APPROACH TO THE DIAGNOSIS & MOTOR SYMPTOMS OF PARKINSON'S DISEASE

OLTCC CONFERENCE. OCT 22, 2023

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DISCLOSURES

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LEARNING OBJECTIVES

1. Discuss a basic approach to recognizing Parkinsonism and non-motor and motor features of Parkinson's disease (PD).

2. Provide an approach to initiating levodopa and monitoring response.
    - Briefly review adjunctive treatments.

3. Review the management of motor complications of Parkinson's disease in Geriatric patients.

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QUICK SURVEY

Please complete ☺

WHY IS PARKINSON'S DISEASE IMPORTANT TO DISCUSS?

Prevalence = 1% over age 60[1]

Fastest growing neurological disease (>AD) - Prevalence projected to double from 2015 to 2040 [2]

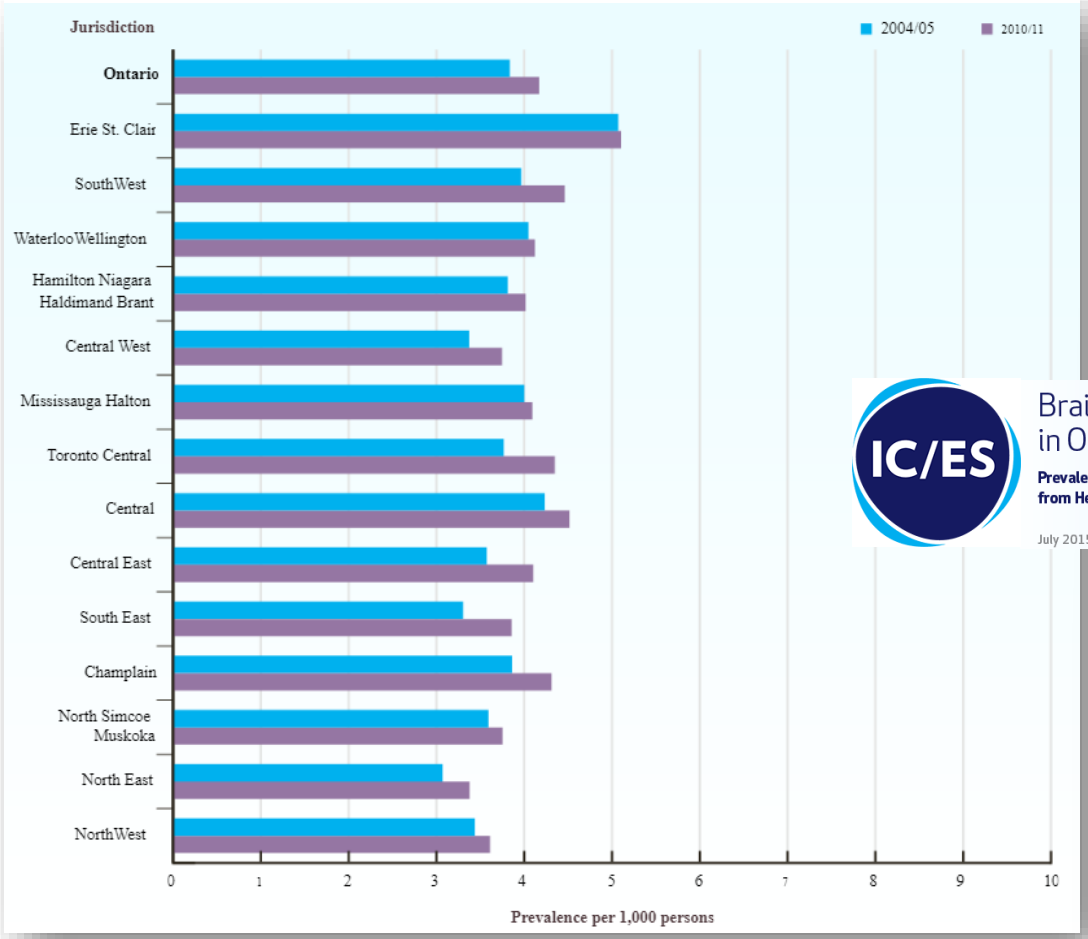
Over 90% of persons with parkinsonism ≥ 60 y.o. [3]

Complexity of PD with motor and non motor features, and high prevalence of frailty = "Geriatric Syndrome" [4]

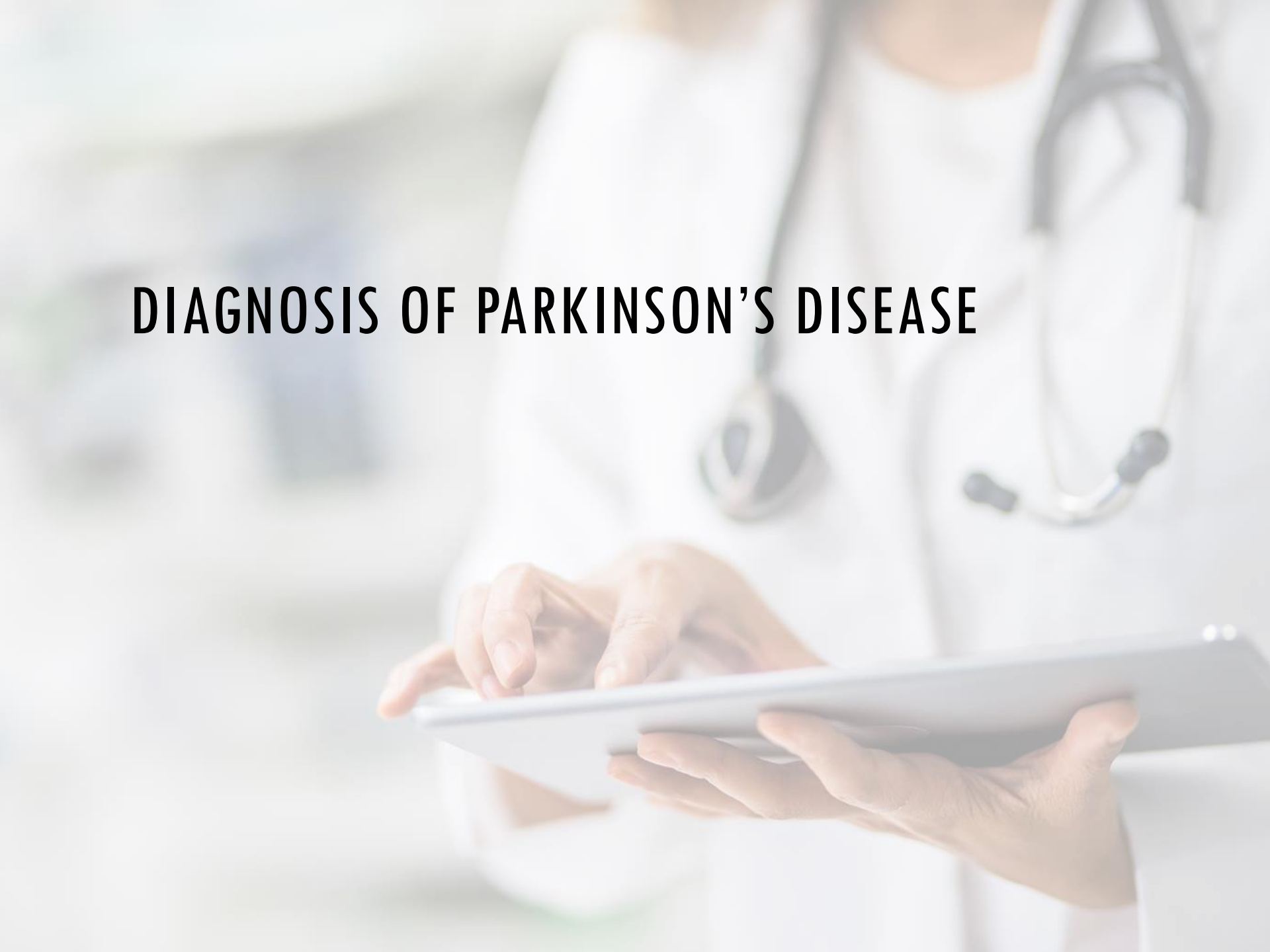
1. Connolly, B et al. JAMA 2014; 311 (1) 1670-83
2. Dorsey ER, Bloem BR. *JAMA Neurol*. 2018;*75*(1):9–10.
3. Guttman, M. et al.. Mov. Disord. 2003, 18: 313-19.
4. Lauretani F. et al. Arch Ger and Geriatrics 54(2012): 242-246

