A Parkinson Disease Primer

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Faculty/Presenter Disclosure

- **Faculty: Elizabeth Slow**
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  None to be disclosed

Mitigating Potential Bias

The information presented in this CME program is based on recent information that is explicitly “evidence-based”.

This CME Program and its material is peer reviewed and all the recommendations involving clinical medicine are based on evidence that is accepted within the profession; and all scientific research referred to, reported, or used in the CME/CPD activity in support or justification of patient care recommendations conforms to the generally accepted standards

Objectives:

- PD Timeline:

i. Early Stage

ii. Mid Stage

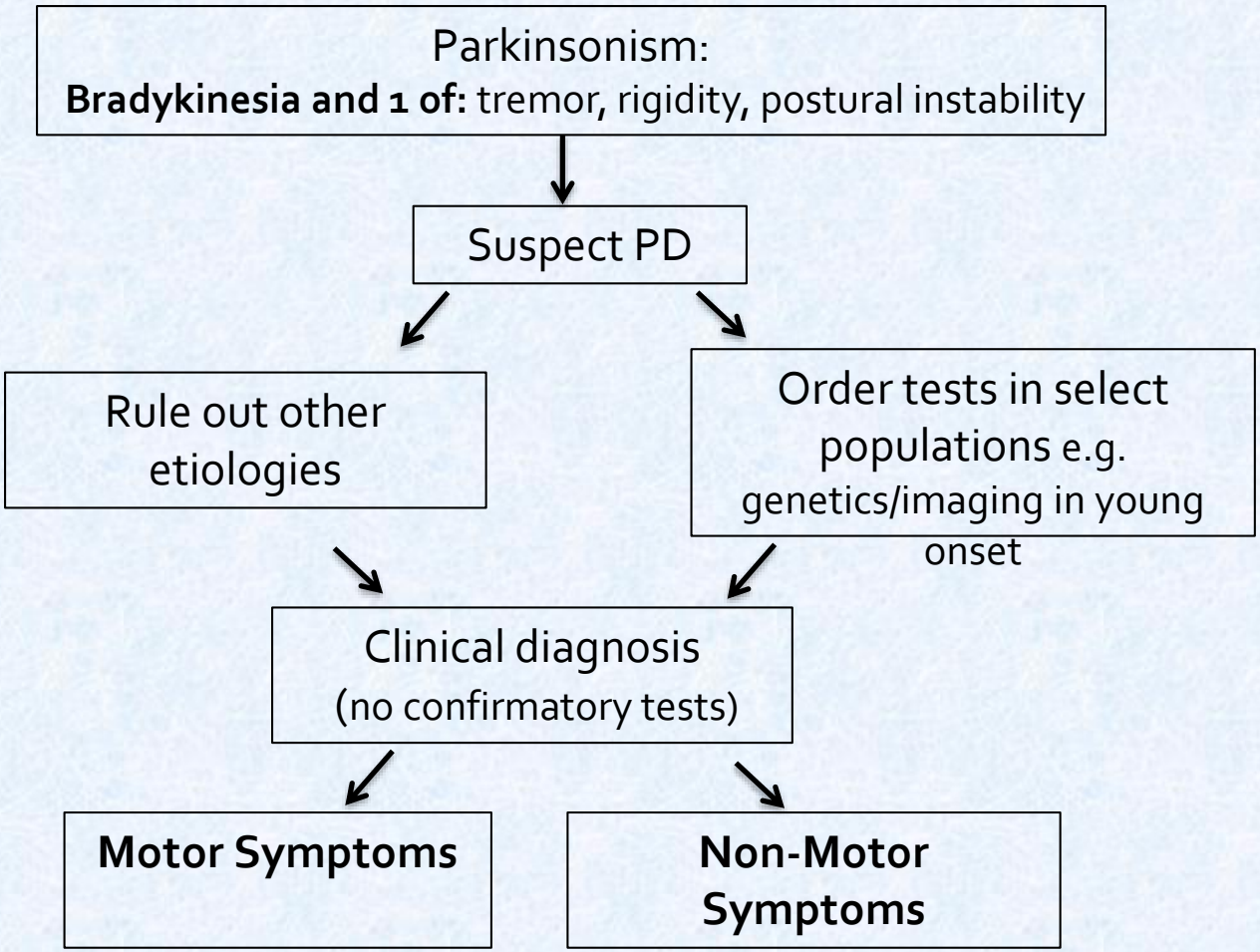
iii. Late Stage

- 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

Parkinsonism	*Distinguishing Features*
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.,

Slow EJ, Lang AE. Neurology. Parkinsonism and Related Disorders. In: Singh AK, editor(s). Scientific

