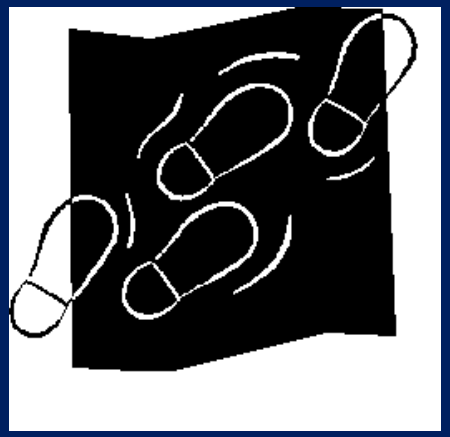
Motor Fluctuations

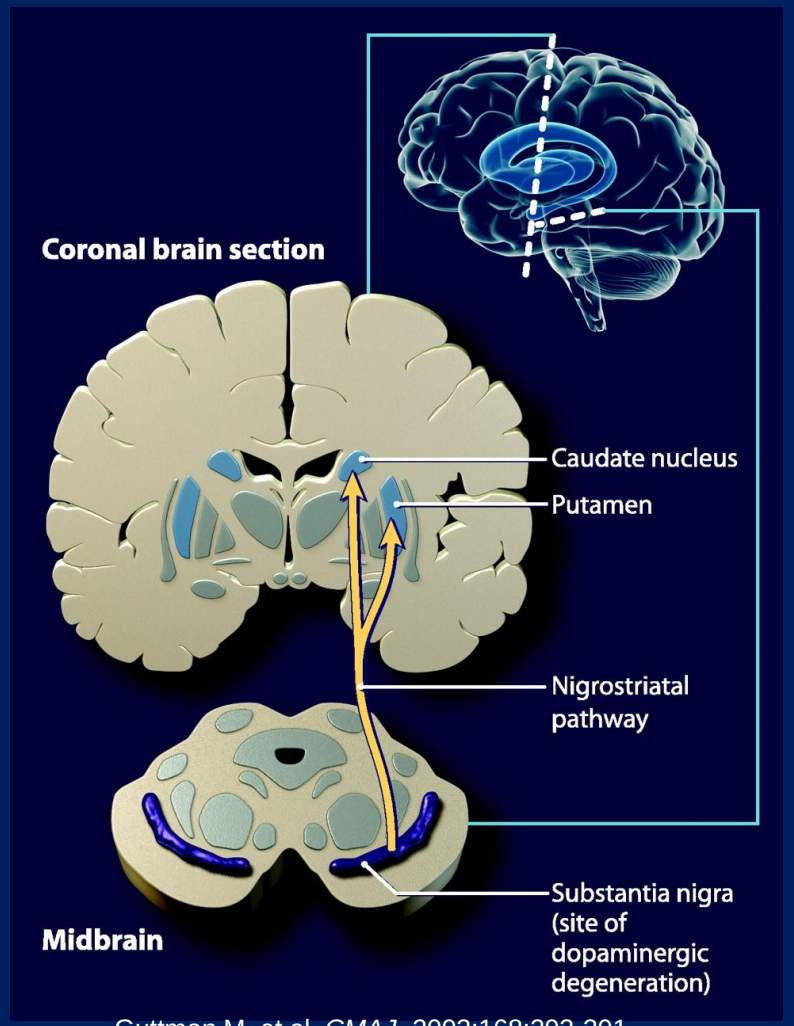


Stephen Grill, MD, PHD

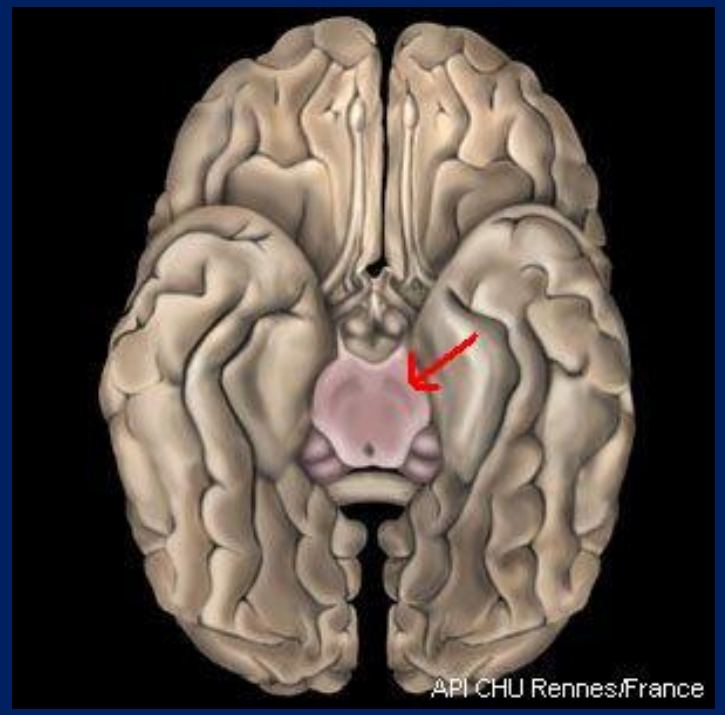
Parkinson's and Movement Disorders Center of Maryland
and
Johns Hopkins University

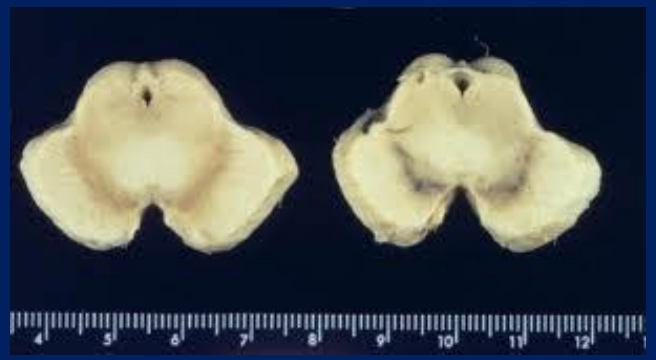
- I have no financial interest with any entity producing marketing, re-selling, or distributing healthcare goods or services consumed by, or used on patients
- I will not be discussing the use of off-label products or services or will point out any off-label uses

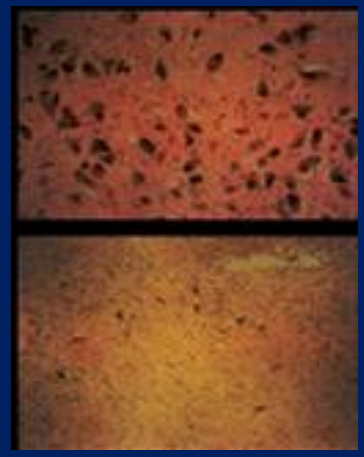
Loss of Dopamine (DA) Containing Neurons in PD



Guttman M, et al. *CMAJ*. 2003;168:293-301.





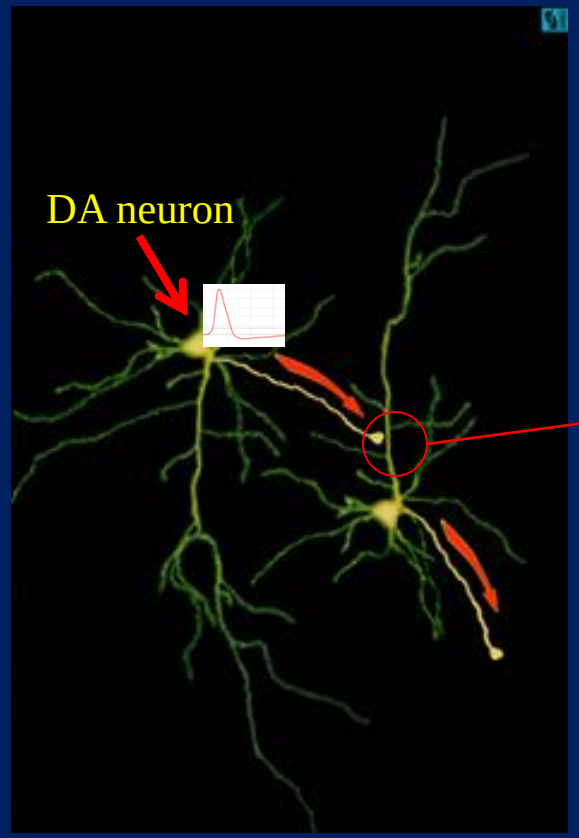


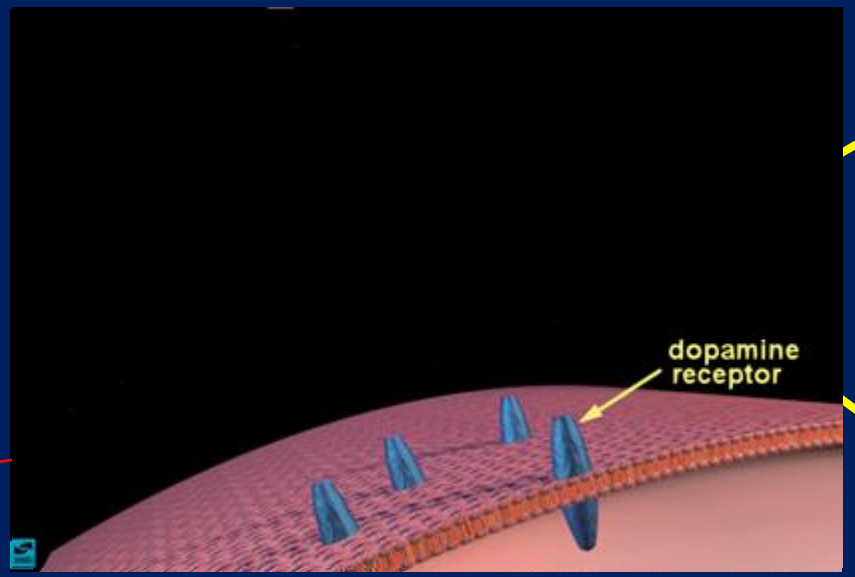
Loss of DA neurons (lower)

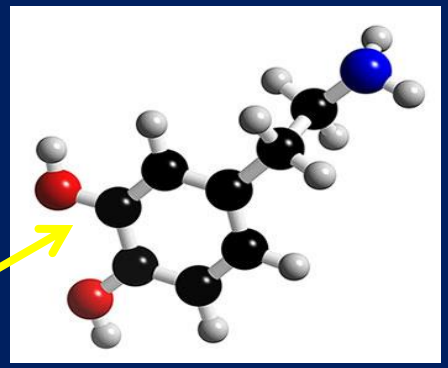
DA Neuron

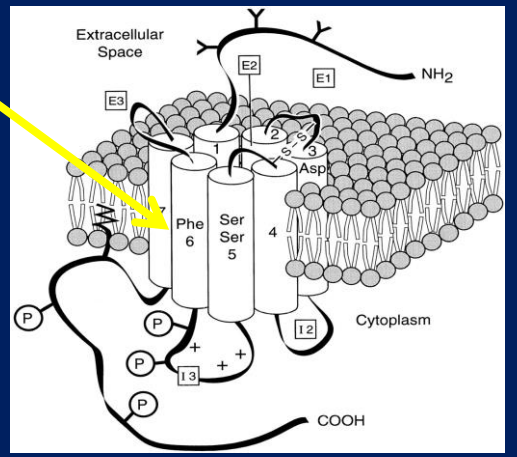
Loss of DA neurons in **Substantia Nigra** responsible for motor symptoms