WHY IS PARKINSON'S DISEASE IMPORTANT TO DISCUSS?

EXHIBIT 10.4 Age- and sex-adjusted* prevalence of parkinsonism (including Parkinson's disease) per 1,000 persons aged 40 years and older, in Ontario and by Local Health Integration Network, 2004/05 and 2010/11



DIAGNOSIS OF PARKINSON'S DISEASE



CANADIAN GUIDELINES ON PARKINSON'S DISEASE (CGPD) 2019

Grading scheme from NICE (UK), EFNS (Europe) and SIGN (Scotland):

Level A – High quality meta-analyses, or RCTs with low bias

Level B – High quality case-control or cohort studies with very low bias, and high causality

Level C – Case-control or cohort with low bias and moderate causality

Level D – Case reports; Expert opinion

GPP – Recommended best practice based on guideline development group

CMAJ 2019 Sept 9: 191: E989- 1004

CGPD 2019: DIAGNOSIS AND PROGRESSION

PD should be suspected in people presenting with tremor, stiffness, slowness, balance problems or gait disorders (Grade: D; GPP; Source: NICE)

PD can be diagnosed using **MDS** clinical diagnostic criteria (Grade: GPP; Source: CAN)*

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CGPD 2019: DIAGNOSIS AND PROGRESSION

Patients with suspected PD with **substantial disability or exclusion criteria/red flags should be seen by a specialist** with expertise in movement disorders (Grade C, GPP; Source: SIGN)*

CT/MRI should not be used routinely to diagnose PD (C; SIGN)

Recognize poor specificity of Dx of PD in early stage (C; SIGN)

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MDS DIAGNOSTIC CRITERIA

Specificity at least 90%

Parkinsonism – bradykinesia plus either rigidity or rest tremor[1]

Clinically established PD:

- **Absence of absolute exclusion criteria; at least 2 supportive criteria; no 'red flags'**

Absolute exclusion criteria

- Cerebellar signs
- Supranuclear gaze palsy
- Established diagnosis of BVFTD
- Parkinsonism restricted to the lower limbs only for >3 years
- Treatment with an antidopaminergic, or with dopamine-depletion agents
- Absence of response to levodopa
- Sensory–cortical loss
- No evidence for dopaminergic deficiency on functional imaging
- Other parkinsonism-inducing condition

Red flags

- Rapid deterioration of gait
- Absence of motor symptom progression over 5 years
- Early bulbar dysfunction
- Respiratory dysfunction
- Early severe autonomic failure
- Early recurrent falls due to misbalance
- Disproportionate anterocollis
- Absence of common non-motor features of disease during >5 years
- Pyramidal tract signs
- Bilateral symmetric presentation

Supportive criteria

- **A clear and dramatic positive response to dopaminergic therapy**
- Levodopa-induced dyskinesia
- Documentation of resting tremor of a limb
- A positive diagnostic test of either olfactory loss or cardiac sympathetic denervation on scintigraphy

Postuma et al. Mov Disord 2015;30(12):1591–1601

IDENTIFYING PARKINSONISM

Motor Symptoms:

Early

Shaking Stiff Muscle Shuffling Gait
(Tremor 70%) ↓ arm swing

Moderate

Slow Movement
Axial rigidity

Advanced

Freezing of Gait, Falls
Postural Instability
Dysphagia

Autonomic Dysfunction:

Bowel: Constipation (60%) w slow GI motility
Bladder: (30%) Nocturia, OAB
BP: (30%) Orthostatic Hypotension

Neuropsychiatric Symptoms:

Deprivation of Sleep (60%): RLS, RBD(50%), OSA
Depression and/or Anxiety (40%)
Dementia w/wo Psychosis (40% or more)

RBD (often preceding PD by median of 14 years)

Physical examination demonstration

FINDINGS OF PD

MDS DIAGNOSTIC CRITERIA… SIMPLIFIED

Consider alternatives…

1. **Poor levodopa responsiveness**
2. **Unusual neurologic symptoms/findings**
3. **Overly fast or slow progression**
4. **Clear alternate explanations (drugs, strokes, tumours, NPH)**

Supportive criteria

- A clear and dramatic positive response to dopaminergic therapy
- Levodopa-induced dyskinesia
- Documentation of resting tremor of a limb

ALTERNATIVES TO CONSIDER…

VASCULAR PARKINSONISM

Early bilateral/symmetric parkinsonism

Findings restricted to lower limbs for >3 y

Lack of progression of motor symptoms or absence of nonmotor symptoms after 5 y

DRUG-INDUCED PARKINSONISM

Use of dopamine receptor blocker (typical antipsychotics, metoclopramide) or dopamine-depleting agent

Upper > lower limb findings

Frank et al. Can Fam Physician. 2023 Jan;69(1):20-24.

