

Treatment of Parkinson 2

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DRUGS USED IN ALZHEIMER'S DISEASE

Dementia of the Alzheimer type has three distinguishing features:

- 1) Accumulation of senile plaques (β -amyloid accumulations),
- 2) formation of numerous neurofibrillary tangles, and
- 3) loss of cortical neurons, particularly cholinergic neurons.

Current therapies aim to either improve cholinergic transmission within the CNS or prevent excitotoxic actions resulting from overstimulation of NMDA-glutamate receptors in selected areas of the brain. Pharmacologic intervention for Alzheimer's disease is only palliative and provides modest short-term benefit. None of the available therapeutic agents alter the underlying neurodegenerative process.

Disease	Differences from AD	Treatment Notes
Common Irreversible Causes		
MCI	No interference with work or social functions 1 in 5 progress to AD	Eliminate or control risk factors for dementia May use CIs, which reduced risk of progression by 40% in one study
Vascular dementia	Includes focal neurological signs and symptoms Radiologic evidence of stroke Onset within 3–6 mo of stroke Abrupt deterioration followed by stepwise progression	Control of cardiac and vascular risk factors CIs and memantine not effective
Lewy body dementia	Fluctuating cognition with pronounced variation in attention and alertness Recurrent visual hallucinations Motor features of PD	Especially avoid typical antipsychotics, which may worsen motor symptoms May use CIs
Dementia of advanced PD	PD onset predates cognitive impairment Usually at latter stages of PD	Especially avoid typical antipsychotics, which may worsen motor symptoms May use CIs
Frontotemporal dementia	Affects personality, behavior, self-care, and language Onset in ages 45–65 with a 2- to 10-yr course	CIs may worsen behavior and cause agitation SSRIs or trazodone may be beneficial

Reversible Causes		
Vitamin B ₁₂ deficiency	Progressive memory loss Vitamin B ₁₂ serum concentration < 300 pg/mL May be anemic also, but folic acid may disguise the anemia	Replace vitamin B ₁₂ according to standard protocols
Hypothyroidism	Deficient or inadequate replacement of thyroxine	Levothyroxine replacement according to standard protocols
Depression	Trouble concentrating and memory Apathy and “I don’t care” responses	Treatment of depression according to standard protocols
NPH	Triad of progressive memory loss, incontinence, and gait abnormality Symptoms improve after lumbar puncture	Surgical placement of ventricular shunt

AD = Alzheimer disease; CI = cholinesterase inhibitor; MCI = mild cognitive impairment; NPH = normal pressure hydrocephalus; PD = Parkinson disease; SSRI = selective serotonin reuptake inhibitor.

Assessment Tools

1. Folstein MMSE

- a. 30-point scale; higher is better function
- b. Untreated AD: Score usually decreases 3 or 4 points a year.
- c. Heavily relies on verbal and language skills, so less accurate if education is poor

2. SLUMS examination

- a. 30-point scale; higher number is better function
- b. Includes adjustment of scores for lower educational status

3. Montreal Cognitive Assessment

- a. 30-point scale; higher number is better function
- b. Less reliant on verbal or language skills

4. Mini-Cog assessment

- a. 5-point scale; higher number is better function
- b. Easiest to administer; takes 3 minutes

New Diagnostic Guidelines

- 1. Recognizes three phases
 - a. Preclinical, asymptomatic phase
 - b. Symptomatic, predementia phase (MCI)
 - c. Dementia phase

	MMSE (out of 30)	Examples of Cognitive Loss	Examples of Functional Loss
Mild	20–24	Some short-term memory loss; word-finding problems	Loss of IADLs such as laundry, housekeeping, and managing medications; may get lost in familiar places
Moderate	10–19	Disorientation to time and place, inability to engage in activities and conversation	Needs assistance with ADLs such as bathing, dressing, and toileting
Severe	< 10	Loss of speech and ambulation, incontinence of bowel and bladder	Dependency in basic ADLs such as feeding oneself; often needs around-the-clock care

ADLs = activities of daily living; IADLs = instrumental activities of daily living; MMSE = Mini-Mental State Examination.

