Parkinson's Treatment
"Tips & Pearls"

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Objective Comparisons for Optimal Drug Therapy

The RxFiles Academic Detailing Program
Saskatoon City Hospital
701 Queen Street, Saskatoon, SK S7K 0M7
Phone 306-655-8506 ; Fax 306-655-7980; www.RxFiles.ca

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 onset within the first year. Drug benefits must be evaluated against any side effects to ensure benefits outweigh the risks. Individualize therapy!

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, SSRI's & 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 ~1week 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 tid ac.
Hypotension: ensure adequate water & salt intake; consider midodrine 7.5-15mg/d, domperidone or fludrocortisone 0.05-0.4mg/d.

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 SK.)

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 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.

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Generic/TRADE (Strength & forms)	Class/Mechanism of Action/ Pregnancy category [7]	Side effects / Contraindications CI	√ = Therapeutic Use / Comments / Drug Interactions DI	INITIAL & MAX DOSE	USUAL DOSE RANGE	$ /30d
Levodopa/benserazide **PROLOPA** =P 50/12.5, 100/25, 200/50mg cap **Levodopa/carbidopa** [8] **SINEMET**/generic =S 100/10^{S};100/25^{S};250/25^{S}mg IR tab; 100/25,200/50mg^{S} **CR** tab: 70% bioavailable vs immediate release **Oral liquid form** [9,10] manufactured by some pharmacies **carbidopa/levodopa/ entacapone STALEVO** [11] -not in 🇨🇦 yet 50= 12.5/50/200 100= 25/100/200 150= 37.5/150/200mg tab (don't cut these doses in half) (PARCOPA: rapid dissolving form of levo/carbidopa avail in USA only [12], DUODOPA: levo/carbidopa gel for Intraduodenal infusion avail. in Europe[13])	**Dopamine precursor**: Levodopa (LD): **most** potent med available for PD {regular tab/cap: peak level at ~30minutes & ~4hr duration} Benserazide & carbidopa are peripheral dopamine **decarboxylation inhibitors** which ↓ nausea from levodopa. (≥75mg **carbidopa** [14] blocks enzyme; may need up to 200mg) C **-all**	**Common**: GI: **nausea**, vomiting, anorexia; CNS: headache, confusion, dizziness, **hallucinations**, mood changes, **nightmares**, insomnia, depression; rash, alopecia, discolored urine, dark saliva/sweat & ↑**libido. Dose unresponsiveness** & freezing, **fluctuations** (**wearing off**, on-off), **dyskinesia** (chorea, **peak dose**, diphasic & dystonia[off period; hand/foot in AM]). **Serious**: dyskinesia, **↓BP**, psychosis, arrhythmias, sudden sleep, blood dyscrasia, neuroleptic malignant syndrome (esp. after abrupt D/C med), malignant melanoma, anemia & possible ↑ gambling behavior. CI: MAOI use, caution if psychosis history, glaucoma,sympathomimetic amines & may activate melanoma. Correct ↓BP SE by: ↑water & salt intake, midodrine [7.5-30mg/d], domperidone,fludrocortisone [0.05-0.4mg/d] & adjust antihypertensive & TCA doses.	√ idiopathic, postencephalitic & symptomatic PD esp. if pt rigid, bradykinesia or **elderly**. Not useful for freezing. For restless leg sx (eg. 100/25@hs). -initiate PD tx with either levodopa **or** a DA; levodopa provides **superior motor benefit** but is assoc. with an **↑risk of dyskinesia**. [1 American 2002] -**wearing off**, on-off phenomena, sudden offs & freezing & dyskinesia incl. painful dystonia affect ≤ 70% of pts **within 5yr of starting** levodopa. [15] -**No** evidence that CR levodopa [16 (Koller)] better than regular release, but may help to **give CR @HS if early morning OFF** episodes occurring -on-off phenomenon (reduced by giving smaller, more frequent levodopa doses **or** adding DA) -can be given up to 4hrs before surgery -may slow progression or ↓ severity of sx [(NEJM'04) 17] -avoid abrupt withdrawal→worsen PD/cause NMS DI: ↓ effect of levodopa: antipsychotics, iron [↓ absorption], isoniazid, metoclopramide & pyridoxine [only if levodopa alone ; no effect if bens./carbidopa used]. ↑ toxicity: MAOI's, antihypertensive agents	P 50/12.5mg bid ↑q3-7d Max 2g/d S 50/12.5mg bid ↑q3-7d Max 2g/d Dosing frequency is 3-6x/day for regular release. An adequate trial is often ~3months of 200/50mg qid, but most pts. respond to lower dosages. ↑ **dose** by **20-30% if switching** to **CR** if want equivalent dose. CR useful sometimes since duration of action is 25% longer [2]	100/25mg tid-qid cc 200/50mg tid cc (contains phenylalanine) 100/25mg tid-qid cc 250/25mg tid cc 100/25mg CR tid cc 200/50mg CR bid-tid cc **Chew** tabs & carbonated drink will ↑absorption [even useful for IR tab] esp. **good for severe early morning** Sx. ↑ **protein** foods [18] may ↓ absorption. Take **cc** if nausea; **ac** for ↑ absorption of regular formulation **Domperidone** [5-10-20mg tid ac] to ↓ nausea / hypotension	54-70 87 45-58 49 76 60-86 ~20