ALTERNATIVES TO CONSIDER…

PARKINSON'S PLUS SYNDROMES

Early recurrent falls within 3 y of onset

Rapid progression of gait impairment leading to use of walker by 3 y and a wheelchair by 5 y

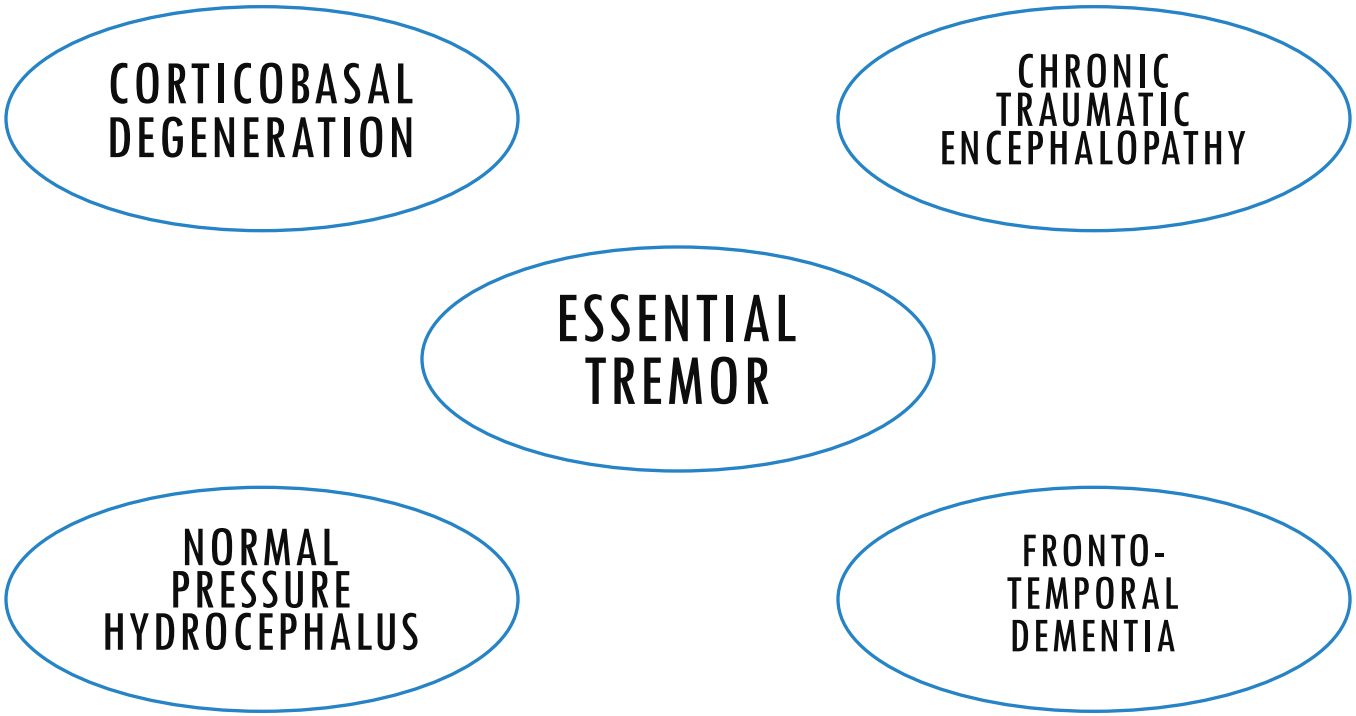
Severe autonomic failure within 5 y of onset, cerebellar findings, stridor (MSA)

Downward vertical gaze palsy or slowing of downward vertical saccades (PSP)

Early cognitive impairment and visual hallucinations, either spontaneous or with low-dose levodopa (DLB)

Frank et al. Can Fam Physician. 2023 Jan;69(1):20-24.

ALTERNATIVES TO CONSIDER…



INITIATING LEVODOPA

CGPD 2019: PHARMACOLOGIC THERAPY IN EARLY PD

Patients considered to have possible PD may benefit from trial of dopamine replacement therapy (Grade: GPP, Source: SIGN)

Individualize therapy based on patient lifestyle, needs, goals, clinical circumstances, frailty, risks from medications (GPP; NICE)

Levodopa can be used in early PD (A; NICE) at as low a dose as possible to maintain function (A: NICE)

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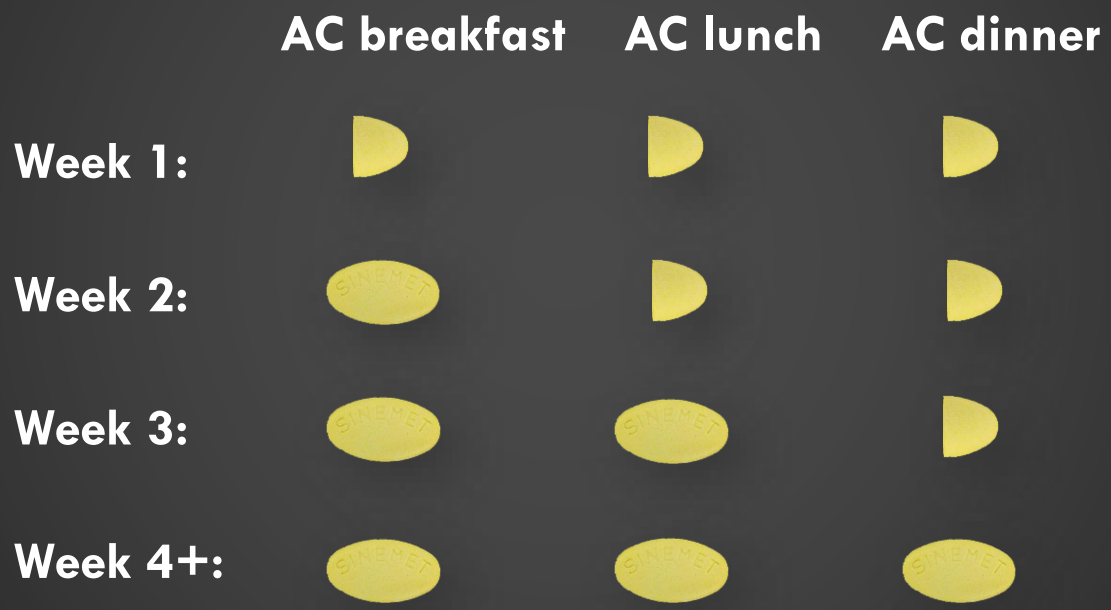
LEVOCARB UPTITRATION: VERSION 1



*30-60 min ac meals

LEVOCARB UPTITRATION: VERSION 2

Weeks 1-2:    **WITH meals**

Weeks 3-4:    **AC meals**

Weeks 5+:    **AC meals**

LEVODOPA DOSING & PEARLS*

Absorption

- EMPTY stomach
- Can crush tablet and/or mix in carbonated drink to speed onset
- Avoid co-administration with iron

