The James J. and Joan A. Gardner Family Center for Parkinson's Disease and Movement Disorders

Optimizing Parkinson's Symptomatic Management through Enhanced Drug Delivery

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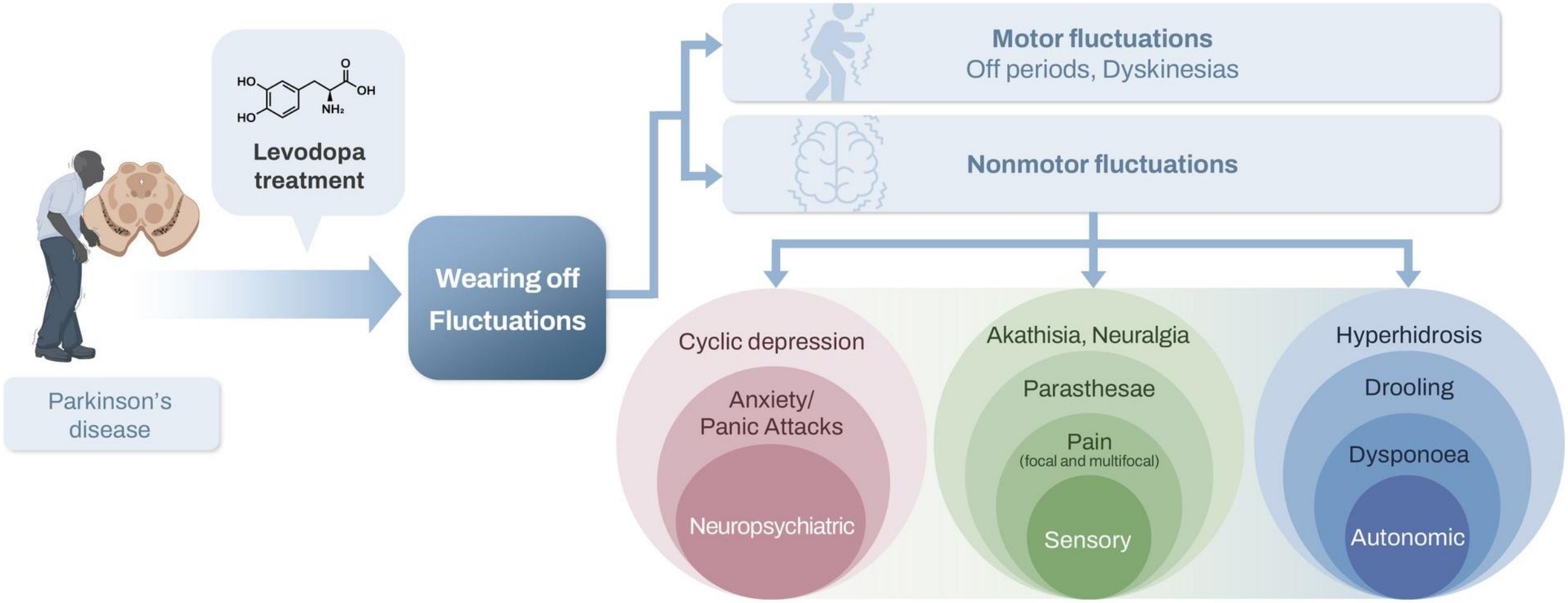
Disclosures

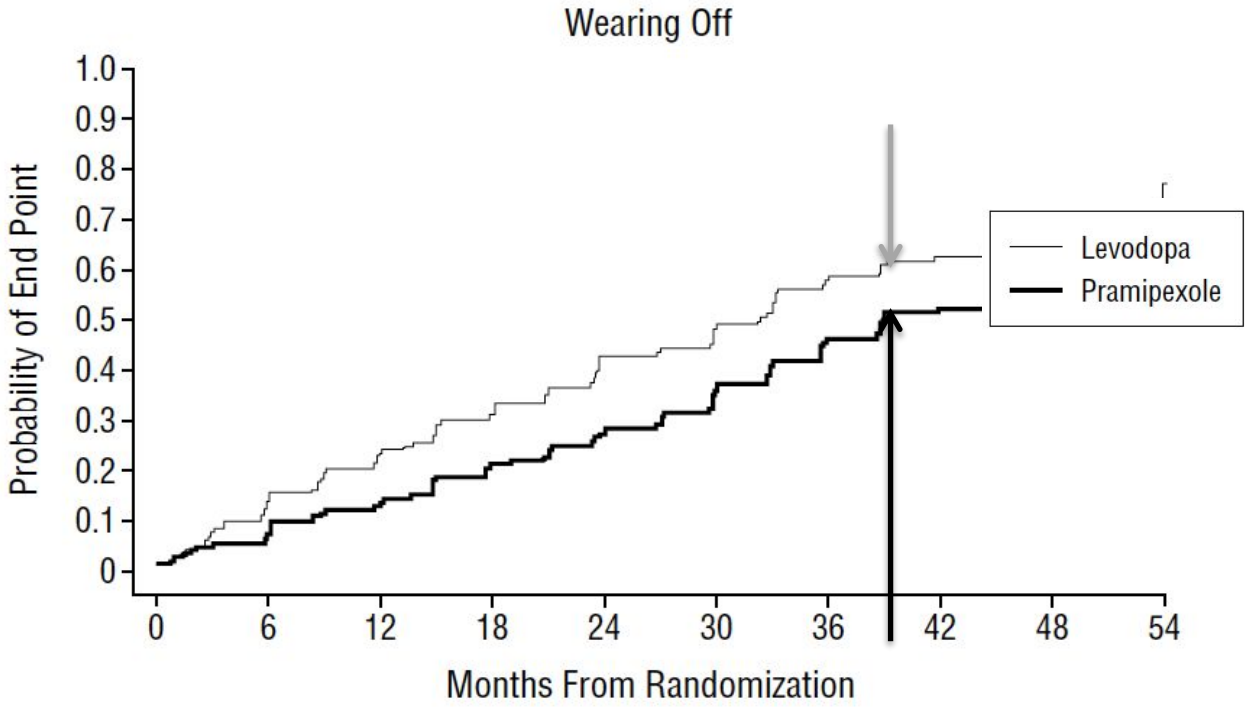
- **Research**: NIH, Michael J Fox Foundation
- **Consultant/scientific Advisory Board**: Mitsubishi Tanabe Pharma America (formerly, Neuroderm), Amneal, Acorda, Abbvie, Bial, Kyowa Kirin, Supernus (formerly, USWorldMeds), NeuroDiagnostics, Inc (SYNAPS Dx), Intrance Medical Systems, Inc., Merz, Praxis Precision Medicines, Citrus Health, and Herantis Pharma
- **Data Safety Monitoring Board (DSMB) Chair**: AskBio-GDNF gene therapy trials
- **Speaker's Bureau**: Amneal, Supernus
- **Royalties**: Lippincott Williams & Wilkins, Cambridge University Press, and Springer
- **Cofounder of Regain Therapeutics** and co-inventor of the patent "Compositions and methods for treatment and/or prophylaxis of proteinopathies." I have relinquished the right to any personal income from future treatments.

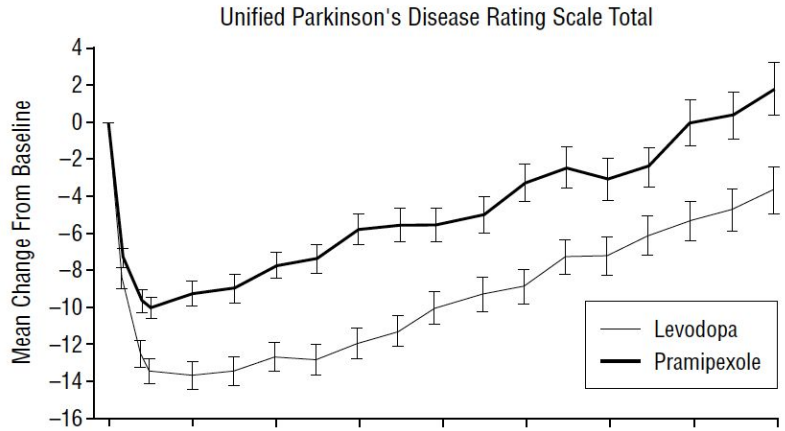
Dopaminergic drug delivery remains suboptimal

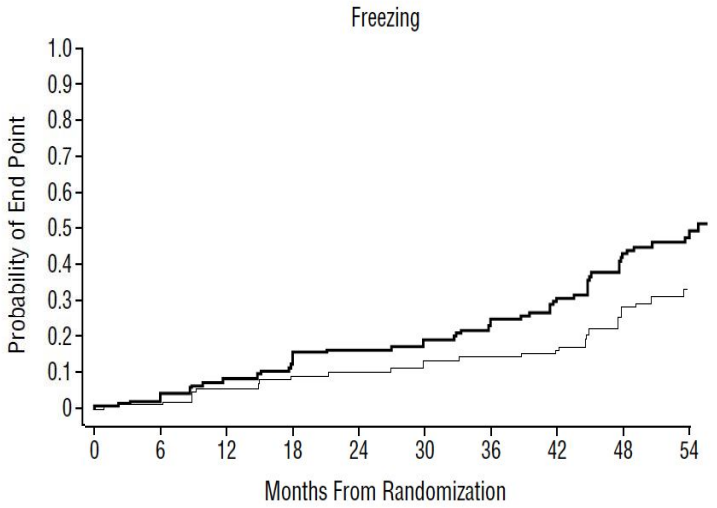


Boura I et al J Mov Disord 2025 Jan;18(1):1-16.

Motor fluctuations: Clinical practice has suffered from misinterpreted clinical trials



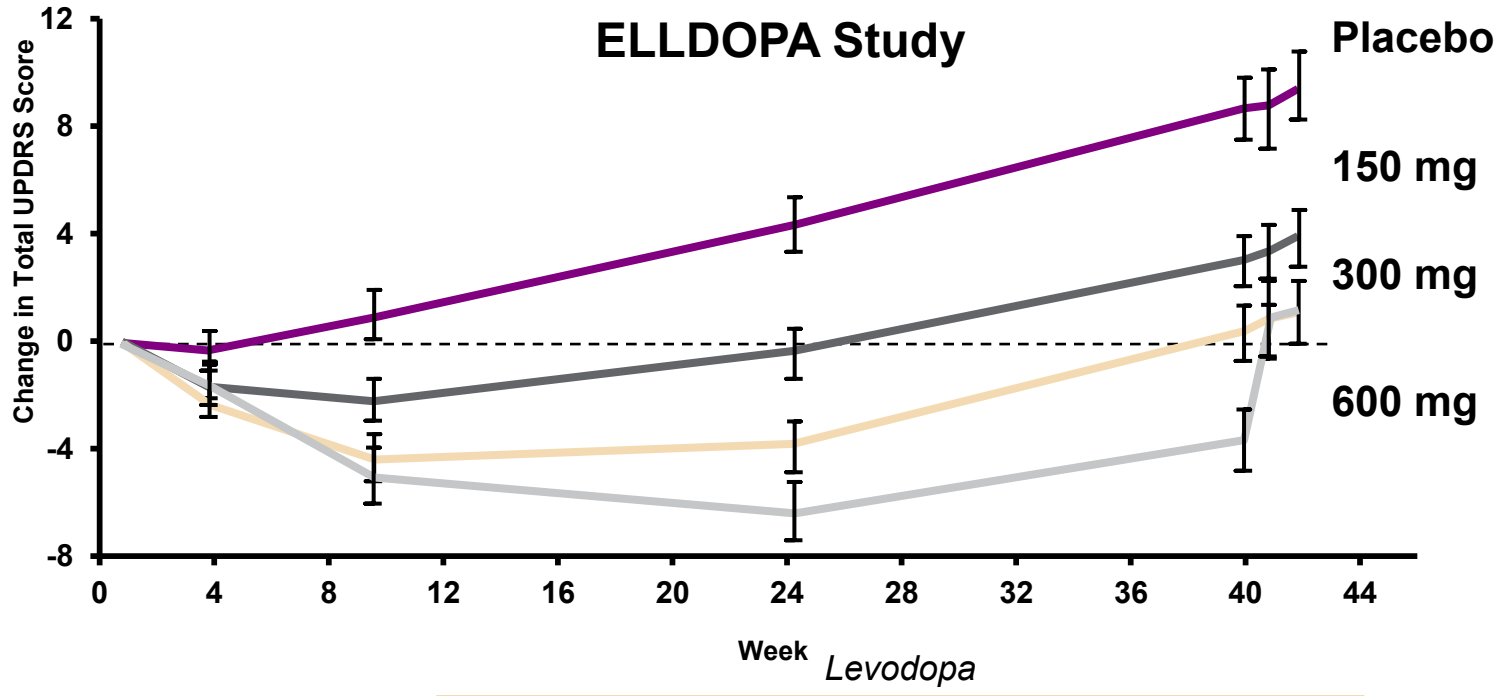




When disability is mild –or the replacement low– there is no “OFF” recognition

CALM-PD, PSG., Arch Neurol. 2004;61:1044-1053.

