Hudson Valley Community Seminar on Parkinson's disease and other Movement Disorders

Medical treatment of moderate to advanced PD

Patient and Caregiver Symposium

April 23, 2022

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WMC Health | MidHudson Regional Hospital
Westchester Medical Center Health Network

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All Roads Lead to Rome

One of the running themes for discussion in our office is the small world we live in. Although the Hudson Valley is huge, we always seem to be running into people who are connected.

A story linked to this year's Top Doctors feature is my new favorite small-world anecdote. Every year, we receive the list of Top Doctors from Castle Connolly Medical Ltd., a healthcare research and information company. Our team then selects a handful of doctors to interview for profiles in the article. We choose these doctors based on a variety of factors including specialty, hospital, medical group, location, and gender.

This year, out of 410 doctors on our list, we managed to pick two doctors with a very strong connection — which was only discovered during the interviews. Writer Melissa F. Pheterson first spoke to Fabio Danisi, MD, who mentioned going to medical school in Italy. That same evening she spoke to Barbara Chatr-Aryamontri, MD, who also mentioned studying in Italy. "I asked if she knew Dr. Danisi," says Melissa, not really expecting that she did. "She said, 'Yes, he's my husband.'"

When Melissa told me about this coincidence, I asked her to go back to the doctors and interview them as a married couple. That writeup didn't really work with our feature, so I'm sharing it here:

Collaboration and Cappuccino

Fabio Danisi, MD, and Barbara Chatr-Aryamontri, MD, met in their first year of medical school in Rome. In December, they celebrate their 25th anniversary.

As MidHudson Hospital's associate director of neurology, Dr. Danisi focuses on the treatment of movement disorders such as Parkinson's disease. As director of the sleep lab at HealthAlliance Hospital: Broadway Campus, Dr. Chatr-Aryamontri has restored harmony and peace to marriages, including her own, by helping couples get a good night's rest.

"At first, I really didn't believe I snored," says Dr. Danisi, when his wife insisted he become her patient. "I figured, she's a sleep doctor; she thinks the whole world snores. But our daughter said, 'Yes, Dad, I can hear it across the house!'" The diagnosis: mild sleep apnea.

"Fabio thought I should go to the sleep lab too, because I drink an enormous amount of coffee," says Dr. Chatr-Aryamontri.

"She won't speak to me until I bring her coffee. And it has to be cappuccino," Dr. Danisi adds.

Sharing and pooling their knowledge has allowed both to grow in their fields and provide better care. "Part of my expertise has evolved through working closely with Fabio for patients that needed my support," says Dr. Chatr-Aryamontri. "It's a unique niche to know so much about sleep disorders associated with movement disorders." Both also advocate for healthcare reform and draw attention to urgent public health matters, such as the looming crisis of Alzheimer's in an aging population.

She's a pulmonologist at a hospital in Kingston; he's a neurologist at a hospital in Poughkeepsie. They met in Rome, and found their way into our feature.

"It bores our children to tears to hear us talk shop at the dinner table," says Dr. Danisi. "But we learn a lot from each other. It's nice to compare notes, share stories, and have an extra set of eyes and ears."

In our feature on page 56, we present the full list of 410 Top Doctors, as voted on by their peers, and more interviews with physicians — although not nearly as intimate as this one.

Kathryn Walsh
Editor in Chief

PHOTO BY TOSHA TASAKI

Initial monotherapy - what are the choices?

(PHYSIOLOGIC) AGE & RISK OF:

- Motor complications
  - Younger patients at higher risk
  - PD onset before age 40 years is associated with a dyskinesia frequency of 94% after 5 years of treatment
- Short term side effects
  - Older patients more likely to experience sedation, cognitive impairment, psychosis, orthostasis
  - Symptomatic therapy must be tailored to individual characteristics
    - Clinical features such as: RLS? EDS? h/o ICD? Tremor predominant? Dystonia?
    - Comorbidities and concomitant medications
- R Kurlan: “Levodopa phobia”: A new iatrogenic cause of disability in Parkinson disease
  Neurology 2005

Symptomatic therapy prolongs survival

PD life expectancy:

1967: **9.4** years from onset to death [1]
1993: **13.1** [2]
2016: **14.6** (±7.7) years [3]

average PD onset age: 60 years
relevant comparator: 23.3 years

Observational prospective study of 198 pts followed for a mean of 18 months (15-20): [4]

- left untreated →
  - clinically important, possibly reversible **deterioration** in all eight domains of the PDQ-39
    - in motor and non-motor domains
      - cognition, bodily discomfort, emotional well being and communication
- treatment is started →
  - PDQ-39 scores remain stable and show no deterioration
    - regardless of whether they are prescribed levodopa or other anti-PD treatments

1. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967
2. Hughes et al. A clinicopathologic study of 100 cases of Parkinson's disease. Arch Neurol 1993.
3. De Pablo-Fernandez et al. Association of autonomic dysfunction with disease progression and survival in Parkinson disease. JAMA Neurol 2017
4. Grosset et al. Self reported health status in PD left untreated. JNNP 2007

Rajput et al. Timely levodopa (LD) administration prolongs survival in Parkinson's disease. Parkinsonism Relat Disord. 1997

Rajput AH. Levodopa prolongs life expectancy and is non-toxic to substantia nigra. Parkinsonism Relat Disord. 2001

"Based on these observations we conclude that PS survival is negatively influenced if LD use is delayed until H&Y Stage 2.5"

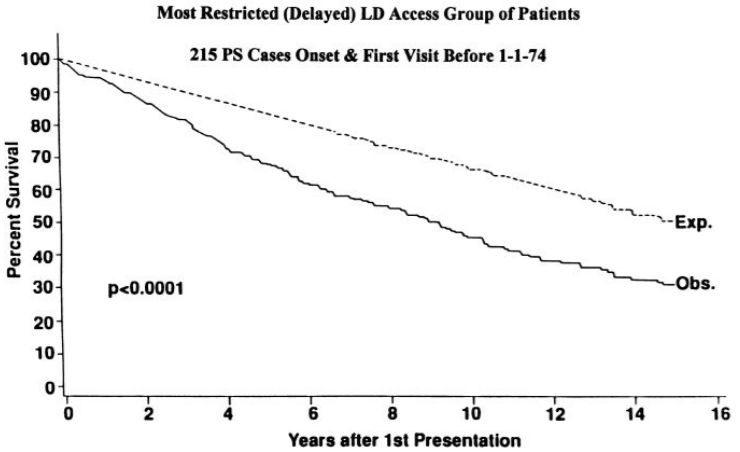


Fig. 2. Survival in 215 patients who had the most restricted levodopa access is compared with that expected in the regional matched population. Survival in the patients is significantly reduced.

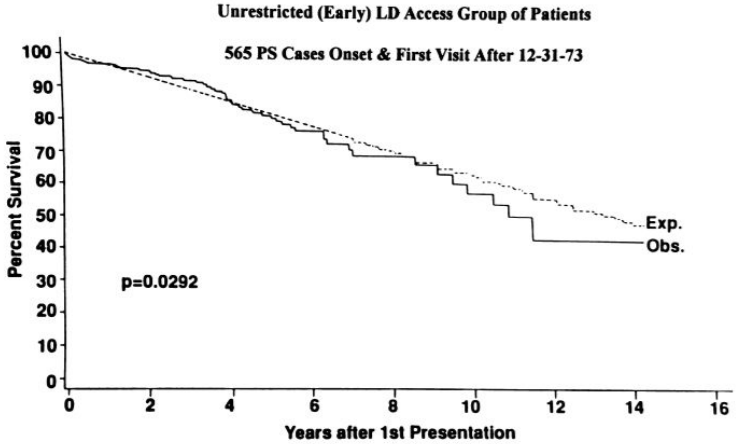
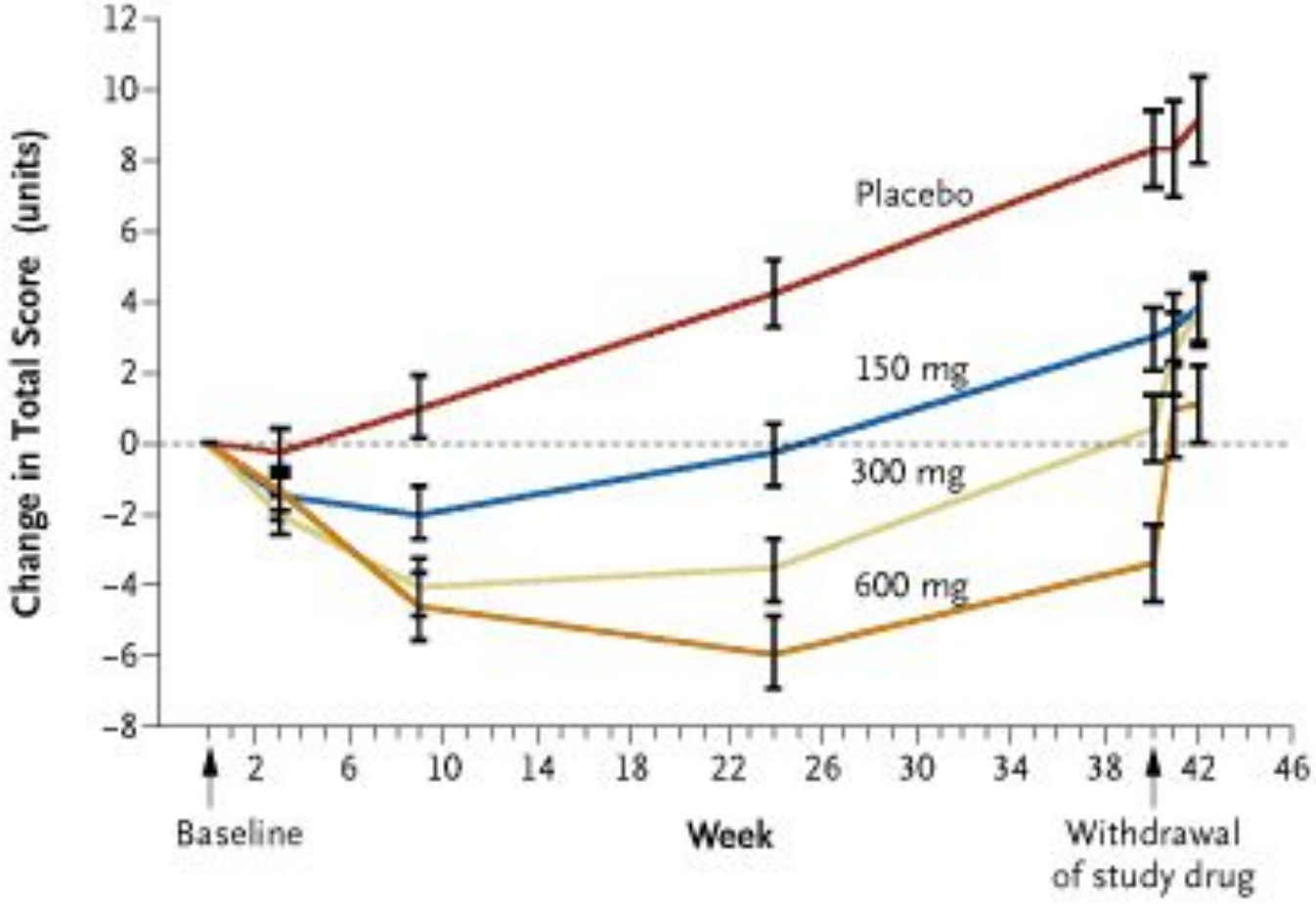


