MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Treatment of Motor Symptoms of Parkinson's Disease

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Parkinson's Preceptorship Program
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Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.

Some Things We Know about PD

1. Motor symptoms (including tremor, slowness, stiffness) are due to lack of dopamine related to loss of specific dopamine-producing brain cells.

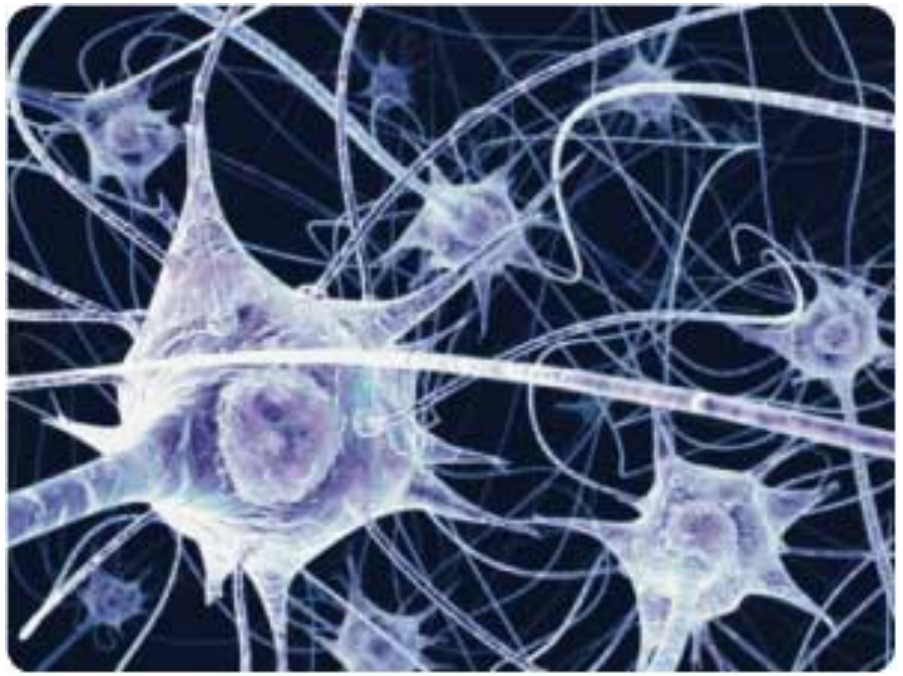
2. Abnormal protein deposits called Lewy bodies are found in the brain (the basis for definite diagnosis).

3. “Non-motor” symptoms are also present in Parkinson’s disease.

4. PD is likely due to a combination of genetic and environmental factors.

Thinking about Parkinson's Medications

- *"Neuroprotective"*
  - Treatments that protect the brain from further damage (i.e., slow disease progression)
- *"Symptomatic"*
  - Treatments that treat PD symptoms (i.e. reduce tremor, stiffness, slowness)
- *"Neurorestorative"*
  - Treatments that reverse neurodegeneration



Currently Available Medications for PD

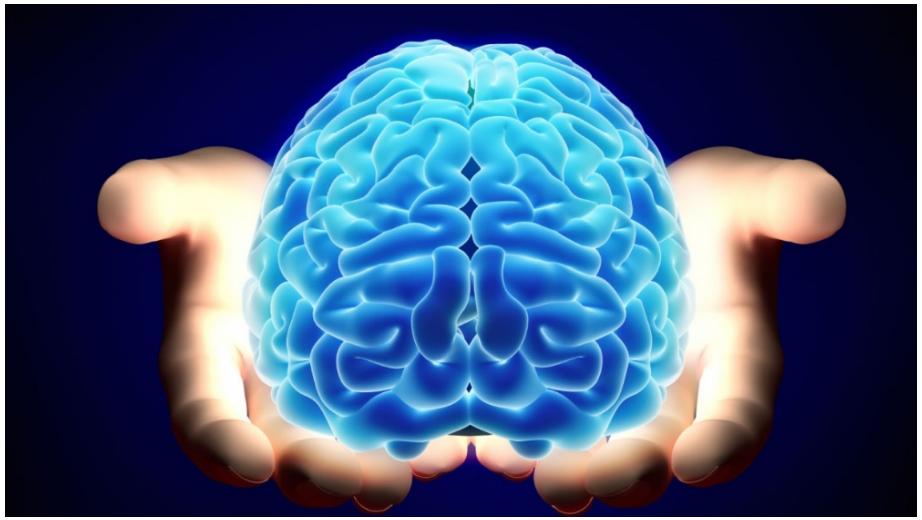
- *Dopaminergic agents*
  - Levodopa (given with carbidopa)
  - Dopamine agonists
    - Pramipexole
    - Ropinirole
    - Rotigotine
    - Apomorphine
- *COMT inhibitors*
    - Entacapone
    - Tolcapone
    - Opicapone
- *Amantadine*
- *MAO-B inhibitors*
    - Selegiline
    - Rasagiline
    - Safinamide
- *Adenosine A2A receptor antagonist*
    - Istradefylline
- *Anticholinergics* *(primarily useful for tremor)*
    - Trihexyphenidyl
    - Benztropine

Why We Need New Medications for PD

- Lack of disease-modifying treatments
- Limitations and side effects of existing treatments
- “Non-motor” symptoms and gait/balance issues often unresponsive to current medications

