

Treatment of Parkinson disease

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BCPS

Drugs for Neurodegenerative Diseases

Most drugs that affect the central nervous system (CNS) act by altering some step in the neurotransmission process. Drugs affecting the CNS may act presynaptically by influencing the production, storage, release, or termination of action of neurotransmitters. Other agents may activate or block postsynaptic receptors. These concepts are useful in understanding the etiology and treatment strategies for the neurodegenerative disorders that respond to drug therapy: Parkinson's disease, Alzheimer's disease, multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS)

NEUROTRANSMISSION IN THE CNS

The basic functioning of neurons in the CNS is similar to that of the autonomic nervous system (ANS). For example, transmission of information in both the CNS and in the periphery involves the release of neurotransmitters that diffuse across the synaptic cleft to bind to specific receptors on the postsynaptic neuron. In both systems, the recognition of the neurotransmitter by the membrane receptor of the postsynaptic neuron triggers intracellular changes. However, several major differences exist between neurons in the peripheral ANS and those in the CNS. The circuitry of the CNS is more complex than that of the ANS, and the number of synapses in the CNS is far greater. The CNS, unlike the peripheral ANS, contains networks of inhibitory neurons that are constantly active in modulating the rate of neuronal transmission. In addition, the CNS communicates through the use of multiple neurotransmitters, whereas the ANS uses only two primary neurotransmitters, acetylcholine and norepinephrine.

SYNAPTIC POTENTIALS

In the CNS, receptors in most synapses are coupled to ion channels. Binding of the neurotransmitter to the postsynaptic membrane receptors results in a rapid but transient opening of ion channels. Open channels allow specific ions inside and outside the cell membrane to flow down their concentration gradients. The resulting change in the ionic composition across the membrane of the neuron alters the postsynaptic potential, producing either depolarization or hyperpolarization of the postsynaptic membrane, depending on the specific ions and the direction of their movement.

