

# Speech and voice response to a levodopa challenge in late-stage Parkinson's disease patients

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## BACKGROUND

Parkinson's disease (PD) patients are affected by hypokinetic dysarthria, characterized by hypophonia and dysprosody, which worsens with disease progression. Speech disorders affect nearly 90% of PD patients and have a negative impact on quality of life. Levodopa's (L-dopa) effect on quality of speech is inconclusive; no data are currently available for late-stage PD (LSPD).

## OBJECTIVE

❖ To assess the modifications of speech and voice in LSPD following an acute L-dopa challenge.

## METHODS

❖ LSPD patients (Schwab and England <50/Hoehn Yahr >3 [MED ON]) performed several vocal tasks before and after an acute L-dopa challenge;  
 ❖ The following was assessed: a) **respiratory support for speech** (time duration of vowel /a/ prolongation); b) **voice quality** (fundamental frequency [F<sub>0</sub>]); c) **voice stability** (pitch break time, and jitter); d) **voice variability** (standard deviation [SD] of speaking F<sub>0</sub> during sentences [Sentence F<sub>0</sub>SD]); e) **speech rate** (syllables/sec); f) motor performance (**MDS-UPDRS-III**) and **mAIMS**.

❖ All voice samples were recorded and analyzed by a speech and **language therapist blinded** to patients' therapeutic condition using **Praat 5.1 software**.

## RESULTS

### Patients

- 24/27 (14 men) LSPD patients succeeded in performing voice tasks;
- Median age and disease duration of patients was 79 [IQR: 71.5-81.7] and 14.5 [IQR: 11-15.7] years, respectively;
- There were no differences in demographic or clinical variables between men and women (Table 1). Indeed, they presented similar MDS-UPDRS II-III-IV scores, axial signs score, S&E and HY stages, although women had a slightly, but not statistically significant, worse HY stage.

Patients data	LSPD (n= 24)	LSPD MALE (n=14)	LSPD FEMALE (n=10)	p - value
Age (yrs)	79 [71.5-81.7]	77.5 [70.7-81.2]	79 [73.5-85]	ns
Age at disease onset (yrs)	64.5 [54.5-69.5]	62.5 [55-67]	65 [51.5-71.5]	ns
Disease duration	14.5 [11-15.7]	13.5 [8.7-17]	15 [11.7-17.2]	ns
Education (yrs)	4 [4-11]	4 [4-12]	5 [4-10.5]	ns
S&E (ON/OFF)	40/35 [40-40.7 / 22.5-40]	40/30 [40-40/ 40-40]	40/30 [27-50 / 17.5-50]	ns
HY (ON/OFF)	4 [2-4] / 4 [2-4.75]	3 [2-4] / 3 [2-4]	4 [4-5] / 4 [4-5]	ns
PDD (n (%))	14 (58%)	10 (71%)	4 (40%)	ns
MMSE	22.5 [21.2-25]	22.5 [22-24.2]	22.5 [16-27.2]	ns
MMSE (demented/non-demented)	22 [17-23.7] / 25 [23-26.7]	22 [21.7-24.2] / 23 [22.2-25.2]	17 [13-19.5] / 27 [25-28.5]	
LEDD (mg)	1037 [902-1272]	1100 [990-1303]	905 [742-1257]	ns
MDS-UPDRS-II	31 [27-38]	32 [29.2 - 38.5]	30 [20.5-38]	ns
MDS-UPDRS-III (MED ON/MED OFF)	50 [40-54]/64 [52-77]	50 [42.5-55.2]/61[53-76]	50 [37.5-62.5] /64 [48-79.5]	ns
Axial sign (MED ON/MED OFF)	8 [6-13] /10 [7-13]	8 [6-13]/10 [7-13.2]	8 [6.5-12]/ 10 [7-13.5]	ns
MDS-UPDRS-IV	4 [2-9.5]	5 [2-8.5]	4 [0-11.2]	ns

**Table 1.** Values are presented as median [IQR, 25th–75th percentile] if no otherwise specified; ns: not significant. LEDD: L-dopa equivalent daily dose; PDD: Parkinson's disease with dementia; MMSE: mini mental state examination. S&E: Schwab and England score; HY: Hoehn Yahr Stage; ns: non-significant; P value is the results for male vs. female scores' comparison.

