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Pathophysiology of Motor Fluctuations

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Funded by PARKINSON'S UK CHANGE ATTITUDES. FIND A CURE. JOIN US.

Oxford Parkinson's Disease Centre

UNIVERSITY OF OXFORD

NHS Oxford University Hospitals NHS Foundation Trust

Disclosures

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M Hu is an advisory founder and shareholder of NeuHealth Digital Ltd (company number: 14492037), a digital biomarker platform to remotely manage condition progression for Parkinson's

Talk Outline

Pathophysiology of Motor Fluctuations:

1. Terminology & epidemiology of motor fluctuations
2. The long and short-term response to levodopa
3. Pathophysiological mechanisms of motor fluctuations
4. Non-motor fluctuations
5. The patient experience

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1. **Terminology** & epidemiology of motor fluctuations

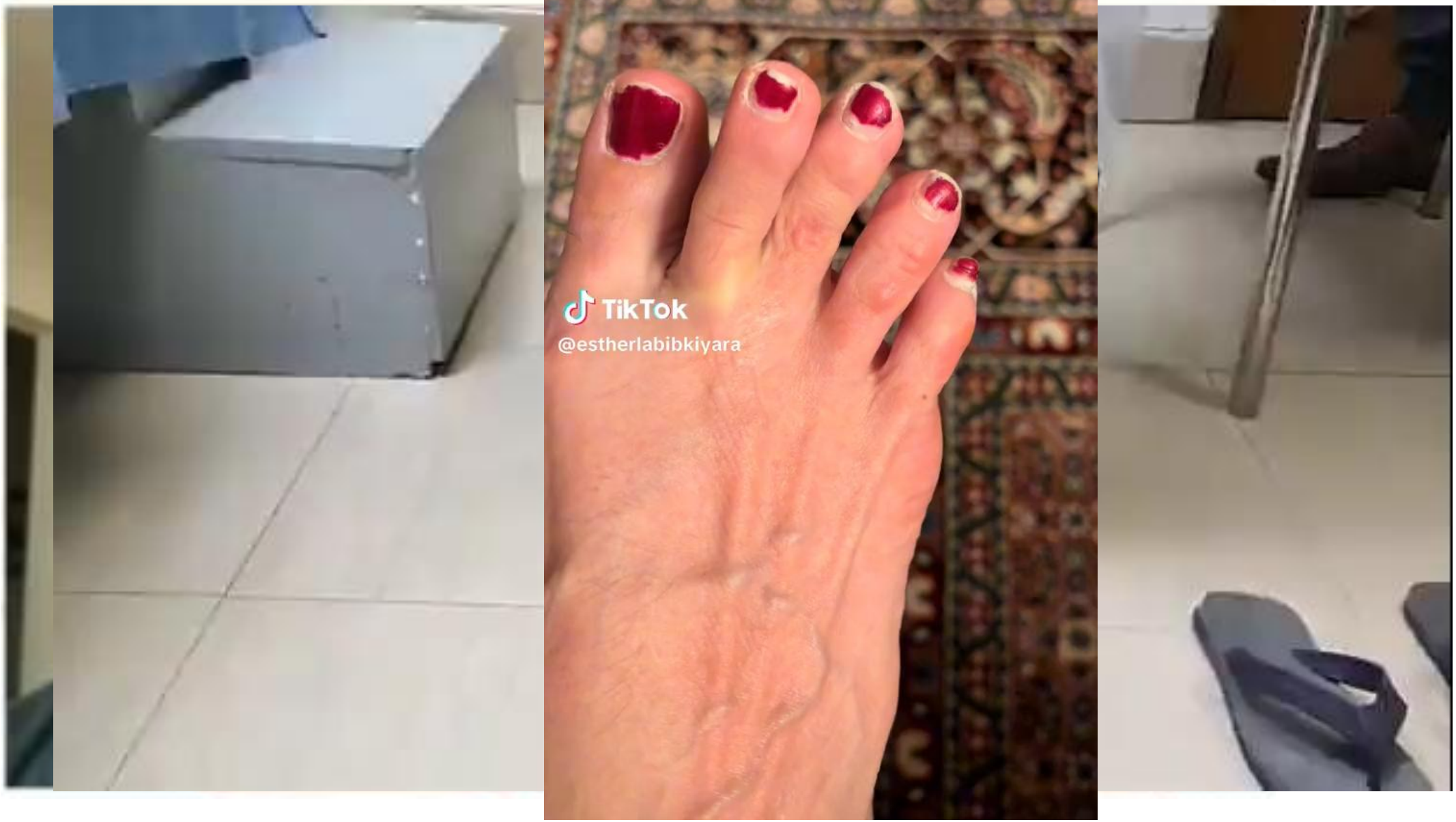
- Over time, duration and reliability of levodopa benefit decline leading to ON times when l-dopa providing good benefit (reduced PD signs and symptoms and improved functional status) and OFF times when PD symptoms or signs re-emerge and functional status declines
- Motor fluctuations = transition between ON and OFF

- OFF can occur gradually (wearing off or end-of-dose deterioration), or rapid (ON-OFF fluctuations, and unexpectedly ('sudden' or 'random' OFFS
- Delayed ON = time to on longer than usual
- Partial ON = suboptimal compared to usual benefit
- Dose failure = no benefit following l-dopa dose
- OFF first thing am = early morning off/akinesia
- Practically defined OFF = 12 hour overnight medication withdrawal
- Fluctuations also occur with other PD meds eg apomorphine