Neuroprotection: The Greatest Need

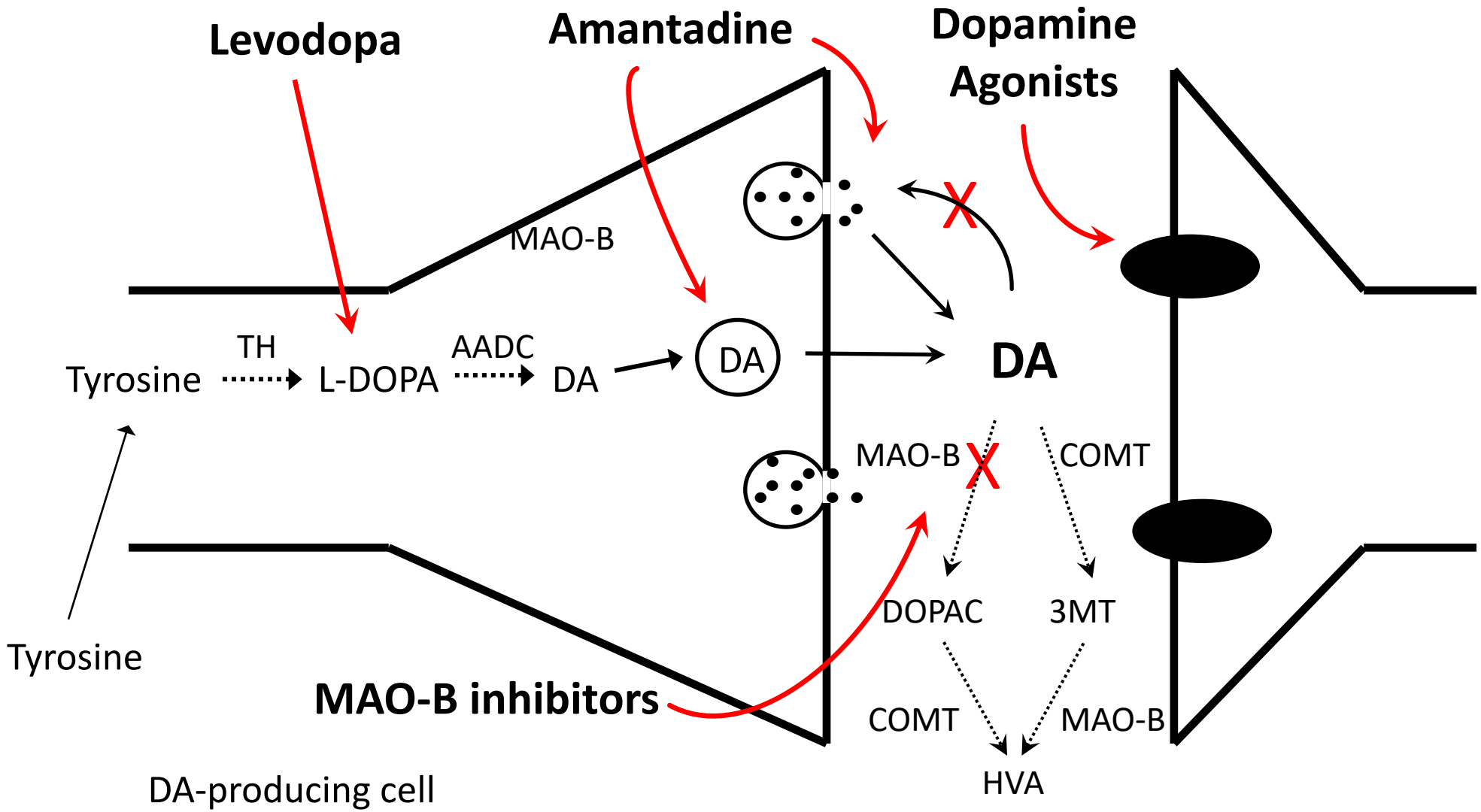
- Challenges in identifying neuroprotective agents
  - Lack of adequate animal models
  - Slow progression of disease
  - Lack of available “biomarkers” to follow progression
  - Availability of effective symptomatic medications may obscure mild disease-modifying effects



Strategies toward Neuroprotection

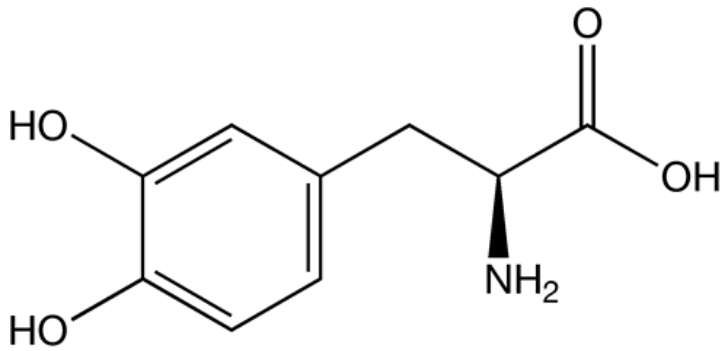
- Drug “repurposing”
  - Isradipine (STEADY-PD3): calcium channel blocker
  - Inosine (SURE-PD3): urate elevation
  - Glucagon-like peptide-1 agonists: diabetes medication
  - Iron-chelating agents
- Targeting α-synuclein
  - Anti-synuclein antibody therapies
  - Active immunization
  - Nilotinib (NILO-PD): leukemia treatment
- Genetic targets for PD
  - Glucocerebrosidase (*GBA)*
  - LRRK2