Fig. 3. Comparison of survival in 565 parkinsonian patients who had an unrestricted levodopa access compared with the age and sex matched regional population. The survival is significantly shorter in patients.

Elldopa study

Parkinson Study Group. NEJM 2004



Randomized delayed start trial of levodopa in 445 patients with PD:

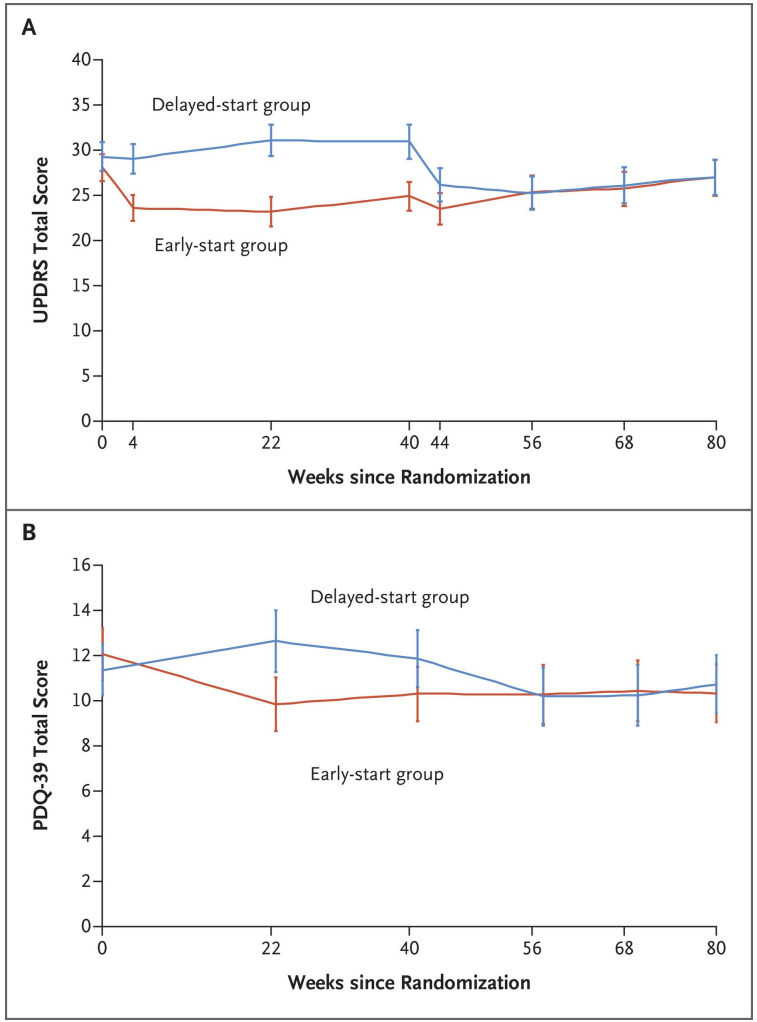
- 222 to the early-start group
- 223 to the delayed-start group

- Patients recruited from 50 community hospitals and 7 academic hospitals in the Netherlands [1]
  - carbidopa/levodopa 25/100 mg three times per day x 80 weeks (**early-start group**) ***vs***
  - placebo three times per day for 40 weeks followed by carbidopa/levodopa 25/100 mg three times per day for 40 weeks (**delayed-start group**)

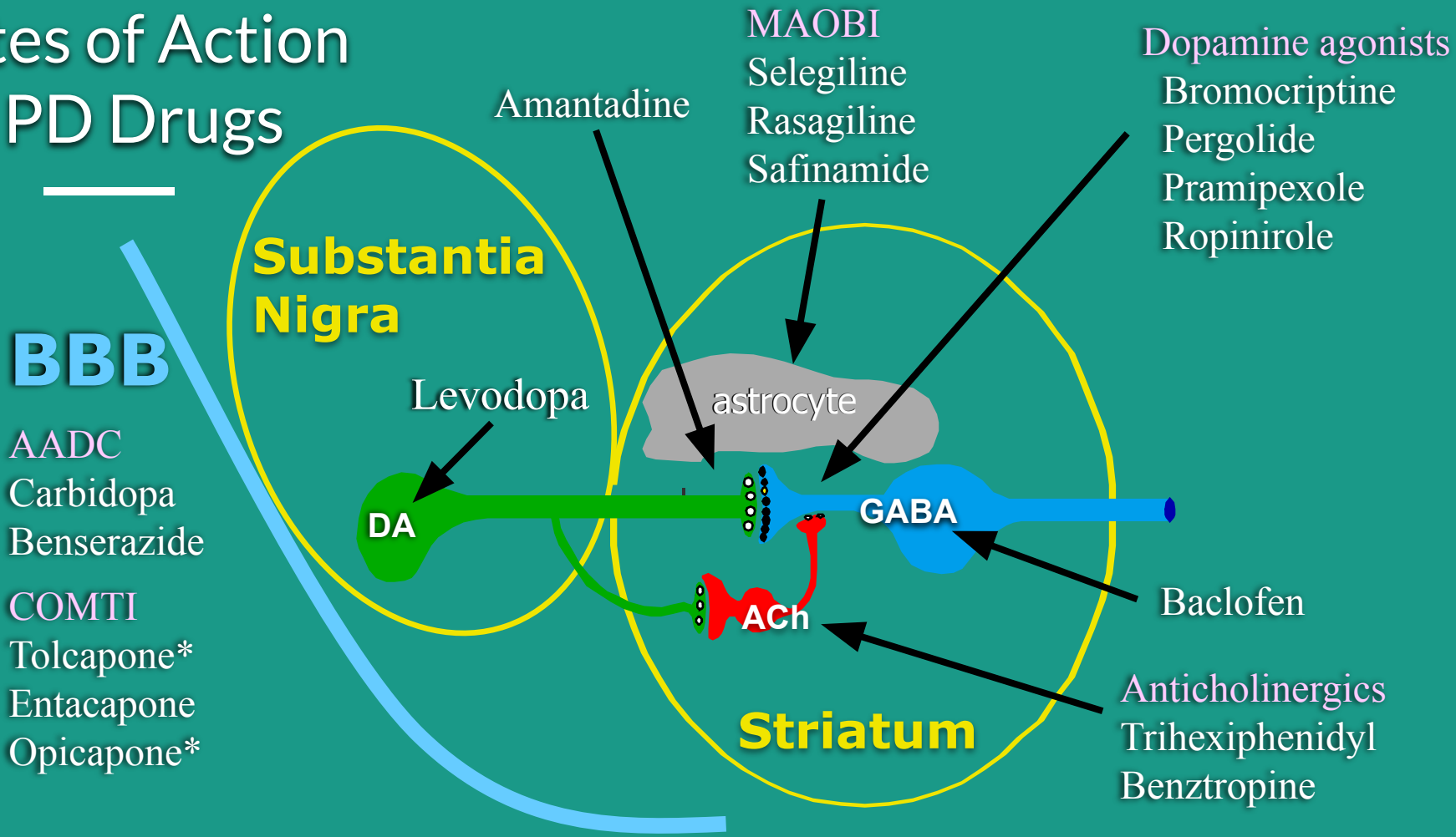
- No significant between-group difference at week 80
  - → Levodopa had no disease modifying effect over the course of 1.5 years

- Rates of **dyskinesia** and levodopa-related **fluctuations** in motor response did not differ significantly between the two groups
  - → No reason to delay therapy

