Understanding Motor Symptoms and Oral Drug Therapies for Parkinson Disease

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History of PD

History of Parkinson's Disease

- First references to tremor and palsy appear in ancient Hindu texts which date to 2500 BC
- Described by James Parkinson in 1817 as the "shaking palsy"
- Renamed "Parkinson's Disease" by Charcot in 1877

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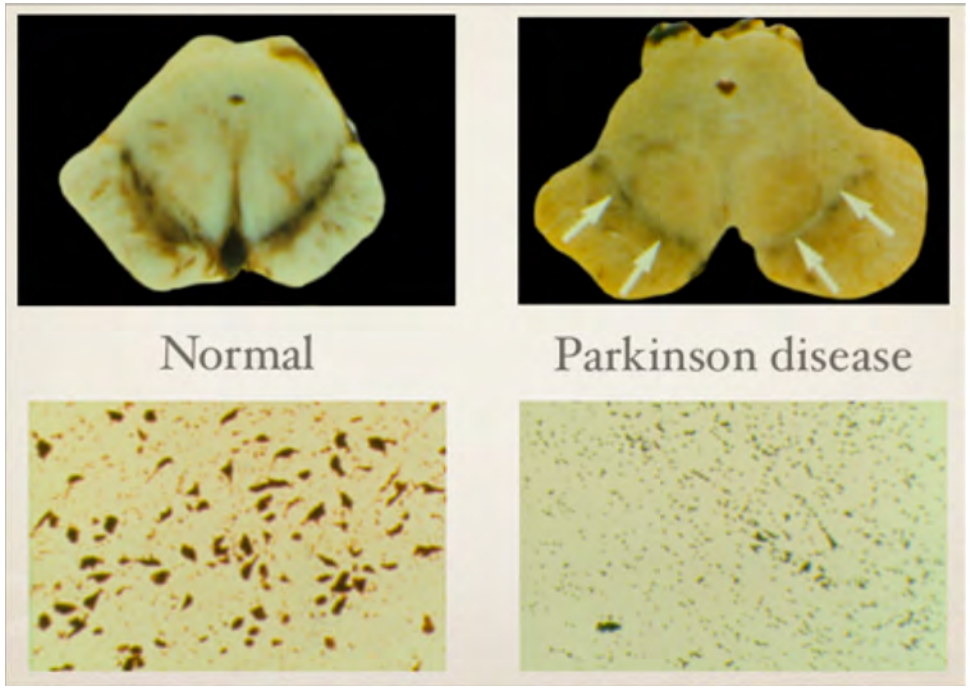
Parkinson Disease Depicted in Art