Timing

- Ensure on-time administration
- Do NOT withdraw suddenly

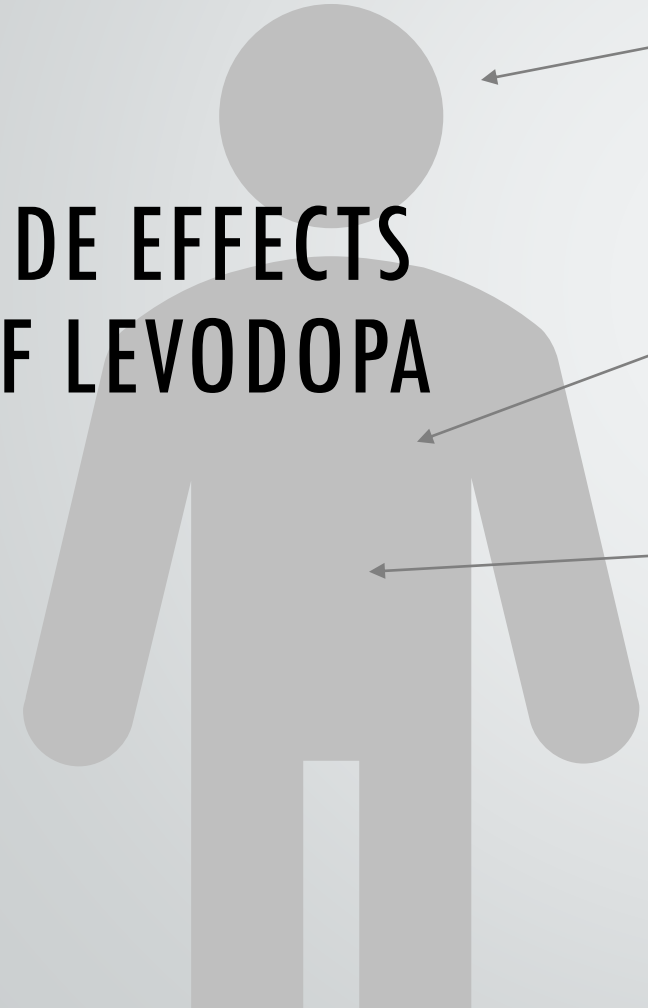
LEVODOPA DOSING & PEARLS*

Sinemet CR – for hs dosing only, 70% bioavailability

- Do NOT crush

100/25 or 200/50 mg
LU: 64/65

SIDE EFFECTS OF LEVODOPA



Neuropsychiatric

- Confusion, psychosis (*caution with dementia)

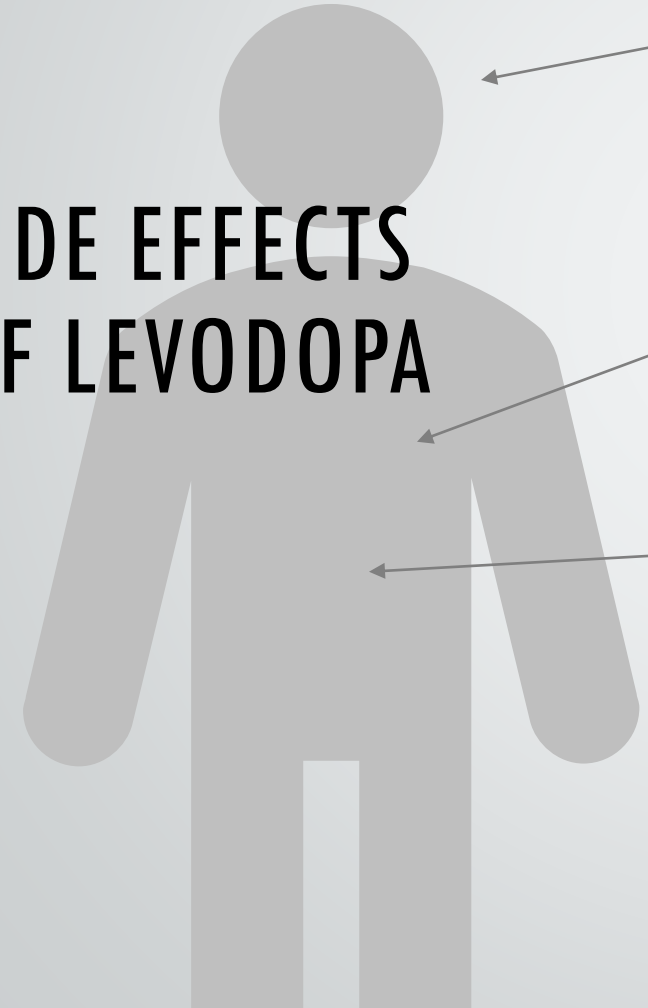
Cardiovascular

- Orthostatic hypotension, dizziness

GI

- Nausea

SIDE EFFECTS OF LEVODOPA



*DOMPERIDONE (BLOCKS DOPAMINE PERIPHERALLY)
- HELPFUL FOR NAUSEA, DIZZINESS

Neuropsychiatric

- Confusion, psychosis (*caution with dementia)

- REDUCE ANTIHYPERTENSIVES
- REFER TO NON-MOTOR TALK!

Autonomic

- Orthostatic hypotension, dizziness

- TRY PROLOPA (NO LU)
- TAKE WITH NON-PROTEIN SNACK

GI

- Nausea, diarrhea

ADJUNCTIVE TREATMENTS

CGPD 2019: PHARMACOLOGIC THERAPY IN EARLY PD

DA agonists may be used in early PD (A, NICE) – but due to higher risk of A/E, discourage use in older patients over 70

Insufficient evidence to recommend amantadine in early PD (A; SIGN)

Anticholinergics should not be used as first line tx in early PD (B: SIGN)

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ENTACAPONE

- Inhibits L-dopa metabolism by catechol O-methyltransferase
- Add entacapone to select doses of levodopa to address wearing off
- SE: nausea, dyskinesia, diarrhea++, orange brown stain (teeth/urine)

Add 200 mg to select dosing times

Vs.