### Baseline voice and speech characteristics

- No differences were found between men and women for breath support and voice stability at baseline;
- In MED OFF, **respiratory breath support and pitch break time** of LSPD patients were worse than the normative values of non-parkinsonian (Table 2).
- Mean **jitter** values were in the normal range (Table 2), although results were borderline for men and SD showed a tendency for higher values.
- F<sub>0</sub>SD was in the normal range (Table 2). However, due to the low level of cooperation of LSPD patients, we adopted an 8-word (14 syllables) declarative sentence (syntactically simple) that in European Portuguese is expected to have a low level of voice variability compared to complex sentences or text reading, which are normally used for this task

	PD Patients (N=24)		Normal value	
	MALE (N=14)	FEMALE (N=10)	MALE	FEMALE
Respiratory support for speech	5.8 [4.4-11.5.8]		22.97 (1.1) ^	
Vowel duration (sec)				
Voice stability				
Pitch break time (sec)	1.24 [0.2-2.6.1]		NA*	
Jitter (%)	0.8 [0.5-1.1]		≤ 0.5-1%	
Voice variability F <sub>0</sub> SD (Hz)	2.4 [1.6-4]		2-4Hz	
Voice quality (Hz) F <sub>0</sub>	125 [104-152]	202 [160-226.8]	128 (36)**	198 (44)**

**Table 2 .** Values for LSPD patients are presented as median [IQR, 25th–75th percentile]. Values for healthy subjects are presented as mean (SD), as reported in literature (Maslan J. et al., 2011; Barkana BD & Zhou JA, 2015; Colton & Casper, 1996; Titze IR, 1993). F<sub>0</sub>: fundamental frequency; F<sub>0</sub>SD: fundamental frequency standard deviation; NA\*: not available (healthy voices should have no trouble in maintaining voicing during a sustained vowel. Thus is 0% of voice breaks. No standard values are available). ^: normal value for vowel duration are referred to a healthy population aged between 71 and 80 years old. \*\*: normal value for voice quality are referred to a healthy population aged between 55 and 80 years old.

### Voice features and PD severity

- A positive correlation was found between disease duration and voice quality (R=0.51; p=0.013) and a negative one with speech rate (R= -0.55; p=0.008).
- Motor impairment (MDS-UPDRS-III) had a moderate significant correlation with respiratory support for speech (R= -0.43; p=0.045) and pitch break time (R= -0.565; p=0.006).
- No correlations were found between voice and speech features and axial motor impairment, neither between speech rate and freezing.

### L-dopa challenge test

- The median L-dopa dose for the test was 375 mg (IQR: 277-375).
- L-dopa significantly improved MDS-UPDRS-III score (20%; IQR: 11.5%-32%);
- Sub-analysis of MDS-UPDRS-III scores for axial signs showed a significant median improvement after L-dopa intake for all the sub-items, except speech;
- None of voice and speech variables changed significantly after L-dopa intake as assessed by automatic analysis (Table 3).
- Equally, separate analysis of non-demented and demented patients showed no modification of speech and voice variables following L-dopa intake.

	LSPD patients (N= 24)		
	MED OFF	MED ON	p - value
MDS-UPDRS-III	64 [52-77]	50 [40-54]	<0.001
Speech	2 [1-3]	2 [1-3]	0.83
Freezing of gait	3 [1-4]	2 [0-3]	<0.05 (0.01)
Postural Stability	3 [2-4]	3 [2-3]	<0.05 (0.014)
Gait	3 [2-4]	3 [2-3]	<0.05 (0.01)
Axial Signs	10 [7-13]	8 [6-13]	<0.05 (0.01)
HY	4 [2-4.75]	4 [2-4]	0.7
mAIMS	0	1 [0-6.75]	0.04
Voice Respiratory support for speech			
Vowel duration (sec)	5.8 [4.4-11.5]	7 [3.6-10.6]	0.6
Voice stability			
Pitch break time	1.2 [0.2-2.6]	0.8 [0.07-2.5]	0.9
Jitter	0.8 [0.5-1.1]	0.7 [0.4-1]	0.5
Voice quality F <sub>0</sub>	154 [123-209]	162 [147-203]	0.2
Voice variability SentenceSF <sub>0</sub> SD	31 [19-51]	29 [20-40]	0.5
Speech rate	5 [3.6-5.6]	5 [4.2-5.7]	0.2

**Table 3.** Values are presented as median [IQR, 25th–75th percentile]. Statistical significant results are in bold. Axial Signs: sum of item 3.1, 3.10-3.12 of the MDS-UPDRS-III. P - value is the results of MED OFF versus MED ON scores. mAIMS: Modified Abnormal Involuntary Movement Scale.

## CONCLUSION

- ❖ **Speech is severely affected among LSPD patients.**
- ❖ **This is the first report on L-dopa response of speech and voice in a sample of LSPD patients**
- ❖ **No effect of L-dopa was found on speech and voice by means of both automated analysis and clinical evaluation, although patients had a moderate positive motor response, even present for some axial signs, with the exception of speech.**
- ❖ **Our findings highlight the need for alternative non-dopaminergic/non-pharmacologic treatments to specifically target and improve communication of LSPD patients**