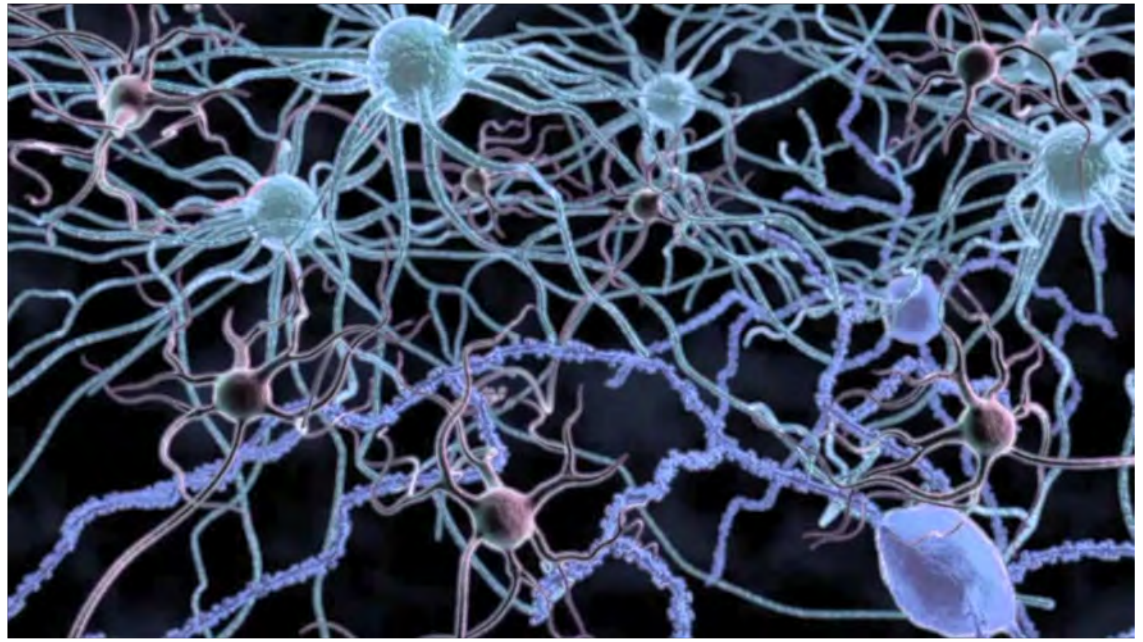
The Good Samaritan, Rembrandt, 1633

St. Hugo of Grenoble, Zurbaran, 1600s

Pathology and Epidemiology of PD

Pathology of PD





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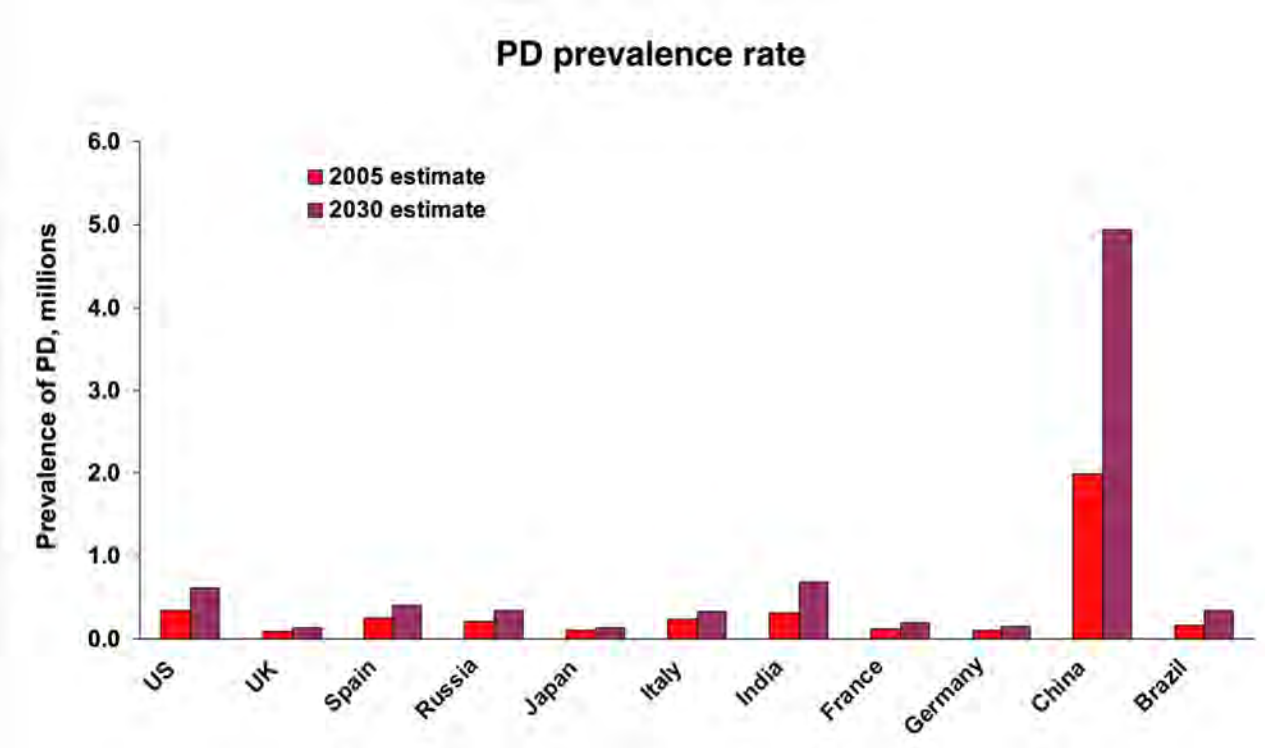
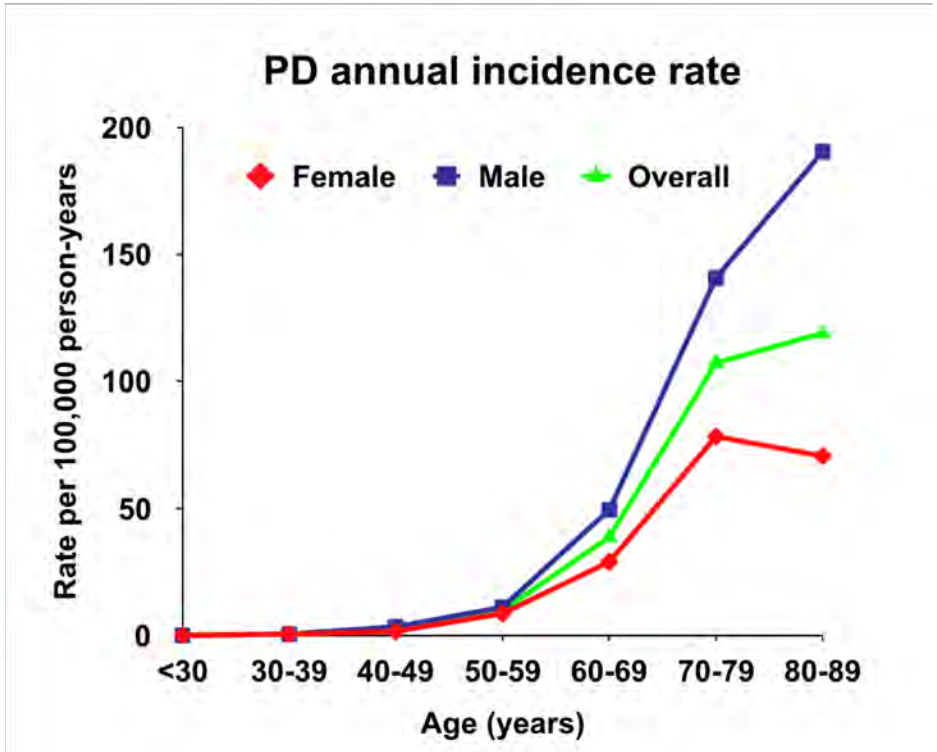
Epidemiology of PD