Bromocriptine [19,20,21,22,23] **PARLODEL**/generic 2.5^{S} mg tab; 5mg cap ergot derivative to D1,2 **Cabergoline** [24,25] **DOSTINEX** 0.5^{S} mg tab {☎✆ hyperprolactinemia} ergot derivative to D2 **Pergolide** [26] **PERMAX** 0.05^{S},0.25^{S},1^{S} mg tabs ergot derivative to D1,2 **Pramipexole** [27,28,29,30,31] **MIRAPEX** 0.25^{S},0.5^{S},1^{S},1.5^{S} mg tabs non-ergot derivative to D2,3,4 **Ropinirole** [32,33,34] **REQUIP** 0.25,1,2,5mg tab non-ergot derivative to D2,3,4	**Dopamine agonist** [35,36] **(DA)** (active at various receptors eg. $D_{1,2,3}$ or $_4$ subtype) B for bromocriptine, cabergoline & pergolide; but pramipexole & ropinirole are a C {lack evidence for any one being better than another} {starter packs may be available for dose titration}	**Common**: GI: **nausea**, vomiting **{may use domperidone to ↓nausea}**, anorexia; CNS: headache, **confusion**, dizziness, depression, **dyskinesia**, **hallucinations**; **↓BP**, alopecia & ankle **edema.** **Serious**: seizures, stroke, MI, sudden **sleep episodes** [37,38,39], gambling [40] & {(**ergot derivatives:** pulmonary & retroperitoneal fibrosis, digital spasms, limb/skin pain & Raynaud's like phenomena may occur); Cardiac valve dx [0.005%] with pergolide.[41,42,43] Consider echo at baseline.} CI: protease inhibitors & sibutramine with ergot agents; caution if psychosis & if uncontrolled hypertension	√idiopathic PD, (galactorrhea +/- amenorrhea, hypogonadism, prolactin-secreting adenoma, acromegaly, prevent postpartum lactation, NMS [bromocriptine]), restless leg Sx -initiate at low dose & ↑ gradually **over 4-6weeks** -for initial PD, levodopa **or** a DA can be used; but DA may have **less motor complications** with tx, but ↑ hallucinations, somnolence & edema than levodopa tx. [1 American 2002] Not useful for freezing. -at low doses DA have less benefit but still ↑SE -↓ levodopa dose often possible after adding DA -possible preference in **young** (**<50yrs**) PD pts [2,44] -can be given up to 4hrs before surgery DI: ↓ effect therapy: antipsychotics, metoclopramide, nitroglycerin [↓ benefit of NTG] & omeprazole [for ropinirole] ↑ toxicity: (amantadine, cimetidine, diltiazem, quinidine, quinine, triamterene & verapamil [with pramipexole only]), ciprofloxacin [with ropinirole], (clarithromycin, erythromycin, fluvoxamine [also with ropinirole], itraconazole, propranolol & protease inhibitors [esp with bromocriptine, cabergoline & pergolide]), serotonin meds like SSRIs/MAOI [↑ risk of serotonin syndrome] & sibutramine.	1.25-2.5mg bid ↑q1-2wk Usual 2.5-20mg bid 0.25mg od ↑q2wk Max 5mg od 0.05mg od ↑q7d Max 1.5mg tid {use lower doses if also on Sinemet} 0.125mg tid ↑q7d Max 1.5mg tid 0.25mg tid ↑q7d Max 8mg tid	5mg tid cc 10mg tid cc -less useful as mono tx [2] 1mg od 3mg od 0.25mg tid 0.5mg tid 1mg tid 0.5-1mg tid cc 1.5mg tid cc 🍎 (0.5,1,1.5mg tabs same $) 1-2mg po tid cc 3mg tid cc 5mg tid cc	110 215 850 2500 100 200 330 230 230 125 240 340
Benztropine **COGENTIN**/generic 2^{S} tab; 2mg/2ml inj **Ethopropazine** **PARSITAN** 50^{S} mg tab **Procyclidine** **KEMADRIN**/generic 5^{S}mg,2.5mg✗▼tab;2.5mg/5ml elixir **Trihexyphenidyl** **ARTANE**/generic 2^{S}, 5^{S} mg tabs; 0.4mg/ml soln ✗▼	**Anticholinergics** C **–all** **-blocks cholinergic activity in the brain** **Best to taper & discontinue over several days (~7) when stopping!**	**Common**: CNS: **confusion**, **drowsiness**, headache, **slow memory; anticholinergic**: dry mouth, blurred vision, urinary retention, **constipation** etc.; rash, ↑ HR & ↓ sweating (over heating). **Serious**: ↑ HR, delirium & psychosis CI: narrow angle glaucoma, ileus, BPH, myasthenia gravis, obstructive uropathy	√PD tremor (unknown if better for tremor vs other Sx) [45 Cochrane'03], useful for foot dystonia, ↓drooling[3] & drug induced EPS. As mono or adjunct tx more effective than placebo in improving motor fx.[1 American 2002] Neuropsychiatric & cognitive **SE esp in elderly.** Withdraw very slowly to prevent PD exacerbations. Switching to another anticholinergic may be of use. DI: Worsen Parkinson's Sx with: antipsychotics, cholinergics (eg. donepezil, galantamine, rivastigmine) ↑ toxicity with: anticholinergics (eg. amantadine, TCA's,OTCs)	0.5-1mg hs ↑q5d Max 2mg tid 25mg od Max 500mg/d 2.5mg bid ↑q5d Max 5mg qid 1-2mg hs ↑5qd Max 5mg tid	1mg bid 2mg bid 50mg bid 100mg bid 2.5mg tid cc 5mg tid cc 2mg tid cc 5mg bid cc	9 12 21 34 9 10 11 14