OFF is in the ON of the beholder



Levodopa

Adverse Motor Event	*Placebo (N = 90)*	*150 mg/day (N = 92)*	*300 mg/day (N = 88)*	*600 mg/day (N = 91)*	*P-value*
	Number (percent)				
Dyskinesia	3 (3.3)	3 (3.3)	2 (2.3)	15 (16.5)	< 0.001
Wearing off	12 (13.3)	15 (16.3)	16 (18.2)	27 (29.7)	0.06

UPDRS = Unified Parkinson's Disease Rating Scale

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

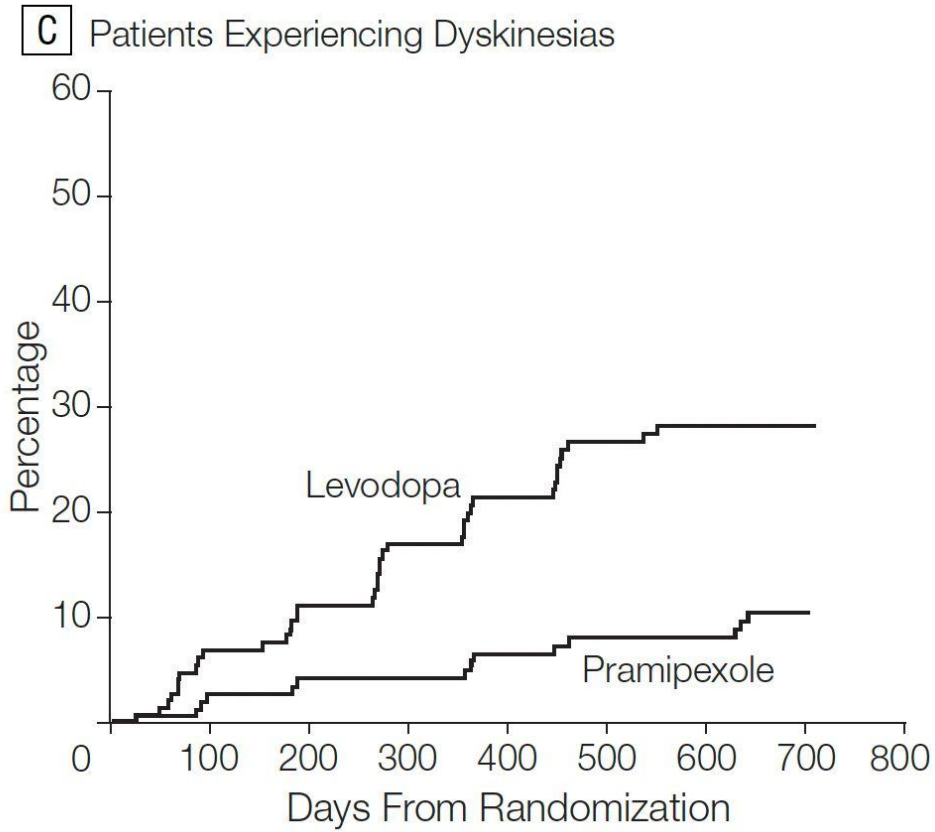
When does the clock begin to tick for dyskinesia?

56-year-old woman with right arm and right shoulder pain for 11 years and progressive gait impairment for 5 years

Three months later, after reaching a levodopa dose of 600 mg/day [patient also developed dyskinesias]


Wearing off and dyskinesia appeared within weeks!

Dyskinesia: What did clinical trial data say? (1/2)

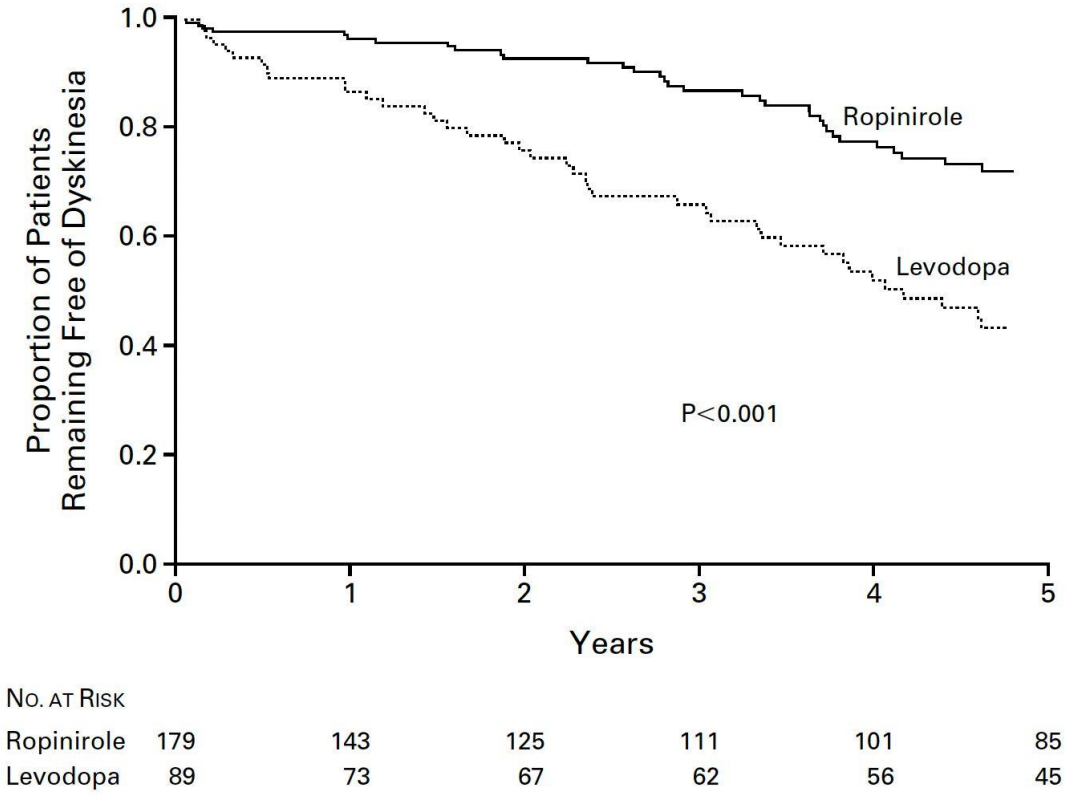


Pramipexole vs L-dopa

- **Conclusions**: "Fewer patients receiving initial treatment for PD with pramipexole developed dopaminergic motor complications than with levodopa therapy."

CALM-PD Study, JAMA 2000

Dyskinesia: What did clinical trial data say? (2/2)



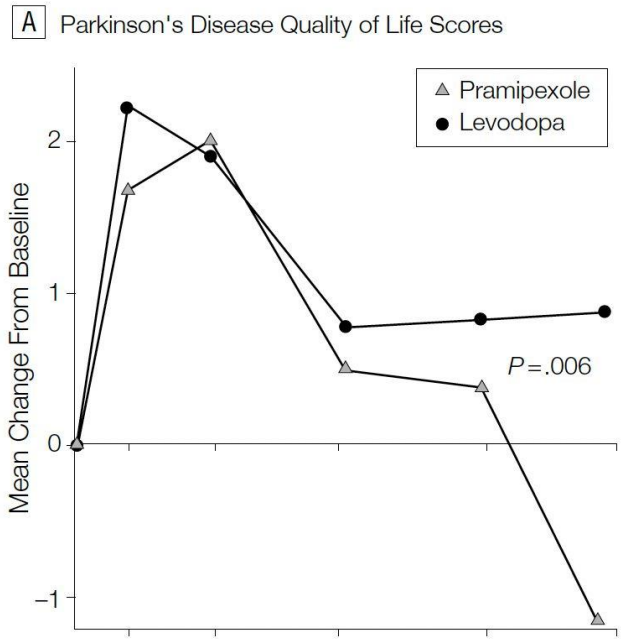
Ropinirole vs L-dopa

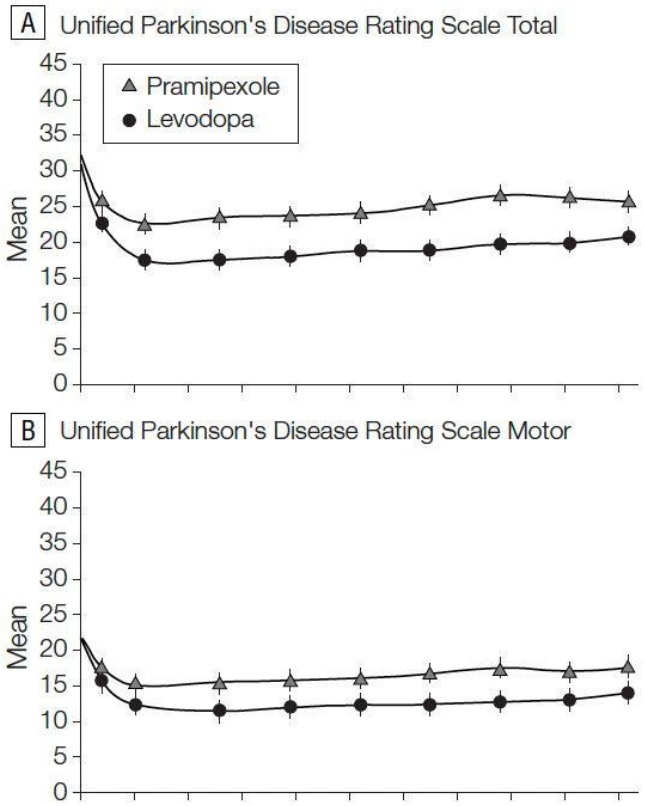
- **Conclusions**: "Early Parkinson's can be managed successfully for up to five years with a reduced risk of dyskinesia by initiating treatment with ropinirole alone"

056 Study, NEJM 2000

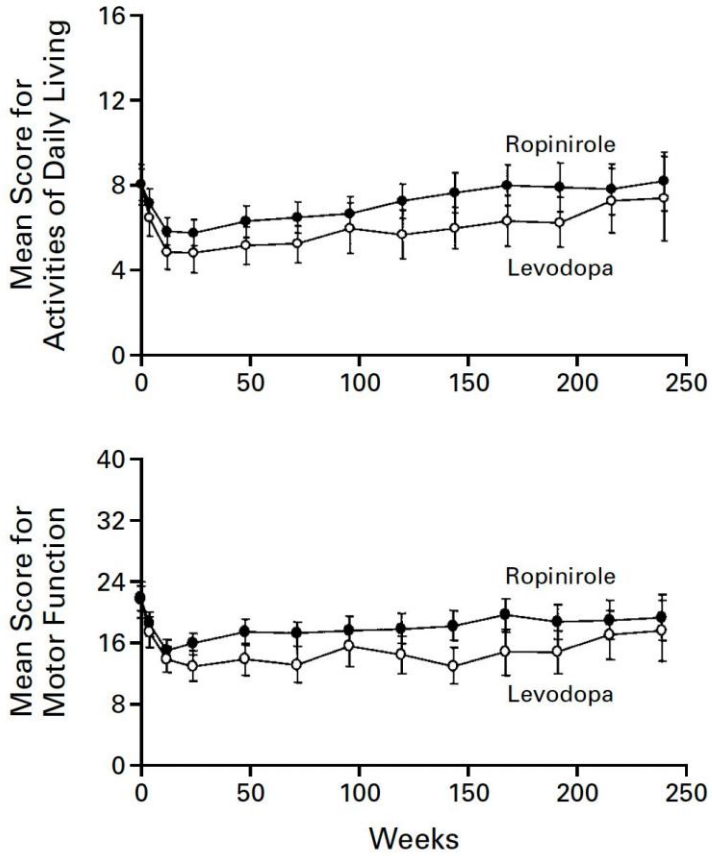
The other side of the coin: levodopa superiority

CALM-PD Study, JAMA 2000





056 Study, NEJM 2000

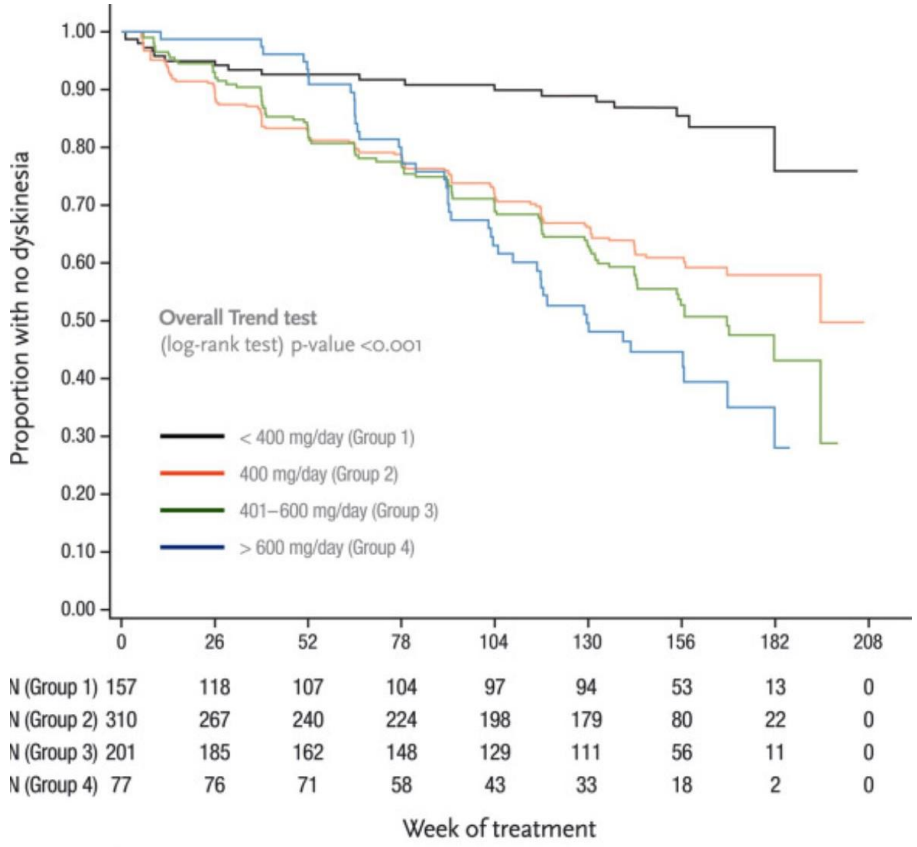


- **In both comparisons, the motor function, activities of daily living, and quality of life were superior in L-dopa-treated patients**