Dopamine: A Neurotransmitter







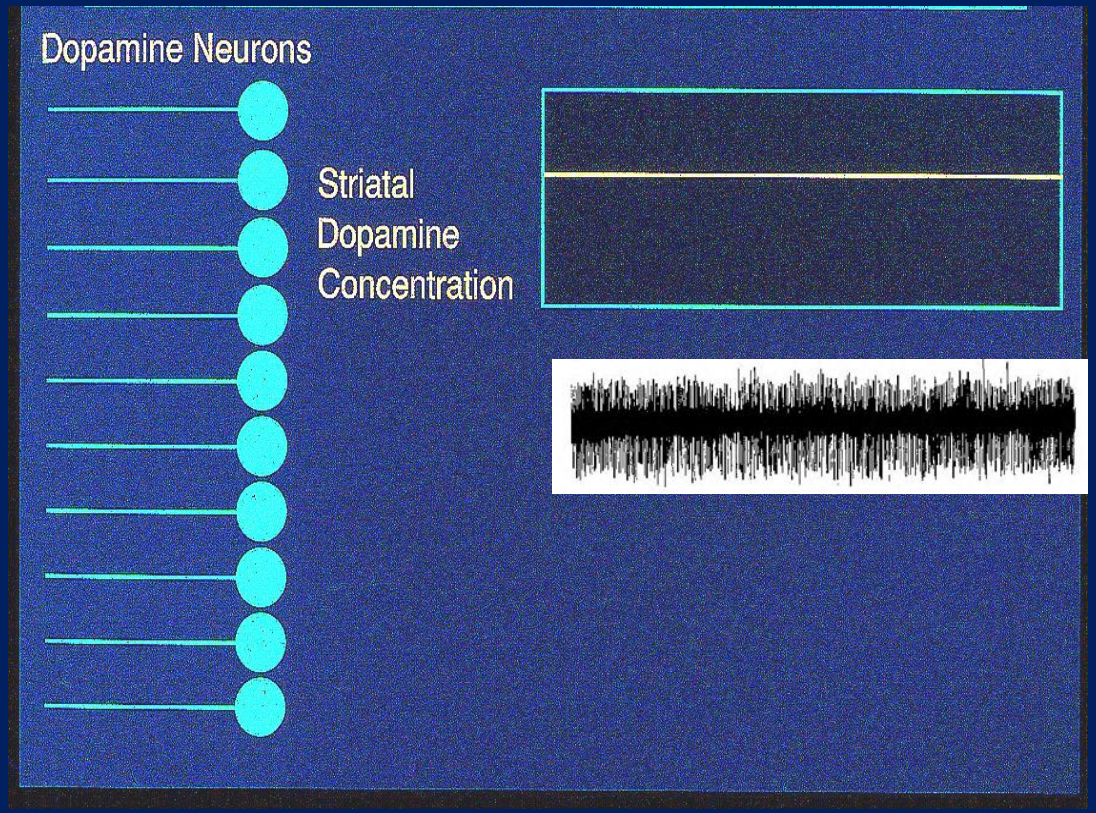


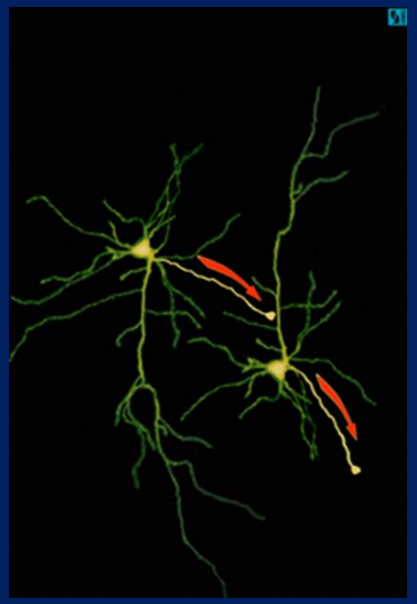
Neurotransmitter: A chemical which transmits a signal from one neuron to another.

What are Dopamine Neurons Doing?

- They are sending a "steady" signal.
- Goal of medications is to "fix" the signal by either:

1. Replacing Dopamine
2. Stimulating Dopamine receptors directly





Hutchison et al 1998 Ann Neurol

Agents Used in the Treatment of Parkinson's Disease

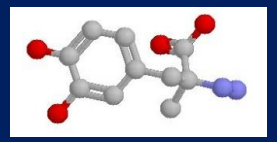
- **Levodopa Preparations**
  - Carbidopa/levodopa IR
  - Rytary
  - Duopa

- **Helper Medications**
  - Dopa decarboxylase inhibitors
    - Carbidopa
    - Benserazide
  - COMT inhibitors
    - Entacapone
    - Tolcapone
  - MAOb inhibitors
    - Selegiline
    - Rasagaline
    - Safinamide

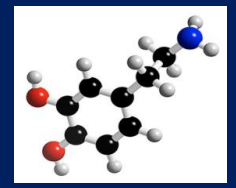
- **Dopamine Agonists**
  - Ropinirole
  - Pramipexole
  - Rotigotine
  - Apomorphine*
- **Anticholinergics**
  - Trihexyphenidyl
  - Benztropine
- **NMDA receptor antagonists**
  - Amantadine
  - Gocovri (Amantadine ER)

Carbidopa/Levodopa (Sinemet®)

- Levodopa is most powerful drug for PD
- Least side effects
- Generic, relatively cheap
- All patients respond
- Improves mortality rate

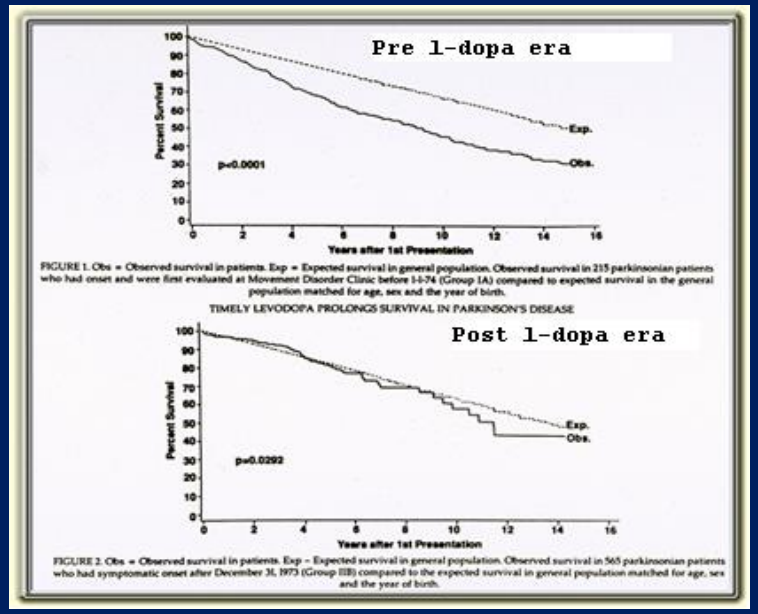


carbidopa

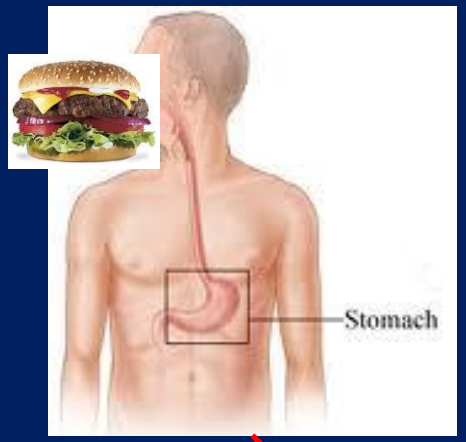


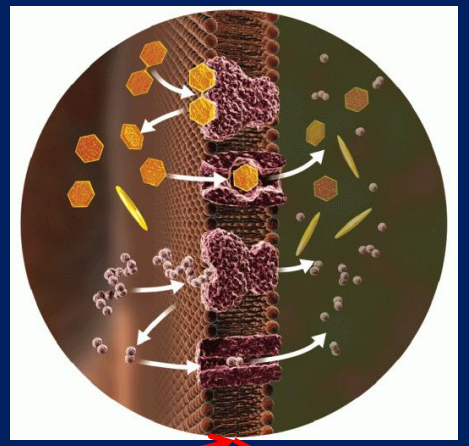
levodopa

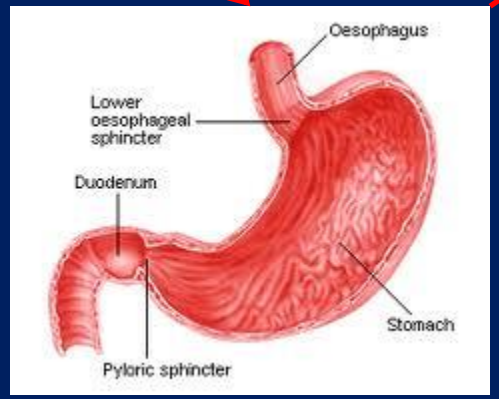
- Response changes over time due to changes in compensatory responses or further loss of nigrostriatal projections
- Chronic use of l-dopa does NOT enhance progression of pathology (Parkinnen et al 2011)

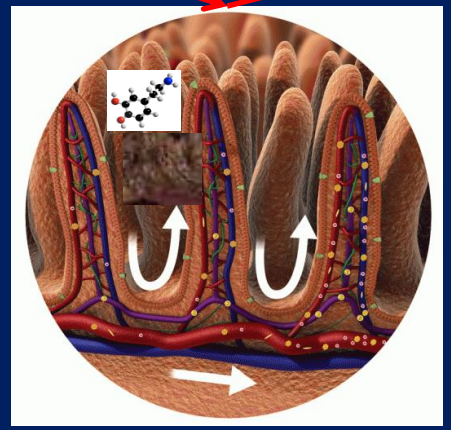


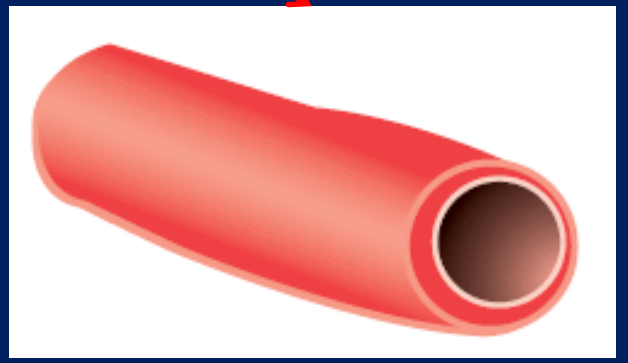
Medications Need to Get to the Brain





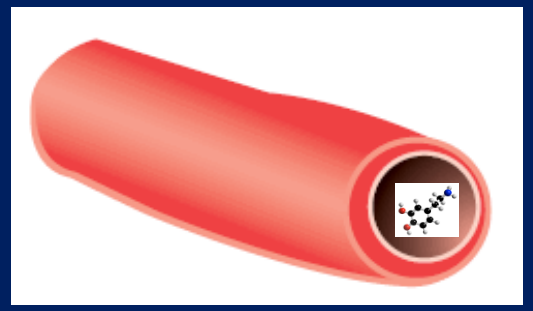




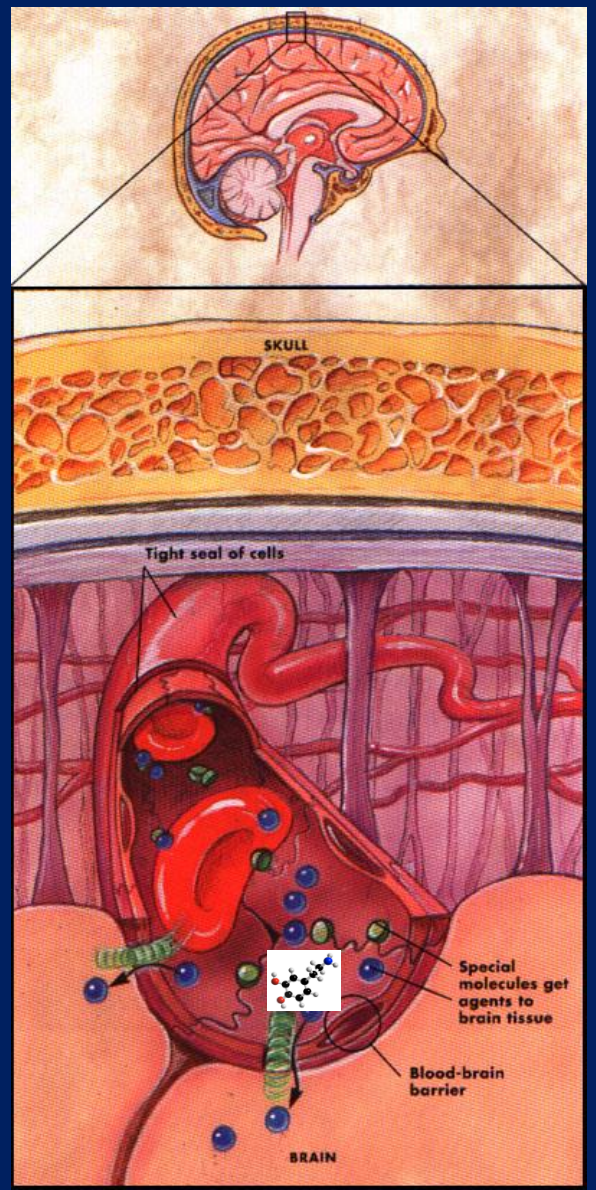


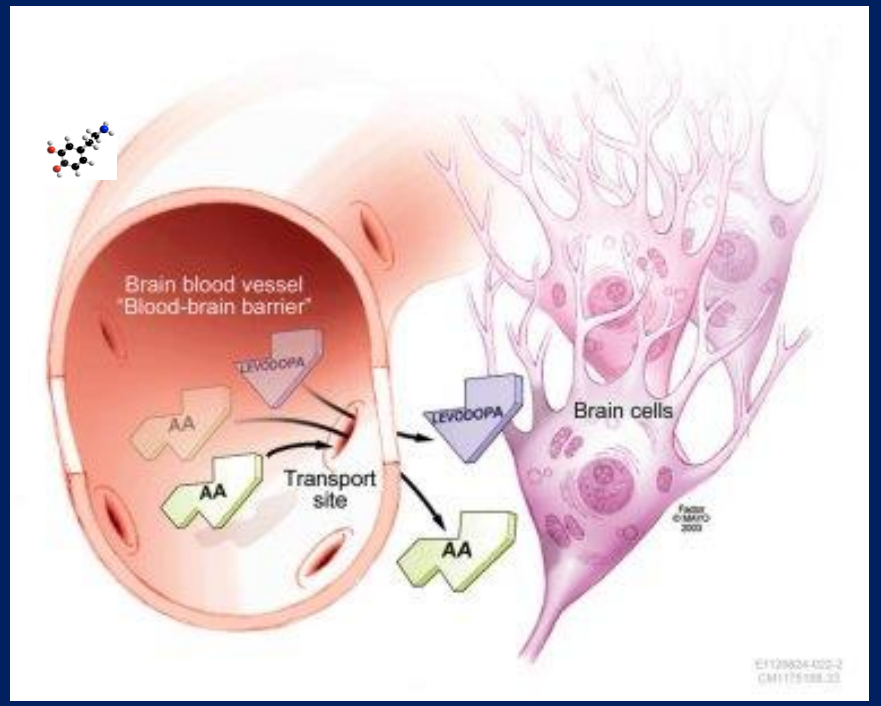
Absorption through gut to blood. L-dopa is an amino acid and is transported through "channels" along with other amino acids. Only a limited number of amino acids can be transported in a given time.

