# Response of non-motor symptoms to levodopa in late-stage Parkinson's disease: results of a levodopa challenge test

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**Abstract**

**Background:** Non-motor symptoms (NMS) are extremely common among late-stage Parkinson's disease (LSPD) patients. Levodopa (L-dopa) responsiveness seems to decrease with disease progression but its effect on NMS in LSPD still needs to be investigated.

**Objective:** To assess the response of blood pressure (BP), pain, fatigue and anxiety to L-dopa in LSPD patients.

**Methods:** 20 LSPD patients, defined as Schwab and England ADL Scale < 50 or Hoehn Yahr Stage >3 (MED ON) and 22 PD patients treated with subthalamic deep brain stimulation (advanced PD group) underwent a L-dopa challenge. BP and orthostatic hypotension (OH) assessment, a visual analogue scale (VAS) for pain and fatigue and the Strait Trait Anxiety (STAI) were evaluated before and after the L-dopa challenge.

**Results:** Systolic BP dropped significantly after L-dopa intake ($p < 0.05$) in LSPD patients, while there was no change in pain, fatigue or anxiety. L-dopa significantly improved ($p < 0.05$) pain and anxiety in the advanced PD group, whereas it had no effect on BP or fatigue. L-dopa-related adverse effects (AEs), namely OH and sleepiness, were more common among LSPD patients. 40% and 65% of LSPD patients were not able to fill out the VAS and the STAI, respectively, while measurement of orthostatic BP was not possible in four LSPD patients.

**Conclusions:** This exploratory study concludes that some NM variables in LSPD do not benefit from the acute action of L-dopa while it can still induce disabling AEs. There is also a need for assessment tools of NMS adapted to these disabled LSPD patients.

## Introduction

Parkinson's disease (PD) is a multisystem disorder characterized by several motor and non-motor symptoms (NMS) [1]. NMS are very common in PD, and their frequency and, in the majority of the cases, their severity increase in more advanced stages [2, 3]. Interestingly, the presence, and above all, the severity of levodopa (L-dopa)-induced motor complications (MCs) seem to decrease in late-stage PD (LSPD), [2, 4] thus probably accounting for the major impact that NMS have on patients' quality of life (QoL). Though frequently underdiagnosed [5], NMS play a major role in the QoL of PD patients and carers [6]. Moreover, 30% of PD patients consider L-dopa-induced non-motor fluctuations more disabling than motor fluctuations [7].
The management of NMS is challenging along all the disease course, [8] but even more in later stages in which patients have usually to decrease dopaminergic therapy due to the occurrence of adverse effects (AEs). [9]. Overall, L-dopa responsiveness seems to decrease with disease progression, but very few studies have indeed investigated L-dopa responsiveness among LSPD patients [4, 10], and even less the benefit of L-dopa on NMS. To assess this, we report the response of NMS to an acute L-dopa challenge in a population of LSPD. To better inform the results a group of advanced stage PD patients submitted to sub-thalamic nucleus deep brain stimulation (STN-DBS) underwent the same protocol.

## Patients and methods

### *Objectives*

Our primary objective was to assess the response of blood pressure (BP), pain, fatigue and anxiety following an acute L-dopa challenge in a LSPD population.

### *Design and recruitment*

We performed a cross-sectional study in a consecutive sample of LSPD patients, recruited during 6 months from the movement disorders outpatient clinic of a tertiary university hospital (Hospital Santa Maria, Lisbon, Portugal). PD was defined according to the UK Brain Bank criteria [11], whereas LSPD was defined as PD patients with either a Schwab and England score (S&E) < 50 (MED ON) or a Hoehn & Yahr stage (HY) >3 (MED ON). As an "active control group", a group of advanced PD patients were included to better inform the interpretation of both the applicability of the assessment tools and the results. Advanced PD patients were defined as patients treated STN-DBS at least three years before and who did not

fulfill the criteria of LSPD. Patients who underwent DBS were excluded from the LSPD group. The Local Ethical Committee approved the study and all patients provided informed consent.

