How to identify Parkinson's disease?
Parkinsonism (PS) is a clinical diagnosis that requires 2 of the following 3: bradykinesia, rigidity & resting tremor (or the THREE S's: slow, stiff & shaky). Postural instability is often a late PD presentation. The majority ~85% of PS cases are idiopathic Parkinson's disease (PD). Other PS variants include multiple system atrophy, progressive supranuclear palsy and drug-induced PS. Lewy body dementia has PS features with dementia 
TREATMENT: After the offending drug is stopped it may take up to 1-4 months for PS symptoms to resolve.

What medications can induce PS?
Select medications can induce PS either acutely or within 3 months of use (eg. amiodarone, amphotericin B, calcium channel blockers, chemotherapy, lithium, meperidine, metoclopramide, neuroleptics, cholinergics, reserpine, SSRIs & valproate). After the offending drug is stopped it may take up to 2-6 months for PS symptoms to resolve.

Is levodopa still the most powerful med?
Levodopa (LD) provides superior motor benefit, but is associated with increased dyskinesias. In early PD, LD use is often delayed to preserve LD usefulness, but LD is very valuable in the elderly. Other early PD considerations are amantadine or selegiline. Initial Sinemet dose is usually 100/25mg bid, increasing in ~1 week if needed. An adequate trial dose is considered to be ≤200/50mg qid x 3 months.

How can I get the Sinemet to work faster?
Chewing the tablets or drinking with carbonated beverages will increase absorption (whereas high protein foods may slow absorption). Clinically this is useful for patients with severe early morning symptoms and/or painful dystonia.

Ways to overcome troubling LD side effects?
Nausea: ensure 75-200mg of carbidopa is being used with LD, LD with food or consider using domperidone 5-10mg po ld ac.
Hypotension: ensure adequate water & salt intake; consider midodrine 7.5-15mg bid, domperidone or fludrocortisone 0.05-0.4mg tid.

Is Sinemet CR best for my patient?
There is no evidence that CR levodopa is better than regular release, but it is more costly. However, if early morning "off" episodes are occurring, giving CR at bedtime may help. Taking with food increases absorption, but overall only 70% is bioavailable (eg. ↑ dose by 20-30% if switching to CR from regular release, if an equivalent dose is desired).

Are there drawbacks to dopamine agonists?
Although not as potent as LD, younger patients may benefit from using dopamine agonists (DA) to delay LD tolerance and dyskinesia. DA's have less motor complications, but more hallucinations, somnolence & edema than LD. If DAs are not titrated both slowly and up to the therapeutic dose, side effects occur without much clinical benefit.

Are anticholinergics in the elderly a good idea?
Although useful for tremor predominant PD but unproven superiority, mild PD symptoms, drooling and dystonia, use in the elderly frequently causes constipation, confusion, and hallucinations. If stopping anticholinergics, taper to prevent PD exacerbations. Using lower doses minimizes toxicity.

How to manage a psychotic PD patient?
It is important to rule out drug induced confusion/hallucinations. In general decrease the dose, or discontinue the drug in the following order: anticholinergic, selegiline, amantadine, DA & then levodopa. Consider quetiapine after other offending drugs are stopped. It may take 1-4 weeks for psychosis to resolve. (Alternately clozapine but requires weekly blood tests, expensive & lacks coverage for this indication %)

How to manage behavior in a PD patient?
Antidepressants (eg. tricyclics,SSRI's) may be required for depression, but rare cases of SSRI's worsening PD are reported.

How to manage wearing off effects in PD patient?
Consider smaller & more frequent LD dosing (liquid forms an option), an addition of Sinemet CR, combination DA & LD, entacapone, amantadine, selegiline, apomorphine SC or possibly decreasing protein in the diet may help. (IF adding DA or entacapone a decrease in LD dose may be needed.)

How to manage dyskinesia in a PD patient?
Dyskinesias are best prevented by avoiding large doses of LD early in the disease. Treat if bothersome; consider lowering LD dose (CR form hard to adjust dose), add amantadine, add/switch to a DA, possibly stop entacapone or selegiline or consider surgery.

How about alternative therapies?
Lack evidence for benefit for vitamins, herbs or chelation; however, broad beans Cowhage provide superior motor benefit. But, broad beans Cowhage do contain LD. PS documented with manganese, but only "shakes" from lead or mercury. PD seems to have a genetic predisposition with environmental factors playing a role. Benefits of Coenzyme Q10 in PD requires further study.
### Levodopa/benserazide

**Generic:** PROLOPA

- 5012.5, 100, 200, 500mg cap

- Levodopa/carbidopa

  **Generic:** SINEMET

- 100/25, 200/50mg cap; CR tab: 200/50mg, 300mg cap

  - Benserazide & carbidopa are peripheral dopamine decarboxylase inhibitors which ↓ nausea from levodopa.

  - Carbidopa/levodopa/entacapone STELAVO

  - Not in USA

- Carbidopa is a dopamine precursor which levodopa can be converted into.

- Levodopa is the primary active component of anti-Parkinson medications.

