Parkinson's Disease:

Management of Associated Symptoms

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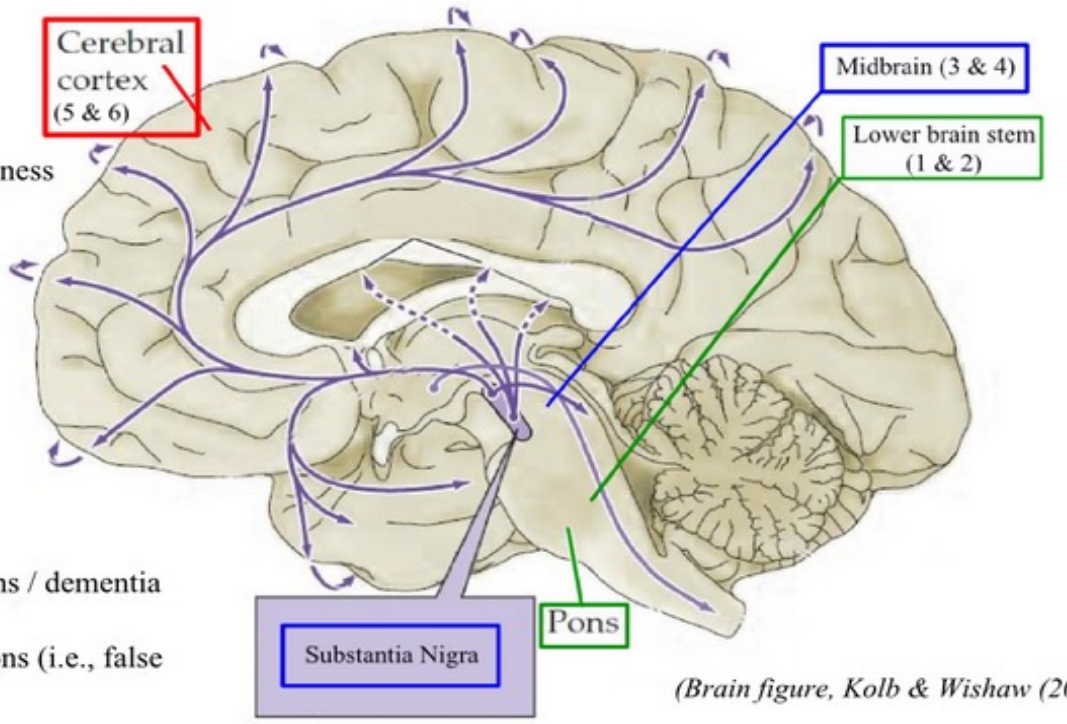
Progression of Parkinson's Disease

Before diagnosis - Stages 1 & 2
- loss of smell
- disturbance of sleep and wakefullness
- lowered blood pressure
- constipation
- anxiety / depression