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

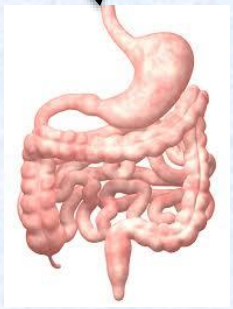
Parkinson Disease: Early

Motor

Tremor
Rigidity
Akinesia/Bradykinesia

Non-Motor

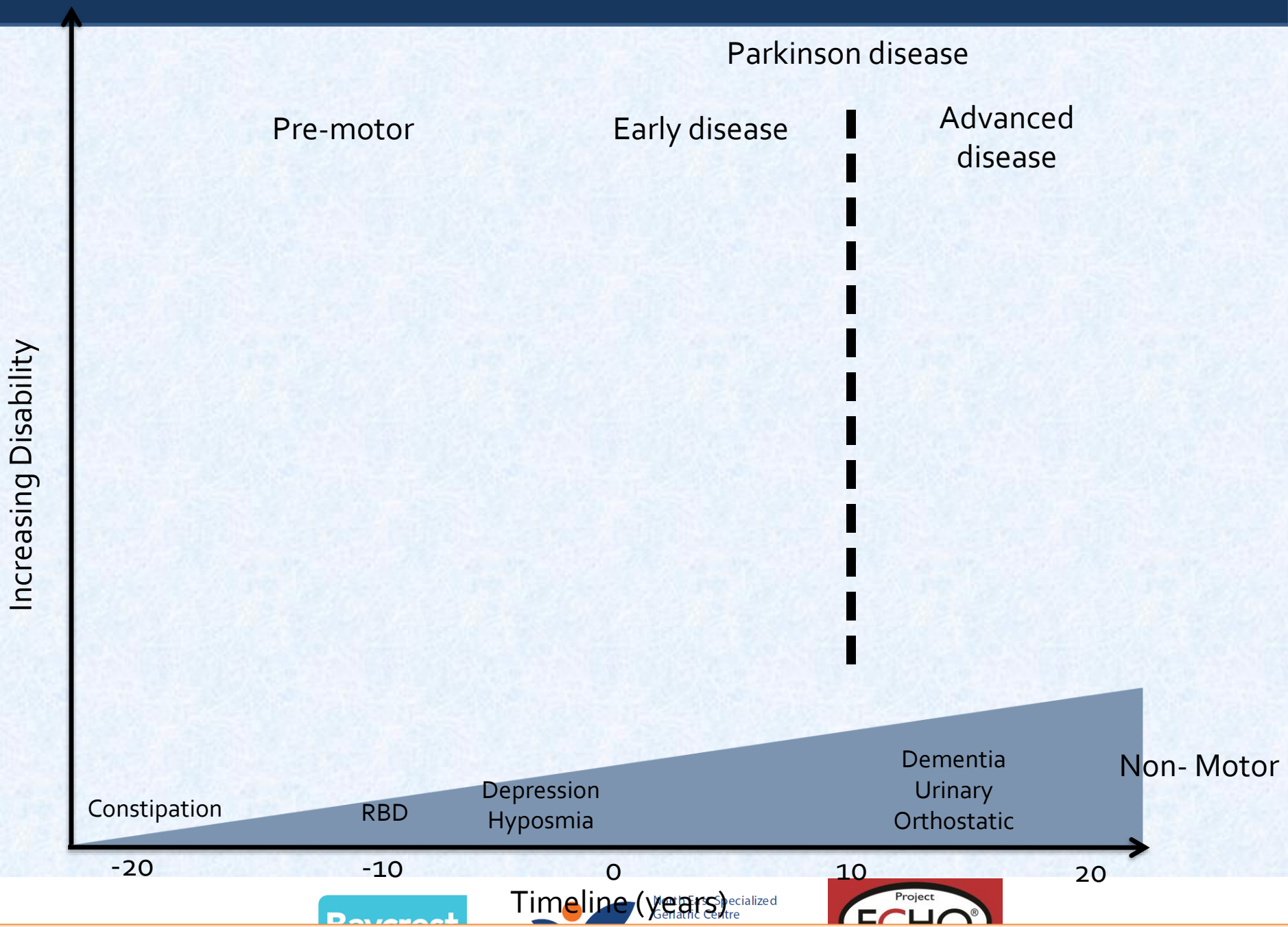
Olfactory loss (75%)