1. **Terminology** & epidemiology of motor fluctuations

- **LID = levodopa induced dyskinesias:**
- **peak dose 90%** (chorea, ballism, stereotopy > dystonia or myoclonus, worse on most affected side)
- **diphasic/biphasic 10%** (immediately before or after l-dopa dose as plasma levels rising or falling (dystonia> ballism, usually LL's
- **Others <2%):** abnormal eye movements (eg stereotyped upgaze or horizontal gaze deviation that are jerky, tonic or more sustained, disordered breathing, involuntary abdominal movements (belly dancers dyskinesias), and punding (compulsive sorting of objects)
- **Painful dystonia** during Off can occur esp early morning akinesia- typically LLs, inversion/plantar flexion of toes > other regions. More common in YOPD.
- **Early lower face dystonia suggests APD** eg MSA

Foot Dystonia in YOPD



RESEARCH ARTICLE

Predictors of Motor Complications in Early Parkinson's D
A Prospective Cohort Study

Kelly MJ, 2019, DOI:10.1002/mds.27783

- Oxford Discovery inception cohort of 734 PD< followed up to max 10 yrs
- 186 LID, 253 OFF periods observed
- Confirmed previous risk factors, additionally good levodopa benefit and baseline non-motor symptoms (MDS-UPDRS I scores) predictive

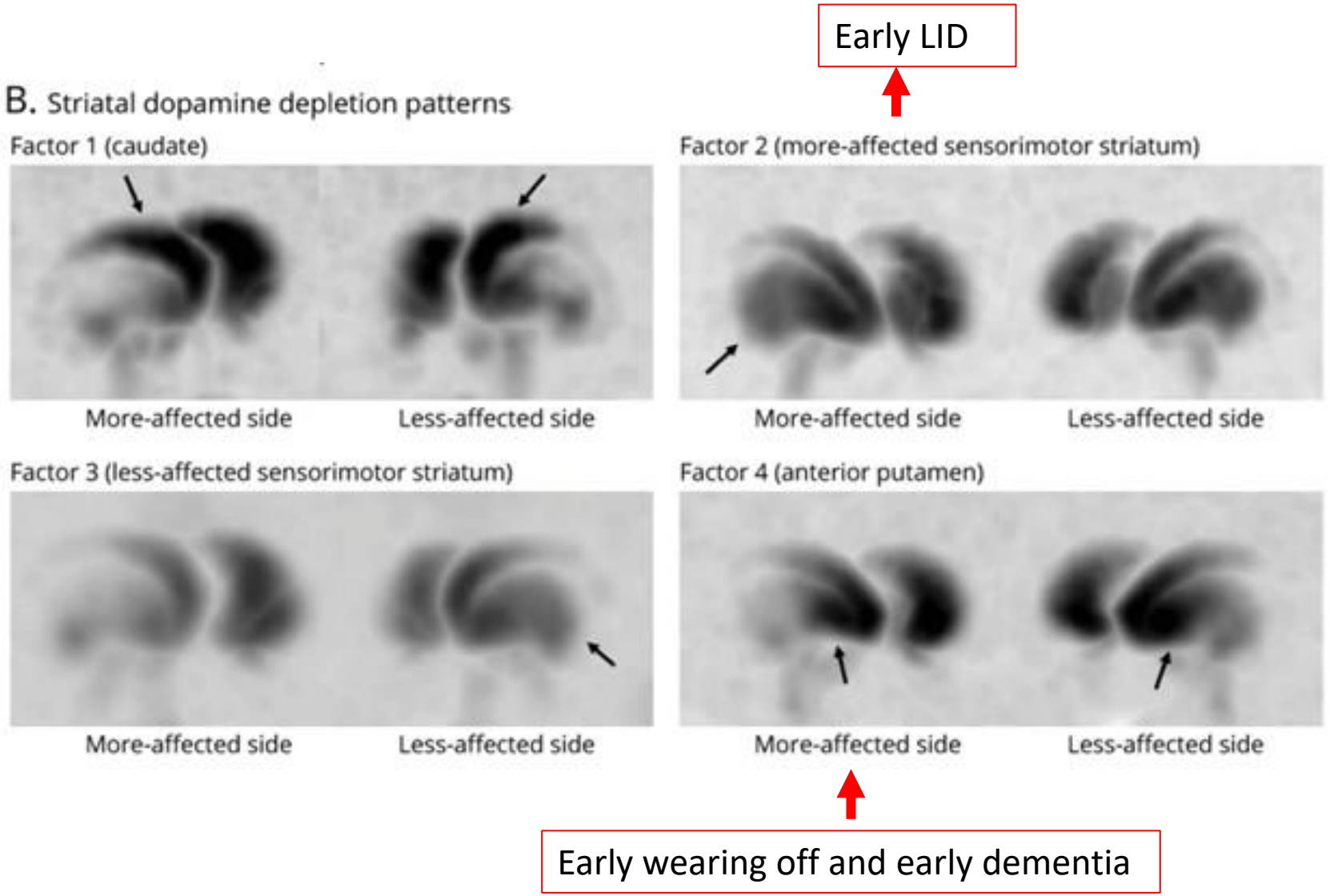
	Variables	Univariable Exp(B) (95% CI)	Univariable P	Multivariable Exp(B) (95% CI)	Multivariable P
Time (Yrs)	Time		0.04		0.49
	<3.5				
	3.5-5	1.31 (0.90, 1.9)	0.16	1.12 (0.75, 1.68)	0.58
	5-6.5	1.57 (1.00, 2.47)	0.05	1.17 (0.70, 1.95)	0.55
	≥6.5	2.02 (1.17, 3.47)	0.011	1.61 (0.88, 2.97)	0.12
Medication Factors	Levodopa dose (mg/100)[a]	1.20 (1.13, 1.28)	<0.001	1.17 (1.09, 1.25)	<0.001
	Medication response[a] (1-Very much improved – 7-very much worse)	0.55 (0.45, 0.66)	<0.001	0.61 (0.49, 0.75)	<0.001
	Levodopa treatment duration (Years)[a]	1.05 (0.97, 1.14)	0.24		
	DA use[a]	0.91 (0.65, 1.28)	0.60		
	MAOBI use[a]	1.24 (0.89, 1.72)	0.20		
Motor Features	MDS-UPDRS II (/5) [a]	1.02 (1.00, 1.044)	0.059		
	MDS-UPDRS III (/5) [a]	0.99 (0.97, 1)	0.044		
	Disease Phenotype[a] (Tremor Dominant)	0.71 (0.51, 0.99)	0.044	-	-
Non-motor Features	MDS-UPDRS I (/5)				
	-Time-varying[a]	1.04 (1.01, 1.07)	0.007	1.23 (1.07, 1.42)	0.005
	-Baseline[c]	1.20 (1.00, 1.42)	0.047		
	MOCA[a] (<22)	0.97 (0.65, 1.45)	0.89		
	BDI		0.005		
	-Time-varying[a]	1.33 (1.09, 1.62)	0.005		
	-Baseline[c]	1.04 (1.01, 1.07)			
	HADS- Anxiety (≥8)				
	-Time-varying[a]	2.05 (1.42, 2.95)	<0.001		
	-Baseline[c]	1.93 (1.30, 2.86)	0.001		
	Sniffin Score[a] (Below 10[th] centile)	1.49 (0.667, 3.32)	0.33		
	QUIP[a,b]	1.13 (0.81, 1.59)	0.48		
	RBDSQ[a,b]	1.20 (0.85, 1.67)	0.30		
	ESS[a,b]	0.83 (0.60, 1.16)	0.29		
	Orthostatic Hypotension[a]	0.98 (0.67, 1.42)	0.90		
	Constipation[a]	0.80 (0.58, 1.1)	0.17		
Patient Factors	Age at symptom onset (Years/3)[c]	0.87 (0.83, 0.92)	<0.001	0.89 (0.84, 0.94)	<0.001
	Age at diagnosis (Years/3)[c]	0.88 (0.83, 0.92)	<0.001		
	Gender[c] (Female)	1.61 (1.17, 2.22)	0.004	-	-
	BMI[a]				
	Continuous	0.99 (0.96, 1.02)	0.51	0.95 (0.92, 0.99)	0.011
	<25	1.41 (1.02, 1.96)	0.037		
	Smoking[c] (Pack years prior to diagnosis)	1.00 (1, 1.01)	0.80		
	Caffeine use[a] (Cups per day)	1.00 (0.94, 1.07)	0.10		
	QRISK2 vascular risk score[a,d] (1-4)	0.94 (0.75, 1.17)	0.58		
	Socioeconomic status[a] (5 point scale)	0.99 (0.86, 1.12)	0.82		
	Education[a] (>12 years)	1.04 (0.75, 1.43)	0.82		
	No. of Cars[a] (>2)	1.20 (0.87, 1.65)	0.27		
	No. of Bedrooms[a] (4+)	0.94 (0.68, 1.30)	0.70		
	Job status[a] (Supervisor)	0.74 (0.54, 1.03)	0.08		

