

# *Dopamine Drugs: Why do their beneficial effects fluctuate?*

September 26, 2010



TEXAS A&M

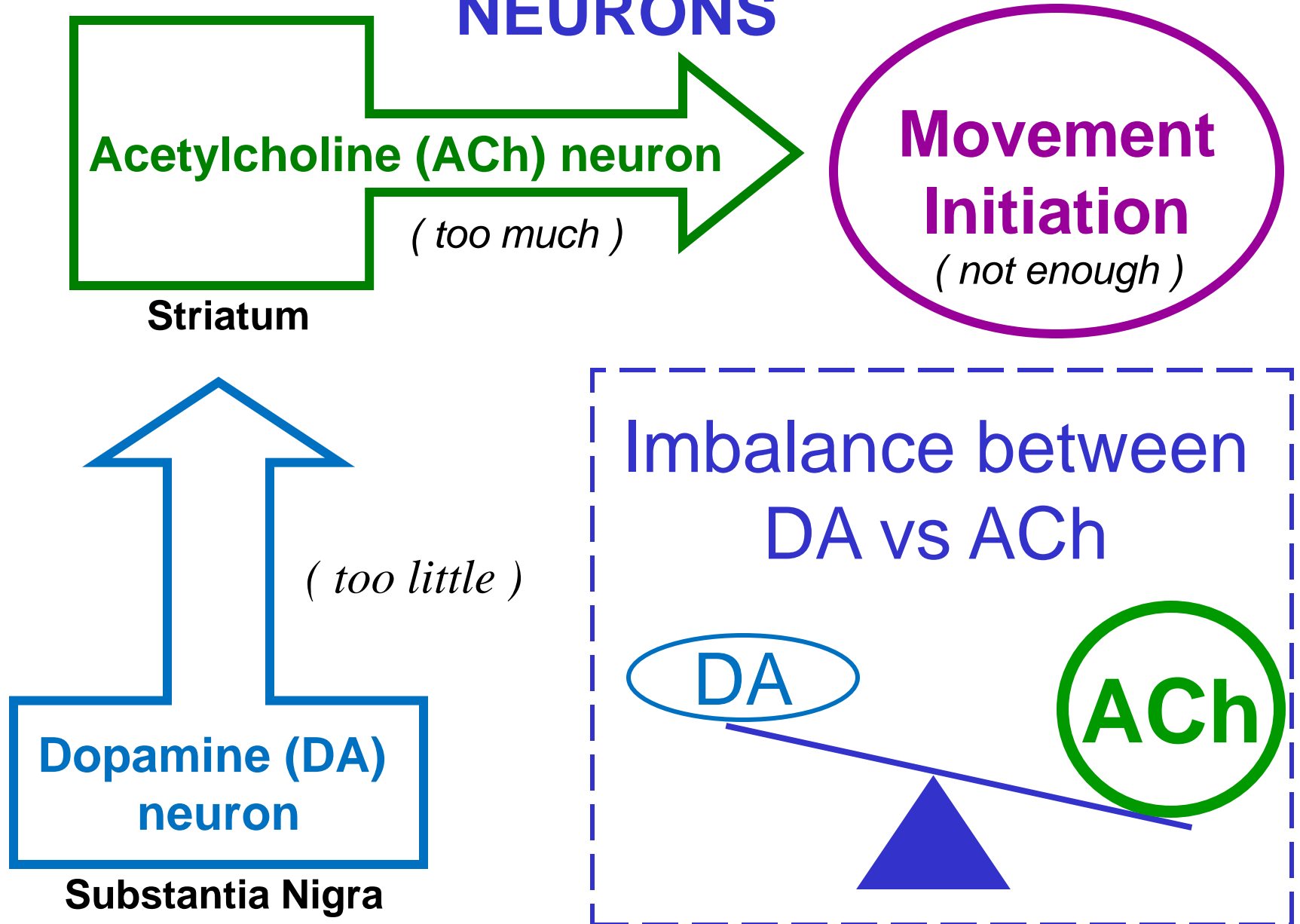
HEALTH SCIENCE CENTER  
COLLEGE OF MEDICINE

Gerald (Gerry) D. Frye  
Joseph H. Shelton Professor of  
Neuropharmacology &  
Neurotoxicology  
Department of Neuroscience and  
Experimental Therapeutics

Phone: 979-845-2888; E-mail:  
gdfrye@medicine.tamhsc.edu  
<http://medicine.tamhsc.edu/basic-sciences/next/faculty/gerald-frye.html>



# LOSS of NIGRO-STRIATAL DOPAMINE NEURONS



# Why are some PD drugs used in combination

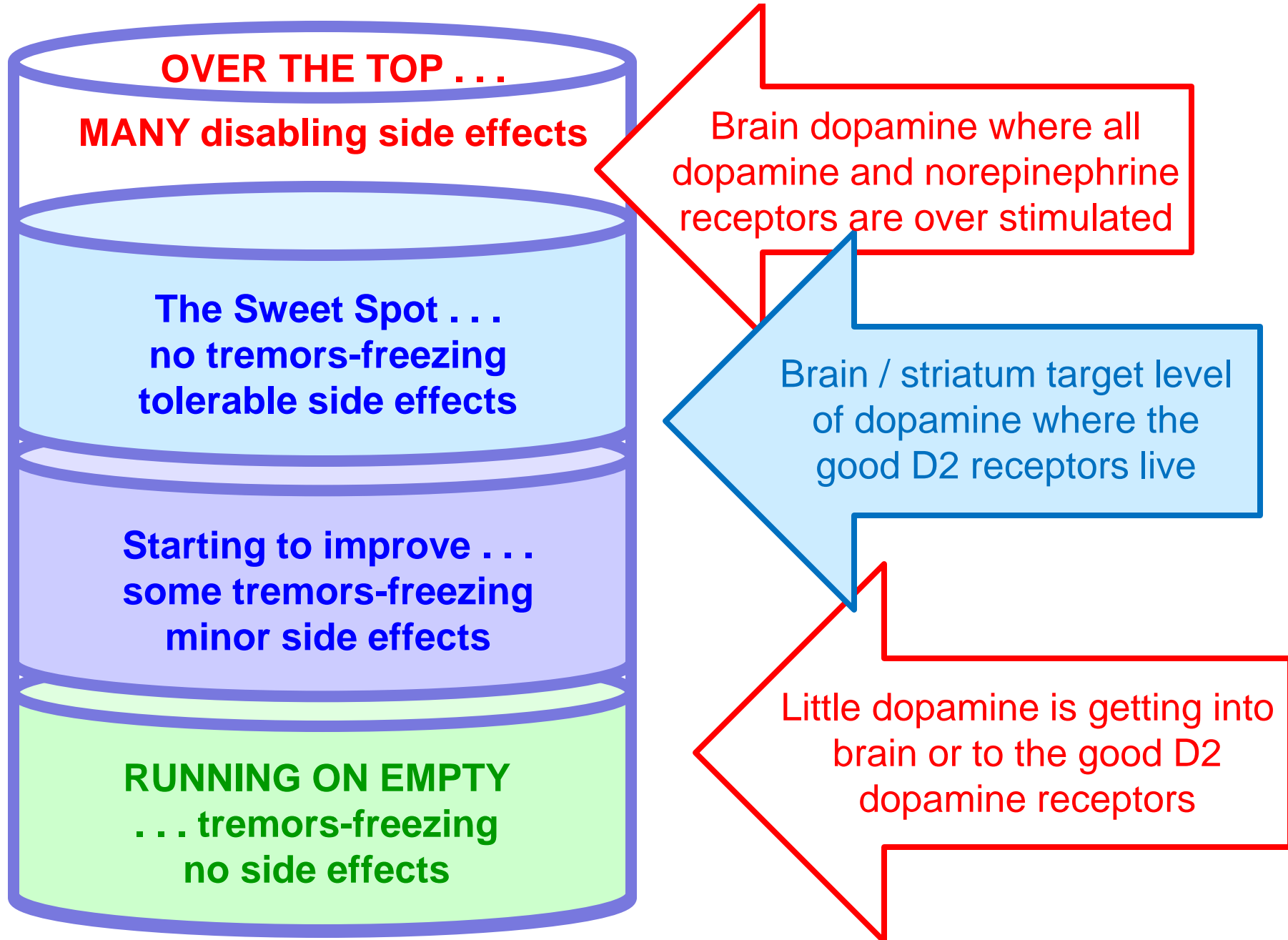
**No single drug is a magic bullet!**

THE GOAL for combining drugs:

- - Increase effectiveness of treatment.
- - Decrease side-effects of treatment.

