50TH ANNIVERSARY
Parkinson Society British Columbia

Motor Symptoms

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From Moving Forward Together Conference, October 26, 2019, Burnaby, BC

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OBJECTIVES

- Review motor symptoms and evaluation
- Discuss treatment strategies, including references to the most recent Canadian guideline for Parkinson disease (CMAJ, September 2019)
- Briefly discuss the Saskatchewan Movement Disorders Program, including the role of clinicopathological studies and research

DISCLOSURES

- I am a movement disorders neurologist (clinician), not a basic scientist or neurosurgeon
- Some of what I will discuss is my personal views, which may differ from published guidelines
- I have received research support from the Dr. Ali Rajput Endowment for Parkinson's Disease and Movement Disorders (managed by Royal University Hospital Foundation) and am co-investigator on a grant funded by Parkinson Canada

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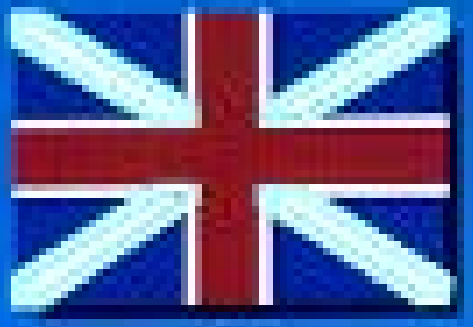
"Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured."



Dr. James Parkinson
"An ESSAY on the SHAKING PALSY"
1817

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James Parkinson (1755-1824)

- Photo – not available (first known photograph did not appear until 1826)

- Multiple interests
  - Surgeon-apothecary, medical writer, advocate for the underprivileged and an outspoken critic of the government; amateur chemist, and best known during his lifetime for his work in geology and paleontology
    (Parent A. A tribute to James Parkinson. *Can J Neurol Sci*. 2018; 45:83-89)

- Original paper reported on what he observed in 6 people

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EPIDEMIOLOGY

- The second most common neurodegenerative disease affecting humans (after Alzheimer's)
- Parkinson's disease (PD) affects 1% of the general population age 60 years and older
  - Nearly all studies show slight but definite male preponderance
- Canadian census data from 2016
  - 1,173,080 people ages 60+ in British Columbia → ***about 12,000 persons in the province with PD***
- For policy makers:
  - Recent abstract by Tanner et al. at MDS International meeting in Nice, France (Sept/19) estimated **total annual cost of PD in USA of over $50 billion**

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Cardinal features of Parkinson's disease (PD)

- **The 3 S's:**
  - ***Slow (bradykinesia)***
  - ***Stiff (rigidity)***
  - ***Shaky (resting tremor)***

- Need 2 of 3 to make a diagnosis

- PD is a clinical diagnosis i.e. need to interview and examine

- Typically asymmetric – side of onset is worst as a rule

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Bradykinesia

- Literally “slow movements”
  - may encompass terms akinesia (lack of movement), bradykinesia (slow movement), and hypokinesia (reduced amplitude of movement)
- Upper limbs
  - finger tap, pronation/supination, hand open/close
- Lower limbs
  - heel tap, toe tap

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Rigidity

- Passively move joint (wrist; also elbow, knees, neck)

- Cogwheeling (ratchety feel throughout) vs lead-pipe (smooth increased tone throughout)
  - Can see both types with PD, though classically cogwheeling

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Tremor in PD

- About 70% have tremor as a presenting feature of PD
- Classic parkinsonian tremor is a *resting tremor*
  - Limb fully support against gravity
  - Sometimes most obvious in certain positions (e.g. arms on armrests)
  - Upper limb tremor may be most obvious with walking or standing
- “Pill rolling” tremor; frequency 4-6 Hz
- Upper and lower limbs (often asymmetric i.e. one side worse than the other), jaw, lips

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Resting tremor not the only type of tremor observed in PD

- Deuschl et al (2012) described three types of tremor in PD:
  - Type I - classic parkinsonian rest tremor (RT)
    - Similar 4-6 Hz with rest and posture (occ up to 9 Hz in early PD)
  - Type II – RT, and postural/action tremor (PT/AT) of different frequencies
    - PT/AT higher (>1.5 Hz) and non-harmonically related frequency to RT
    - Mild form of AT present in almost every parkinsonian pt
  - Type III, pure PT or AT
    - Isolated PT/AT do occur in PD with frequency 4-9 Hz
    - Common in akinetic-rigid (slow and stiff) variant of PD