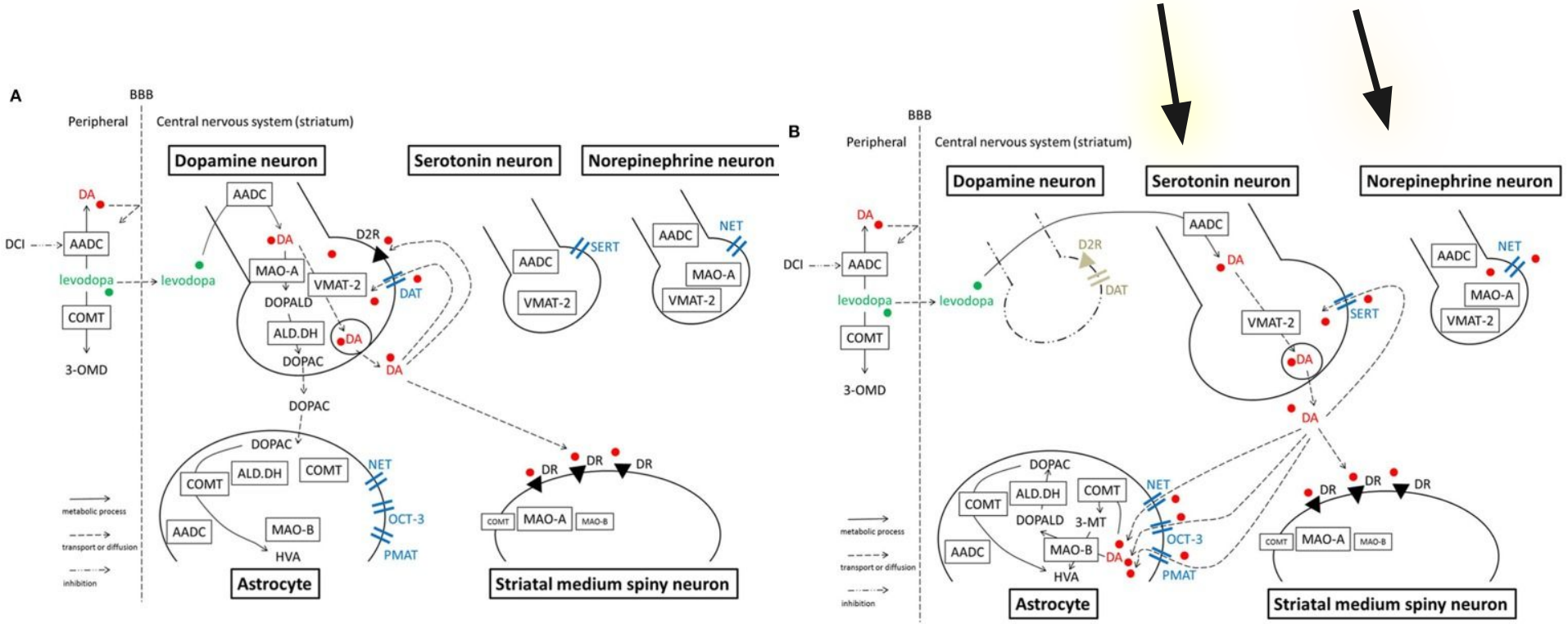
1. Verschuur CVM et al; LEAP Study Group. Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease. N Engl J Med. 2019 Jan 24;380(4):315-324


A
UPDRS Total Score
Delayed-start group
Early-start group
0
5
10
15
20
25
30
35
40
0
4
22
40
44
56
68
80
Weeks since Randomization
B
PDQ-39 Total Score
Delayed-start group
Early-start group
0
2
4
6
8
10
12
14
16
0
22
40
56
68
80
Weeks since Randomization

Sites of Action of PD Drugs

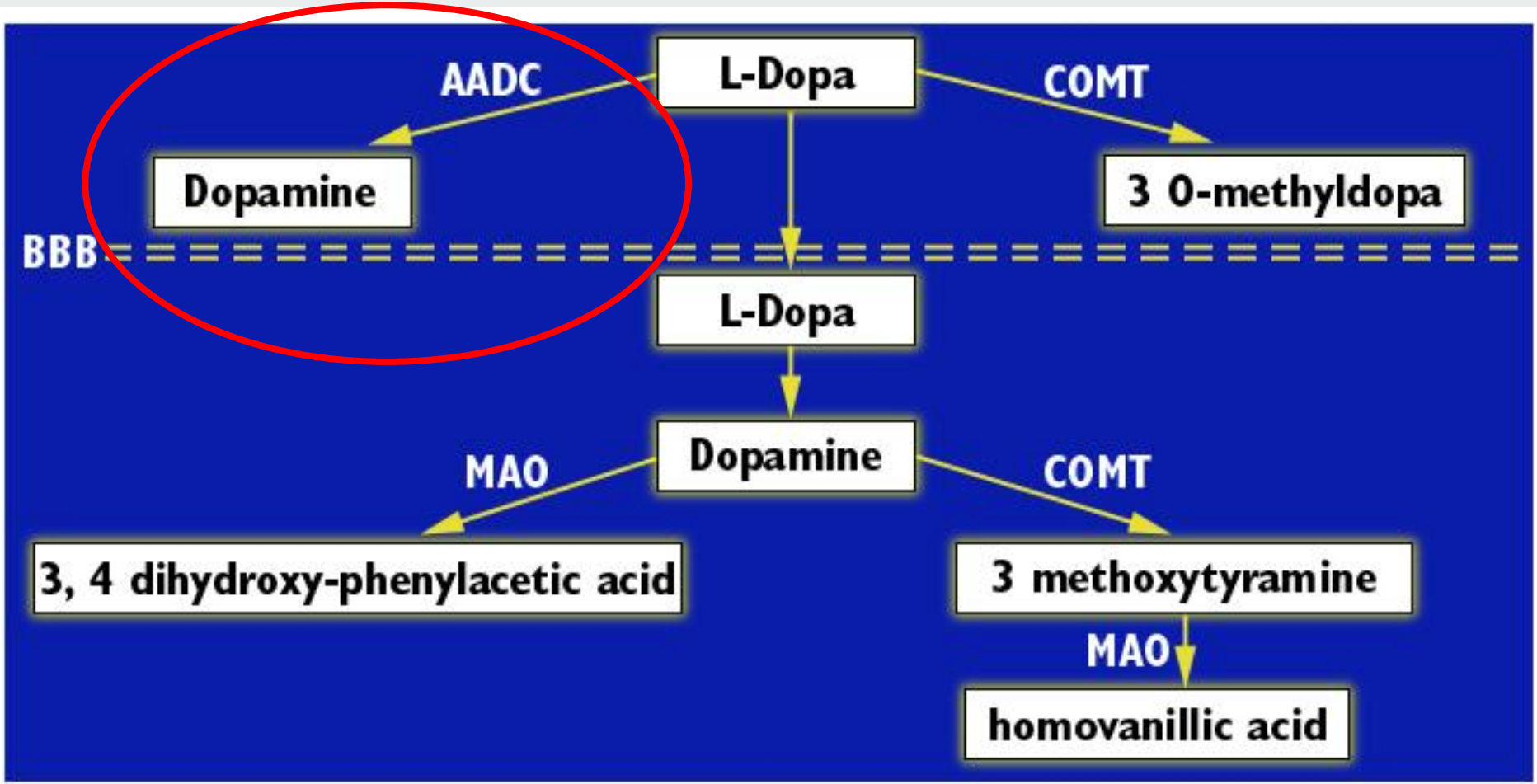


LD-DA metabolism in normal (A) and DA-denervated (B) striatum



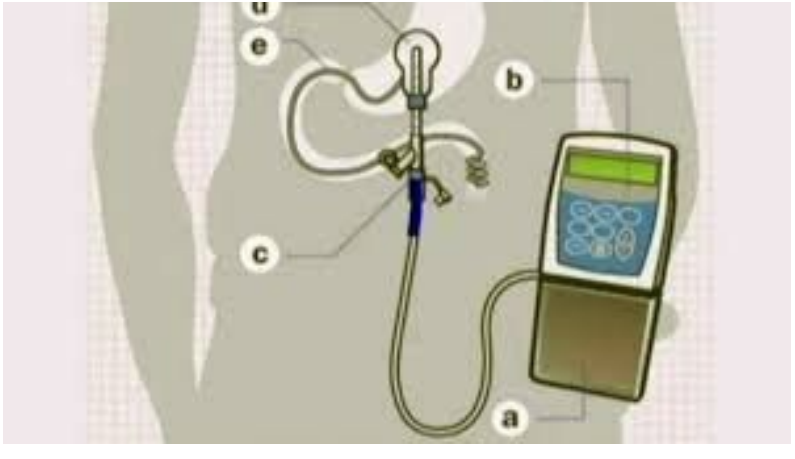
Nishijima et al. What Mechanisms Are Responsible for the Reuptake of Levodopa-Derived Dopamine in Parkinsonian Striatum? Front Neurosci 2016

Levodopa Metabolism



Dopamine precursors

- Sinemet (Carbidopa/Levodopa)
- Sinemet CR
- Stalevo (Carbidopa/Levodopa/Entacapone)
- Rytary
- Duopa
- Lodosyn (carbidopa) AADC
- Inbrija (inhaled levodopa)
    - Rescue drug bypasses GI tract