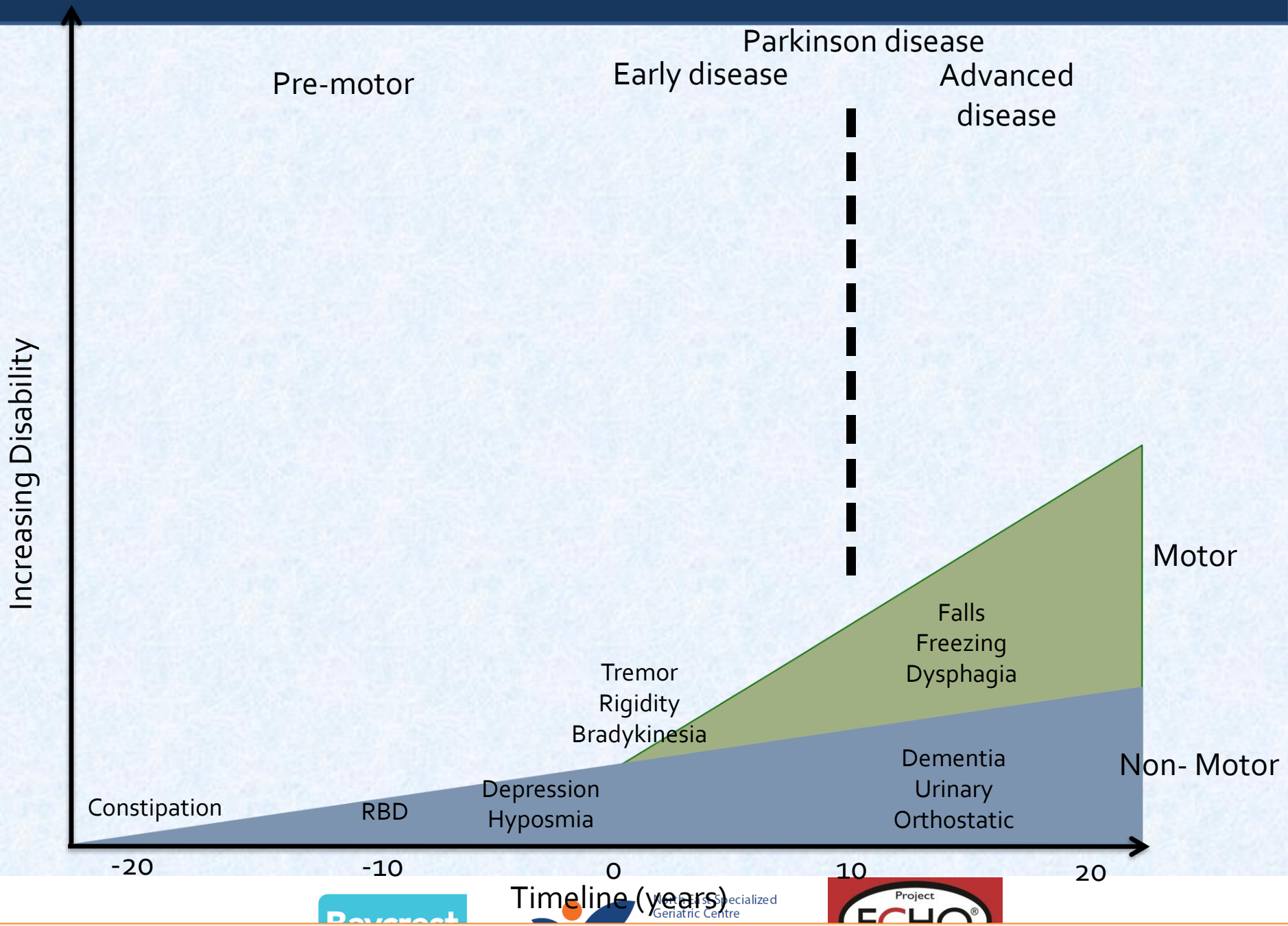
Constipation

RBD (30%)

Pre-Motor



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



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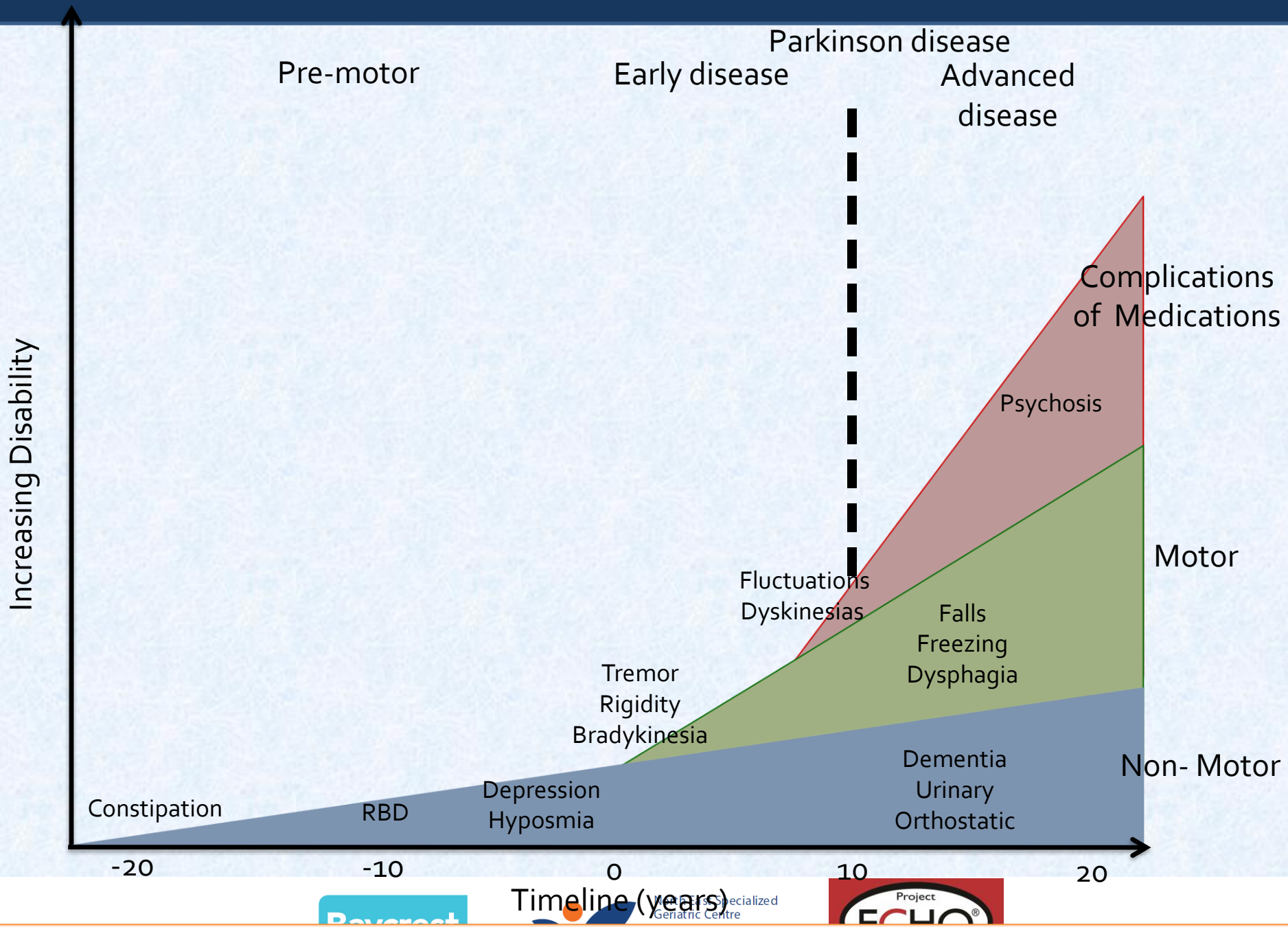

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Case

ID: 60 M teacher, healthy, no meds

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

No autonomic, cognitive, psychiatric

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

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Normal EOMs, no orthostatic drop

What is the recommended initial therapy?