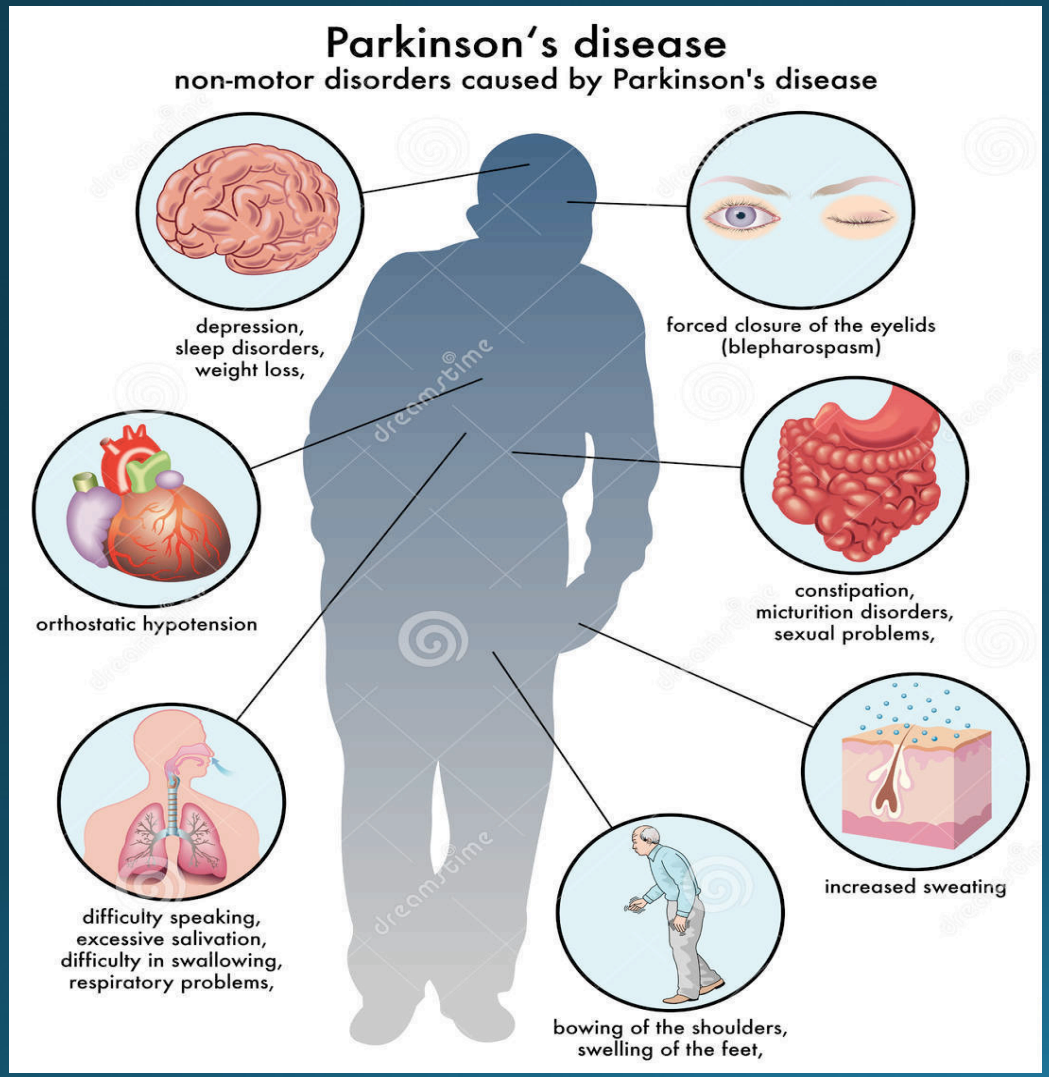
At diagnosis - Stages 3 & 4
- movement problems
- subtle thinking problems

Later disease - Stages 5 & 6
- worsening movement problems
- more significant thinking problems / dementia
- worsening anxiety / depression
- hallucinations / paranoia / delusions (i.e., false beliefs)



(Brain figure, Kolb & Wishaw (2003))

Non-motor Symptoms



Early nonmotor symptoms		
Hyposmia	May precede diagnosis	25-97
Fatigue	May precede diagnosis	~ 60
Depression	May precede diagnosis	~ 25
Rapid eye movement sleep behavior disorder (RBD)	May precede diagnosis by 15 y or more[4]	~ 30
Constipation	May precede diagnosis	~ 30
Late symptoms		
Treatment-resistant axial symptoms	5-10 y after symptom onset	
Freezing/postural instability/falls		~ 90 by 15 y
Dysphagia		~ 50 by 15 y
Psychiatric disturbances	5-10 y after symptom onset	
Anxiety		~ 55
Autonomic disturbances	5-10 y after symptom onset	
Postural lightheadedness		~ 15
Sialorrhea		~ 30
Urinary urgency		~ 35
Nocturia		~ 35
Sexual dysfunction		~ 20
Cognitive impairment:	Likelihood increases with time since symptom onset	
Mild cognitive impairment		~ 35 at diagnosis, 50 after 5 y
Dementia		>80 at 20 y after diagnosis

[a] Frequency of symptoms are estimated from a composite of studies.[129-133]

[b] Some patients can present with an isolated parkinsonian rest tremor, but without bradykinesia the diagnosis of Parkinson disease cannot be made clinically.

[c] Based on the UK Parkinson Disease Society Brain Bank Clinical Diagnostic Criteria, bradykinesia is essential for the diagnosis of Parkinson disease.

Connolly BS, Lang AE. Pharmacological Treatment of Parkinson Disease. JAMA April 23/30, 2014 Volume 311, Number 16

Motor Fluctuations

- ON TIME:
  - Characterized by good control of PD symptoms.
- OFF TIME:
  - Occurs when medication has worn off before the next scheduled dose and symptoms return or worsen motor such as tremor slowness and non-motor symptoms.
  - Nearly 50% of patients will develop motor fluctuations within 2-5 years of starting therapy.