A. Excitatory pathways

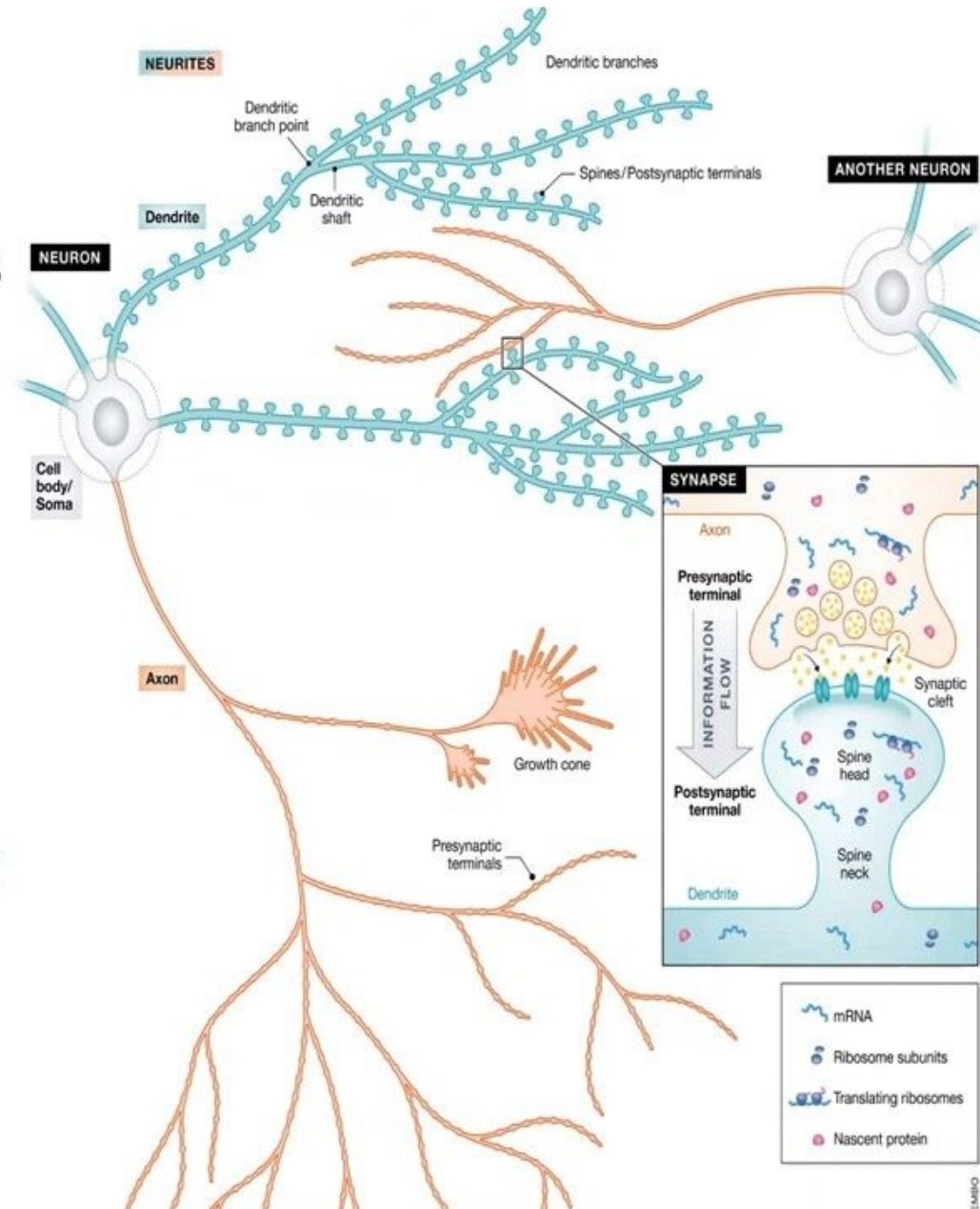
- Neurotransmitters can be classified as either excitatory or inhibitory, depending on the nature of the action they elicit. Stimulation of excitatory neurons causes a movement of ions that results in a depolarization of the postsynaptic membrane. These excitatory postsynaptic potentials (EPSP) are generated by the following: 1) Stimulation of an excitatory neuron causes the release of neurotransmitters, such as glutamate or acetylcholine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of sodium (Na^+) ions. 2) The influx of Na^+ causes a weak depolarization or EPSP, that moves the postsynaptic potential toward its firing threshold. 3) If the number of stimulated excitatory neurons increases, more excitatory neurotransmitter is released. This ultimately causes the EPSP depolarization of the postsynaptic cell to pass a threshold

B. Inhibitory pathways

Stimulation of inhibitory neurons causes movement of ions that results in a hyperpolarization of the postsynaptic membrane. These inhibitory postsynaptic potentials (IPSP) are generated by the following: 1) Stimulation of inhibitory neurons releases neurotransmitters, such as γ -aminobutyric acid (GABA) or glycine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of specific ions, such as potassium (K^+) and chloride (Cl^-). 2) The influx of Cl^- and efflux of K^+ cause a weak hyperpolarization, or IPSP, that moves the postsynaptic potential away from its firing threshold. This diminishes the generation of action potentials

Combined effects of the EPSP and IPSP

Most neurons in the CNS receive both EPSP and IPSP input. Thus, several different types of neurotransmitters may act on the same neuron, but each binds to its own specific receptor. The overall action is the summation of the individual actions of the various neurotransmitters on the neuron. The neurotransmitters are not uniformly distributed in the CNS but are localized in specific clusters of neurons, the axons of which may synapse with specific regions of the brain. Many neuronal tracts, thus, seem to be chemically coded, and this may offer greater opportunity for selective pharmacological modulation of certain neuronal pathways.



OVERVIEW OF PARKINSON'S DISEASE

Parkinsonism is a progressive neurological disorder of muscle movement, characterized by tremors, muscular rigidity, bradykinesia, and postural and gait abnormalities. Most cases involve people over the age of 65 years. The exact etiology is unknown. The disease often manifests itself between the ages of 50 and 60 years, among whom the incidence is about 1 in 100 individuals. It was first described by James Parkinson in 1817; therefore, it is named after him.

Etiology

The cause of Parkinson's disease is unknown for most patients. 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.