### Dopamine precursor: Levodopa

- Levodopa (LD): most potent med available for PD (regular tab/cap: peak level at ~30min & ~4hr duration)

- Levodopa/carbidopa: GI: ↓ bradykinesia, dyskinesia, & constipation.

- Levodopa provides superior motor benefit but is associated with ↑ risk of dyskinesia.

### Conclusion

- Levodopa is the primary active component of anti-Parkinson medications.

- Levodopa is the most effective medication for Parkinson's disease.

### Anticholinergics

- All: blocks cholinergic activity in the brain.

  - Best to taper & discontinue over several days (~7) when stopping!

  - CNS: confusion, drowsiness, headache, slow memory; anticholinergic: dry mouth, blurred vision, urinary retention, constipation; embarrassment; rash, ↑ HR & ↓ sweating (over heating).

  - Serous: ↑ hallucinations, confusion, dizziness, depression, hallucinations.

  - BP: psychosis, arrhythmias, sudden sleep, blood dyscrasia, neuroleptic malignant syndrome (esp. after abrupt D/C med), malignant melanoma, anemia & possible ↑ gambling behavior.

  - MAO: side effects which can include confusion, depression, dizziness, hallucinations, hypertension, & anxiety.

  - Correct: levodopa/entacapone is often ~3 months of 200/50mg qid, but most pts. respond to lower dosages.

  - Use lower doses if on Sinemet.

  - Serous: ↑ toxicities: MAOIs, anticholinergic agents.

  - Toxicity: ↑ nausea from levodopa.

  - Notice that levodopa, anticholinergic, and antihistamine medications can cause significant side effects.

  - Consider an alternative medication or adjust the dosage accordingly.

### Bromocriptine

- 1.25-2.5mg bid Tq1-2wk

- Usual 2.5-20mg bid

- 1.5mg tid Q2wk Max 5mg od

- 0.5mg od Tq2wk Max 5mg od

- 0.05mg od Tq7qd Max 1.5mg tid

- 0.25mg od Tq7qd Max 1.5mg tid

- 0.25mg tid Max 7.5mg tid

- 0.5mg tid Max 15mg tid

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<table>
<thead>
<tr>
<th>Generic/TRADE (Strength &amp; forms)</th>
<th>Class/Mechanism of Action/ Pregnancy category</th>
<th>Side effects / Contraindications</th>
<th>= Therapeutic Use / Comments / Drug Interactions</th>
<th>INITIAL &amp; MAX DOSE</th>
<th>USUAL DOSE RANGE</th>
</tr>
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<tbody>
<tr>
<td><strong>Amantadine 46</strong> SYMMENTREL/generic 100mg cap; 100mg/10ml syrup</td>
<td>NMDA receptor antagonist blocks reuptake/ release of dopamine via N-methyl-D-aspartate antagonist (NMDA)</td>
<td>Common: CNS (esp in elderly confusion, drowsiness, nightmares, light headedness, insomnia; anticholinergic effects, irritability, (less when ↓ dose for age &amp; renal fx); GI upset, ↓BP, ankle edema &amp; rose colored motting on legs. Serious: seizures, psychiatric illness, arrhythmias, visual impairment, neuropenia, hallucinations &amp; ↓BP.</td>
<td>PD-modest effect (early to help with tremor, later to ↓dyskinesia, may help ON effect, better tolerated in young PD pts), antiviral-influenza A, drug induced EPS -300 mg/d ↓dyskinesias-45% but lasted &lt;8months - unknown whether safe &amp; effective for levodopa induced dyskinesias -48 Cochrane 2003, may ↓fatigue -avoid abrupt withdrawal-worsen PD/cause NMS ↓ effect of therapy with ↓ antipsychotics &amp; live influenza vaccine may be less effective ↑ level of therapy with: trihexyphenidyl</td>
<td>100mg od ↑7qd</td>
<td>Max 200mg bid</td>
</tr>
<tr>
<td><strong>Entacapone 49,50,51,52,53 COMTAN</strong> 200mg tab</td>
<td>Inhibits reversible COMT (peripheral catechol O-methyl-transferase; decreases the GI metabolism of levodopa to prolong the half life &amp; area under the curve without affecting the peak concentration; therefore ↑ effect in the brain)</td>
<td>Common: nausea, vomiting, ↑dyskinesias, urine discoloration, abdominal pain, ↑sweating, mood changes &amp; daytime sleepiness. Serious: dyskinesia, ↓BP, diarrhea (may present even weeks to months after starting), hallucinations &amp; NMS</td>
<td>↓idiopathic PD with wearing-off Sx at end of dose ↓ for motor complications to ↓ off time ↓ levodopa. ↑ end of dose wearing off, to ↓ levodopa dose, &amp; modestly improve motor &amp; disability ↓ in pts who are not experiencing motor fluctuations while on levodopa, entacapone does not improve motor scores but improves some quality-of-life measures ↓-300 mg/d</td>
<td>100-200mg</td>
<td>Max 1.6 g/d (with each levodopa dose given)</td>
</tr>
<tr>
<td><strong>Selegiline 56,57,58,59,60,61 ELDERLY/generic</strong> 5mg tab (also known as deprenyl)</td>
<td>Irreversibly inhibits monoamine oxidase type B (MAO-B) to decrease the metabolism of dopamine</td>
<td>Common: nausea, dizziness, orthostatic hypotension, abdominal pain, hallucinations, dyskinesia, rash, insomnia &amp; alopecia. Serious: arrhythmia, TH↑, ↓BP esp. with doses &gt;10mg/d, anemia, ↓ BP, meperidine</td>
<td>ADJOINT for PD (may aid wearing off effects) ↓ improves disability scores &amp; delays need for levodopa without ↑ mortality; may ↓ freezing? has very mild symptomatic benefit with ↑ in quality of life measures NMS</td>
<td>2.5-5mg od</td>
<td>Max 5mg bid</td>
</tr>
<tr>
<td><strong>Rasagiline AGILECT 0.5-1mg od not in CR yet</strong></td>
<td></td>
<td></td>
<td></td>
<td>5mg po od cc</td>
<td>5mg po od cc</td>
</tr>
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</table>

