Drugs for Parkinson's Disease

(modified November 2024)

The chart below outlines the place in therapy of common meds used to treat Parkinson's motor symptoms (tremor, rigidity, bradykinesia).[1] Tips for managing motor symptoms in more advanced disease and other therapeutic pearls are also included. **Tapering** is covered in **footnote a**. For a **general overview of treatment**, see **footnote e**. **Footnotes c and d** give tips for management of **dyskinesias** and **motor fluctuations**, respectively. Click here for an algorithm presenting a general stepwise approach to Parkinson's disease pharmacotherapy.

Drug or Drug Class	Role in Therapy	Adverse Effects/Monitoring	Comments
Carbidopa-levodopa (*Sinemet* [US], generics; *Sinemet CR* [generic only]; *Parcopa* [US], generic only; *Rytary* [US]; *Duopa* [US]; *Duodopa* [Canada]; *Dhivy* [US]; *Crexont* [US]) Levodopa: *Inbrija* (US) Levodopa-benserazide (*Prolopa* [Canada]) Carbidopa-levodopa-entacapone (*Stalevo,* generics [US]) Foscarbidopa-foslevodopa (*Vyalev*)	• Most effective drug for Parkinson's motor symptoms.[3,7] • Can be used first-line, especially in older patients (e.g., >65 to 70 years of age).[1,3,7]	•Highest risk of **dyskinesias** (see **footnote c**) and **motor fluctuations** (on-off, wearing off) (see **footnote d**).[3] •Lower risk of neuropsychiatric side effects than dopamine agonists.[3] •Treatment of neuropsychiatric effects includes stopping anticholinergics and amantadine, reduce or stop other antiparkinson agents, and levodopa dose reduction (last-line).[7] •Other side effects include nausea (take with food*), loss of appetite, orthostasis (worse with dopamine agonists), discolored sputum (*Inbrija*), cough (*Inbrija*).[1,3,25] *Food impairs absorption, and amino acids from dietary protein compete for transport into the brain. Taking on an empty stomach may improve efficacy as disease advances.[3] *Prolopa* (Canada) may cause less nausea.[17]	• Choose an immediate-release product (generic, or triple-scored *Dhivy*) for initial therapy for ease of titration.[1] • Generic controlled-release formulations have poor absorption, delayed onset, less predictable effects, and require a higher dose.[2,18] Can be used for overnight control or wearing off.[2,7] • Oral disintegrating tablets (US only) available for patients with difficulty swallowing. • As the disease advances, other medications will be added.[1] This may require reduction in the levodopa dose to minimize dyskinesias.[1] • *Inbrija* is a levodopa breath-actuated inhaler: Onset ~10 min. Lasts at least 1 hr.[25] ~$38/dose.[b] Not for patients with lung disease.[25] • Combo with entacapone may help with end of dose wearing off.[3] • Foscarbidopa-foslevodopa (*Vyalev*) subcutaneous infusion is reserved for treatment-refractory, debilitating motor fluctuations.[19]

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Dopamine agonist (pramipexole [*Mirapex* (Canada), generics; *Mirapex ER* (US), generics], ropinirole, ropinirole extended-release (US), rotigotine [*Neupro*])	• Not as effective as carbidopa-levodopa for Parkinson's symptoms.[1,7] • Can be used first-line in younger patients (e.g., <70 years of age).[7] • Can be added to levodopa to reduce off time, improve symptoms, or manage dyskinesias due to levodopa.[1,2]	• Side effects generally similar to carbidopa-levodopa.[1] Lower risk of motor complications.[3,7] Higher risk of hallucinations, nausea, excessive sleepiness, impaired impulse control (warn patient/caregiver), and orthostatic hypotension.[3,7]	• There is no proof of a meaningful difference in efficacy or safety among these drugs/dosage forms.[3,7] • Avoid in patients with a history of addiction, impaired impulse control, cognitive impairment, excessive daytime sleepiness, or psychosis.[3] • A study using a low-dose pramipexole/rasagiline combo for early disease has been completed.[28]
Monoamine oxidase type B (MAO-B) inhibitors (selegiline generic tablets or capsules [US], *Zelapar* [US]; rasagiline [*Azilect*], generics; safinamide [*Xadago*, US; *Onstryv*, Canada]) Note that transdermal selegiline (*Emsam*) has not been studied for Parkinson's disease. It is FDA-approved for depression only.[20] It achieves higher plasma levels than oral.[20]	• Mild benefit in early disease when activities of daily living are not yet impaired.[3,4,7,27] • Can be used first-line (not safinamide)[1,15,26] • Can be added to levodopa to reduce off time.[2,15,26] • Insufficient evidence of neuroprotection.[3,7]	• Considered well-tolerated.[1] Lower risk of neuropsychiatric side effects than dopamine agonists, and lower risk of dyskinesias than levodopa.[1,3] • Common side effects include constipation, dry mouth (selegiline, rasagiline), vivid dreams (selegiline), headache, nausea (less with safinamide).[18,24] • May cause hallucinations, confusion, or orthostasis, especially with selegiline plus levodopa.[4,23] • Agitation and insomnia are most common with selegiline (less with *Zelapar*); dose in morning and/or at noon.[18,24] • May worsen dyskinesias when used with levodopa; may require dopaminergic med dose reduction when added.[15,24,26] • Many potential **drug interactions** due to MAO inhibition (see **footnote f**).	• Rasagiline and safinamide are better studied for reducing off time, but no proof they work better than selegiline. All increase "on time" by about one hour more than placebo, similar to entacapone.[1] • Safinamide is a reversible MAO-B inhibitor; the others are irreversible. The clinical significance of this difference is unknown. Safinamide is also glutamatergic. Animal models suggest this may confer neuroprotection, and post hoc clinical trial analysis suggests it may provide analgesia.[22]