Getting l-dopa from Blood to Brain



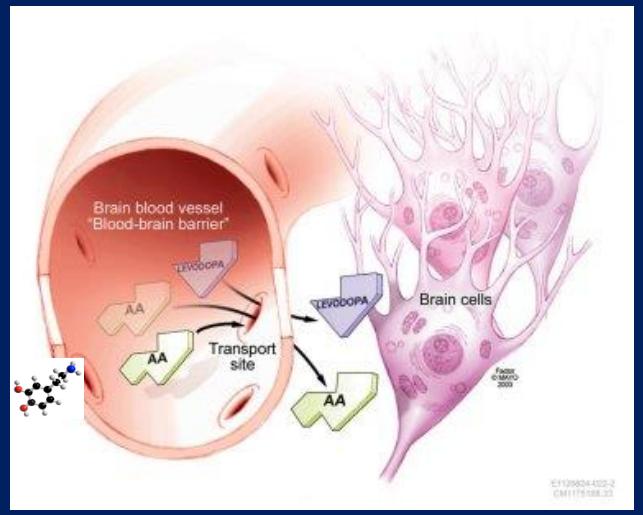
Blood-Brain Barrier:
L-dopa will not simply diffuse into brain. It has to get through a barrier by being transported with other amino acids through channels.

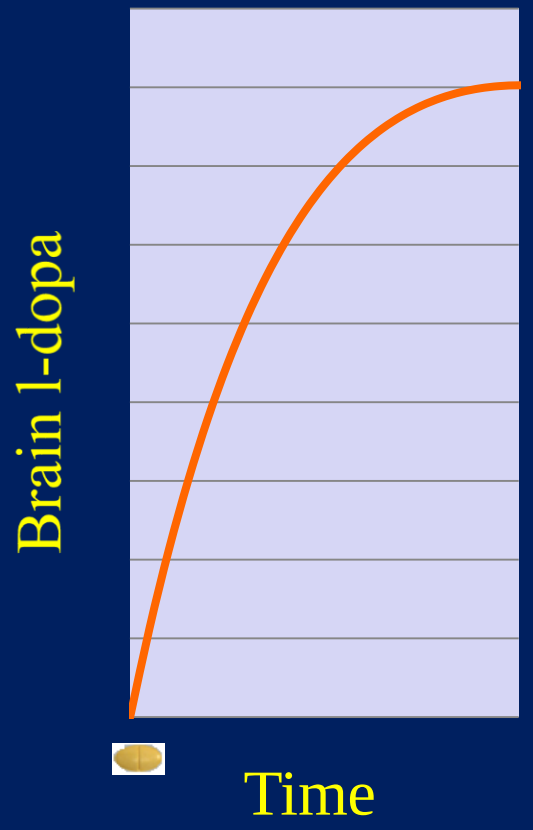




It Takes Time to Get the l-dopa to the Brain

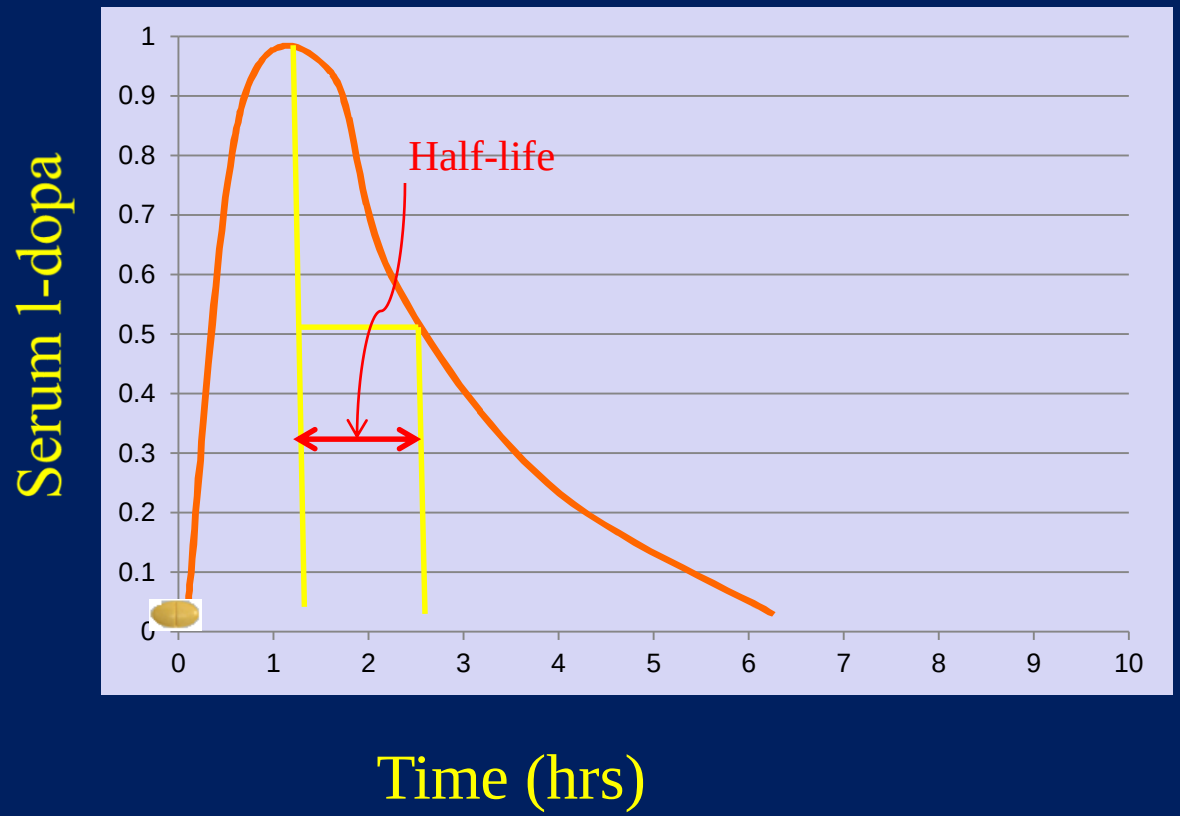
- It takes time for the l-dopa to get absorbed through the gut and then into the brain. Usually about 15-30 minutes





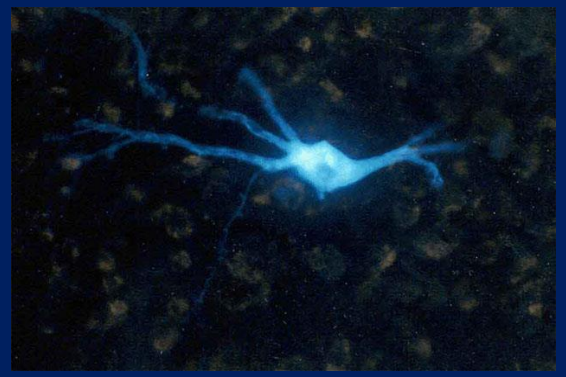
How Long Does DA Remain in Your System?

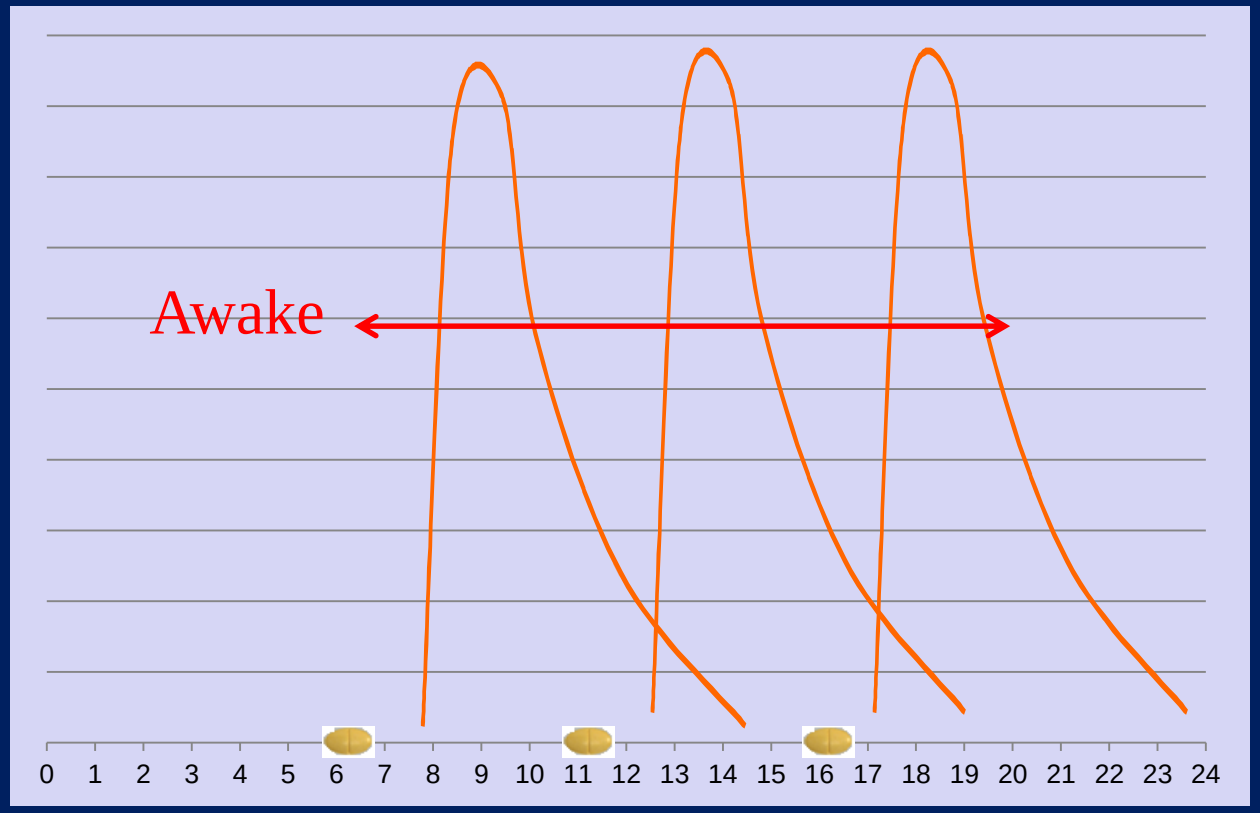
- The “half –life” is the amount of time it takes for ½ of the l-dopa to be cleared from your system.
- This is not changed significantly as the disease progresses.
- In early disease, dopamine can be stored in the neurons so benefit from carbidopa/levodopa lasts longer than the half-life.