PARKINSON'S DISEASE

Motor Skill Symptoms



BRADYKINESIA

(mask-like face; decreased blinking, degrading fine motor skills)



VOCAL SYMPTOMS



RIGIDITY AND POSTURAL INSTABILITY



TREMORS



WALKING OR GAIT DIFFICULTIES



DYSTONIA

(repetitive muscle movements that makes body parts twist)

Nonmotor Skill Symptoms

MENTAL/BEHAVIORAL ISSUES*

SENSE OF SMELL

SWEATING AND MELANOMA

GASTROINTESTINAL ISSUES (urinary issues, weight loss, sexual concerns)

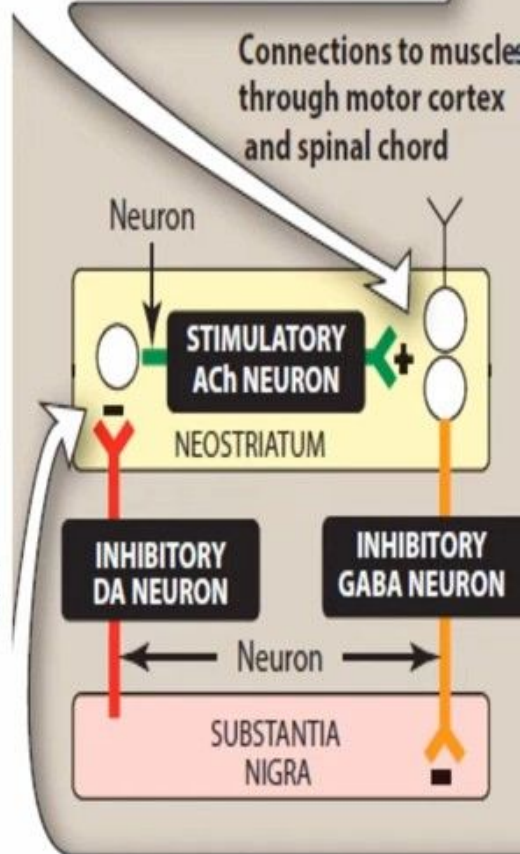
PAIN

*includes depression, anxiety, fatigue, sleep problems, and cognitive ability and personality changes

1. Substantia nigra: The substantia nigra, part of the extrapyramidal system, is the source of dopaminergic neurons that terminate in the neostriatum. Each dopaminergic neuron makes thousands of synaptic contacts within the neostriatum and therefore modulates the activity of a large number of cells. These dopaminergic projections from the substantia nigra fire tonically rather than in response to specific muscular movements or sensory input. Thus, the dopaminergic system appears to serve as a tonic, sustaining influence on motor activity, rather than participating in specific movements.

2. Neostriatum: Normally, the neostriatum is connected to the substantia nigra by neurons that secrete the inhibitory transmitter GABA at their termini. In turn, cells of the substantia nigra send neurons back to the neostriatum, secreting the inhibitory transmitter dopamine at their termini. This mutual inhibitory pathway normally maintains a degree of inhibition of both areas. 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. This triggers a chain of abnormal signaling, resulting in loss of the control of muscle movements.

2 Loss of the inhibitory effect of dopamine results in more production of acetylcholine, which triggers a chain of abnormal signaling leading to impaired mobility.



