

A Parkinson Disease Primer



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TWH: Movement Disorders
Neurologist



Faculty/Presenter Disclosure

- **Faculty: Elizabeth Slow**
- **Relationships with financial sponsors:**
 - Civitas Pharmaceuticals (part of a clinical trial)

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- This program has **NOT** received financial support other than the support of the MOHLTC
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None to be disclosed

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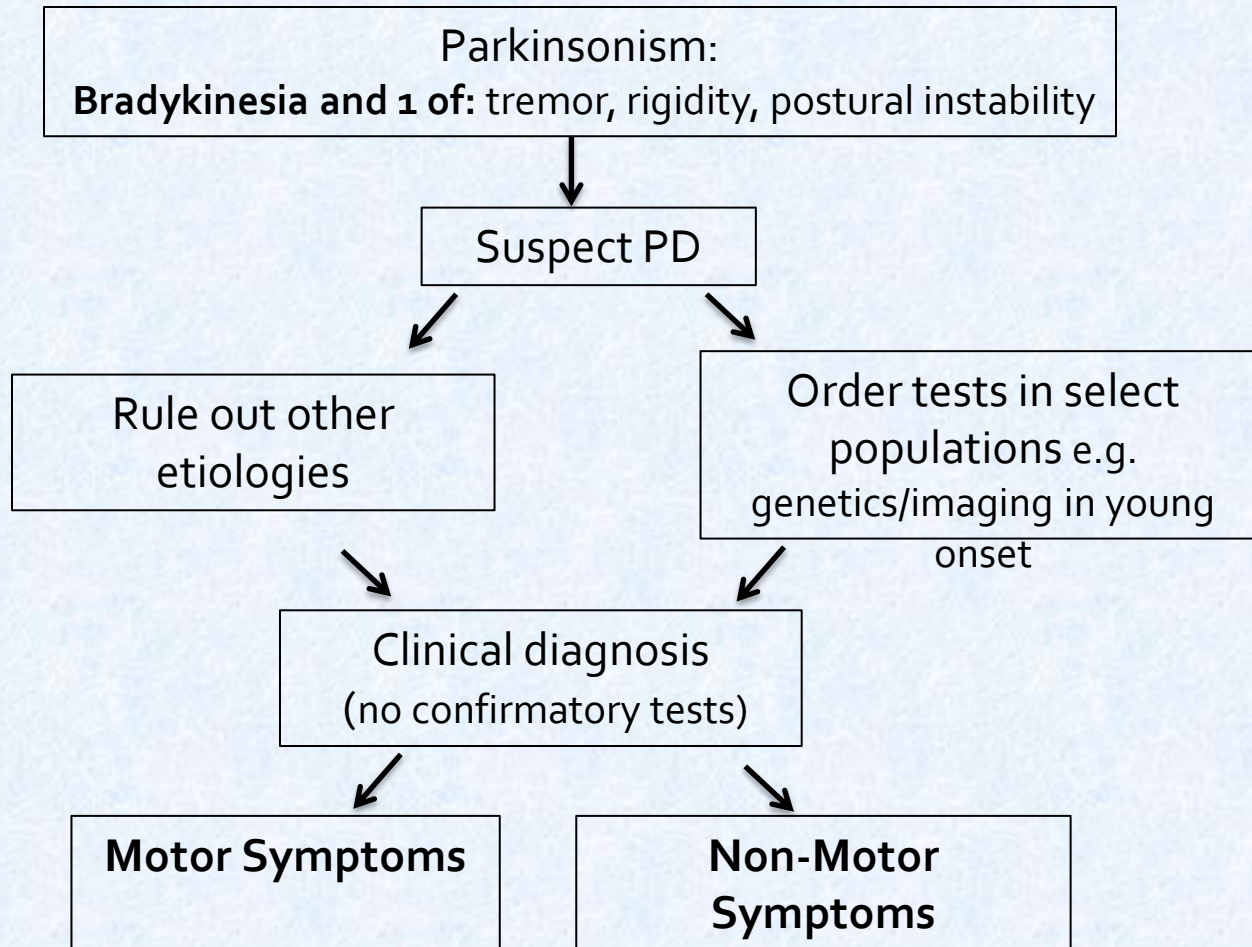
Objectives:

- PD Timeline:
 - i. Early Stage
 - ii. Mid Stage
 - iii. Late Stage
- Treatment: Motor and Non-motor Symptoms at each stage

PD Demographics

- Prevalence 1% over the age of 60 (incidence increases with age)
- Male: Female ratio 1.5:1
- Mean age of onset =65
- 90% sporadic, 10% genetic
- Increased risk with head injury, pesticide exposure
- Decreased risk with smoking and caffeine consumption, Appendix removal?

PD Diagnosis



Adapted from Grimes et al., Canadian Guidelines on Parkinson Disease Treatment. Can J Neurol Sci. 2012; 39: Supp 4. S1-S30.

Parkinsonism Differential

<i>Parkinsonism</i>	<i>Distinguishing Features</i>
Multiple system atrophy	Prominent dysautonomia, cerebellar dysfunction (ataxia), pyramidal tract signs, stimulus-sensitive myoclonus, respiratory symptoms (apnea, stridor), prominent dysarthria
Progressive supranuclear palsy	Early falls, vertical supranuclear gaze palsy, cognitive and behavioral changes
Corticobasal degeneration	Cognitive dysfunction, apraxia, alien limb, cortical sensory loss; asymmetrical rigidity, dystonia; stimulus-sensitive myoclonus
Dementia with Lewy bodies	Dementia, visual hallucinations, fluctuating level of consciousness, sensitivity to neuroleptics, REM sleep behavior disorder
Normal pressure hydrocephalus	Cognitive impairment, urinary symptoms, lower-body parkinsonism ("gait apraxia")
Vascular parkinsonism	"Lower-body parkinsonism," additional neurologic signs (e.g., spasticity, weakness)
Drug-induced parkinsonism	Can have all the features of classic parkinsonism of PD, including rest tremor; generally symmetrical; can be accompanied by other drug-induced movement disorders (e.g.,

Supportive criteria for the diagnosis of PD

- Unilateral onset
- Rest tremor
- Progressive
- Persistent asymmetry primarily affecting side of onset
- Excellent response(70%-100%) to levodopa
- Severe levodopa-induced dyskinesia
- Levodopa response for 5 years or more
- Clinical course of 10 years or more