Generic/TRADE (Strength & forms)	Class/Mechanism of Action/ Pregnancy category [7]	Side effects / Contraindications CI	√ = Therapeutic Use / Comments / Drug Interactions DI	INITIAL & MAX DOSE	USUAL DOSE RANGE	$ /30d
Amantadine [46] SYMMETREL/generic 100mg cap; 100mg/10ml syrup	**NMDA receptor antagonist** blocks reuptake/↑ release of dopamine via N-methyl-D-aspartate antagonist (NMDA) C	**Common**: CNS: (esp in elderly) **confusion**, drowsiness, nightmares, light headedness, **insomnia**; anticholinergic effects, irritability, (less when ↓ dose for age & renal fx); GI upset, ↓BP, ankle **edema** & rose colored mottling on legs. **Serious**: seizures, psychiatric illness, arrhythmias, visual impairment, neutropenia, hallucinations & **↓BP.**	√ 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 <8months [47] - unknown whether safe & effective for levodopa induced dyskinesias [48 Cohrane 2003]; may ↓fatigue? -avoid abrupt withdrawal→worsen PD/cause NMS DI: ↓ effect of therapy with : antipsychotics & live influenza vaccine may be less effective ↑ amantadine levels with: triamterene	100mg od ↑7qd Max 200mg bid	100mg bid (8am & 12 noon; or od) 100mg tid Trial for ~2weeks before deciding if tx ineffective. [3]	33 45
Entacapone [49,50,51,52,53] COMTAN 200mg tab **Tolcapone** TASMAR 200mg tab -restricted for only previous pts (b/c of ↑LFT's) Phone: 613-941-2108 **carbidopa/levodopa/ entacapone** STALEVO -not in 🇨🇦 yet 50= 12.5/50/200 100= 25/100/200 150=37.5/150/200mg tab (do not cut dose in half)	**Inhibits reversible COMT** (peripheral catechol O-methyl-transferase: decreases the GI metabolism of levodopa to prolong the half life & area under the curve without affecting the peak concentration; therefore ↑ effect in the brain) C	**Common**: **nausea**, vomiting, **↑ dyskinesias**, **urine discoloration**, abdominal pain, ↑ sweating, mood changes & daytime sleepiness. **Serious**: dyskinesia, ↓BP, **diarrhea** (may present even weeks to months after starting), hallucinations & NMS. CI: dobutamine, dopamine, epinephrine, isoproterenol, MAOIs, history of NMS	√ idiopathic PD with wearing-off Sx at end of dose -for **motor complications** to **↓ off time** ~1.5hrs/day (eg. end of dose wearing off), to ↓ levodopa dose, & modestly improve motor & disability [54 Cochrane 2004] -in pts who are **not** experiencing motor fluctuations while on levodopa, entacapone does **not** improve motor scores but improves some quality-of-life measures [55] -combo with levodopa can ↑ levodopa levels ~25% thus **↓ levodopa dose to minimize dyskinesias** & this combo prolongs the levodopa effect DI: ↑HR with dobutamine, dopamine, epinephrine & isoproterenol; chelates with iron	100-200mg Max 1.6 g/d	200mg po tid 200mg po qid (with **each** levodopa dose given)	165 215
Selegiline [56,57,58,59,60,61] ELDEPRYL/generic 5ς mg tab ☎ (also known as deprenyl) Rasagiline AGILECT 0.5-1mg od -not in 🇨🇦 yet	**Irreversibly inhibits monamine oxidase type B** (MAO-B) to decrease the metabolism of dopamine C	**Common**: **nausea**, dizziness, orthostatic hypotension, abdominal pain, hallucinations, dyskinesia, rash, **insomnia** & alopecia. **Serious**: arrhythmia, ↑HR, ↑BP esp. with doses >10mg/d, anemia CI: meperidine	√ adjunct for PD (may aid wearing off effects) -improves disability scores & delays need for levodopa without ↑ mortality [62]; may ↓ freezing? -has very mild symptomatic benefit with **no evidence** for neuroprotective benefit [1 American 2002] -stop 10days before anesthetic (has amphetamine metabolites) DI: ↑ toxicity with: atomoxetine, **amphetamines**, bupropion, buspirone, **dextromethorphan**, entacapone, ephedrine, **meperidine**, methylphenidate, miconazole, mirtazapine, phenylephrine, pseudoephedrine, **SSRI's**, TCA's, venlafaxine	2.5-5mg od **Max 5mg bid** (given earlier in the day to ↓ insomnia)	5mg po od cc 5mg am & noon (Often used in earlier rather than later PD) Tyramine intake should not be a concern with typical doses	42 78