How PD medications work



Levodopa

- Precursor to *DOPAMINE*
- Still most effective drug for Parkinsonian symptoms
- Given with *CARBIDOPA* (Carbidopa/levodopa = Sinemet)
- Available in multiple formulations
  - Oral (immediate release, controlled release, extended release)
  - Intestinal gel
  - Inhalation powder
- Limitations of levodopa
  - Short-acting
  - "Motor fluctuations"



Dopamine Agonists

- Chemicals that mimic the action of dopamine in the brain
- Bind to postsynaptic dopamine receptors
- Multiple agonists currently available on market
  - Oral: pramipexole, ropinirole
  - Patch: rotigotine
  - Injectable: apomorphine
  - Sublingual film: apomophine

Side Effects of Dopamine Agonists

- Nausea
- Dizziness, postural hypotension
- Excessive daytime sleepiness
- Confusion, hallucinations
- Leg swelling (edema)
- Impulse control disorders
- “Dopamine agonist withdrawal syndrome”

Impulse Control Disorders

- “Behaviors that are performed repetitively, excessively, and compulsively to an extent that interferes with major areas of life functioning”
- PD patients at increased risk of developing one or more of 4 major ICDs
  - Gambling
  - Buying
  - Hypersexuality
  - Eating behaviors
- Associated with greater functional impairment, decreased quality of life, increased caregiver burden

Impulse Control Disorders in PD

- ICDs present in 13.6% of patients
- ICDs significantly more likely with dopamine agonists
- Higher rate of ICDs if first-degree relative with gambling problem

Table 2. ICD Frequencies by Dopamine Agonist Treatment Status

ICD Type	Treatment Status (N=3090)[a]	No. (%)		OR (95% CI)[b]	*P* Value[c]
		Current ICD	No Current ICD		
Any ICD	No dopamine agonist	72 (6.9)	978 (93.1)	2.72 (2.08-3.54)	<.001
	Dopamine agonist	348 (17.1)	1692 (82.9)		
Problem/pathological gambling	No dopamine agonist	24 (2.3)	1026 (97.7)	2.82 (1.81-4.39)	<.001
	Dopamine agonist	130 (6.4)	1910 (93.6)		
Pathological gambling only	No dopamine agonist	17 (1.6)	1033 (98.4)	2.15 (1.26-3.66)	.004
	Dopamine agonist	72 (3.5)	1968 (96.5)		
Compulsive sexual behavior	No dopamine agonist	18 (1.7)	1032 (98.3)	2.59 (1.55-4.33)	<.001
	Dopamine agonist	90 (4.4)	1950 (95.6)		
Compulsive buying	No dopamine agonist	30 (2.9)	1020 (97.1)	2.53 (1.69-3.78)	<.001
	Dopamine agonist	147 (7.2)	1893 (92.8)		
Binge-eating disorder	No dopamine agonist	18 (1.7)	1032 (98.3)	3.34 (2.01-5.53)	<.001
	Dopamine agonist	114 (5.6)	1926 (94.4)		

