

# Supplementary Material

## Sex Is the Main Determinant of Levodopa Clinical Pharmacokinetics: Evidence from a Large Series of Levodopa Therapeutic Monitoring

**Supplementary Table 1.** Demographic, clinical, therapeutic data, and lifestyles collected within levodopa therapeutic monitoring

1. Age (y)
2. Sex (m/f)
3. Weight (kg)
4. Height (cm)
5. Body mass index (kg/cm<sup>2</sup>)
6. Duration of parkinsonism (y)
7. Duration of LD therapy (y)
8. LD test dose (mg)
9. LD daily dose (mg/day)
10. LD equivalent daily dose (LEDD) (mg/day)
11. Dopa decarboxylase inhibitors (carbidopa/benserazide)
12. Cotherapy with dopaminergic agonists (yes/no)
13. Cotherapy with MAO inhibitors (yes/no)
14. Cotherapy with amantadine (yes/no)
15. Non antiparkinsonian cotherapies
16. MDS UPDRS part III scale "off" score
17. MDS UPDRS part III scale "on" score
18. H&Y scale "off" score
19. Coffee consumption (yes/no)
20. Alcohol consumption (yes/no)
21. Cigarette smoke consumption (yes/no)

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LD, levodopa; MDS UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; H&Y, Hoehn & Yahr.

**Supplementary Table 2.** Levodopa kinetic-dynamic therapeutic monitoring protocol

Time (min)	LD test dose	Blood drawing	Alternate finger tapping test	TUG test	Blood pressure and heart rate measurement	Standard breakfast	Semi-quantitative scales	Dyskinesia rating
-10			x *	x *	x			x
-5		x	x *	x *			x "off"	
0	x							
+15		x	x	x				x
+30		x	x	x				x
+45		x	x	x				x
+60		x	x	x	x		x "on"	x
+75		x	x	x		x		x
+90		x	x	x				x
+120		x	x	x				x
+150		x	x	x				x
+180		x	x	x				x

-10, -5, baseline pre-levodopa dose measurements; \*, average values; LD, levodopa; TUG, Timed Up and Go.

**Supplementary Table 3.** Demographic and clinical-therapeutic variables comparisons between patients with a diagnosis of Parkinson's disease or atypical parkinsonism

Variables	PD (n=373)	AP (n=121)	P
Age (y)	65 (57 - 72)	71 (64 - 75)	<0.001
Weight (kg)	73 (63 - 83)	72 (64 - 80)	0.467
Height (cm)	170 (163 - 175)	166.5 (161 - 174)	0.074
BMI (kg/cm <sup>2</sup> )	25.2 (23.0 - 28.4)	25.7 (23 - 28.4)	0.692
Sex			
Male – n° (%)	230 (61.7)	76 (62.8)	0.821
Female – n° (%)	143 (38.3)	45 (37.2)	
Duration of parkinsonism (y)	4 (3 - 8)	4 (3 - 6)	0.082
Duration of LD therapy (y)	2 (1 - 5)	2 (1 - 4)	0.240
LD test dose (mg/kg)	1.41 (1.23 - 1.75)	1.43 (1.25 - 1.82)	0.677
LD daily dose (mg/day)	300 (200 - 400)	300 (200 - 400)	0.573
LEDD (mg/day)	368.5 (200 - 600)	359 (200 - 500)	0.184
MDS-UPDRS part III (“off”)	24 (15 - 33)	37 (25.5 - 48)	<0.001
H&Y scale (“off”)	2 (2 - 2)	2.5 (2 - 3)	<0.001
Dopa decarboxylase inhibitors			
Carbidopa – n° (%)	83 (22.3)	37 (30.6)	0.063
Benserazide – n° (%)	290 (77.7)	84 (69.4)	
Antiparkinsonian cotherapies			
Dopamine agonists – n° (%)	181 (48.5)	31 (25.6)	<0.001
MAO-B inhibitors – n° (%)	60 (16.1)	14 (11.6)	0.226
Amantadine – n° (%)	21 (5.6)	6 (5)	0.778
Other cotherapies			
Antihypertensive – n° (%)	146 (39.1)	69 (57)	0.001
Heart disease – n° (%)	57 (15.3)	42 (34.7)	<0.001
Cholesterol lowering – n° (%)	52 (13.9)	30 (24.8)	0.005
Gastrointestinal disorders – n° (%)	31 (8.3)	29 (24)	<0.001
Antidiabetic – n° (%)	19 (5.1)	11 (9.1)	0.110
Ipothyroidism – n° (%)	22 (5.9)	6 (5)	0.698
Antidepressant – n° (%)	107 (28.7)	45 (37.2)	0.078
Antipsychotic – n° (%)	9 (2.4)	6 (5)	0.156
Prostatic hypertrophy – n° (%)§	45 (19.6)	23 (30.3)	0.052
Coffee consumption – n° (%)	257 (69.8)	79 (66.9)	0.555
Alcohol consumption – n° (%)	155 (42.6)	46 (38.7)	0.451
Cigarette smoke consumption – n° (%)	46 (12.5)	13 (10.9)	0.647

Values are expressed as median (interquartiles). PD, Parkinson's disease; AP, atypical parkinsonism; BMI, body mass index; LD, levodopa; LEDD, levodopa equivalent daily dose; MDS UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; H&Y, Hoehn & Yahr; MAO-B, monoamino oxidase-B. §calculated on males.