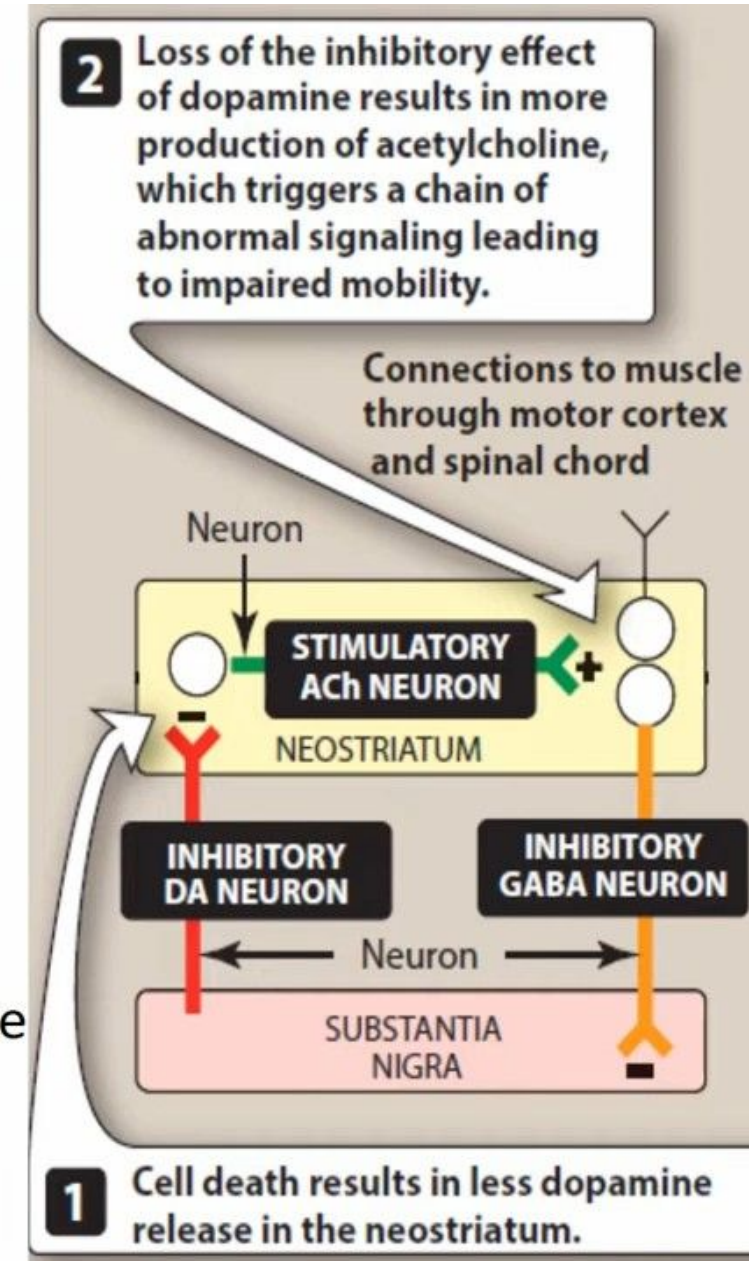
1 Cell death results in less dopamine release in the neostriatum.

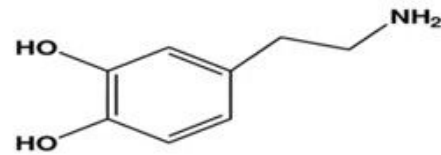
Strategy of treatment

In addition to an abundance of inhibitory dopaminergic neurons, the neostriatum is also rich in excitatory cholinergic neurons that oppose the action of dopamine. Many of the symptoms of parkinsonism reflect an imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons. 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**.

DRUGS USED IN PARKINSON'S DISEASE

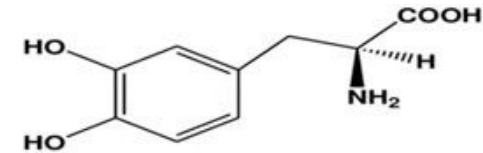
Many currently available drugs aim to maintain CNS dopamine levels, or signaling, as constant as possible. These agents offer temporary relief from the symptoms of the disorder, but they do not arrest or reverse the neuronal degeneration caused by the disease.





Dopamine

Too Polar
Cannot cross blood brain barrier



Levodopa

Non-polar
Can cross blood brain barrier

Levodopa and carbidopa

Levodopa is a metabolic precursor of dopamine. It restores dopaminergic neurotransmission in the neostriatum by enhancing the synthesis of dopamine in the surviving neurons of the substantia nigra. In early disease, the number of residual dopaminergic neurons in the substantia nigra (typically about 20% of normal) is adequate for conversion of *levodopa* to dopamine. Thus, in new patients, the therapeutic response to *levodopa* is consistent, and the patient rarely complains that the drug effects “**wear off**.” Unfortunately, with time, the number of neurons decreases, and fewer cells are capable of converting exogenously administered *levodopa* to dopamine. Consequently, motor control fluctuation develops. Relief provided by *levodopa* is only symptomatic, and it lasts only while the drug is present in the body.