Patterns of striatal dopamine depletion in early Parkinson disease

Prognostic relevance

Chung SJ, 2020, DOI:10.1212/WNL.0000000000009878

- ^{18}F-FP-CIT PET at baseline in 205 drug naïve PD
- Assessed effect of 4 striatal subregions to predict LID, OFF, FOG and dementia at FU (6.84 +/- 1.8 yrs)



Talk Outline

Pathophysiology of Motor Fluctuations:

1. Terminology & epidemiology of motor fluctuations
2. **The long and short-term response to levodopa**
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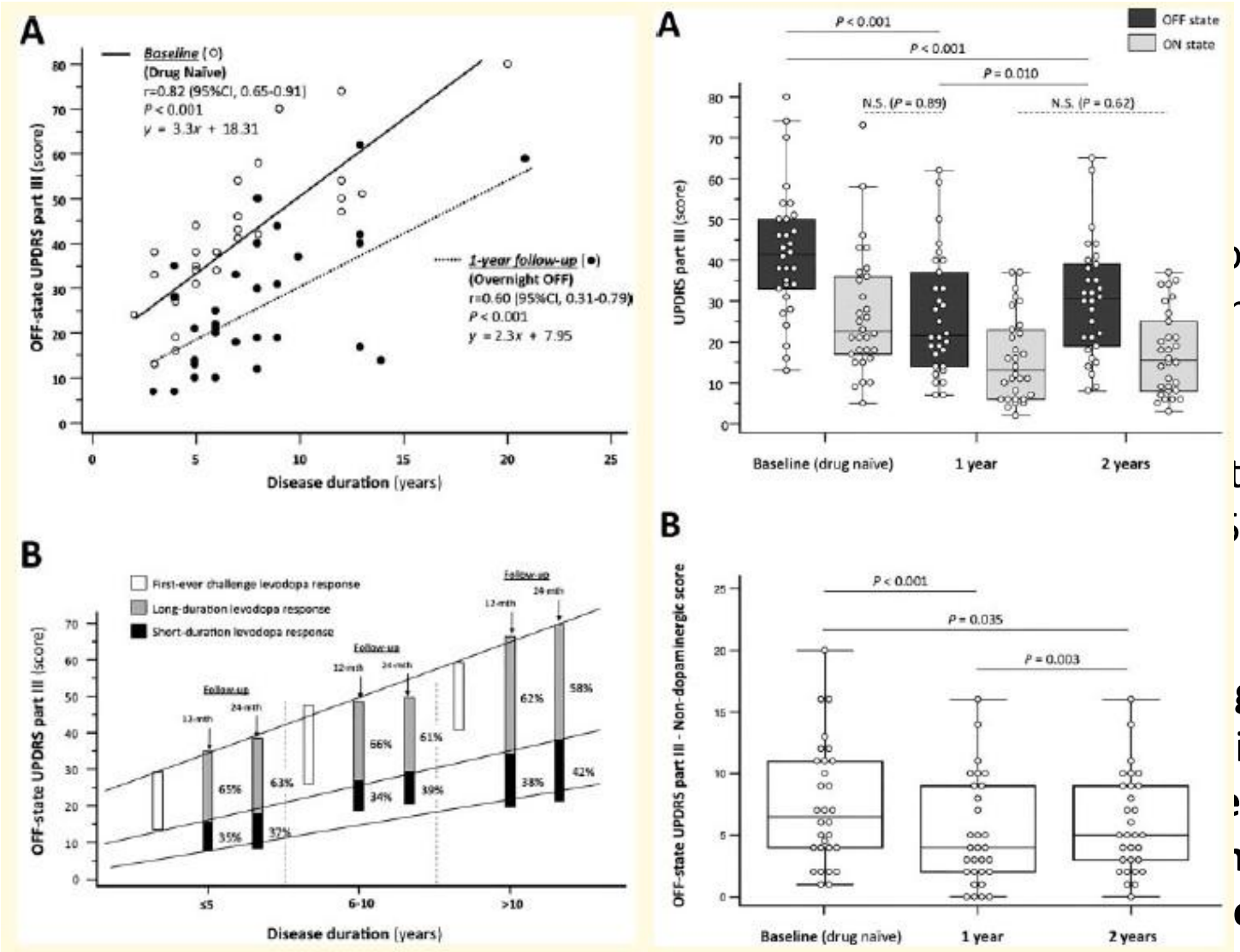
2. The long and short-term response to levodopa (LDR & SDR)