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Motor Features of PD

Cardinal Motor Features of PD

Resting tremor	• 70% of patients • “Pill-rolling” tremor in hands • Can involve lips, chin, jaw, legs
Bradykinesia	• 80% to 90% of patients • Most disabling symptom of PD
Rigidity	• >90% of patients • “Cogwheel” (fluctuating) or “lead pipe” (continuous)
Postural instability	• Indicative of advanced-stage PD • Frequent cause of falls

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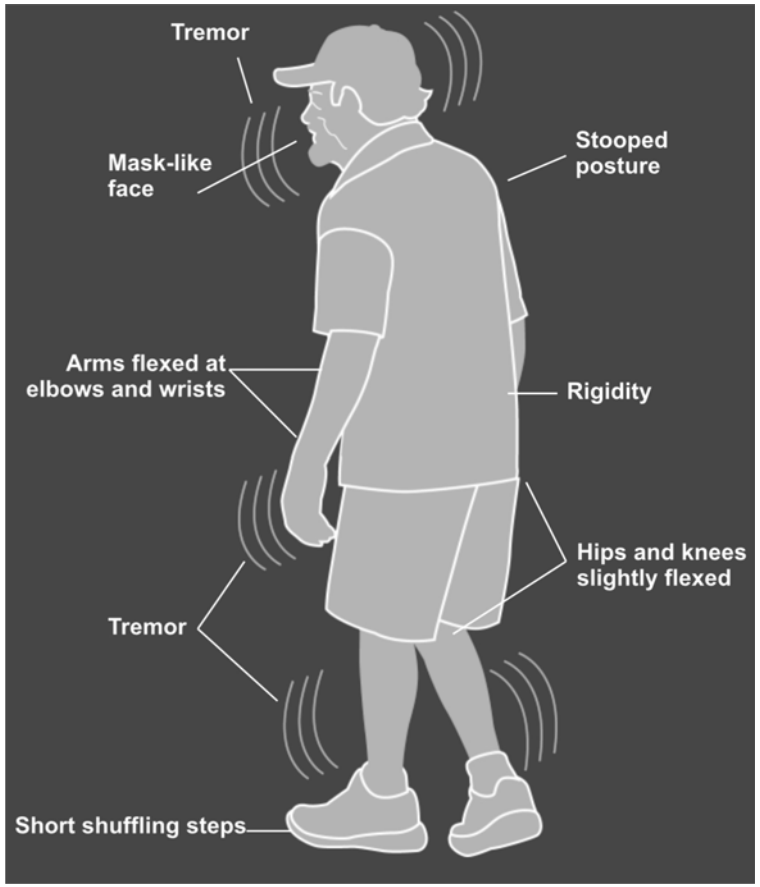
Associated Motor Features of PD

- Stooped posture
- Small handwriting
- Decreased arm swing
- Cramping
- Difficulty swallowing
- Changes in facial expression
- Shuffling