Mechanism of action:

a. **Levodopa:** Dopamine does not cross the blood–brain barrier, but its immediate precursor, *levodopa*, is actively transported into the CNS and converted to dopamine. *Levodopa* must be administered with *carbidopa*. Without *carbidopa*, much of the drug is decarboxylated to dopamine in the periphery, resulting in diminished effect, nausea, vomiting, cardiac arrhythmias, and hypotension.

b. **Carbidopa:** *Carbidopa*, a dopamine decarboxylase inhibitor, diminishes the metabolism of *levodopa* in the periphery thereby increasing the availability of *levodopa* to the CNS. The addition of *carbidopa* lowers the dose of *levodopa* needed by four- to five-fold and, consequently, decreases the severity of adverse effects arising from peripherally formed dopamine.

Therapeutic uses: *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. In approximately two-thirds of patients with Parkinson's disease, *levodopa-carbidopa* substantially reduces the severity of symptoms for the first few years of treatment. Patients typically experience a decline in response during the 3rd to 5th year of therapy. Withdrawal from the drug must be gradual.

3. Absorption and metabolism: The drug is absorbed rapidly from the small intestine (when empty of food). *Levodopa* has an extremely short half-life (1 to 2 hours), which causes fluctuations in plasma concentration. This may produce fluctuations in motor response, which generally correlate with the plasma concentration of *levodopa*, or perhaps give rise to the more troublesome “**on-off**” phenomenon, in which the motor fluctuations are not related to plasma levels in a simple way. Motor fluctuations may cause the patient to suddenly lose normal mobility and experience tremors, cramps, and 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.

Adverse effects:

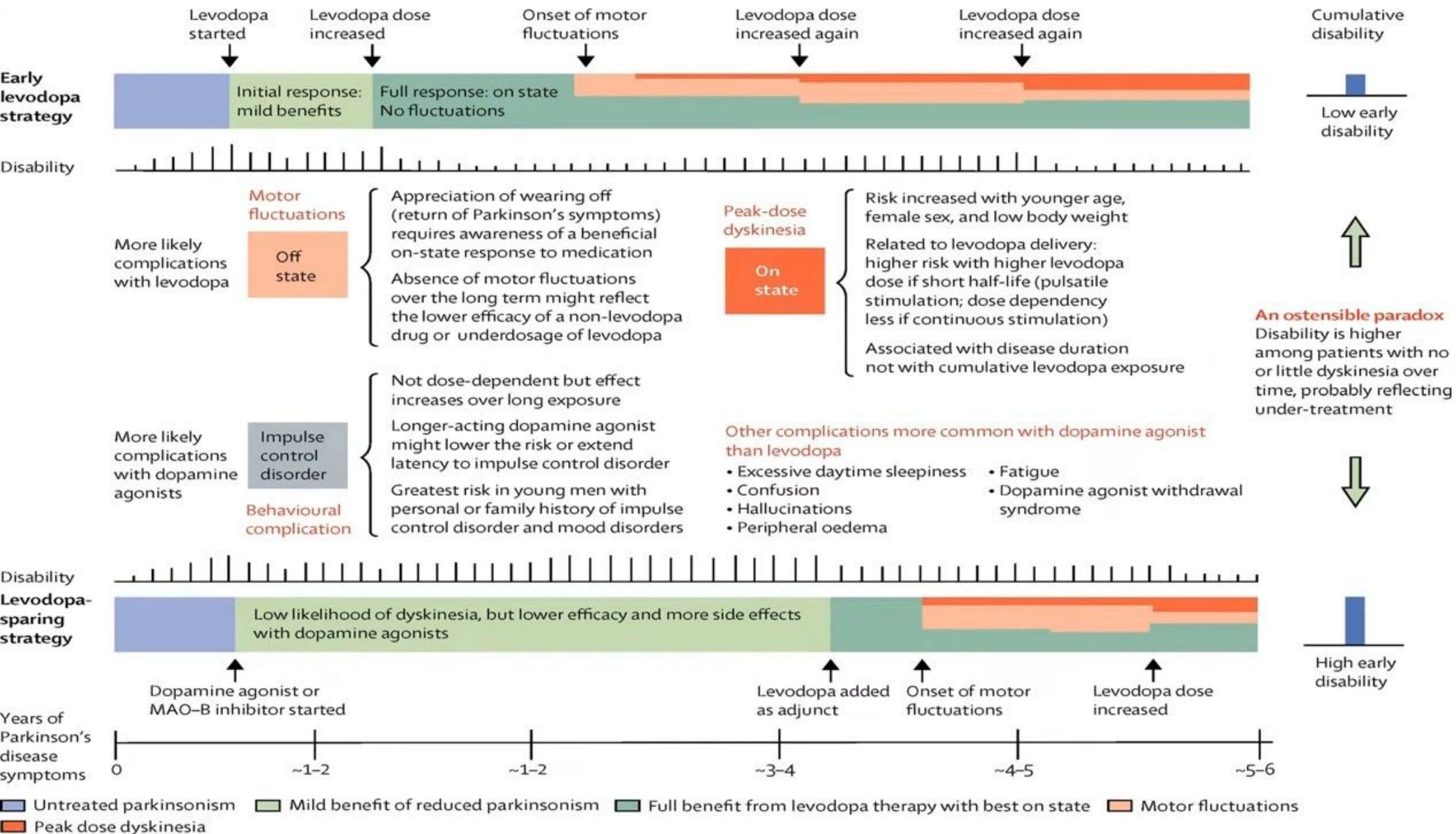
a. Peripheral effects: Anorexia, nausea, and vomiting occur because of stimulation of the chemoreceptor trigger zone. Tachycardia and ventricular extrasystole result from dopaminergic action on the heart. Hypotension may also develop. Adrenergic action on the iris causes mydriasis. In some individuals, blood dyscrasias and a positive reaction to the Coombs test are seen. Saliva and urine may turn brownish color because of the melanin pigment produced from catecholamine oxidation.

