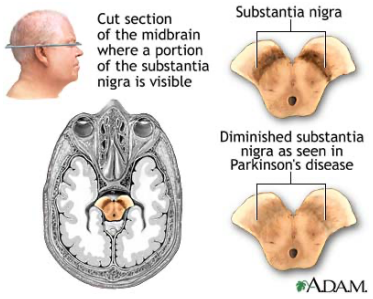
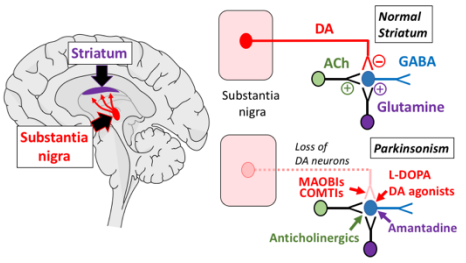
Pharmacologic Management of Parkinson's Disease

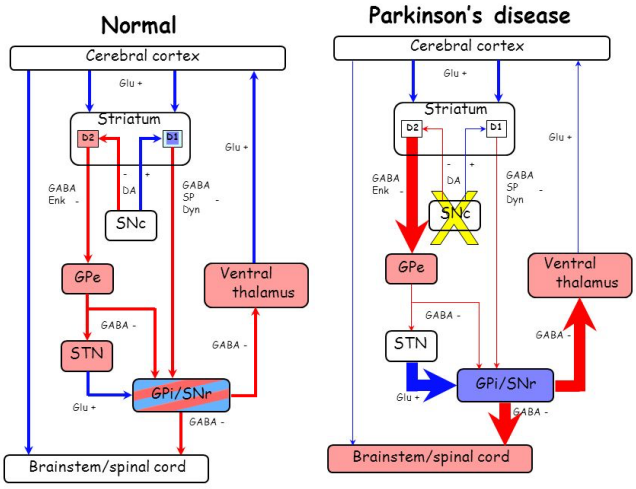
Pathophysiology



- PD results from a loss of dopaminergic neurons in the nigrostriatal tracts of the brain and the development of abnormal intraneuronal protein aggregates called Lewy bodes that interfere with neuronal function
  - Lewy body pathology ascends to the medulla oblongata in preclinical stages (causing anxiety, depression, and olfactory disturbance), ascending the midbrain (causing motor dysfunction), and spreading eventually to the cortex (causing cognitive and behavioral changes)
- the pigmented neurons within the basal ganglia have dopaminergic fibers, and in PD, these dopamine producing neurons are progressively depigmented and lost
  - the loss of dopamine (DA) neurons results in loss of dopamine-mediated inhibition of acetylcholine neurons
  - when the balance of dopamine (DA) and acetylcholine (ACh) is lost, there is a relative increase in cholinergic activity

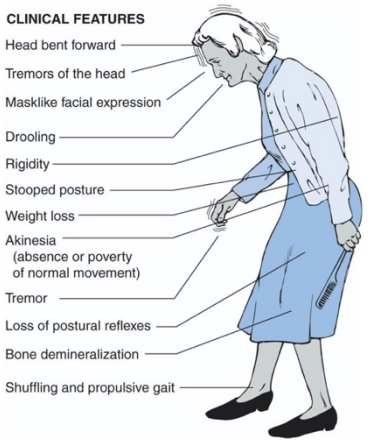


- in PD, reduced dopaminergic activation of the D_1 and D_2 receptors in the striatum results in a net inhibitory tone on the thalamus
  --> leading to decreased motor cortical activity (hypokinesis)
- dopaminergic therapies help restore functional activity within the D_1 and D_2 pathways with the latter primarily responsible for mediating clinical improvements



Diagnosis

- the clinical diagnosis of PD is based on the presence of bradykinesia and at least one of three other features: muscular rigidity, resting tremor, and postural instability
  - asymmetry of motor features is supportive of the diagnosis of PD
  - tremor is not always present at the time of diagnosis
  - postural instability typically occurs in later stages of PD
- overall, the diagnosis of PD cab be made with a high level of confidence in a patient who has bradykinesia (along with rest tremor and/or rigidity), prominent asymmetry, and a good response to dopaminergic therapy
  - to confirm the diagnosis of PD, a therapeutic trial of levodopa (L-dopa) is considered
  - a positive response to L-dopa, evidenced by an improvement in motor function, supports the diagnosis of PD
- note: medication-induced parkinsonism can mimic PD and must be excluded
  - drugs that block D2 receptors are include antipsychotics (e.g., haloperidol), metoclopramide (Reglan), and prochlorperazine (Compazine)



