ANTI PARKINSON DRUGS

From Lippincott

By Fatima Haider

Parkinsonism is a progressive neurological disorder of muscle movement, characterized by tremors, muscular rigidity, bradykinesia (slowness in initiating and carrying out voluntary movements), and postural and gait abnormalities.
The disease is correlated with destruction of dopaminergic neurons in the substantia nigra with a consequent reduction of dopamine actions in the corpus striatum, parts of the basal ganglia system that are involved in motor control
In Parkinson's disease, destruction of cells in the substantia nigra results in the degeneration of the nerve terminals that secrete dopamine in the neostriatum. Thus, the normal inhibitory influence of dopamine on cholinergic neurons in the neostriatum is significantly diminished, resulting in overproduction or a relative overactivity of acetylcholine by the stimulatory neurons

Secondary parkinsonism: Drugs such as the phenothiazines and haloperidol, whose major pharmacologic action is blockade of dopamine receptors in the brain, may produce parkinsonian symptoms (also called pseudoparkinsonism). These drugs should be used with caution in patients with Parkinson's disease

Therapy is aimed at restoring dopamine in the basal ganglia and antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine balance.

ANTI PARKINSON DRUGS

	MOA	**THERAPEUTIC USES**	**ADVERSE EFFECTS**	**OTHER POINTS**
LEVODOPA and CARBIDOPA	-Levodopa is a metabolic precursor of dopamine.Levodopa cross BBB	-The effects of levodopa on the CNS can be greatly enhanced by coadministering carbidopa. Without carbidopa,	-Motor fluctuations -Motor fluctuations may cause the patient to suddenly lose normal mobility and experience tremors, cramps, and	-Levodopa high life = 1-2 hrs -The drug is absorbed rapidly from the small intestine (when empty of food)

	-Carbidopa is a dopamine decarboxylase inhibitor that does not cross the blood–brain barrier	much of the drug is decarboxylated to dopamine in the periphery, resulting in nausea, vomiting, cardiac arrhythmias, and hypotension. -Levodopa in combination with carbidopa is an efficacious drug regimen for the treatment of Parkinson's disease. It decreases rigidity, tremors, and other symptoms of parkinsonism.	immobility. -Ingestion of meals, particularly if high in protein, interferes with the transport of levodopa into the CNS. Thus, levodopa should be taken on an empty stomach, typically 30 minutes before a meal -Anorexia, nausea, and vomiting occur because of stimulation of the chemoreceptor trigger zone - Tachycardia and ventricular extrasystoles result from dopaminergic action on the heart. -Hypotension may also develop. -Adrenergic action on the iris causes mydriasis. -In some individuals, blood dyscrasias and a positive reaction to the Coombs test are seen. -Saliva and urine are a brownish color because of the melanin pigment produced from catecholamine oxidation. -Visual and auditory hallucinations and abnormal involuntary movements (dyskinesias) may occur. These effects are the opposite of parkinsonian symptoms and reflect overactivity of dopamine in the basal ganglia. -Levodopa can also cause mood changes, depression, psychosis, and anxiety	-The vitamin pyridoxine (B6) increases the peripheral breakdown of levodopa and diminishes its effectiveness -Concomitant administration of levodopa and non-selective monoamine oxidase inhibitors (MAOIs), such as phenelzine, can produce a hypertensive crisis caused by enhanced catecholamine production. Therefore, concomitant administration of these agents is contraindicated. - Cardiac patients should be carefully monitored for the possible development of arrhythmias. -Antipsychotic drugs are generally contraindicated in Parkinson's disease
SELEGILINE (also called deprenyl) and RASAGILINE	-Selegiline selectively inhibits monoamine oxidase (MAO) type B (metabolizes dopamine) at low to moderate doses.	-By decreasing the metabolism of dopamine, selegiline increases dopamine levels in the brain -When selegiline is	-Selegiline is metabolized to methamphetamine and amphetamine, whose stimulating properties may produce insomnia if the drug is administered later than mid-afternoon.	