Jankovic. J Neurol Neurosurg Psychiatry 2008;79:368-376

Case

ID: 65 M teacher, healthy, no meds

HPI: 3 year progressive R hand rest tremor, stiffness of right shoulder, mild difficulties using R hand, occasional dragging R leg

5 year history of olfactory loss, 10 year history of RBD

No autonomic, cognitive, psychiatric

Exam: mild increased tone right, rest tremor R hand, bradykinesia R hand, decreased arm swing R

Normal EOMs, no orthostatic drop

Parkinson Disease: Early

Motor

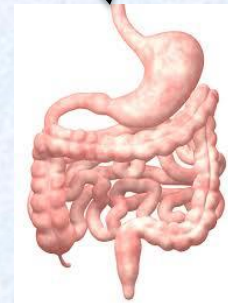


Tremor
Rigidity
Akinesia/Bradykinesia

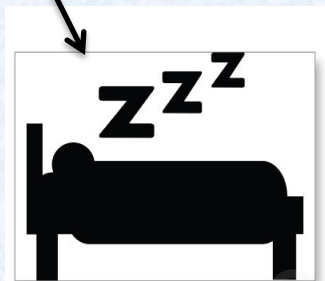
Non-Motor



Olfactory loss
(75%)

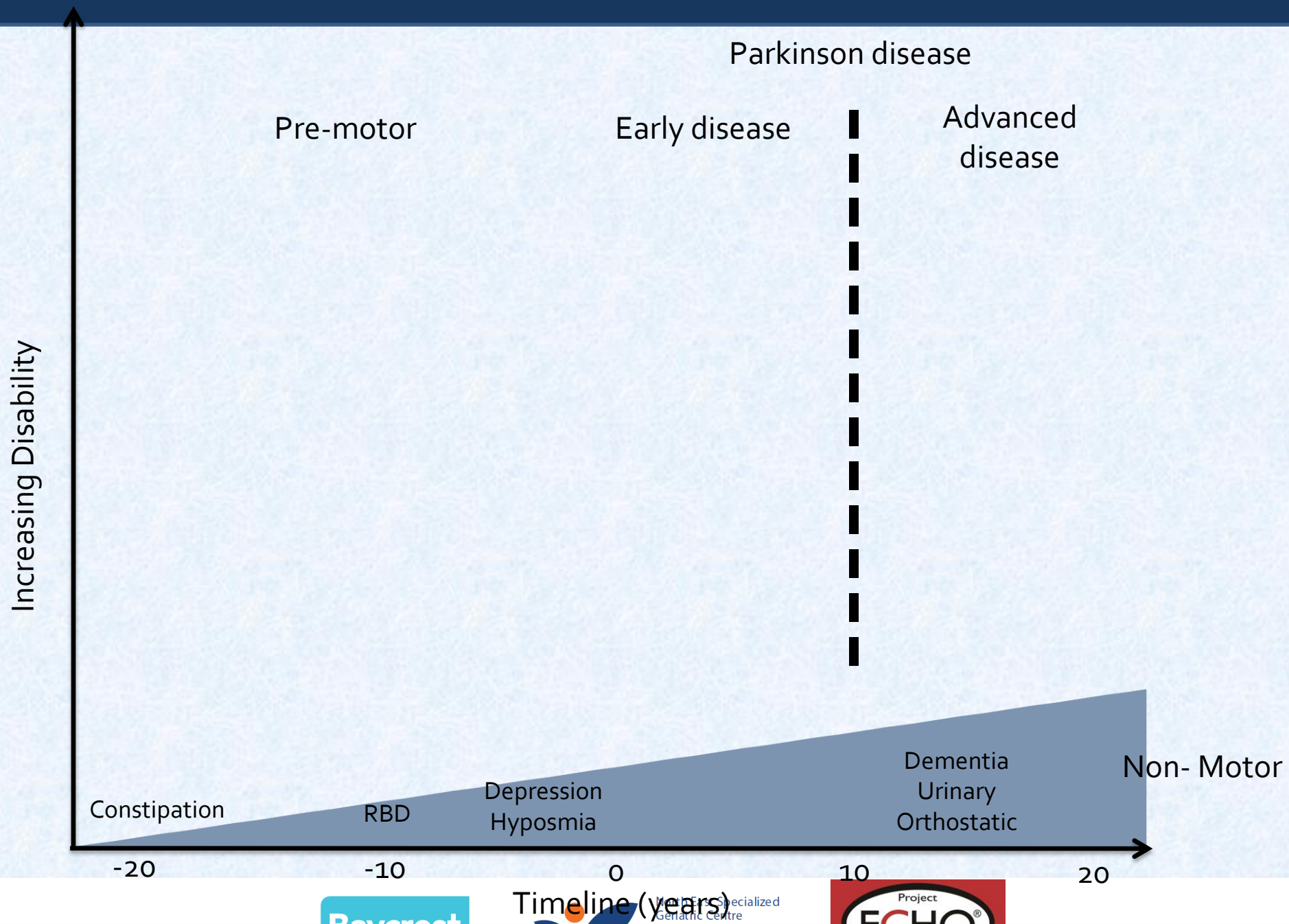


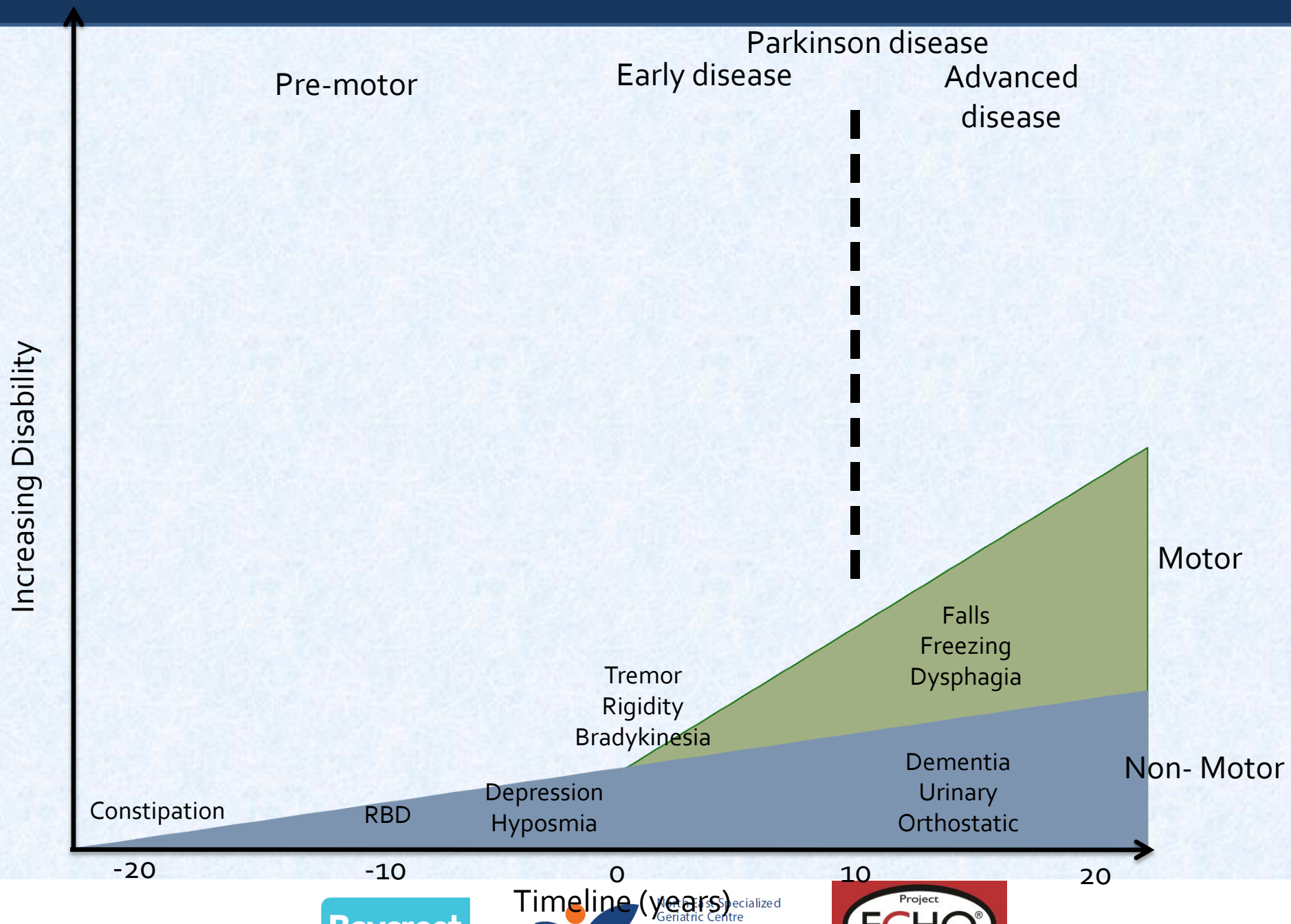
Constipation



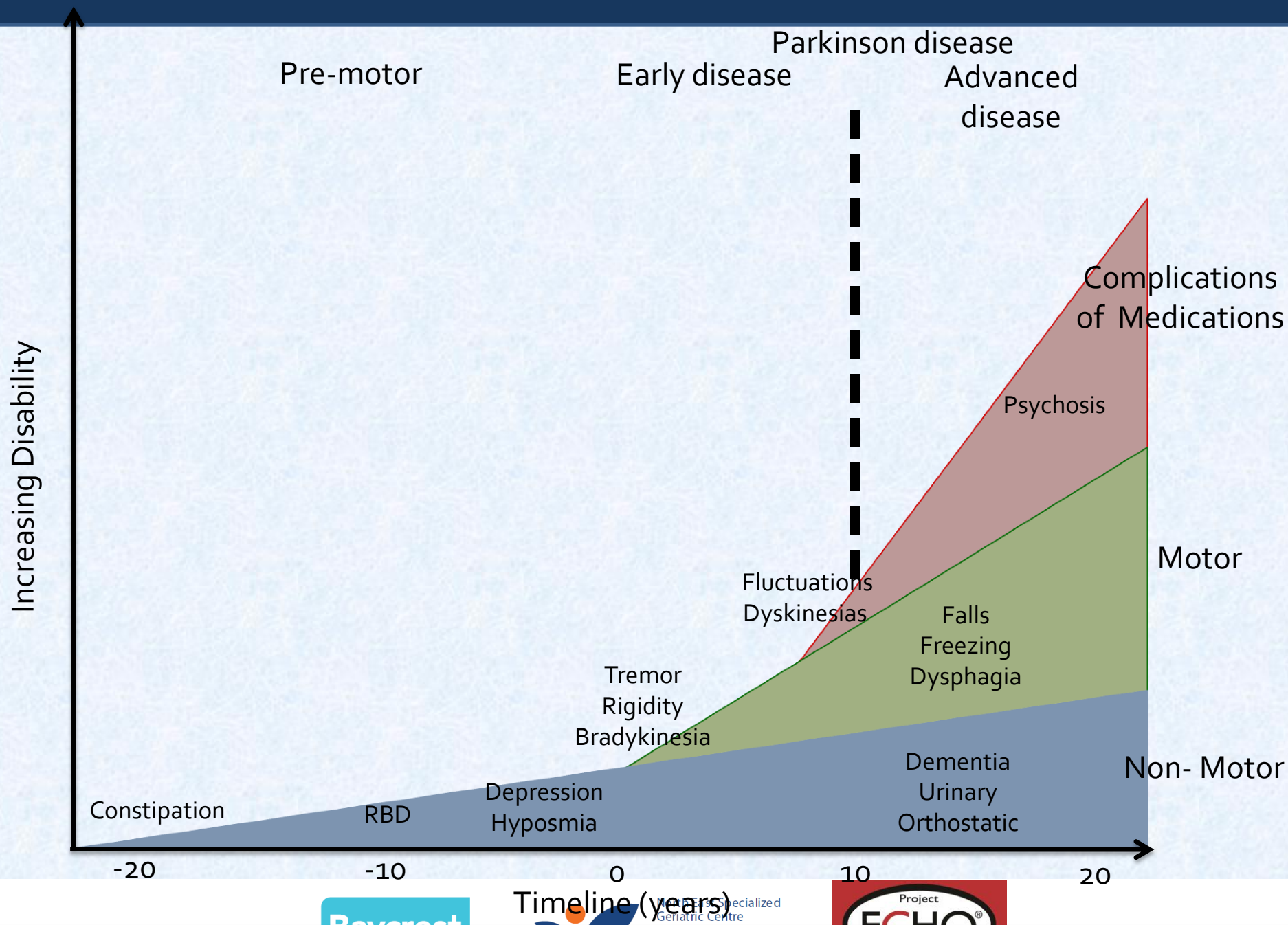
RBD (30%)