Staging of Parkinson's Disease

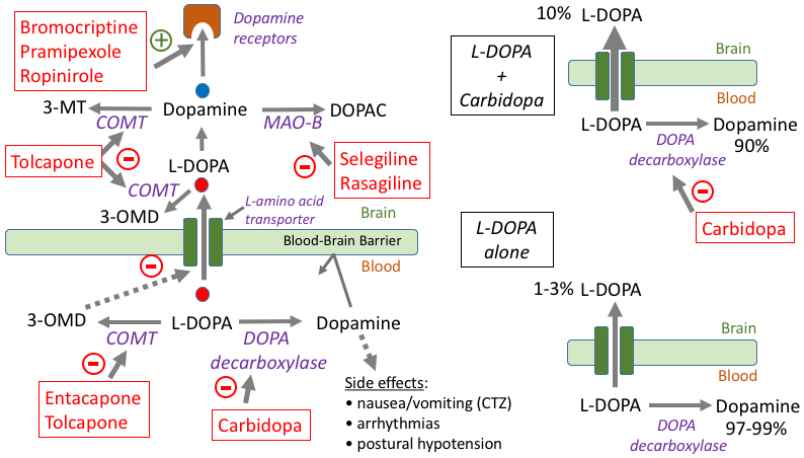
- the Hoehn and Yahr scale is used to assess the degree of stability and determine the rate of disease progression relative to treatment
- stage 1-2: patients have mild disease and does not interfere with activities of daily living (ADLs) or work and usually requires minimal or no treatment
- stage 3: daily activities are restricted and employment may be significantly affected unless effective treatment is initiated
- stage 3-4 (advanced disease): most patients require a double or triple drug therapy strategy
- state 5: patients are severely incapacitated and do not respond well to drug therapy
  DBS (deep brain stimulator) is a pulse generator, surgically implanted in a pouch beneath the clavicle --> sends electrical impulses to the thalamus --> reduces PD symptoms

Non-Pharmacologic Therapy

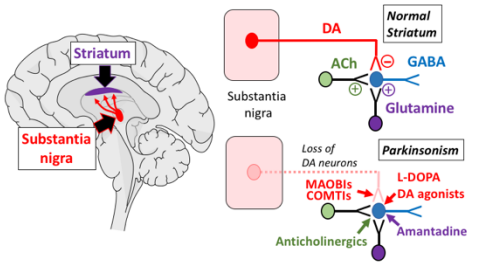
- the importance of nonpharmacologic, supportive care cannot be overemphasized
- exercise, physical and occupational therapy, and good nutritional support can be beneficial at the earlier stages to improve mobility, increase strength, and enhance well-being and mood
- psychological support is often necessary in dealing with depression and other related problems
- newly diagnosed patients and their family members need to be educated about what to expect from the disease and the various forms of treatment available
- the support of family members is vital in establishing an overall effective therapeutic plan

Pharmacologic Therapy

- since the pathophysiologic feature of PD is the progressive loss of dopamine from the nigrostriatal tracts in the brain, drug therapy for the disease is aimed at replenishing the supply of dopamine
- replenishing the supply of dopamine is accomplished through one, or a combination of the following methods:
  (1) administering exogeneous dopamine in the form of a precursor (levodopa)
  (2) stimulating dopamine receptors within the striatum with dopamine agonists (e.g., pramipexole, ropinirole), or
  (3) inhibiting the major metabolic pathways that are responsible for the degradation of levodopa and its metabolites
    - carbidopa: aromatic L-amino acid decarboxylase (ADD)
    - COMT inhibitors (e.g., entacapone, tolcapone)
    - MAO-B inhibitors (e.g., selegiline, rasaligine)

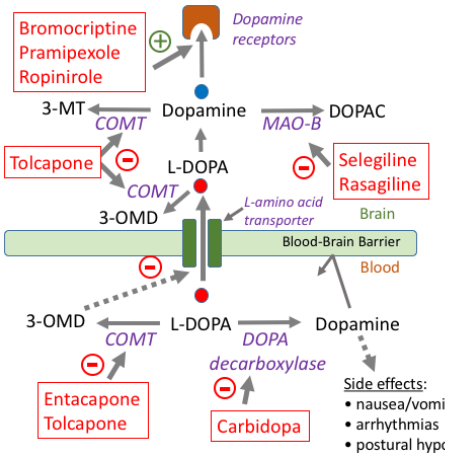


- anticholinergic agents (e.g., benztropine, trihexyphenidyl) are also used; however, they are solely efficacious for the cholinergic-mediated tremors, and their routine use is limited by CNS side effects (especially in older patients)
- amantadine, a unique agent used as an antiviral, is also used occasionally to provide modest benefits via both dopaminergic and non-dopaminergic (inhibition of glutamate) mechanisms