Some drugs are always taken together (e.g. Sinemet = Levo-dopa + carbidopa) - carbidopa alone has no anti-PD effects but improves Levo-dopa effects / reduces side-effects!

# Keeping the Glass Half Full is the Challenge?



# Keeping the Glass Half Full IS THE Challenge !

<u>Dose Number/Time</u>	<u>Drug</u>	<u>Strength</u>	<u>Amount</u>	<u>Type</u>	
1	6:00 a.m.	<u>Sinemet</u>	25/100	1 tablet	PD
		<u>Mirapex</u>	1 mg	½ tablet	PD
2	9:00 a.m.	<u>Sinemet</u>	25/100	1 tablet	PD
		<u>Mirapex</u>	1 mg.	½ tablet	PD
		<u>Amantadine</u>	100 mg.	1 tablet	PD
		<u>Aspirin</u>	81 mg.	1 tablet	PD
3	12:00 noon	<u>Sinemet</u>	25/100	1 tablet	PD
		<u>Mirapex</u>	1 mg.	1 tablet	PD
4	3:00 p.m.	<u>Sinemet</u>	25/100	1 tablet	PD
5	5:30 p.m.	<u>Sinemet</u>	25/100	1 tablet	PD
		<u>Mirapex</u>	1 mg.	1 tablet	PD
		<u>Metoprolol</u>	25 mg.	1 tablet	BP
6	9:00 p.m.	<u>Amlodipine</u>	10 mg.	1 tablet	BP
		<u>Aricept</u>	5 mg.	1 tablet	MD
		<u>Sinemet</u>	25/100	1 tablet	PD
		<u>Clonidine</u>	0.1 mg.	1 tablet	BP*

\* Rescue drug used if and when systolic BP exceeds 180.

(Type abbreviation – PD = Parkinson's disease, BP = Blood pressure, BT = Blood thinner and MD = Mind drug.)

<u>Daily dosages:</u>	<u>Drug</u>	<u>Strength</u>	<u>Amount</u>	<u>Total</u>
	<u>Sinemet</u>	25/100	6 tablets	600 mg.
	<u>Metoprolol</u>	25 mg.	1 tablet	25 mg.
	<u>Mirapex</u>	1 mg.	3 tablets	3 mg.
	<u>Amantadine</u>	100 mg.	1 tablet	100 mg.
	<u>Aspirin</u>	81 mg.	1 tablet	81 mg.
	<u>Amlodipine</u>	10 mg.	1 tablet	10 mg.
	<u>Aricept</u>	5 mg.	1 tablet	5 mg.



# Keeping the Glass Half Full is the Challenge?

RESPONSE  
(improvement)

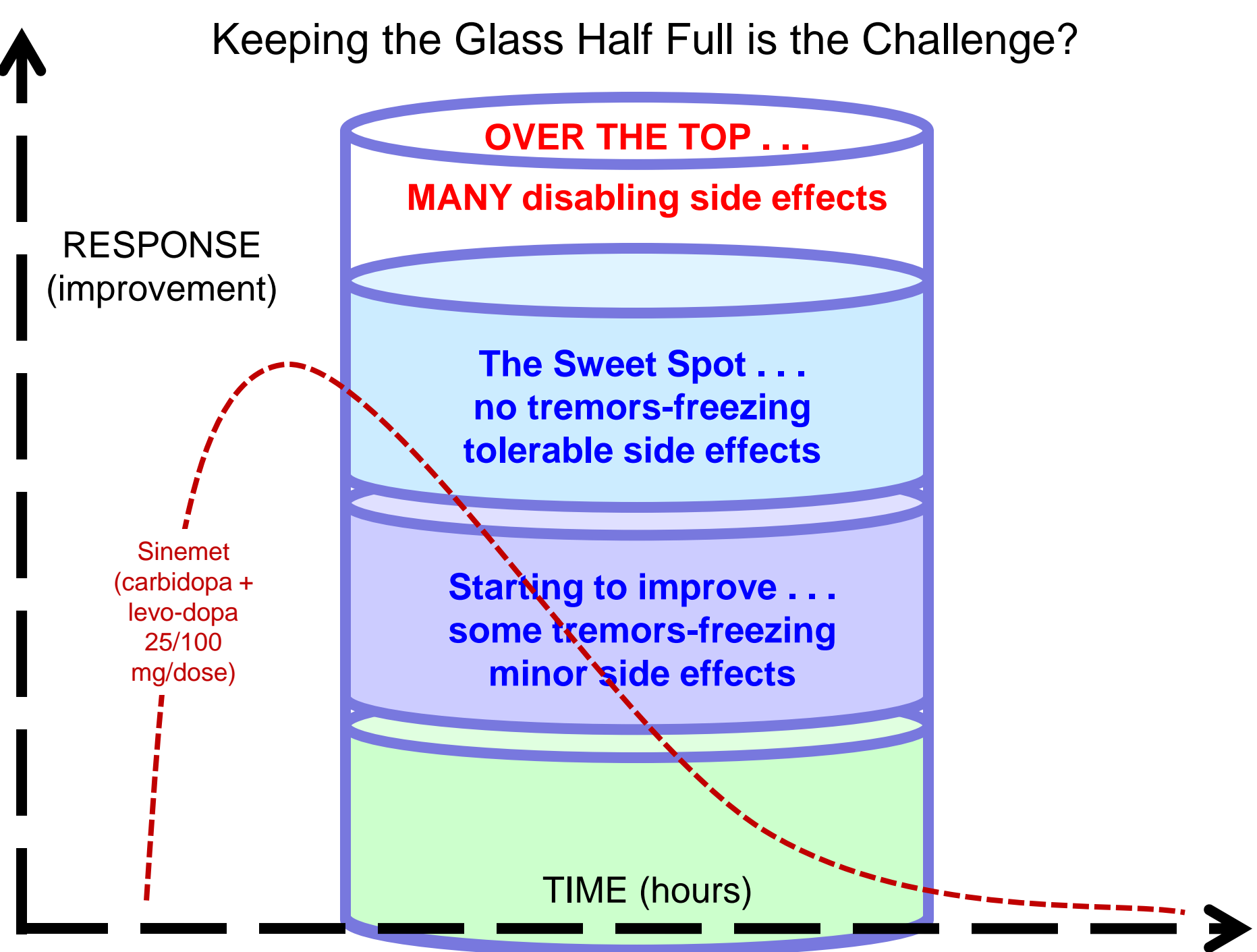
Sinemet  
(carbidopa +  
levo-dopa  
25/100  
mg/dose)