Non-medical therapy options in early PD

- Exercise +++++++++
- No drug treatment may be the option.
- The timing of symptomatic therapy is individual
  - degree of functional impairment
  - lifestyle of patient
  - Age of patient
  - Co morbidities

PD Motor Treatment: Medications

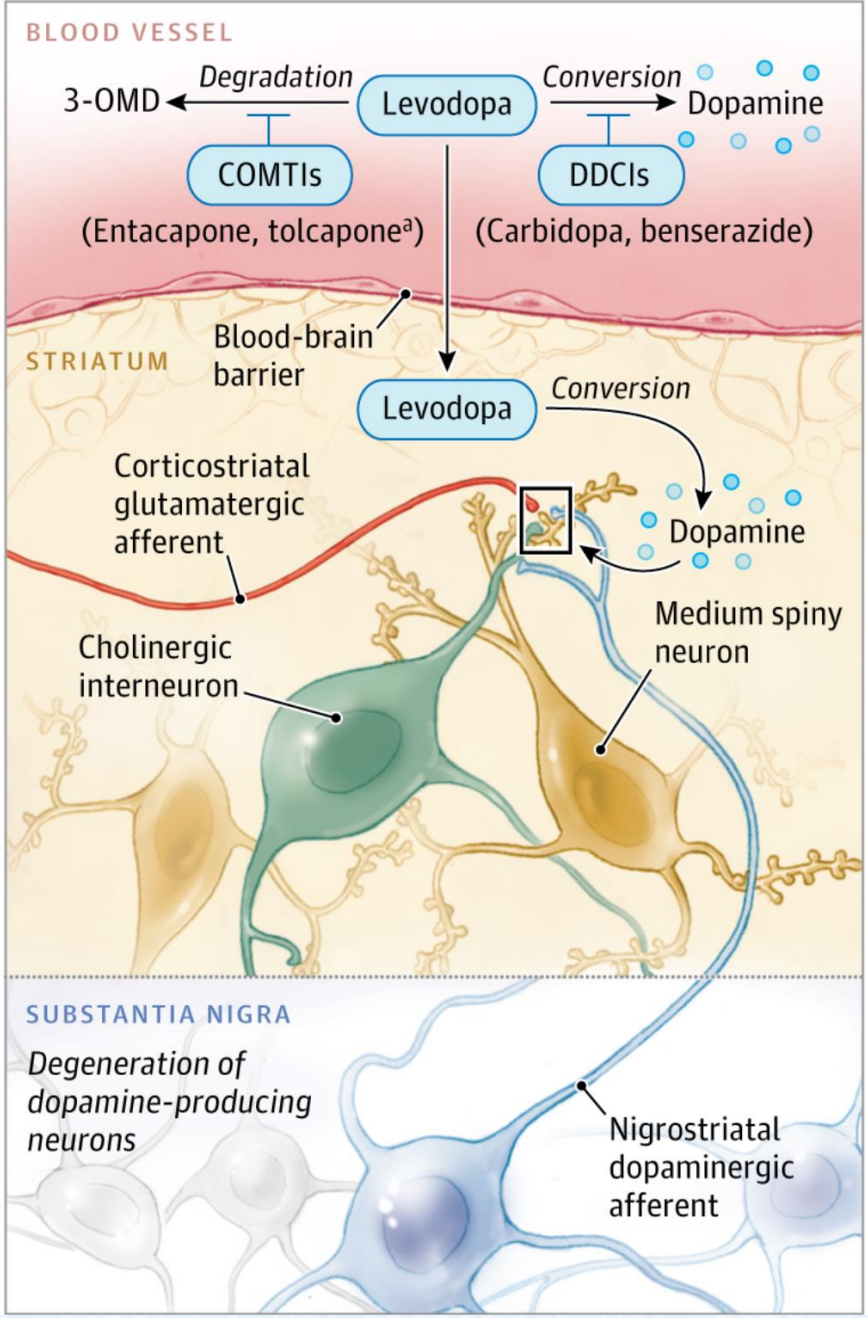
1. Levodopa:

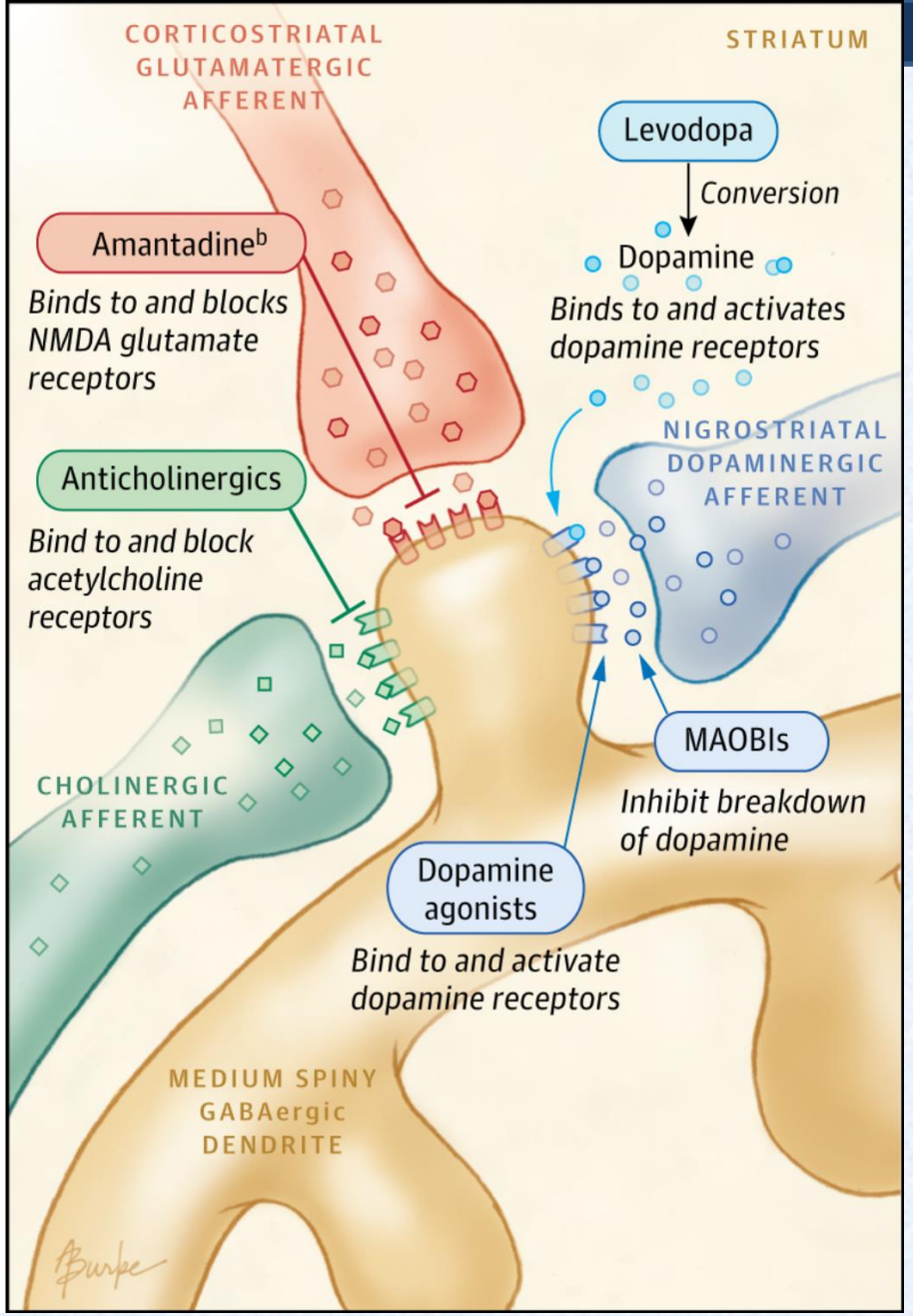
2. Dopamine Agonists: pramipexole, ropinirole, **rotigitine (patch), apomorphine (injectable)**