Combo pill "Stalevo":
200 mg entacapone
100 mg levodopa
25 mg carbidopa

DOPAMINE AGONISTS

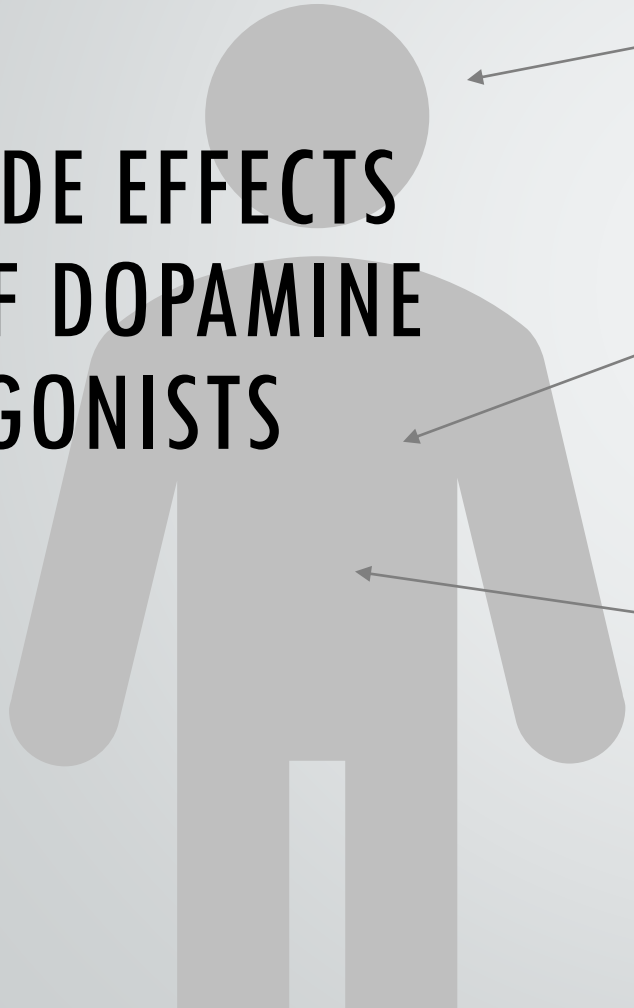
- Directly stimulate dopamine receptors
- As initial therapy, tend to cause *less dyskinesia* than levodopa (eventually require addition of levodopa)
- Should be **used in caution (or even avoided) in older adults** due to side effects
- Need to uptitrate very gradually

TID

TID

Q24h patch

SIDE EFFECTS OF DOPAMINE AGONISTS



Neuropsychiatric

- Confusion, psychosis (more than levodopa)
- *Impulse control disorder, anxiety/obsessive symptoms
- *Dopamine agonist withdrawal syndrome

Cardiovascular

- Orthostatic hypotension, dizziness
- *Edema

GI

- Nausea

AMANTADINE

Mainly for reducing dyskinesia

Use minimal dose due to anticholinergic side effects, hallucinations, confusion, insomnia (avoid hs dosing)

AMANTADINE

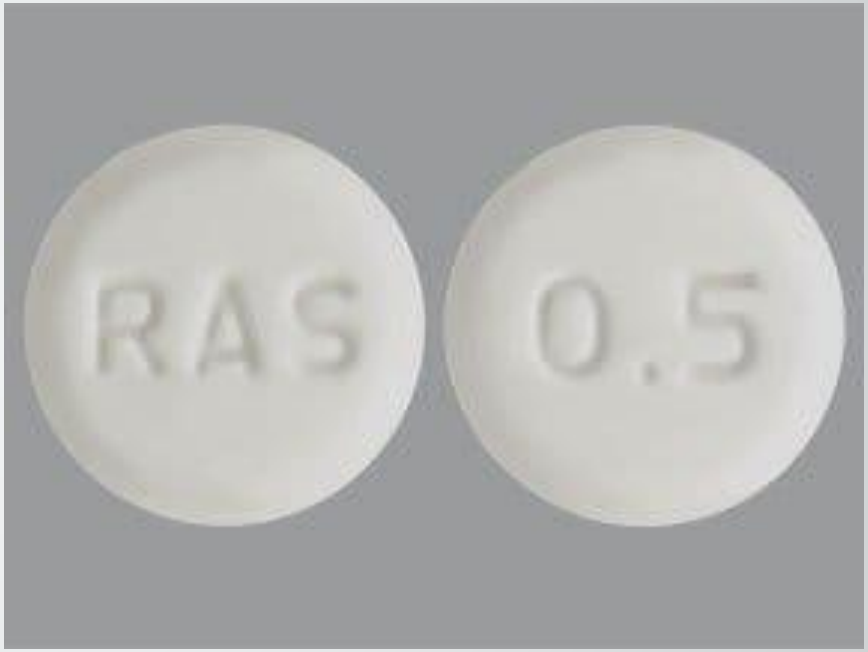
Initial dose: 100 mg daily, then 100mg bid after 1 week (lower dose if renal impaired, liquid formulation available)

Avoid abrupt withdrawal (may worsen PD)