Drug	Starting Dose	Maintenance Dose	Dosage Forms	Pharmacologic Properties	Comments
Cholinesterase Inhibitors					
Donepezil	5 mg daily	10 mg daily May increase to 23 mg/day	Tablets Orally disintegrating tablets	Acetylcholinesterase inhibitor; metabolized in part by CYP2D6 and CYP3A4 Protein binding 96%	Labeled for mild to moderate and moderate to severe AD
Rivastigmine	1.5 mg twice daily 4.6-mg patch daily	3–6 mg twice daily 9.5-mg patch daily; may increase to 13.3-mg patch daily	Capsules Oral solution Transdermal patch	Acetyl- and butyryl-cholinesterase inhibitor Nausea, vomiting, and diarrhea seem more intense than with other CIs	Labeled for mild to moderate and moderate to severe AD as well as mild to moderate dementia with Parkinson disease Skin reactions with patch
Galantamine	4 mg twice daily	8–12 mg twice daily 8–24 mg ER once daily	Tablets Oral solution ER capsules	Selective competitive, reversible acetylcholinesterase inhibitor and nicotine receptor modulator Metabolized in part by CYP2D6 and CYP3A4	Preferable to administer with food Renal dosing adjustment necessary
Glutamatergic Therapy					
Memantine	5 mg once daily 7 mg ER once daily	10 mg twice daily 28 mg ER once daily	Tablets Oral solution ER capsules	<i>N</i> -methyl-D-aspartate receptor antagonist that blocks glutamate transmission	Labeled for moderate to severe AD; may be used in combination with acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors

Numerous studies have linked the progressive loss of cholinergic neurons and, presumably, cholinergic transmission within the cortex to the memory loss that is a hallmark symptom of Alzheimer's disease. It is postulated that inhibition of acetylcholinesterase (AChE) within the CNS improves cholinergic transmission, at least at those neurons that are still functioning. The reversible AChE inhibitors approved for the treatment of Alzheimer's disease include *donepezil*, *galantamine*, and *rivastigmine*. These agents have some selectivity for AChE in the CNS, as compared to the periphery. *Galantamine* may also augment the action of acetylcholine at nicotinic receptors in the CNS. At best, these compounds may provide a modest reduction in the rate of loss of cognitive functioning in Alzheimer patients. *Rivastigmine* is the only agent approved for the management of dementia associated with Parkinson's disease and also the only AChE inhibitor available as a transdermal formulation. *Rivastigmine* is hydrolyzed by AChE to a carbamate metabolite and has no interactions with drugs that alter the activity of CYP450 enzymes. The other agents are substrates for CYP450 and have a potential for such interactions. Common adverse effects include nausea, diarrhea, vomiting, anorexia, tremors, bradycardia, and muscle cramps.

NMDA receptor antagonist

Stimulation of glutamate receptors in the CNS appears to be critical for the formation of certain memories. However, overstimulation of glutamate receptors, particularly of the NMDA type, may result in excitotoxic effects on neurons and is suggested as a mechanism for neurodegenerative or apoptotic (programmed cell death) processes. Binding of glutamate to the NMDA receptor assists in the opening of an ion channel that allows Ca^{2+} to enter the neuron. Excess intracellular Ca^{2+} can activate a number of processes that ultimately damage neurons and lead to apoptosis. *Memantine* is an NMDA receptor antagonist indicated for moderate-to-severe Alzheimer's disease. It acts by blocking the NMDA receptor and limiting Ca^{2+} influx into the neuron, such that toxic intracellular levels are not achieved. *Memantine* is well tolerated, with few dose-dependent adverse events. Expected adverse effects, such as confusion, agitation, and restlessness, are often indistinguishable from the symptoms of Alzheimer's disease. Given its different mechanism of action and possible neuroprotective effects, *memantine* is often given in combination with an AChE inhibitor.

MULTIPLE SCLEROSIS

Definitions

1. Autoimmune disorder with areas of CNS demyelination and axonal transaction
2. Clinical course
 - a. Clinically isolated syndrome; first clinical presentation for which the criterion of dissemination in time has not been met to diagnose MS
 - b. Classified as relapsing or progressive disease; subclassified according to disease activity and progression: Relapsing-remitting: 85% of patients at diagnosis, develops into progressive disease in 50% of patients within 10 years

Treatment

1. Acute relapses are treated with **corticosteroids**.
 - a. Intravenous methylprednisolone: Usual dose is 1 g/day as one dose or as divided doses for 3–5 days.
 - b. Oral prednisone: Usual dose is 1250 mg/day given every other day for five doses.
 - c. Intravenous adrenocorticotrophic hormone
 - d. Neurologic recovery is the same with or without an oral prednisone taper.
2. Disease-modifying therapies

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Interferons (Avonex, Betaseron, Extavia, Plegridy, Rebif)

- i. Mechanism of action: Suppress T-cell activity, down-regulate antigen presentation by major histocompatibility complex class II molecules, decrease adhesion molecules and matrix metalloproteinase 9, increase anti-inflammatory cytokines, and decrease inflammatory cytokines
- ii. Adding polyethylene glycol to interferon- β 1a decreases the frequency of injections.
- iii. Injection site reactions: More common in subcutaneously administered products. May help to bring a drug to room temperature before injection, ice the injection site, and rotate injection sites
- iv. Flu-like symptoms: Usually dissipate in 2–3 months. May help to inject the dose in the evening. Begin at the 0.25- to 0.5-mg dose and slowly increase, and use ibuprofen or acetaminophen.
- v. Neutralizing antibodies: Develop in some patients 6–18 months after treatment begins; frequency and administration route affect neutralizing antibody development; relapse rates are higher in patients with persistently high antibody titers; antibodies may disappear even during continued treatment; show cross-reactivity with other β -interferons