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Other (motor) features of PD

- Micrographia
  - Small handwriting
- Hypophonia
  - Softer speech
- Hypomimia
  - Reduced facial expression
- Gait and postural abnormalities

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Gait & posture in PS

- Reduced armswing
- Flexed posture
- Slow, shuffling gait
- Propulsion &/or retropulsion
- Gait freezing

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Hoehn & Yahr (H&Y) staging

- Stage 1 — Unilateral findings
- Stage 2 — Bilateral findings
- Stage 3 — Unstable posture
- Stage 4 — Markedly unstable; walks alone (cane, walker)
- Stage 5 — Wheelchair/bedbound

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Biochemistry and pathology (brief!)

- Dopaminergic cell loss in substantia nigra pars compacta
  →Approx 50% striatal dopamine deficiency before motor features apparent

- In the SNc
  - Neuronal loss and gliosis
  - Lewy body

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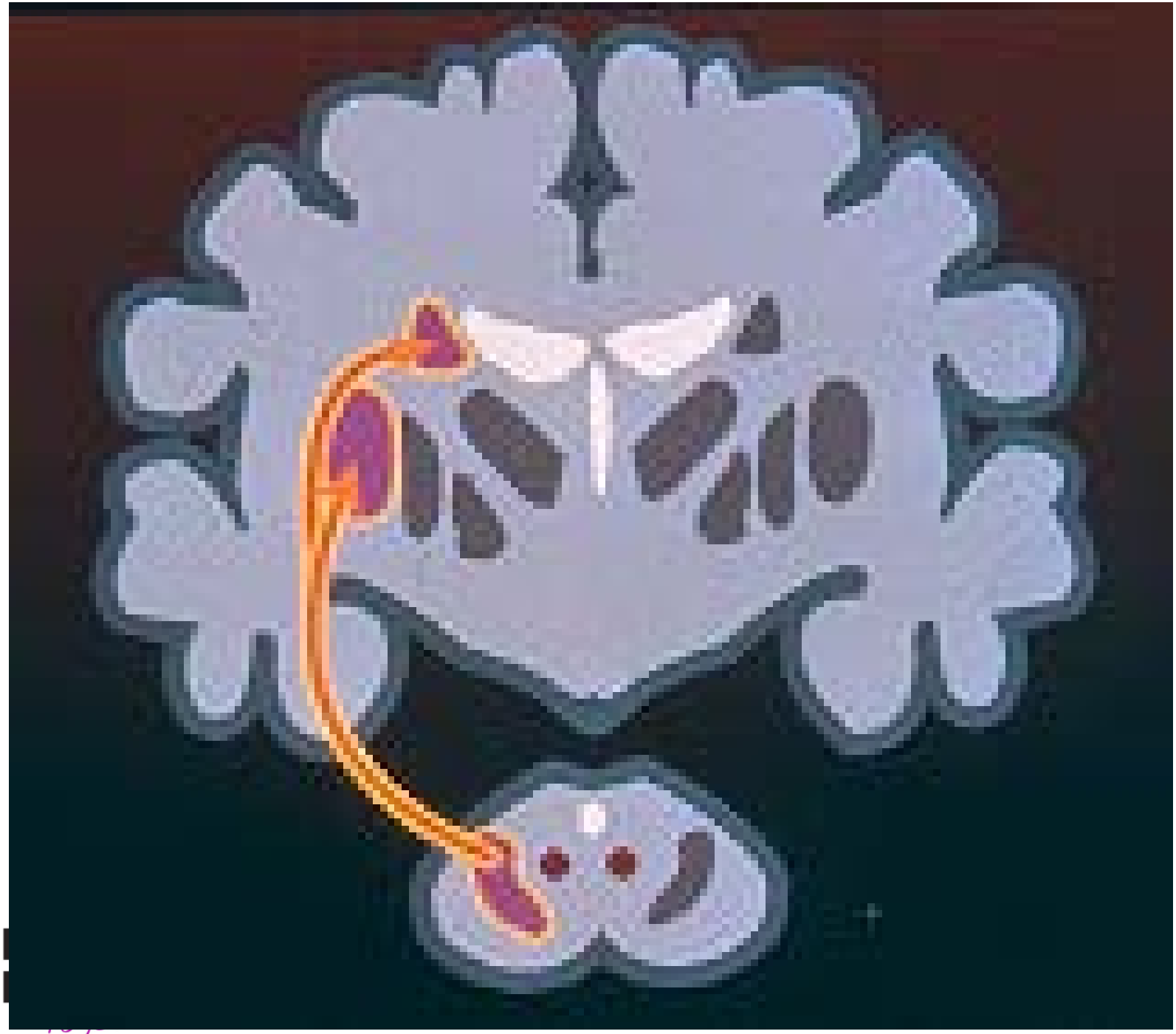