b. CNS effects: 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 behavioral effects such as mood changes, depression, psychosis, and anxiety due to exacerbation of pre-existing psychotic symptoms. There are also occasional late-onset dream alterations, visual hallucinations, and drug-induced psychoses characterized by paranoia and confusional states.

Dyskinesias: Dyskinesias are the major limiting factor in therapy with *levodopa* and may occur in 80% of patients. They are characterized by a variety of repetitive involuntary abnormal movements affecting the face, trunk, and limbs. Dyskinesias may be relieved by decreasing the dose of *levodopa*, but parkinsonian symptoms may deteriorate. Akinesia paradoxia, a sudden freezing of movement, may follow an episode of dyskinesia and is often precipitated by stress.



Some patients may experience an end-of-dose akinesia or “wearing-off” (worsening of symptoms) before the next dose is due. Each dose of *levodopa* improves mobility for a period of time and is followed by the rapid return of muscle rigidity and akinesia before the end of the dosing interval. Increase in dose and frequency of *levodopa* administration usually relieves these symptoms but may also induce dyskinesia. An “on-off” effect might also occur, in which rapid fluctuation between showing no beneficial effects of levodopa and showing beneficial effects with dyskinesias occurs. Clinical improvement may be seen with sustained release formulation of *levodopa/carbidopa*. Hence, *levodopa/carbidopa* should never be stopped suddenly.



Interactions and contraindications:

The **vitamin pyridoxine (B6)** increases the peripheral breakdown of *levodopa* and diminishes its effectiveness. Concomitant administration of *levodopa* and nonselective 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. In many **psychotic** patients, *levodopa* exacerbates symptoms, possibly through the buildup of central catecholamines. Cardiac patients should be carefully monitored for the possible development of **arrhythmias**. **antipsychotic** drugs are generally contraindicated in Parkinson's disease, because they potently block dopamine receptors and may augment parkinsonian symptoms. However, low doses of atypical antipsychotics, such as ***quetiapine or clozapine***, are sometimes used to treat *levodopa*-induced psychotic symptoms. The use of *levodopa* is also contraindicated in patients with **narrow-angle glaucoma and peptic ulcer** disease.