Both pivotal L-dopa vs DA trials (CALM-PD and 056) 2000

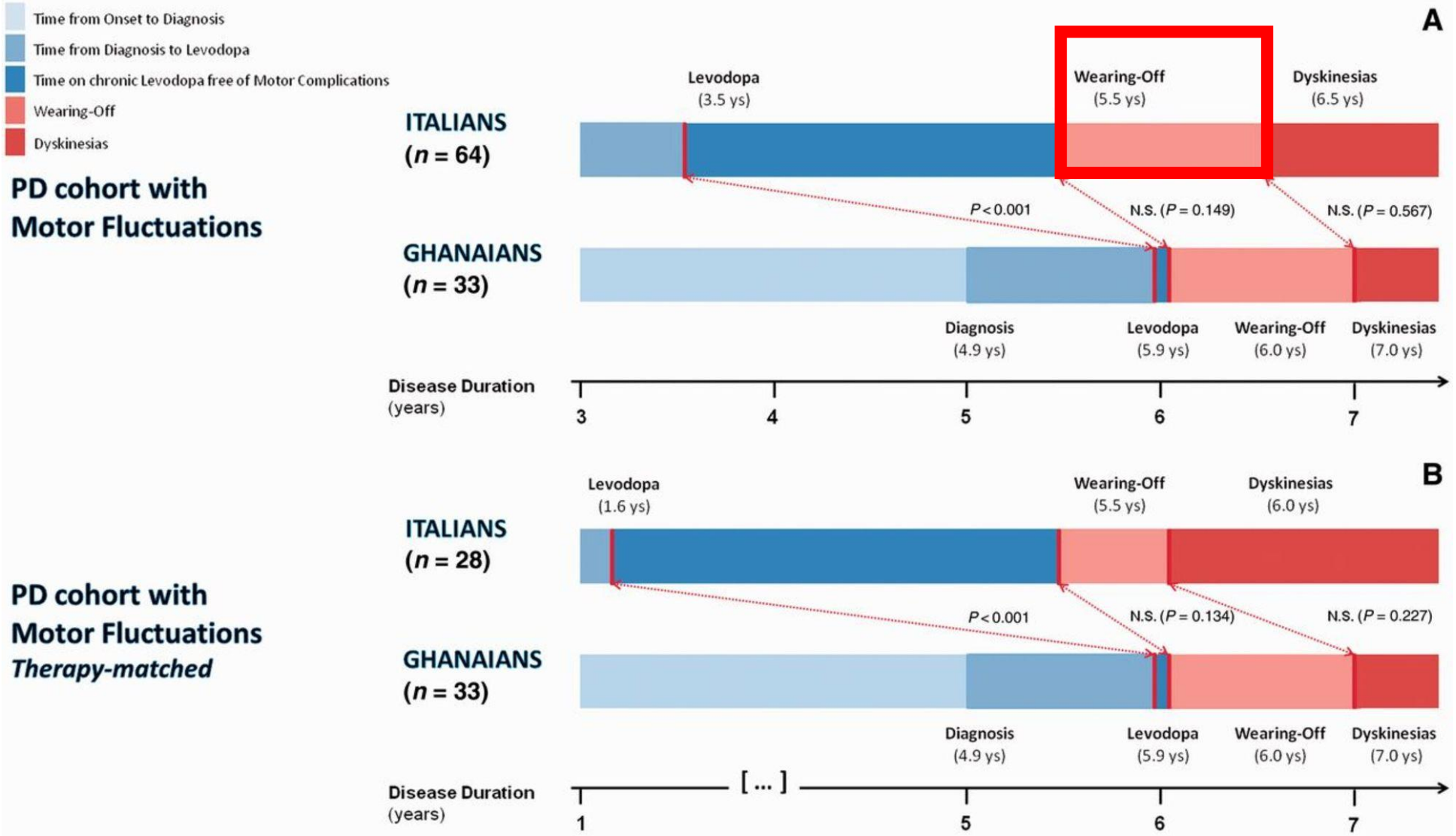
Factors predictive of the development of dyskinesia and wearing-off in Parkinson's disease (STRIDE-PD)

- Dose-dependent increased risk of developing dyskinesia and wearing-off
- The factors predictive of dyskinesia, in rank order, were **young age at onset, higher levodopa dose, low body weight, female gender, and more severe UPDRS Part II**.
- "Physicians should use the lowest dose of levodopa that provides satisfactory clinical control to minimize the risk of both dyskinesia and wearing-off"



Olanow CW et al, Mov Disord 2013 Jul;28(8):1064-71.

Motor fluctuations (OFF) and dyskinesia are **not associated with the duration of levodopa therapy**, but rather with disease duration



Cilia R et al. Brain. 2014;137(10):2731-2742. doi:10.1093/brain/awu195

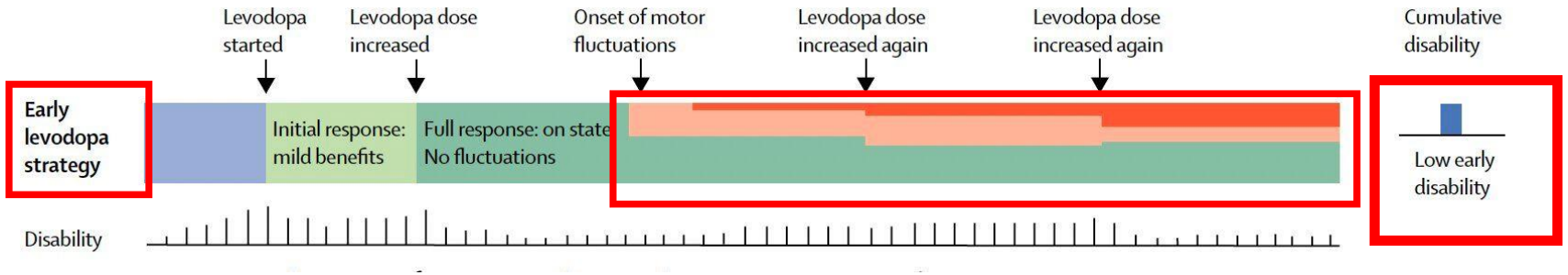
Dyskinesia as "measure of success"

	bPD	mPD	*p* value
Motor features			
Wearing-off in between L-dopa doses bPD ($n=210$) mPD ($n=142$)	77.6%	54.2%	$<.001$
Moderate to severe dyskinesia bPD ($n=208$) mPD ($n=149$)	19.2%	10.7%	.038

'Benign PD' (bPD): H&Y ≤ 3, normal cognition, and S&E ≥ 70 after ≥20 years (n = 210)
'Malignant PD' (mPD): H&Y > 3, S&E < 70, and dementia <10 years (n = 155).

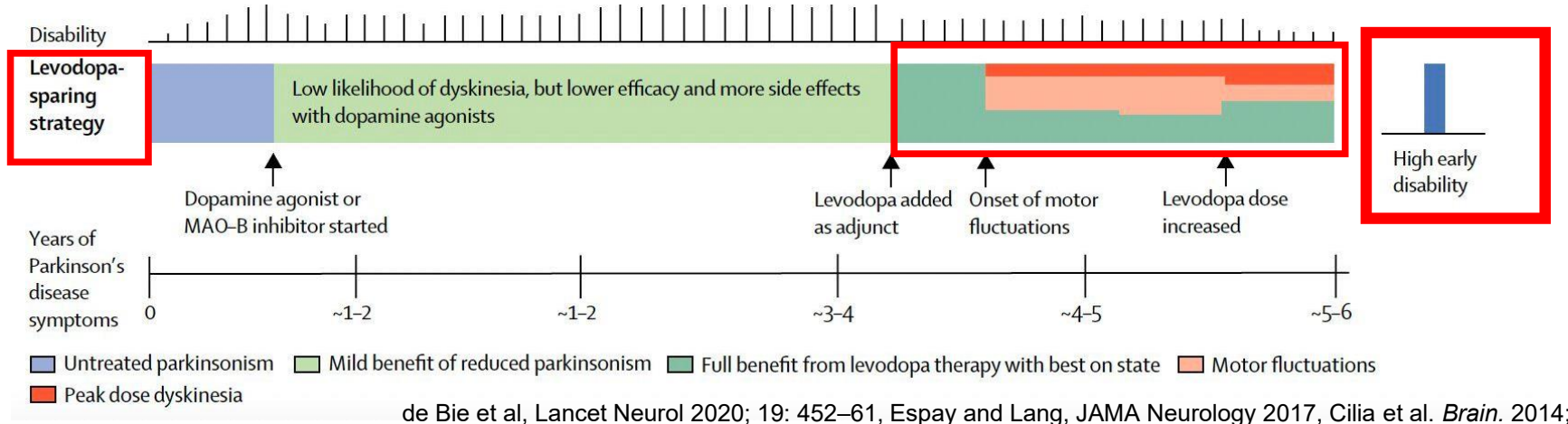
- Malignant PD: more depression, hallucinations, dysautonomia, and RBD
- The odds of malignant PD were significantly reduced by the presence of dyskinesia and wearing-off.

Merola et al, Benign versus malignant Parkinson disease: **the unexpected silver lining of motor complications.** Journal of Neurology (2020) 267:2949–2960



- Early levodopa: larger response and overall lower cumulative disability despite dyskinesia
- Dopamine agonists don't delay dyskinesia; they are largely incapable of generating it

An ostensible paradox
Disability is higher among patients with no or little dyskinesia over time, probably reflecting under-treatment



de Bie et al, Lancet Neurol 2020; 19: 452–61, Espay and Lang, JAMA Neurology 2017, Cilia et al. *Brain.* 2014;137(Pt 10):2731-2742.

Levodopa is the best dopamine replacement –if imperfect

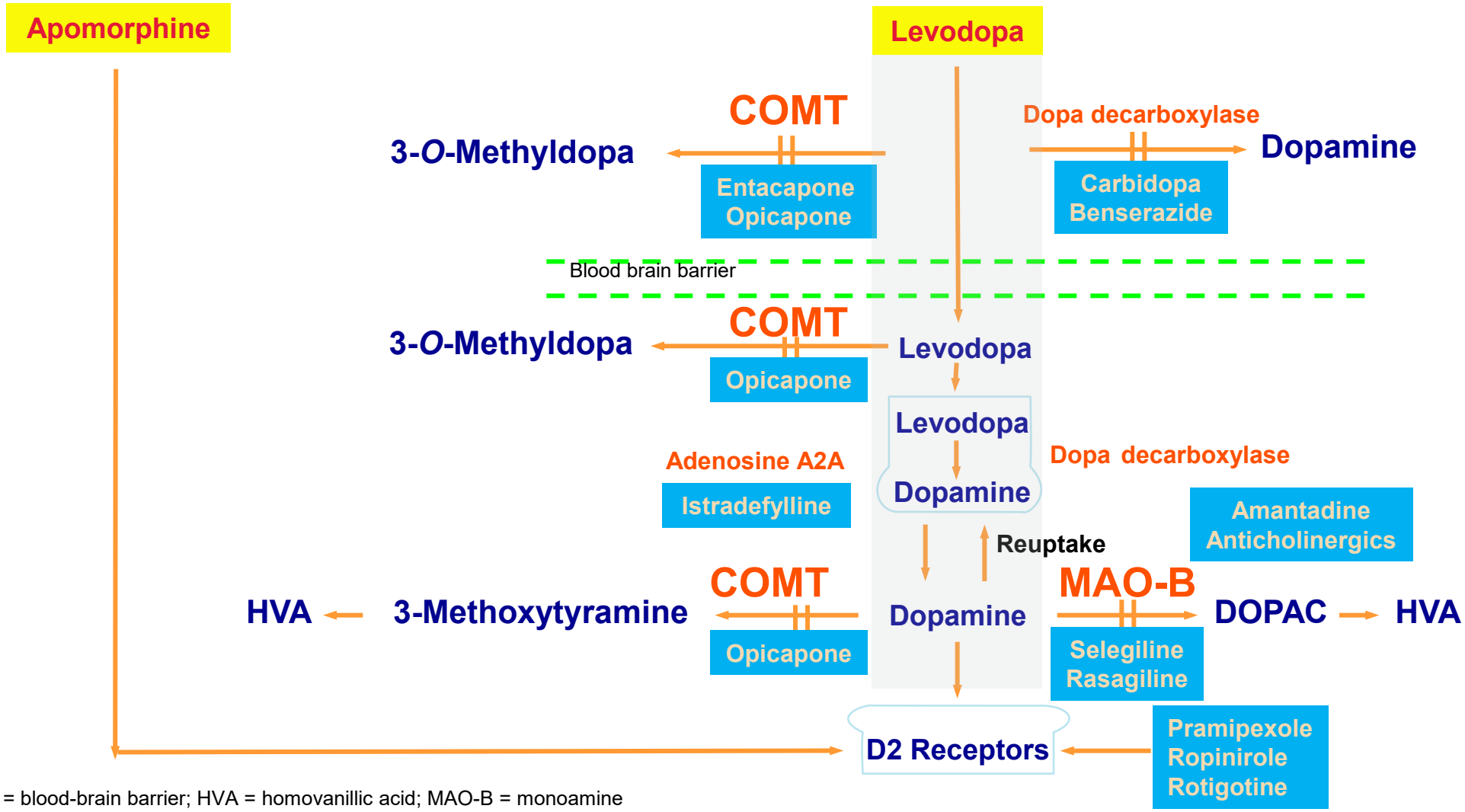
- Only levodopa can restore motor function. Dopamine agonists are largely incapable of doing so, or generating dyskinesia (SQ apomorphine is only equipotent drug)

- The clock for dyskinesia development begins to tick with disease onset rather than with levodopa initiation

- Dyskinesia is an artifact of the method of administration of levodopa rather than an intrinsic molecular effect of levodopa itself.