Natural history of motor symptoms in Parkinson's disease and the long-duration response to levodopa

Cilia R et al, 2011,
DOI: doi:10.1093/brain/awaa181

- 30 African l-dopa naïve PD patients (age at onset 58 +/-14 yrs, disease duration 7 +/- 4 yrs) began l-dopa monotherapy with baseline, 1 yr and 2y FU
- SDR: (natural OFF versus ON state UPDRS-III 41.9± 15.9 versus 26.8± 15.1)
- At 1 yr FU, OFF state UPDRS-III score after overnight withdrawal of levodopa was considerably lower than natural OFF (26.5± 14.9; P50 .001), effect not modified by disease duration
- At 2 yr FU, motor signs after overnight OFF (30.2± 14.2) were still 30% milder than natural OFF (P = 0.001). The ON state UPDRS-III at the first-ever levodopa challenge was similar to the overnight OFF score at 1-year follow-up and the two conditions were correlated

2. The long and short-term response to levodopa (LDR & SDR)



Cilia R et al, 2011,
DOI: doi:10.1093/brain/awaa181

- …a treatment resulted in a 31% lower annual …nts/year) with a lower model's variance
- …ts and estimated that the magnitude of the …% of total motor benefit provided by
- **…g the long-duration response to levodopa** …inson's disease and the long-duration **…es increasing its magnitude to improve …ndomized clinical trials on disease-…e Parkinson's disease progression**.

2. The long and short-term response to levodopa (LDR & SDR)

Review

2011, DOI:10.1016/j.parkreldis.2011.03.014

The long-duration response to levodopa: Phenomenology, potential mechanisms and clinical implications

Elise Anderson*, John Nutt

- Cotzias GC (NEJM 1967) "It is of interest that the onset of improvement when sufficient DOPA was given was rapid (within two or three hours), whereas the reestablishment of the baseline state with abrupt termination of the drug, after prolonged therapy, was much longer (four to fourteen days) "
- ' Long duration response (LDR) to l-dopa in PD is sustained motor improvement over days- builds up over days-weeks or repeated dosing, decays over weeks once l-dopa stopped
- SDR comes on within mins of l-dopa administration, lasts minutes to hours, broadly paralleling l-dopa levels post dose
- Acutely stopping long-term l-dopa leads to initial motor decline as SDR fades, then gradual deterioration over days as LDR fades
- However, LDR is predominant response in early PD, influencing SDR