	It does not inhibit MAO type A (metabolizes norepinephrine and serotonin) unless given above recommended doses, where it loses its selectivity. -Rasagiline, an irreversible and selective inhibitor of brain MAO type B, has five times the potency of selegiline.	administered with levodopa, it enhances the actions of levodopa and substantially reduces the required dose.		
Catechol-O-methyltransferase inhibitors (ENTACAPONEand TOLCAPONE)	Normally, the methylation of levodopa by COMT to 3-O-methyldopa is a minor pathway for levodopa metabolism. However, when peripheral dopamine decarboxylase activity is inhibited by carbidopa, a significant concentration of 3-O-methyldopa is formed that competes with levodopa for active transport into the CNS	-Inhibition of COMT by these agents leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of levodopa, and greater concentrations of brain dopamine. Both of these agents reduce the symptoms of “wearing-off” phenomena seen in patients on levodopa−carbidopa.	- diarrhea, postural hypotension, nausea, anorexia, dyskinesias, hallucinations, and sleep disorders. -Most seriously, fulminating hepatic necrosis is associated with tolcapone use. Therefore, it should be used, along with appropriate hepatic function monitoring, only in patients in whom other modalities have failed. Entacapone does not exhibit this toxicity and has largely replaced tolcapone	-The dosage may need to be adjusted in patients with moderate or severe cirrhosis.
Dopamine receptor agonists Ergot derivative: bromocriptine		-Apomorphine is an injectable dopamine agonist that is used in severe and advanced stages of the disease to supplement oral medications	-hallucinations, confusion, delirium, nausea, and orthostatic hypotension are more common as compared to levodopa, whereas dyskinesia is less prominent. -In psychiatric illness, bromocriptine may cause the mental condition to worsen. -It should be used with caution in patients with a history of myocardial infarction or	

			peripheral vascular disease. - Because bromocriptine is an ergot derivative, it has the potential to cause pulmonary and retroperitoneal fibrosis.	
Dopamine receptor agonists Non ergot drugs: Apomorphine, pramipexole, ropinirole, and rotigotine		-Apomorphine is used for acute management of the hypomobility “off” phenomenon in advanced Parkinson’s disease. -Rotigotine is administered as a once-daily transdermal patch that provides even drug levels over 24 hours. -These agents alleviate the motor deficits in patients who have never taken levodopa and also in patients with advanced Parkinson’s disease who are treated with levodopa. -Dopamine agonists may delay the need to use levodopa in early Parkinson’s disease and may decrease the dose of levodopa in advanced Parkinson’s disease -Unlike the ergotamine derivatives, these agents do not exacerbate peripheral vascular disorders or cause fibrosis	-Nausea, hallucinations, insomnia, dizziness, constipation, and orthostatic hypotension are among the more distressing side effects of these drugs, but dyskinesias are less frequent than with levodopa - dosage adjustments are needed in renal dysfunction. -	-Cimetidine inhibits renal tubular secretion of organic bases and may significantly increase the half-life of pramipexole -The fluoroquinolone antibiotics and other inhibitors of the cytochrome P450 (CYP450) 1A2 isoenzyme (for example, fluoxetine) may inhibit the metabolism of ropinirole, requiring an adjustment in ropinirole dosage.
AMANTADINE	Amantadine has several effects on a number of neurotransmitters	-This antiviral drug, used to treat influenza, has an antiparkinsonian action.	-cause restlessness, agitation, confusion, and hallucinations - at high doses, it may induce acute toxic	

	implicated in parkinsonism, including increasing the release of dopamine, blocking cholinergic receptors, and inhibiting the N-methyld-aspartate (NMDA) type of glutamate receptors.		psychosis. -Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth also may occur. -Amantadine is less efficacious than levodopa, and tolerance develops more readily.	
ANTI MUSCARINIC AGENTS (benztropine, Trihexyphenidyl. Procyclidine, biperiden)	Blockage of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission, since it helps to correct the imbalance in the dopamine/acetylcholine ratio		-can induce mood changes -produce xerostomia (dryness of the mouth), constipation, and visual problems typical of muscarinic blockers -interfere with gastrointestinal peristalsis and are contraindicated in patients with glaucoma, prostatic hyperplasia, or pyloric stenosis	