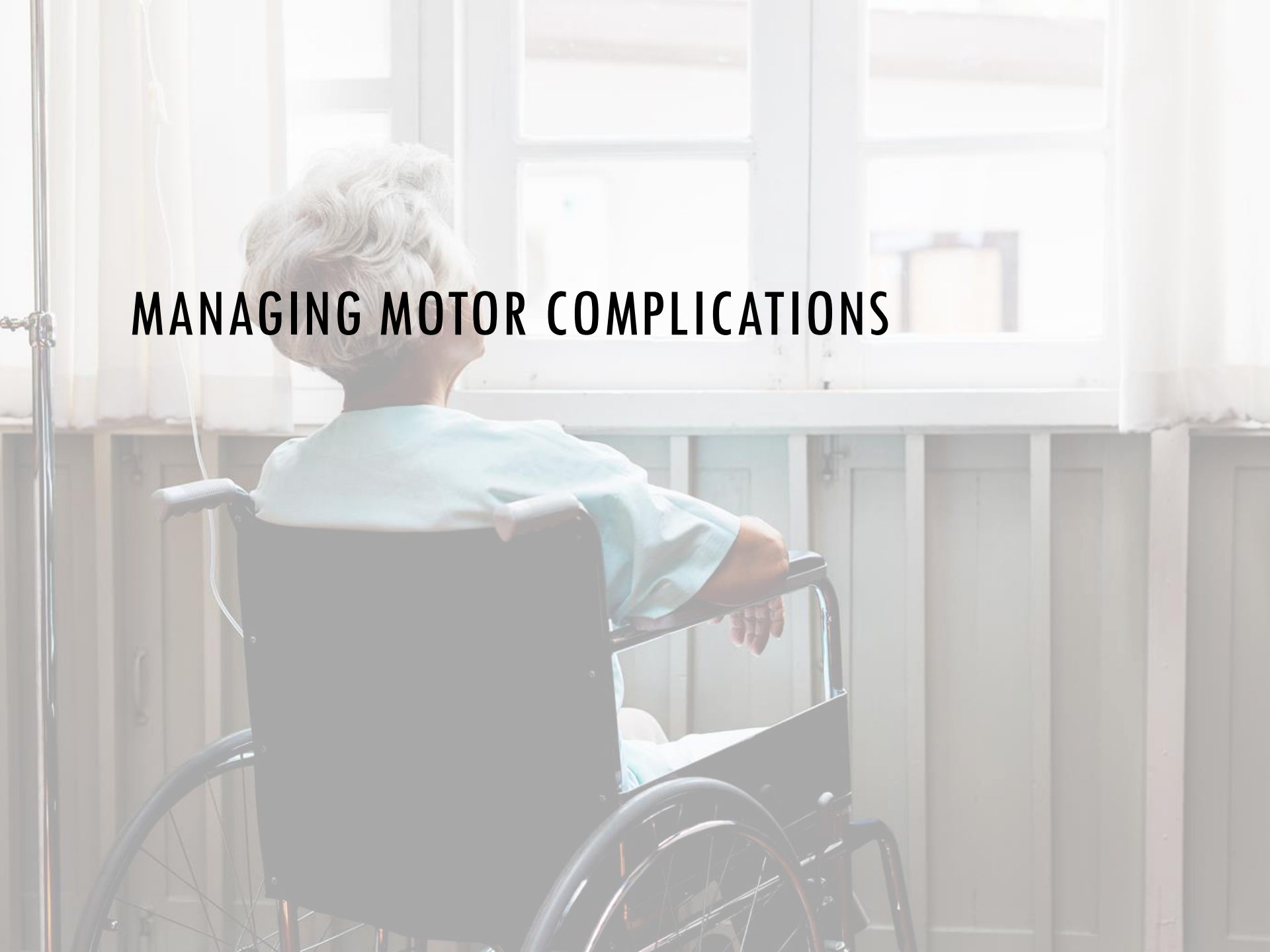
Taper by reducing 50mg every week

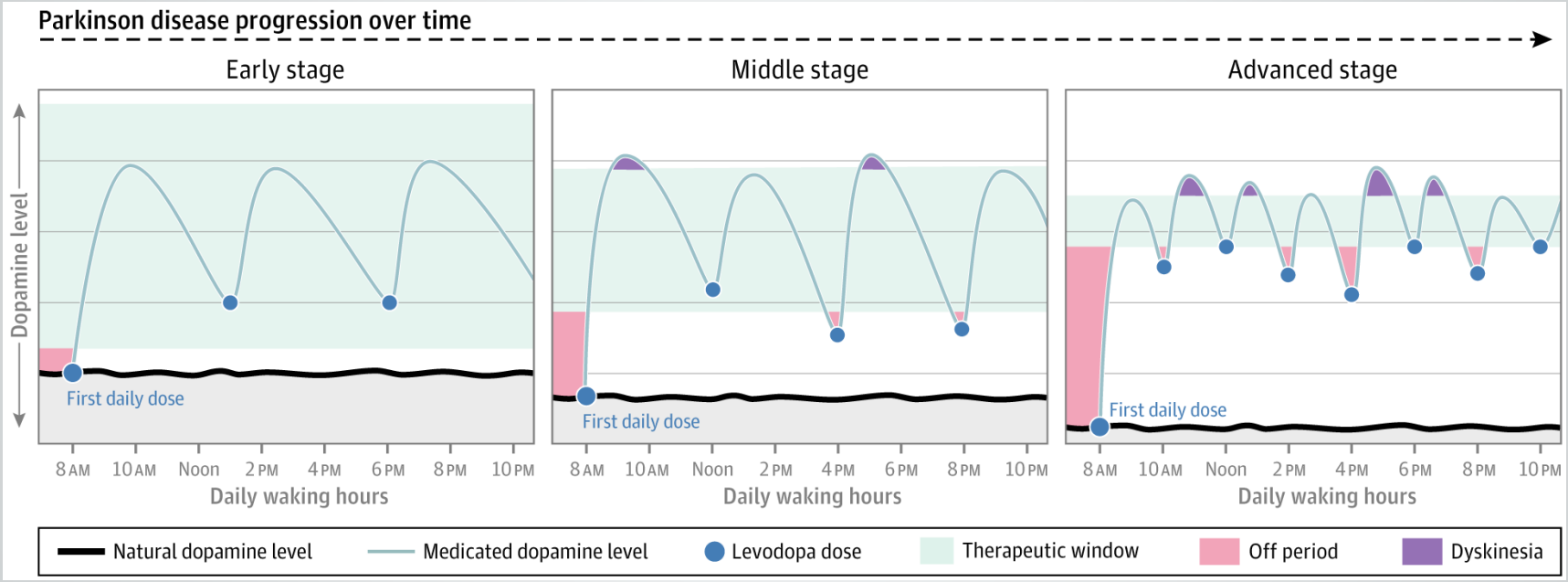
MAO-B INHIBITORS

- Can be monotherapy or adjunct
- Selegiline 10mg /day
- Rasagiline 1mg/day (requires EAP)
- Safinamide (Xadago)
- Small symptomatic effect and potential disease modifying not excluded



MANAGING MOTOR COMPLICATIONS





Armstrong et al. JAMA. 2020 Feb 11;323(6):548-560.

OPTIONS FOR "WEARING OFF"

1. Ensure no constipation and take levodopa 30 – 45 min ac meals
2. Increase levodopa frequency
3. Increase individual dose
4. Add adjunct or refer for advanced therapies

Arch Neurol 2005;62:241-8
Lancet 2005;365:947-54
Neurology 2006;66:983-95

ANXIETY & MOTOR SYMPTOMS

- If main wearing off sx = tremor, may consider non-pharmacologic mx +/- tx anxiety
- Recommend having a low threshold for diagnosis of depression & anxiety (often under-diagnosed, misinterpreted as normal for PD)
- Mirtazapine 3.75 -15 mg qhs if poor sleep, poor appetite with weight loss, keep dose as low as possible if RBD or RLS
- Sertraline is preferred over Escitalopram or Citalopram if concern for QT prolongation (i.e concurrent use of domperidone and Cholinesterase Inhibitors)

FREEZING OF GAIT

Big steps

Visual: target on floor/ground

- Tape across doorway threshold
- Laser pointer/laser beam on walker
- Look beyond obstacle

Auditory:

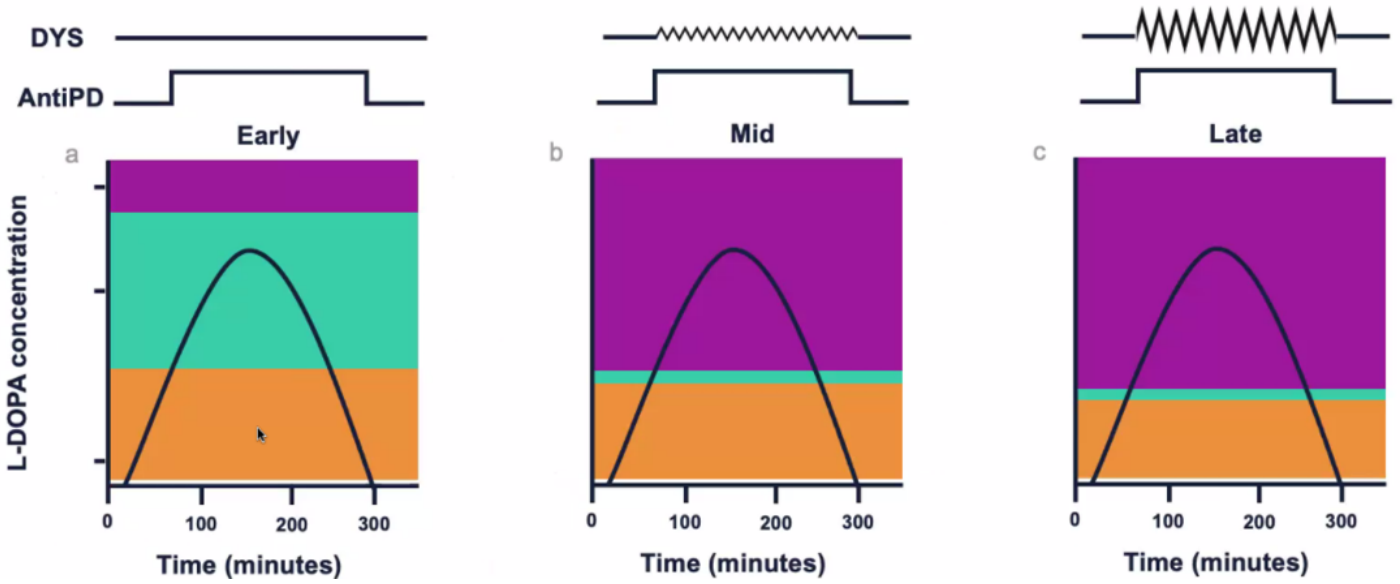
- Counting with marching
- Music/metronome