Weintraub et al., Arch Neurol 2010;67:589

Dopamine Agonist Withdrawal Syndrome

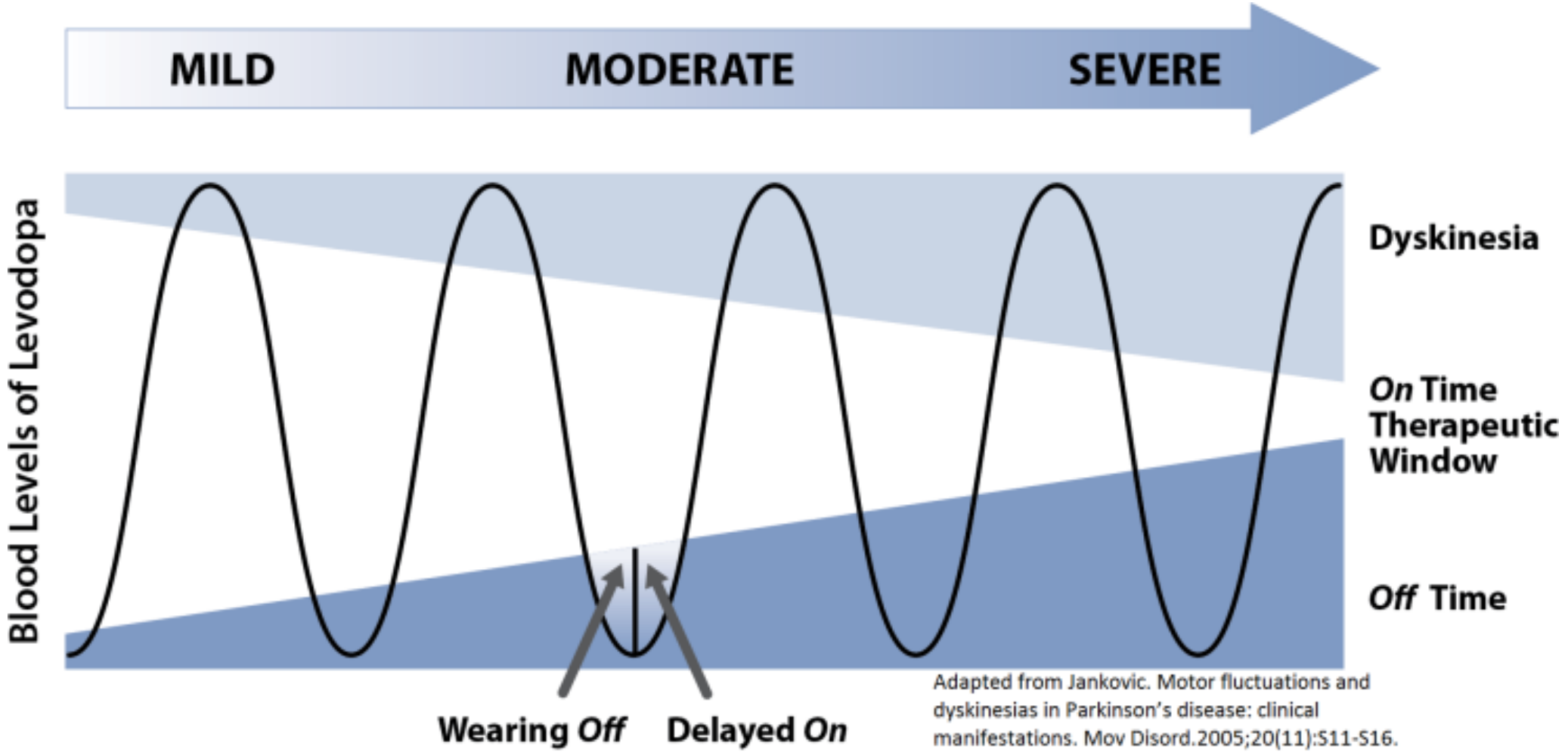
- Symptoms of DAWS
  - Anxiety/panic attacks, depression
  - Agitation, irritability
  - Suicidal ideaton
  - Fatigue
  - Orthostatic hypotension
  - Nausea/vomiting
  - Drug craving
- Impulse control disorders major risk factor for DAWS
- No effective treatments

Dopamine Agonist vs. Levodopa

- Levodopa more effective for treatment of motor symptoms
- Higher incidence of short-term side effects (sleepiness, hallucinations, edema) with dopamine agonist
- *Increased risk of motor fluctuations, dyskinesias with levodopa therapy*

Parkinson Study Group, JAMA 2000;284:1931-38.
Rascol et al., N Engl J Med 2000;342:1484-91.