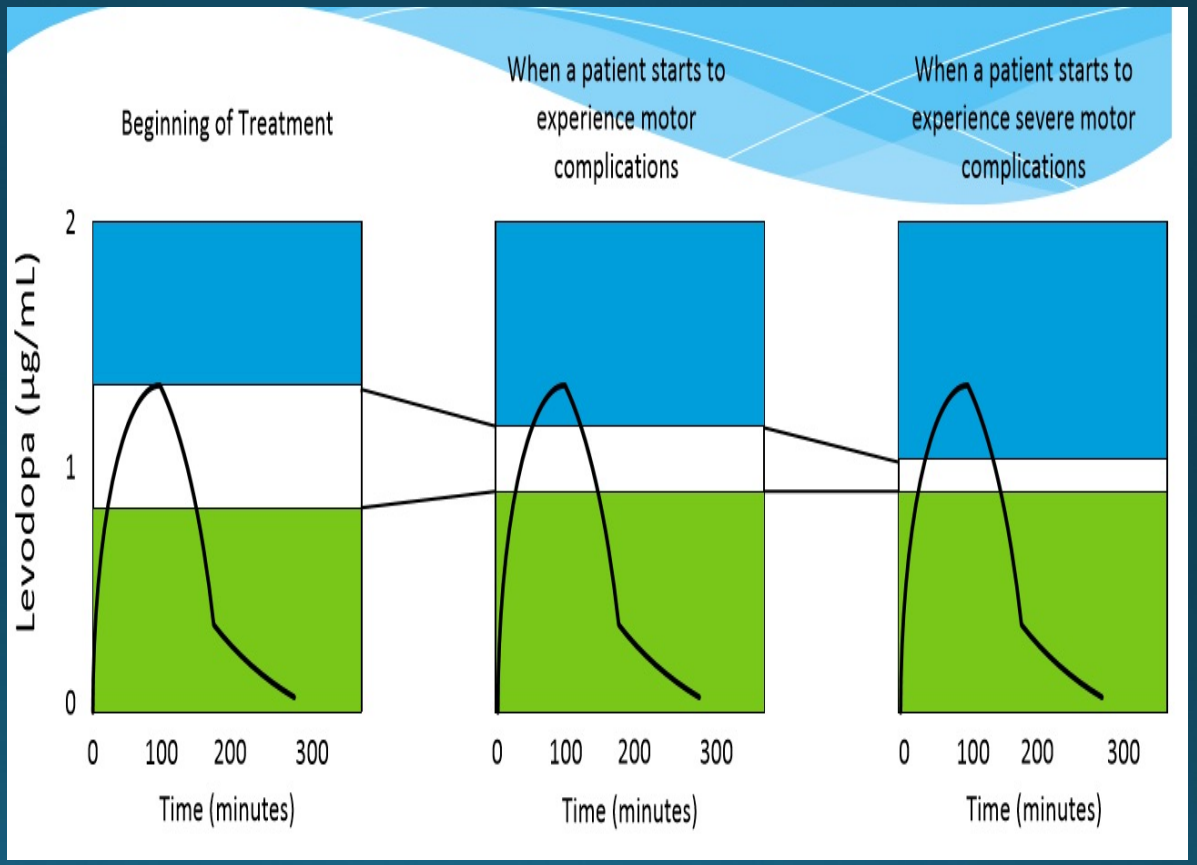
Non-motor Fluctuations

- Sensory/pain
  - tingling or tightening sensation.
  - Akathesia, Diffuse pain
- Mental
  - Anxiety, Fatigue, Irritability
  - Depression, slow thinking, hallucinations
- Autonomic Dysfunction
  - Drenching sweats, facial flushing, dry mouth
  - Dyspnea, Dysphagia, Constipation

Reason for Motor Fluctuations

- Diminished capacity of striatal nerve terminals to store and release dopamine.
- Striatal function more dependent on plasma levels of levodopa.
- Pathological modification of striatal receptors.
- Related to delivery of LD in a pulsatile mode

- Risk Factors: Higher levodopa doses more often related to the severity of underlying disease.
- Early onset (age <4 years of PD)