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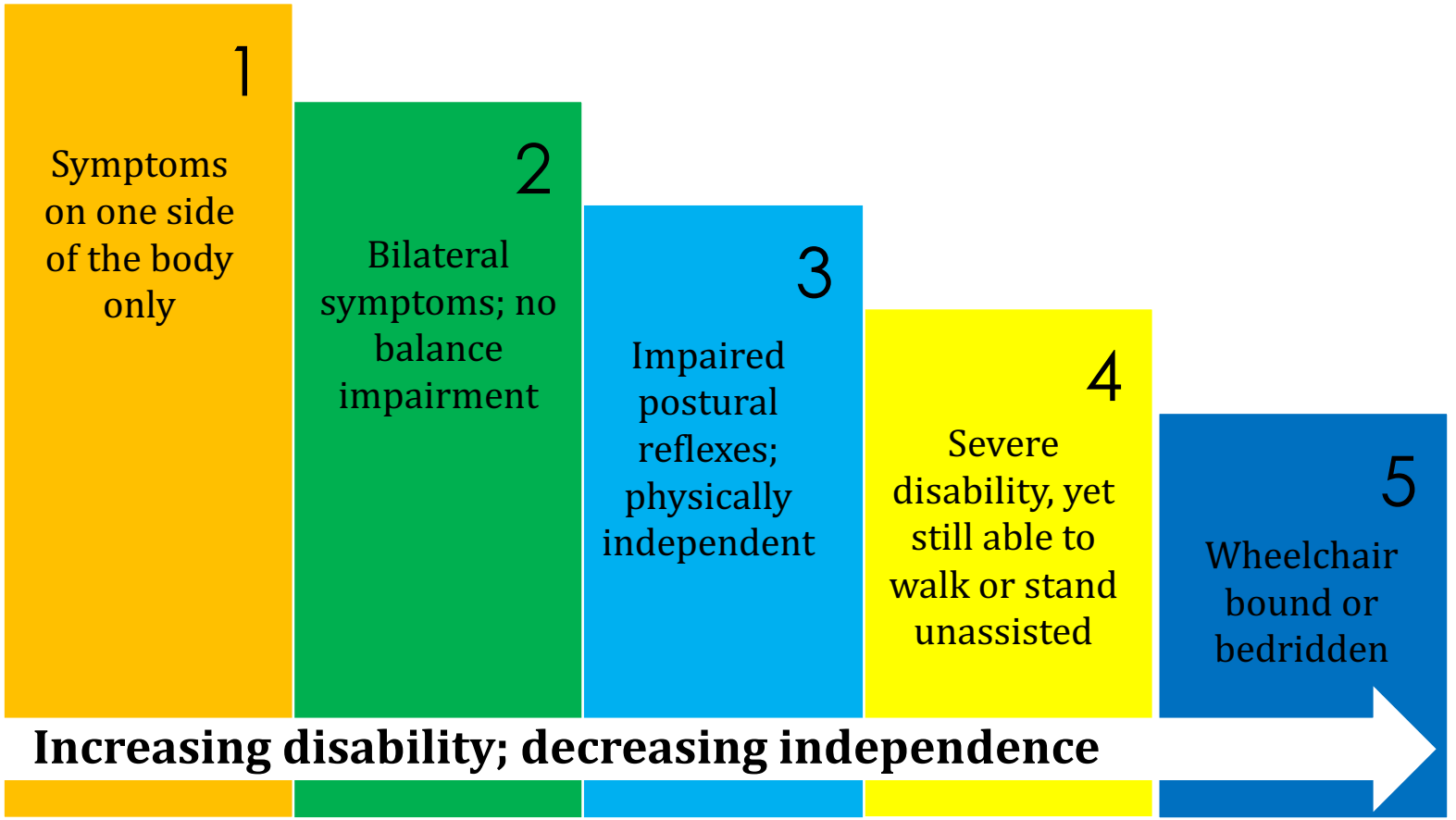
Disease Progression



Hoehn and Yahr Staging

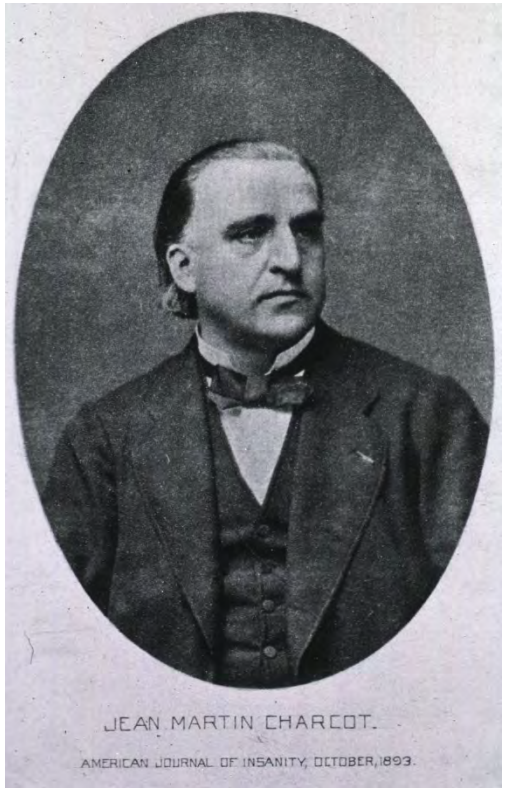
Pathophysiology of Motor Symptoms

- Most motor symptoms are the result of diminished dopamine levels in the brain
- Tremor, rigidity, and bradykinesia (slowing of movement) thus typically improve with drugs that increase either dopamine itself or a dopamine-like substance in the brain
- Too much dopamine can cause involuntary movements (dyskinesia)
- Some symptoms tend to be resistant to dopaminergic treatments
  - Tremor may be difficult to control in a minority of patients
  - Postural stooping and speech difficulty is often resistant to drug treatment
  - Freezing of gait sometimes responds and sometimes does not