Motor fluctuations in PD

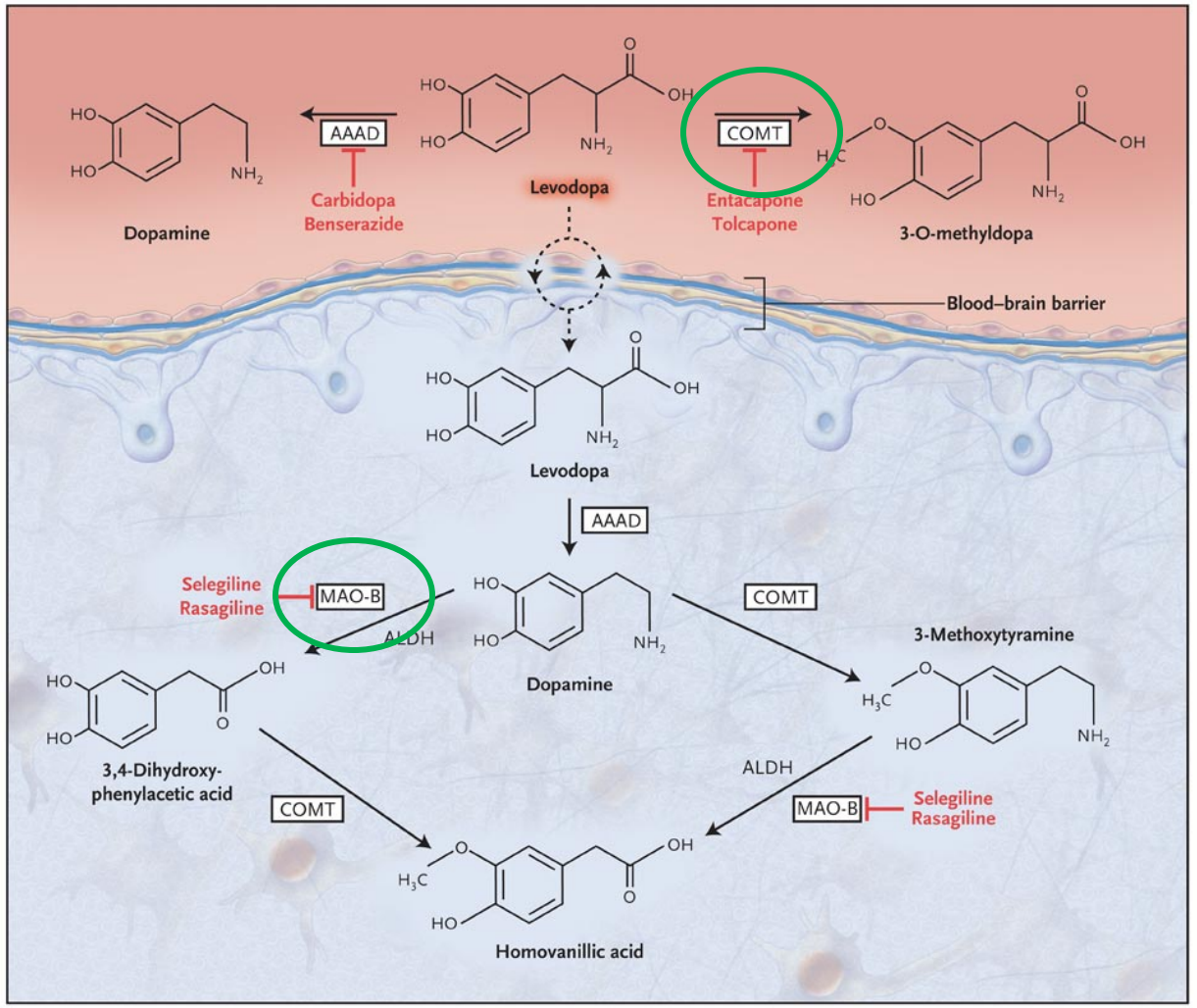


Adapted from Jankovic. Motor fluctuations and dyskinesias in Parkinson's disease: clinical manifestations. Mov Disord.2005;20(11):S11-S16.

Definitions of “On” and “Off”

- “On” — Good symptomatic benefit from PD medication
- “Off” — Loss of symptomatic benefit from PD medication on failure of usual benefit to occur
- Wearing “off” — Re-emergence of PD symptoms prior to next scheduled dose
- Delayed “on” — Dose takes longer to take effect than usual
- Dose failure — Dose fails to improve symptoms
- “On/Off” — Unpredictable between “on” and “off” without correlation to medication intake

Treatment of PD: Enzyme Inhibitors



LeWitt , New Engl J Med 359:2468, 2008

COMT and MAO-B inhibitors

- Block dopamine breakdown, extend duration of action of levodopa
- Currently available COMT inhibitors
  - Entacapone (also available in combination with C/L)
  - Tolcapone (rarely associated with serious liver damage)
  - Opicapone (once daily)
- Currently available MAO-B inhibitors
  - Selegiline
  - Rasagiline
  - Safinamide

Istradefylline

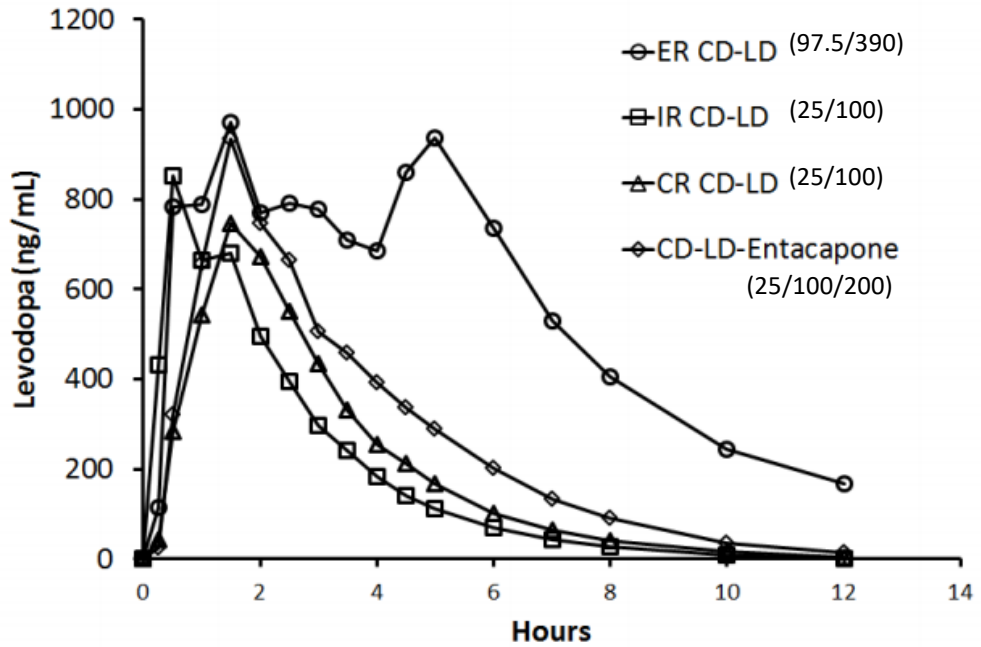
- Adenosine-2A receptor (A2A) antagonist
- FDA-approved as add-on therapy to treat off periods in PD patients on levodopa
- Multiple RCTs: reduces OFF time, increases ON time without troublesome dyskinesias
- Initially rejected by FDA in 2008, approved in Japan in 2013
- Approved in August 2019 based on additional post-marketing data

Strategies to Reduce On/Off Fluctuations

- Improve *"Pharmacokinetics"* of medication
  - Longer-acting medications
  - Continuous delivery
- *"On-demand"* medications for treatment of off periods