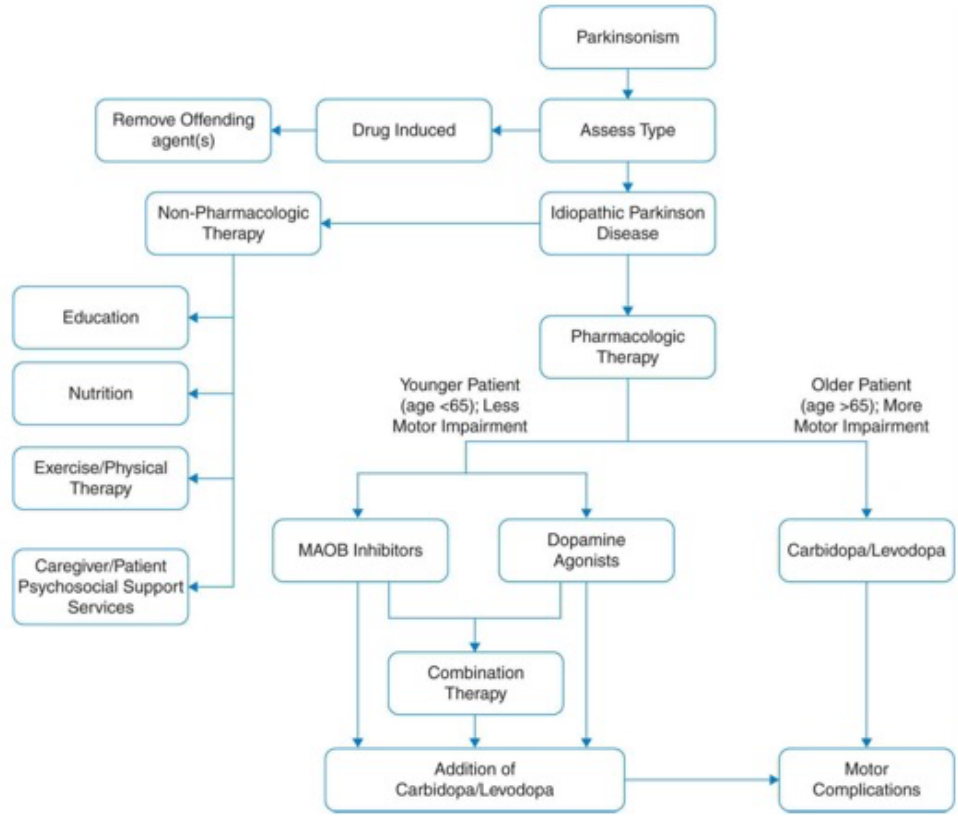
Pharmacologic Therapy: General Considerations

- most clinicians agree that treatment for PD should begin when the patient begins to experience functional impairment as defined by the following:
  (1) threat to employment status
  (2) symptoms affecting the dominant side of the body, or
  (3) bradykinesia or rigidity
- despite advances in pharmacologic treatment for PD, no therapy has been proven to be disease-modifying or neuroprotective; therefore, therapy continues to be symptomatic, and levodopa remains the most effective agent for PD
  - when to begin treatment with levodopa is still being debated by clinicians since the efficacy of levodopa decreases with long-term use and the risk of dyskinesias increases with long-term levodopa use
  - when escalating doses of levodopa introduces a high frequency of undesirable side effects (e.g., dyskinesia), dopamine agonists and MAO-B inhibitors are used to augment dopamine levels
- dopamine agonists bind directly to dopamine receptors and do not require metabolic conversion to an active form
  - dopamine agonists have a longer half-life than levodopa formulations, reducing the need for multiple daily dosing
  - although ADLs and motor features are improved to a greater degree with levodopa, dopamine agonists are associated with fewer dyskinesias
  - against levodopa as initial therapy, dopamine agonists delay the onset of dyskinesias
    - studies have demonstrated that patients were less likely to experience dyskinesias with ropinirole, compared with levodopa, at the end of a 5-year evaluation (20% vs 45%)