Oral Drug Treatment for PD

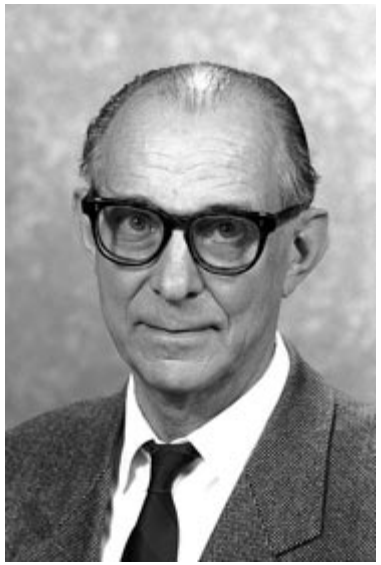
History of Oral Drug Treatments

- Bella donna alkaloids (anticholinergic agents) were first suggested and widely used by Charcot in the 1860s
- He also suggested "vibratory therapy" having observed that after riding in a carriage, some PD symptoms improved
- The importance of dopamine in the basal ganglia was established by Hornykiewicz in 1960, and levodopa was proved to be effective using controlled clinical trials in 1969



Charcot

Hornykiewicz



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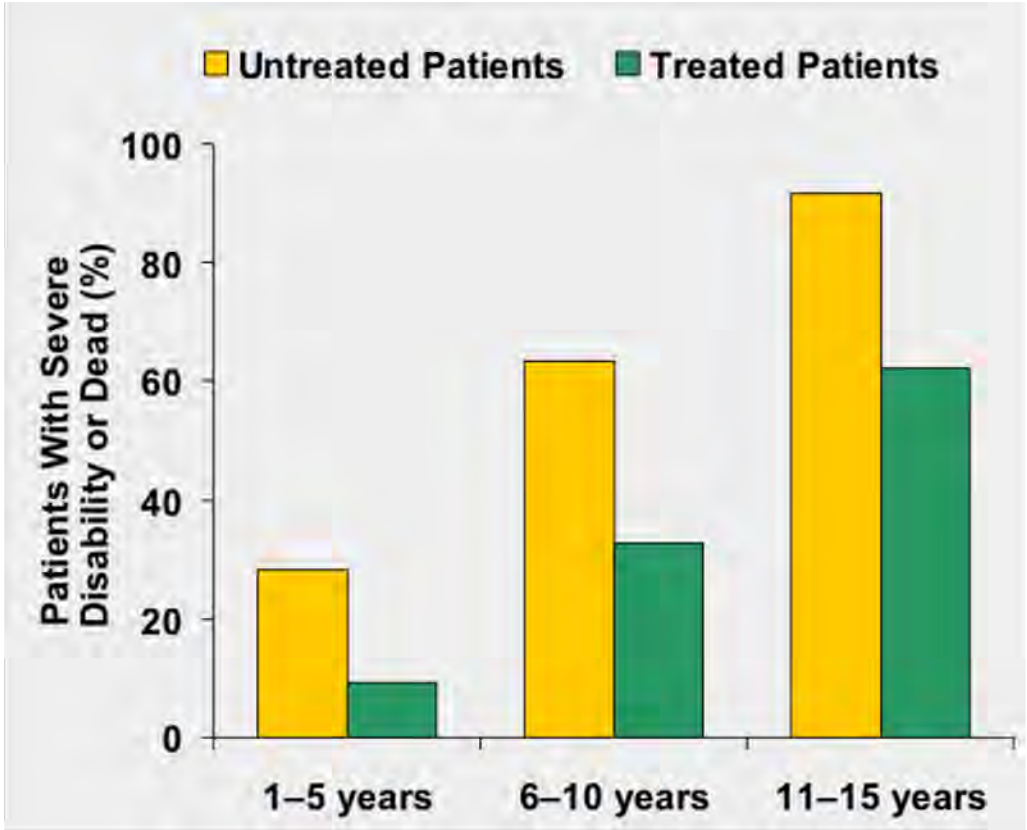
Levodopa's Long Ride

- Levodopa is a naturally-occurring amino acid which is the biochemical precursor to dopamine
- In spite of being discovered 50 years ago, levodopa is still the most effective and one of the best tolerated drugs for PD
- It works by traveling from the GI tract to the blood, then from the blood into the brain, and once in the brain, the amino acid is collected in dopaminergic neurons where it is converted into dopamine and released into the basal ganglia
- This drug therefore corrects much of the biochemical problem in the brains of PD patients

Levodopa in Different Stages of PD

- In early PD, almost any form of levodopa works well because the brain still has a number of intact neurons which uptake and release dopamine
- As the disease progresses, however, the duration of effect of levodopa shortens because the half-life of the amino acid in the blood stream is short, and there are insufficient remaining neurons to store and release dopamine
- As the neuron loss continues, patients become dependent on real-time absorption of levodopa, and thus its short half-life is reflected in short response times (the “on” and “off” effects, motor fluctuations)
- Additionally, the short pulses of dopamine release in the basal ganglia abnormally change the firing pattern of these neurons often resulting in dyskinesia when the drug is otherwise helping

Benefits of Levodopa



Hoehn MM. *Adv Neurol*. 1986;45:457-461.