Newer Forms of Levodopa Delivery

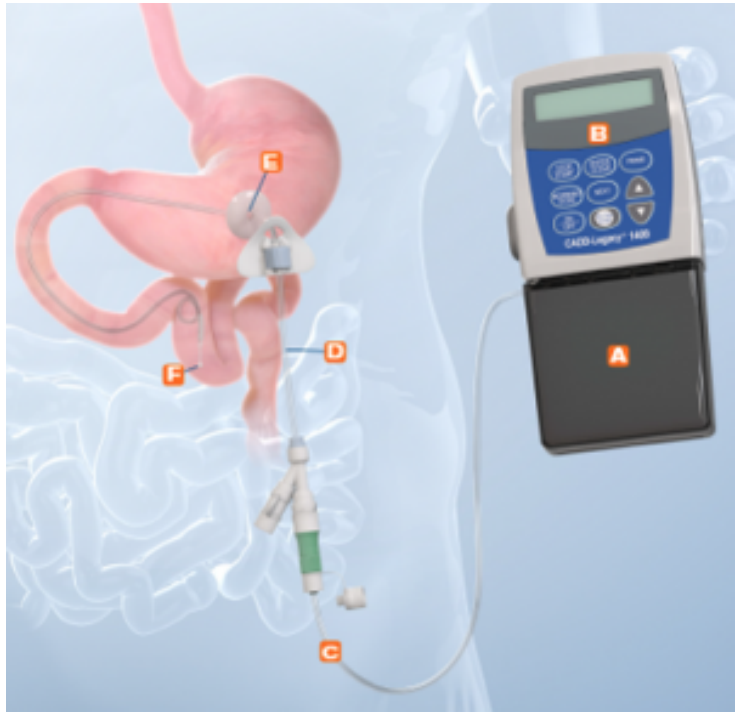
- Extended release carbidopa/levodopa
  - Combination of beads that release levodopa both rapidly and slowly
  - Lasts in bloodstream ~ 4-5 hrs



Hsu et al., J Clin Pharmacol 55:995, 2015

Continuous Levodopa Delivery Systems

- Carbidopa and levodopa enteral gel
  - Levodopa directly and continuously infused into the intestine
  - Requires infusion port (“J-tube”)
  - Allows initial morning dose, extra doses



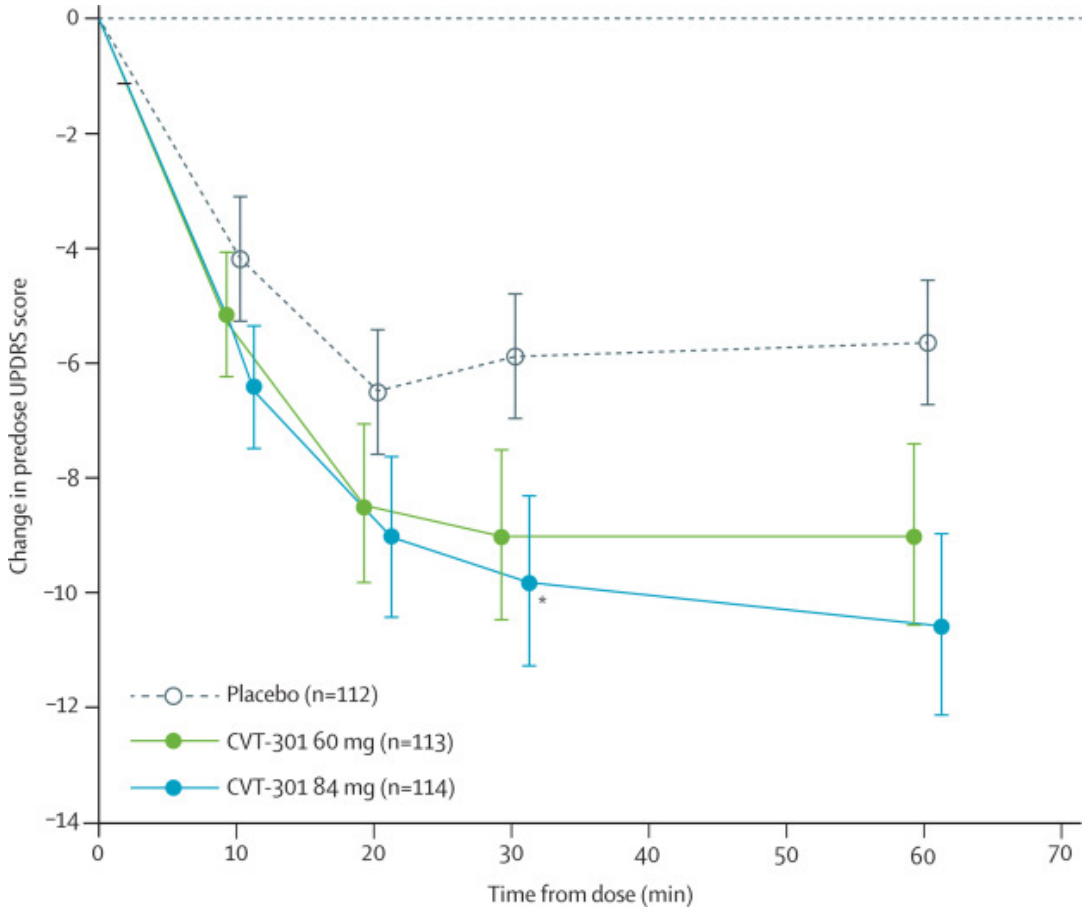
- Levodopa “pump patch”: in development

“On-Demand” Medications

- *Apomorphine (injectable)*
  - Approved in 2004
  - Indication: “Acute, intermittent treatment of hypomobility, “*off*” episodes (“end-of-dose wearing-*off*” and unpredictable “*on-off*” episodes) in patients with advanced Parkinson’s disease (PD)”
  - Advantages: Rapidly acting, adjustable dose
  - Disadvantages: injection
  - Main side effects: nausea/vomiting (pretreatment with trimethobenzamide recommended), headache, lightheadedness