**OVER THE TOP . . .**  
**MANY disabling side effects**

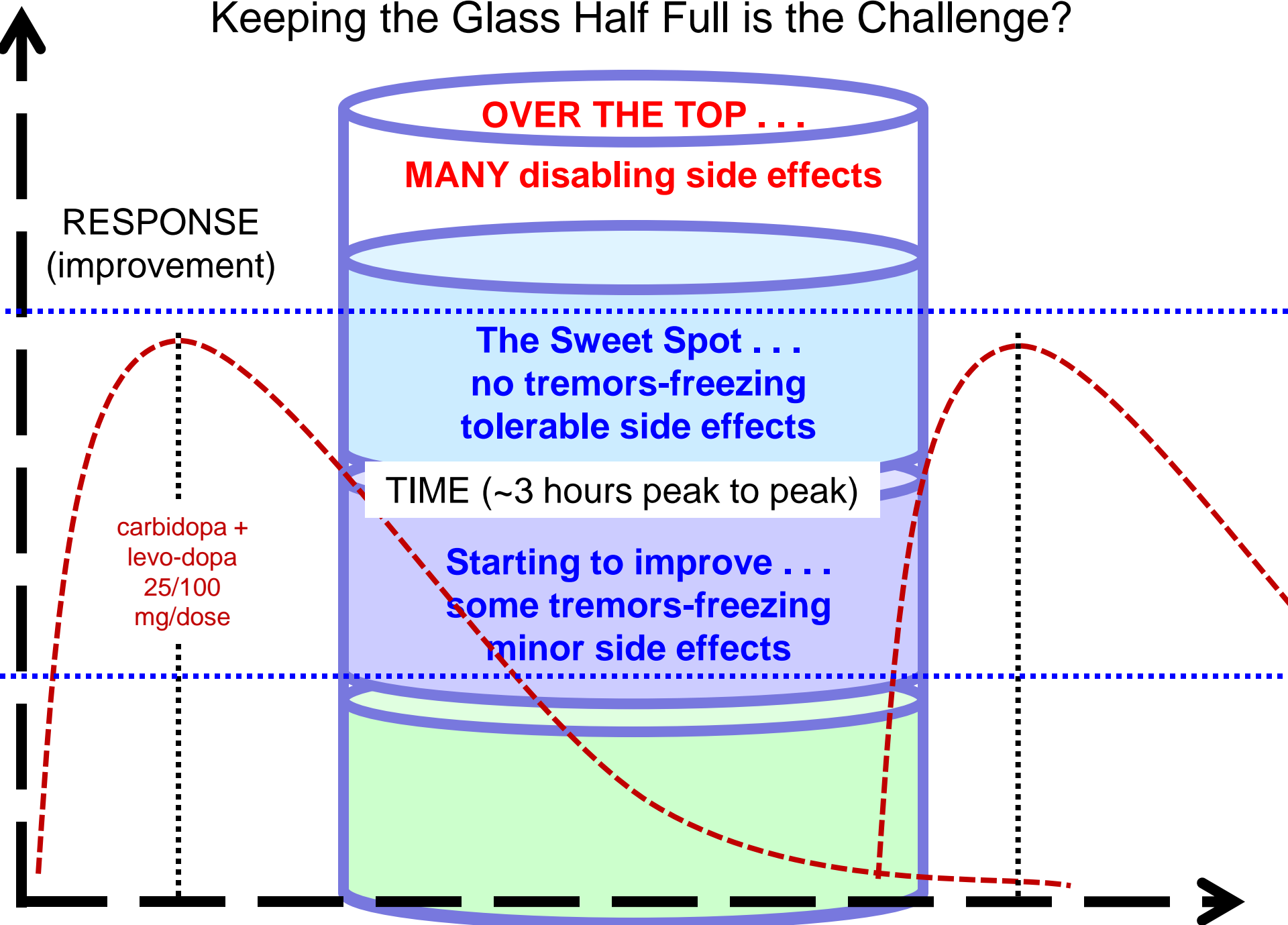
**The Sweet Spot . . .**  
**no tremors-freezing**  
**tolerable side effects**

**Starting to improve . . .**  
**some tremors-freezing**  
**minor side effects**

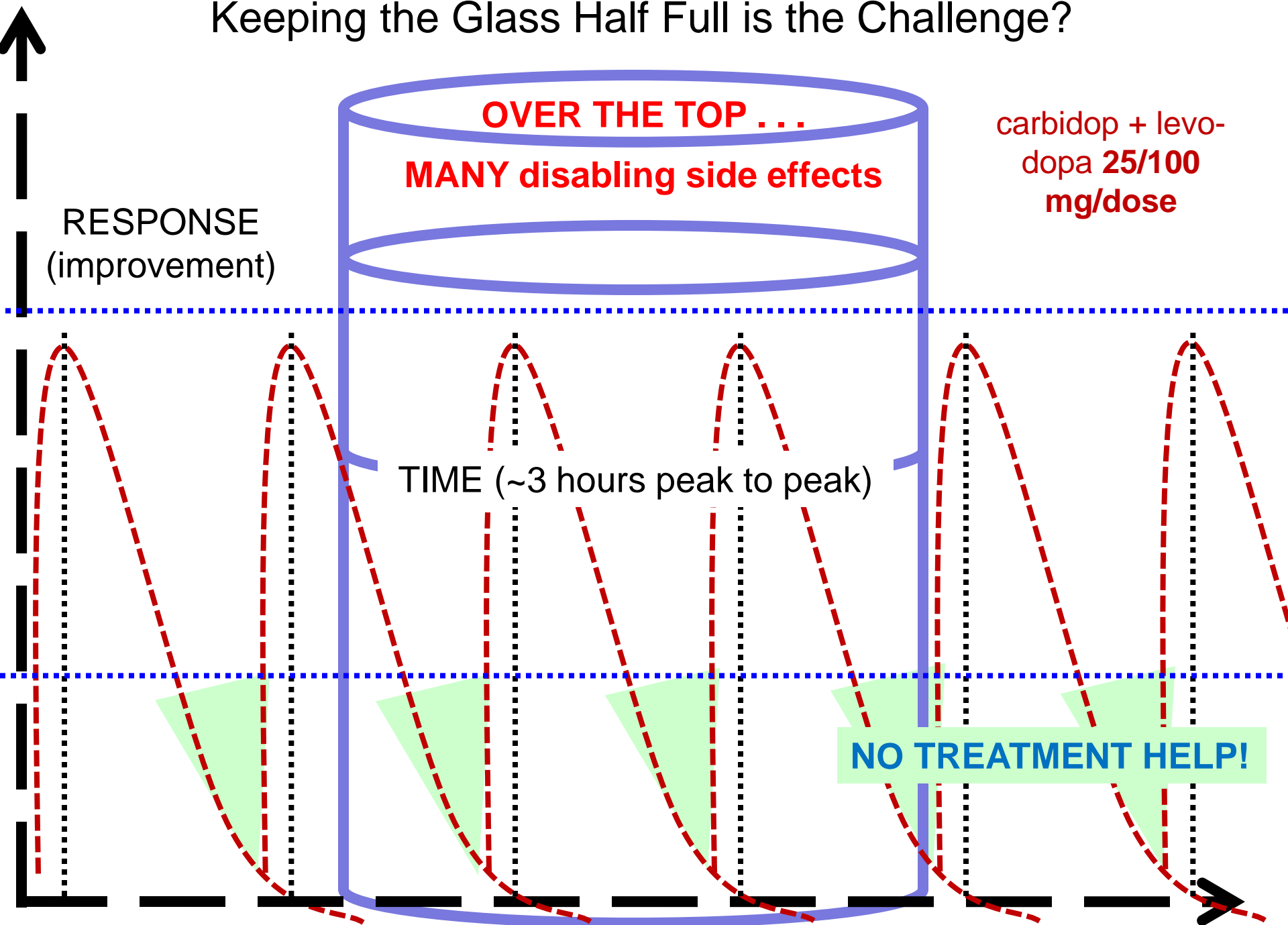
TIME (hours)