3. Monoamine-B Inhibitors: selegiline, rasagiline, **safinamide**

4. COMT inhibitor: entacapone

5. Anti-cholinergics: e.g. trihexyphenidyl





Connolly and Lang. Pharmacological Treatment of Parkinson Disease. JAMA. 2014, 311; 1670-1683

PD Motor Treatment: Age>65

1. Levodopa
2. Dopamine Agonists: ~~p~~ramipexole, ropinirole, rotigitine (patch)
3. Monoamine-B Inhibitors: selegiline, rasagiline
4. COMT inhibitor: entacapone
5. Anti-cholinergics: e.g. ~~tri~~hexyphenidyl

Treatment: Levodopa


EDITORIAL

Levodopa: 50 Years of a Revolutionary Drug for Parkinson Disease

Stanley Fahn, MD[1] and Werner Poewe, MD[2]

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, **Rotigitine**
- 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, Safinamide

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…

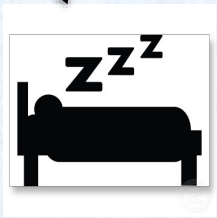
ID: 65 M teacher with 3 year history of possible PD

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

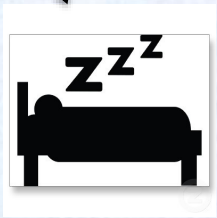
Now noticing at 3.5 hours very immobile until next dose “kicks in”

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

Parkinson Disease-Mid

Motor

Non-Motor



Medication Complications

Peripheral: N/V, OH

Central: Motor fluctuations and dyskinesias

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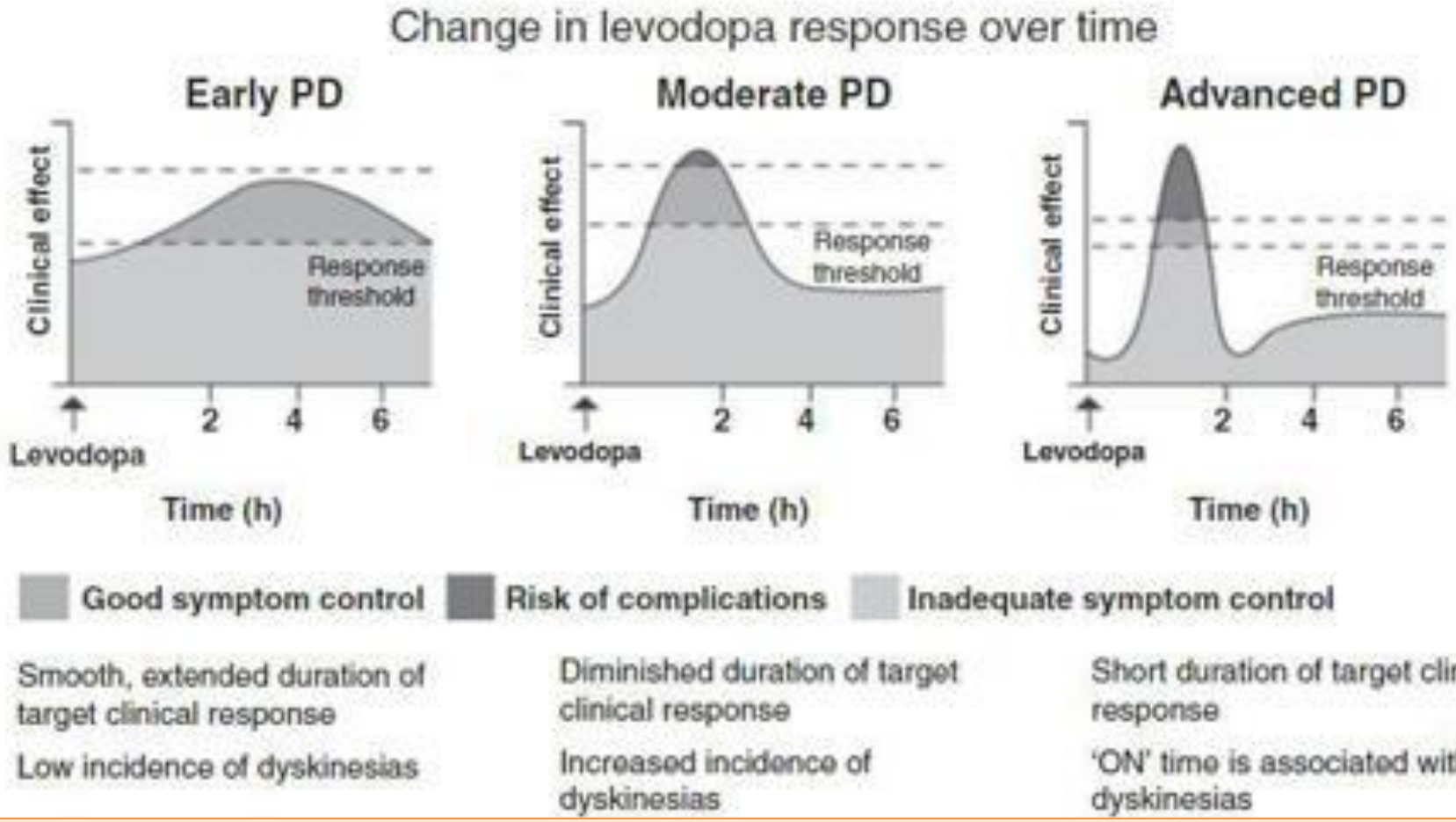
Motor Fluctuations in PD