Selegiline, rasagiline, and safinamide

Selegiline, also called *deprenyl*, selectively inhibits monoamine oxidase (MAO) type B, the enzyme that metabolizes dopamine. It does not inhibit MAO type A (metabolizes norepinephrine and serotonin) unless given above the recommended doses, where it loses its selectivity. By decreasing the metabolism of dopamine, *selegiline* increases dopamine levels in the brain. When *selegiline* is administered with *levodopa*, it enhances the actions of *levodopa* and substantially reduces the required dose. Unlike nonselective MAOIs, *selegiline* at recommended doses has **little** potential for causing hypertensive crises. However, the drug loses selectivity at high doses, and there is a risk for severe hypertension. Otherwise these drugs are well tolerated. *Selegiline* is metabolized to *methamphetamine* and *amphetamine*, whose stimulating properties may produce insomnia if the drug is administered later than mid-afternoon. **Rasagiline**, an irreversible and selective inhibitor of brain MAO type B, has five times the potency of *selegiline*. Unlike *selegiline*, *rasagiline* is not metabolized to an *amphetamine*-like substance.

Safinamide is also a selective inhibitor of MAO type B indicated for use as an adjunct to *levodopa-carbidopa*. These drugs should be avoided in patients taking selective serotonin re-uptake inhibitors (**SSRIs**), **tricyclic antidepressants**, and **meperidine**, as concomitant therapy may precipitate serotonin syndrome

Catechol-O-methyltransferase inhibitors

Normally, the methylation of *levodopa* by catechol-O-methyltransferase (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. ***Entacapone* and *tolcapone*** selectively and reversibly inhibit COMT. 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*. The two drugs differ primarily in their pharmacokinetic and adverse effect profiles. *Entacapone* acts only in the periphery. It decreases the metabolism of *levodopa* and makes more *levodopa* available to the brain. *Tolcapone* acts in both the periphery and the brain by inhibiting the degradation of dopamine.

Pharmacokinetics:

oral absorption of both drugs occurs readily and is not influenced by food. They are extensively bound to plasma albumin, with a limited volume of distribution.

Tolcapone has a relatively long duration of action (probably due to its affinity for the enzyme) compared to *entacapone*, which requires more frequent dosing. Both drugs are extensively metabolized and eliminated in feces and urine. The dosage may need to be adjusted in patients with moderate or severe cirrhosis.

Adverse effects:

Both drugs exhibit adverse effects that are observed in patients taking *levodopa-carbidopa*, including 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* in clinical practice.