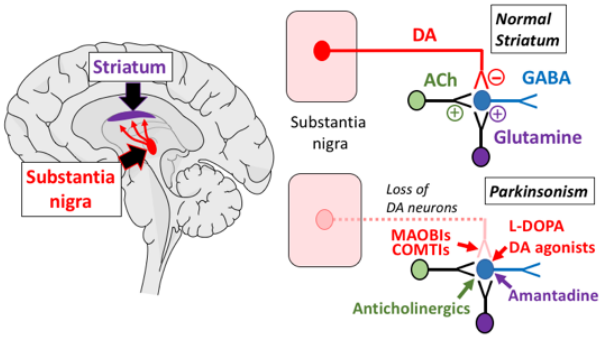
  - regardless of initial therapy chosen, due to disease progression, levodopa therapy will eventually be required, motor complications will develop, and disability will be present
- MAO-B inhibitors are an alternative method of enriching dopamine supply in early disease by irreversible inhibition of MAO-B
  - recent studies have indicated that MAO-B inhibitors are at least as effective as dopamine agonists in early therapy of PD
- disease severity, degree of functional impairment, life expectancy, and age should guide therapeutic drug selection in early PD
- in younger patients (i.e., age < 65 years), patients with milder disease, initiating of levodopa sparing therapy with either a dopamine agonist or MAO-B inhibitor is recommended
- initiating of levodopa therapy later in the course of PD delays the development of motor complications, especially the troubling peak-dose, levodopa-induced dyskinesias, which eventually develop with advancing PD
- in older patients (i.e., age > 65 years), patients with more significant functional impairments, or those with limited life expectancy, use of levodopa is recommended since more symptomatic benefits are associated with levodopa compared to dopamine antagonist and MAO-B inhibitors

Treatment Algorithm for Management of Early Parkinson's Disease



Anticholinergic Agents

- since dopamine provides negative feedback to acetylcholine neurons in the striatum, degradation of dopamine neurons in PD results in a relative increases in striatal cholinergic activity
- Increase in cholinergic activity is believed to contribute to the tremors in PD and anticholinergics are used to specifically target tremor
    - although tremor may improve with dopaminergic drugs with restoration of balance between dopamine and ACh, tremors may still persistent

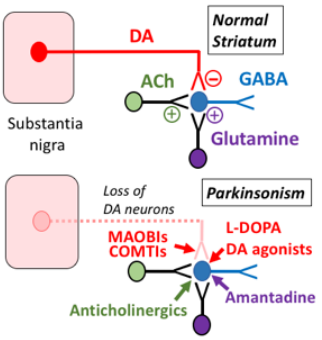


- since anticholinergics cause undesirable anticholinergic side effects (i.e., dry mouth, blurred vision, constipation, urinary retention, drowsiness, confusion, etc…), and have poor efficacy with relieving bradykinesia and rigidity, they are no longer used as 1st-line agents

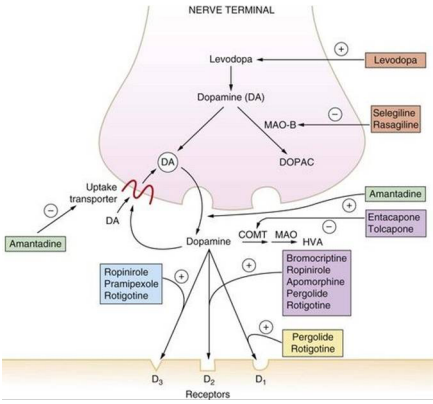
Anticholinergic Agents				
Benztropine (Cogentin)	0.5-, 1-, and 2-mg tablets Injection: 1 mg/mL	0.5 mg every day increased by 0.5 mg every 5–6 days	1–3 mg given every day to BID	Constipation, xerostomia, dry skin, dysphagia, confusion, memory impairment
Trihexyphenidyl (Artane)	2- and 5-mg tablets Liquid: 2 mg/5 mL	1–2 mg/day increased by 1–2 mg every 3–5 days	6–15 mg divided TID to QID	Constipation, xerostomia, dry skin, dysphagia, confusion, memory impairment

- anticholinergics are reserved for the treatment of resting tremor early in the disease, particularly in younger patients with preserved cognitive function

Amantadine (Symmetrel)