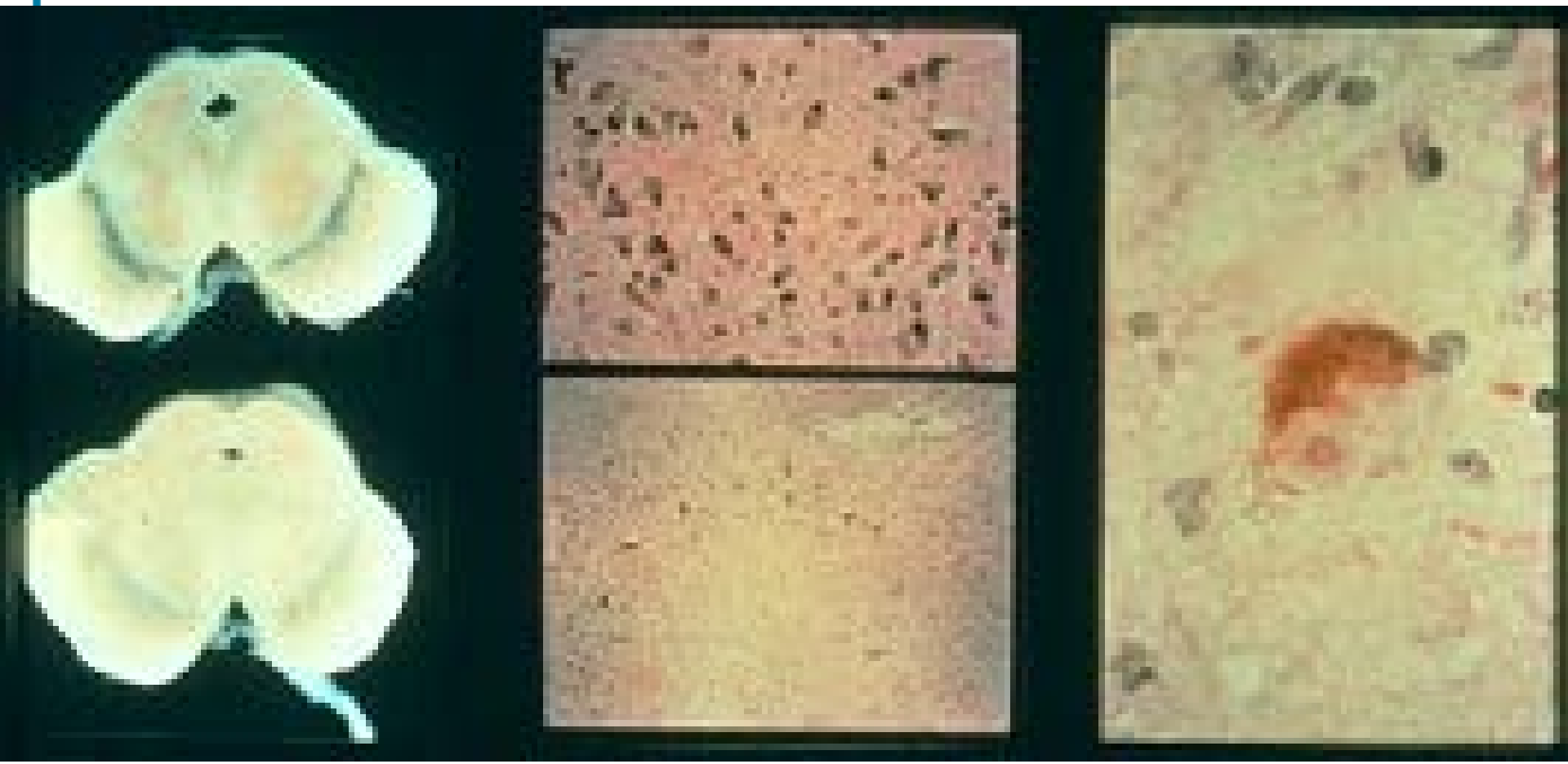

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Motor symptoms reported by people with PD