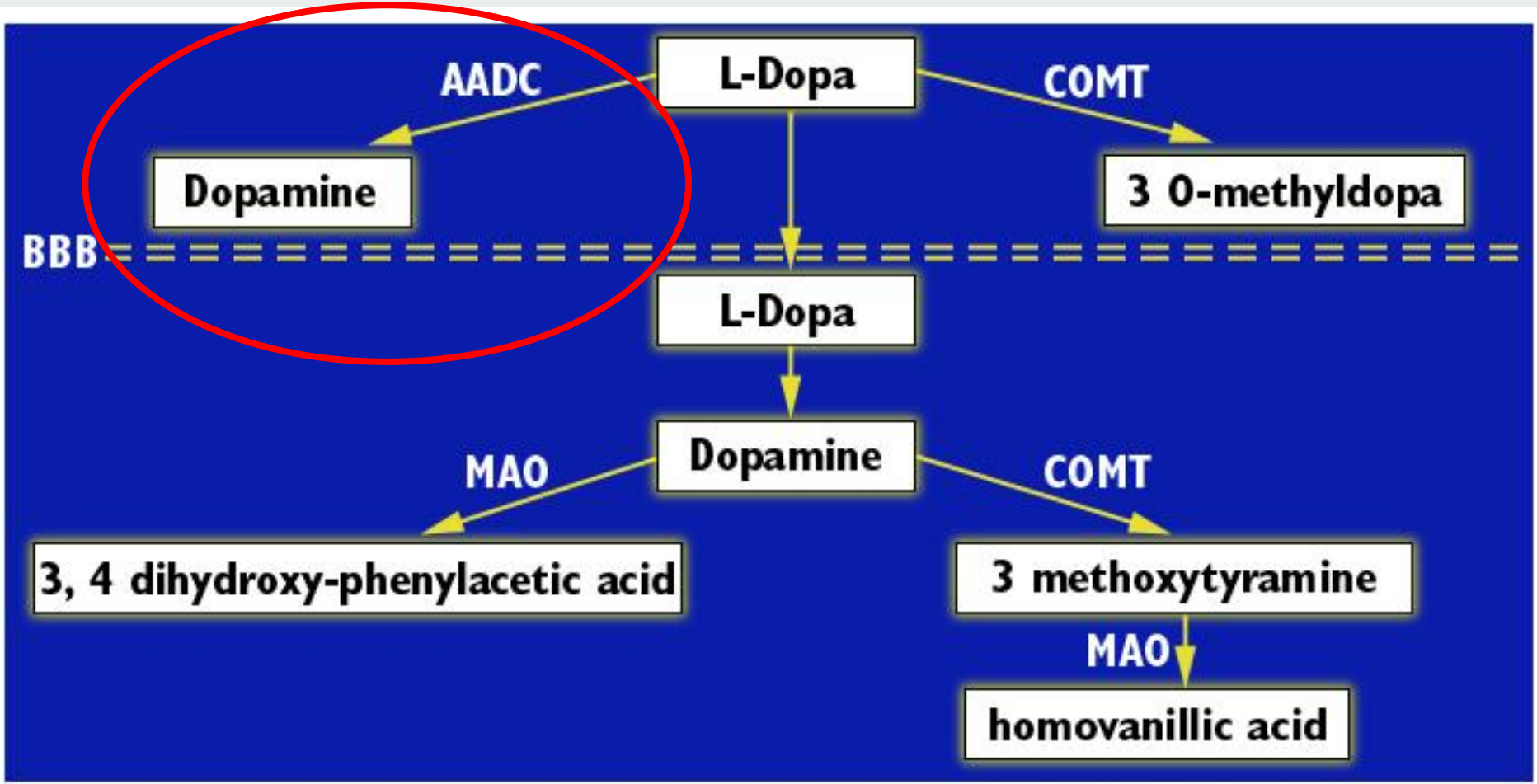
Levodopa characteristics

- First trial in PD patients 1961 - Cotzias first to report clinical efficacy in 1967
- Most effective symptomatic therapy; “gold standard”
- Almost all patients will require at some point
- Administered with carbidopa to reduce peripheral conversion to dopamine
- Absorption limited in duodenum by dietary protein
- Most common early, acute side effects:
    - **Nausea**
    - **Vomiting**
    - **Postural hypotension**

Peripheral Dopa-Decarboxylase Inhibitors

- Inhibit decarboxylation of peripheral LD
- Amplify central delivery of LD; minimize peripheral adverse effects
- Used only in combination with LD
  - Carbidopa in US, Benserazide in Europe
- No antiparkinsonian effect when given alone
- Use >75 mg carbidopa daily for AADC inhibition
  - Lodosyn = carbidopa alone
  - Don’t use Sinemet 10/100

Levodopa Metabolism

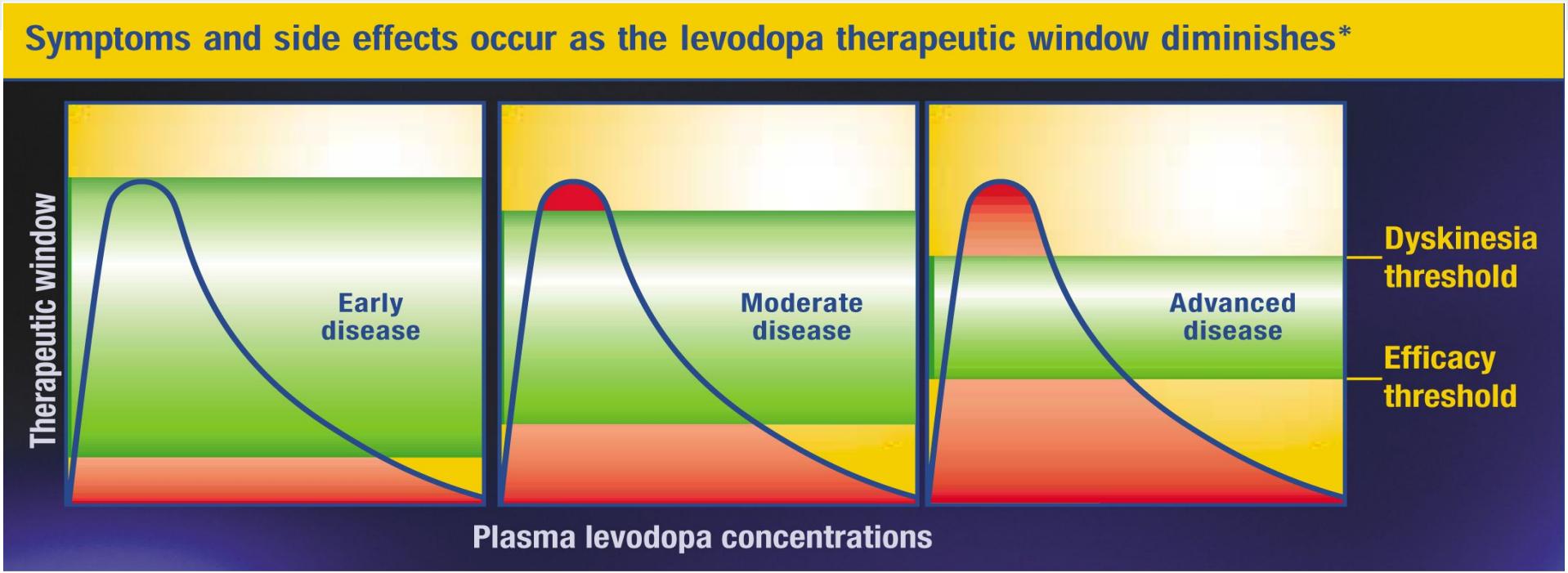


Levodopa/Carbidopa Formulations

	Onset	Duration	
"Liquid Sinemet"	*5-10 min*	*½-1 hr*	
Parcopa	*15-30 min*	*1½-3½ hr*	
Immediate Release	*20-40 min*	*2-4 hr*	
Controlled Release	*30-60 min*	*3-6 hr*	(dose conversion ~ 1 : 1.3)
Rytary	*30-60 min*	*4-6 hr*	(dose conversion ~ 1 : 1.8)
Inbrija	*5-15 min*	*1-2 hr*	(levodopa alone)
Duopa intestinal gel	*continuous infusion via PEG-J*		

Motor Complications Associated With Long Term LD Therapy

- Smooth clinical response for up to 5 years
- ~10% risk of motor complications per year of treatment
- After “honeymoon”, slow “wearing off” of clinical benefit from LD dose due to increased symptoms
- Motor fluctuations:
  - end of dose OFF
  - “ON-OFF” response
  - delayed ON
  - dose failures
- Dyskinesias



Over time, pulsatile stimulation leads to brittle response that parallels plasma levels.
When levodopa effects wear off, parkinsonian symptoms re-emerge.
Narrowing of the “therapeutic window”.

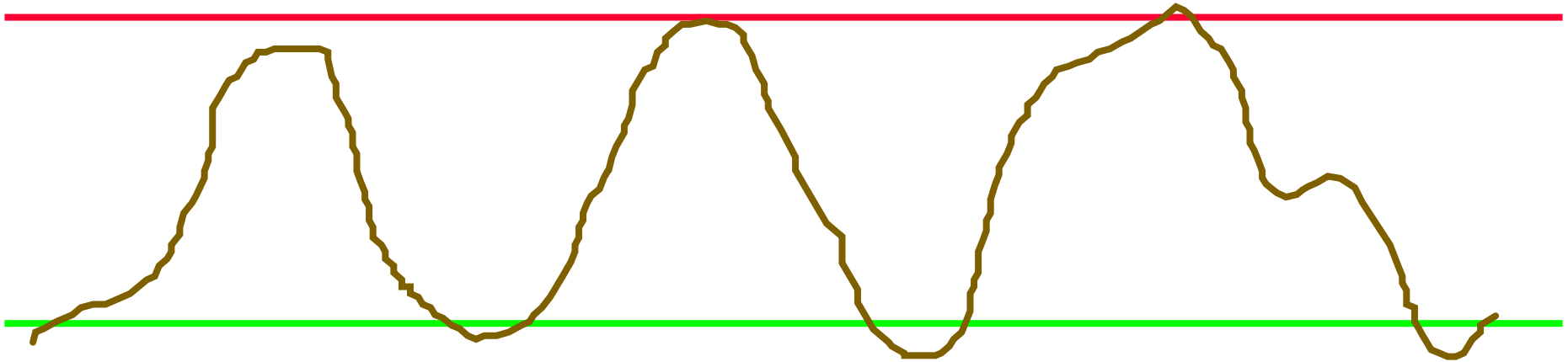
Possible Causes of Response Fluctuations to Levodopa

- Short half-life (1.75 to 2.5 hrs with decarboxylase inhibitor) resulting in pulsatile stimulation of striatal dopamine receptors
- Loss of synthetic and storage capacity for dopamine in the brain
- Altered bioavailability of levodopa
- Delayed gastric emptying
- Poor absorption
- Competition for transit across the blood-brain barrier (amino acids)
- Changes in receptor sensitivity