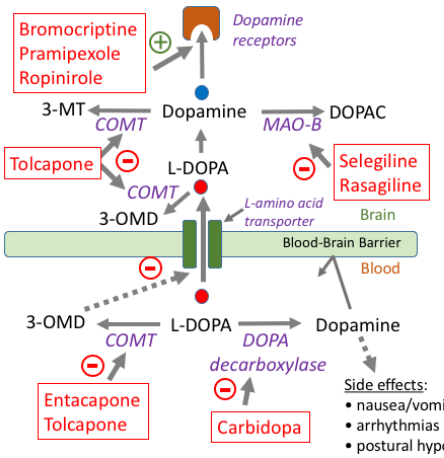


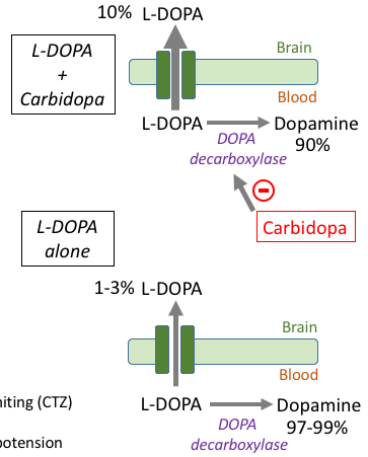
- amantadine is antiviral agent used for influenza; however, it was found to also reduce symptoms of PD in about 50% of patients
- MOA: (1) amantadine augments the release of DA and inhibits DA reuptake --> increases DA concentrations in synapse and (2) amantadine is also an NMDA antagonist --> blocks glutamate transmission
- in PD, amantadine is limited by the development of tachyphylaxis within 1-3 months
- although amantadine can be used for managing symptoms of tremor, rigidity and bradykinesia, guidance suggests reserving amantadine for use in patients whom dyskinesia is not adequately managed with other agents
- SEs: confusion, dizziness, dry mouth, and hallucinations with elderly patients being particularly prone to develop confusion
- dose: 100 mg daily; increase by 100 mg every 1-2 weeks (max daily dose : 300 mg); doses in excess of 200 mg/day are associated with increased adverse effects and should be used cautiously



Carbidopa / Levodopa

- L-dopa is the immediate precursor of dopamine and, in combination with a peripherally acting L-amino acid decarboxylase inhibitor (carbidopa), remains the most effective drug for the symptomatic treatment of PD
- L-dopa crosses the BBB, whereas carbidopa does not --> increased amounts of L-dopa are transported to the brain and peripheral adverse effects of dopamine (nausea/vomiting, arrhythmias) are reduced





- regardless of the initial therapeutic agent used, ultimately all patients with PD will require L-dopa
- as the motor features of PD become progressively more severe, use of higher dosages of L-dopa are required; however, in patients with severe PD, the usual maximal dose tolerated is approx. 1000-1500 mg/day

Motor Complications of L-Dopa

- long-term L-dopa therapy is associated with a variety of motor complications, of which end-of-dose "wearing off" (motor fluctuations) and L-dopa peak-dose dyskinesias are the 2 most commonly encountered
- the approx. risk of developing either motor fluctuations or dyskinesia with L-dopa is 10% per year; however, motor complications can occur as early as 6 months after starting L-dopa therapy, especially if excessive doses are used initially

Carbidopa / Levodopa (cont.)

End-of-Dose "Wearing Off"

- the terms "off" and "on" refer to periods of poor movement (i.e., return to tremor, rigidity, or slowness) and good movement respectively
- end-of-dose "wearing off" prior to the next dose of medication is related to the increasing loss of neuronal storage capability for dopamine as well as the short half-life of L-dopa
- with the progressive loss of neurons and storage capacity, patients become more increasing more dependent on exogenous carbidopa/L-dopa; and the peripheral pharmacokinetic properties of L-dopa increasingly become the determinant of central dopamine synthesis
- with advancing PD, the duration of action of a single carbidopa/L-dopa dose progressively shortens, and in some cases may produce benefits for as little as 1 hour
- as a result of end-of-dose "wearing off" effects, the following possible treatment options may be implemented:
  (1) increase frequency of carbidopa/L-dopa doses,
  (2) add either a COMT inhibitor (e.g., entacopone) or a MAO-B inhibitor (e.g., rasagiline, selegiline) to extend the duration of action of L-dopa,
  (3) add a dopamine agonist (e.g., pramipexole, ropinirole) to carbidopa/L-dopa regimen
  (4) switch carbidopa/L-dopa tablet to Rytary, a carbidopa/L-dopa IR/ER capsule containing beads that dissolve at different rates --> allows for a 4-5 hour duration for management of motor fluctuations (note: Sinemet CR tablet has not demonstrated compelling evidence for reducing motor fluctuations)