DYSKINESIA

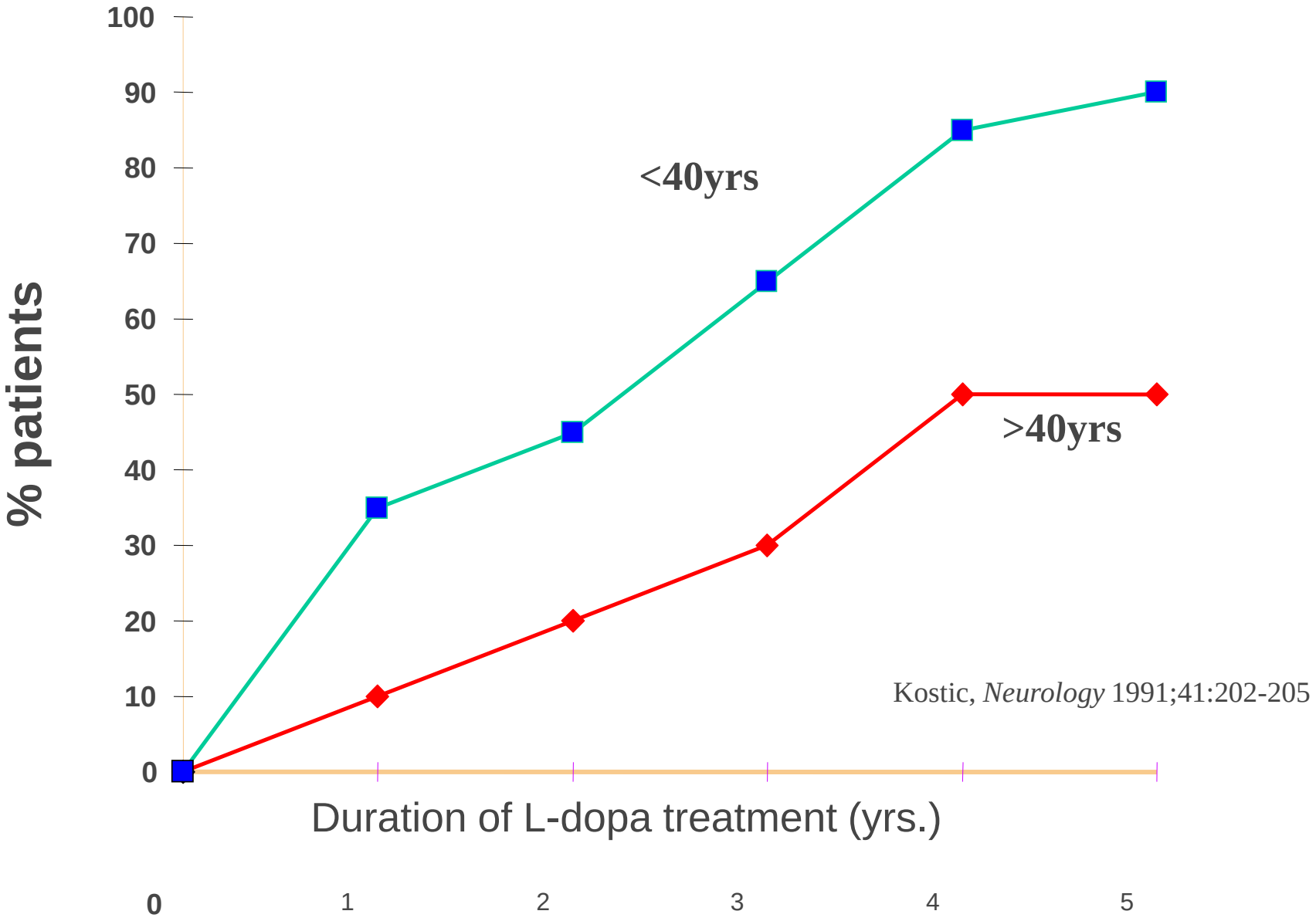
- Involuntary movements: mild jerks to twisting movements
- Abnormal response by the dopamine-deprived brain to non-physiologic pulsatile levodopa stimulation
- May occur at any time, but usually at peak levodopa level (1 hr after taking the dose)

DYSKINESIA

- The response to levodopa changes over the course of Parkinson's disease and the therapeutic window for oral levodopa becomes narrower
- As the therapeutic window narrows, the patient has more "off" time and more dyskinesia with levodopa treatment