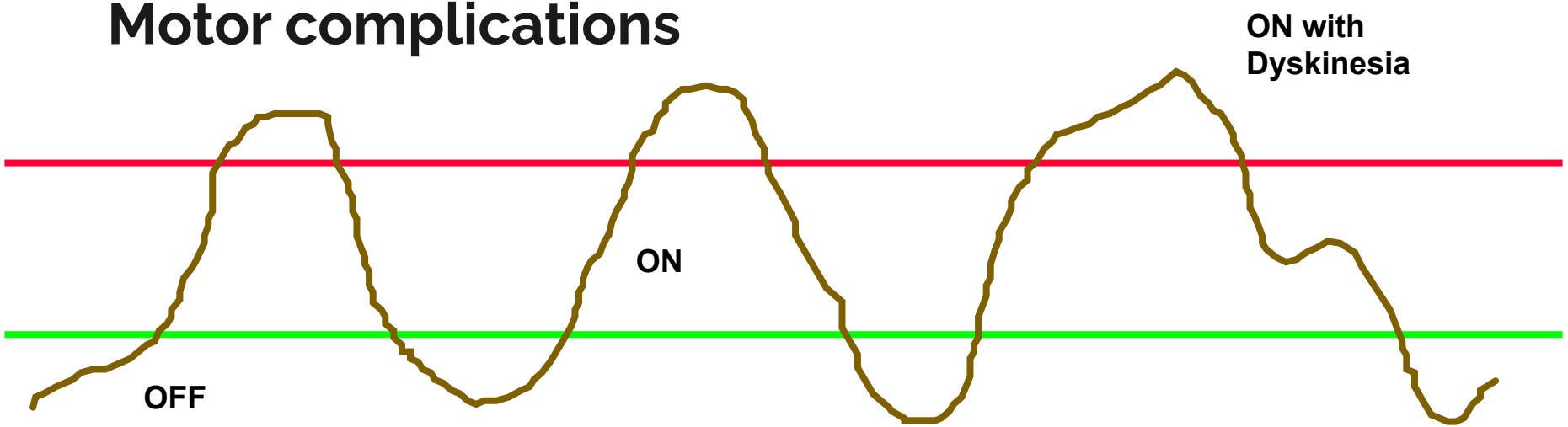
Nonmotor Fluctuations

Sensory/pain	Tingling sensation	Akathisia
	Tightening sensation	Diffuse pain
Cognitive/psychiatric	Anxiety	Depression
	Fatigue	Slow thinking
	Irritability	Hallucinations
Autonomic	Drenching sweats	Dyspnea
	Facial flushing	Dysphagia
	Dry mouth	Constipation

Motor complications



Motor complications



Nutt et al: Dyskinesia and the antiparkinsonian response always temporally coincide: a retrospective study. Neurology 2010

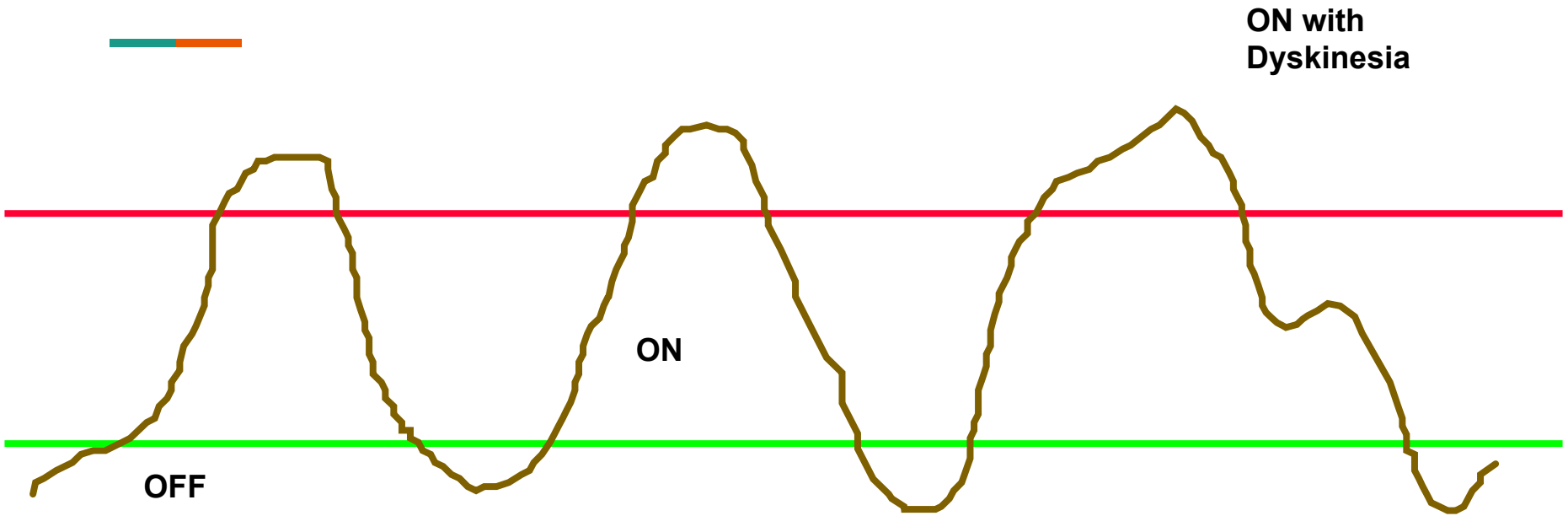
Levodopa induced dyskinesia (LID)

- Cumulative dose of levodopa, age of PD onset, medication half life
- Much earlier in patients from pre-levodopa era: longer duration, greater PD severity
- Levodopa era: therapy for 4–6 years:
  - ≅ 40% motor fluctuations
  - 30-40 % dyskinesias [1]
    - Severe in 3.2% of all PD pts
    - Severe in 10.7% of pts w dyskinesia [2]
      - Marked improvement among those treated with deep brain stimulation.
- Incident data: clinically important morbidity may be less

1. Ahlskog et al: Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord 2001
2. Turcano et al. Levodopa-induced dyskinesia in Parkinson disease. Neurology Nov 2018

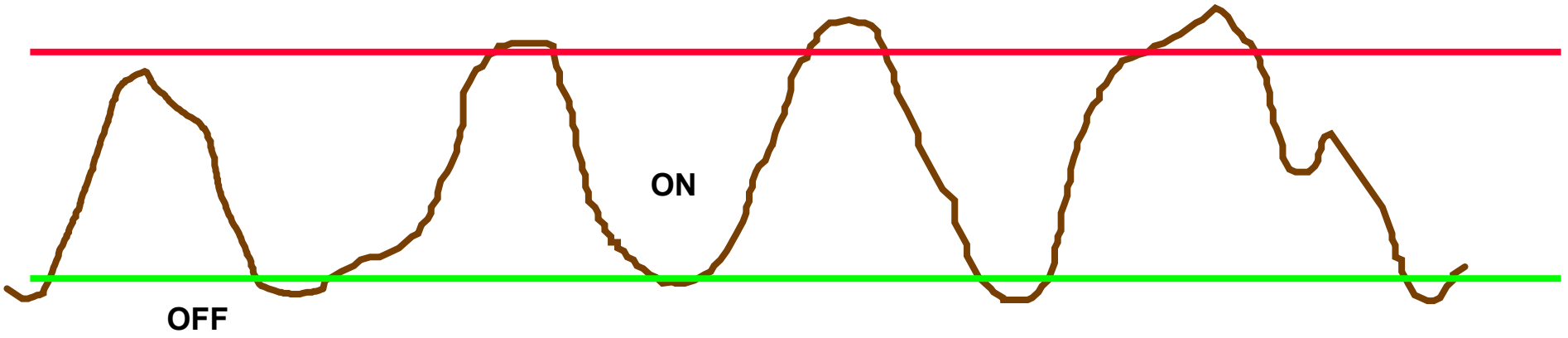
Management of motor complications

- Smaller, more frequent doses of LD
  - Monitor for dose failures
  - “Liquid Sinemet”
- Longer acting levodopa preparations
  - Sinemet CR
  - Rytary
  - Duopa
- Add COMT inhibitor
- Add dopamine agonist
- Amantadine
- Add MAOb inhibitor
- Apomorphine rescue
- Levodopa enteral gel via PEGJ (Duopa)
- Neurosurgical interventions:
  - Pallidotomy
  - Deep Brain Stimulation
    - DBS GPi
    - DBS STN



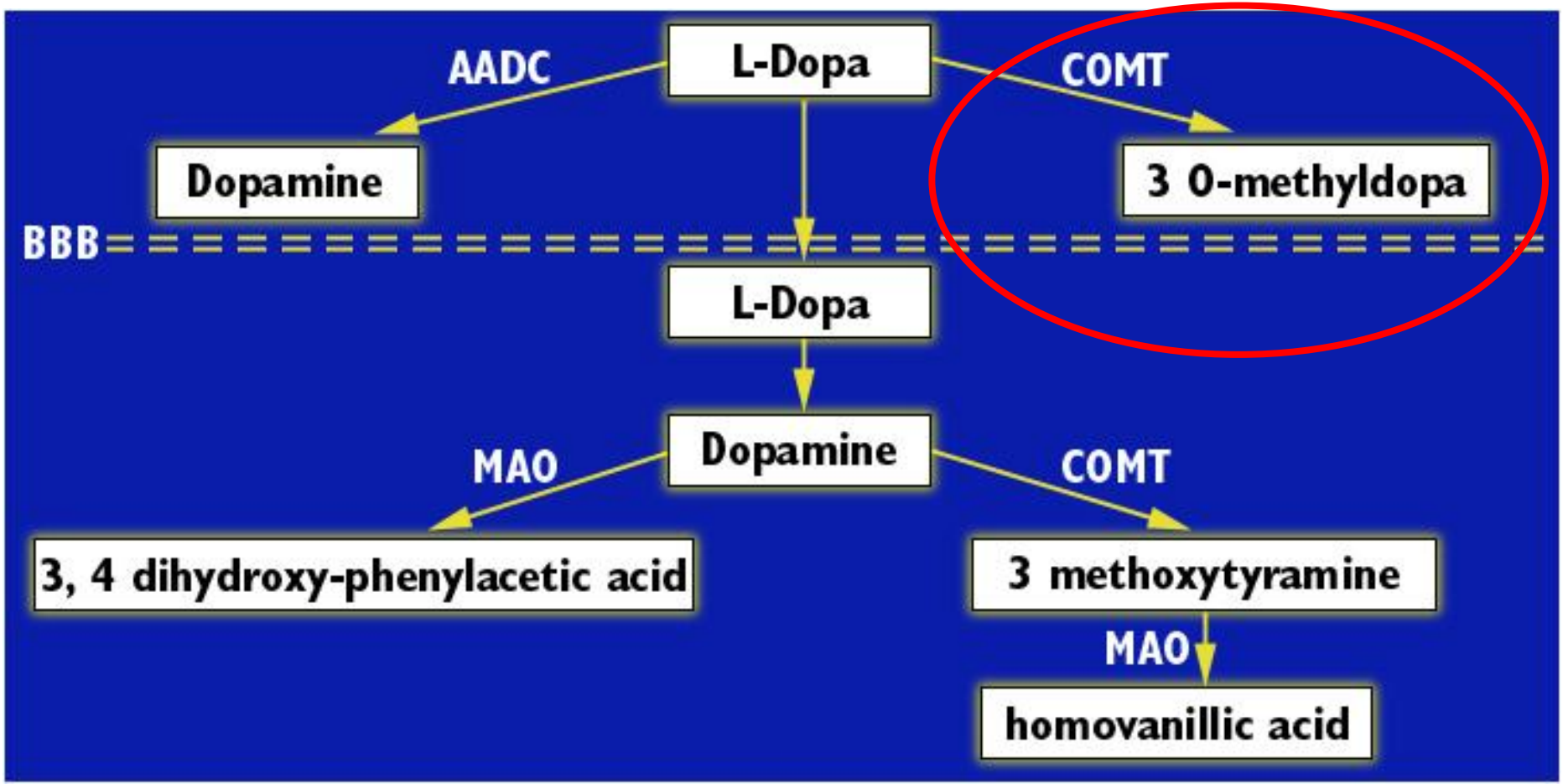
Nutt et al: Dyskinesia and the antiparkinsonian response always temporally coincide: a retrospective study. Neurology 2010

