lovastatin, but not simvastatin, were associated with a lower prevalence of AD. Further study is needed before these agents can be recommended for this use.

• A metaanalysis indicated that EGb 761 (an extract of ginkgo biloba) may have some therapeutic effect at doses of 120 to 240 mg of the standard leaf extract twice daily. Because of limited efficacy data, the potential for adverse effects (e.g., nausea, vomiting, diarrhea, headache, dizziness, weakness, and hemorrhage), and the poor standardization of herbal products, it is recommended that *ginkgo biloba be used only with caution*.

✓ Ginkgo biloba should not be used in individuals taking anticoagulants or antiplatelet drugs, and should be use cautiously in those taking nonsteroidal anti-inflammatory drugs.

• Although initial studies suggest potential effectiveness of huperzine A, it has not been adequately evaluated for treatment of AD.

PHARMACOTHERAPY OF NONCOGNITIVE SYMPTOMS:

• Pharmacotherapy is aimed at treating psychotic symptoms, inappropriate or disruptive behavior, and depression.

• General guidelines are as follows:

(1) use reduced doses,

(2) monitor closely,

(3) titrate dosage slowly,

(4) document carefully, and

(5) Periodically attempt to reduce medication in minimally symptomatic patients.

• Psychotropic medications with anticholinergic effects should be avoided because they may worsen cognition.

Medications Used for Noncognitive Symptoms of Dementia

Drugs	Starting Dose (mg)	Maintenance Dose in Dementia (mg/day)	Target Symptoms
Antipsychotics			Psychosis: hallucinations, delusions, suspiciousness Disruptive behaviors: agitation, aggression
Haloperidol	0.25	1–3	
Olanzapine	2.5	5–10	
Quetiapine	25	100–300	
Risperidone	0.25	0.75–2	
Ziprasidone	20	40–160	
Antidepressants			Depression: poor appetite, insomnia, hopelessness, anhedonia, withdrawal, suicidal thoughts, agitation, anxiety
Citalopram	10	10–20	
Escitalopram	5	20–40	
Fluoxetine	5	10–40	
Paroxetine	10	10–40	
Sertraline	25	75–100	
Venlafaxine	25	75–225	
Trazodone	25	75–150	
Anticonvulsants			Agitation or aggression
Carbamazepine	100	200–600	
Valproic acid	125	500–1,000	

- Cholinesterase inhibitors and memantine are **first-line therapy** in early management of behavioral symptoms. Modest improvement may be achieved.

- Antipsychotic medications have traditionally been used to treat disruptive behaviors and psychosis in AD patients.
- A metaanalysis showed that 17% to 18% of dementia patients showed a modest treatment response to atypical antipsychotics. Adverse events included somnolence, extrapyramidal symptoms, abnormal gait, worsening cognition, cerebrovascular events, and increased risk of death.

- Depression and dementia have many symptoms in common, and the diagnosis of depression can be difficult, especially later in the course of AD.
- Treatment with a selective serotonin reuptake inhibitor is usually initiated in depressed patients with AD.
- Paroxetine causes more anticholinergic side effects than the other selective serotonin reuptake inhibitors. Venlafaxine may also be used.

- Although probably equally effective, the tricyclic antidepressants are usually avoided because of anticholinergic side effects.

Carbamazepine, mean dose 300 mg/day, may improve psychosis and behavioral disturbance in AD patients.

- Oxazepam and other benzodiazepines have been used to treat anxiety, agitation, and aggression, but they generally show inferior efficacy compared with antipsychotics. They can also worsen cognition, cause disinhibition, and increase the risk of falls.