*Assessment of patients*

LSPD patients were first assessed in the practically defined "MED OFF" condition and then 60-90 minutes after L-dopa intake in the best "MED ON" condition [10].

Advanced patients were first assessed in the practically defined "MED OFF" condition and with the neurostimulator switched OFF for at least 60 minutes (MED OFF/STIM OFF), and then after taking the same L-dopa dose as they did in the L-dopa challenge performed for DBS selection years before (MED ON/STIM OFF). The protocol of the L-dopa challenge performed for DBS selection was the same as for LSPD patients, as previously reported [10]. Indeed each patient took her/his usual morning L-dopa equivalent dose plus 50% (supra-maximal dose=150%). L-dopa equivalent daily dose (LEDD) was calculated according to recognized standard conversions [12].

NMS were evaluated using the MDS-UPDRS part I [13], the Non-Motor Symptoms Assessment Scale for PD (NMSS) [14], the Neuropsychiatric Inventory test 12-items [15], and the Geriatric Depression Scale (GDS)[16]. PD with Dementia (PDD) was diagnosed according to the recommendation of the MDS Task Force [17].

Depression was diagnosed if patients scored ≥ 11 on the GDS (mild depression between 11 and 20 points; severe depression between 21 and 30 points). Psychosis was present if patients had an MDS-UPDRS item 1.2 score ≥ 1.

Acute response of BP, pain, fatigue and anxiety to L-dopa were assessed immediately before and 60-90 minutes after L-dopa intake in the best "MED ON" condition. BP was measured in supine and 3 minutes after standing; orthostatic hypotension (OH) was defined as a decrease with standing in systolic blood pressure (SBP) >30 mmHg or in diastolic blood pressure (DBP) >15 mmHg (criteria I), or in SBP >20 mmHg or in DBP >10 mmHg (criteria 2). Pain and fatigue were measured using a visual analogue scale (VAS) (VAS-p for pain and VAS-f for fatigue). Anxiety was assessed with the State Trait of Anxiety Inventory (STAI), which is a psychological inventory consisting of 40 self-report items, 20 items to assess trait anxiety and 20 for state anxiety, each item is scored on a 4-point Likert-type response scale. [18]. For the purpose of our study only the 20 items for state anxiety assessment have been administered to

patients. MDS-UPDRS motor part III [13] was performed in "MED OFF" and then best "MED ON" condition [10]. MDS-UPDRS parts II and IV were used to assess the impact of motor symptoms on activities of daily life and L-dopa-induced MCs, respectively [13].

**Statistical Analysis**

Descriptive statistics of demographic, clinical and therapeutic data were provided for continuous [median and interquartile range (IQR, 25th–75th percentile)] and categorical (count and percentage) variables.

The acute effect of L-dopa on NMS was calculated comparing the median value of BP and the development of OH, and the scores of VAS-p, VAS-f and STAI between MED OFF versus MED ON condition for LSPD patients and between MED OFF/STIM OFF with MED ON/STIM OFF condition for DBS patients. Comparisons were made using the Wilcoxon's signed ranked test or the Fischer's exact test, as appropriate.

Spearman's rank correlation coefficient was used to assess the association between the magnitude of motor (Δ MDS-UPDRS-III) and NMS (ΔVAS-p and Δ VAS-f and Δ STAI) response to L-dopa, and the association between the severity of motor symptoms (MDS-UPDRS-III) and NMS (MDS-UPDRS-I, NMSS NPI-12 items and GDS). Two group comparisons were performed using Fisher's exact test (categorical variables) and Mann-Whitney U-test (continuous variables), as appropriate.

LSPD and DBS patients were not matched for any relevant variables (e.g. age, disease duration, duration of levodopa treatment, etc.) refraining the possibility to perform direct comparison between both groups, thought descriptive statistics are reported. P value <0.05 was considered significant. The software SPSS 21.0 (SPSS, Chicago, IL) was used.

**Results**

***LSPD patients***

*Clinical data and NMS characteristics*

20 LSPD patients were included in the study. All had good response to L-dopa in the past. Demographic, clinical, disability milestones and therapeutic data of these patients have been reported previously [10] and are summarized in Table 1. The application of patients' self-reported scales was hampered due to the presence of dementia and weak collaboration (Tables 1 and 2).