- Upper limbs
  - hands shake, less coordinated, problems with fine tasks, feel “weak”
- Legs
  - shuffle or scuff feet, no longer the ‘fast’ walker, hunched over
- General
  - harder to get out of a chair, get in/out of car, problems getting in/out/turning over in bed, problems putting arms into sleeves or getting dressed, slower to get ready
- ***While one slows with aging, the passage of a couple of years shouldn’t make someone twice as slow***
  - ***Lack of dopamine makes the ‘automatic’ activities ‘less automatic’***

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PD - management

- Despite there being no cure yet for PD, it is the ONLY neurodegenerative disease for which there is effective treatment

- Goals of treatment vary according to the individual, their symptoms, and circumstances

- **Adequate function on the least medication possible**
  - Do not expect all the symptoms to resolve and be as good as you once were, but better than being untreated – a ‘new normal’ for baseline

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Early PD

- If can still do everything at an acceptable level, may choose no treatment initially following the diagnosis
  - As there is no treatment that has a neuroprotective effect, this is reasonable
- No harm if do not treat immediately after diagnosis, other than depriving someone of potential symptomatic benefit of treatment
- No benefit to delaying symptomatic treatment if having difficulty with daily activities

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Anticholinergics

- Includes - Benztropine, Trihexyphenidyl, Ethopropazine
- ‘20% medication’ – helps 20% of people about 20%
- Thought to preferentially help with tremor, but no good evidence to support that; may help people with symptoms of dystonia

- A number of adverse effects – confusion, memory impairment, dry eyes, dry mouth, constipation, urinary retention

- I do not use it very often; will tend to reserve it for younger people with tremor and/or dystonia symptoms – low dose

- Not recommended as first line treatment for early PD (Canadian guideline – grade B)

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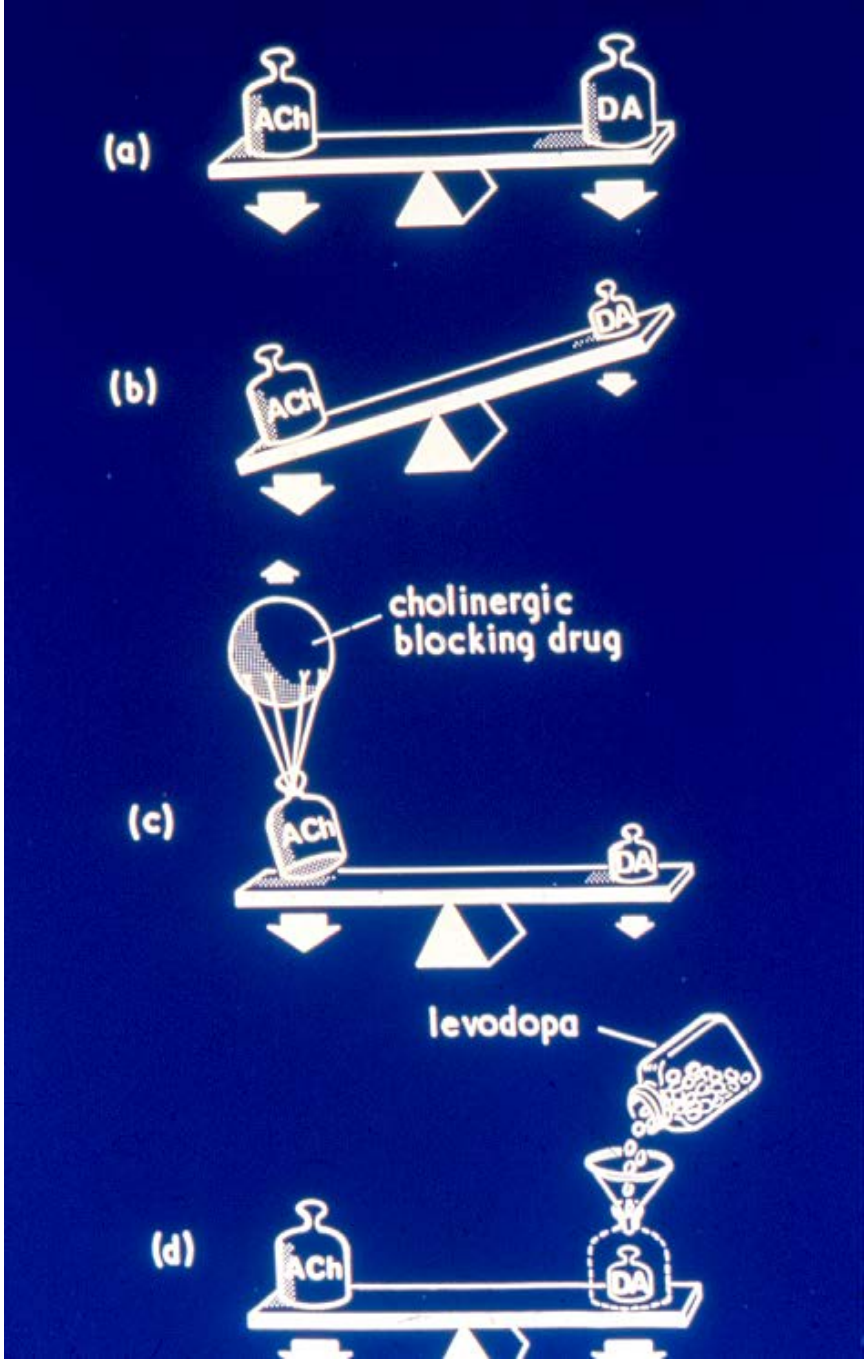