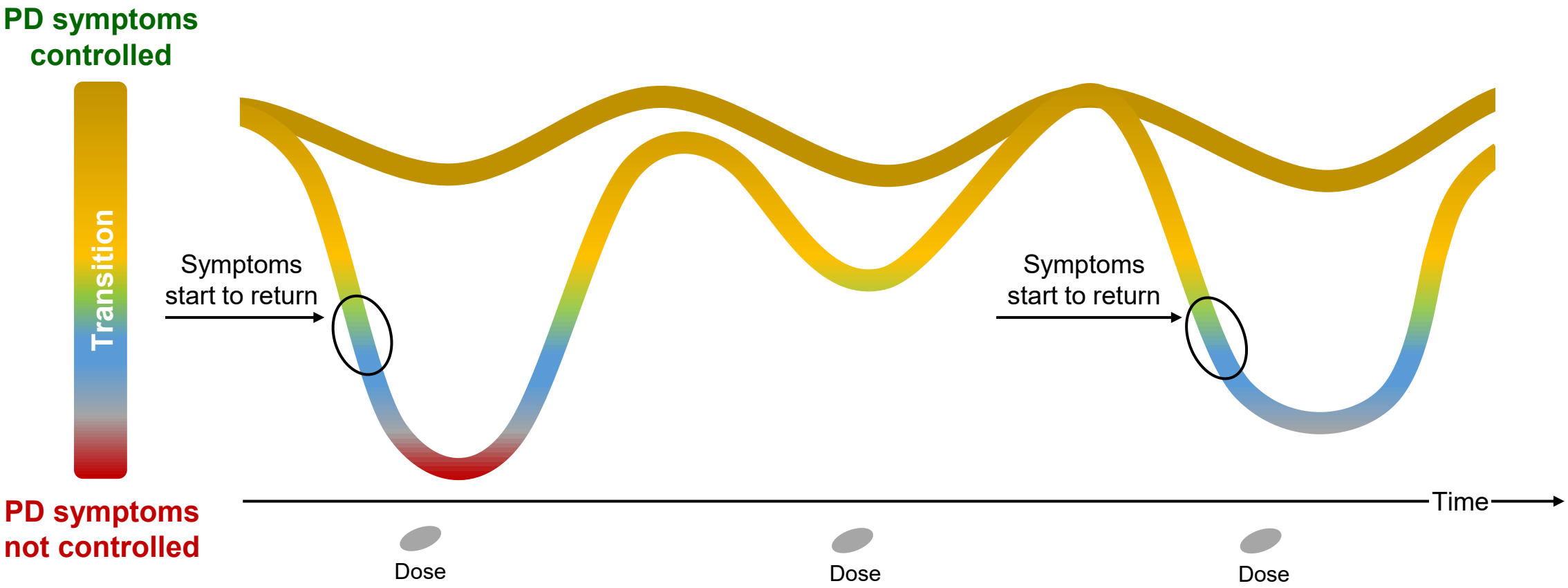
Fahn et. *N Engl J Med.* 2004;351(24):2498-2508.
Antonini et al *Mov Disord.* 2016;31(4):530-537.

The axis of treatment in Parkinson's disease



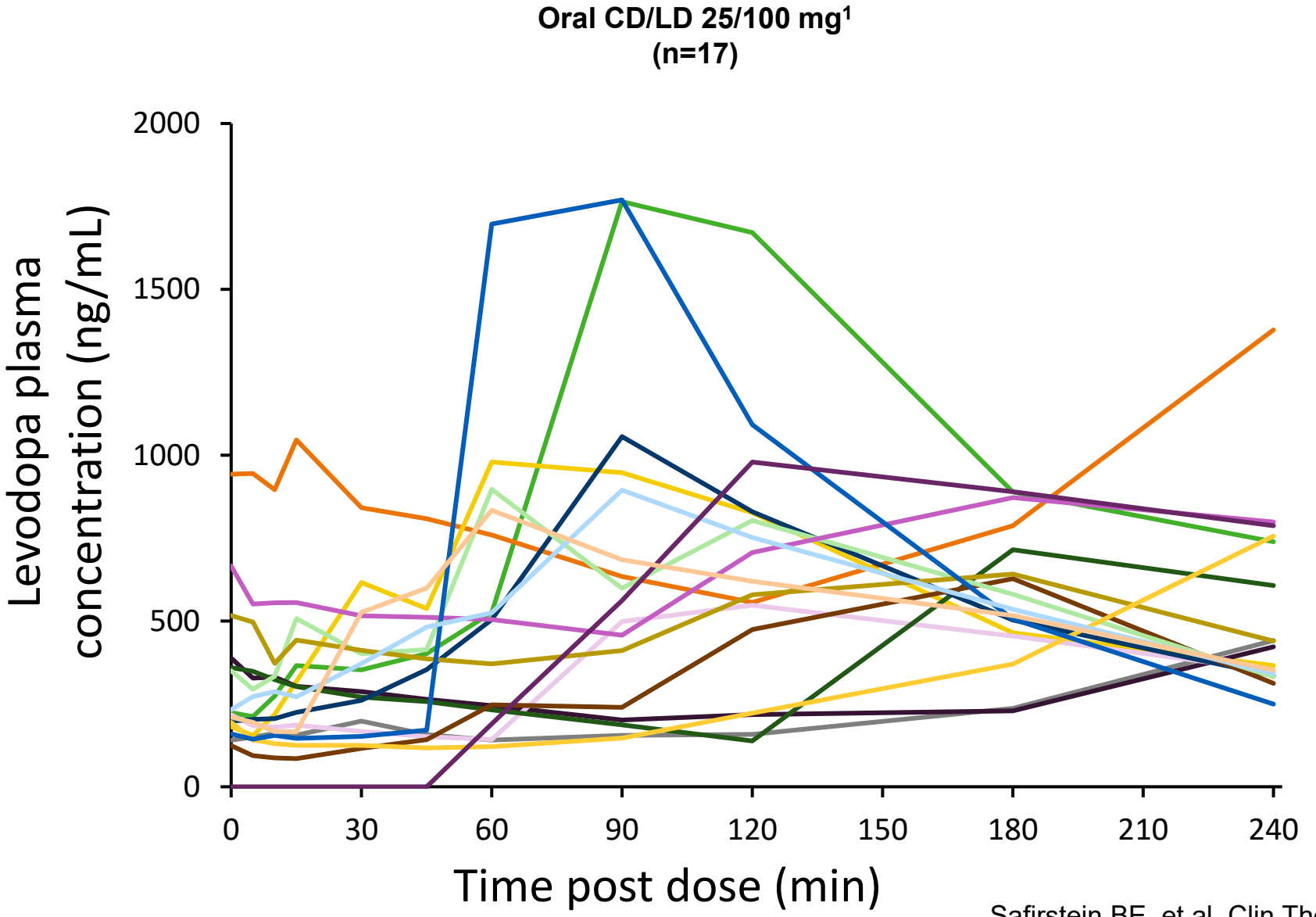
BBB = blood-brain barrier; HVA = homovanillic acid; MAO-B = monoamine oxidase-B; DOPAC = 3,4-dihydroxyphenylacetic acid.

Blood levels of levodopa may bring low brain levels



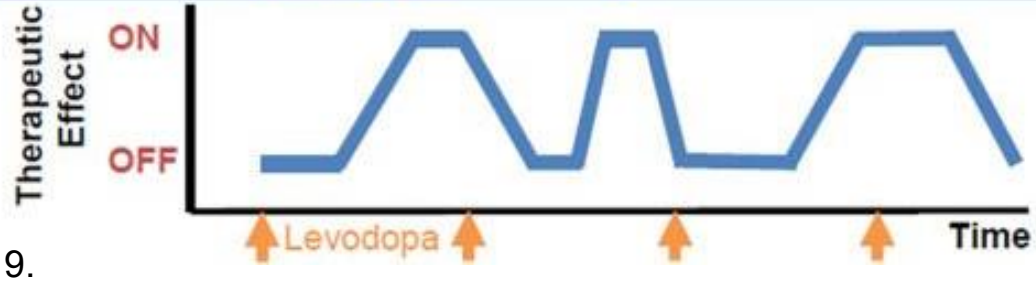
Chou KL, et al. Parkinsonism Relat Disord. 2018;51:9–16; Merims D, et al. Clin Neuropharmacol. 2003;26(4):196–198; Stocchi F, et al. Eur Neurol. 2010;63(5):257–266; Pahwa R, Lyons KE. Curr Med Res Opin. 2009;25(4):841–849

Absorption of IR levodopa varies greatly



Safirstein BE, et al. Clin Ther. 2020;42(6):1034–1046

Where do motor fluctuations come from?

Clinical pattern	Mechanism	
Wearing-off	Levodopa – half-life Pre-synaptic storage	
Delayed-on	Gastric emptying Intestinal absorption	
Dose-failures (No-ON)	Gastric emptying Intestinal absorption Blood–brain barrier transport	
Random ON-OFF	Striatal Pharmacodynamic Changes	

Chaudhuri KR et al, Mov Disord 2018 Jul;33(6):909-919.

Central Mechanisms

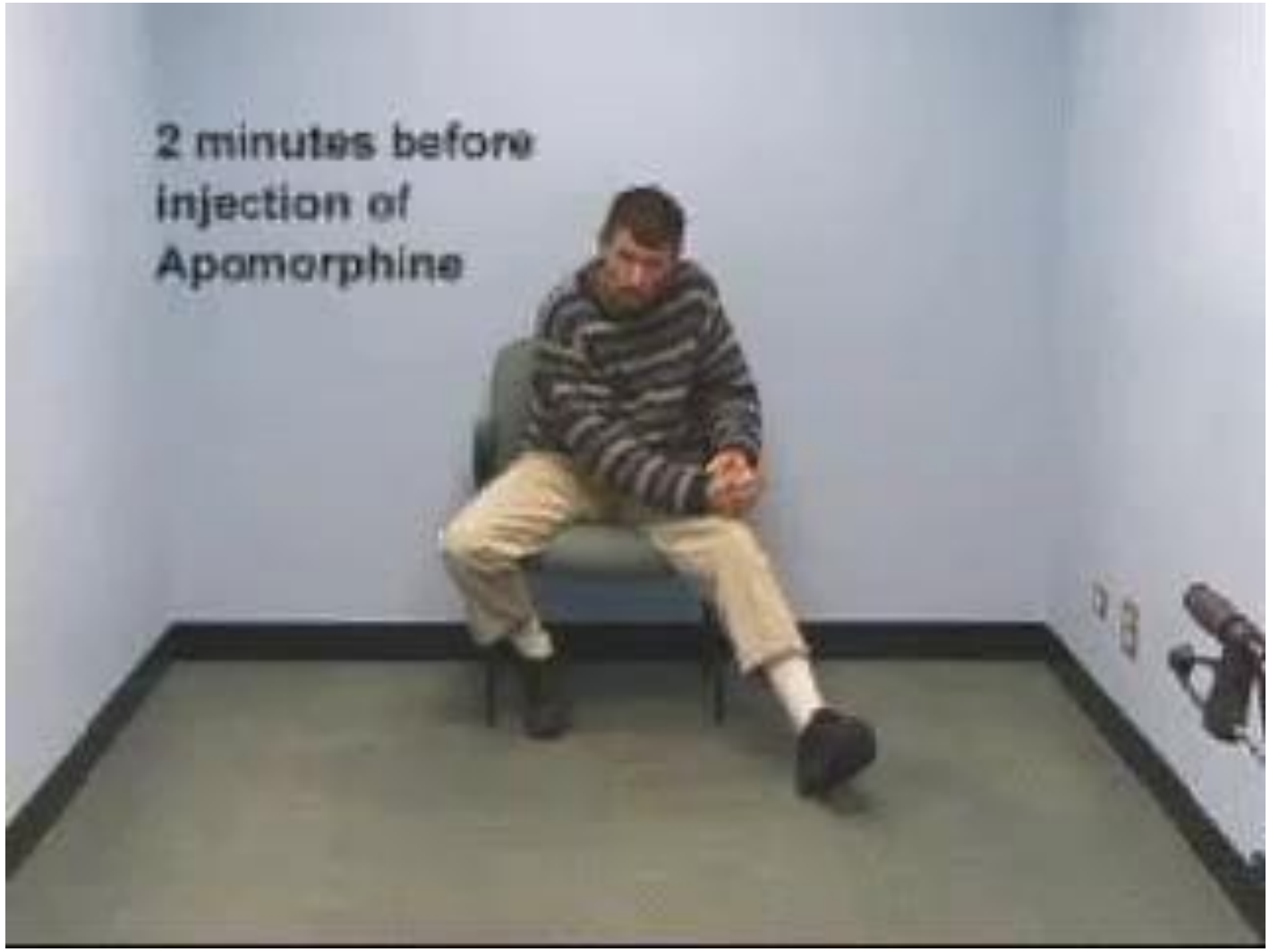
Preceding ON needed

Peripheral mechanisms

- Gastric/first pass
  - Delayed ON
  - Dose Failure
- H pylori
- SIBO
- Gut microbiota?