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:

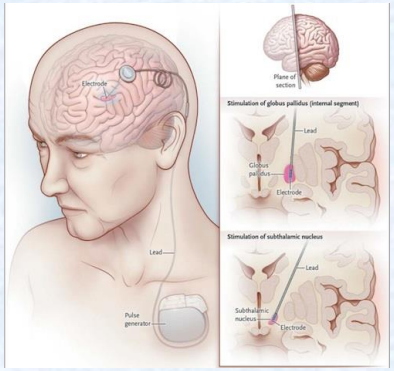
1. Amantadine- **NOT for use in elderly (confusion/hallucinations)**
2. Variation of the above

Advanced Therapies!!

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

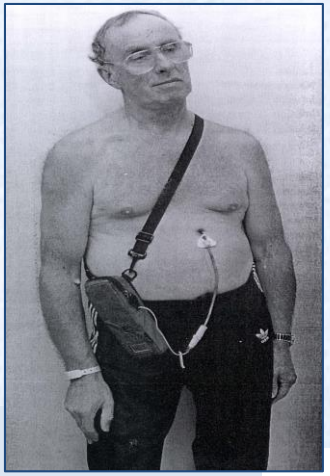
Advanced Therapies: Treatment of Medication-Resistant Motor Fluctuations*

1. Surgery: Deep Brain Stimulation



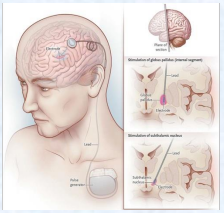
2. Levodopa-carbidopa intestinal gel (LCIG/d*uodopa*)

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



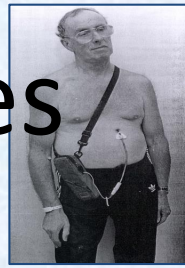
*Requires referral to a Movement Disorders Centre in Toronto (TWH), Hamilton, London, Ottawa

DBS Candidates



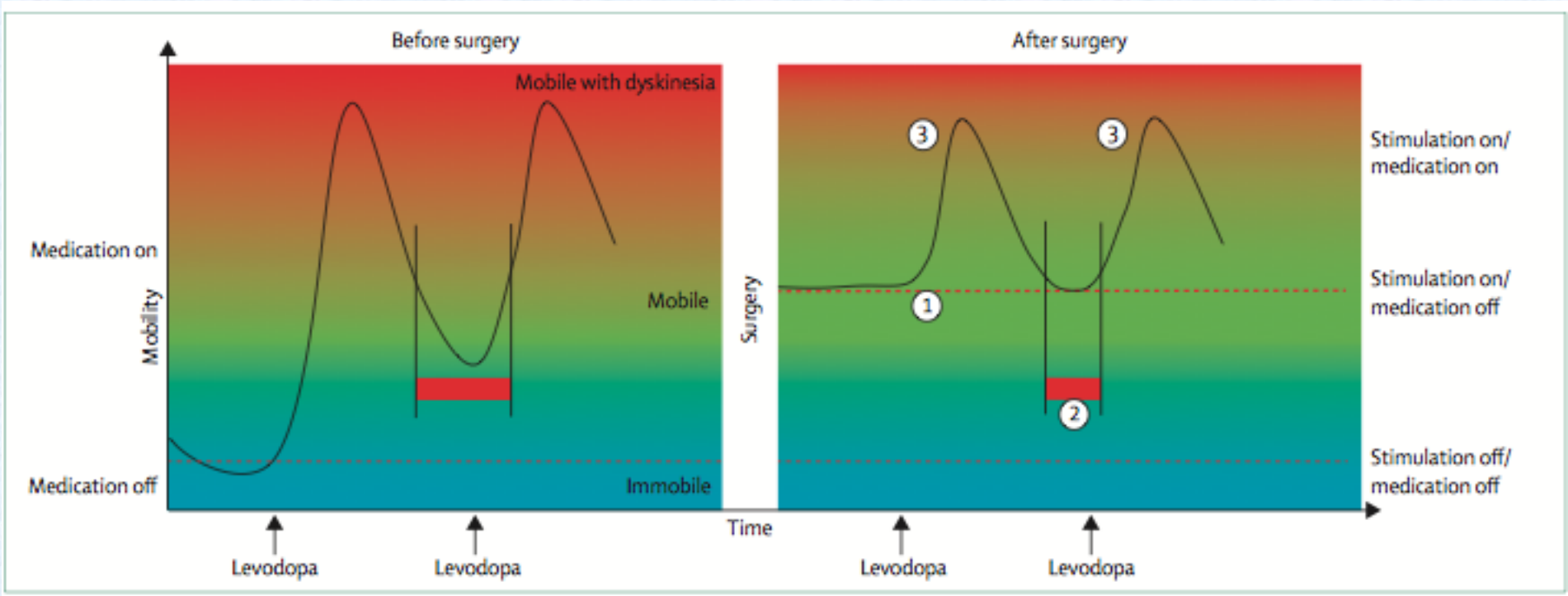
- PD diagnosis
- Levodopa Responsive (30-40%)
- Medically healthy
- No dementia
- No psychosis
- No unstable depression
- <70 (75?)