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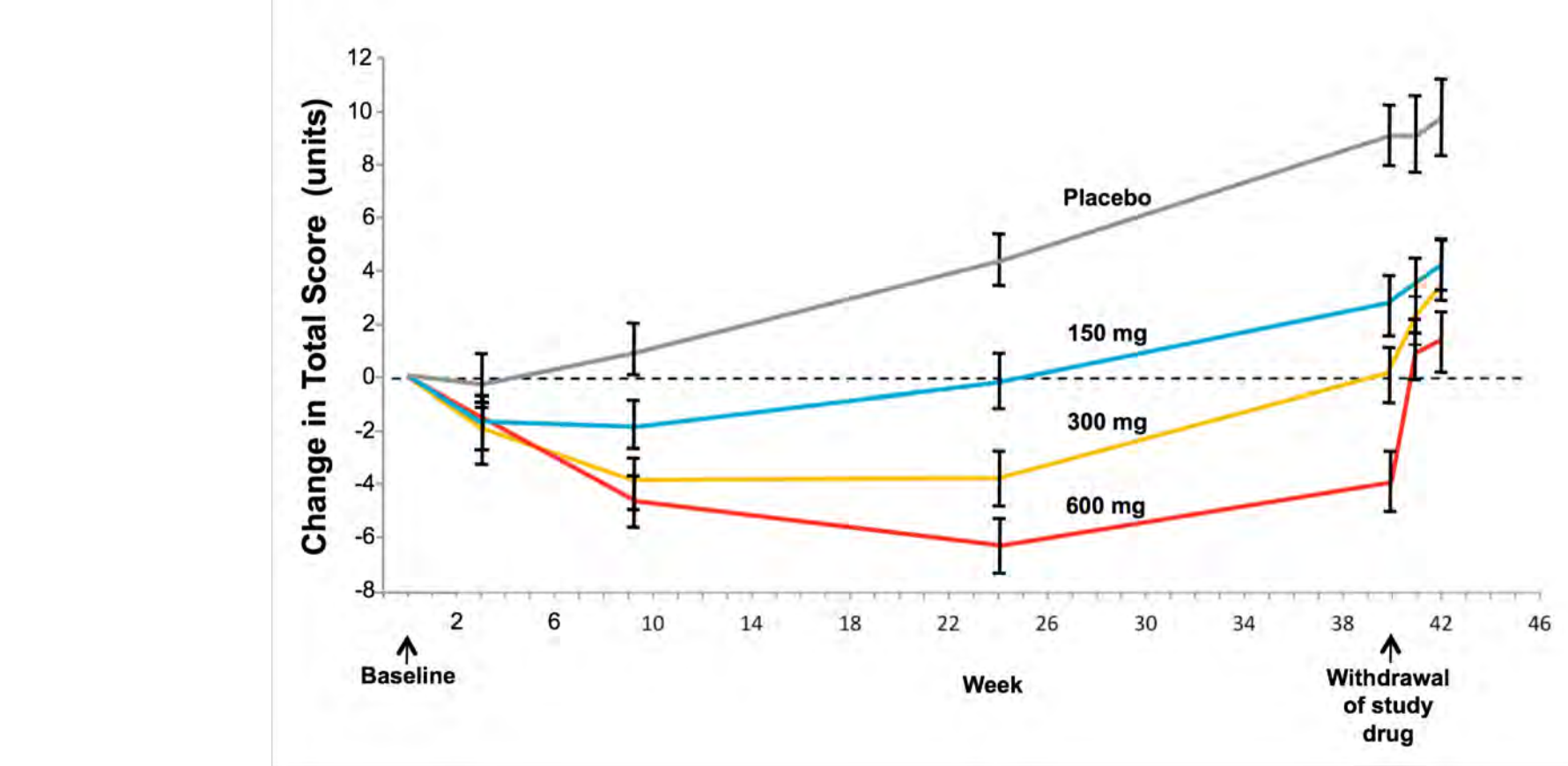
Dose-Response Relationship of Levodopa



Fahn S et al. *N Engl J Med*. 2004;351:2498-2508.