More frequent doses



Dose fractionation with more frequent, smaller levodopa doses:
monitor for dose failures (“no-ON” responses)

Levodopa Metabolism

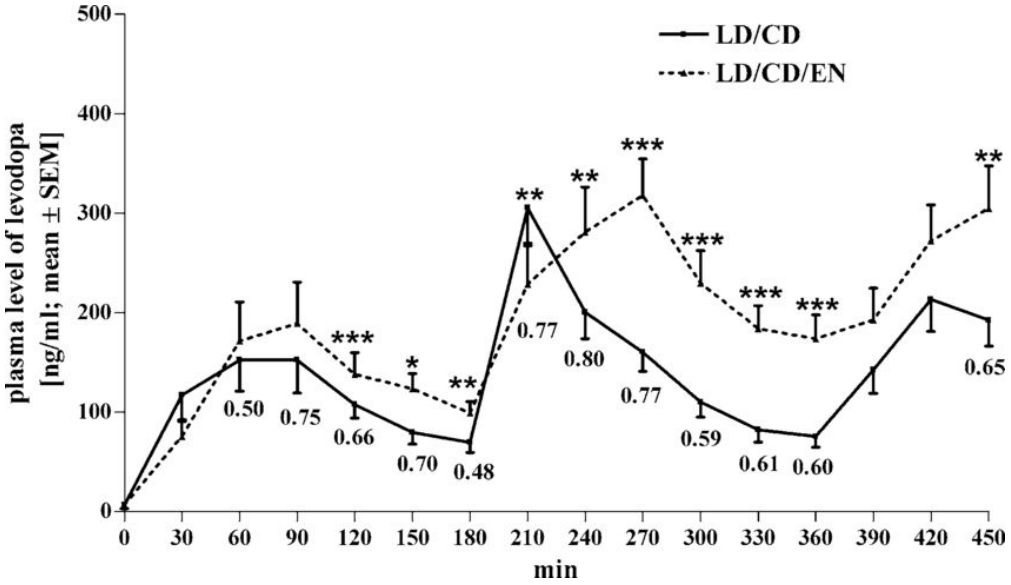


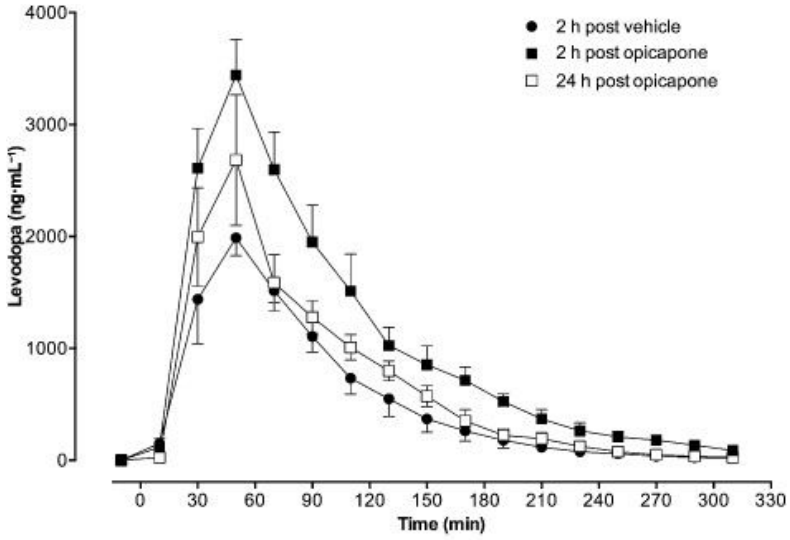
COMT inhibitors

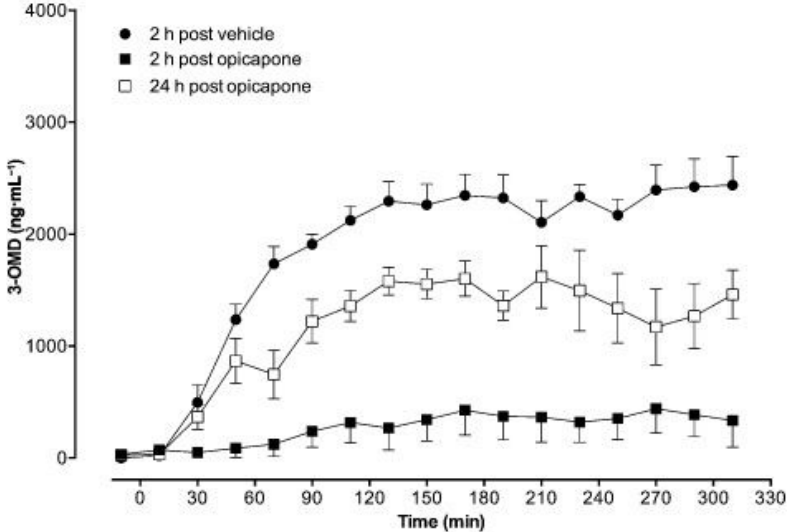
- Prolong the half life of LD, causing less fluctuations in the serum dopa levels
- Increase the AUC by blocking the peripheral degradation of LD

- **Entacapone** taken with each LD dose; no liver function monitoring required; limited efficacy, good s.e. profile
- **Tolcapone** administered tid; liver function monitoring required; very effective
- **Opicapone** (Ongentys) once daily at bedtime; no safety concerns

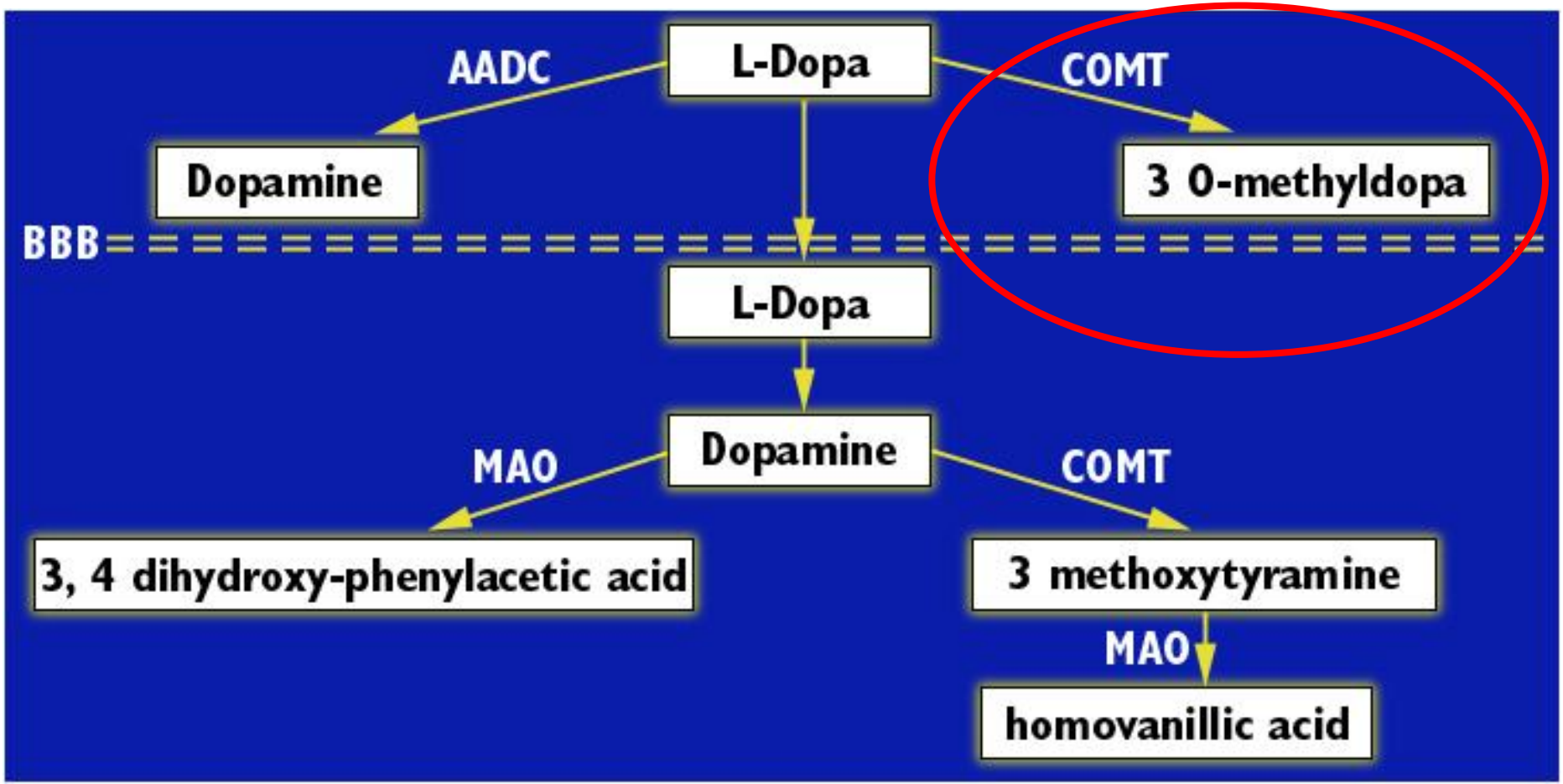
Stocchi et al. Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: **the STRIDE-PD study**. Ann Neurol. 2010