DYSKINESIA MORE COMMON IN YOUNG AND YOUNG ONSET PATIENTS



WEIGHT LOSS / LOW BODY WEIGHT

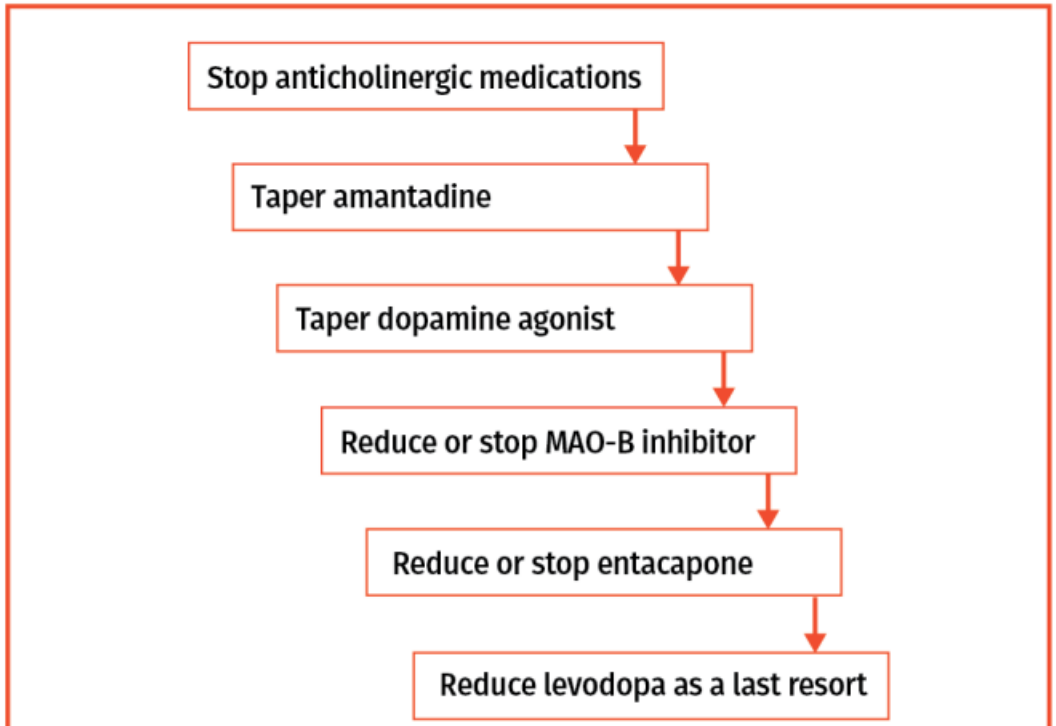
Dopaminergic tx dosing is weight based

WEIGHT LOSS = excessive dopamine stimulation with same dose →

increases psychosis, dyskinesias & **ICD**

Dyskinesias drive more weight loss → vicious cycle

Figure 1. How to reduce polypharmacy in patients with PD and psychosis



MAO-B—monoamine oxidase B, PD—Parkinson disease.
Data from Grimes et al.[4]

Frank et al. Can Fam Physician. 2023 Jan;69(1):20-24.

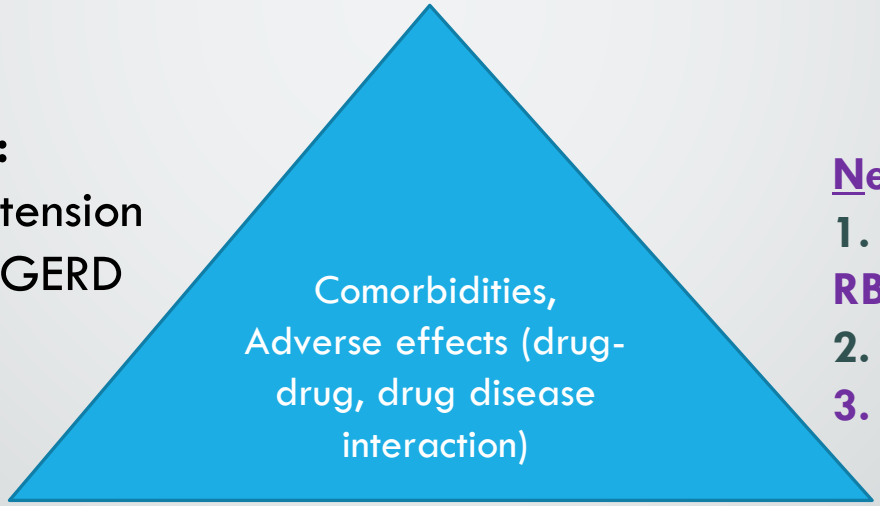
COMPREHENSIVE PARKINSON'S ASSESSMENT: M-A-N

Motor:

1. **TRAP, Motor fluctuations**
2. **Bone health, falls risk**
3. **Dysphagia**

Autonomic:

1. **B**P: Orthostatic Hypotension
2. **B**owel: Constipation, GERD
3. **B**ladder Dysfunction: OAB, UTI



Neuropsychiatric:

1. **D**isturbed Sleep: RBD,RLS,OSA
2. **D**epression/Anxiety
3. **D**ementia/ Psychosis

LATE STAGE PD: ROLE OF THE LTC PHYSICIAN

Recognize and help manage motor and non-motor complications

Referral to OT/PT/SLP

Recognize that cognitive impairment/dementia makes optimal tx of motor symptoms difficult due to dopa → confusion

Support patient and caregiver in

- Goals of care discussion - realistic expectations
- Support decision making using Clinical Frailty Scale
- Prioritize clear mentation > motor "on"

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QUESTIONS

CASE STUDY: PAUL

65 yo retired accountant admitted to LTC with late stage PD, diagnosed at age 45

He won't go to sleep at night and is agitated, calling nurses frequently

Hypersexual with nurses – inappropriate touching and comments

He has lost 10 lb recently and has moderate almost continuous writhing dyskinesias

CASE STUDY: PAUL

Prolopa (Levodopa/Benserazide) 200/50 qid x 14 yr

Rasagiline 1mg daily (MAO-B Inh) x 20 yr

Pramipexole 1.5mg tid (Dopamine Agonist) x 19 yr

Amantadine 100mg bid for dyskinesia x 5y

CASE STUDY: PAUL

Gradually taper off Pramipexole

May consider antidepressant for anxiety (note to pharmacy – aware of potential serotonin syndrome, monitor while on MAO-B inh)

Rx:

Sertraline 25mg daily, Rasagiline 1mg daily

Prolopa 200/50 qid, Amantadine 100mg bid

Patient now complains of end of dose wearing off

CASE STUDY: PAUL

Prolopa (Levodopa/Benserazide) 200/50 qid

Rasagiline 1mg daily (MAO-B Inh)

~~Pramipexole 1.5mg tid (Dopamine Agonist)~~

Amantadine 100mg bid for dyskinesia

Sertraline 25mg daily

Paul now complains of end of dose wearing off…

CASE STUDY: PAUL

With addition of **Entacapone** with the first and third dose of Prolopa 200/50 qid, PD symptoms are managed.

His dyskinesia & hypersexual behaviour much improved with tapering off Pramipexole

However, Paul is now diagnosed with PD dementia with worsening of agitation and hallucinations, seeing deceased relatives…

CASE STUDY: PAUL

Reduce/stop culprit medications:

- stop anticholinergics -> taper off amantadine -> reduce/taper dopamine agonists - > reduce/stop MAO-B/entacapone -> lastly reduce levodopa (CGPD 2019)

Taper off Amantadine by 50mg per week

D/C Rasagiline

Add Quetiapine 6.25-12.5mg bid & HS

Add Donepezil after baseline ECG

CASE STUDY: PAUL

Prolopa (Levodopa/Benserazide) 200/50 qid

Entacapone 200 mg PO BID

~~Rasagiline 1mg daily (MAO-B Inh)~~

~~Pramipexole 1.5mg tid (Dopamine Agonist)~~

~~Amantadine 100mg bid for dyskinesia~~

Sertraline 25mg daily

Quetiapine 6.25-12.5 mg BID and QHS

Donepezil 10 mg daily