# Keeping the Glass Half Full is the Challenge?



# Keeping the Glass Half Full is the Challenge?



# Keeping the Glass Half Full is the Challenge?

carbidop + levo-  
dopa 25/100  
mg/dose

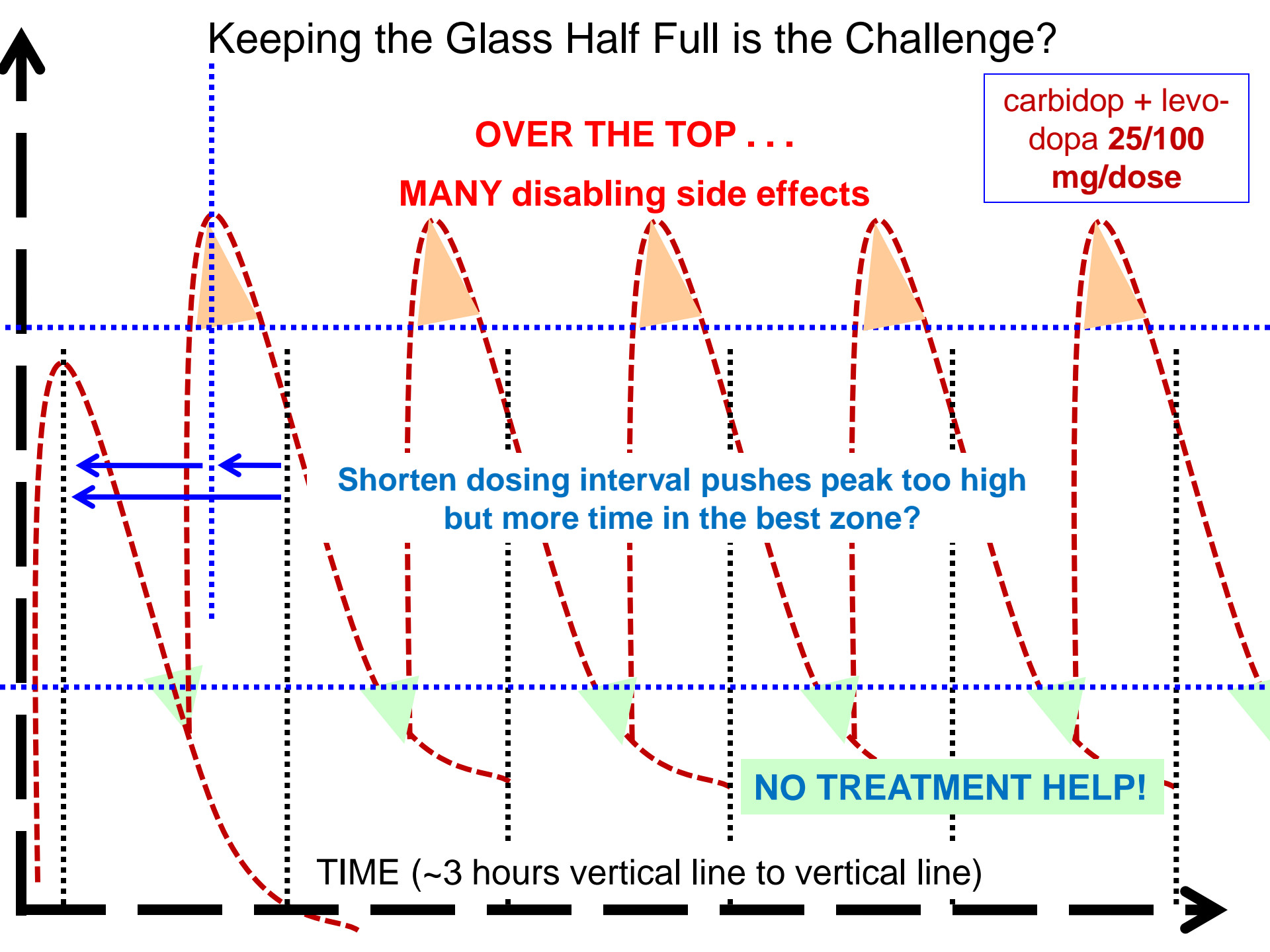
**OVER THE TOP . . .**

**MANY disabling side effects**

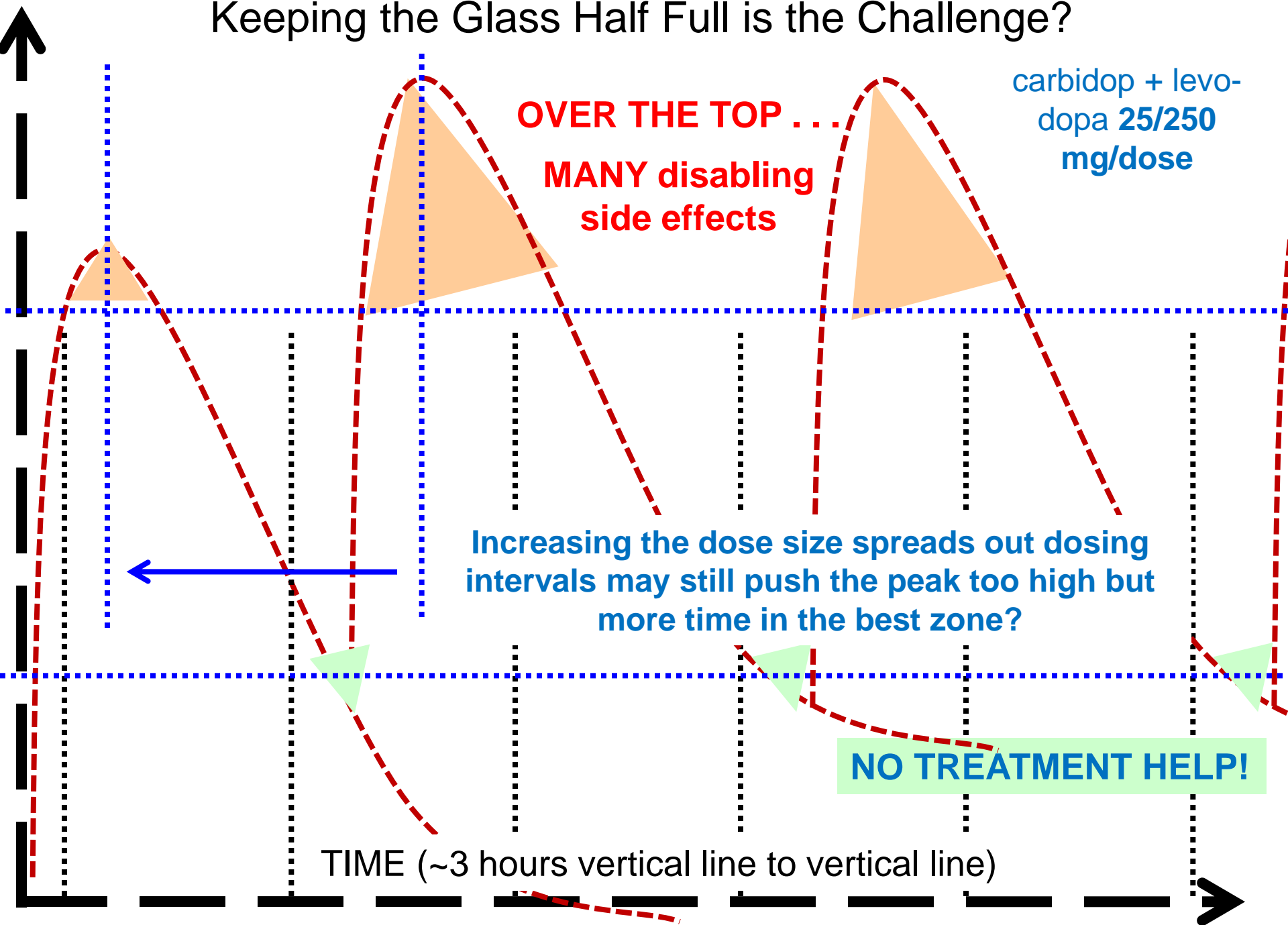
Shorten dosing interval pushes peak too high  
but more time in the best zone?