LD/CD
LD/CD/EN
plasma level of levodopa
[ng/ml; mean ± SEM]
min
0.50
0.75
0.66
0.70
0.48
0.77
0.80
0.77
0.59
0.61
0.60
0.65

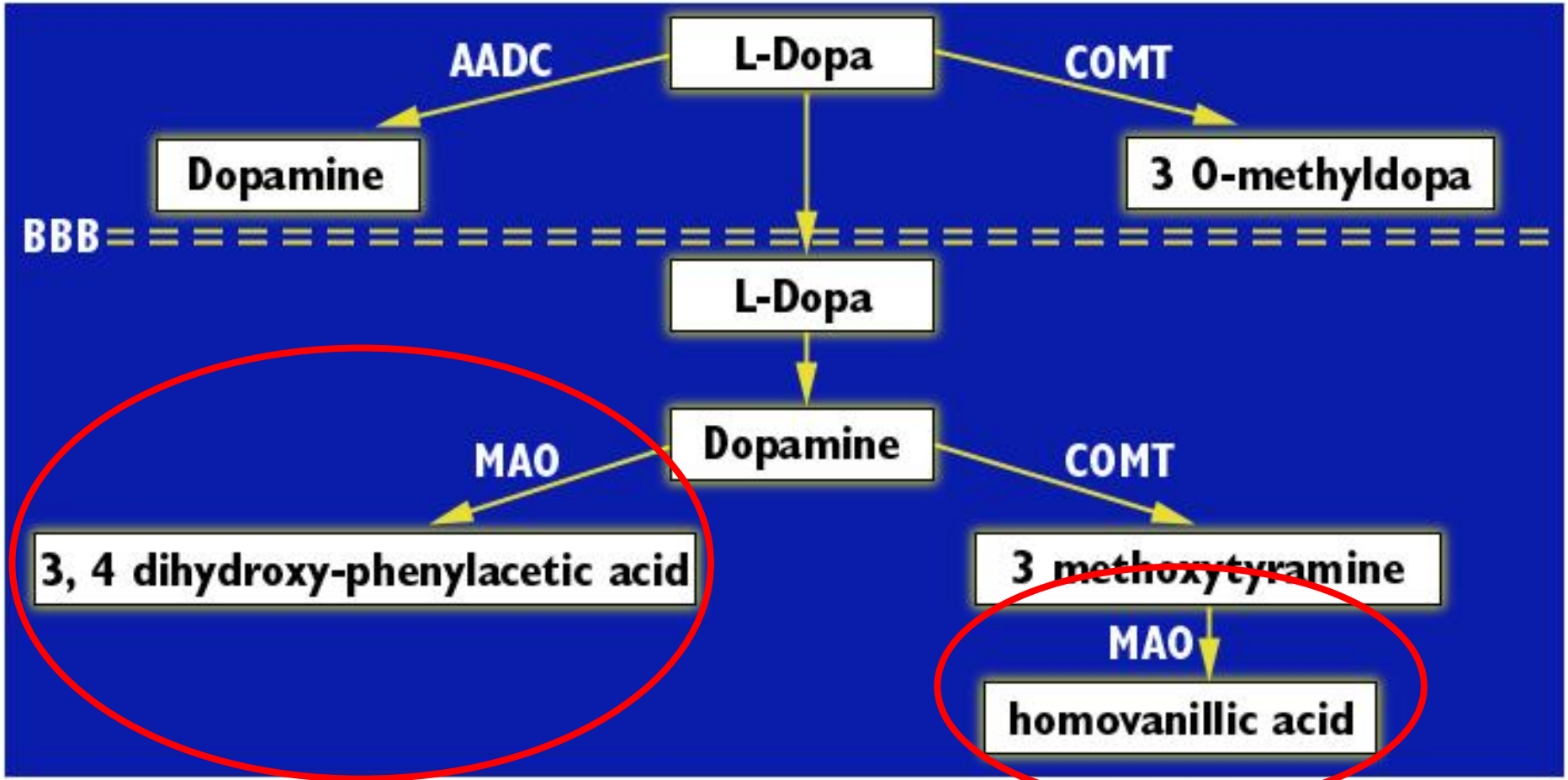

2 h post vehicle
2 h post opicapone
24 h post opicapone
Levodopa (ng·mL⁻¹)
Time (min)


2 h post vehicle
2 h post opicapone
24 h post opicapone
3-OMD (ng·mL⁻¹)
Time (min)

Levodopa Metabolism



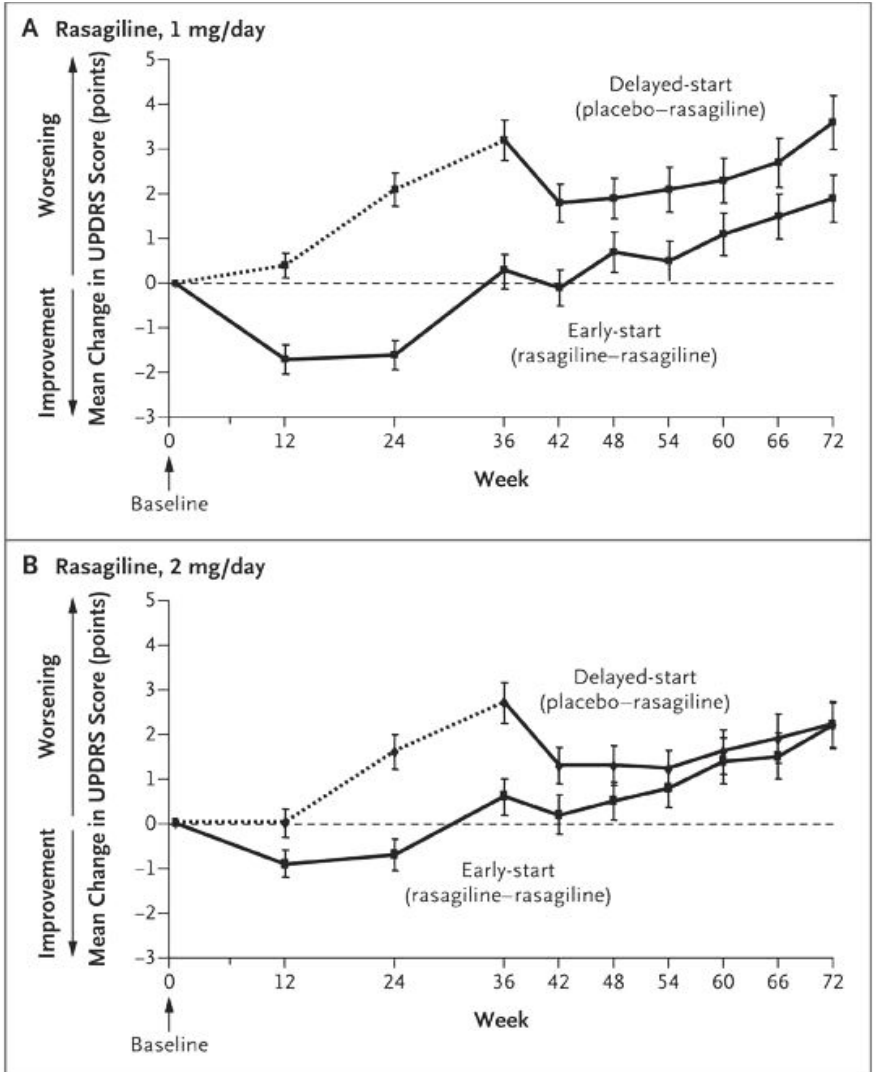
Levodopa Metabolism



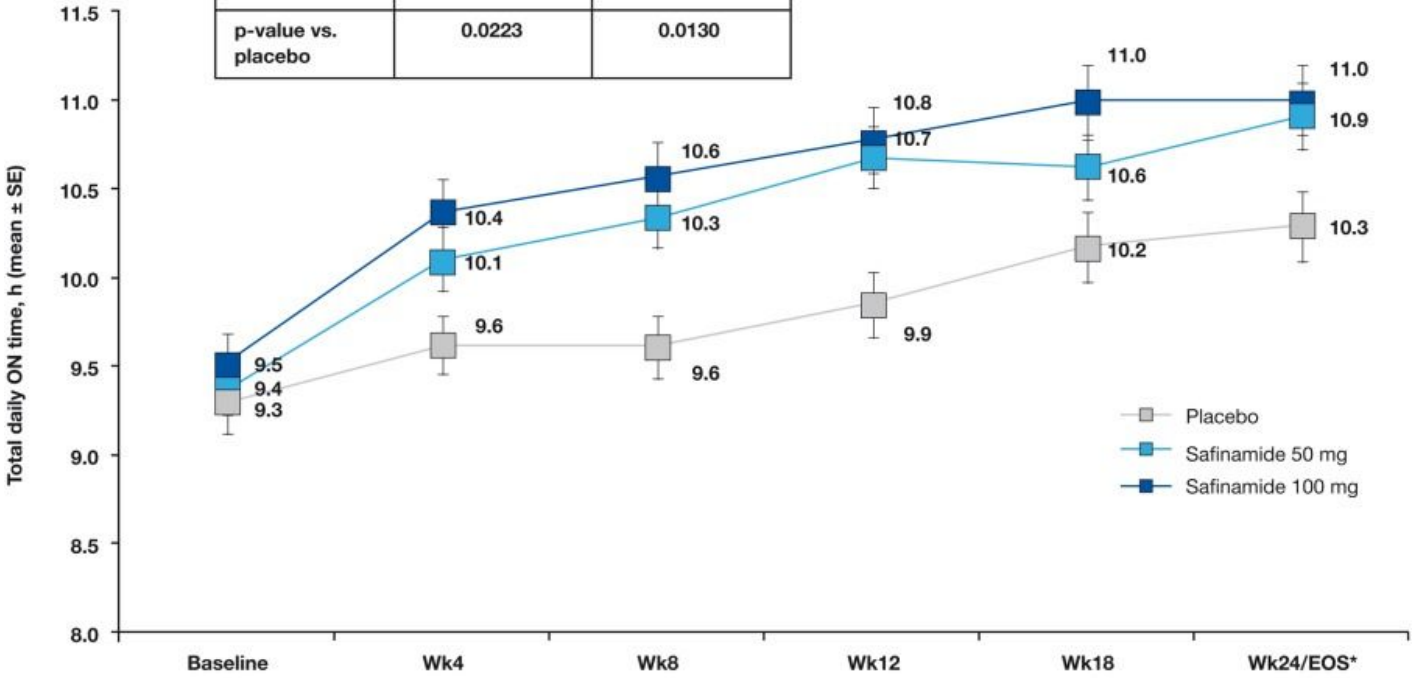
MAOB inhibitors

Safe and well tolerated, not sedating, long acting, mild antidepressant effect
Limited efficacy