“On-Demand” Medications

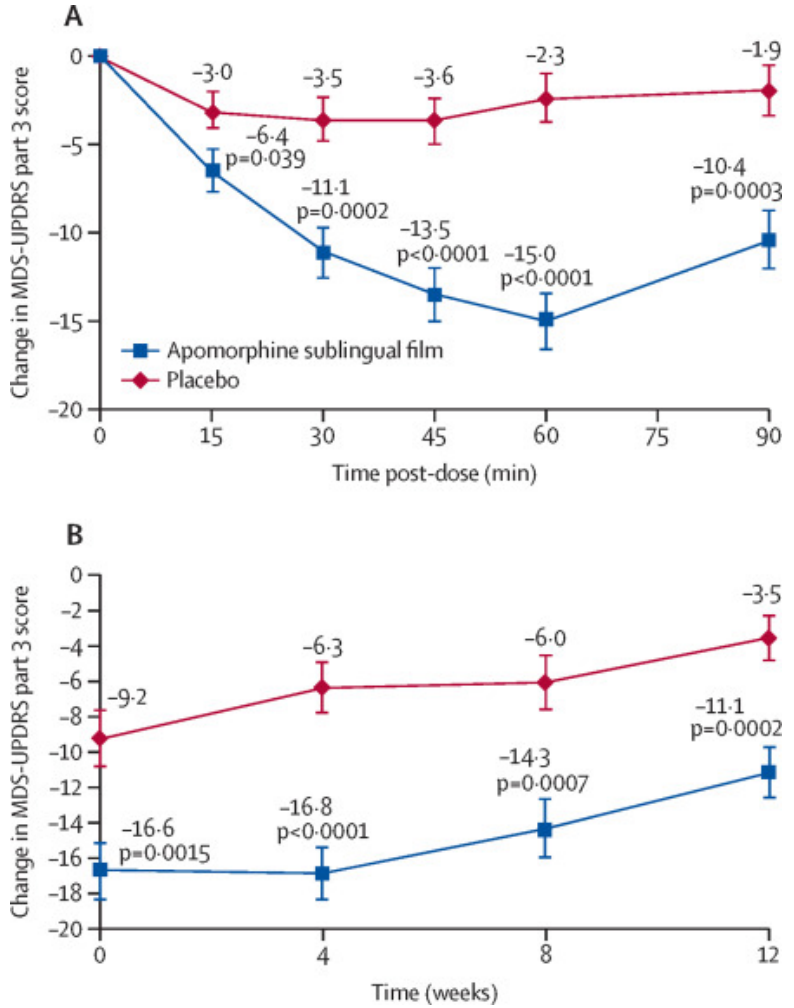
- *Inhaled Levodopa*
  - Approved in December 2018
  - Indication: “Intermittent treatment of OFF episodes in patients with PD treated with CD/LD”
  - Each capsule contains 42 mg levodopa; typical dose 2 capsules up to 5 times a day
  - Action within 10 minutes, bypasses GI tract
  - Main side effects: cough, URI, nausea, sputum discoloration



Lewitt et al., Lancet Neurol 18:145, 2019

“On-Demand” Medications

- *Sublingual Apomorphine*
  - Indication: acute, intermittent treatment of “off” episodes in patients with Parkinson's disease
  - Available in 10-mg, 15-mg, 20-mg, 25-mg, 30-mg strengths
  - Main side effects: nausea, oral/pharyngeal soft tissue swelling/pain, dizziness, sleepiness
  - Contraindicated in patients taking $5HT_3$ antagonists (ondansetron)