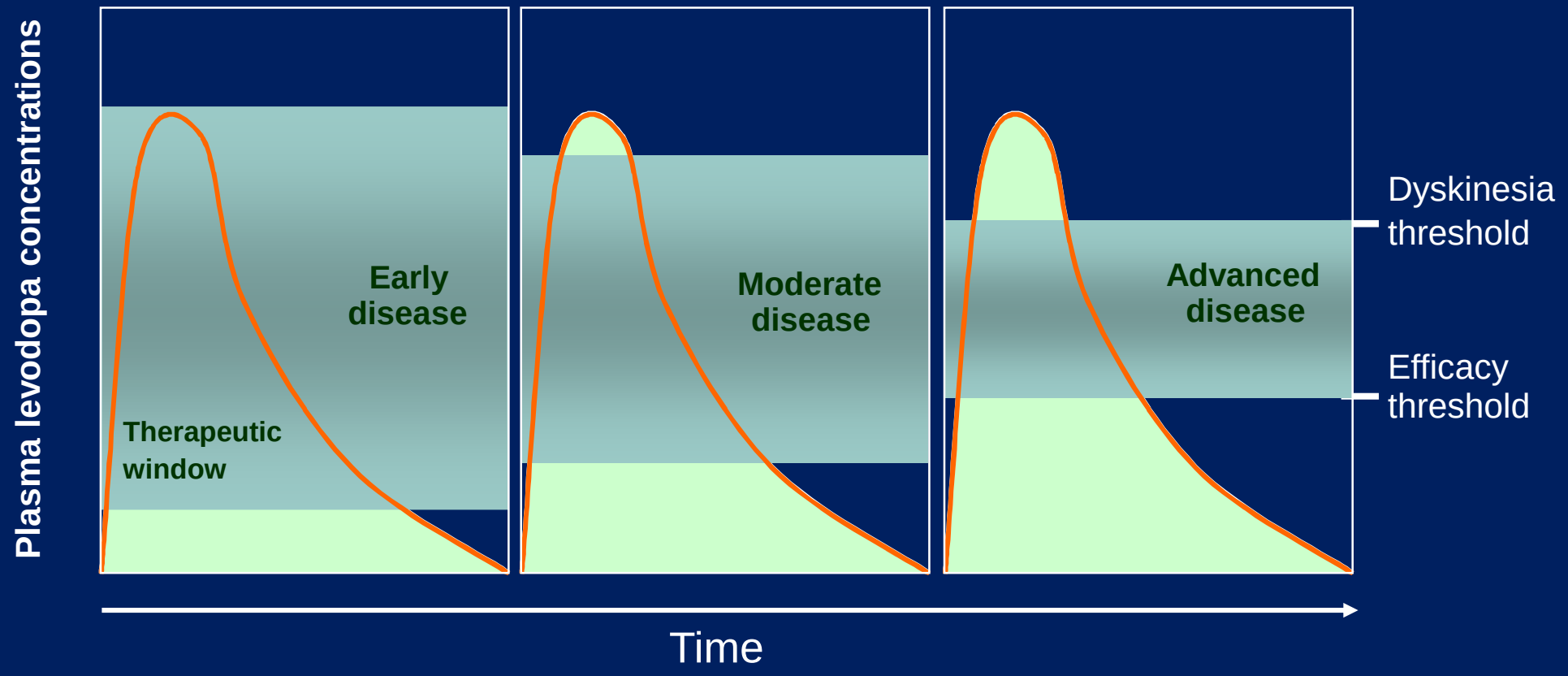
In Early Disease, Carbidopa/levodopa can be taken at 5-7 hour intervals

Dopamine neurons can store dopamine. In early disease, patients are not so dependent on the fluctuations in l-dopa levels in the brain. As more DA neurons are lost, this "buffering" capacity is lost.



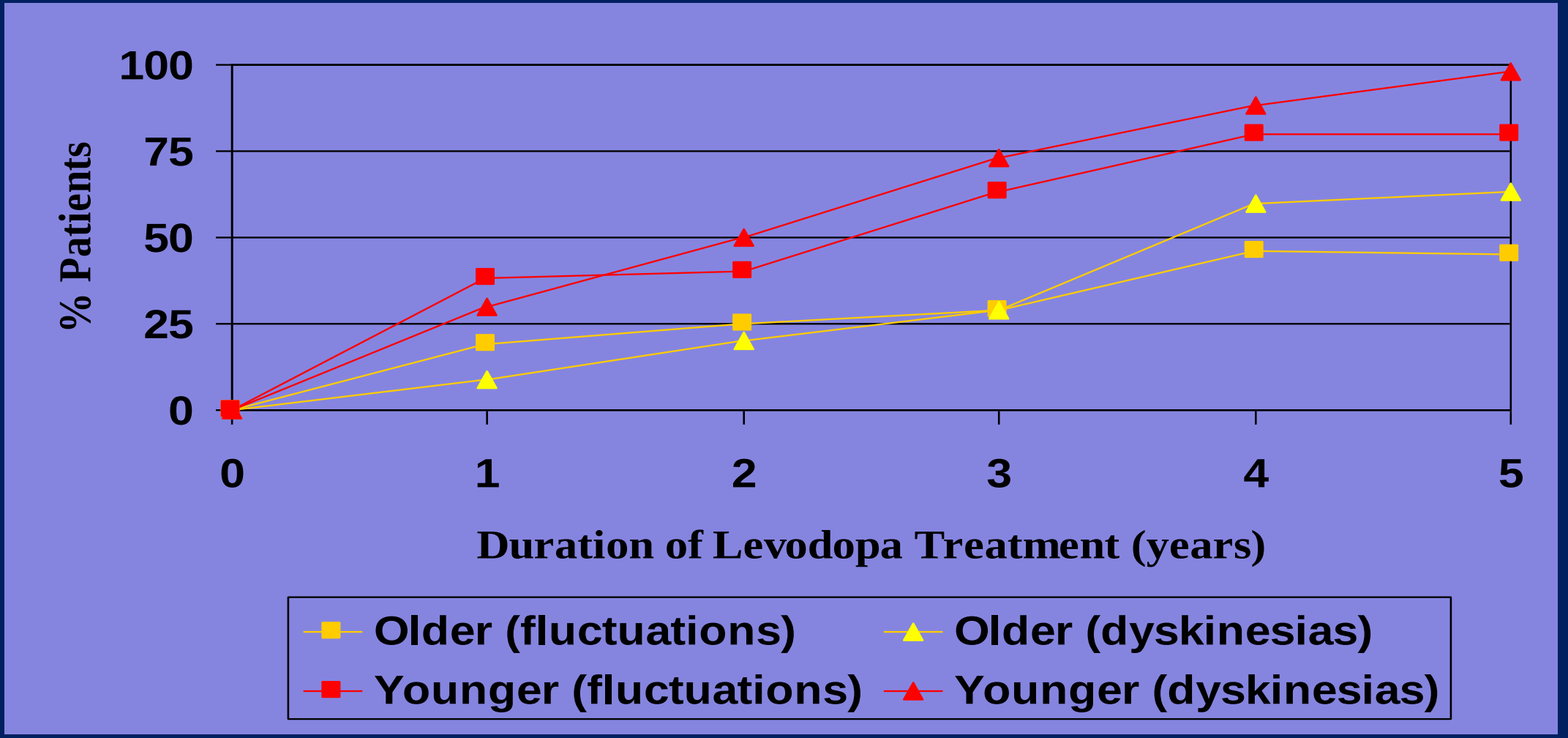


The Levodopa *Therapeutic Window* Narrows with Disease Progression



Obeso et al 2000

How Common are Motor Fluctuations?



What Can Be Done to Reduce Risk of Developing Motor Fluctuations and Dyskinesias?

The ELLDOPA Study

- 361 early PD patients
- Randomized, double-blind, placebo-controlled
- 40 week trial

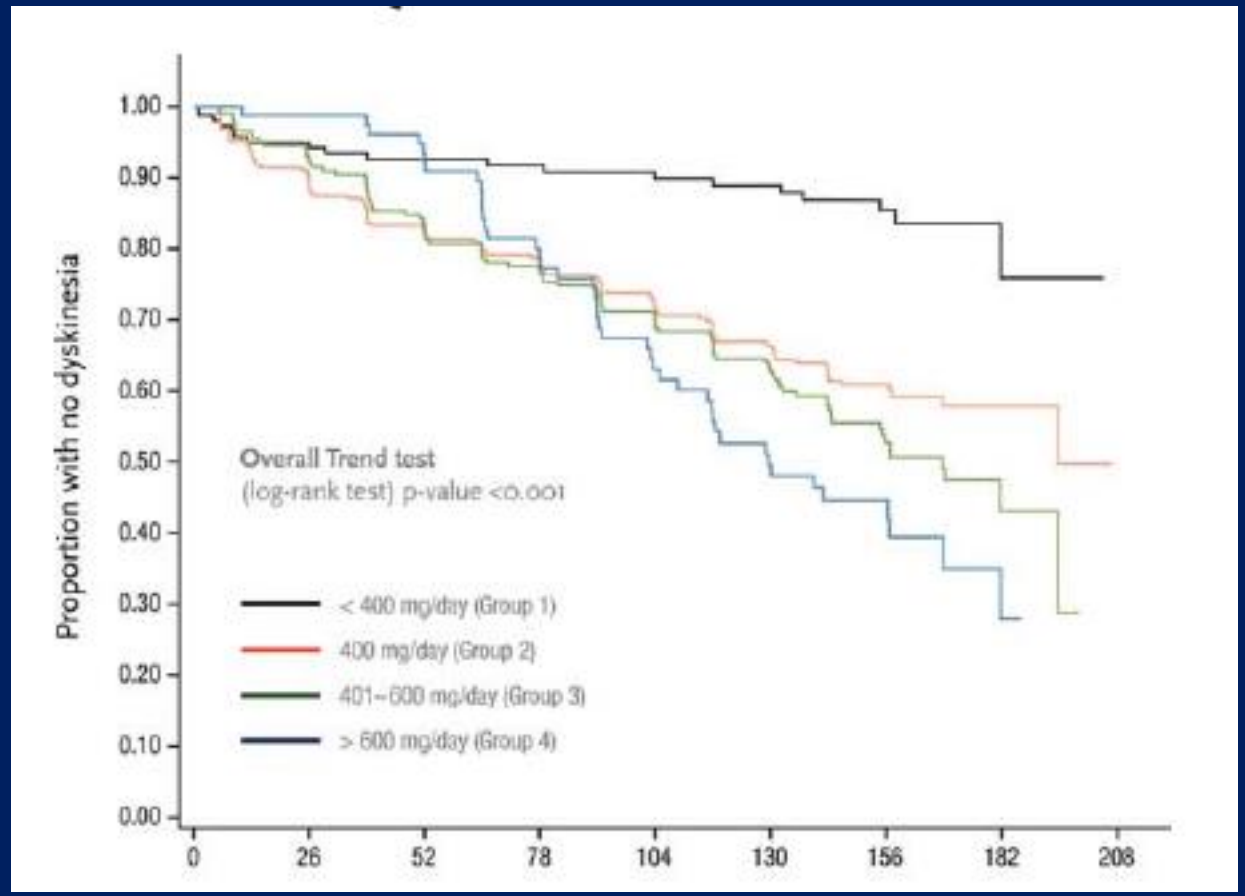
Adverse event	Placebo	Levodopa 150 mg/day	Levodopa 300 mg/day	Levodopa 600 mg/day	P-value (Trend)
Subjects, N	90	92	88	91	
Dyskinesia	3 (3.3)	3 (3.3)	2 (2.3)	15 (16.5)	<0.001
Dystonia	19 (21.1)	19 (20.1)	14 (15.9)	12 (13.2)	0.30
Freezing	13 (14.4)	9 (9.8)	6 (6.8)	5 (5.5)	0.15
On-Off	3 (3.3)	1 (1.1)	0 (0.0)	3 (3.3)	0.26
Wearing-Off	12 (13.3)	15 (16.3)	16 (18.2)	27 (29.7)	0.06

- Keep levodopa dose below 600 mg/day advisable to avoid motor fluctuations

Parkinson Study Group. *N Engl J Med*. 2004;351:2498-2508.