Pre-Motor





Adapted from Kalia and Lang. Parkinson Disease Treatment. Lancet. 2015; 386: 896-912



Adapted from Kalia and Lang. Parkinson Disease Treatment. Lancet. 2015; 386: 896-912

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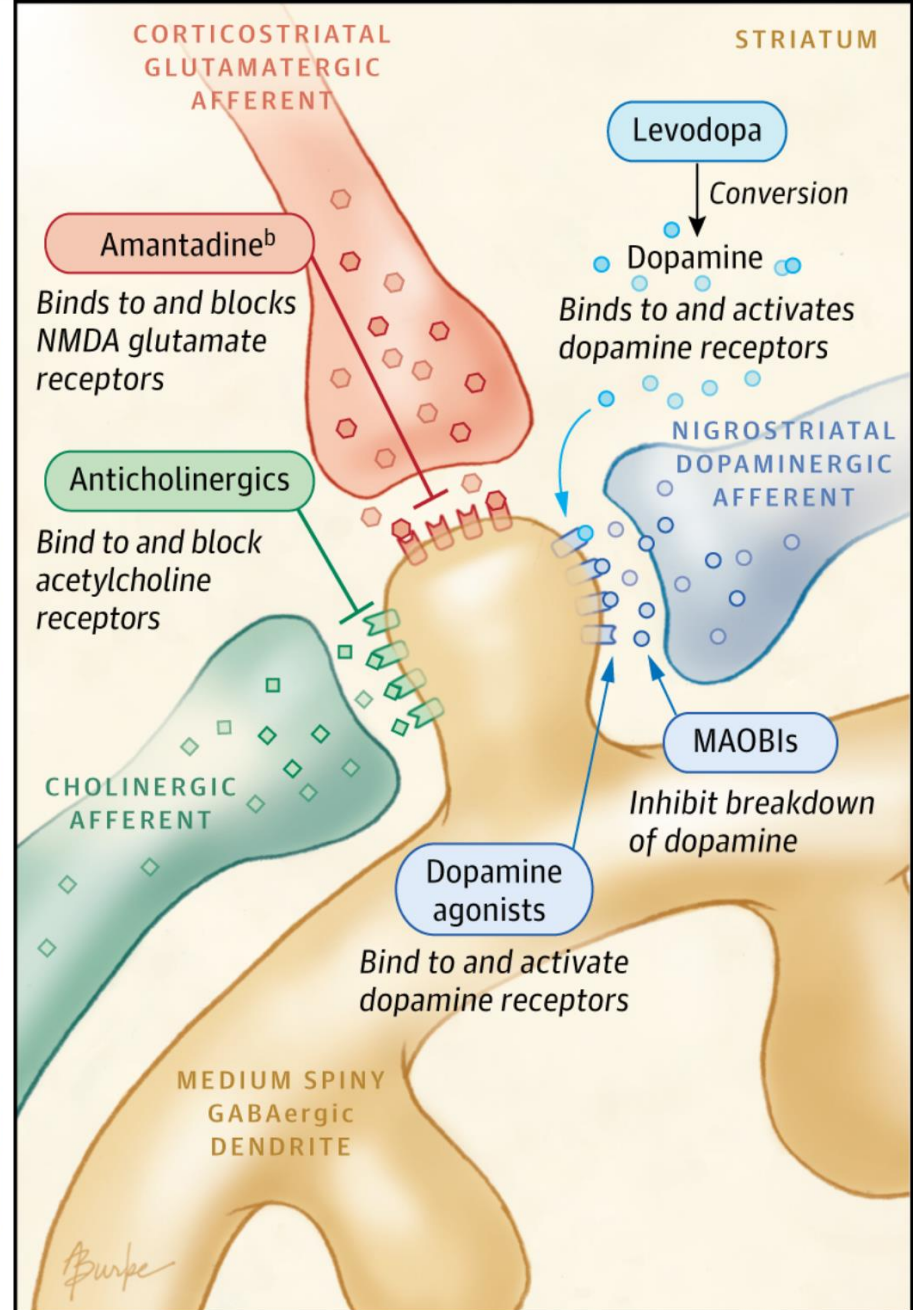
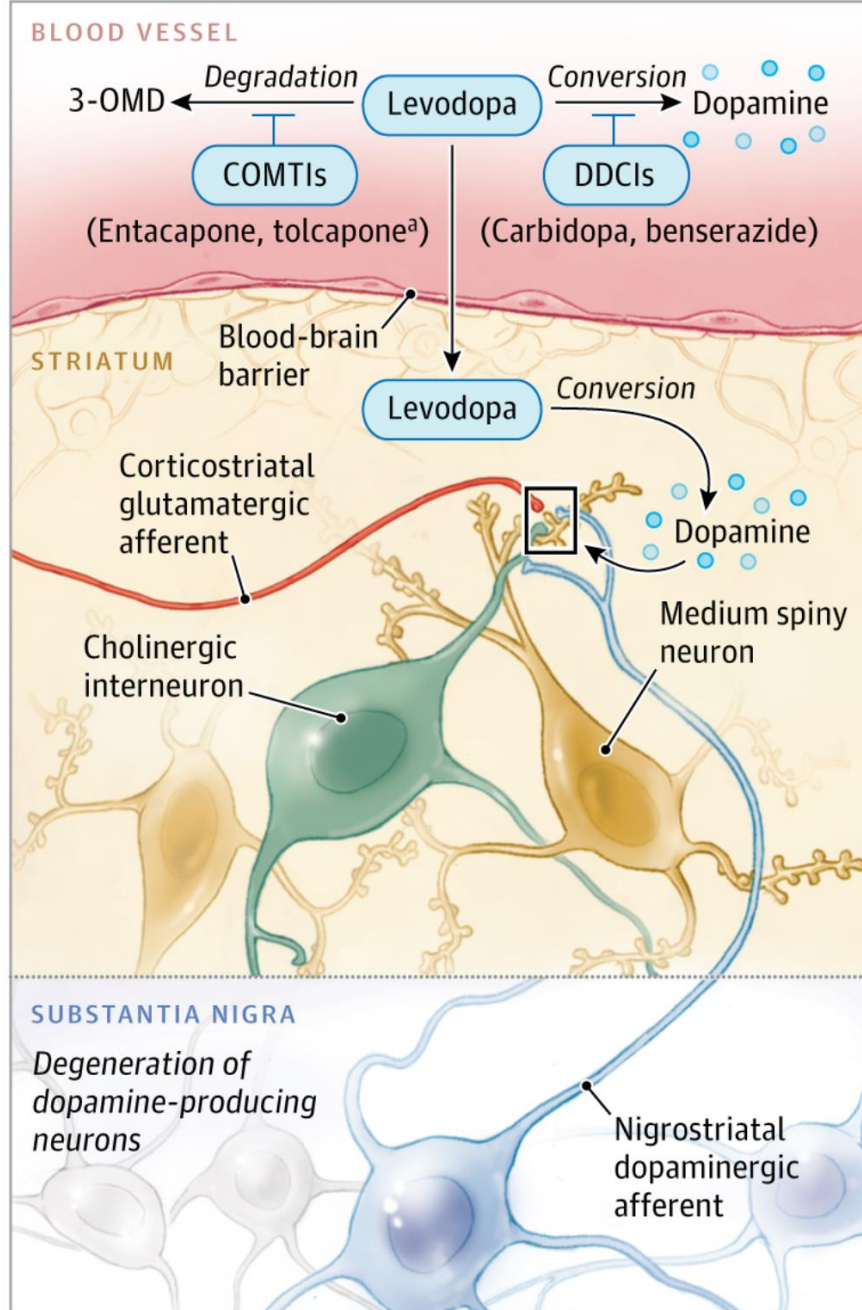
Exam: mild increased tone right, rest tremor R hand, bradykinesia R hand, decreased arm swing R