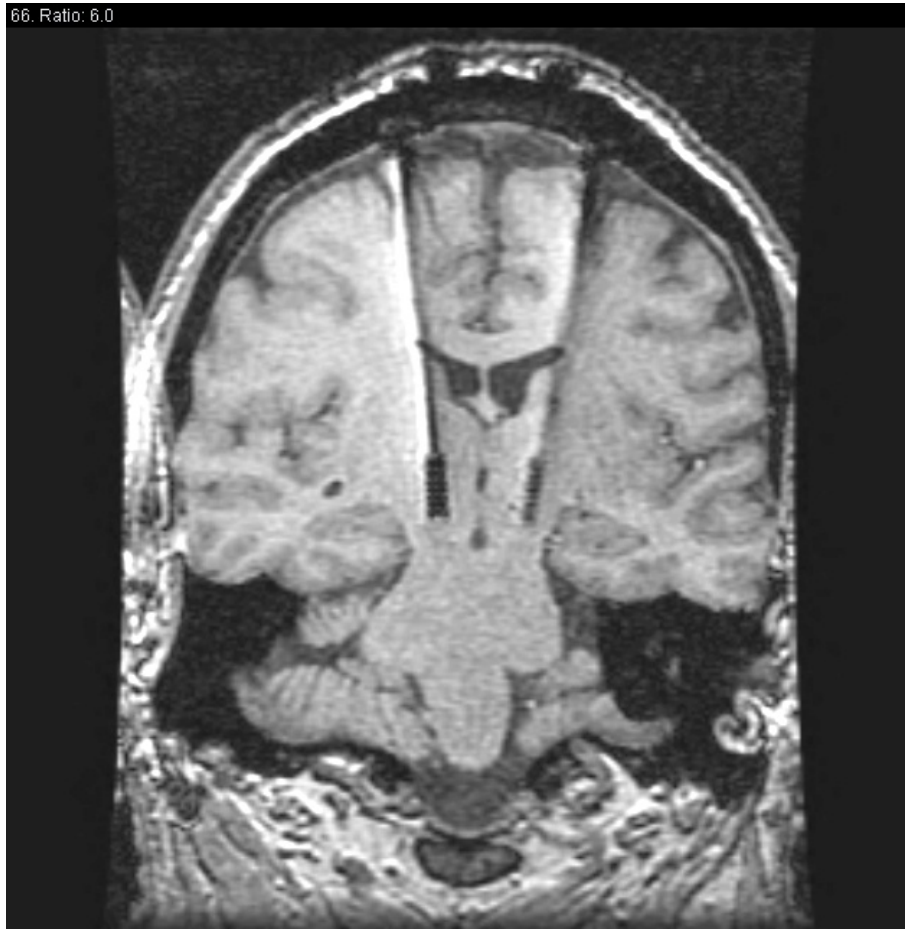


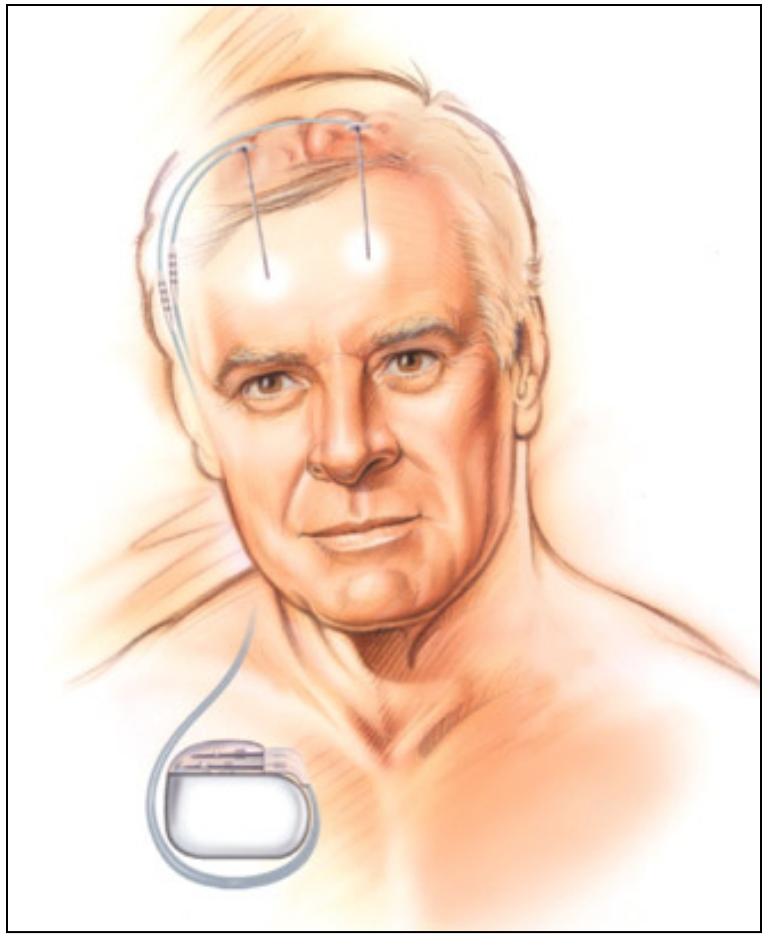
Olanow et al., Lancet Neurol 19:135, 2020

Treatment of Levodopa-induced Dyskinesias

- ***Amantadine***
  - Initially developed as antiviral treatment for influenza (1960s)
  - Promotes dopamine release, blocks dopamine reuptake
  - Antagonist of NMDA-type glutamate receptors
- Available in immediate- and extended-release formulations
- Side effects
  - Nausea
  - Lightheadedness
  - Insomnia
  - Confusion, hallucinations
  - Swelling of the ankles
  - Livedo reticularis

Surgical Management of PD: Deep Brain Stimulation





Deep Brain Stimulation for PD

- Treatment option for patients experiencing motor fluctuations/dyskinesias or medically refractory tremor
- Targets: subthalamic nucleus (STN) or globus pallidus interna (GPi)
- Better motor outcome and quality of life compared to best medical treatment
- Potential negative effects on cognitive function, mood, speech and gait

Summary

- There are currently no treatments available to slow progression of PD.
- Currently available medications that target dopamine pathways are effective in treating motor symptoms of PD.
- Medications have been developed recently to reduce motor fluctuations and treat unpredictable off periods.
- Deep brain stimulation surgery is an effective treatment option for dopamine-responsive PD when limited by motor fluctuations.

Questions?