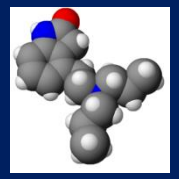
Factors Predictive of the Development of Levodopa-Induced Dyskinesia and Wearing-Off in Parkinson's Disease

Young age at Onset
Higher l-dopa dose
Low body weight
North Americans
Entacapone
Female gender
More severe symptoms

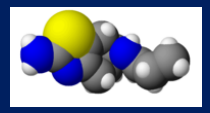


(Olanow et al 2013)

Dopamine Agonists Bind to DA Receptors

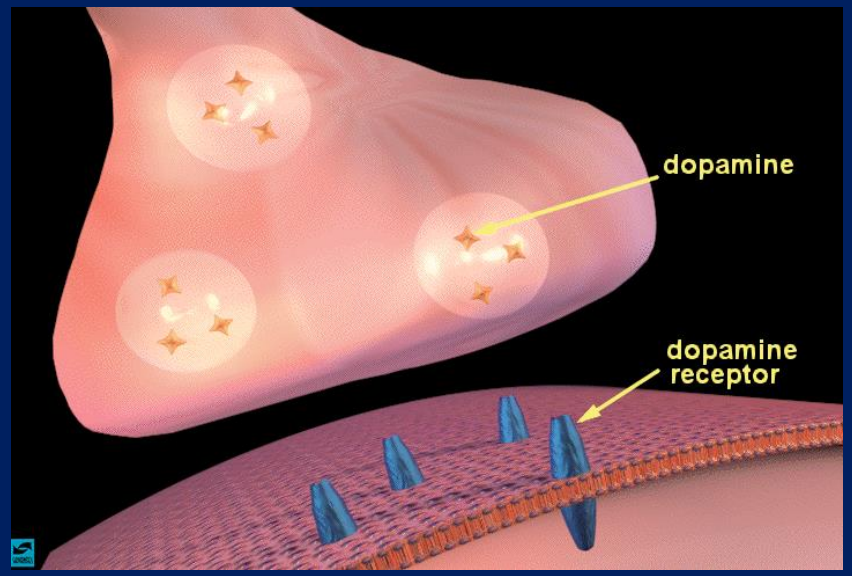


Ropinirole
(Requip ®)



Pramipexole
(Mirapex ®)

Rotigotine
(Neupro ®)



Advantages

- Longer ½ life: 6 hours
- No competition to get absorbed through gut or into brain
- Do not need to be converted
- Extended Release Formulations

Disadvantages

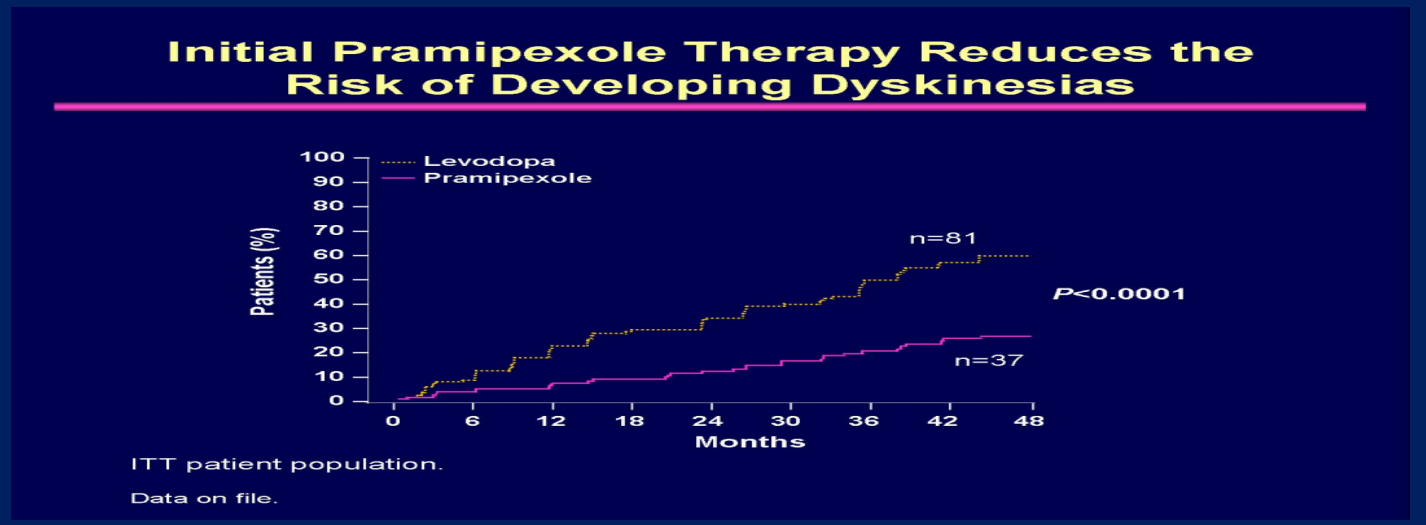
- Not as powerful as l-dopa
- Worse side effects
  - Nausea, tiredness, confusion, hallucinations, orthostatic hypotension, impulse control

Pramipexole vs Levodopa as Initial Treatment for Parkinson Disease

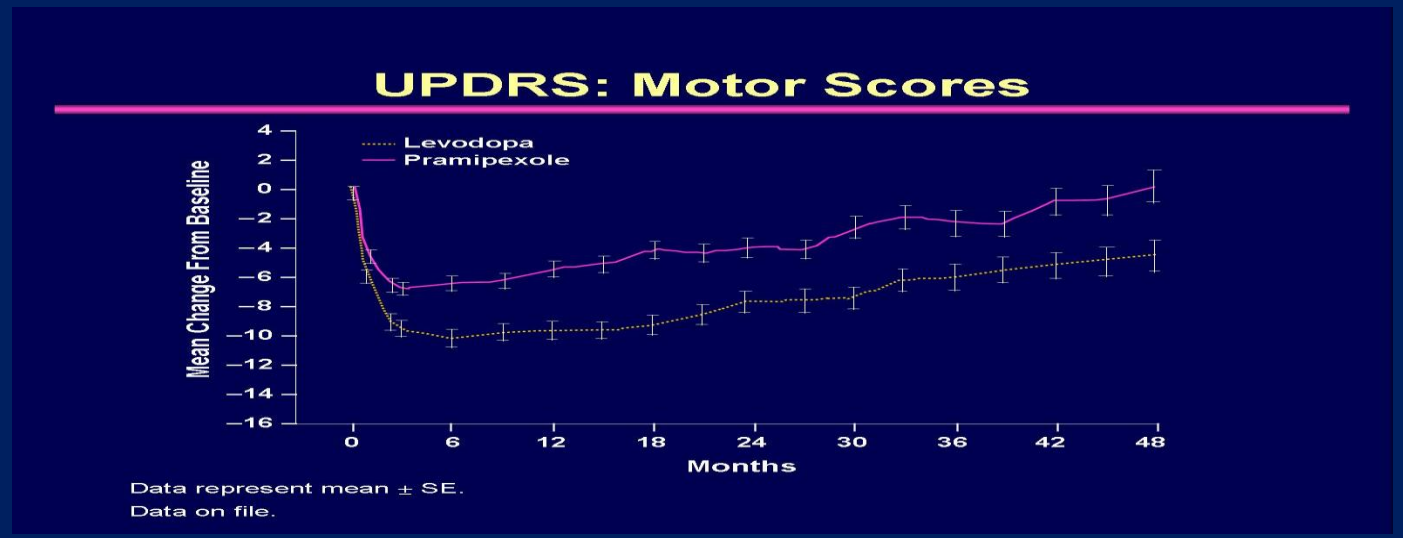
A Randomized Controlled Trial

- Double-blind, 5 year controlled study of l-dopa vs pramipexole

- Reduced risk of dyskinesias in pramipexole group.



Study flaw:
L-dopa patients better treated throughout study.



JAMA 2000

Dopamine agonists in the treatment of early Parkinson's disease: A meta-analysis

William L. Baker [a,b], Dee Silver [c], C. Michael White [a,b], Jeffrey Kluger [d], Jeffrey Aberle [a,b], Aarti A. Patel [e], Craig I. Coleman [a,b,*]

- 25 randomized controlled trials
- DA agonists inferior to l-dopa in treating motor symptoms (2 point higher ADL score and 4 point higher motor score)
- DA agonists result in lower rate of motor fluctuations
- Adverse effects worse in DA agonists with 17.2% withdrawal rate vs 8.8% for l-dopa treated patients

Parkinsonism and Related Disorders 15 (2009) 287–294

DA Agonists

- Less effective vs l-dopa
- Perhaps less risk motor complications
- Probably no long term benefit vs l-dopa
- More side effects
  - Somnolence
  - Leg edema (up to 45%)
  - Constipation
  - Dizziness; hypotension
  - Hallucinations
  - Nausea
  - Impulse control disorders (6-25%)
  - Punding

Fourteen-year final report of the randomized PDRG-UK trial comparing three initial treatments in PD

- **782 patients, randomized, open label***
  - **L-dopa**
  - **Bromocriptine (a dopamine agonist)**
- **Endpoints: Mortality, disability, motor complications**
- **<u>Long term outcomes similar with respect to mortality and motor complications. L-dopa group had sustained better motor functioning</u>**

*L-dopa + selegiline arm stopped prematurely due to increased mortality; not confirmed in other studies

Initiating Medication Therapy in Early PD

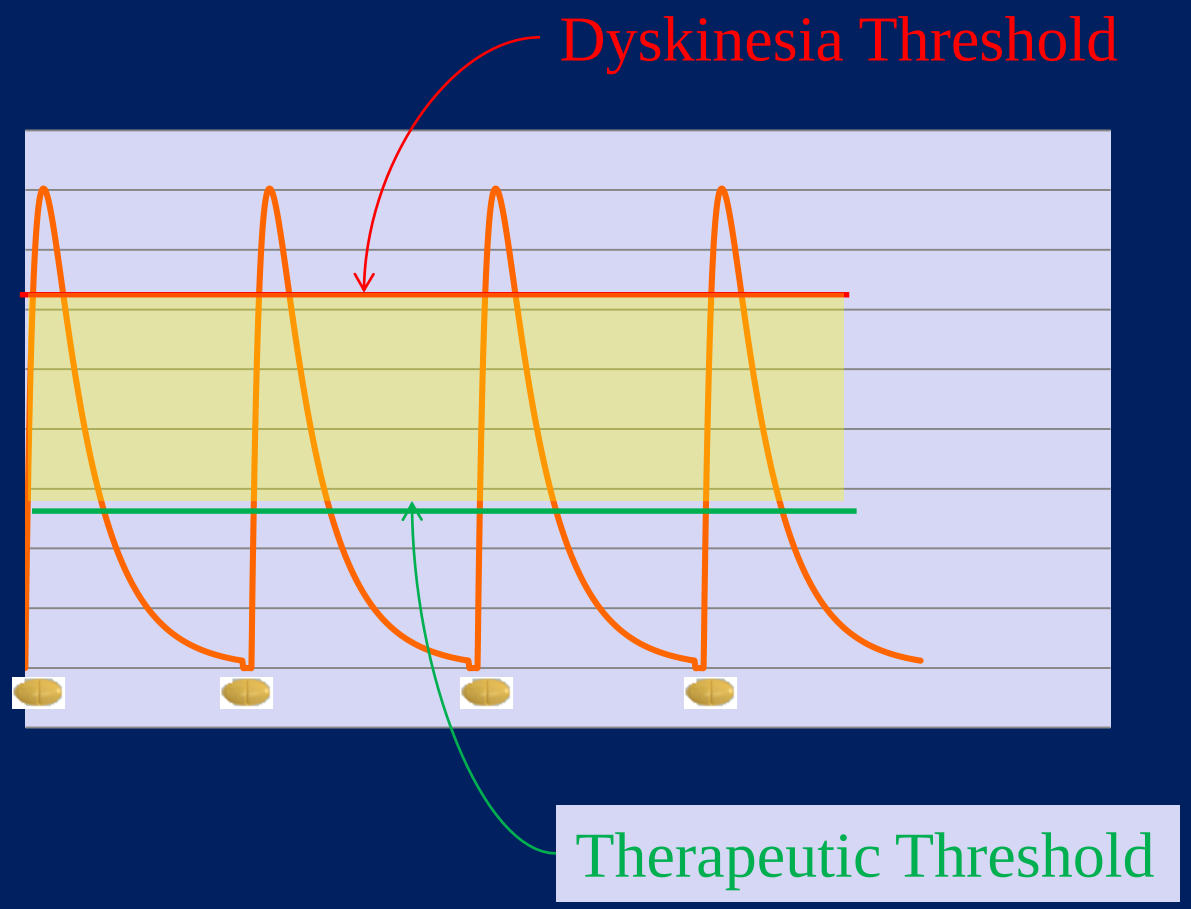
- Consider MAOb-inhibitor (selegiline, rasagaline)*
- Consider DA agonist (pramipexole, ropinirole, rotigotine)
- Prescribe l-dopa at minimum dose needed to provide control of symptoms (usually 300-400 mg/day at about 5 hour intervals)
- Evaluate efficacy at 3 months

*Safinamide not indicated as monotherapy

What Can Be Done to Treat Motor Fluctuations and Dyskinesias?

Therapeutic Window

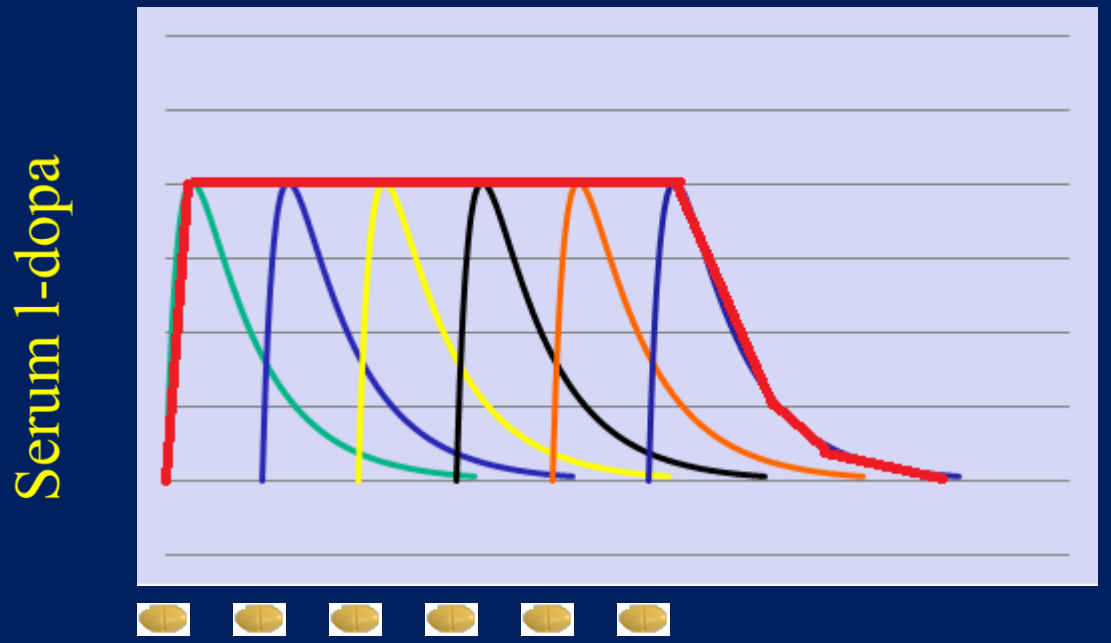
- With advancing disease, people become dependent on fluctuations of l-dopa levels.
- If the level is too low, symptoms are not treated. If the levels are too high, dyskinesias result.