Dimethyl fumarate

- i. Mechanism of action: Antioxidant and cytoprotective; inhibits proinflammatory cytokines, increases anti-inflammatory cytokines
- ii. Adverse effects
 - (a) Skin flushing: Occurs in up to 38% of patients, usually within 30–45 minutes of dosing; involves the face, chest, and neck; dissipates after 15–30 minutes; peaks within first month of therapy and decreases thereafter; aspirin may block flushing, taking with food helps prevent
 - (b) GI events: Occur in up to 41% of patients; peak within first month of therapy and decrease thereafter
 - (c) Lymphocytes decrease by 30% in the first year of therapy and then stabilize.

Glatiramer acetate

- i. Mechanism of action: Decreases type 1 helper T cells; increases type 2 helper T cells; increases production of nerve growth factors
- ii. Injection site reactions: Icing the site before and after injection may help.
- iii. Systemic reactions: May involve flushing, chest tightness, palpitations, anxiety, and shortness of breath; this is noncardiac; recurrence is infrequent

Fingolimod

- i. Mechanism of action: Binds to the S1P receptor 1 expressed on T cells, prevents activation of T cells
- ii. Indicated for patients older than 10 years

iii. Contraindicated in patients with myocardial infarctions, unstable angina, stroke, TIAs, or decompensated heart failure necessitating hospitalization or class III/IV heart failure, history of Mobitz type II second- or third-degree atrioventricular block or sick sinus syndrome unless patient has a pacemaker, baseline QTc interval greater than or equal to 500 milliseconds, or treatment with class Ia or class III antiarrhythmic drugs

iv. Patients must be monitored for bradycardia for 6 hours after the first dose; if therapy is discontinued for more than 2 weeks, patients must be re-monitored.

Adverse effects

(a) Bradycardia: ECG is recommended within 6 months for patients using antiarrhythmics (including β -blockers and calcium channel blockers), those with cardiac risk factors, and those with slow or irregular heartbeat. Heart rate returns to baseline within 1 month of continued dosing.

(b) Atrioventricular conduction delays: First- and second-degree block

(c) Decrease in lymphocytes: A recent CBC should be available before therapy begins. Infections may be more common. discontinue therapy for serious infections; test patients without varicella zoster vaccine or infection history for varicella zoster virus antibodies, and immunize antibody-negative patients (wait 1 month to initiate fingolimod).

(d) Macular edema: Ophthalmologic evaluation at baseline and 3–4 months after fingolimod initiation; a history of uveitis or diabetes mellitus increases risk

(e) Respiratory effects: Decreases in forced expiratory volume over 1 second and diffusion lung capacity for carbon monoxide can occur.

(f) Elevation of liver enzymes

(g) Hypertension: Monitor during treatment.

(h) Extended effects of drug for up to 2 months after discontinuation necessitate extended monitoring for many adverse effects.

Monoclonal antibodies: *Alemtuzumab*, *daclizumab*, *natalizumab*, and *ocrelizumab* are monoclonal antibodies indicated for the treatment of MS. *Ocrelizumab* is the first agent to be approved for primary progressive forms of the disease. These agents can be associated with significant toxicities, such as progressive multifocal leukoencephalopathy with *natalizumab*, serious infections with *daclizumab* and *alemtuzumab*, and autoimmune disorders with *alemtuzumab*. As such, these agents may be reserved for patients who have failed other therapies.

On January 20, 2012, an FDA-issued drug safety communication associated positive tests for John Cunningham virus (JCV) antibodies as a risk factor for progressive multifocal leukoencephalopathy. Thus, patients with all three of the following risk factors – presence of anti-JCV antibodies, longer natalizumab treatment duration (especially beyond 2 years), and previous treatment with an immunosuppressant medication (mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil) – have a 1.1% chance of developing progressive multifocal leukoencephalopathy.

DRUGS USED IN AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is characterized by progressive degeneration of motor neurons, resulting in the inability to initiate or control muscle movement. ***Riluzole*** and ***edaravone*** are indicated for the management of ALS. *Riluzole*, an oral NMDA receptor antagonist, is believed to act by inhibiting glutamate release and blocking sodium channels. *Riluzole* may improve survival time in patients suffering from ALS. *Edaravone* is an intravenous free radical scavenger and antioxidant that may slow the progression of ALS.