Normal EOMs, no orthostatic drop

What is the recommended initial therapy?

PD Motor Treatment: Medications

1. Levodopa:
2. Dopamine Agonists: pramipexole, ropinirole, **rotigotine (patch)**
3. Monoamine-B Inhibitors: selegiline, rasagiline
4. COMT inhibitor: entacapone
5. Anti-cholinergics: e.g. trihexyphenidyl



PD Motor Treatment: Age>65

1. Levodopa

2. Dopamine Agonists: pramipexole, ropinirole, rotigotine (patch)

3. Monoamine-B Inhibitors: selegiline, rasagiline

4. COMT inhibitor: entacapone

5. Anti-cholinergics: e.g. trihexyphenidyl

Treatment: Levodopa

EDITORIAL

Levodopa: 50 Years of a Revolutionary Drug for Parkinson Disease

Stanley Fahn, MD¹ and Werner Poewe, MD²

Available as:

- Sinemet (with carbidopa), Prolopa (with benserazide)
 - IR preparation or CR; (*ER in US- Rytary*)
 - **Levodopa/carbidopa intestinal gel: Duodopa**
- Adverse effects:
 - **Behavioural complications**
 - **Dyskinesias and motor fluctuations**
 - Nausea/GI
 - Orthostatic Hypotension
 - Worsening hallucinations/behavioural

Treatment: Dopamine Agonist

- Drugs: Pramipexole, Ropinirole, **Rotigotine**
- Less well tolerated in elderly patients
- Adverse effects:
 - **Impulse Control Disorder***: hypersexuality, hyperphagia, excessive gambling/shopping (up to 15% of patients)**
 - Nausea/GI
 - Orthostatic Hypotension
 - Worsening hallucinations
 - Ankle edema
 - Sleep attacks



Treatment: Enzyme Inhibitors

1. Monoamine B (MAOB)-Inhibitors: block breakdown of levodopa and patient's intrinsic dopamine

Rasagiline, Selegiline

Theoretical risk of serotonin syndrome with SSRI use but exceedingly rare

2. COMT-Inhibitors: block breakdown of levodopa ONLY (therefore adjunctive therapy with levodopa ONLY)

Entacapone; Stalevo (single pill with levodopa/carbidopa/entacapone)

Side effects: Diarrhea 5% - need to stop drug

Back to the Case...

ID: 65 M teacher with 3 year history of possible PD

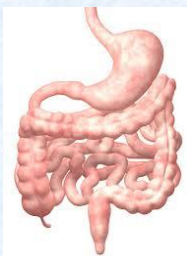
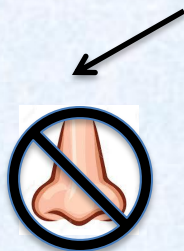
HPI: Started on levodopa with good benefit but feels nausea with every dose

Parkinson Disease- Early

Motor



Non-Motor



Medication Complications



Peripheral:
Nausea;
orthostatic
hypotension

Levodopa Peripheral Side Effects

- Nausea/vomiting can be a complication of starting therapy in up to 15% of patients
- Orthostatic hypotension can be worsened

Treatment:

1. Take with food (e.g. cracker)
2. Additional dose of carbidopa with levodopa
3. Domperidone 30 minutes prior to levodopa dosing

(*** associated with small increased risk in ventricular arrhythmias, sudden cardiac death- 30 mg per day max and not for use in certain populations – e.g. prolonged Qt, CHF, severe liver disease)

***Domperidone Maleate - Association with Serious Abnormal Heart Rhythms and Sudden Death (Cardiac Arrest) - For Health Professionals

Case... five years later

ID: 70 M

Dx: Probable PD

Started on levodopa with excellent response.