2. The long and short-term response to levodopa (LDR & SDR)

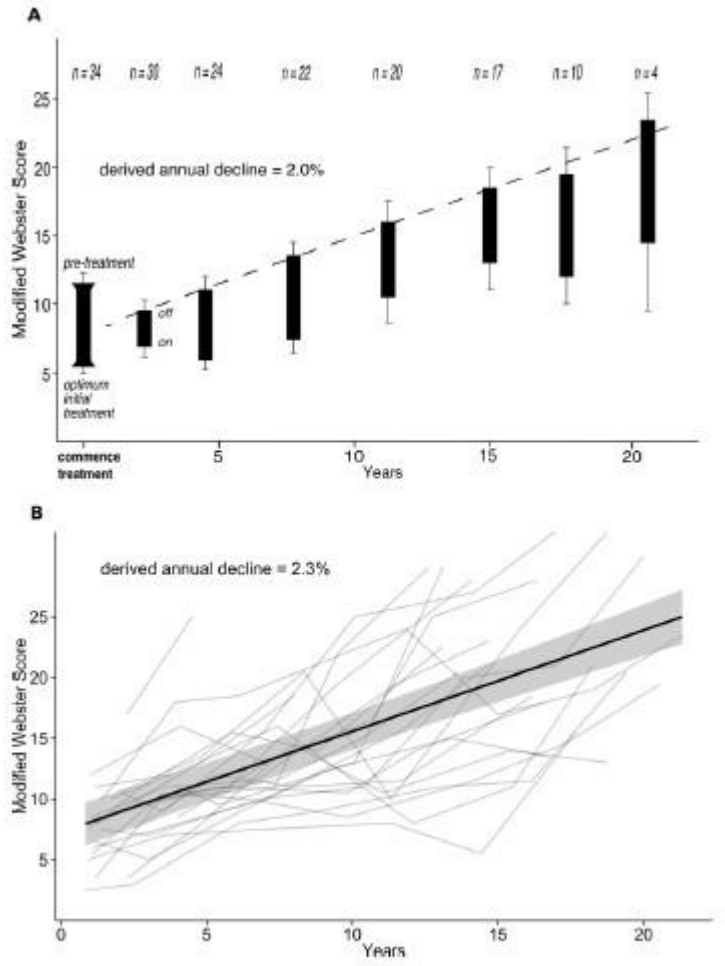


FIG. 1. Rate of motor progression. (A) Trapezium-ended box: initial drug response. Rectangular boxes: L-dopa test-dose measurements. Line of best fit for mean *off* scores. (B) LMER model (solid line) of individual *off* scores (faint lines). Shading of 95% confidence interval.

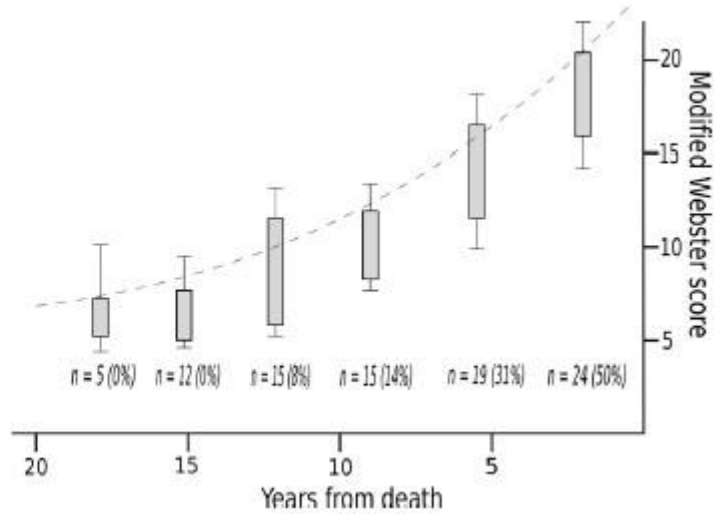
in

Ding C, 2016, DOI:10.1002/mds.26497

TABLE 1. Summary of the multivariable regression factors that determine the progression of motor disability

Factors	β Coefficient	95% Confidence Interval	*P* Value
Initial severity	0.64	0.43–0.85	<0.01
Disease duration and age at commencement of treatment	0.01	0.001–0.02	0.03
Disease duration and demented	0.58	0.35–0.81	<0.01

The R^2 of this model was 0.74.



otor function than those without dementia, with motor
end of disease course
al trial design for neuroprotective PD interventions

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3. Pathophysiological mechanisms of motor fluctuations

Motor Fluctuations in Parkinson's Disease: Central Pathophysiological Mechanisms, Part I

Fabbrini G, 1988, DOI:10.1002/ana.410240303.

Motor Fluctuations in Parkinson's Disease: Central Pathophysiological Mechanisms, Part II

Mouradian MM, 1988, DOI:10.1002/ana.410240304..

Motor fluctuations in Parkinson's disease: pathophysiology and treatment

Colosimo C, 1999, DOI:0.1046/j.1468-1331.1999.610001.x.

Pathophysiology of Motor Fluctuations in Parkinson's Disease

Widnell K, 2005, DOI: 10.1002/mds.20459

3. Pathophysiological mechanisms of motor fluctuations

Key mechanisms include:

- (i) **Reduced buffering capacity** of the brain to manage shifts in levodopa availability occurring with periodic oral l-dopa administration, linked directly to baseline and progressive dopaminergic neuron degeneration

- (ii) **Post synaptic changes at the receptor level** are major determinants for reduced therapeutic window, increasing difficulty with optimal dose adjustment and on-off motor fluctuations

3. Pathophysiological mechanisms of motor fluctuations

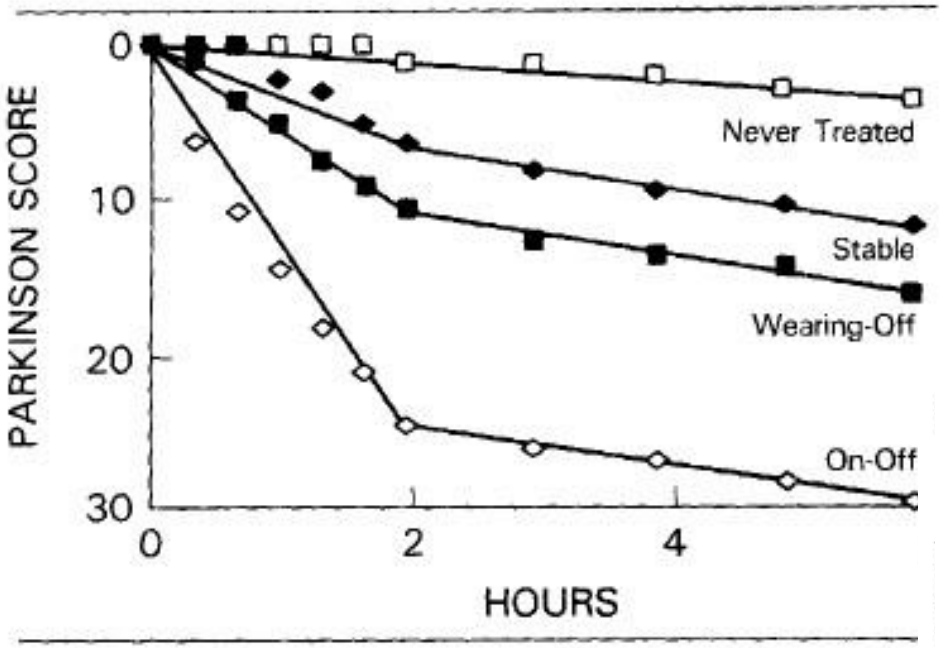
Key mechanisms include:

- (i) **Reduced buffering capacity** of the brain to manage shifts in levodopa availability occurring with periodic oral l-dopa administration, linked directly to baseline and progressive dopaminergic neuron degeneration

- (ii) **Post synaptic changes at the DA receptor level (? triggered by pulsatile stimulation)** are major determinants for reduced therapeutic window, increasing difficulty with optimal dose adjustment and on-off motor fluctuations

- (iii) **Preclinical data demonstrating that alterations in dopaminergic tone** results in cellular adaptations, including gene expression alterations

3. Pathophysiological mechanisms of motor fluctuations



Decline in parkinsonian motor scores following withdrawal of steady-state, optimal-dose, intravenous infusion of levodopa. Eac point is the mean for the number of patients indicated in Tables 1 and 2. Analysis was performed using least-squares linear regression.

f the brain to manage shifts in l
dopa administration, linked dire
uron degeneration Fabbrini G, 198

Conclusions:

-Half lives for decline in anti-PD efficacy and dyskinesia severity differed significantly, ? Different mechanisms

-Motor fluctuation correlated best with initial efficacy decay slope, both LID and motor fluctuations predicted by PD symptom severity

- Progressive DA neuron loss leads to reduced buffering, causing wearing-off

Table 5. Correlations Between Disease- and Levodopa Treatment–Related Factors and Levodopa Efficacy Decay Slopes[a]

	Initial Slope		Terminal Slope	
	r	*p*	*r*	*p*
Variance	0.677	0.007	−0.061	NS
Parkinsonian symptoms				
Duration	0.528	0.0001	−0.036	NS
Severity	0.917	0.0001	0.404	0.01
Levodopa treatment				
Duration	0.546	0.0001	−0.149	NS
Dosage	0.788	0.0001	0.023	NS

[a]Pearson product moment correlation coefficients, *r*, calculated for 48 patients, except for variance (n = 15). Severity of parkinsonian motor fluctuations is expressed in variance (square of standard deviation) of motor scores obtained every 20 minutes for 9 hours. Parkinsonian severity is the score obtained at 6 hours after cessation of the steady-state levodopa infusion. Levodopa dosage was expressed in mg/kg/hr for the optimal oral dose calculated for waking hours.

NS = significant

Table 6. Stepwise Regression Analysis of Levodopa Response Parameters[a]

Response Parameters	Clinical Variables	R^2
Antiparkinsonian efficacy		
Half-time	Levodopa dose	0.479
Initial slope	Parkinsonian severity	0.841
	Levodopa dose	0.881
Variance	Parkinsonian severity	0.479
Dyskinesia severity		
Half-time	Levodopa dose	0.224

[a]A forward linear stepwise regression procedure was used for the inclusion of the variables in the model. All variables are significant and in the sequence presented.

3. Pathophysiological mechanisms of motor fluctuations

(ii) **Post synaptic changes at the DA receptor level (? triggered by pulsatile stimulation)** are major determinants for reduced therapeutic window, increasing difficulty with optimal dose adjustment and on-off motor fluctuations

(iii) **Preclinical data demonstrating that alterations in dopaminergic tone** results in

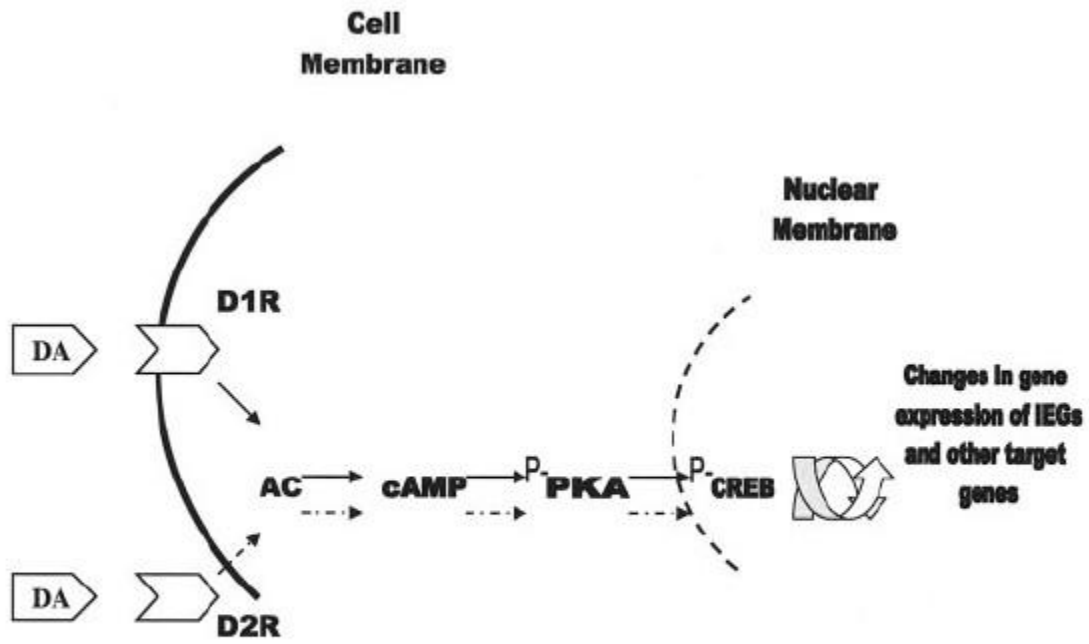


FIG. 2. Two classes of dopamine (DA) receptors exist (D1R and D2R) and differentially activate signal transduction pathways. The D1 receptor increases the activity of adenyl cyclase (AC), which increases levels of cyclic adenosine monophosphate (cAMP), resulting in phosphorylation and activation of protein kinase A (PKA). Activated protein kinase phosphorylates and activates cAMP-response element binding protein (CREB), which leads to changes in gene expression. The D2 receptor decreases the activity of AC, which decreases levels of cAMP resulting in less phosphorylation and decreased activity of PKA. Arrows represent either a positive (full line) or negative (dashed line) effect on the activity of the protein represented in the figure. IEG, immediate early gene.