**NO TREATMENT HELP!**

TIME (~3 hours vertical line to vertical line)



# Keeping the Glass Half Full is the Challenge?

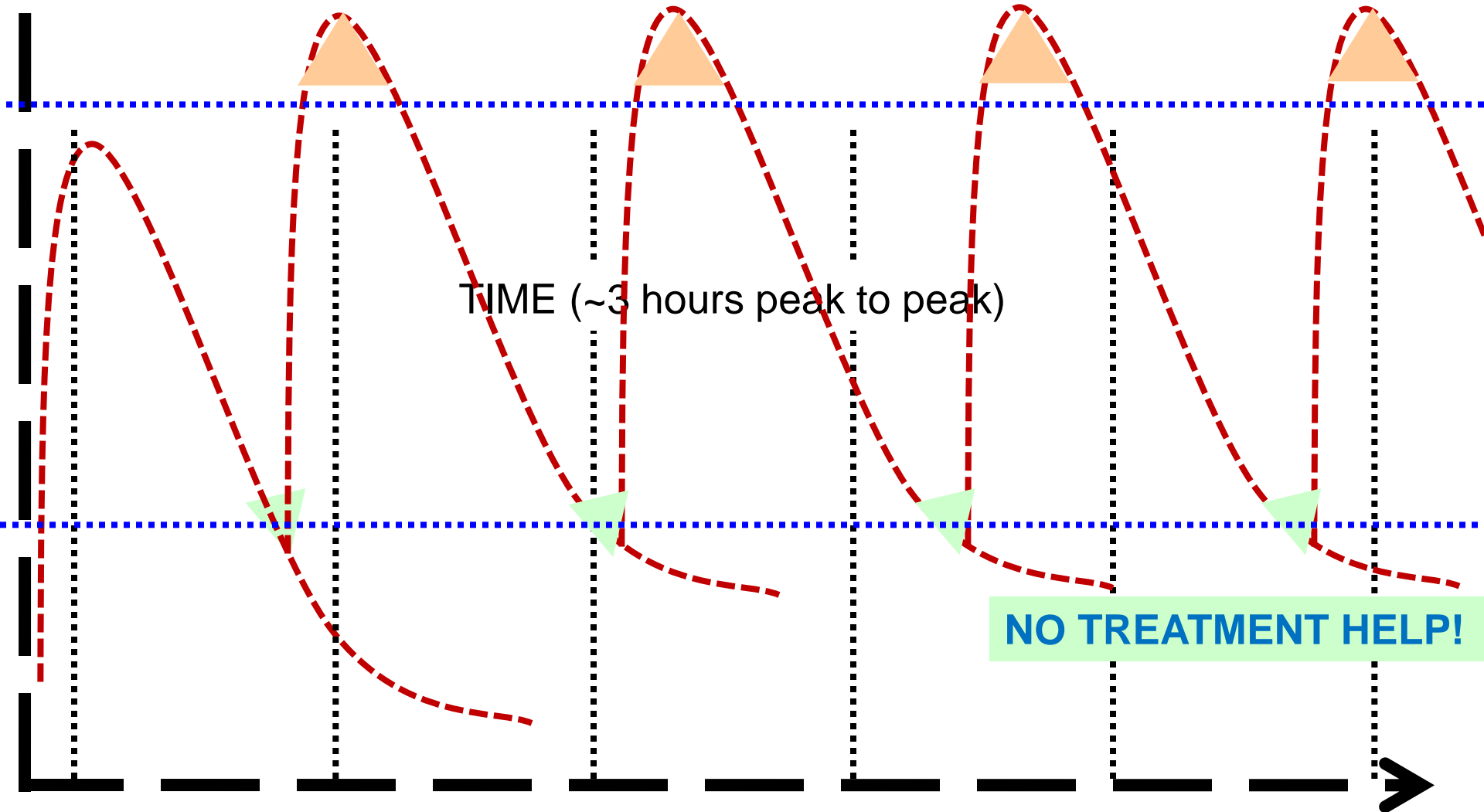


# Keeping the Glass Half Full is the Challenge?

**Add  
entocapone or  
selegiline?**

**OVER THE TOP ...  
MANY disabling side effects**

carbidop + levo-  
dopa + entocapone  
**25/100/200  
mg/dose)**

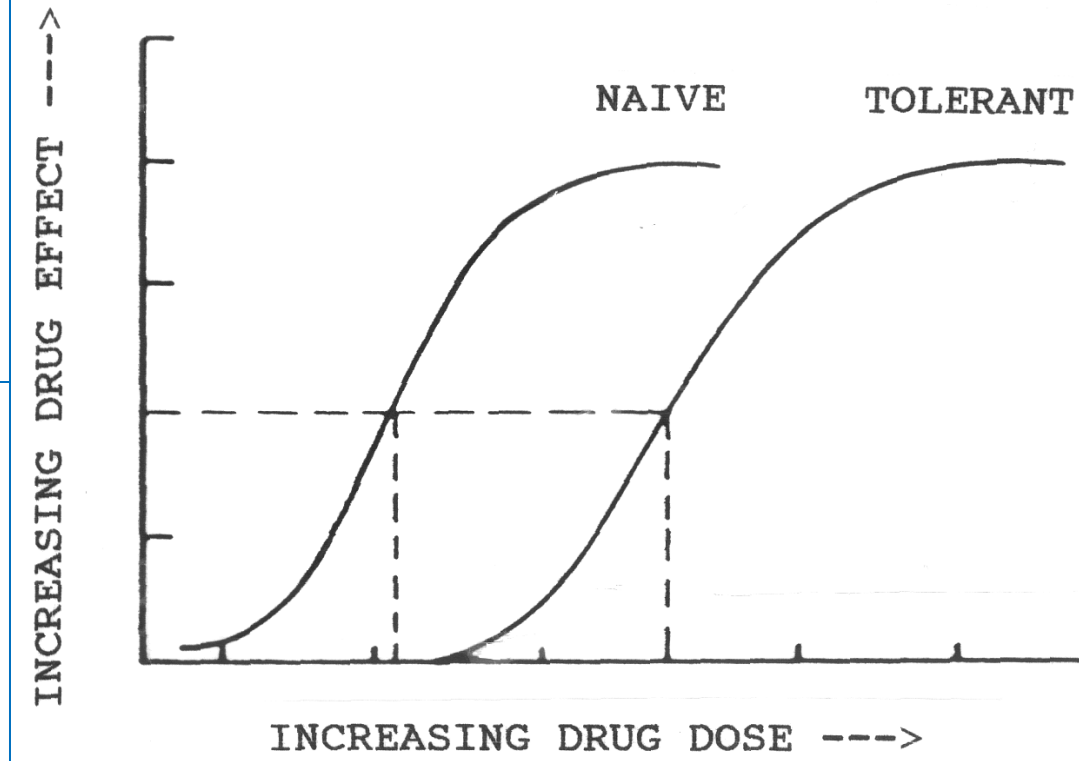


# Tolerance = Decreased Responses to a Drug!

**No good evidence that tolerance develops to L-Dopa**

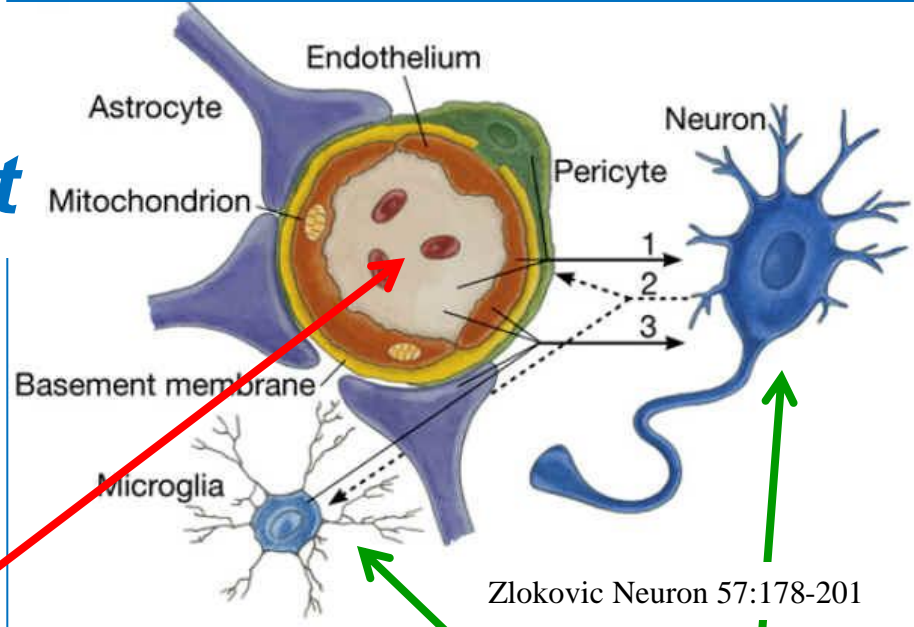
**Metabolic or Dispositional Tolerance**  
is accelerated drug clearance