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



Deutschl 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

DANCING WITH PARKINSON'S

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ROCK STEADY BOXING

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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

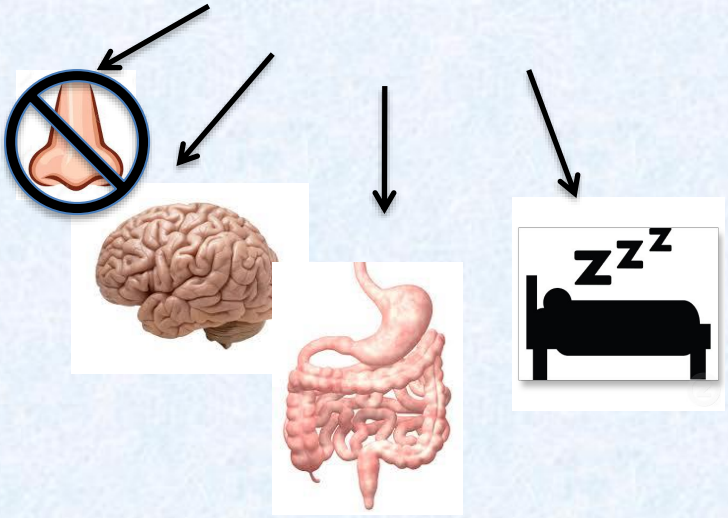
Parkinson Disease- Late

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

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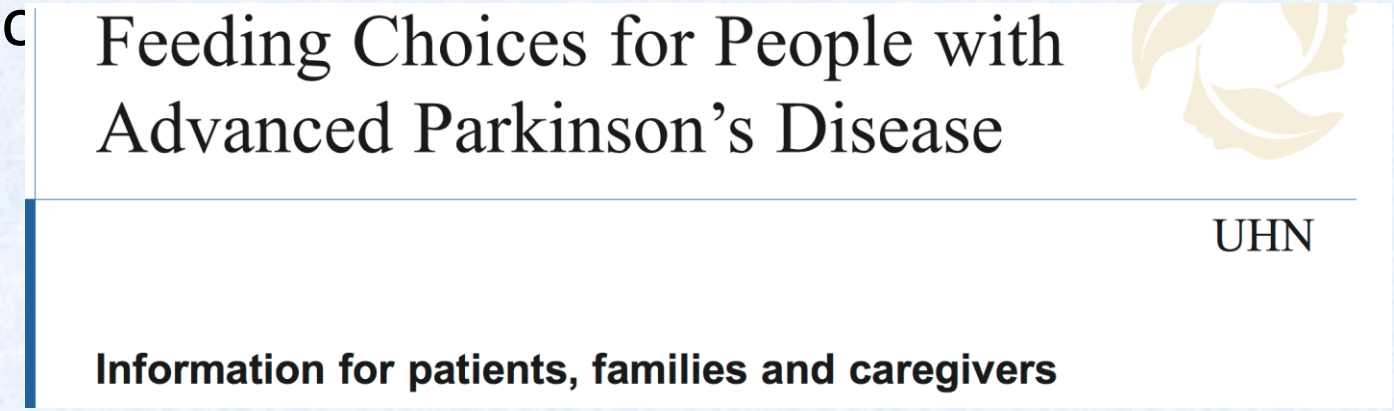
PD Motor Treatment: Advanced Disease

- 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 nutritic


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

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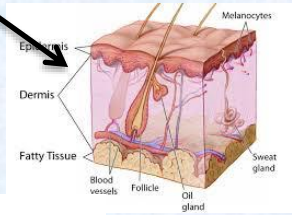
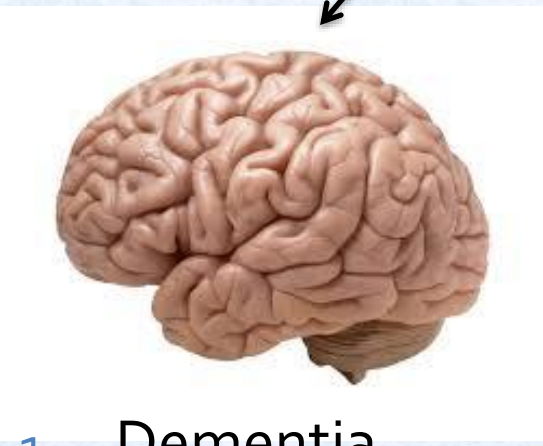
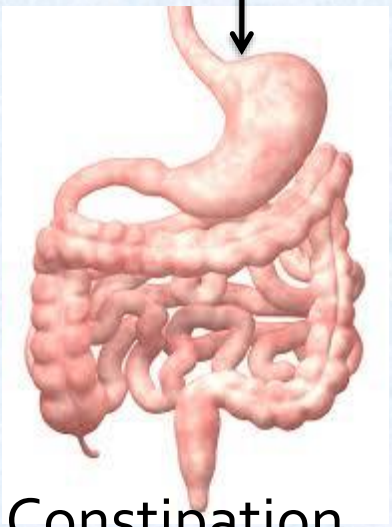
PD: Non-motor