Strategies to Keep DA Stimulation Steady

- **Shorten Dosing Interval**
- Add Helper Medication
  - COMT inhibitors
    - Entacapone (Comtan®)
  - MAOb inhibitors
    - Selegiline, Rasagaline, Safinamide
- Add Dopamine Agonist
  - Ropinirole (Requip®)
  - Pramipexole (Mirapex®)
  - Rotigotine patch (Neupro®)
- Long-acting carbidopa/levodopa: Rytary
- Apomorphine injections
- Continuous Infusion of l-dopa: duopa

Taking Medications at Shorter Intervals Leads to More Steady DA Levels



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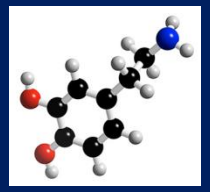
  - Pramipexole (Mirapex®)
  - Rotigotine patch (Neupro®)
- Apomorphine
- Continuous Infusion of l-dopa

Helper Medications Make Dopamine Last Longer by Blocking Enzymes Which Break it Down*

RQPCTRS01 NEW2/6/02

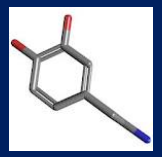
COMT inhibitors block COMT



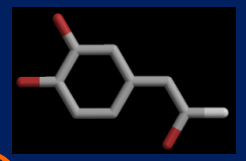
DOPAMINE

MAOb inhibitors block monoamine oxidase

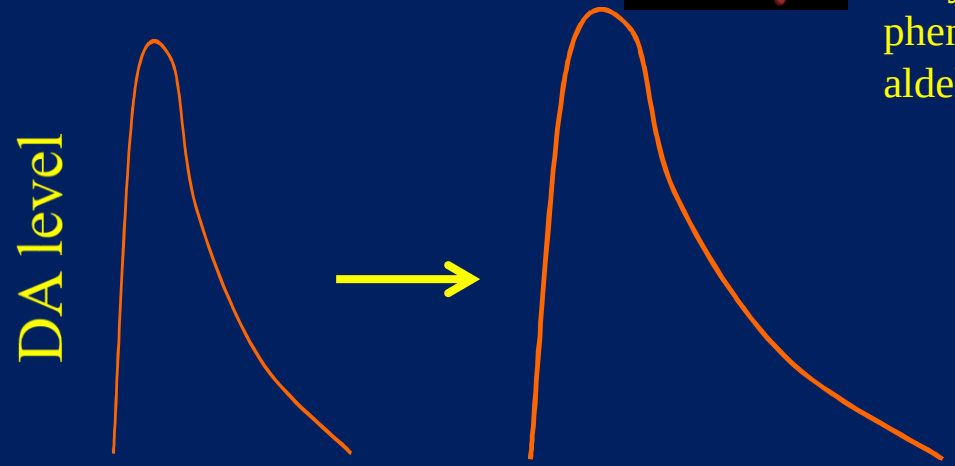
If the enzymes are blocked the dopamine lasts longer



3-Methoxy-Tyramine



Dihydroxy-phenylacet-aldehyde



Helper medications add about 20 minutes of “on” time per dose of levodopa

*COMT inhibition also works outside the brain to block breakdown of l-dopa

Strategies to Keep DA Stimulation Steady

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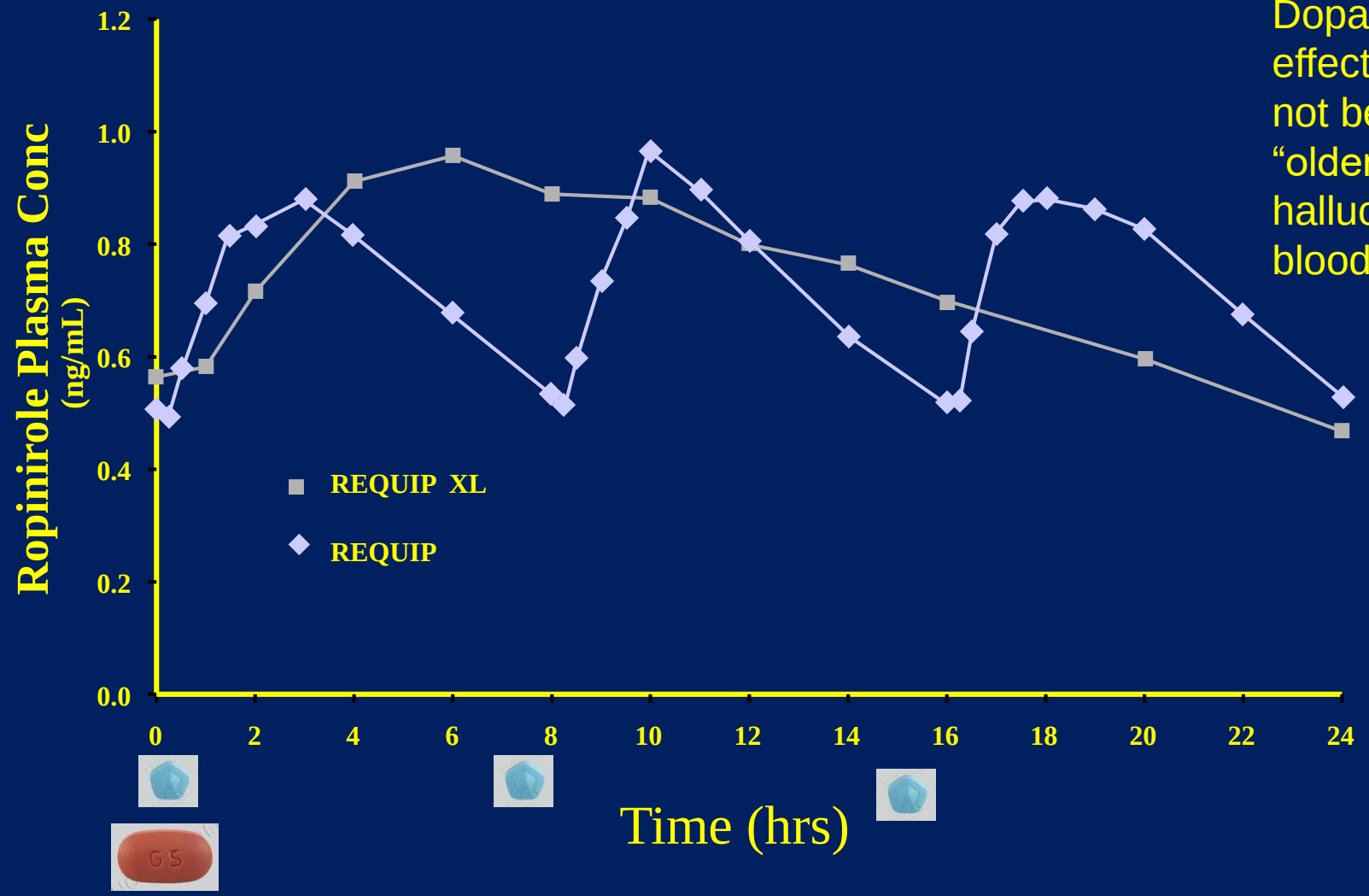
  - Rotigotine patch (Neupro®)
- Apomorphine
- Continuous Infusion of l-dopa

Dopamine Agonist as Add-on Therapy



Dopamine agonists have more side effects than levodopa and should not be used in persons who are “older”, have cognitive problems, hallucinations/delusions or low blood pressure

Strategies to Keep DA Stimulation Steady

- Shorten Dosing Interval
- Add Helper Medication
  - COMT inhibitors
    - Entacapone (Comtan®)
  - MAOb inhibitors
    - Selegiline, Rasagaline (Azilect®)
- Add Dopamine Agonist
  - Ropinirole (Requip®)
  - Pramipexole (Mirapex®)
  - Rotigotine patch (Neupro®)
- Long-acting carbidopa/levodopa: Rytary
- Apomorphine
- Continuous Infusion of l-dopa: duopa

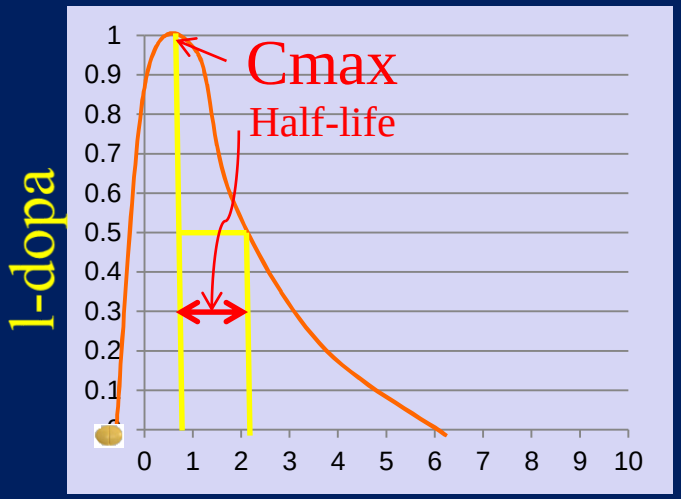
Rytary

- Extended release capsule formulation of carbidopa/levodopa in a 1:4 ratio
- Contains both immediate and extended release components
- Dose often has to be “tweaked”

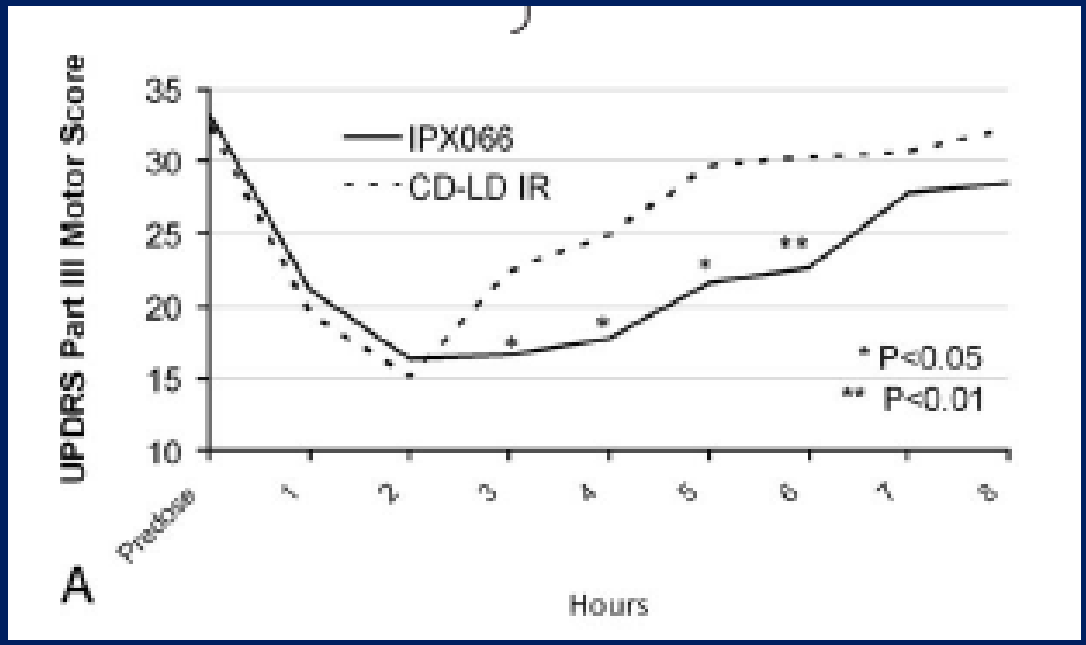
Crossover Comparison of IPX066 and a Standard Levodopa Formulation in Advanced Parkinson's Disease

Robert A. Hauser, MD,[1] Aaron L. Ellenbogen, DO, MPH,[2] Leo Verhagen Metman, MD, PhD,[3] Ann Hsu, PhD,[4] Martin J. O'Connell, PhD,[4] Nishit B. Modi, PhD,[4] Hsuan-Ming Yao, PhD,[4] Sherron H. Kell, MD, MPH,[4] and Suneel K. Gupta, PhD[4]*