Treatment of OFF Periods

- Increase frequency or dose of levodopa administration
- Change formulation of levodopa
- Add dopamine agonist
- Consider adjunctive oral therapies (MAOB-I, Amantadine, Entacapone, opicapone, Istradefylline
- Night time dose for nocturnal symptoms
- Avoid heavy protein meals before levodopa dose
- Subcutaneous and sublingual apomorphine
- Inhaled levodopa (inbrija)
- For patients that continue to have fluctuations consider invasive therapies

Treatment of Dyskinesias (2 types)

- Reduction in individual dose of l-dopa and more frequent administration.
- Add a dopamine agonist and reduce dose of levodopa
- Amantadine
- Propranolol, clozapine and valproate have some efficacy
- Infusion therapies: apomorphine or jejunal levodopa
- Surgery: DBS

Motor Symptoms &Therapies - medical

- Freezing of gait, Wearing off, Dyskinesias, Gait imbalance/ postural instability, Falls, Festination, Propulsion, Tremor (+/- resistant), muscle cramps/ pain (dystonia), blepharospasm, micrographia

- MAO-B inhibitors: selegiline, rasagiline, safinamide
- Dopamine agonists: pramipexole IR/ER, rotigotine, ropinirole, bromocriptine, pergolide
- Carbidopa/Levadopa: lodosyn, sinemet IR/ER, parcopa, stalevo, rytary
- COMT inhibitors: entacapone, tolcapone, opicapone
- Anticholinergics: benztropine, trihexyphenidyl
- Antiglutaminergic agents: amantadine IR/ER
- Toxin injections: botox, myobloc, xeomin, dysport

Motor Symptoms & Therapies – nonmedical

- Freezing of gait, Wearing off, Dyskinesias, Gait imbalance/ postural instability, Falls, Festination, Propulsion, Tremor (+/- resistant), muscle cramps/ pain (dystonia), blepharospasm, micrographia

- Physical and occupational therapy; BIG program, weighted utensils
- Exercise, yoga/ pilates, meditation, Tai Chi, Rock Steady Boxing
- Massage
- Acupuncture
- Home safety evaluation
- Assistive devices: cane, walker, motorized wheelchair
- Sensory tricks
- Support programs/ groups (local vs national)

Motor Symptoms & Therapies – nonmedical

- Sensory tricks:

  -Try another movement: raise an arm, touch your head, point to ceiling; then restart

  -Change direction: if you can't move forward, try stepping sideways or taking a step backwards, then go forward

  -Carry a laser pointer in your pocket; when you freeze – shine the laser in front of your foot and step on the light. This cue can help you restart. (they also make walkers with laser line)

  -Visualize an object on the ground in front of you and try to step over it

  -Wear a metronome on your belt or carry a small one in your pocket – turn it on and the external beat can help you restart

  -Try humming a song and time your restart with the beat of the music

  -Count "1-2-3-go" an then step forward

  -Weight shift side to side to help initiate taking a step

  -March in place a few times and then step forward

  -Don't fight the freeze by trying harder to step forward. Shift your attention from moving the legs to moving the arms, then resume walking forward