Table 3. Intercorrelations Between Therapeutic Window and Dose-Response Slope with Disease Progression and Drug Treatment Factors

	Window		Slope	
Disease/Treatment Factors	r^a	p	r^a	p
Parkinsonian symptoms				
Duration	−0.702	0.001	0.406	NS
Severity[b]	−0.350	NS	0.424	NS
Levodopa treatment				
Duration	−0.721	0.001	0.425	0.01
Dose[c]	−0.591	0.001	0.312	NS

[a]Correlation coefficients were obtained by Pearson's correlation analysis.
[b]Severity is defined as the mean of early morning scores.
[c]Levodopa dose was calculated while patients were on optimal oral therapy in mg/kg/hour during the hours of drug administration.
NS = not significant.

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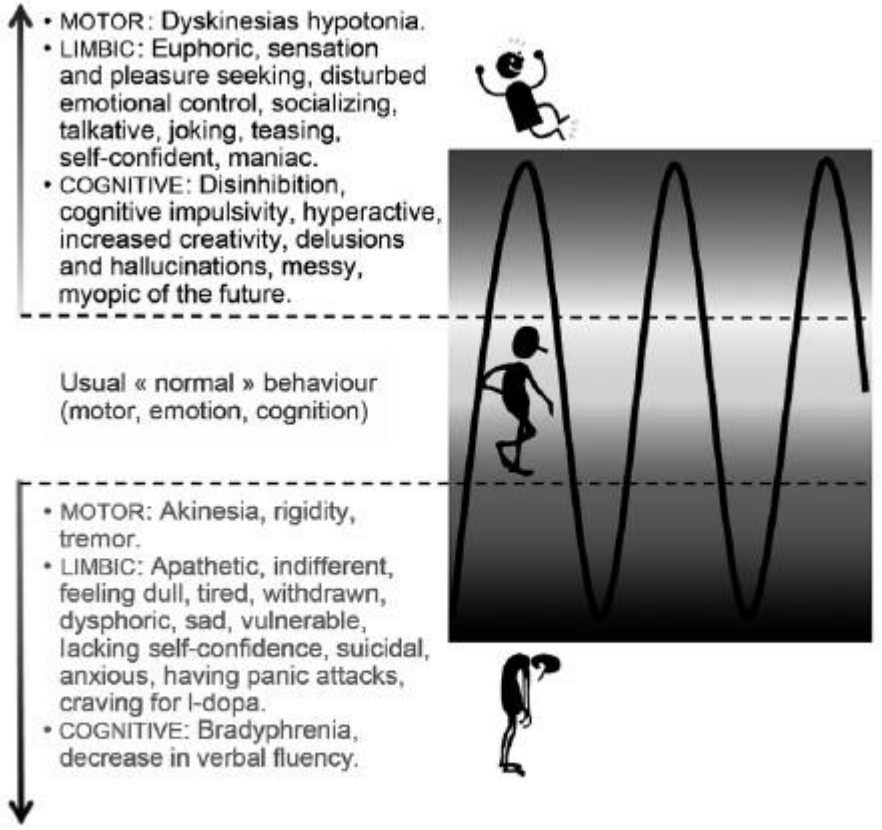
2016, DOI:10.1002/mds.26731

The Hidden

Raul Martínez-Fernández



IG. 1. Neuropsychiatric nonmotor fluctuations that can lead to dopaminergic addiction in a subgroup of patients who attempt to maintain ON uphoric and avoid OFF dysphoric states. Behavioral addictions, such as gambling, hypersexuality, and shopping, induced by dopamine agonists re also frequent. Adapted from Lhommée 2012.

TABLE 1. NMS reported to manifest as NMF

Category	Symptom	Distribution in Motor State
Neuropsychiatric	Depression/sadness	OFF > ON[a]
	Apathy	OFF > ON[a]
	Fatigue	OFF > ON[a]
	Anxiety	OFF > ON[a]
	Panic attack	OFF
	Attention problems	OFF > ON[a]
	Forgetfulness	OFF > ON[a]
	Slowness of thinking	OFF > ON
	Mental emptiness	OFF>ON
	Elevated mood	ON > OFF[a]
	Hallucination	OFF < ON
	Mental hyperactivity	OFF < ON
	Mutism	OFF
	Irritability	OFF > ON
	Aggressive behavior	OFF > ON
	Moaning and screaming	OFF
	Confusion	OFF
	Drowsiness	OFF
Autonomic	Light-headedness	OFF > ON[a]
	Limb edema	OFF > ON
	Abdominal pain	OFF
	Abdominal bloating	OFF > ON
	Constipation	OFF > ON
	Nausea	OFF > ON
	Pyrosis	OFF > ON
	Hunger	OFF
	Sexual disorders	OFF > ON[a]
	Drenching sweats	OFF > ON[a]
	Facial flushing	OFF > ON
	Bladder dysfunction	OFF > ON[a]
	Belching	OFF > ON
	Drooling	OFF > ON
	Swallowing trouble	OFF > ON
	Chilling	OFF > ON
	Cough	OFF > ON
	Stridor	OFF
	Visual disorder	OFF > ON
Sensory	Diffuse pain	OFF > ON[a]
	Neuralgic pain	OFF > ON
	Dysesthesia	OFF
	Akathisia	OFF > ON[a]
	Burning sensation	OFF > ON
	Sensory dyspnea	OFF
	Restless legs	OFF

[a]Significant difference in the frequency of presentation between the ON and the OFF state according to Storch and colleagues.