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

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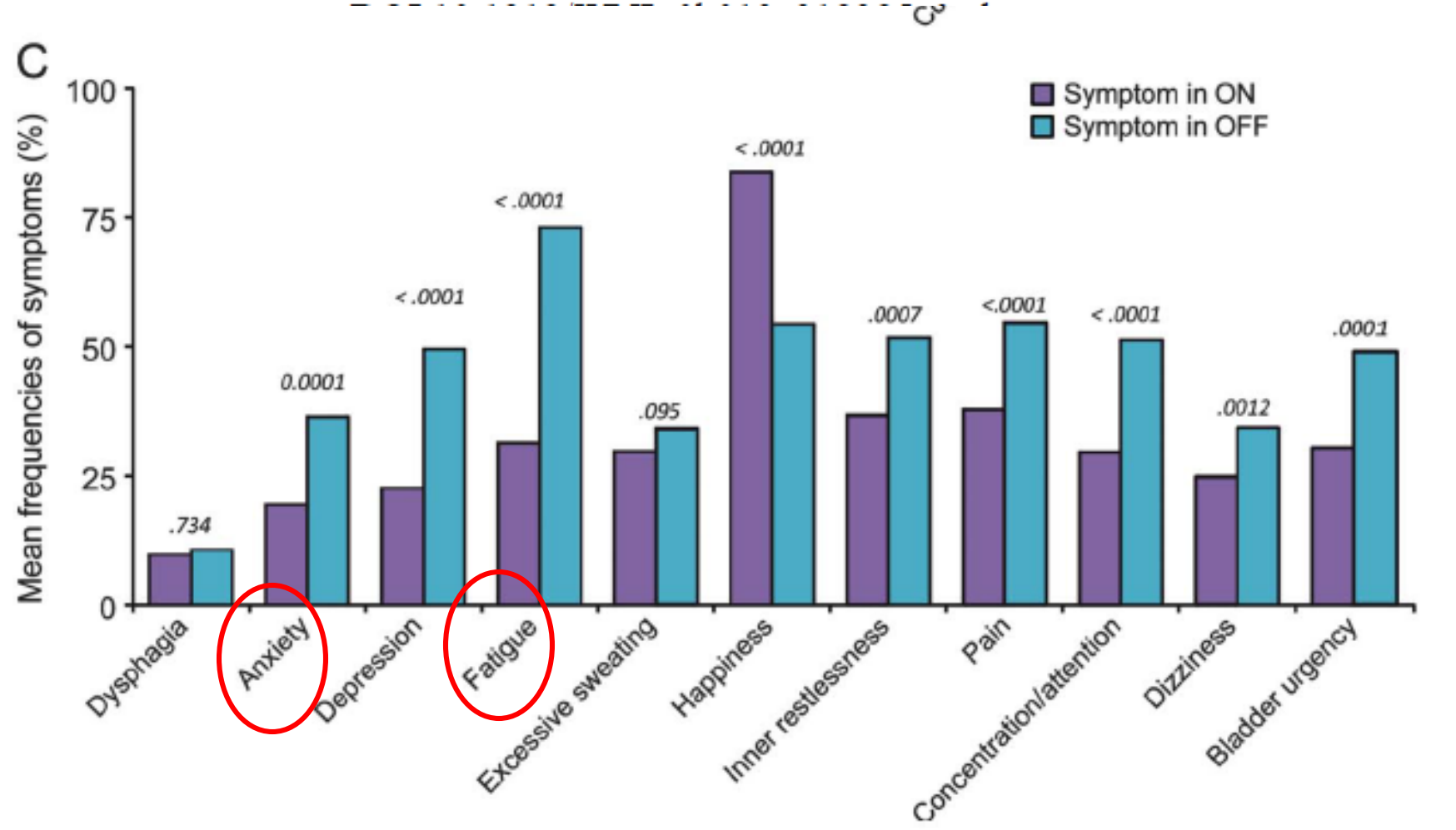
Nonmotor fluctuations in Parkinson disease: Severity and correlation with motor complications

Alexander Storch, Christine B. Schneider, Martin Wolz, et al.

Neurology 2013;80;800-809 Published Online before print January 30, 2013



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

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

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

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

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

Slow EJ, Lang AE. Neurology. Parkinsonism and Related Disorders. In: Singh AK, editor(s). Scientific American Medicine [online]. Hamilton (Canada): Decker Intellectual Properties; 2015.

EXERCISE for PD

- **MDS EBM review conclusions**
  - ***Likely efficacious; Clinically useful* (depending on intervention)**
  - **> 60 RCT** studies since 2011
  - 3 types of interventions
    1. Physio/physical therapy
    2. Movement strategy training with cuing or focused attention
    3. Formalised Patterned exercises

Fox SH et al on behalf of the MDS EBM Committee *2017 in preparation*

Which type of exercise for PD?

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Exercise ? duration

"Evidence suggests that a **minimum of 4 weeks of gait training 8 weeks of balance training** can have positive effects that persist for 3-12 months after treatment completion"

"Sustained strength training, aerobic training, **tai chi or dance therapy lasting at least 12 weeks** can produce long-term beneficial effects".

Mak M et al Long-term effects of exercise and physical therapy in people with Parkinson disease *Nature Reviews Neurology* 2017;**13;** 689–703

Freezing and Falls

- Rarely respond to changes in Levodopa in advanced disease; OFF >>> ON
  - Can also be due to postural hypotension
- Physiotherapy – Several trials
  - Canes, walking aids
  - Tricks, cues – marker on floor; singing, counting to overcome motor block

Drug Class	Drug	Efficacy conclusions	Implications for clinical practice	Safety
EBM reviews of Therapeutics for GAIT	Donepezil	Insufficient evidence for gait	investigational	
	Methylphenidate	Insufficient evidence for gait	investigational	
	Memantine	Insufficient evidence for gait	Investigational	
	Rivastigmine	**Likely efficiacious**	**Possibly Useful**	

Fox SH et al on behalf of the MDS EBM Committee *2017 in preparation*

Cannabidiol

J Psychopharm 2014;28:1088-1092

Cannabidiol 75 mg/d vs. 300 mg/d vs. Placebo, 1:1:1

Double-blind

UPDRS and PDQ-39

21, no dementia or psychiatric conditions

6 weeks

No difference on UPDRS

Placebo and cannabidiol 300 mg/d had different PDQ-39 (P=0.05)

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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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