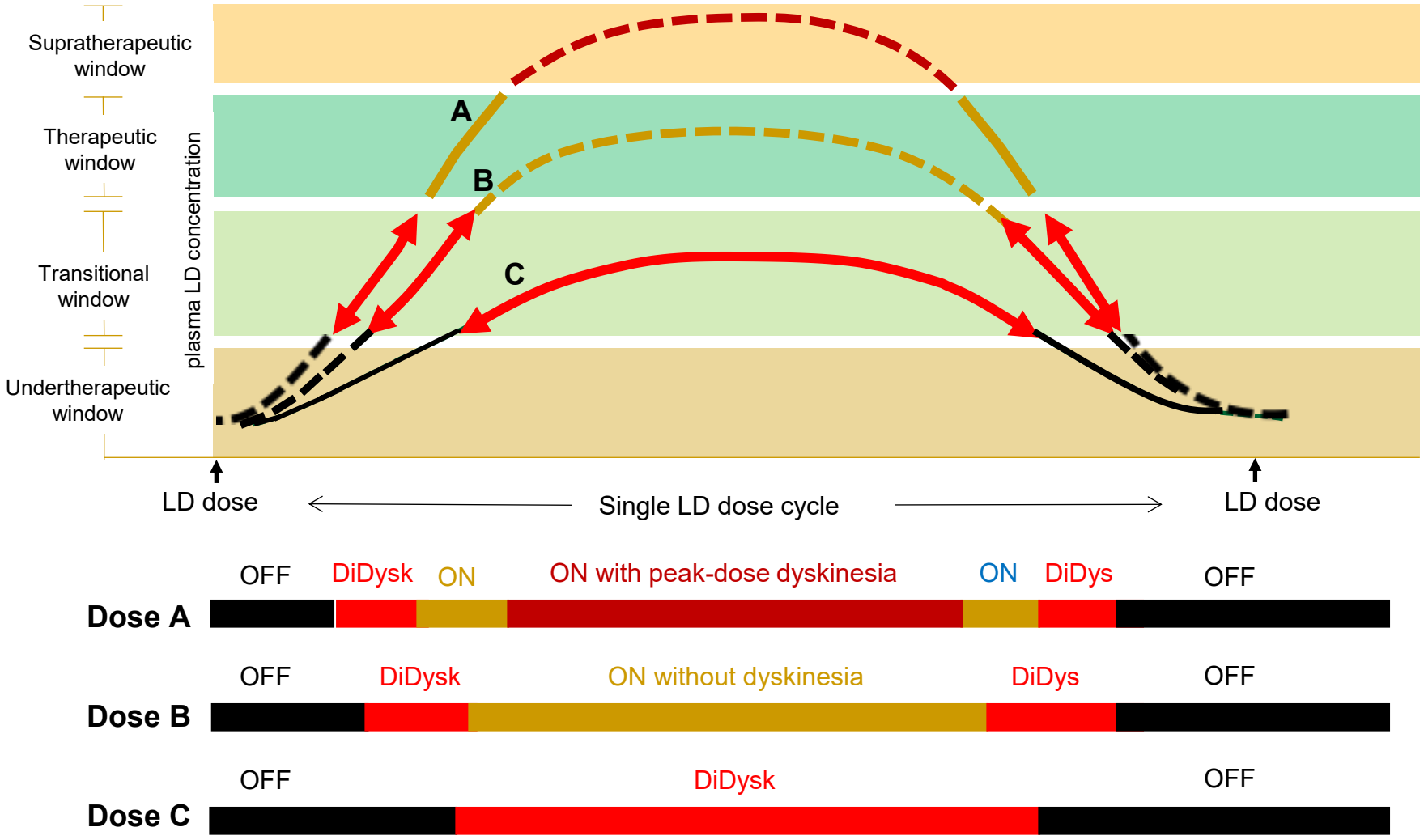
Some "never OFFs" included

A twist in the dyskinesia tale: diphasic dyskinesia



Verhagen Metman and Espay, Neurology 2017

Peak and Low-Dose (diphasic) dyskinesia can be similar



Management differs according to dyskinesia subtype:

Lower dopaminergic dose in peak-dose dyskinesia, higher in diphasic

Espay et al, Ann Neurol 2018

Summary on motor fluctuations

A full ON must be achieved for wearing OFF to be endorsed

OFF is the expression of a low dopaminergic state in PD patients on therapeutic doses of levodopa

No endorsement of OFF >5 years: Possibly undertreated state

OFF is a nearly unavoidable feature of optimally treated PD patients

Dopamine agonists don’t just “delay” dyskinesia

Dopamine agonists are largely incapable of generating dyskinesia without co-administered levodopa

Strategies minimize fluctuations (today's focus: red)

Oral therapies

Oral levodopa dose adjustments

- Increase IR levodopa dosing or frequency
- Switch to extended-release L-dopa

Adjunctive therapies

- Dopamine agonists
- COMT/MAO-B inhibitors
- Amantadine

Non-surgical

Subcutaneous therapies

- Foslevodopa infusion
- Levodopa infusion
- Apomorphine infusion

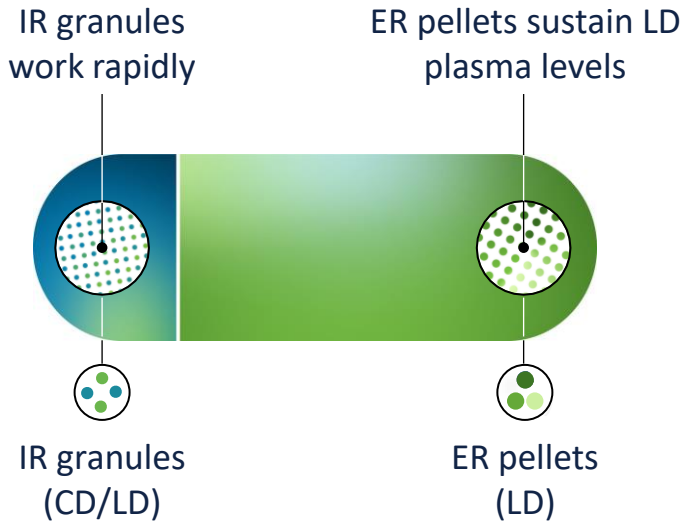
Surgical

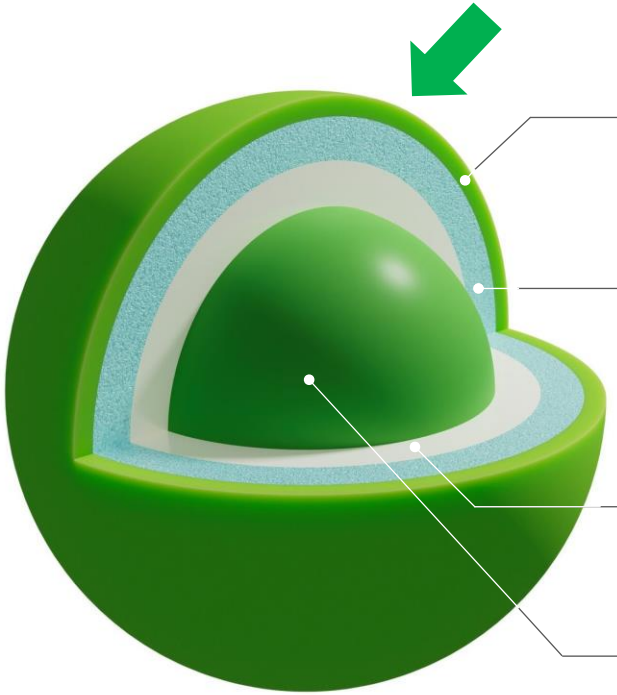
Surgical therapies

- LCIG infusion
- Deep brain stimulation
- Focused ultrasound

CD, carbidopa; COMT, catechol-O-methyltransferase; IR, immediate-release; LCIG, levodopa–carbidopa intestinal gel; LD, levodopa; MAO-B, monoamine oxidase B

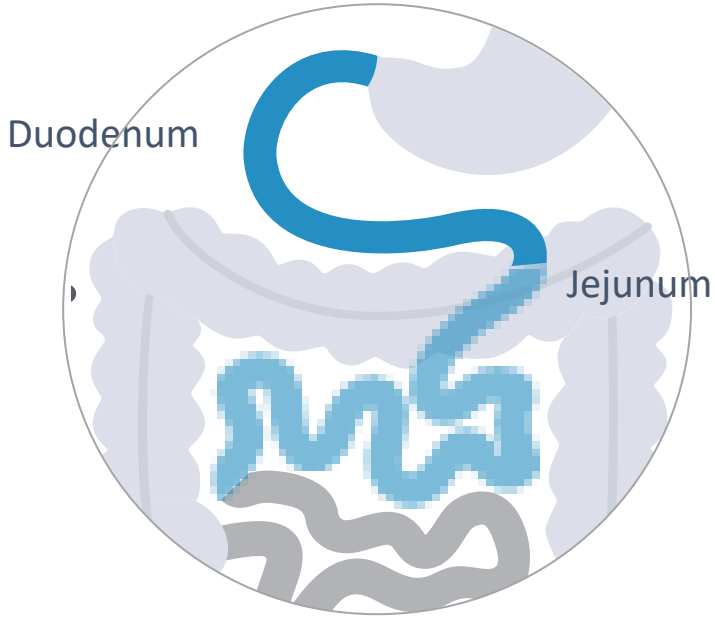
Extended-release levodopa 2.0: newest technology



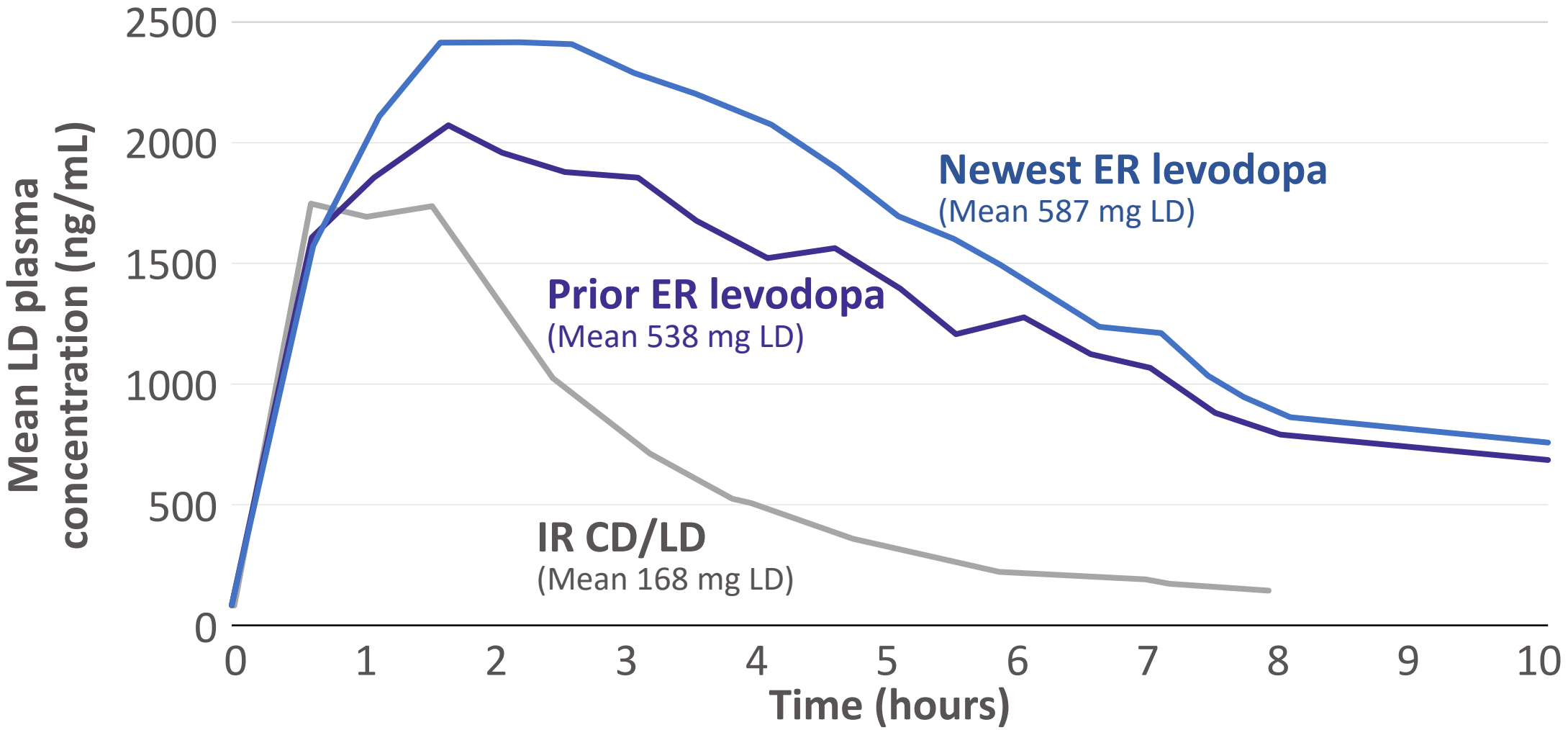


(Technology behind Crexont)