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Amantadine

- Available as red capsule (100 mg) or liquid
- Typical starting dose 100 mg twice/day (morning and noon), can go up to 100 mg three times/day
  - if significant kidney problems, only 100 mg once/day
- Overall mild benefit, if helps tend to notice it quickly
- Adverse effects – confusion, hallucinations, lower limb swelling, livedo reticularis (lattice like discoloration)
- I will still use it occasionally – my impression is more potent and better tolerated than the anticholinergics
- There is insufficient evidence to support the use of amantadine in the treatment of patients with early PD. (Canadian guideline – grade A)

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Monoamine Oxidase-B (MAO-B) inhibitors

- Selegiline; Rasagiline – both irreversible inhibitors
- Work by inhibiting breakdown of dopamine in the brain
- They each have mild symptomatic benefit
- Well tolerated; AE similar to what see with levodopa
  - Caution with SSRIs, narcotics – may cause serotonin syndrome
- Neuroprotective benefits not borne out by studies
  - Selegiline delays need for levodopa by 9 months
  - Rasagiline study met 3 of 4 endpoints but not all to justify ‘neuroprotection’
- MAO-B inhibitors may be used as a symptomatic treatment for people with early PD. (Canadian guideline - grade A)

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Safinamide

- Reversible selective MAO-B inhibitor
- Brand name Onstryv (Xadago rest of the world)
- Approved in Canada in January 2019
  - Still going through common drug review to determine its availability in different provincial formularies
- Indicated as add-on therapy for those on levodopa who have wearing off

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Dopamine agonists

- Pramipexole
- Ropinirole
- Rotigotine (transdermal)
- (Bromocriptine – ergot derived)

- Second most potent class of medications after levodopa

- Stimulate dopamine receptors directly

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Dopamine agonists

- Thought of as levodopa sparing strategy → lower risk of dyskinesias by delaying use of LD

- However:
  - *Once compared to time to start using LD – rates of dyskinesia the same*

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Dopamine agonists (cntd)

- Adverse effects:
  - Sleepiness, confusion, hallucinations, psychosis, lower limb edema and discoloration
  - ** Impulse control disorders (ICD) – gambling, sexual behavior, cleaning, shopping, eating
  - Need to caution patients and family members about this

- No good evidence one agonist is better than another

- Ergot-derived agonists (e.g. bromocriptine) should not be used as first line treatment because of potential risk of pulmonary and cardiac fibrosis (Canadian guideline – grade B)

- Dopamine agonists may be used as a symptomatic treatment for people with early PD. (Canadian guideline - grade A)