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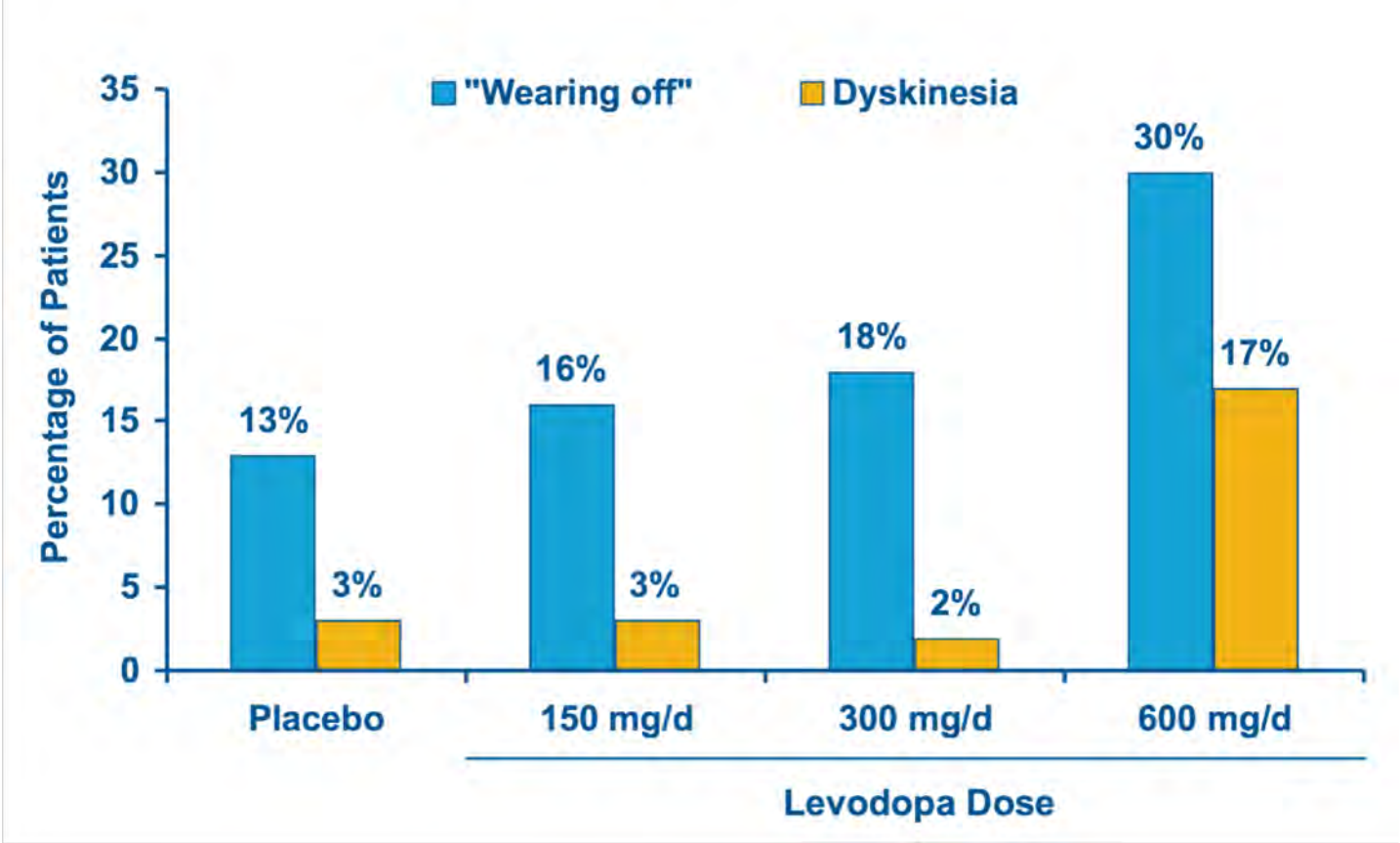
Adverse Events with Levodopa



Fahn S et al. *N Engl J Med*. 2004;351:2498-2508.

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Levodopa Phobia

- Refers to a "fear of starting levodopa" that is found in many patients
- Based on several ideas:
  - that levodopa is "toxic" to the brain (cell culture experiments)
  - levodopa causes dyskinesia
  - dopamine agonists (which can be used to delay levodopa) cause less dyskinesia
- The facts are:
  - levodopa is not toxic to the intact brain
  - it is disease severity, not dose or duration of levodopa, that is the main cause of dyskinesia
  - dopamine agonists are NOT safer than levodopa, the reverse is true