Result: longer time of adherence of levodopa to the areas of greatest absorption



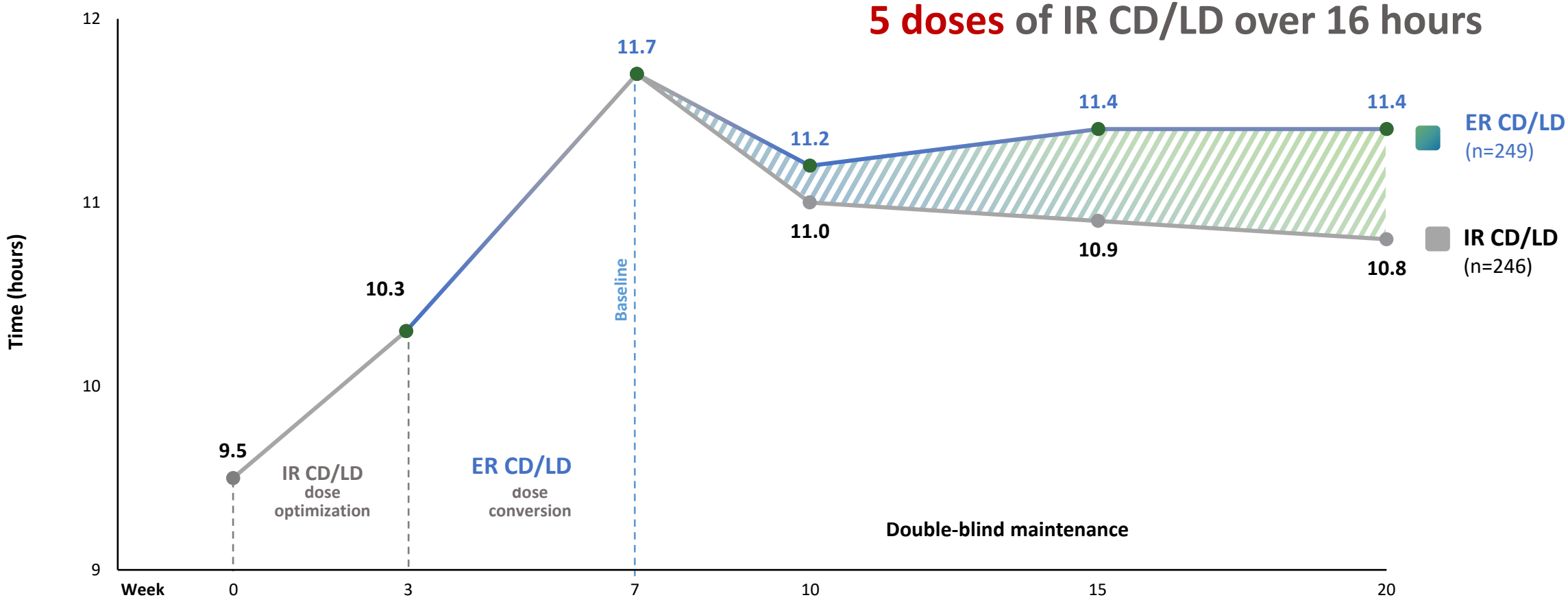
Measuring levels in blood



Modi NB et al. *Clin Neuropharmacol*. 2019;42(1):4-8.

More "Good On" time

0.5 hours difference in "Good On" time:
3 doses of ER CR/LD over 24 hours
versus
5 doses of IR CD/LD over 16 hours



Hauser RA et al. *JAMA Neurol*. 2023;80(10):1062-1069.

Less "Off" time

0.5 hours difference in "Off" time:
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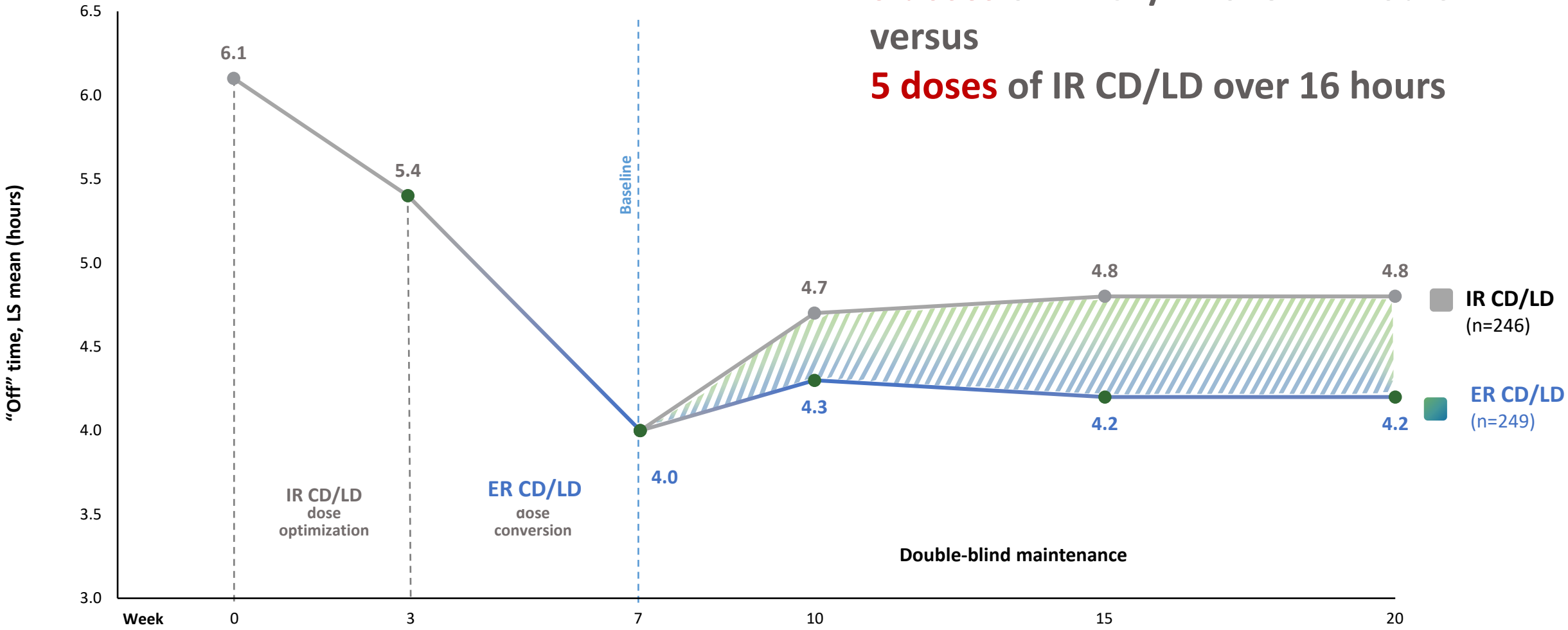
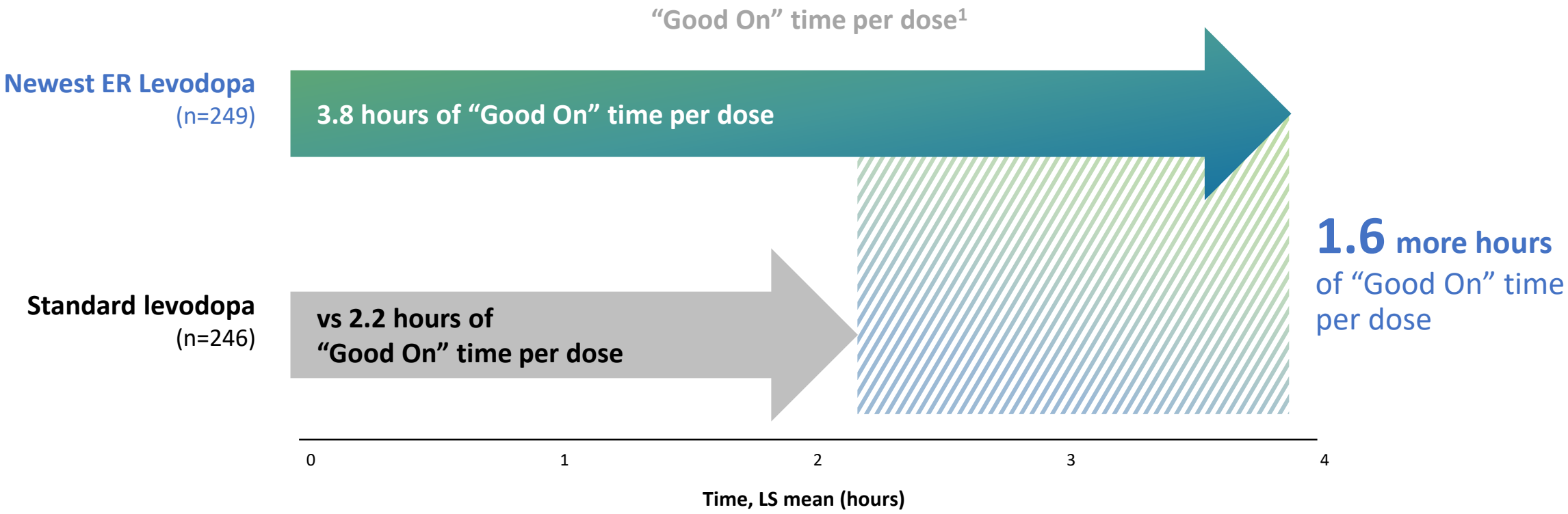


Hauser RA et al. *JAMA Neurol*. 2023;80(10):1062-1069.

"Good On" time per dose

A 70% increase vs standard immediate-release levodopa



Hauser RA et al. *JAMA Neurol*. 2023;80(10):1062-1069.

Similar side effect profile as standard levodopa

	Dose conversion period	Double-blind period	
ADVERSE REACTION	ER Levodopa (n=589)	ER Levodopa (n=256)	Standard levodopa (n=250)
Nausea	5%	4%	1%
Anxiety	2%	3%	0%
Dizziness	3%	2%	1%
Dyskinesia	7%	2%	0.4%
Constipation	2%	2%	0.4%
Headache	2%	1%	0%
Vomiting	2%	1%	0%
Insomnia	2%	1%	0.4%

Adverse reactions leading to discontinuation during dose conversion: dyskinesia, dizziness, and nausea

Hauser RA et al. *JAMA Neurol*. 2023;80(10):1062-1069.

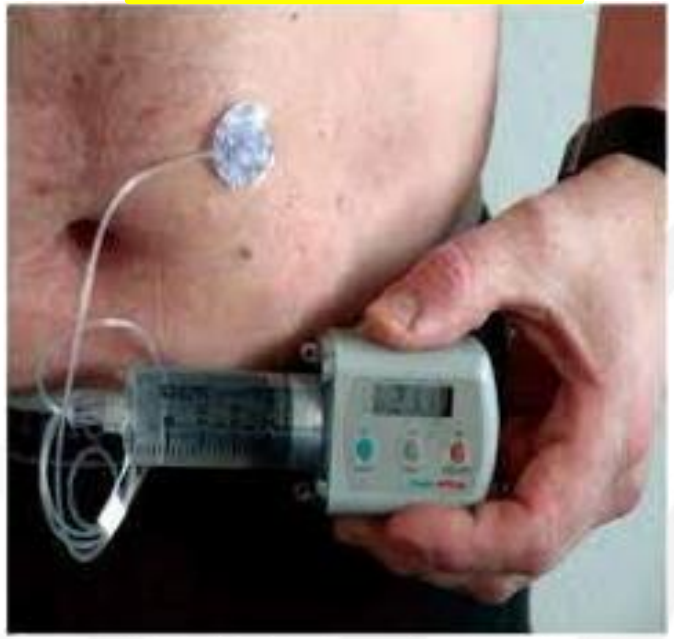
Subcutaneous infusions

Foslevodopa infusion

Vyalev.com

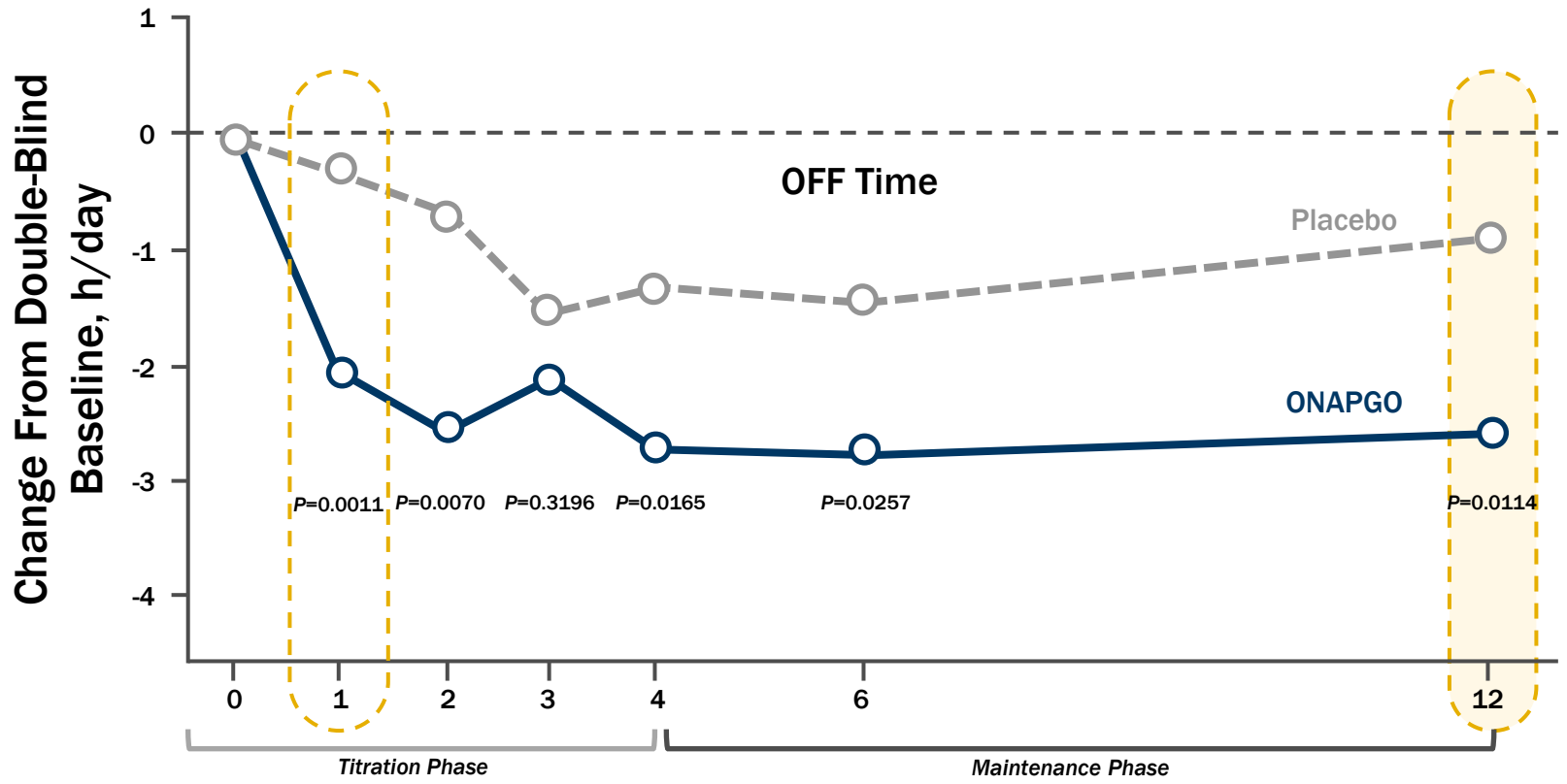
https://www.uchealth.org/today/vyalev-pump-eases-off-periods-for-advanced-parkinsons-patients/