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Levodopa (LD)

- Dopamine (DA) deficiency in striatum discovered in 1960 (Hornykiewicz)
  - i.v. levodopa tx (1961)
  - Large doses D,L - Dopa (Cotzias 1967)
- Large proportion catabolized (broken down) peripherally and not available (dopamine doesn't cross the blood-brain barrier)
- Dopa-decarboxylase inhibitors (carbidopa or benserazide) inhibit peripheral catabolism

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Levodopa (cntd)

- Half-life (t ½) only 1.5-2 hours
  - CR (controlled release) increases duration of benefit but delays onset
  - bioavailability is about 30% less of CR vs regular (i.e. 4 pills of CR equals 3 pills of regular
- Typical starting dose100/25 mg levodopa/carbidopa (Sinemet) or levodopa/benserazide (Prolopa) 3 times/day
  - This dose may not be enough, depending on severity of symptoms and size of person

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Levodopa (cntd)

- Competes with protein for absorption across the gut; best absorbed on empty stomach (30 minutes before a meal or 60 minutes after)
  - If need to eat something to settle stomach, suggest something without a lot of protein

- Peripheral adverse effects:
  - Nausea/vomiting, orthostasis (blood pressure drops when stand up, feel dizzy)

- Central adverse effects:
  - hallucinations, psychoses, confusion
  - motor fluctuations

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Levodopa (cntd)

- **Levodopa remains *the most effective drug* to manage PD motor symptoms**

- Levodopa may be used as a symptomatic treatment for people with early PD. (Canadian guideline - grade A)

- The dose should be kept as low as possible to maintain good function in order to reduce the development of motor complications. (Canadian guideline - grade A)

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Motor Fluctuations

- Wearing off
  - predictable loss of benefit from medication prior to next dose
  - persons will tell you of these symptoms

- Dyskinesias
  - excessive movement secondary to medical treatment (typically from levodopa); most common are “peak dose” dyskinesias
  - Most commonly seen with levodopa treatment, can be seen with other anti-Parkinson medications too
  - Persons (and even others) may not have noticed mild DK

- On/Off
  - unpredictable worsening between doses

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Differentiating dyskinesias from tremor

- Dyskinesias
  - Non-stereotyped movements
  - “flowing” from one movement to next
  - Minimal parkinsonian findings during peak dose dyskinesias i.e. little stiffness or slowness (though involuntary movements may interfere)
- Tremor
  - Rhythmic, repetitive movements (“movement about an axis”)
  - Worsens as medications wear off
  - Other parkinsonian features (slowness and stiffness) often worse as medication wears off as well

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Motor fluctuations

- Estimated 40% persons develop motor fluctuations within 4-6 years of levodopa treatment (Ahlskog and Muenter *Mov Disord* 2001)

- More recent study – duration of illness and levodopa dose determines development of motor fluctuations, and not duration of therapy (Cilia et al. *Brain* 2014)

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Management of wearing off

- Simplest approach – take levodopa dose sooner
- Addition of dopamine agonist – has longer half life than levodopa – am not keen to use in those much older than age 70
- Dopamine agonists (oral [pramipexole, ropinirole] or transdermal [rotigotine]) may be considered for the management of motor complications in patients with advanced PD. (Canadian Guidelines grade A)

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Management of wearing off (cntd)

- COMT inhibitor (Entacapone) – inhibits peripheral breakdown of levodopa
  - Allows one more hour of ‘on’ time per day
  - Take with each dose of levodopa, maximum 8x/day
  - Can worsen dyskinesias; diarrhea; orange discoloration of urine, sweat, saliva

- MAO-B inhibitors inhibit central breakdown of dopamine and can also help wearing off
  - Allows one more hour of ‘on’ time per day; may also worsen DK

- Catechol-*O*-methyltransferase inhibitors (entacapone) and MAO-B inhibitors (rasagiline) may be considered for the reduction in off-time in patients with advanced PD who have motor fluctuations. (Canadian guideline - grade A)

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Medical management of dyskinesias

- Can reduce amount of levodopa, however in some people that can worsen symptoms of ‘off’
  - Smaller, more frequent doses of levodopa can help but not always practical

- Dopamine agonists have a longer half life and may be preferable to levodopa (as a levodopa-sparing effect), but themselves can also cause dyskinesias