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Catechol-O-methyl transferase (COMT) inhibitors (entacapone [*Comtan*, generics]; opicapone [US; *Ongentys*]; tolcapone [US; *Tasmar*, generics]) Carbidopa-levodopa-entacapone (*Stalevo,* generics [US])	• Adjunct to carbidopa-levodopa for "wearing off;" not for monotherapy.[2,9] • Prolongs the duration of action of levodopa.[9]	• Addition of COMT inhibitor can increase carbidopa-levodopa side effects (e.g., dyskinesias, confusion).[2,9] Levodopa dose may need to be decreased.[1] • COMT inhibitors cause discolored urine (e.g., reddish brown, rust-colored), nausea, and diarrhea.[2,9] • Tolcapone requires liver function test monitoring.[2] • Opicapone can cause low blood pressure/dizziness and weight loss.[9]	• Combo product with carbidopa-levodopa plus entacapone (*Stalevo*) available. Decreases pill burden and may cost less than separate Rxs for *Comtan* plus carbidopa-levodopa. • Entacapone should be administered with each carbidopa-levodopa dose.[2] Tolcapone is dosed three times daily, starting with the first dose of carbidopa-levodopa.[5] Opicapone is dosed once daily at bedtime.[9]
Adenosine antagonist (istradefylline [*Nourianz*, US])	• Adjunct to carbidopa-levodopa for treatment of "off" episodes.[10]	• Seems to pose a relatively low risk of dyskinesias, hallucinations, or impulsive behaviors (no head-to-head-studies).[10,18] • Dyskinesia is the most common side effect.[10] • Behaviors or hallucinations may respond to dose reduction.[10] • May also cause constipation, dizziness, nausea, or insomnia (<10% of patients).[10] • Max dose is 20 mg with strong CYP3A4 inhibitors.[10]	• Once-daily dosing.[10] Initial dose titration not required.[10] • Reduces "off" time by less than an hour per day compared to placebo.[10]
Amantadine (generic tablets [US], capsules, syrup; *Gocovri* [US]; *Osmolex ER* [US]) *Continued…* Amantadine,	• Insufficient evidence for early disease.[7] • Added to levodopa in later disease for dyskinesias or "off" episodes.[7,29]	• Side effects include dizziness, orthostatic hypotension, falls, nausea, dry mouth, constipation, depression, insomnia, abnormal dreams, confusion, hallucinations, peripheral edema, livedo reticularis (cosmetic problem only).[1,18,29]	• Efficacy may wane after weeks or months.[1] • May require dose reduction or avoidance in kidney impairment.[1,29,30] • In the event of psychotic symptoms, stop amantadine first, then adjust other Parkinson's medications.[7]