Apomorphine infusion



https://medicaldialogues.in/neurology-neurosurgery/news/continuous-subcutaneous-infusion-delivery-of-apomorphine-beneficial-in-treating-parkinsons-disease-120250

Apomorphine infusion (TOLEDO study)



ONAPGO n =	53	51	50	50	47	44	42
Placebo n =	51	50	46	41	38	37	33

OFF time

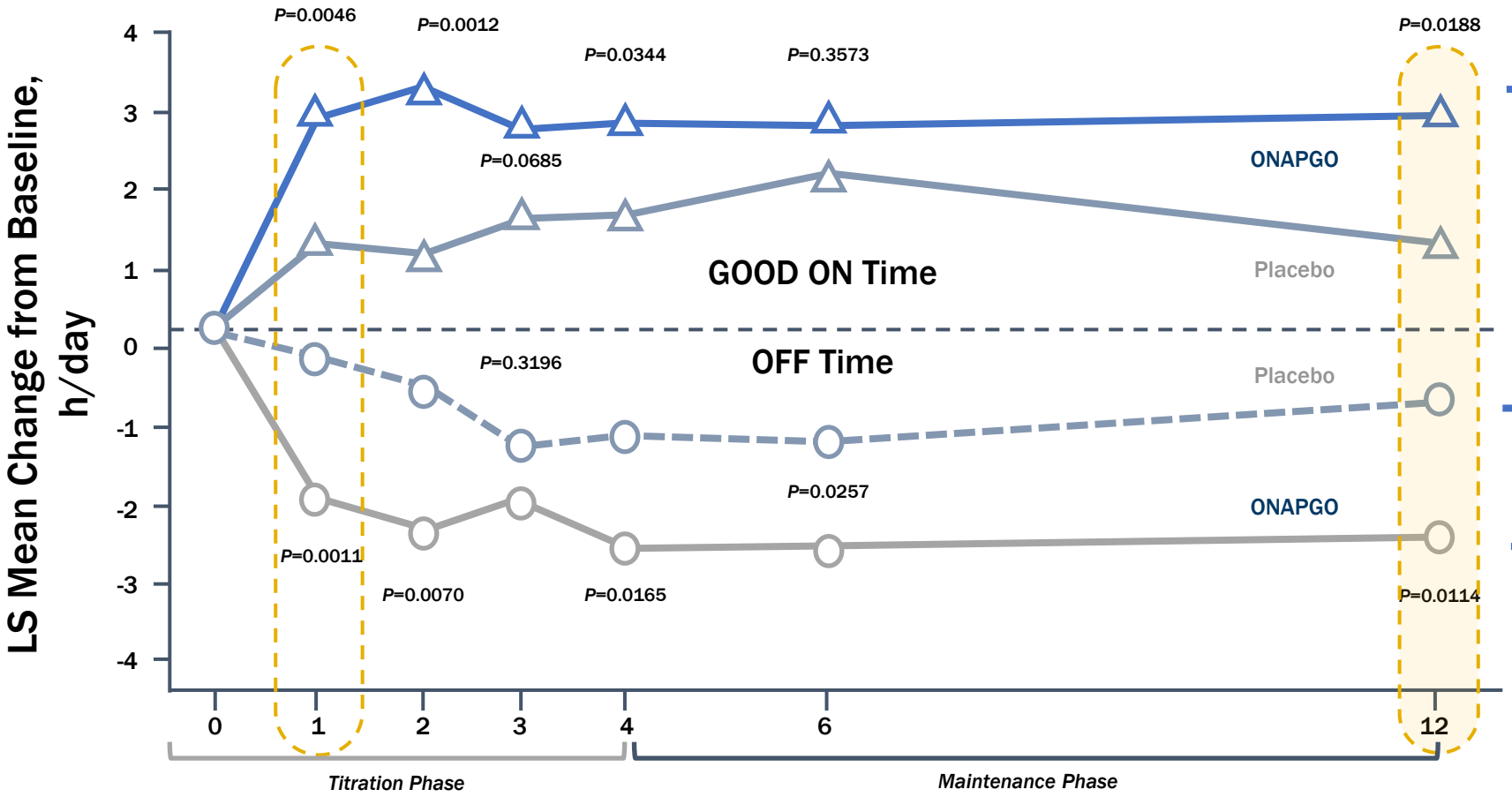
-0.9 h/day

-2.6 h/day

Reductions in daily OFF time as early as Week 1

Katzenschlager R, et al. Lancet Neurol. 2018;17(9):749-759.

Apomorphine infusion: ON time



ONAPGO n =	53	51	50	50	47	44	42
Placebo n =	51	50	46	41	38	37	33

'Good ON' time

+ 2.8 h/day

+ 1.1 h/day

OFF time

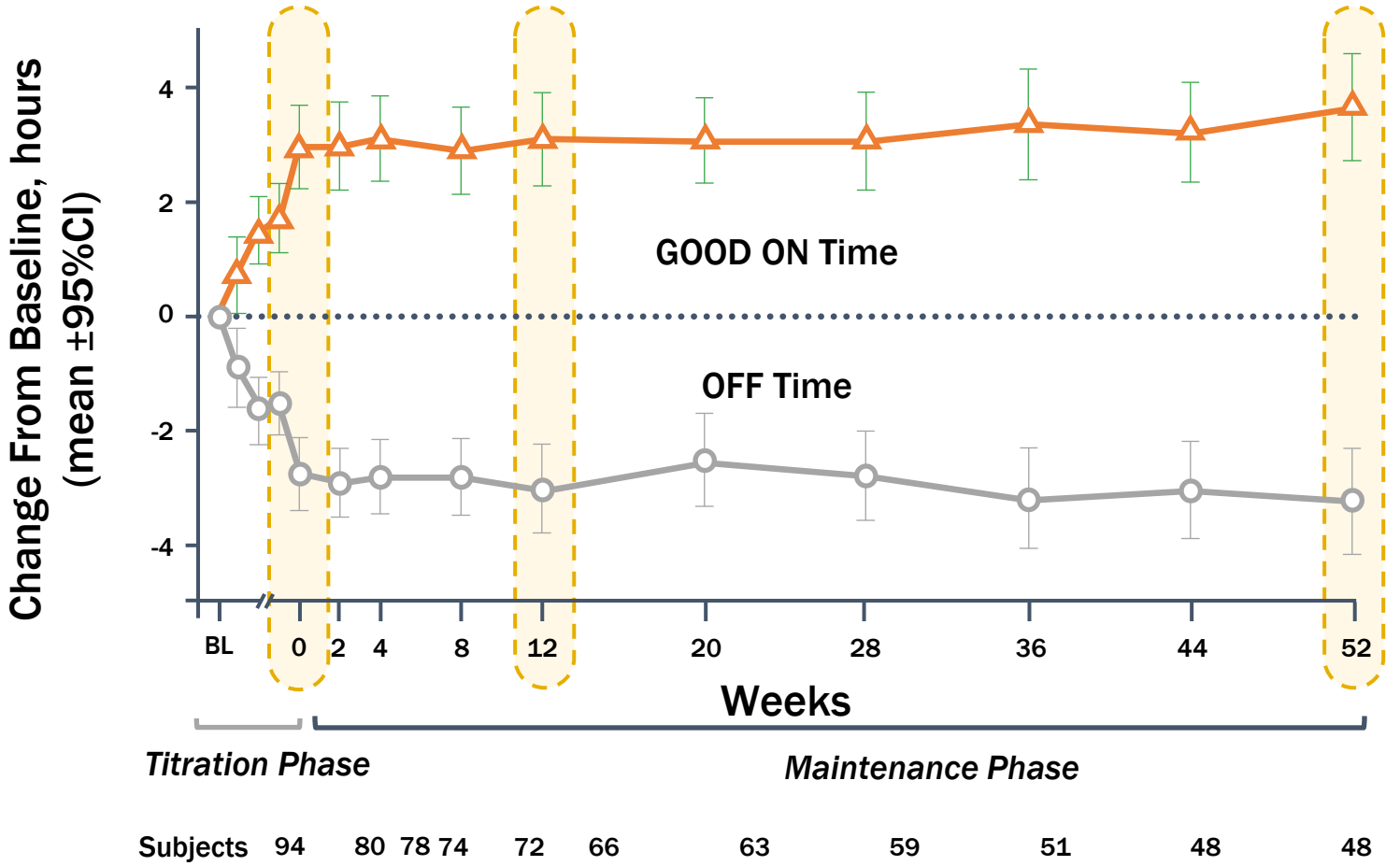
- 0.9 h/day

- 2.6 h/day

Increases in ON and reductions in OFF time as early as Week 1

Katzenschlager R, et al. Lancet Neurol. 2018;17(9):749-759.

Open-label Apomorphine study (InfusON study)



'Good ON' time

+ 3.7 h/day

OFF time

- 3.2 h/day

Increases in ON and reductions in OFF time as early as Week 1

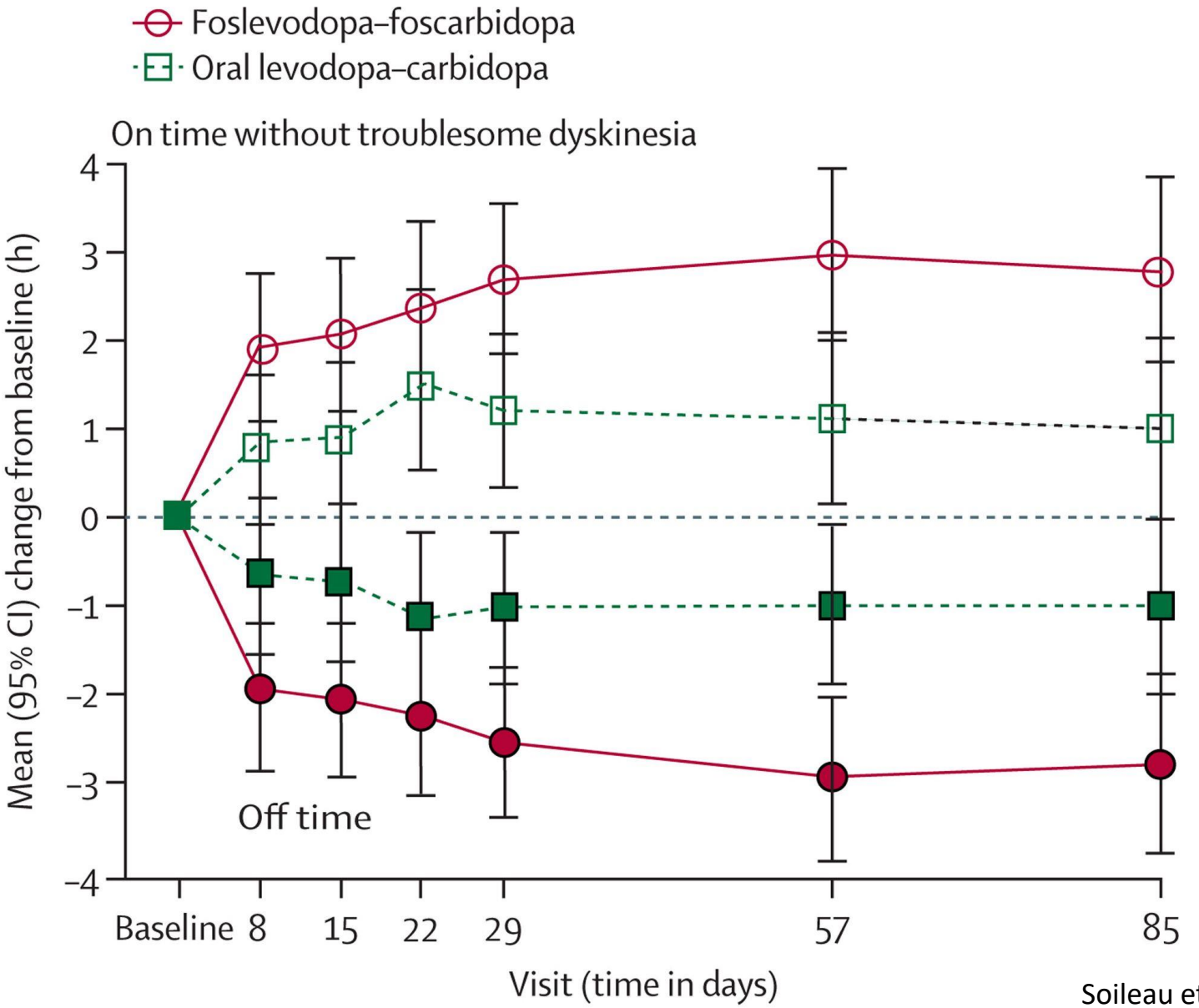
Isaacson SH, et al. J Parkinsons Dis 2025;0(0).