- Amantadine is the only medication that can be added to improve dyskinesias without needing to adjust other medications
  - Amantadine is recommended for the treatment of dyskinesia in PD (200–400 mg/d). (Canadian guideline - grade A)

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Medical management of acute ‘off’

- Challenging

- Subcutaneous apomorphine infusions or injections may be considered for the management of severe motor complications, but should be provided only in units that have sufficient experience and resources. (Canadian Guideline - grade C)

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Gait and freezing

- No medical therapy that specifically targets this or has been shown to be particularly effective (assuming on maximum and/or appropriate doses of medications to control other motor symptoms)
- Visual cues, listening to music may assist
- Physical activity helpful to maintain mobility

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Tremor

- Some people tremor refractory to anti-parkinsonian medication, yet other symptoms under good control
- Striatal dopamine deficiency only moderate correlation with tremor (as opposed to slowness and stiffness, which have much better correlation)
- Use of beta blockers can be tried
- Deep brain stimulation (DBS) of thalamus can help refractory tremor but does not improve other parkinsonian features

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Levodopa-Carbidopa Intestinal Gel (LCIG a.k.a. Duodopa)

- Reduces ‘off’ time by > 4 hours; ‘on’ time without troublesome DK increase > 4 hours
- Requires neurologist, nursing care, and gastroenterologist
- Not for those with significant cognitive or behavioural issues, and those who don’t have the appropriate support to maintain it
- An option for those who may not be candidates for DBS
- ** I have no personal experience with using LCIG
- Intrajejunal levodopa-carbidopa enteric gel administered through percutaneous gastrostomy may be considered for the reduction of off-time or to reduce dyskinesia. (Canadian guidelines - grade C)

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Deep brain stimulation (DBS)

- Indications: may benefit both dyskinesias and wearing off
- Dyskinesias can improve 70%+, either directly (globus pallidus interna, or GPi) or (partly) indirectly (subthalamic nucleus, or STN)
- GPi stimulation does not generally allow much reduction in medication dose, while STN stimulation can allow for greater reduction in dose
- Does not improve ‘on’ function, but improves ‘off’ period scores
- Overall, both STN and GPi stimulation allow > 4 hours more ‘on’ time per day
- Both STN (subthalamic nucleus) and GPi (globus pallidus interna) beneficial
- Thalamic DBS may be considered for those with disabling tremor

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DBS – candidates and limitations

- Improvement in motor score by 30% with levodopa (comparing ‘on’ with ‘off’ state)
- Generally healthy (i.e. no condition that will expect to dramatically reduced life expectancy or significantly interfere with the surgical procedure or recovery)
- No significant cognitive or psychiatric symptoms
- Age typically < 70 years old
- Unfortunately, *no significant benefit with axial symptoms (gait, balance, speech, swallowing)*

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General rules of management

- Good rest
- Reasonable diet
- Be physically, socially and cognitively active
  - Many different physical activities can benefit
- Any physical, medical, mental or social stresses can transiently worsen the motor symptoms of parkinsonism

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Medications

- **Everyone with Parkinson's disease is different – what works best for someone may not work well for you**

- Take medications on time; allowed some leeway if out of usual schedule

- When traveling, <u>always</u> have medications available
  - Plan for extra day at the front and the back end to accommodate recovering from change in usual schedule
  - Can still do things, but take into account slowness and fatigue

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Research potential of clinico-pathological studies

Contributions from the Saskatchewan Movement Disorders Program (SMDP)

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Review article

- Open access

- Can J Neurol Sci. 2015 Mar;42(2):74-87. doi: 10.1017/cjn.2015.13.
- **Saskatchewan movement disorders program.**
- Rajput AH[1], Rajput A[1].
- PMID:25804247 PMCID: PMC4416358
- DOI: 10.1017/cjn.2015.13 [Indexed for MEDLINE]
- Free PMC Article

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4416358/

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Accompanying editorial

- Open access

- Can J Neurol Sci. 2015 Mar;42(2):70-1.
- **The Saskatchewan Movement Disorders Program: Commitment Pays Off.**
- Lang, AE Stoessl AJ.
- PMID: 27482556 PMCID: PMC4416360
- DOI: 10.1017/cjn.2015.9 [Indexed for MEDLINE]
- Free PMC Article

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4416360/

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