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5. The patient experience

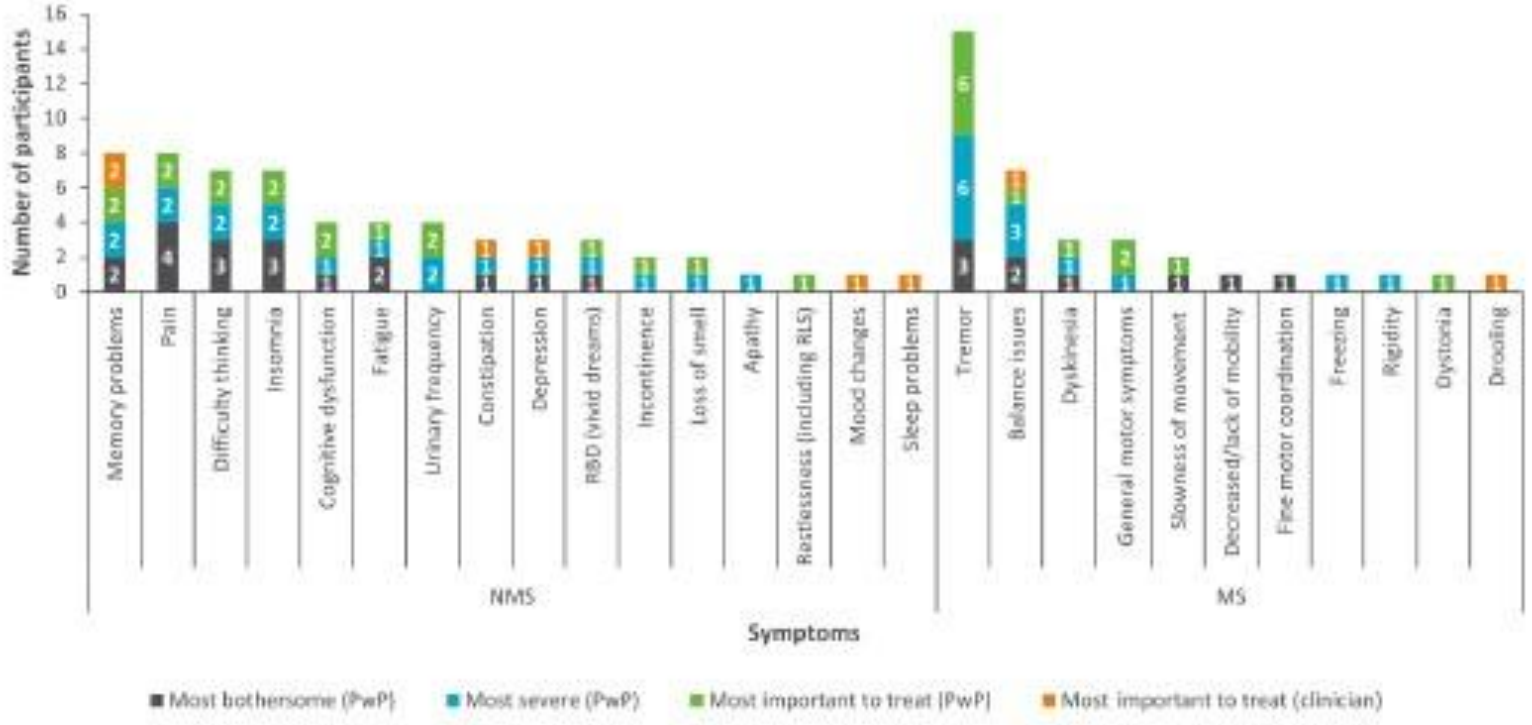

Fig. 3 Overview of symptoms considered most bothersome, most severe, and most important to treat. $N = 20$ PwP discussed the most bothersome and severe symptoms, $n = 17/20$ PwP and $N = 3$ clinicians discussed the most important to treat symptoms. *MS* motor symptoms, *NMS* Non-motor symptoms, *PwP* persons with advanced Parkinson's disease, *RBD* REM sleep behavior disorder, *RLS* restless legs syndrome

/10.1007/s40120-025-00747-5

)N-OFF motor

3 PD clinicians
igidity and balance
n, apathy, pain, sleep
nsory dysfunction
ysical social

5. The patient experience

CURE PARKINSON'S

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CHANGE ATTITUDES.
FIND A CURE.
JOIN US.

Thanks! the OPDC Discovery Cohort Team

Back (L-R): Jamil Razzaque *(Research Practitioner)*, Luca Ratti *(Neurologist)*, Katarina Gunter *(DPhil Student)*, Timothee Aubourg *(Postdoctoral Scientist)*, Karolien Groenewald *(Clinical Research Fellow & Dphil Student)*, Ludo van Hillegondsberg *(Clinical Research Fellow & Dphil Student)*, Johannes Klein *(Senior Clinical Research Fellow & Honorary Consultant Neurologist)*, Richard Wade-Martins *(Professor of Molecular Neuroscience)*

Front (L-R): Tanja Zerenner *(Senior Research associate in Medical Statistics)*, Michele Hu *(Professor of Clinical Neuroscience & Consultant Neurologist)*, Jessica Welch *(Senior Clinical Project Manager)*, Monique Da Gama *(Research Administrator)*, Adriana Nastasa *(Research Administrator)*, David Gordon *(Core Research Scientist)*, Tamir Eisenstein *(Postdoctoral Researcher)*, Livia Civitelli *(Research Fellow in Molecular Neuroscience)*