TABLE 76-5 Common Motor Complications and Possible Initial Treatments

Effects	Possible Treatments
End-of-dose "wearing off" (motor fluctuation)	Increase frequency of carbidopa/L-dopa doses; add either COMT inhibitor or MAO-B inhibitor or dopamine agonist; add or switch to extended-release carbidopa/L-dopa (ie, Rytary); use L-dopa inhalation
"Delayed on" or "no on" response	Give carbidopa/L-dopa on empty stomach; use carbidopa/L-dopa ODT; avoid carbidopa/L-dopa SR; use apomorphine subcutaneous or L-dopa inhalation
Start hesitation ("freezing")	Increase carbidopa/L-dopa dose; add a dopamine agonist or MAO-B inhibitor; utilize physical therapy along with assistive walking devices or sensory cues (eg, rhythmic commands, stepping over objects)
Peak-dose dyskinesia	Provide smaller doses of carbidopa/L-dopa; reduce dose of adjunctive dopamine agonist; add amantadine

COMT, catechol-*O*-methyltransferase; MAO, monoamine oxidase; ODT, orally disintegrating tablet; SR, sustained release.

Combination Agents				
Carbidopa–levodopa (immediate release)/entacapone (Stalevo)	12.5-/50-/200-, 18.75-/75-/200-, 25-/100-/200-, 31.25-/125-/200-, 37.5-/150-/200-, 50-/200-/200-mg tablets	Titrate with individual dosage forms (carbidopa/levodopa and entacapone) first, then switch to combination tablet	Varies (see individual drugs)	See individual drugs
Dopamine Replacement				
Carbidopa–levodopa (regular) (Sinemet)	10-/100-, 25-/100-, and 25-/250-mg tablets	25/100 mg BID, increased by 25/100 mg weekly to effect and as tolerated	30/300 to 150/1,500 mg divided TID to QID	Nausea, orthostatic hypotension, confusion, dizziness, hallucinations, dyskinesias, blepharospasm
Carbidopa–levodopa (CR) (Sinemet CR)	25-/100- and 50-/200-mg tablets	25/100 mg BID (spaced at least 6 hours apart), increased every 3–7 days	50/200 to 500/2,000 divided QID	Same as regular Sinemet
Carbidopa–levodopa (ER) (Rytary)	23.75-/95-, 36.25-/145-, 48.75-/195-, 61.25-/245-mg capsules	23.75/95 mg TID; may increase to 36.25/145 mg TID on day 4 and titrate to response	Variable	Same as regular Sinemet
Carbidopa–levodopa (enteral suspension) (Duopa)	4.63-/20-mg/mL in 100-mL cassette	Total daily dose administered over 16 hours	Variable	Same as regular Sinemet
Carbidopa–levodopa ODT (Parcopa)	10-/100-, 25-/100-, and 25-/250-mg tablets	25/100 TID, increased every 1–2 days; if transferring from regular levodopa <1,500 mg/day, start 25/100 mg TID to QID (start 25/250 mg TID to QID if already on >1,500 mg/day of regular levodopa)	25/100 to 200/2,000 divided TID to QID	Same as regular Sinemet; may occur more rapidly than with regular Sinemet

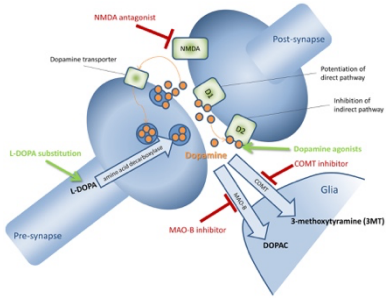
Carbidopa / Levodopa (cont.)

End-of-Dose "Wearing Off"

- for rapid relief of acute off episodes, apomorphine (a SC administered short-acting dopamine agonist) or a L-dopa dry powder for inhalation may be administered as needed