Increasing levodopa overtime to 2tabs q4H with good response

Now noticing at 3.5 hours very immobile until next dose “kicks in”

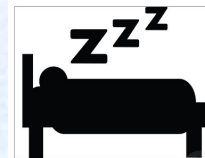
Also, at middle of dose has “wiggly movements” which are bothersome

Parkinson Disease-Mid

Motor



Non-Motor



Medication
Complications

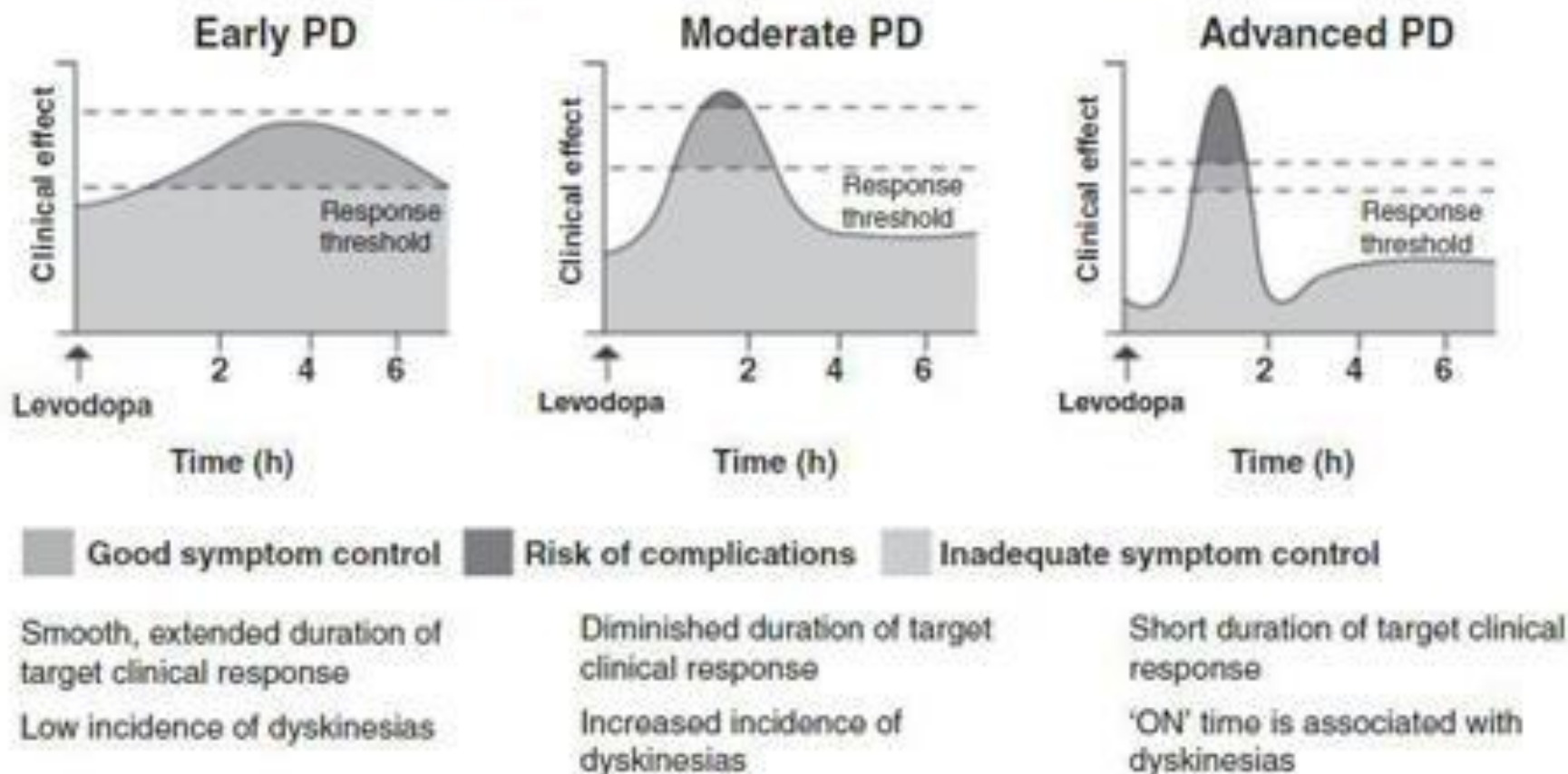


Peripheral: N/V, OH

Central: Motor
fluctuations and
dyskinesias

Motor Fluctuations in PD

Change in levodopa response over time



Adapted from: Obeso JA et al. In: Olanow CW, Obeso JA, eds. Beyond the Decade of the Brain. Vol 2.

Treatment of Motor Fluctuations:

Wearing Off:

1. Addition of COMT or MAO-B inhibitor: reduce off time by 1.5 hr/day (Level A)
2. Addition of Dopamine agonist: reduce off time by 15% (Level B)
3. Change of timing/amount of levodopa

Dyskinesias:

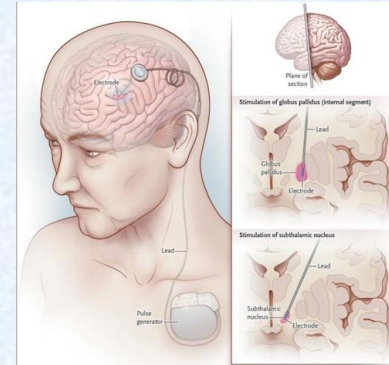
1. Amantadine- **NOT for use in elderly (confusion/hallucinations)**
2. Variation of the above

Advanced Therapies!!

Grimes et al., Canadian Guidelines on Parkinson Disease Treatment. Can J Neurol Sci. 2012; 39: Supp 4. S1-S30

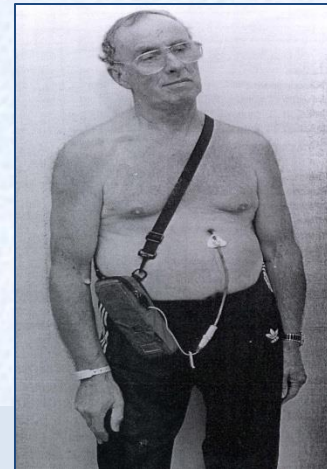
Advanced Therapies: Treatment of Medication-Resistant Motor Fluctuations*

1. Surgery: Deep Brain Stimulation



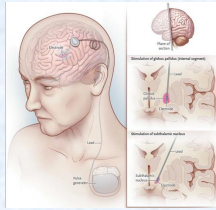
2. Levodopa-carbidopa intestinal gel (LCIG/*duodopa*)

Approval for use and drug benefit coverage Ontario 2014 (used in Europe since 2004)