**Supplementary Table 4.** Levodopa pharmacokinetic variables by different test doses

LD test dose (mg)	C <sub>max</sub> (mg/L)	AUC <sub>0-180 min</sub> [(mg/L) x min]	t <sub>max</sub> (min)
50	1.12 (0.60-1.44)	64.13 (47.45-90.08)	30 (30-45)
100	1.80 (1.33-2.30)	131.00 (107.30-158.00)	30 (30-45)
150	2.41 (1.82-3.04)	203.10 (166.60-250.10)	45 (30-75)
200	4.11 (2.96-5.15)	304.50 (242.60-389.90)	45 (30-45)

Data are expressed as median (interquartiles); LD, levodopa; C<sub>max</sub>, peak plasma concentration; AUC<sub>0-180 min</sub>, area under the 3h plasma concentration-time curve; t<sub>max</sub>, time to peak plasma concentration.

**Supplementary Table 5.** Differences in demographic and clinical-therapeutic variables between “responder” and “non-responder” subgroups

Variable	Responders (n=409)	Non-responders (n=91)	p
Weight (kg)	72 (63-81)	76 (69-87)	0.008
BMI (kg/cm <sup>2</sup> )	25.01 (22.66-28.38)	26.39 (24.22-28.52)	0.021
Sex			
Female - n° (%)	170 (41.6)	22 (24.2)	0.002
Male – n° (%)	239 (58.4)	69 (75.8)	
Duration of parkinsonism (y)	5 (3-7)	3 (2-5)	<0.001
Duration of LD therapy (y)	2 (1-5)	1.25 (0.75-3)	0.006
LD daily dose (mg/day)	300 (200-450)	300 (200-400)	0.043
LEDD (mg/day)	400 (200-600)	300 (200-400)	0.002
Dopamine agonist cotherapy - n° (%)	191 (46.7)	25 (27.5)	0.001
Antihypertensive drugs - n° (%)	166 (40.6)	51 (56.0)	0.007
Gastrointestinal agents - n° (%)	42 (10.3)	19 (20.9)	0.005
Cholesterol lowering drugs - n° (%)	57 (13.9)	26 (28.6)	0.001

Values are expressed as median (interquartiles). BMI, body mass index; LD, levodopa; LEDD, levodopa equivalent daily dose.

**Supplementary Table 6.** Differences in demographic and clinical-therapeutic variables between non-dyskinetic and dyskinetic patients

<b>Variable</b>	<b>Non-dyskinetic (n=360)</b>	<b>Dyskinetic (n=139)</b>	<b>p</b>
Weight (kg)	75 (66-85)	68 (59-77)	<0.001
BMI (kg/cm <sup>2</sup> )	25.84 (23.42-28.69)	24.24 (22.22-27.58)	0.004
Sex			
Female - n° (%)	118 (32.8)	74 (53.2)	<0.001
Male - n° (%)	242 (67.2)	65 (46.8)	
Duration of parkinsonism (y)	3 (2-6)	7 (4.5-10)	<0.001
Duration of LD therapy (y)	1.5 (0.5-3)	5 (2-8)	<0.001
LD daily dose (mg/day)	250 (200-400)	400 (300-600)	<0.001
LEDD (mg/day)	300 (200-460)	515 (382-782)	<0.001
MDS-UPDRS part III “off”	25 (15-35)	32 (23-42)	<0.001
H&Y “off”	2 (2-2)	2 (2-3)	<0.001
Dopamine agonist cotherapy - n° (%)	136 (37.8)	80 (57.5)	<0.001
MAO-B inhibitors - n° (%)	45 (12.5)	30 (21.6)	0.011
Clinical diagnosis			
PD - n° (%)	255 (71.8)	117 (84.8)	0.003
AP - n° (%)	100 (28.2)	21 (15.2)	
Amantadine - n° (%)	7 (1.9)	20 (14.4)	<0.001
Antihypertensive drugs - n° (%)	167 (46.4)	49 (35.3)	0.024
Antidepressant drugs - n° (%)	101 (28.1)	53 (38.1)	0.029
Cigarette smoke consumption- n° (%)	35 (9.9)	25 (18.2)	0.011

Values are expressed as median (interquartiles). BMI, body mass index; LD, levodopa; LEDD, levodopa equivalent daily dose; MDS UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; H&Y, Hoehn & Yahr; MAO-B, monoamino oxidase-B.