=↓ dose for renal dysfunction ς=scored tab χ=Non-formulary Sask ☎=Exception Drug Status Sask. ⊗=not covered by NIHB ▼=covered by NIHB **ac**=before meals **BP**=blood pressure **cc**=with meal **CI**=contraindication **CR**=control release d=day **DA**=dopamine agonist **D1,2,3,4**= dopamine receptors subtypes D/C=discontinue **DI**=drug interaction **Dx**=disease **EPS**=Extrapyramidal symptoms **fx**=function **HS**=bedtime **HR**=heart rate **IR**=immediate release **NMS**=neuroleptic malignant syndrome **n/v**=nausea/vomiting **pc**=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: **Resting** 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, ↓BP, bladder dysfx & lack resting tremor. **Drug Induced**:[63] may take2-6 months to resolve amphotericin B, calcium channel blockers, chemotherapy, cholinergic, lithium, meperidine, **metoclopramide**, **neuroleptics**, reserpine, SSRI's & valproate. **Assoc. problems**:[64] depression/anxiety/psychosis, ↓BP,neurogenic bladder,sexual dysfx,dementia,dysarthia,dysphagia,dermatitis seborrheic, sleep & bowel changes.

Adjunct Meds: Psychotic Sx: clozapine☎▼(~6.25-75mg/d, agranulocytosis 0.6%)[65,66,67] or quetiapine (~25-150mg/d)[68,69,70]; botox (focal dystonia & sialorrhea)[71]; Dementia Sx: donepezil & rivastigmine☎ ⊗but ↑ N/V/ tremor [72,73,74]; modafinil ALERTEC ☎▼(200mg/d to ↓excessive daytime sleepiness)[75]; beta blockers (lack evidence) [76]; apomorphine special access(DA:2-6mg SC 3-5x/d prn with domperidone for off-state episodes) [77,78,79] & vitamin E (NOT beneficial: [80] DATATOP)

Red Flags: early severe dementia; prominent early instability; early autonomic dysfx; no response to levodopa ~1g/d; presence of extra ocular movements, ataxia or corticospinal tract signs.

Rule out: Alzheimer with EPS, Benign essential tremor, Corticobasal degeneration, Diffuse Lewy body dx, Drug-induced EPS, Focal lesions, Infectious-postencephalitic, Multisystem atrophy, Progressive supranuclear palsy, vascular-lacunar state & Wilson dx.

Non Drug: involve patient & family for education, support, exercise, physiotherapy, speech therapy, occupational therapists (for mobility, safety & driving skills) & nutrition counselling.

Wearing off: [1-5] consider **smaller & more frequent LD** dosing [liquid form option], an **addition of Sinemet CR**, **combo DA & levodopa**, **COMT inhibitor**, amantadine, selegiline or apomorphine SC. (↓ protein in diet may help)
Dyskinesia: [1-5 If bothersome] consider ↓levodopa dose [CR 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**: [1-5 May take 1-4 wk 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. [81,82]

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