	Rytary	Carbidopa/ Levodopa IR
Tmax (h)	2.0 +/- 1.1	0.87+/- 0.5
Time to reach 50% Cmax (h)	0.78 +/- 040	0.76 +/- 0.47
Duration above 50% Cmax	4.0 +/- 2	1.4 +/- 0.7



Time (hrs)



Movement Disorders, 2011

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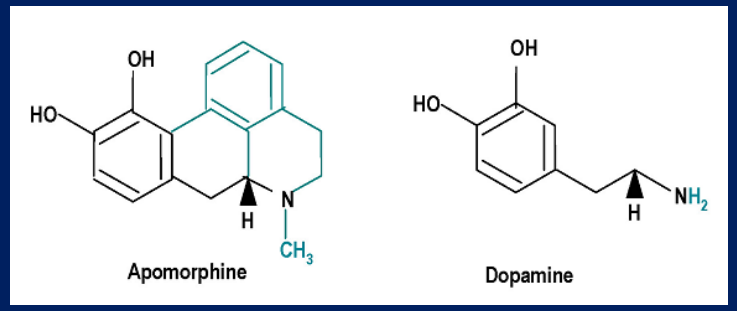
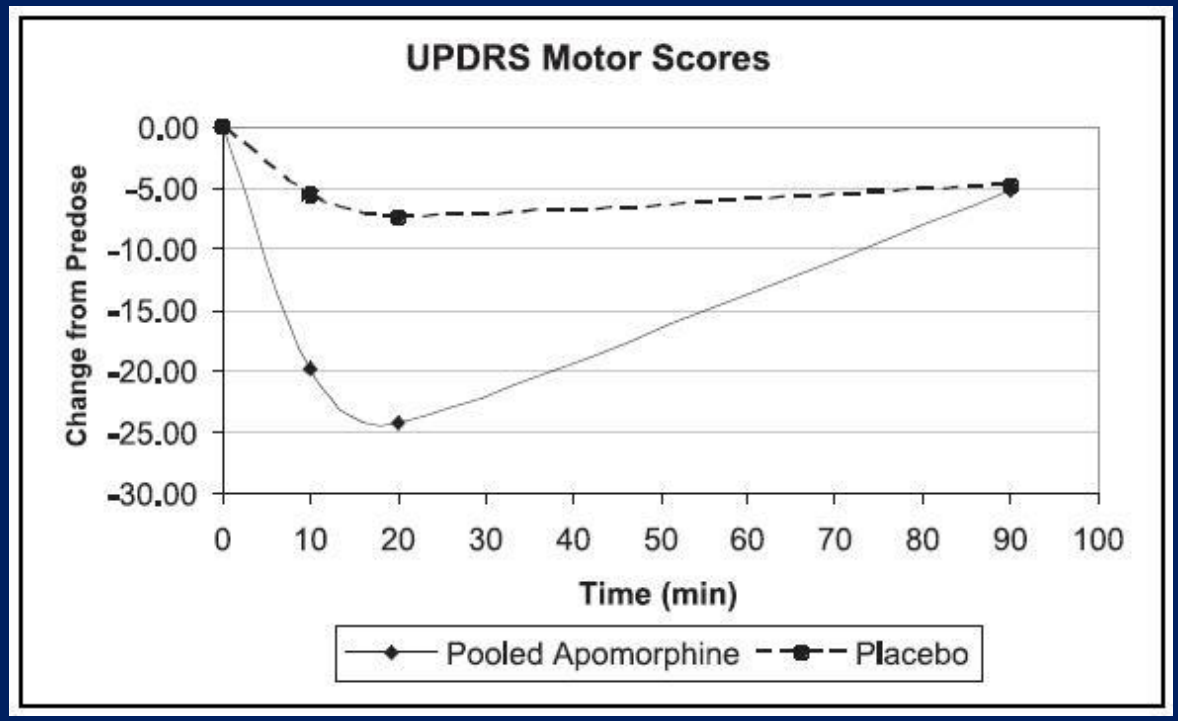
- Long-acting carbidopa/levodopa: Rytary
- Apomorphine
- Continuous Infusion of l-dopa: duopa

Apomorphine (Apokyn)

- Dopamine agonist administered subcutaneously
- Indicated for acute, intermittent “off” episodes
- Effective for about an hour
- Helpful first in AM, unexpected off times, security blanket





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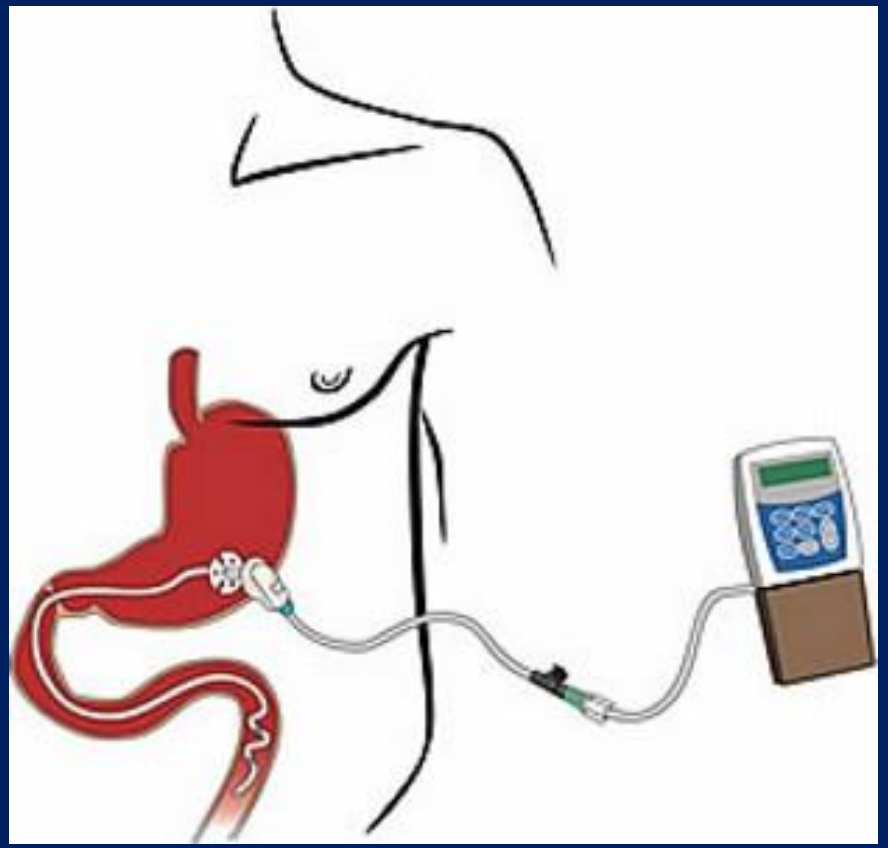
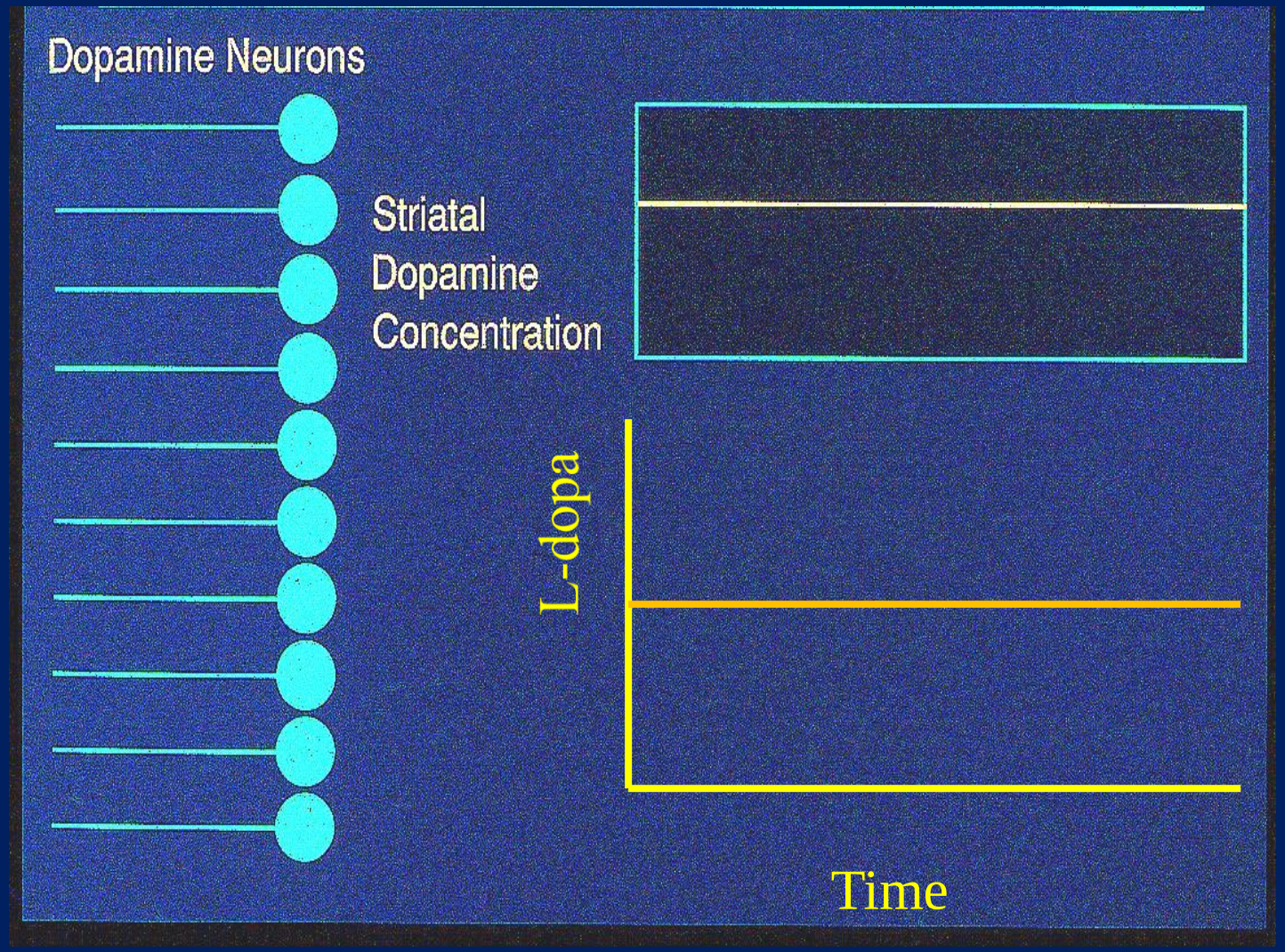
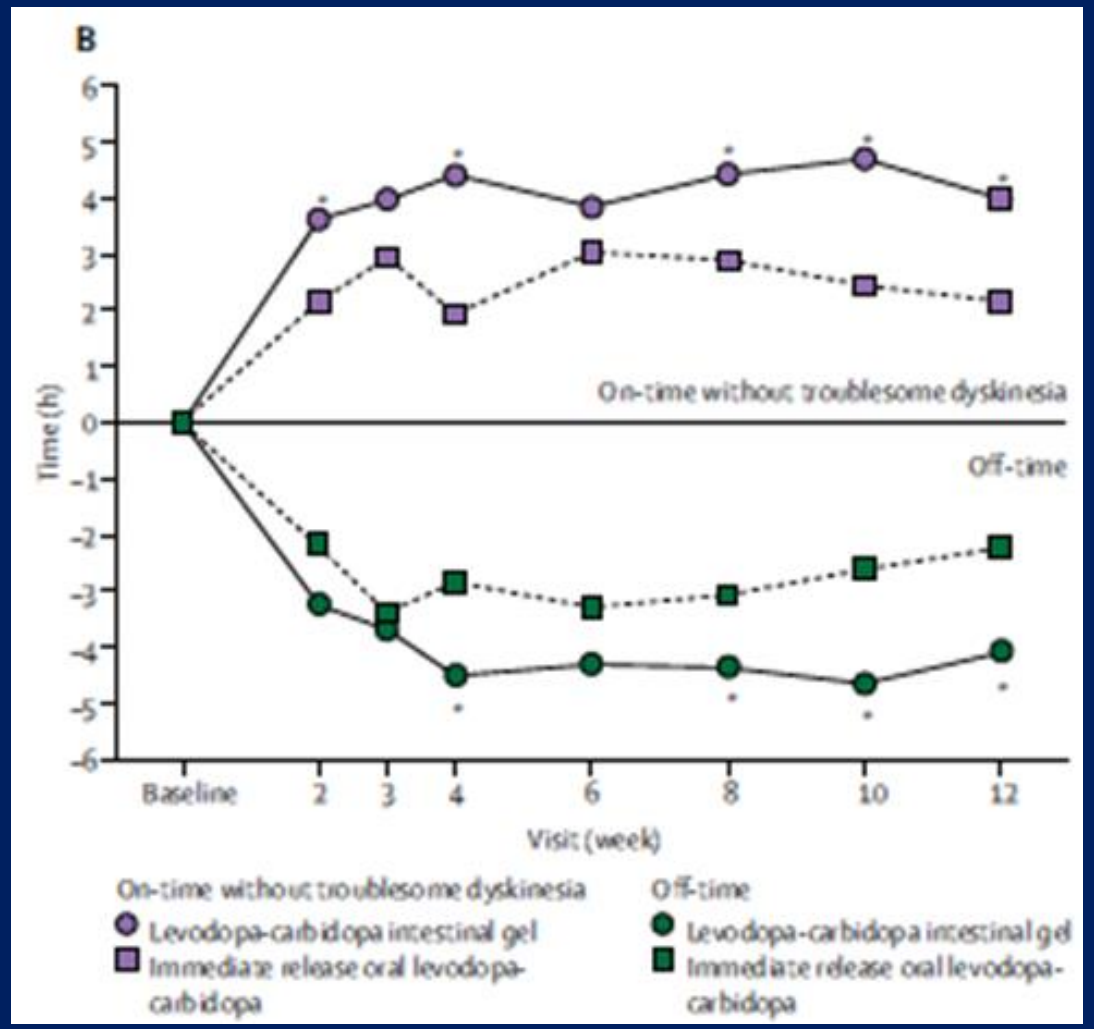
- Apomorphine
- Continuous Infusion of l-dopa (Duopa)