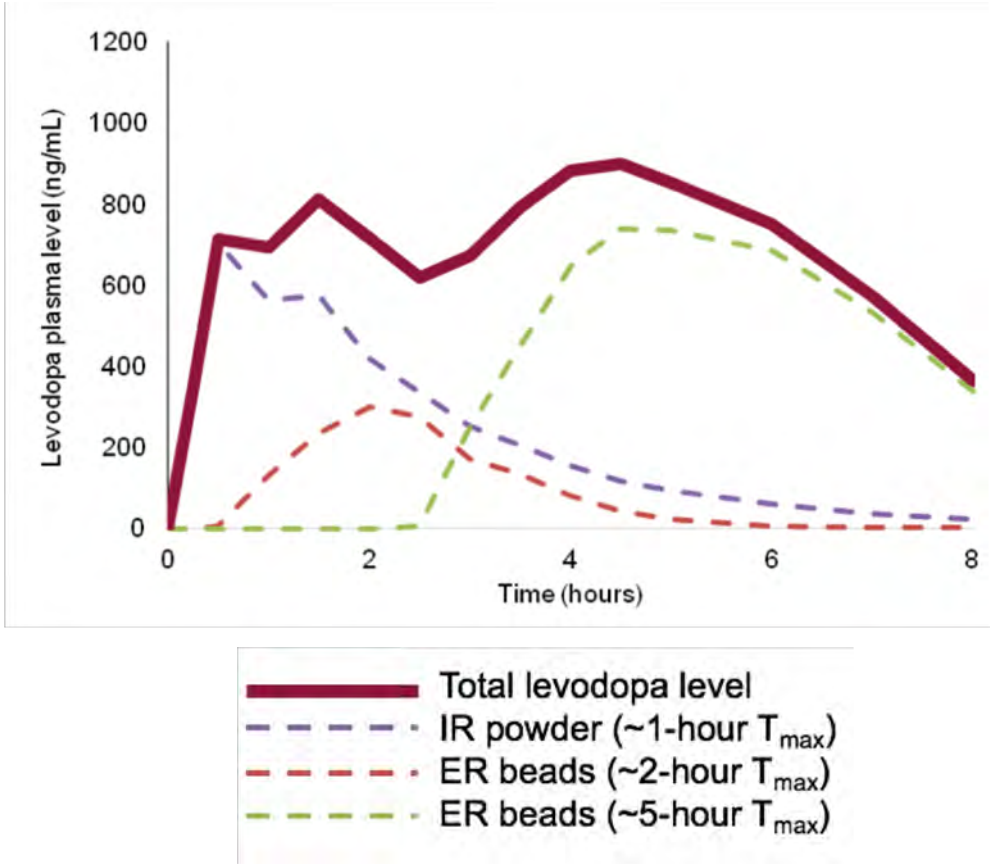
Titova et al. *npj Parkinson's Disease* 2018;4:31

Evolution of Levodopa Preparations

- Levodopa alone helped PD but with severe nausea due to breakdown into dopamine in the blood stream
- The first advance was to combine it with carbidopa to prevent peripheral breakdown which helped with nausea and promoted greater transport to the brain
- The original form of carbidopa-levodopa is referred to as “IR” levodopa (Sinemet®) and has a half-life of 1.5 hours, launched in 1975
- The first improvement on IR levodopa was the introduction of controlled release carbidopa-levodopa (Sinemet® CR) which has a longer half life but a long delay of absorption as well, launched in 1991
- Both the IR and the CR forms of levodopa are associated with motor fluctuations and dyskinesia, and the CR form is associated with unpredictable effects caused by delayed absorption

Extended Release CD/LD Capsules

- Released in 2015 as brand name Rytary®
- A major advance due to a truly longer half life
- Exhibits significant advances in helping to control motor fluctuations
- Unfortunately remains expensive, and many insurance companies continue to place roadblocks to access



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Other Oral Drugs for PD

Class	Agent	Monotherapy	Add-on
MAO-B inhibitors	Azilect® (rasagiline tablets)	•	•
	Eldepryl® (selegiline hydrochloride)		•
	Zelapar® (selegiline hydrochloride)		•
Dopamine agonists	Apokyn® (apomorphine hydrochloride injection)		•
	Mirapex® (pramipexole dihydrochloride)	•	•
	Mirapex ER® (pramipexole dihydrochloride) extended-release tablets	•	•
	Neupro® (rotigotine transdermal system)	•	•
	Parlodel® (bromocriptine mesylate) tablets, USP; (bromocriptine mesylate) capsules, USP		•
	Requip® (ropinirole tablets)	•	•
	Requip XL® (ropinirole XL)	•	•
Amantadine	Amantadine hydrochloride, USP tablets	•	•
COMT inhibitors	Comtan® (entacapone) tablets		•
	Tasmar® (tolcapone)		•
CD/LD/COMT inhibitor	Stalevo® (carbidopa, levodopa and entacapone) tablets		•

Conclusions

- In early PD, patients do well on many different drugs, but the best drug by far in terms both of benefit produced and lowest risk of side effects is levodopa
- Levodopa should not be withheld from any patient who has more than trivial symptoms of PD
- Patients who are afraid of starting levodopa should be educated about its effectiveness and safety
- In advanced PD, all oral drugs have limitations which opens up opportunities for non-oral drugs and brain surgery to address dyskinesia and motor fluctuations