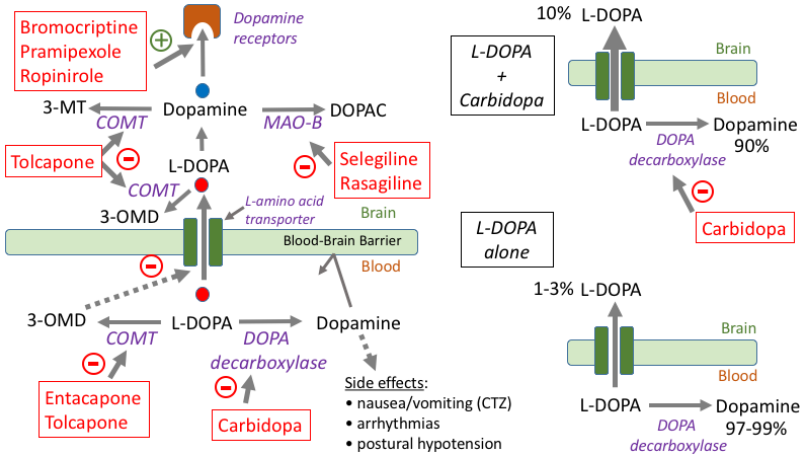
Dyskinesias

- another complication of L-dopa therapy is "on" period dyskinesias that are involuntary movements usually involving the neck, trunk, and lower/upper extremities
- dyskinesias are usually associated with peak striatal levels of dopamine levels --> "peak-dose" dyskinesia
- to counteract peak-dose dyskinesia, the following strategies should be considered:
  (1) the carbidopa/L-dopa dose can be lowered but given more frequently
  (2) add a dopamine agonist
  (3) add amantadine (NMDA-receptor antagonist) since glutamate overactivity may also be involved with dyskinesias
- despite accompanying dyskinesias, most patients prefer to be in an "on" rather than an "off" (or akinetic) state; however, for some patients, dyskinesias can be more disabling than parkinsonism



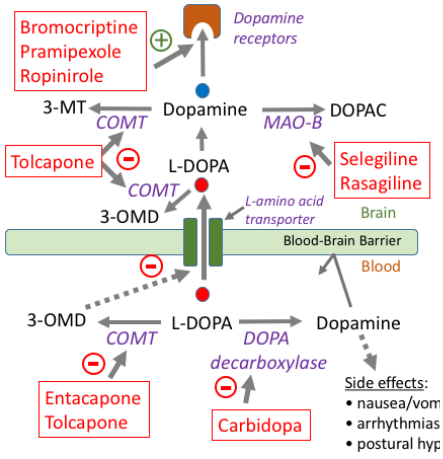
Catechol-O-Methyltransferase Inhibitors (COMT-Inhibitors): Entacapone and Tolcapone

- entacapone and tolcapone are selective, reversible, and potent COMT-inhibitors that increase the amount of L-dopa available for transport across the BBB to prolong its therapeutic effect
- use of these agents is associated with increased on-time and a decrease in the daily L-dopa dose
- tolcapone is associated with cases of fatal, acute fulminant liver failure and requires strict liver function monitoring
- because of the risk for hepatoxicity associated with tolcapone, entacapone is the preferred COMT-inhibitor
- SEs: most side effects of entacapone are consistent with increased L-dopa concentrations (dyskinesias (50-60%), dizziness (10-25%), nausea (15-20%), and hallucinations (1-14%); other SEs include: urine discoloration (11-40%), diarrhea (10%), and abdominal pain (6%)



COMT Inhibitors				
Entacapone (Comtan)	200-mg tablet	200 mg with each administration of carbidopa/levodopa, up to 8 tablets daily	3–8 tablets daily	Diarrhea, dyskinesias, abdominal pain, urine discoloration
Tolcapone (Tasmar)	100-mg tablet	100 mg TID	300–600 mg divided TID	Diarrhea, dyskinesias, - abdominal pain, urine discoloration, hepatotoxicity

Dopamine Agonists



- the 1st generation dopamine agonists (bromocriptine) were derived from ergot alkaloids and are now rarely used because of increased risk of retroperitoneal pleural and pericardial fibrosis, and cardiac valve fibrosis
- the 2nd generation dopamine agonists include: pramipexole, ropinirole, apomorphine, and rotigotine
- dopamine agonists stimulate dopamine receptors and are useful as monotherapy in mild-to-moderate PD, and also as adjuncts to carbidopa/L-dopa therapy to reduce "off" time in patients with motor fluctuations
- apomorphine, derived from morphine but lacks narcotic properties, is available only in injectable form for use as a rescue agent in the treatment of hypomobility "off" episodes with PD
    - apomorphine is administered SC (2-6 mg) and produces an "on" response within 20 mins, with a duration up to 100 mins
    - nausea/vomiting are the most common side effects, and prior to administration, patients should be premedicated with the antiemetic trimethobenzamide (Tigan)
- rotigotine is a once-daily transdermal formulation
- SEs: nausea, confusion, drowsiness, hallucinations, lower-extremity edema, and orthostatic hypotension