**Notes:**
- ↓ dose for renal dysfunction = scored tab ≠ Non-formulary Sask. = Exception Drug Status Sask. ≠-not covered by NIHB ≠-covered by NIHB ac=before meals BP=blood pressure cc=with meal ac=contraindication CR=control release d=daily DA=dopamine agonist D1,2,3,4= dopaminergic receptors subtypes D/C=discontinue DI=dopamine interaction Dx=disease EPS=Extrapyramidal symptoms fx= function HS=bedtime heart rate IR=immediate release NMS=neuroleptic malignant syndrome ∪=nausea/vomiting pe=after meals PD=Parkinson's disease Pt=patient Sx=symptoms Sz=seizure SE=side effect UPDRS=Unified Parkinson's Disease Rating Scale Tx=treatment wt=weight
- **Epidemiologic:** 100,000 Canadians affected, 0.4% general population, ~3% in >65yr age group, lack of substantia nigra dopamine containing neurons. Website of interest: www.parkinson.ca
- **Symptoms:** Rhythmic asymmetric tremor (~70% of pts) hands (pill rolling), feet, lips or jaw (not usually head or neck). Rigidity (~90% of pts) -lead pipe, cogwheel often in neck, trunk & limbs.
- **Bradykinesia (~70% of pts)-slowness of all movements incl. walking. Postural instability-often later presentation, shuffling gait, narrow base, festination, freezing & falls. Micrographia frequently present.
- **Diagnosis:** Classic one-sided signs, resting tremor & good tx response. Atypical ~20%, early falls, LBP, bladder dysfx & lack resting tremor. Drug induced: ~5% may take 4 months to resolve antimetabolites B, calcium channel blockers, chemotherapy, cholinergic, lithium, meperidine metoclopamidene, neuroleptics, reserpine, SSRIs & valporate Asoc: problems: 63 depression/anxiety/psychosis, ↓BP, neurogenic bladder, sexual dysfx, dizziness, dysarthria, dysphagia, dermatitis neuropathy, sleep & bowel changes. Adjunct Meds: Psychotic Sx: clozapine**~10=6.5-25mg/d, agranulocytosis 0.6%-6.88, 69.76, 70, 71, 72, 73; quetiapine (~25-150mg/d)10, 11, 12, 13; 14; beta blockers (lack evidence) 76, apomorphine special access (DA2-6mg SC 3-5x/d with dopomine for off-state episodes) 77,78 & vitamin E (NOT beneficial) 80 DATATOR
- **Red Flags:** Early severe Bradykinesia; prominent early instability; early autonomic dysfx; no response to levodopa ~1g/d; presence of extra ocular movements, ataxia or corticospinal tract signs.
- **Non Drug:** Involve patient & family for education, support, exercise, physiotherapy, speech therapy, occupational therapists (for mobility, safety & driving skills) & nutrition counseling.

**Wearing off:** ~ consider smaller & more frequent LD dosing based from experience, an addition of Sinemet CR, combo DA & levodopa, COMT inhibitor, amantadine, selegiline or apomorphine SC. (↓ protein in diet may help)

**Dyskinesia:** ~10% in earlier stage consider ↓levodopa dose OR form hard to adjust dose, add amantadine, add ↑/switch DA, possibly D/C COMT/selegiline or consider surgery. **Tremor:** if predominant consider amantadine/anticholinergics esp. in young. If drug induced confusion/hallucination: ↑-30 may take 2-4w to resolve, meds in following order—anticholinergic, selegiline, amantadine, DA & then levodopa. Consider tx with quetiapine or clozapine after other possible offending drugs are D/C.

**Treat when disability present, to control Sx & ↑ function, add meds slowly, good history & listen to timing of Sx; deterioration may be due to stress, ↓ sleep or new med. If poor medical control may consider surgery.** 47,48
References: www.RxFiles.ca


Clinical trials

7 Briggs GG, Freeman RK, Surerr JY. Drugs in Pregnancy and Lactation 6th Ed. 2002


Clinical trials