Drug or Drug Class	Role in Therapy	Adverse Effects/Monitoring	Comments
continued			• *Gocovri* is taken at bedtime. Levels peak in the morning to cover dyskinesias and "off" time through the day, then decrease toward evening to limit effects on sleep.[32] • *Osmolex ER* approval based on bioavailability compared to immediate-release amantadine.[30]
Anticholinergics (trihexyphenidyl, benztropine)	• Could be used to target tremor in early disease in patients <60 years of age.[27]	• Side effects include dry mouth, urinary retention, constipation, confusion, hallucinations, short-term memory impairment, blurred vision.[1,8]	• In the event of psychotic symptoms, stop anticholinergic first, then adjust other Parkinson's medications.[7]
Apomorphine (*Apokyn*, generics [US], *Kynmobi*, *Movapo* [Canada])	• For acute, intermittent treatment of "off" episodes in advanced disease.[2,6,12-14]	• Initial titration in a monitored setting required (measure supine and sitting blood pressure, and pulse).[6,12-14] • Can pre-treat with an antiemetic (trimethobenzamide [US] recommended), but **not** a 5-HT3 antagonist (e.g., ondansetron) due to risk of profound hypotension (contraindication).[6,12-14] Canada: can use domperidone, but consider QT prolonging effect.[6,13] Avoid antidopaminergic antiemetics.[6,12-14] • Other labeled warnings: hypotension, syncope, falls, QT prolongation, cardiac events, psychosis, excessive sleepiness, priapism, dyskinesia, impaired impulse control, withdrawal, hemolytic anemia, oral mucosal irritation (sublingual).[6,12-14] • Other side effects, runny nose; **subcutaneous**: yawning, edema; **sublingual**: oral and pharyngeal tissue swelling, pain, and paresthesia.[6,12-14]	• Subcutaneous injection (*Apokyn*, *Movapo*) or sublingual film (*Kynmobi*).[6,12-14] • Short duration of action. Average frequency of dosing in clinical trials was three times daily for the subcutaneous injection, and two times daily for the sublingual product.[6,13,14] • May require dose reduction or avoidance in kidney impairment.[6,12-14] • Avoid with severe liver impairment (Child-Pugh Class C).[6,12-14]

a. **Tapering**: Safinamide labeling recommends reducing the dose to 50 mg for one week before discontinuation.[15,26] See our chart, *Common Oral Medications that May Need Tapering*, for general information about tapering dopaminergic Parkinson's disease medications.
b. **Cost** is wholesale acquisition cost (WAC). Medication pricing by Elsevier, accessed June 2023.
c. **Dyskinesias**: Risk factors include younger age, higher levodopa dose (due to high peak), and longer disease duration.[2,3,31] Individualize treatment based on comorbidities, drug side effects, and patient preferences and goals.[7] Reduce levodopa dose and give more frequently; cautiously add a dopamine agonist; reduce dose of any concomitant COMT or MAO-B inhibitor; add amantadine; or switch to levodopa gel (*Duopa* [U.S.], *Duodopa* [Canada]).[2,7,21]
d. **Motor fluctuations (e.g., wearing off, on-off)**: Individualize treatment based on comorbidities, drug side effects, and patient preference and goals.[7] Add a COMT inhibitor or MAO-B inhibitor, dopamine agonist (e.g., rotigotine, ropinirole XL), istradefylline, or apomorphine or *Inbrija* [U.S.] rescue, or give lower levodopa doses more frequently.[1,2,10,25] Enhance levodopa absorption; advise taking levodopa 30 minutes before eating, treat constipation, and advise avoiding high protein meals during the day.[2] Could switch to *Rytary* or *Crexont* (longer duration vs immediate-release) to increase "good" on-time/dose by 1.16 h for *Rytary* or 1.55 h for *Crexont*, vs immediate-release products).[16] (See product labeling or www.rytary.com for dose conversion.) Switching to levodopa gel is another option.[2] Controlled-release levodopa (i.e., generic *Sinemet* CR) does not reduce off-time better than immediate-release,[1] but despite absorption problems, could be tried at bedtime to provide more stable levodopa levels overnight.[2] Note that add-ons pose the risk of causing peak-dose dyskinesia.[2]
e. **Brief overview of treatment**. Initial treatment options include levodopa, a dopamine agonist, or a monoamine oxidase type B (MAO-B) inhibtor.[1] Levodopa is the most effective agent, while dopamine agonists are less tolerable.[3] All patients will eventually require levodopa.[1] After a period of good control, motor fluctuations (e.g., wearing off, on-off phenomenon) and dyskinesias develop in almost all patients within ten years.[1,2] Management may include changing the levodopa regimen, dose reduction of concomitant agents, or cautious addition of another agent.[2]
f. **MAO-B drug interactions**: antidepressants (commonly combined, however), tramadol, meperidine, methadone, dextromethorphan, fentanyl, amphetamines, other MAO inhibitors (e.g., linezolid).[3,11,15,26] Check product labeling for contraindications, and monitor patients on other combinations (e.g., for agitation, confusion, delirium, diarrhea, fever, increased heart rate, hyperreflexia, clonus, tremor).[11]

Parkinson's Disease Therapy Algorithm

See our *Parkinson's Disease Therapy* algorithm for further information

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