**Behavioral or Learned Tolerance**  
learning offsets impairment

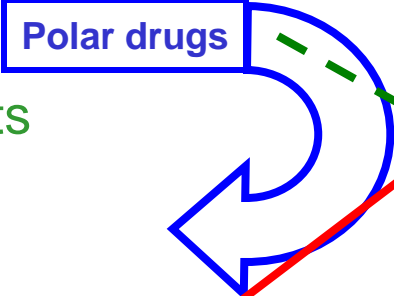


**Functional or Cellular Tolerance - neuronal resistance**

# Blood Brain Barrier Pharmacological Impact



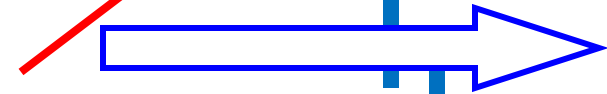
diphenoxylate



Antidiarrheal effects

morphine

Constipation



heroin

Constipation



Weak CNS effects

Strong CNS effects

Faster / stronger /  
euphoric effects

**BLOOD**

**BRAIN**

**OTHER EXAMPLES:**

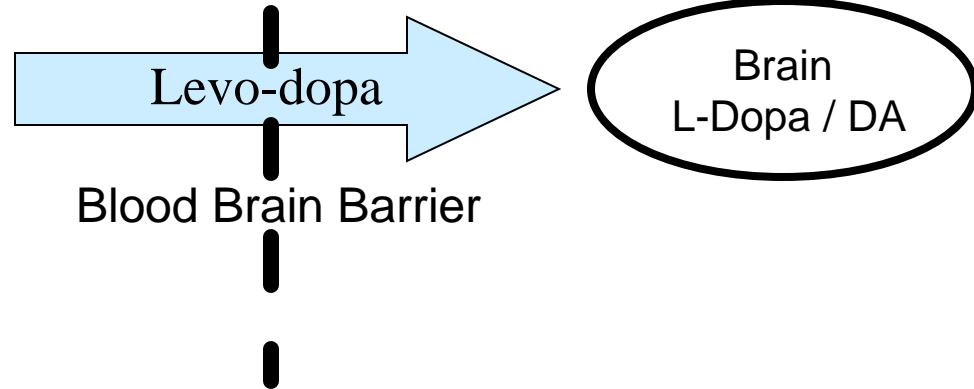
L-dopa vs carbidopa & dopamine

diphenhydramine vs loratidine

# Levo-dopa Therapy

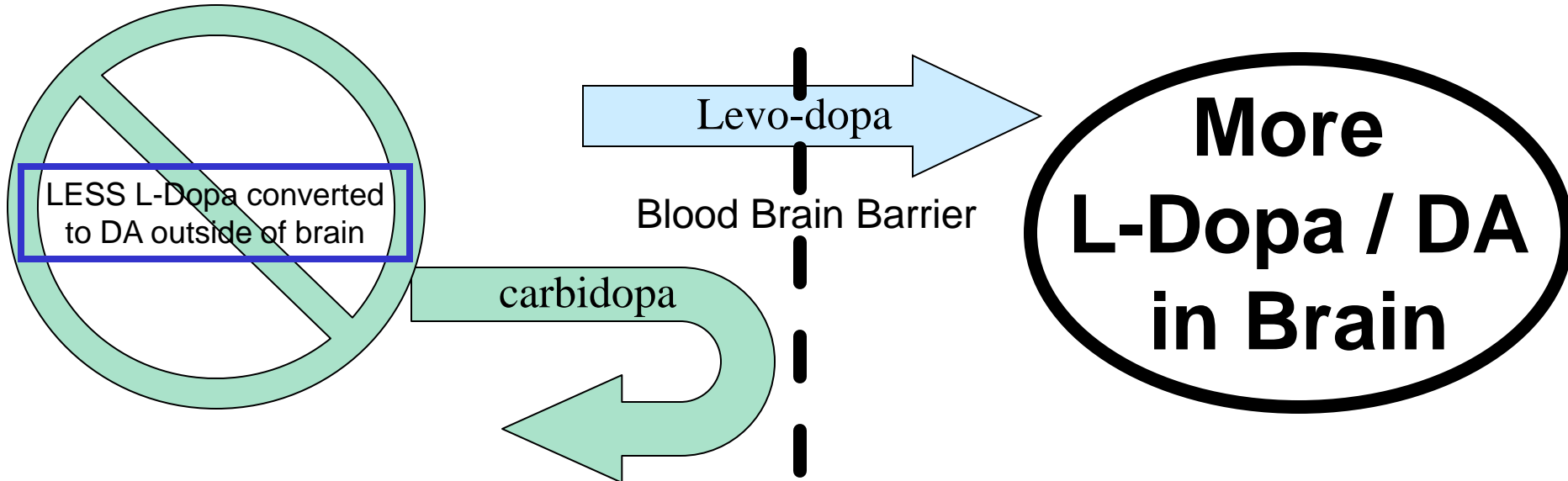
## L-Dopa therapy alone

**MOST L-Dopa converted to dopamine (DA) outside of brain**

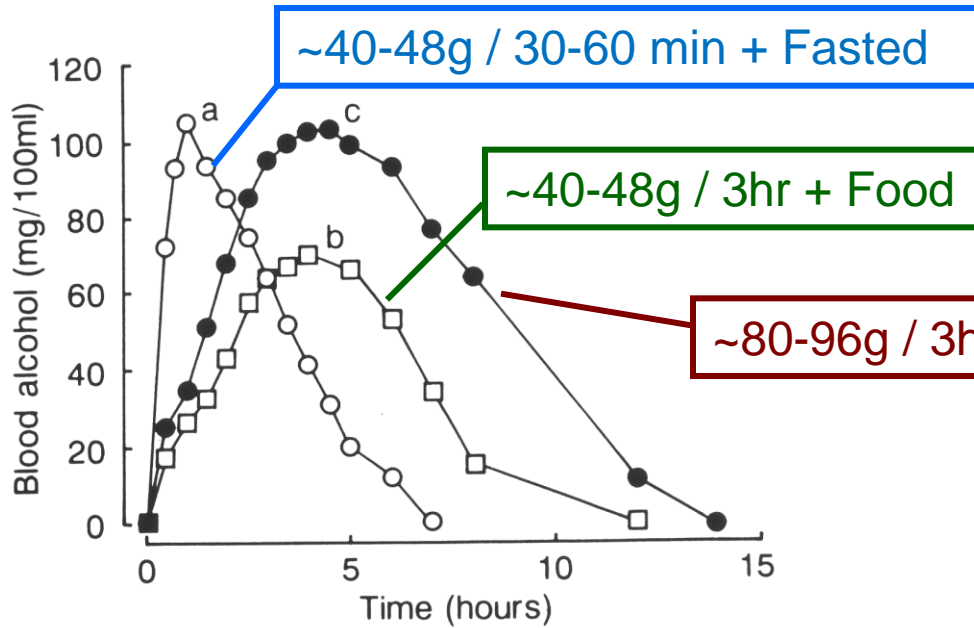


## L-Dopa + carbidopa or entacapone

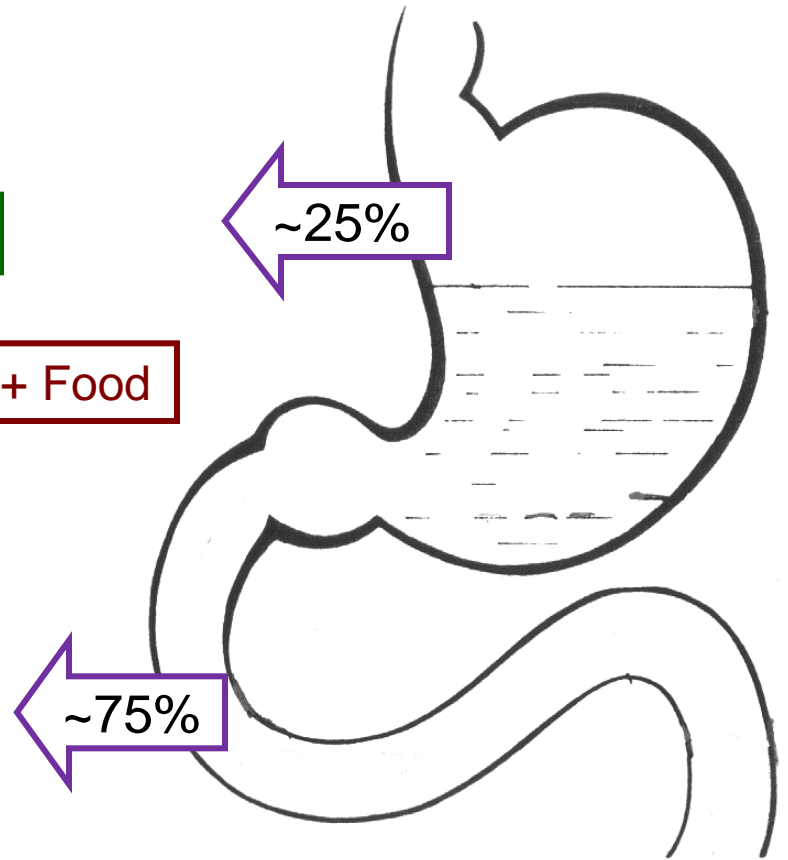
**LESS L-Dopa converted to DA outside of brain**



# After Oral Ethanol / L-Dopa Consumption



Alcohol passes easily from small intestine no pumps required.