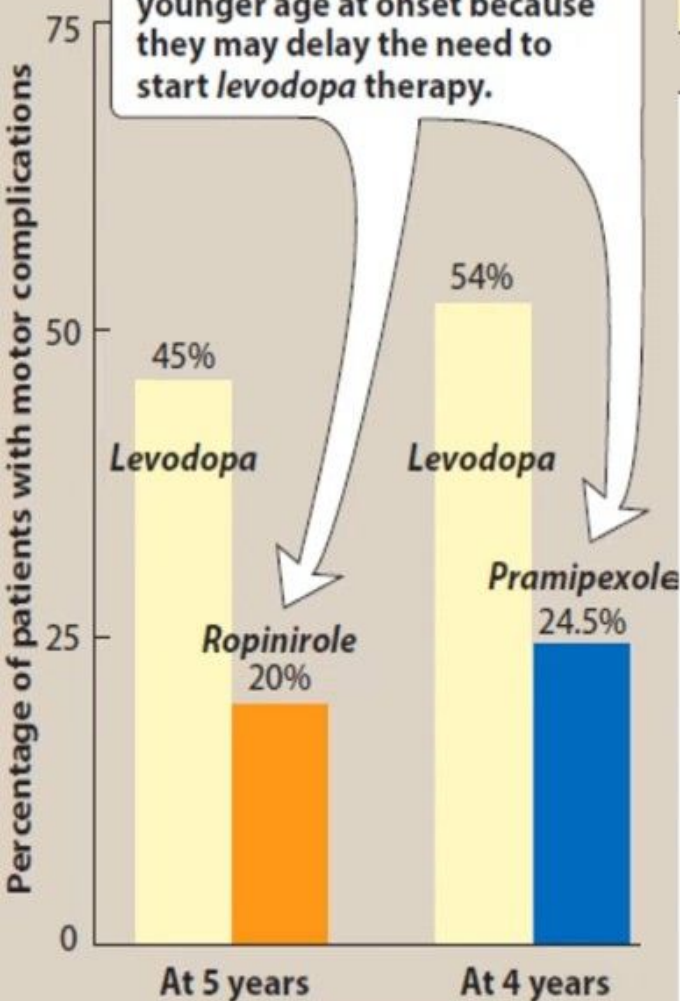
Dopamine receptor agonists

This group of antiparkinsonian compounds includes ***bromocriptine***, an ergot derivative, and the nonergot drugs, ***ropinirole***, ***pramipexole***, ***rotigotine*** and ***apomorphine***. These agents have a longer duration of action than that of *levodopa* and are effective in patients exhibiting fluctuations in response to *levodopa*. Initial therapy with these drugs is associated with less risk of developing dyskinesias and motor fluctuations as compared to patients started on *levodopa*. *Bromocriptine*, *pramipexole*, and *ropinirole* are effective in patients with Parkinson's disease complicated by motor fluctuations and dyskinesias. However, these drugs are ineffective in patients who have not responded to *levodopa*. *Apomorphine* is an injectable dopamine agonist that is used in severe and advanced stages of the disease to supplement oral medications. Adverse effects severely limit the utility of the dopamine agonists

Apomorphine, pramipexole, ropinirole, and rotigotine:

These are nonergot dopamine agonists that are approved for the treatment of Parkinson's disease. *Pramipexole* and *ropinirole* are orally active agents. *Apomorphine* and *rotigotine* are available in injectable and transdermal delivery systems, respectively. *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 adverse effects of these drugs, but dyskinesias are less frequent than with *levodopa*. *Pramipexole* is mainly excreted unchanged in the urine, and 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, *fluvoxamine*) may inhibit the metabolism of *ropinirole*, requiring an adjustment in *ropinirole* dosage.

Dopamine agonists delay motor complications and are most commonly initiated before *levodopa* in patients who have mild disease and a younger age at onset because they may delay the need to start *levodopa* therapy.



CHARACTERISTIC	PRAMIPEXOLE	ROPINIROLE	ROTIGOTINE
Bioavailability	> 90%	55%	45%
V _d	7 L/kg	7.5 L/kg	84 L/kg
Half-life	8 hours ¹	6 hours	7 hours ³
Metabolism	Negligible	Extensive	Extensive
Elimination	Renal	Renal ²	Renal ²

Amantadine

It was accidentally discovered that the antiviral drug *amantadine* has an antiparkinsonian action. *Amantadine* has several effects on a number of neurotransmitters implicated in parkinsonism, including increasing the release of dopamine, blocking cholinergic receptors, and inhibiting the *N*-methyl-d-aspartate (NMDA) type of glutamate receptors. The drug may cause restlessness, agitation, confusion, and hallucinations, and, at high doses, it may induce acute toxic psychosis. Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth also may occur. *Amantadine* is less efficacious than *levodopa*, and tolerance develops more readily. However, *amantadine* has fewer adverse effects

Antimuscarinic agents

The antimuscarinic agents are much less efficacious than *levodopa* and play only an adjuvant role in antiparkinsonism therapy. The actions of ***benztropine*** and ***trihexyphenidyl*** are similar, although individual patients may respond more favorably to one drug or the other. Blockade of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission, since it helps to correct the imbalance in the dopamine/acetylcholine activity. The antimuscarinic agents have a significant effect on tremors and rigidity but little effect on bradykinesia and postural reflexes. These drugs are often used in the tremor-predominant Parkinson's disease. These can also be used in combination with *levodopa*. These agents can induce mood changes and confusion and produce xerostomia, constipation, and visual problems typical of muscarinic blockers. They interfere with gastrointestinal peristalsis and are contraindicated in patients with glaucoma, prostatic hyperplasia, or pyloric stenosis. To avoid precipitating these conditions, these agents should not be administered to patients who are taking other drugs with anticholinergic activity such as tricyclic antidepressants and antihistamines. They can also cause urinary retention in elderly males.