Side effect profile of apomorphine infusion

	ONAPGO, % (n=54)	Placebo, %(n=53)
Infusion site nodule	44	0
Nausea	22	9
Somnolence	22	4
Infusion site erythema	17	4
Dyskinesia	15	0
Headache	13	4
Insomnia	11	2
Dizziness	9	4
Hypotension	7	0
Asthenia	7	0
Fatigue	7	2
Constipation	7	6
Vomiting	7	4

Katzenschlager R, et al. Lancet Neurol. 2018;17(9):749-759.

Foslevodopa infusion pivotal trial



'Good ON' time

+ 2.7 h/day

+ 1.0 h/day

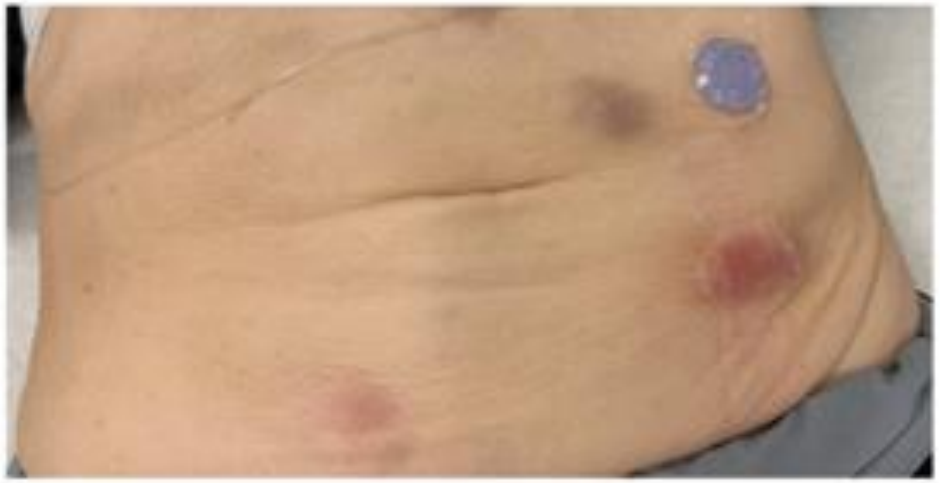
OFF time

- 1.0 h/day

- 2.8 h/day

Soileau et al, Lancet Neurol 2022 Dec;21(12):1099-1109

Side effects



Neimann et al 2021

	Oral levodopa-carbidopa	Foslevodopa-foscarbidopa
Adverse events of special interest		
Infusion site events	8 (12%)	53 (72%)
Hallucinations or psychosis	2 (3%)	11 (15%)
Falls and associated injuries	17 (25%)	13 (18%)
Somnolence	1 (1%)	1 (1%)
Polyneuropathy	2 (3%)	2 (3%)
Weight loss	1 (1%)	1 (1%)
Most frequent adverse events‡		
Infusion site erythema	1 (1%)	20 (27%)
Infusion site pain	1 (1%)	19 (26%)
Infusion site cellulitis	0	14 (19%)
Infusion site oedema	0	9 (12%)
Dyskinesia	4 (6%)	8 (11%)
Fall	12 (18%)	6 (8%)
Infusion site bruising	2 (3%)	6 (8%)
Infusion site haemorrhage	0	6 (8%)
Infusion site nodule	0	6 (8%)

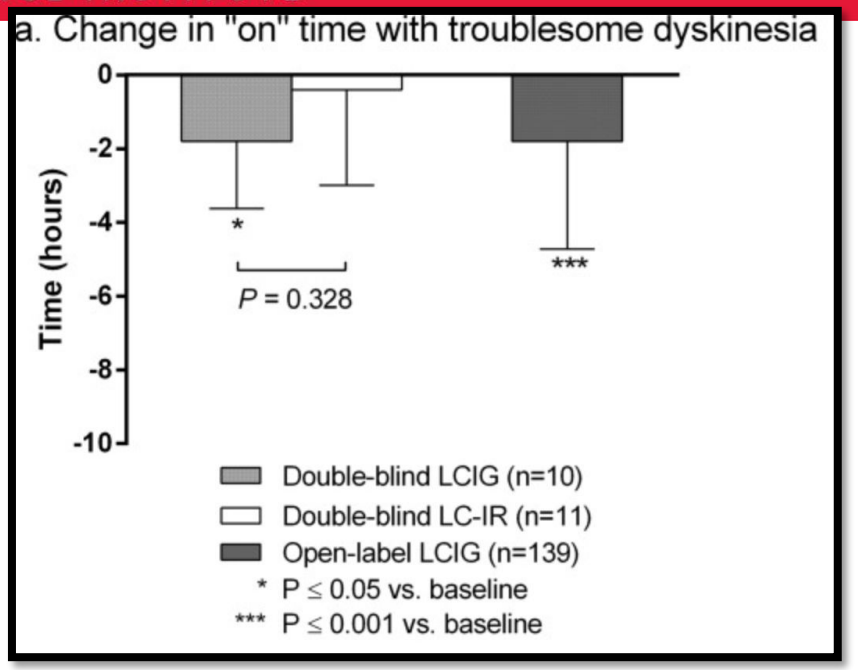
Soileau et al, Lancet Neurol 2022 Dec;21(12):1099-1109

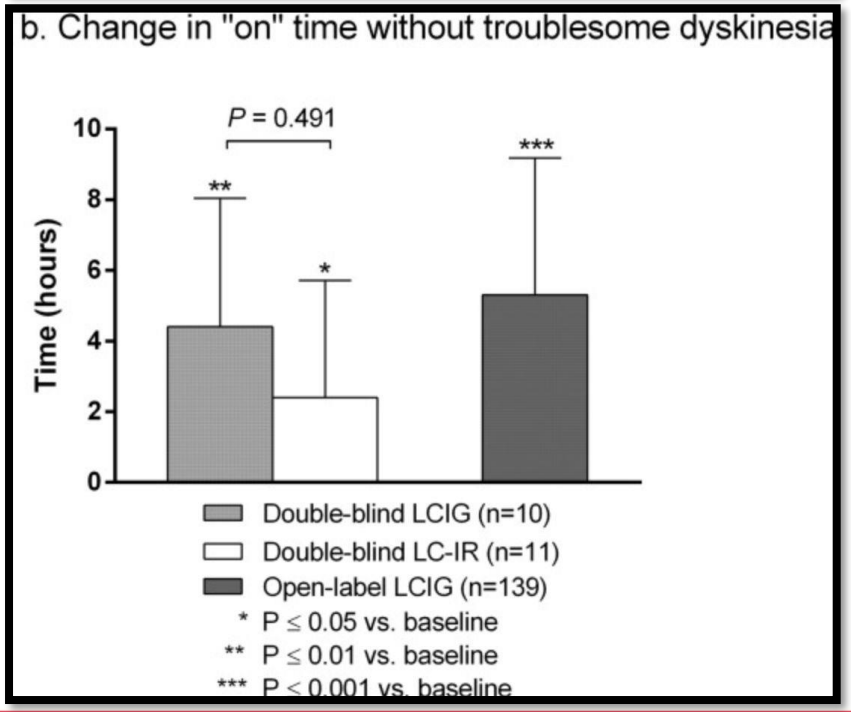
A note about dyskinesia with infusions*

Lower dyskinesia despite increased levodopa exposure

- Observed after the 2nd week of treatment with LCIG
- The mean levodopa dose was ~90 mg higher than baseline and ~400 mg higher in the longer, open-label study.
- Improvement may be related to change in levodopa pharmacokinetics

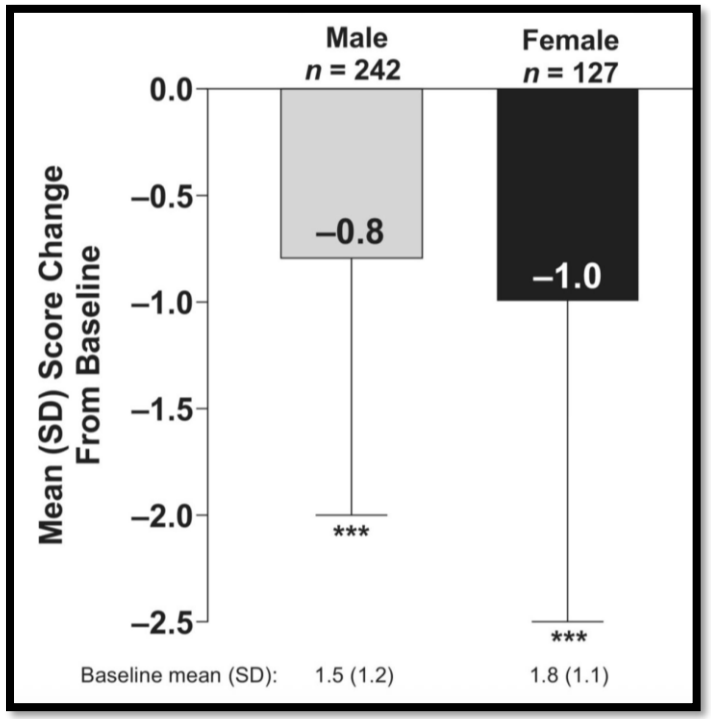
(Note: peripheral levodopa levels, including Cmax, were not measured in these studies)



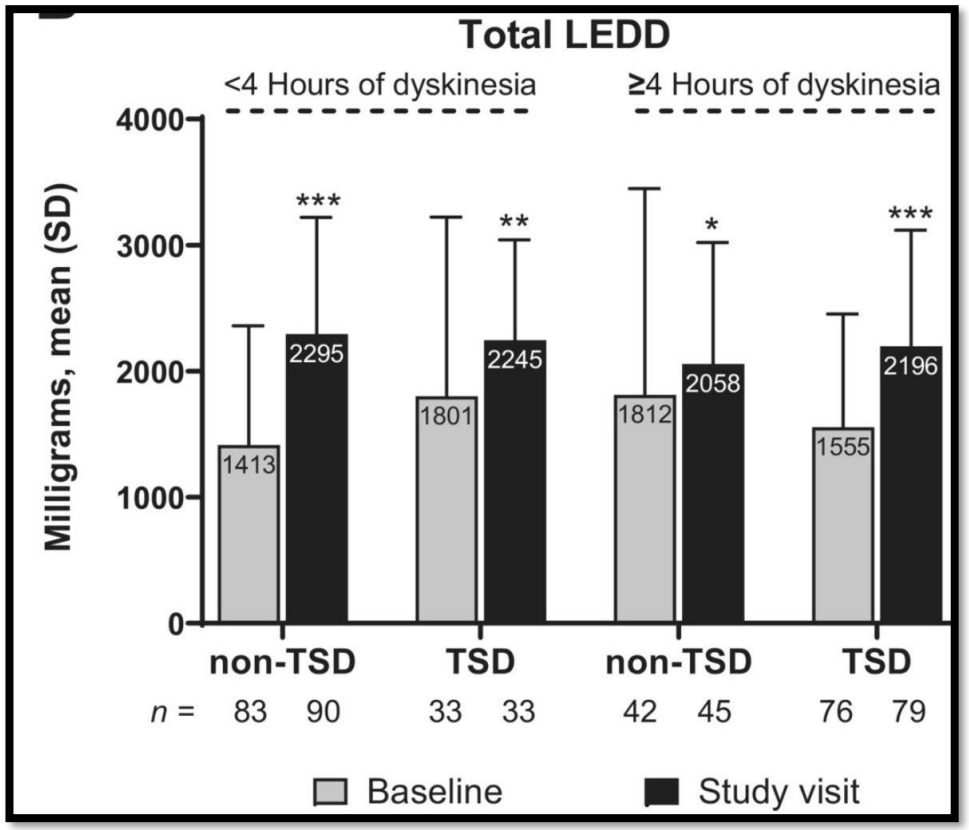


Antonini et al, Mov Disord 2016 Apr;31(4):530-7.

Lower dyskinesia despite increased levodopa exposure



Lower dyskinesia duration and severity



- A significant increase in mean total LEDD was observed from baseline to study visit, regardless of how much or what type of dyskinesia (TSD, non-TSD) there was

Fasano et al, Mov Disord Clin Pract 2025 (in press)

More levodopa and less dyskinesia?*

- Better PK profile with attenuation of peak effect
- More physiologic delivery to dopamine receptors
- A subset of dyskinesia is diphasic (low-dose) –which improves with higher dose of levodopa

- *At least in the short term

Candidates for Extended-release levodopa (Crexont) and Infusion systems (Onapgo, Vyalev):

- **Severe motor fluctuations** between "on" and "off" (Crexont)
- **Troublesome dyskinesia** (Onapgo, Vyalev)
- **Levodopa effect is short-lived**, requiring frequent dosing (Crexont)
- **Swallowing problems** making it hard to take pills (Onapgo, Vyalev).
- Considering but not ready for deep brain stimulation (Onapgo, Vyalev)
- Having a caregiver who can assist is very helpful for infusion systems

Soileau et al, J Neurol 2025;272(6):416.

Infusion delivery systems: old dogs, new tricks

- **Apomorphine and Levodopa** remain the most effective symptomatic treatments
- **Their benefits are enhanced through novel delivery** technologies: ER capsules and SQ infusion systems
- **Key goal: extension of the "Good ON" time** with corresponding reductions in "off" time
- Pre-existing dyskinesia is reduced with higher but sustained levodopa delivery, even at higher doses
- Future studies may assess if early ER L-dopa and SQ infusion may delay the onset of wearing off & dyskinesia