**No tissue barriers to Alcohol – BUT there are to L-dopa / dopamine! They cross into the blood unevenly – mainly from upper small intestine.**

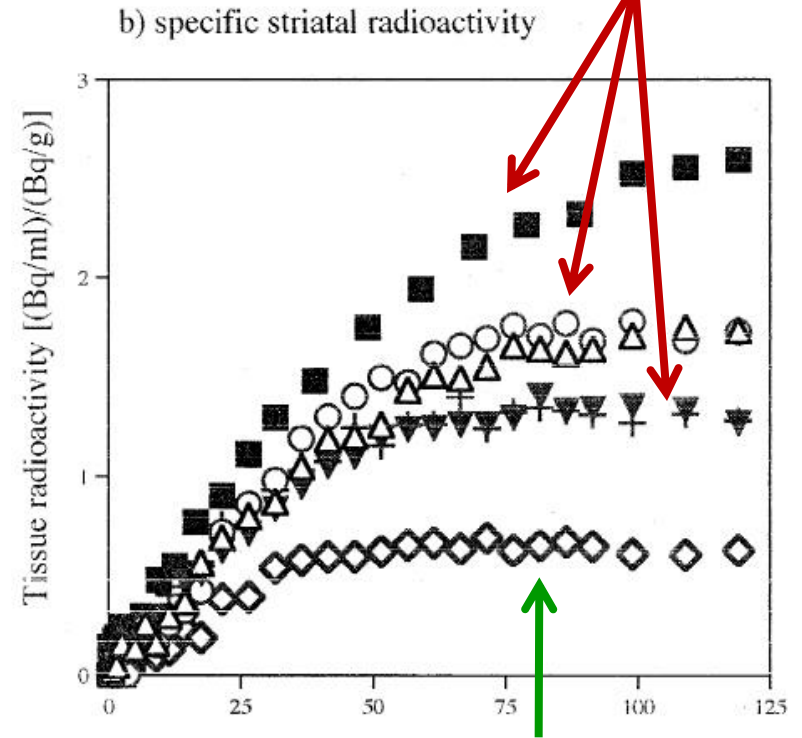
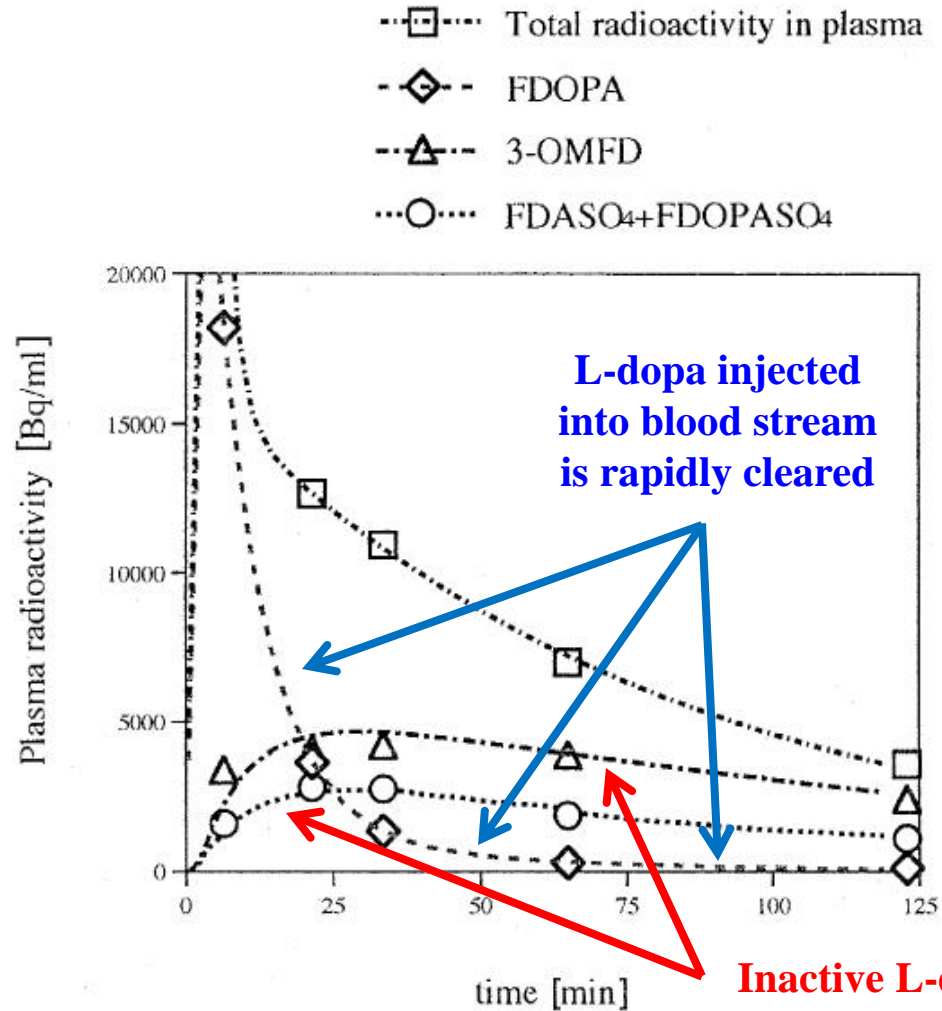
Food slows absorption by slowing stomach emptying

# Absorbed Dopa rapidly metabolized by enzymes

Radioactive tracer studies in rhesus monkeys

## AAAD or COMT

**L-dopa in brain after injection into blood stream with AAAD and/or COMT inhibitors**



Psylla et al., 1997 Brain Res. 767:45-54, 'Cerebral 6-[<sup>18</sup>F]fluoro-L-DOPA uptake in rhesus monkey: pharmacological influence of aromatic amino acid decarboxylase (AAAD) and catechol-O-methyltransferase (COMT) inhibition'

# Modified L-Dopa to improve absorption - EXPERIMENTAL

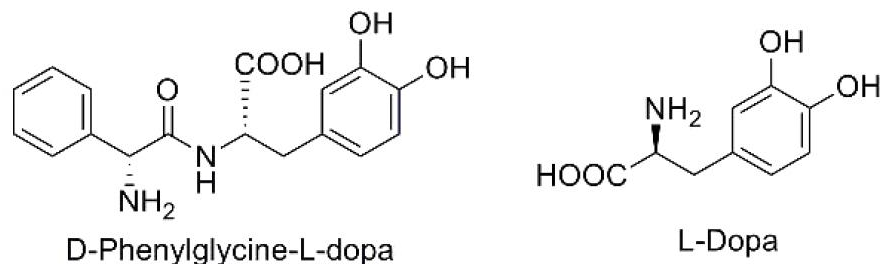


Figure 1 The structures of *d*-phenylglycine-*l*-dopa and *l*-dopa.