Dopamine Agonists				
Bromocriptine (Parlodel)	2.5-mg tablet, 5-mg capsule	1.25 mg BID, titrate slowly as tolerated (2.5 mg/day every 2-4 weeks)	10–40 mg divided TID; Max 100 mg/day	Orthostatic hypotension, confusion, dizziness, hallucinations, nausea, muscle cramps; retroperitoneal, pleural, pericardial fibrosis; cardiac valve thickening
Pramipexole (Mirapex, Mirapex ER)	Immediate release: 0.125-, 0.25-, 0.50-, 0.75-, 1-, 1.5-mg tablets ER: 0.375-, 0.75-, 1.5-, 2.25-, 3-, 3.75-, 4.5-mg tablets	Immediate release: 0.375 mg divided TID; titrate weekly by 0.125–0.25 mg/dose ER: 0.375 mg once daily; titrate weekly by 0.75 mg/dose	Immediate release: 1.5–4.5 mg divided TID ER: 1.5–4.5 mg once daily	Orthostatic hypotension, confusion, dizziness, hallucinations, nausea, somnolence
Ropinirole (Requip, Requip XL)	0.25-, 0.5-, 1-, 2-, 3-, 4-, 5-mg tablet XL: 2-, 4-, 6-, 8-, 12-mg tablets	0.25 mg TID; titrate weekly by 0.25 mg/dose XL: 2 mg once daily; titrate weekly by 2 mg/day	3–12 mg divided TID XL: 3–12 mg once daily	Orthostatic hypotension, confusion, dizziness, hallucinations, nausea, somnolence
Apomorphine (Apokyn)	10 mg/mL injection	Initial 2-mg subcutaneous test dose; begin with 2 mg; increase by 1 mg every few days	2–6 mg TID	Orthostatic hypotension, drowsiness, yawning, injection site reactions, nausea, vomiting (administer with trimethobenzamide, not 5-hydroxytryptamine-3 [5-HT_3] antagonists)
Rotigotine (Neupro)	1,-, 2-, 3-, 4-, 6-, 8-mg/24 hour transdermal delivery system	Early stage: 2 mg/24 hour; Advanced stage: 4 mg/24 hour; titrate weekly by 2 mg/24 hour; Application site should be rotated daily between abdomen, thigh, hip, flank, shoulder, or upper arm and do not use same site within 14 days	4–6 mg/24 hour	Hallucinations, nausea, vomiting, anorexia, somnolence, insomnia, dizziness, hyperhidrosis, visual disturbance, peripheral edema, and application site reactions; avoid in patients with known sulfite sensitivity

Monoamine Oxidase-B Inhibitors

- selegiline (Eldeprel) and rasagiline (Azilect) are selective MOA-B inhibitors which interfere with degradation of dopamine, resulting in prolonged dopaminergic activity
- a common concern with these agents is the potential for interactions with drugs that have serotoninergic activity --> serotonin syndrome
    - concomitant use of SSRI is not contraindicated, but should be used cautiously
- SEs: agitation, insomnia, hallucinations, and orthostatic hypotension

Monoamine Oxidase-B Inhibitors (cont.)

Monoamine Oxidase Type B (MAO-B) Inhibitors				
Selegiline (Eldepryl)[a]	5-mg tablet, capsule	5 mg every morning; may increase to 5 mg BID (5 mg with breakfast and 5 mg with lunch)	5–10 mg/day	Insomnia, dizziness, - nausea, vomiting, - xerostomia, - dyskinesias, mood changes; use caution when coadministered with - sympathomimetics or serotoninergic agents (increased risk of serotonin syndrome); avoid tyramine-containing foods
Selegiline ODT (Zelapar)	1.25-mg tablet	1.25 mg every day; avoid food or liquids for 5 minutes before and after administration; may increase to 2.5 mg every day after 6 weeks	1.25–2.5 mg every day	Insomnia, dizziness, - nausea, vomiting, - xerostomia, - dyskinesias, mood changes; use caution when coadministered with - sympathomimetics or serotoninergic agents (increased risk of serotonin syndrome); avoid tyramine-containing foods
Rasagiline (Azilect)	0.5-, 1-mg tablets	0.5–1 mg once daily	0.5–1 mg/day	Similar to selegiline
Safinamide (Xadago)[b]	50-, 100 mg tablets	50 mg once daily; dose may be increased after two weeks to 100 mg once daily	50-100 mg/day	Similar to selegiline

[a]A transdermal formulation is also available, but not approved for use in PD.

[b]Approved only for use as adjunctive treatment to levodopa/carbidopa in patients experiencing "off" episodes.

BID, twice daily; COMT, catechol-*O*-methyltransferase; MAO-B, monoamine oxidase type B; ODT, orally disintegrating tablet; QID, four times daily; TID, three times daily.