*Requires referral to a Movement Disorders Centre in Toronto (TWH), Hamilton, London, Ottawa

DBS Candidates



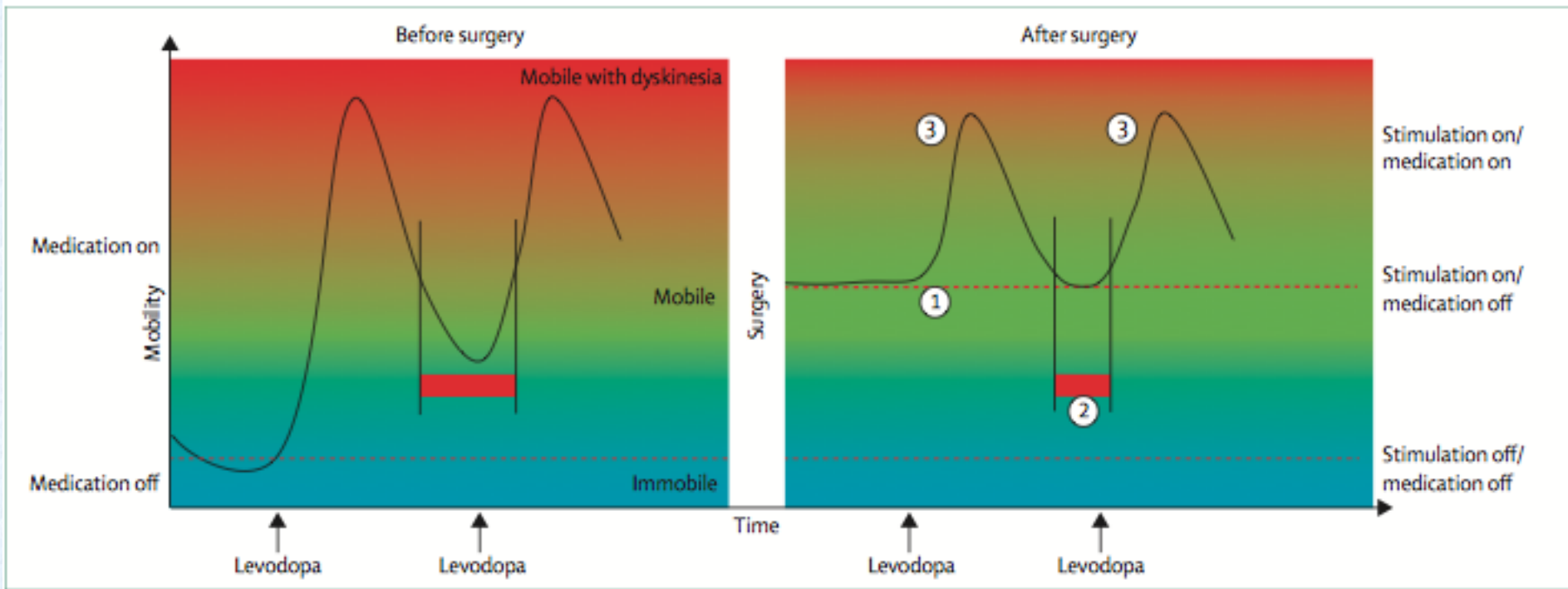
- PD diagnosis
- Levodopa Responsive (30-40%)
- Medically healthy
- No dementia
- No psychosis
- No unstable depression
- <70 (75?)

LCIG Candidates



- PD diagnosis
- Levodopa Responsive (30-40%)
- Medically healthy
- *MCI/mild dementia OK*
- *Mild psychosis OK*
- *Mild depression OK*
- *No age limit*

DBS, LCIg Benefits – decrease ON time
with bothersome dyskinesia and OFF time



Deuschl and Agid, Subthalamic neurostimulation for Parkinson's disease with early fluctuations: balancing the risks and benefits. *Lancet Neurol* 2013. 12:1025-34.

Olanaw et al., Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. *Lancet Neurology*. 2014. 13 (2) 141-149

Case... eight years later

ID: 73 M

STN DBS 2 years ago with good benefit on motor fluctuations, dyskinesias

On levodopa, entacapone

Has had a few falls in the past month

His voice is soft and his wife finds it difficult to hear him at times

Parkinson Disease- Late

Motor



Tremor
Rigidity
Akinesia/Bradykinesia

Hypophonia
Postural Instability
Gait Disorder (Freezing)
Dysphagia

Non-Medical Management

SPEECH

- Speech therapy
- Singing

FALLS

- Walker/Wheel chair
- Occupational Therapist assessment
- Rule out hypotension
- PT, Tai Chi, Exercise



Geriatric Centre
Centre gériatrique
spécialisé du Nord-Est



Slide courtesy Veronica Bruno MD

Case... ten years later

ID: 75 M

STN DBS 4 years ago with good benefit on motor fluctuations, dyskinesias

On levodopa, entacapone

Has difficulties standing up at times, 1 syncope

Severe constipation

Also, his wife feels he is repeating himself and misplacing items

Parkinson Disease- Late

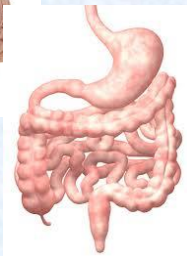
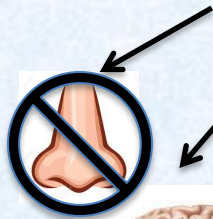
Motor



Tremor
Rigidity
Akinesia/Bradykinesia

Postural Instability/Gait
(FOG)
Dysphagia

Non-Motor



1. Cognitive/Psychiatric
2. Autonomic
3. Sleep Disorders

Medication Complications



Peripheral: N/V,
orthostatic
hypotension

Central: Motor
complications

Central:
Behavioural

PD Motor Treatment: Advanced Disease

- ❑ Development of levodopa-resistant motor symptoms e.g. freezing of gait, instability, falls
- ❑ Previously responsive symptoms may become less levodopa-responsive
- ❑ Increased likelihood of levodopa-induced complications in advanced disease e.g. hallucinations, behavioural changes
- ❑ **BUT...** many patients can continue to have levodopa-responsive parkinsonism in advanced disease
- ❑ There may be non-motor features that also respond to levodopa e.g. anxiety, pain