  -Tennis ball trick

Non-Motor Symptoms &Therapies

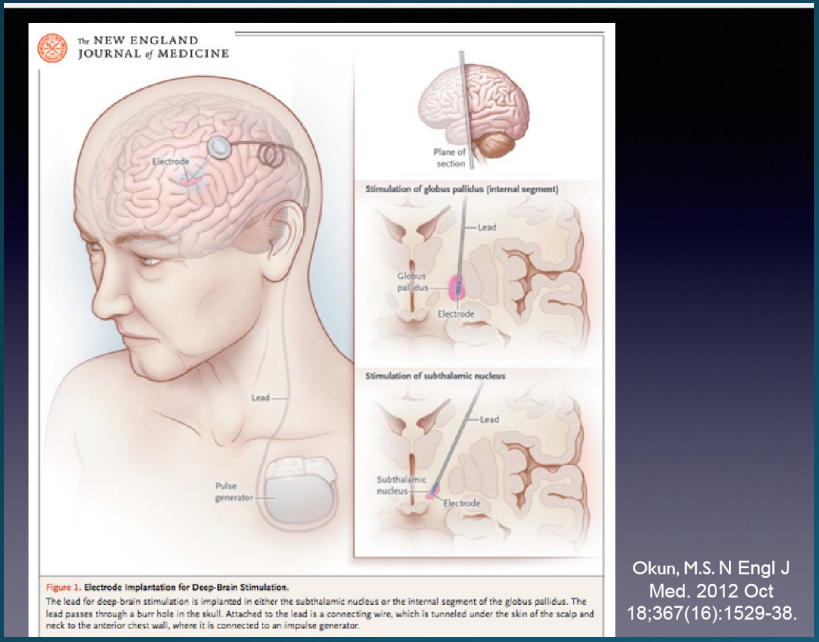
- Depression/ anxiety, akathesia: escitalopram, duloxetine, levadopa adjustment
- Pseudobulbar Affect: Nuedexta (dextromethorphan/ quinidine) – avoid ETOH and MAOBi
- Sun-downing, vivid dreams, RBD, fragmented sleep, snoring, insomnia, nocturia: melatonin, clonazepam, levadopa ER
- Daytime fatigue, Orthostatic hypotension, LE edema: conservative mgmt., fludrocortisone, midodrine, droxidopa
- Hallucinations: rivastigmine, quetiapine, pimavanserin
- Memory loss (MCI vs dementia): donepezil, memantine IR/XR, namzaric, rivastigmine, galantamine

Non-Motor Symptoms &Therapies

- Sialorrhea (drooling): salivary gland toxin injections (myobloc, botox, xeomin)
- Hypophonia, Dysphonia, Dysarthria: speech therapy, LSVT LOUD program, vocal cord injections
- Dysphagia, aspiration PNA: salivary gland injections, speech/ swallow therapy, diet modifications
- Anosmia, decreased appetite: appetite stimulants (megace, megastrol)
- Constipation: (avoid Metamucil)
  - -increase physical activity and hydration
  - -1 cup applesauce, 1 cup bran or wheat germ, 1 to 1/2 cup prune juice. Take 4oz BID
  - -daily stool softener (senna-S)
  - -Docusate 100mg twice per day and can increase to three times a day if needed
  - -daily Citrucel
  - -Miralax 1 capful daily or Lactulose 15-30mL/day -stimulant laxatives
  - -Senna 1-2 tablets nightly or bisacodyl 5-15mg/day
  - -Mag citrate 150-300mL per day if needed

Surgical Options

Surgery-DBS Pallidum or STN



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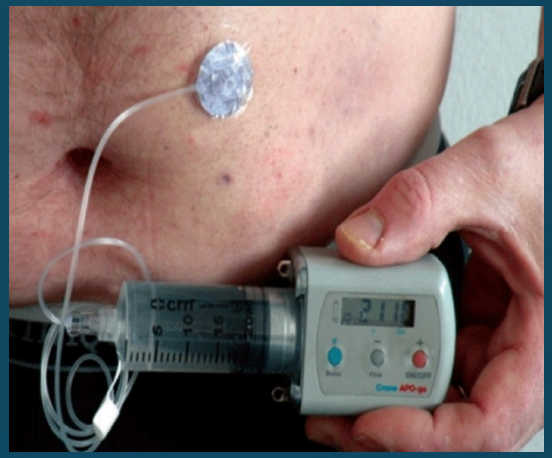
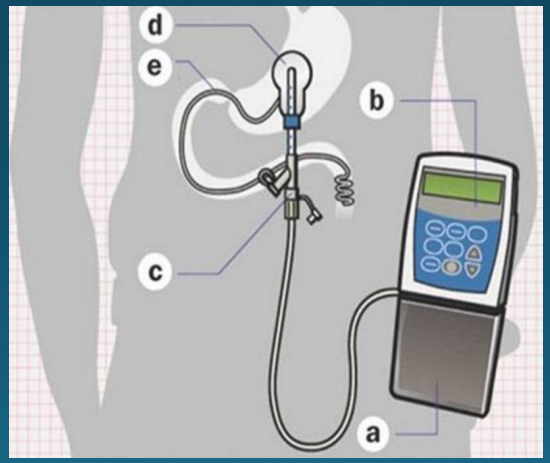


Apokyn subcutaneous pump



Levodopa-carbidopa intestinal gel (LCIG)

Potential Future Therapies:

- Apokyn subcutaneous pump
- Levodopa subcutaneous pump
- Chemotherapeutic therapies
- Longer acting formulations of carbidopa/ levadopa

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