- **Selegiline**
  - PO (Eldepryl), ODT (Zelapar), Transdermal (Emsam)
  - Side effects: insomnia, hallucinations, nausea (rarely), orthostatic hypotension
- **Rasagiline** (Azilect)
  - Well tolerated, no effect on disease progression (ADAGIO delayed start study)
- **Safinamide** (Xadago)
  - ***Reversible*** MAOBI, inhibits glutamate release via VG Na and Ca channels, inhibits dopamine reuptake.
  - More selective for MAOB
  - FDA approved as add-on therapy to Levodopa
    - Effective as initial monotherapy or add-on to DA
  - Well tolerated, low incidence of AEs (dyskinesia)


A Rasagiline, 1 mg/day
Worsening
Improvement
Mean Change in UPDRS Score (points)
5
4
3
2
1
0
−1
−2
−3
Delayed-start
(placebo–rasagiline)
Early-start
(rasagiline–rasagiline)
0
12
24
36
42
48
54
60
66
72
Week
Baseline
B Rasagiline, 2 mg/day
Worsening
Improvement
Mean Change in UPDRS Score (points)
5
4
3
2
1
0
−1
−2
−3
Delayed-start
(placebo–rasagiline)
Early-start
(rasagiline–rasagiline)
0
12
24
36
42
48
54
60
66
72
Week
Baseline

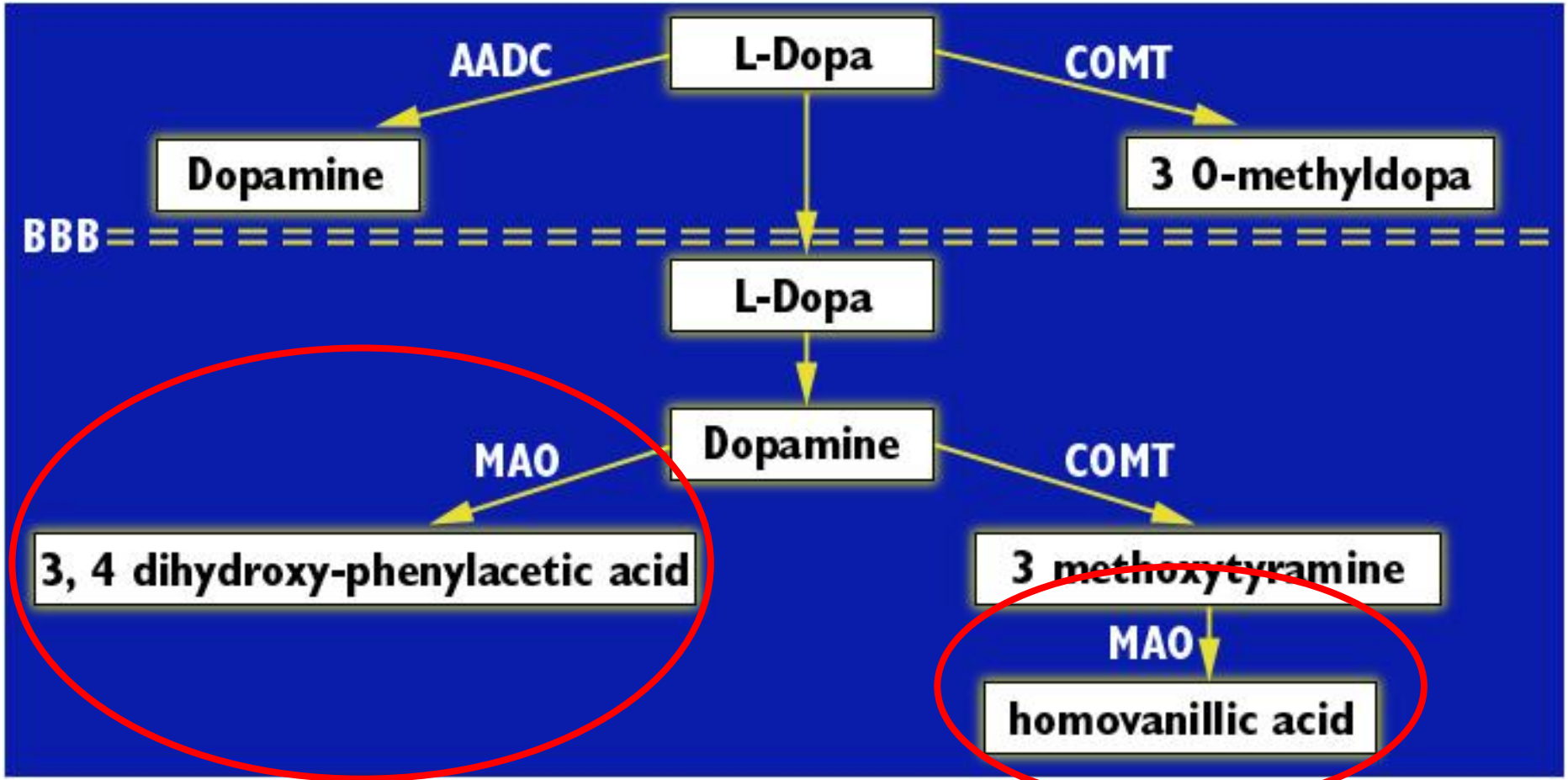
	Safinamide 50 mg	Safinamide 100 mg
LS Mean	1.23	1.28
LS Difference vs. placebo	0.51	0.55
95% CI of LS Difference	(0.07, 0.94)	(0.12, 0.99)
p-value vs. placebo	0.0223	0.0130



* ON time = ON time without dyskinesia + ON time with minor dyskinesia

Borgohain R. et al. Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. Mov Disord. 2014. 29: 229-237

Levodopa Metabolism

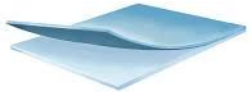


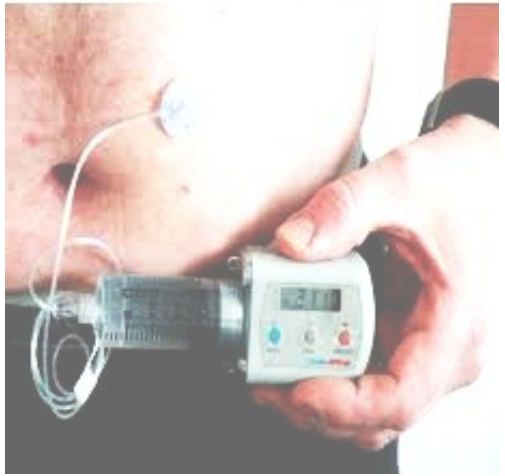
Dopamine agonists

- Act directly on dopamine receptors without metabolic conversion
- Longer $t_{1/2}$ than LD: Monotherapy delays motor complications
- Adjuncts to LD in advanced PD, lower dosage of LD
- More acute side effects than LD
  - Neuropsychiatric effects more frequent with agonists
    - Somnolence,
    - Sleep attacks,
    - Psychosis,
    - Impulse control disorders
      - Failure to resist an impulse, drive or temptation to perform an act that is harmful to the person or to others.
  - Peripheral edema, headaches, dizziness, nausea

Apomorphine

- D1/D2 agonist
- Parenteral delivery
  s.c., i.v., sublingual, intranasal, rectal
- Rapid “off” period rescue
  - 2-5 mg s.c.; pen injection systems
- Treatment of unpredictable, frequent motor fluctuations
- SE: nausea, vomiting, hypotension
  - trimethobenzamide 250 mg t.i.d.
  - domperidone 20 mg t.i.d.; not available in U.S.





Amantadine

- Antiviral agent; limited antiparkinsonian activity
- May increase dopamine release or inhibit its reuptake
- May act as dopamine receptor agonist
- May be weak NMDA antagonist
- Monotherapy in early PD to delay need for LD

- Adjunct to LD in advanced PD to decrease dyskinesias
- New extended release formulation (Gocovri ™) approved for treatment of dyskinesia
    - No head-to-head trial comparing ER vs IR amantadine re: controlling dyskinesias

- **Side effects: hallucinations, confusion, insomnia, nightmares, peripheral edema**

Management of motor complications

- Smaller, more frequent doses of LD
  - Monitor for dose failures
  - **“Liquid Sinemet”**
- Longer acting levodopa preparations
  - Sinemet CR
  - **Rytary**
  - **Duopa**
- Add COMT inhibitor
- Add dopamine agonist
- Amantadine
- Add MAOb inhibitor
- **Apomorphine** rescue
- Levodopa enteral gel via PEGJ (**Duopa**)
- Neurosurgical interventions:
  - Pallidotomy
  - **Deep Brain Stimulation**
    - DBS GPi
    - DBS STN

QUESTIONS??