The Duopa Pump Can Theoretically Keep Dopamine Constant





Duopa is Superior to Oral Levodopa in Reducing Off Time but There are Some Risks



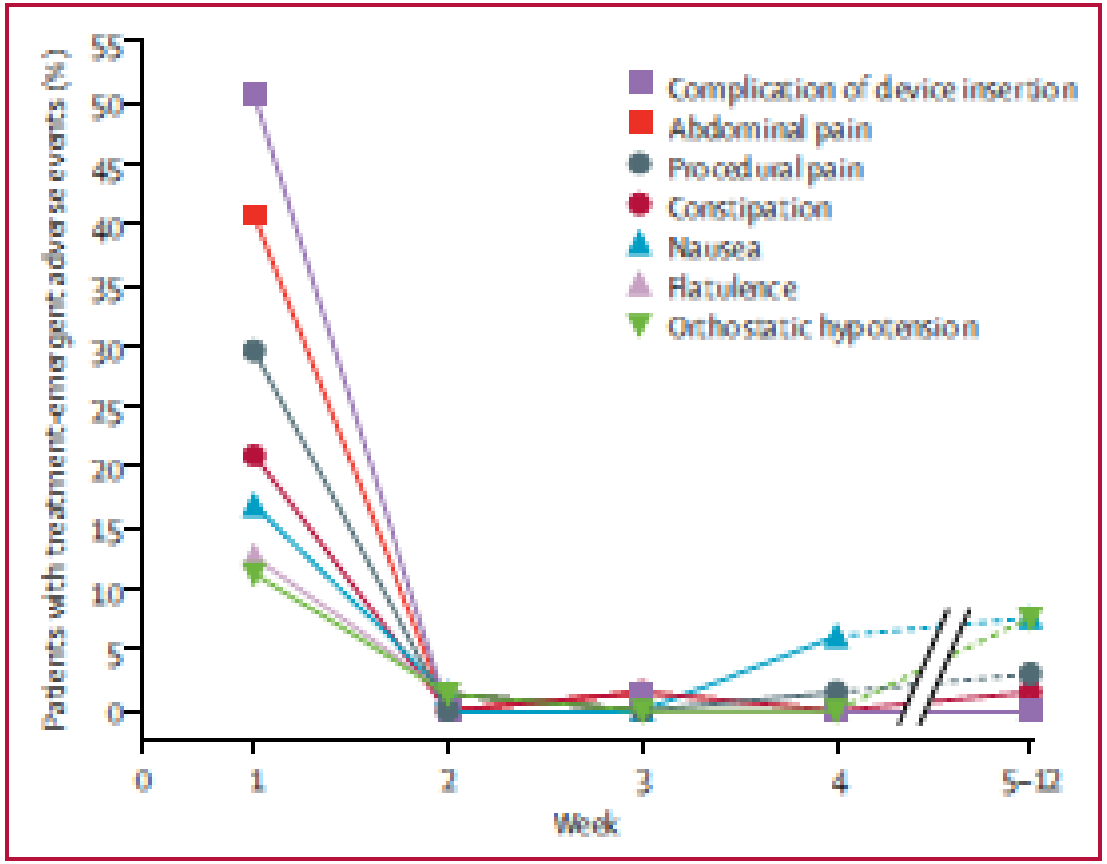
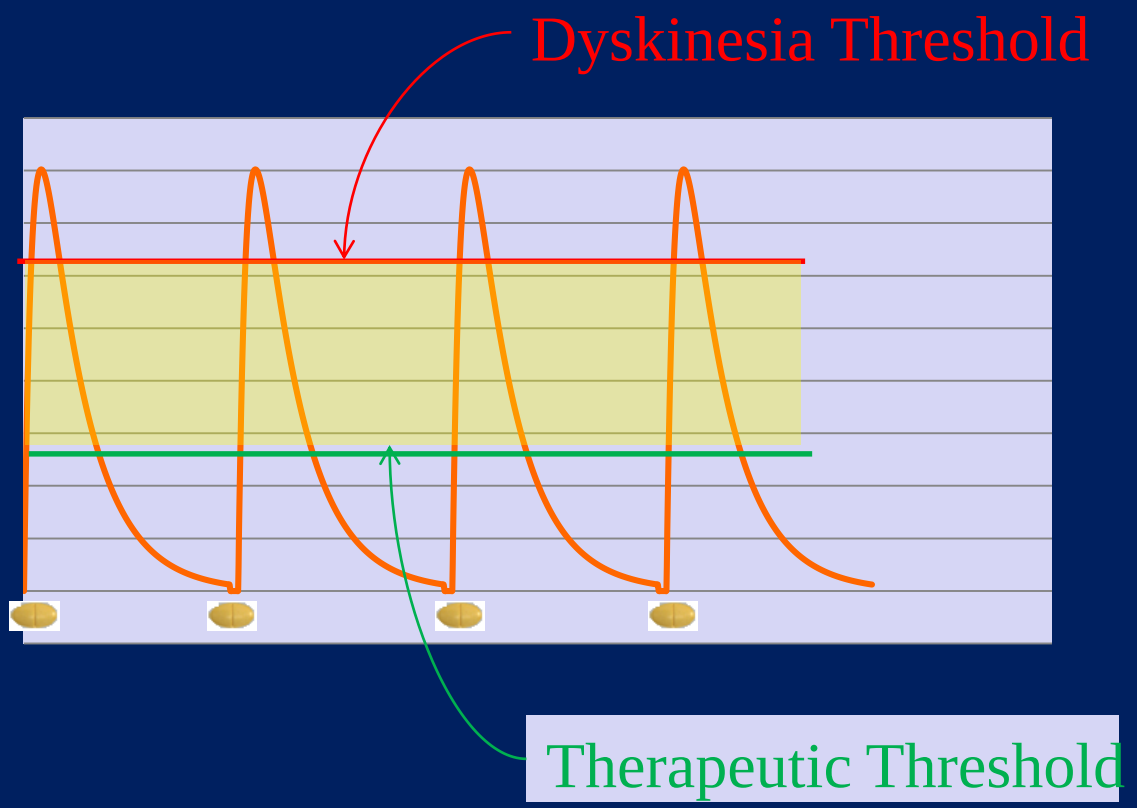


Figure 3: Timing of treatment-emergent adverse events reported by >10% of patients

(Olanow et al 2014)

Management of Dyskinesias

- Take smaller but more frequent doses of levodopa
- Amantadine, Amantadine ER (Gocovri)
- Deep Brain Stimulation

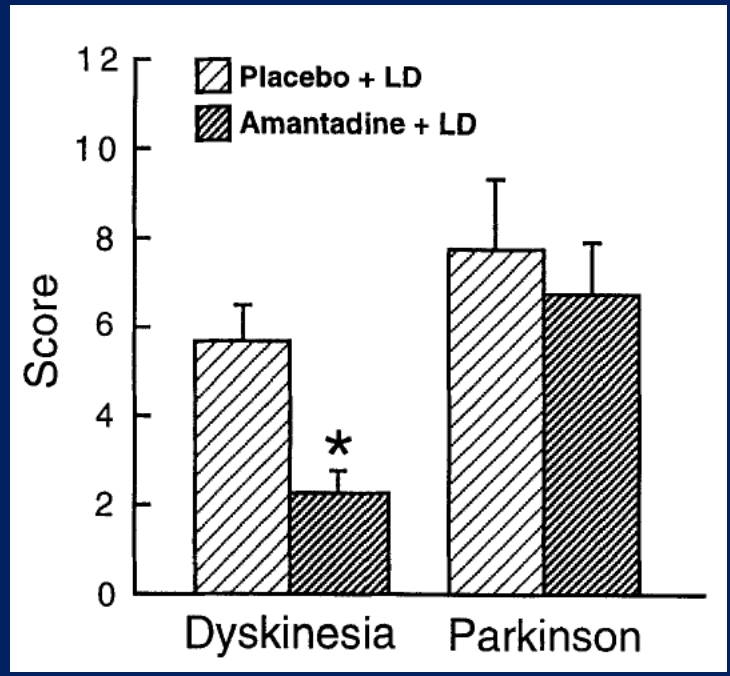


Amantadine

- Has inhibitory effects against influena virus; indicated as anti-viral agent in 1960's
- Tried in PD in and found to help PD motor symptoms
- Began to be used to treat dyskinesias in 1990's
- Thought to antagonize glutamate NMDA receptors and cholinergic muscarinc receptors, thought to play a role in development of dyskinesias. Also increases dopamine synthesis

Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease

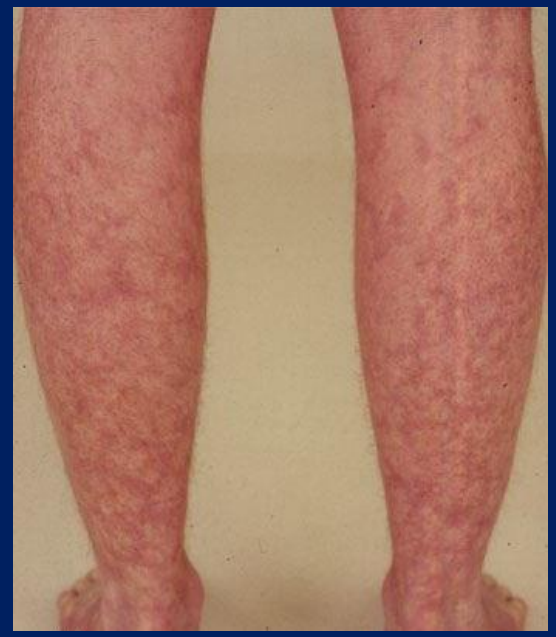
- Double-blind, placebo-controlled, cross-over study
- Eighteen patients with advanced PD
- Patients received 100 mg, 3-4 times per day
- Evaluated during an IV levodopa infusion, along with carbidopa
- Subsequent studies confirmatory
- Benefit persists over time (Ory-Magne et al 2014)



(Verhagen et al 1998)

Amantadine: Adverse Effects

- Neuropsychiatric
- Withdrawal syndrome
- Serotonin Syndrome
- Impulse Control Disorders?
- Orthostatic hypotension
- Livedo reticularis (40%)
- Corneal problems
- Peripheral edema
- Somnolence



Amantadine ER (Gocovri)

- Long-acting formulation
- Taken once daily at bedtime
- Formulated to slowly rise during sleep achieving high levels during waking hours
- May be better tolerated than Amantadine IR

	Pahwa et al. (2015)	Pahwa et al. (2017)	Oertel et al. (2017)
Amantadine dose (mg)	340	274	274
Constipation (%)	23.8 vs 9.1	15.9 vs 5.0	8.1 vs 0
OH symptoms (%)	28.6 vs 4.5	22.2 vs 0	10.8 vs 0
Hallucination (%)	23.8 vs 0	31.7 vs 1.7	8.1 vs 5.3
Dry mouth (%)	19.0 vs 0	17.5 vs 0	13.5 vs 2.6
Confusion (%)	14.3 vs 4.5	–	–
Nausea (%)	14.3 vs 4.5	–	13.5 vs 2.6
Edema (%)	–	23.8 vs 0	–
Livedo reticularis (%)	–	9.5 vs 0	–

Percentage of patients with each adverse event in the amantadine vs placebo groups is shown

OH orthostatic hypotension

(Perez-Lloret 2018)

Conclusions/Summary

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