Swallowing in Advanced PD

- Videofluoroscopy swallowing assessment
- Coughing on liquids or solids is common
- Dietary modification often necessary – use of thickeners
- Careful hand feeding can be as effective as PEG for nutritive

Feeding Choices for People with
Advanced Parkinson's Disease



UHN

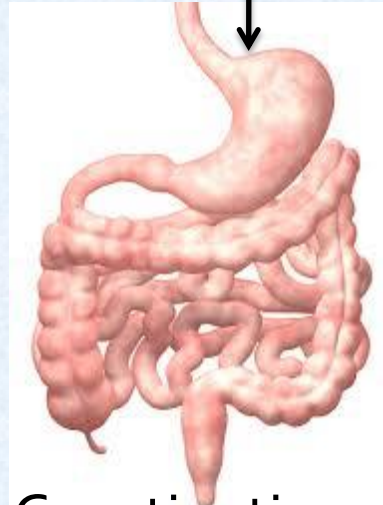
Information for patients, families and caregivers

http://www.uhn.ca/PatientsFamilies/Health_Information/Health_Topics/Documents/Feeding_Choices_Advanced_Parkinson_Disease.pdf

PD: Non-motor



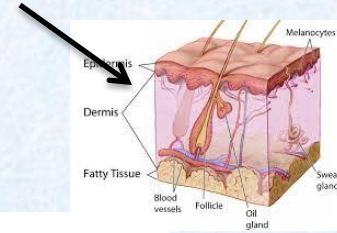
1. Dementia
2. Hallucinations
3. Depression
4. Anxiety
5. Apathy



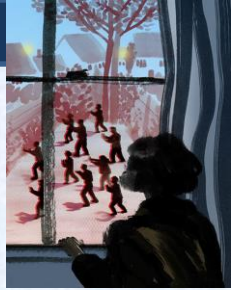
1. Constipation
2. Urinary Symptoms
3. Orthostatic Hypotension
4. Erectile Dysfunction
5. Drooling



1. REM Sleep Behaviour Disorder
2. Insomnia
3. Excessive Daytime Sleepiness



Psychosis/Hallucinations

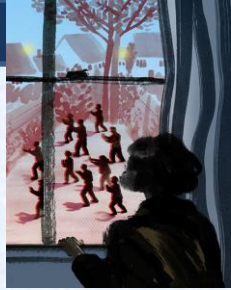


- Tend to be well-formed animals or people
- Increased likelihood with disease duration (up to 70% with 20 years disease) and in the setting of dementia
- Other risks: vision problems, medications, infections

Treatment:

- Rule out infections/other causes
- Stop offending medications (anticholinergics; amantadine>DA>levodopa)
- Medications: quetiapine, cholinesterase inhibitors, clozapine
- Not all hallucinations require treatment

Psychosis/Hallucinations



- Tend to be well-formed animals or people
- Increased likelihood with disease duration (up to 70% with 20 years disease) and in the setting of dementia
- Other risks: vision problems, medications, infections

Treatment:

Quetiapine and Clozapine are the only two “safe” anti-psychotics in PD and related disorders

amantadine > DA > levodopa)

- Medications: quetiapine, cholinesterase inhibitors, clozapine
- Not all hallucinations require treatment

Memory Loss/Dementia

Likelihood increases with disease duration (up to 80% at 20 years duration)

Characterized by slowing of thinking, difficulties with decision making, less flexible thinking; eventual memory problems

Treatment

- Stop offending medications (anticholinergics, TCAs, amantadine, dopamine agonists)
- Medication: Acetyl-cholinesterase Inhibitors, Memantine

Connolly B, Fox SH. Treatment of cognitive, psychiatric, and affective disorders associated with Parkinson's disease. Neurotherapeutics. 2014

Anxiety and Depression



- Can predate PD
- PD can cause or worsen existing depression and or anxiety
- **Treatment:**
 - Psychotherapy
 - Medications (TCA-for depression; SSRI, SNRI)
 - ECT for severe depression
 - “Secondary anxiety disorder:” Associated with “off-periods” or low-levodopa levels: adjust levodopa dosing

Autonomic Dysfunction

SIALORRHEA

Candy, gum

Meds: Atrovent, atropine, Botulinum Toxin injections

CONSTIPATION

Make certain the Bowel Routine is working (senokot, lactulose, PEG)

URINARY PROBLEMS

Modifications: Urinal/commode at bedside

- Appropriate garments and bedsheets
- Condom catheters

Medications: Variety, many with anticholinergic side effects, newer meds with less side effects; botox

ORTHOSTATIC HYPOTENSION

Increase water intake, salt in the diet if possible
Fludrocortisone, midodrine, domperidone

Sleep

RBD

Bed safety

Medications: **melatonin**, clonazepam, quetiapine

Excessive Daytime Sleepiness

Check Blood pressure! , review medications, review overnight sleep

Treat any of the above

Medication: Modafinil, Methylphenidate (occasional)

Insomnia

Sleep Hygiene

Medications:

Initiation: Melatonin, zopiclone

Maintenance: Sinemet CR, treat nocturia

Dopaminergic Medication Behavioural Complications

Impulse control disorder	Includes pathologic gambling, hypersexuality, compulsive shopping, and binge eating
Punding	Repetitive, often purposeless stereotyped behaviors (e.g., continual handling or sorting of objects)
Dopamine dysregulation syndrome	Compulsive overuse of dopaminergic therapy (above what is necessary for treatment of motor symptoms)

Treatment: Decrease dopaminergic medication

Pain in PD

- Prevalence ranges from 40% to 85%, frequently located in the lower limbs
- ½ of all PD patients complain about MSK pain, which has likely worsened with deconditioning and lack of rehabilitation
- Pain may fluctuate with on/off periods (levodopa-responsive?)
- Only 52.4% of PD patients with pain used analgesics, most often non-opioids
- No foundation of evidence for PD pain treatment
- Can respond to traditional pain therapies (e.g. acetaminophen, ROM exercise)
- Opioids problematic due to side effects (constipation, psychoactive metabolites) but occasionally useful

Broen MP, Braaksma MM, Patijn J, Weber WE. Prevalence of pain in Parkinson's disease: a systematic review using the modified QUADAS tool. Mov Disord. 2012

Questions?

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