## Absorption fraction calculations

$$BA = \frac{\frac{AUC_{oral} \cdot k_{oral}}{dose_{oral}}}{\frac{AUC_{iv} \cdot k_{iv}}{dose_{iv}}} \times 100\%$$

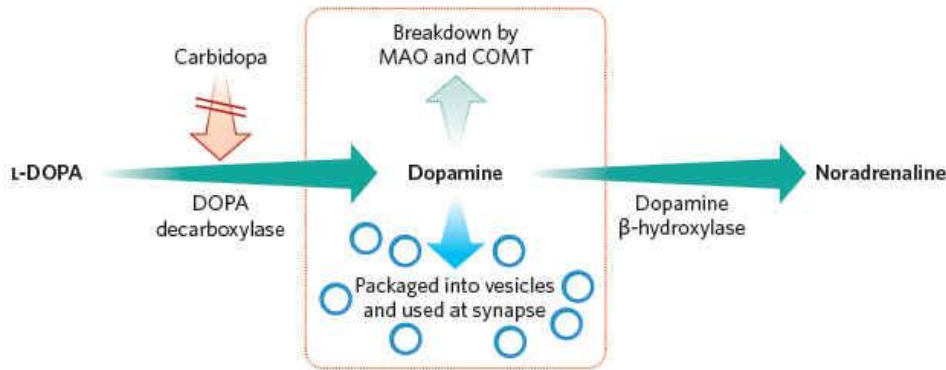
By linking L-dopa to an amino acid (D-phenylglycine) scientists have created a small peptide (protein) that gets taken up across the small intestine by the PepT1 transporter.

## HOW IT WOULD WORK?

L-dopa (amino acid like) + L-dopa-D-phenylglycine (peptide) = TWICE AS MUCH L-dopa getting in to brain. BUT the peptide takes longer to be broken down to dopamine (LONGER DOPAMINE DOSING)

Wang et al., 2010 J. Biomed. Sci. 17:71, 'Evidence of d-phenylglycine as delivering tool for improving *l*-dopa absorption'

# The Next Big Thing in PD Therapy?



In the early days, dopamine was only a precursor to make norepinephrine! Abbott Nature August 26, 2010 [www.nature.com/outlooks](http://www.nature.com/outlooks) p56-57.



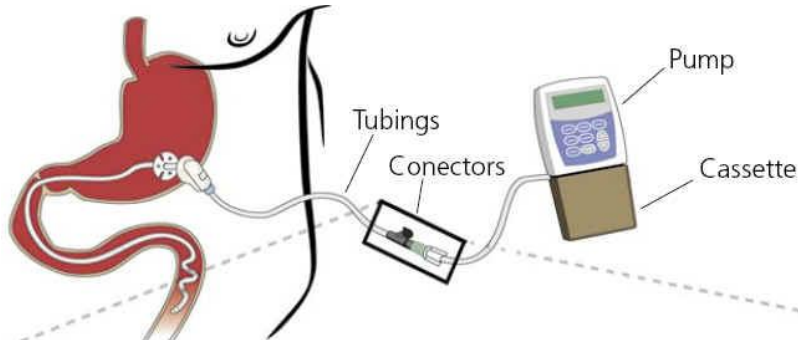
## Trickle down L-dopa therapy? Duodopa!!!!!!!!!!!!

### Contents

Duodopa contains the following:

- Levodopa (L-dopa) 20 mg/ml
- Carbidopa 5 mg/ml
- Thickening agent (Carmellose sodium)
- Water

A 100 ml cassette contains 2000 mg of L-dopa and 500 mg of carbidopa.  
(1 ml contains 20 mg L-dopa and 5 mg carbidopa).



**53 years since dopamine is found to be a transmitter!**  
Arvid Carlsson a Swedish scientist wins the 2000 Nobel Prize in Medicine for discovering dopamine is a transmitters / l-dopa as a precursor. Abbott, Nature 447:368-370, 2007.

“I won it 40 years after my discovery,” he jokes. “Einstein won his some 20 years after his discovery. So I guess my work was twice as complicated as Einstein’s.”

“What is clear is that stabilizing the blood levels greatly ameliorates these undesirable effects. “

by Alison Abbott is *Nature's Senior European Correspondent.*

# Steering between Benefits / Side Effects . . . . the Ever Present Challenge for Dopamine Therapy

**Beneficial Effects of L-dopa**

Least Improved  
Tremor

Most Improved  
Bradykinesia, Rigidity,  
Depression

**Side-Effects of L-dopa**

Tachycardia  
Arrhythmia

Nausea, vomiting  
anorexia

Anxiety  
Agitation  
Insomnia

Dyskinesia

Orthostatic  
hypotension

Hallucination  
Delirium  
Psychosis

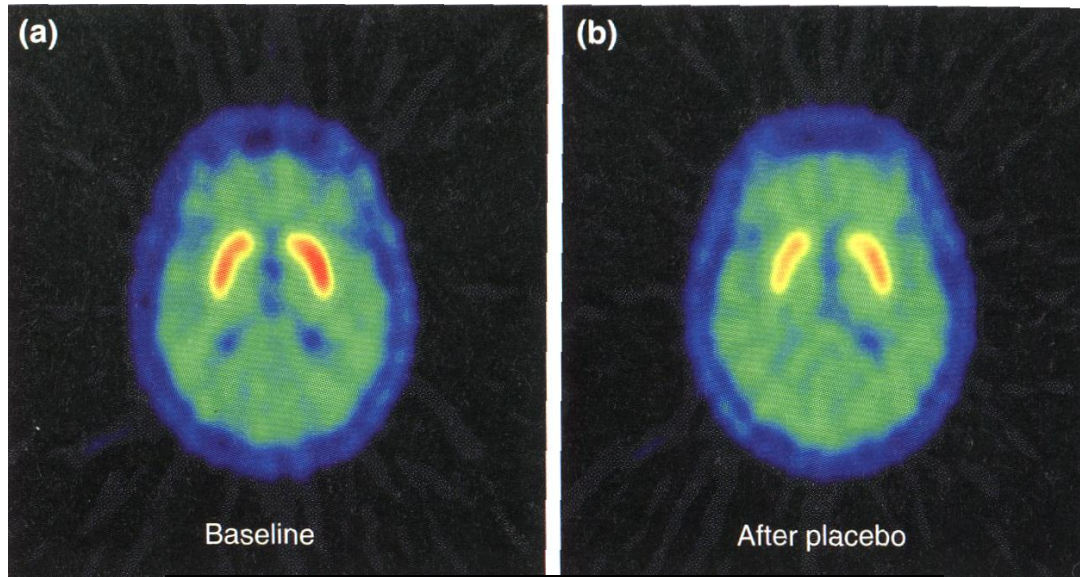


Scylla and Charybdis of the Greek Poet Homer's Odyssey guard a narrow waterway that is essential to pass.

# Take Advantage of the Placebo Effect Mechanism?

Untreated binding

Saline / placebo injection



Fuente-Fernandez & Stoessl TINDS 25: 302, 2002

On LEFT: Placebo treatment causes dopamine release that reduces labeling. (Axial [ $^{11}\text{C}$ ]-raclopride PET scan showing dopamine D2 receptor localization in the striatum of a PD volunteer)

Two Parkinson's patients and correlation between subjective report, arm rigidity, subthalamic nucleus neuron firing frequency (black arrow indicates giving placebo thought to be the potent D2 agonist apomorphine) LEFT placebo responder / RIGHT non-responder)