NMS were very frequent and affected all domains (Table 1). PDD was diagnosed in 70% of the patients and hallucinations and psychosis were present in 45% of the cases. Depression was

very frequent according to the GDS (88%) and 35% of all cases were taking antidepressants (Table 1).

The overall severity of NMS was moderate-high (MDS-UPDRS part I items scoring ≥ 2 points), namely "cognition", "depressed mood", "anxious mood", "apathy", "day-time sleepiness", "urinary problems", "pain", "light-headedness and fatigue". The NPI-12 documented the presence of "agitation/aggression", "irritability/lability" and "aberrant motor behaviour" in about one-third of the patients. In the NMSS the domains of "mood", "memory", "urinary", "sleep/fatigue", "gastrointestinal" and "sexual" were universally affected (Table 1). The frequency of several NMS was similar across the MDS-UPDRS part I, the NPI-12 and the NMS scales (Table 1).

The caregivers of six patients (30%) reported that their relative frequently spent several hours per day in a sort of apathetic state, with their eyes closed but apparently not asleep, as they replied if questioned. Among these patients, five (25%) reported the frequent occurrence of a "drowsiness state" 30-40 minutes after L-dopa intake, while anxiety occurring 15-30 minutes before L-dopa intake was reported by two.

*Levodopa acute challenge test*

The median L-dopa dose for the test was 315 mg [IQR: 277-375]. The median MDS-UPDRS part III score was 67 [IQR: 60.5-78.2] in MED OFF and 57 [IQR: 50.2-64] in MED ON, with a significant improvement of 11.3% [IQR: 6%-23%] ($p<0.001$) (Table 2).

Measurement of BP in orthostatism was not possible in four patients (20%) due to their difficulty in keeping a standing position. Median change of SBP was statistically different between MED OFF versus MED ON ($p < 0.005$). Three and four patients (according to criteria I and II, respectively) developed OH in MED ON, which was symptomatic in only one (Table 2).

Twelve patients (60%) succeeded in completing the VAS scales and 7 (35%) completed the STAI. Pain, fatigue and anxiety did not change significantly after L-dopa intake. There was no correlation between either the ΔVAS-p or ΔVAS-f and the ΔMDS-UPDRS part III while the ΔSTAI correlated with the ΔMDS-UPDRS part III ($R= 0,686$; $p <0.005$). The score of the STAI was not significantly different between fluctuators (score of MDS-UPSRS part IV item 4.3 ≥ 1) and non-fluctuators. Moderate correlation was found between MDS-UPDRS part III (MED ON) and MDS-UPDRS part I ($R=0,675$; $p < 0.05$), GDS ($R=0,634$; $p < 0.005$) and NMSS ($R=0,695$; $p< 0.05$), but not with NPI-12 items, indicating that a worse motor condition was associated with more severe NMS. Severity of motor parkinsonism was not significantly different between demented and non-demented patients, whereas PDD patients had worse scores of MDS-UPDRS parts I and II compared to non-demented patients.

No serious AEs occurred during the test. Six patients (30%) reported moderate drowsiness or fell asleep after L-dopa. The occurrence of L-dopa- related AEs was not associated with neither

longer disease duration, older age, age at PD onset, PDD, L-dopa dose nor with a worse motor score (MED ON).

***Advanced PD patients***

*Clinical data and NMS characteristics*

22 DBS patients were included in the study and, overall, NMS were less severe in advanced patients compared to LSPD (Table 1). No advanced patient was demented, 18% reported hallucinations and depression was diagnosed in 59% of patients. The following items scored ≥ 2 points in the MDS-UPDRS part I, indicating moderate-high severity: "depressed mood", "anxious mood", "apathy", "pain", "urinary problems", "constipation" and "fatigue". Interestingly, joint and skeletal deformities were absent.

*Levodopa acute challenge test*

The median L-dopa dose for the test was 350 mg [IQR: 287-450]. The MDS-UPDRS-III score improved significantly (52.5 versus 27; 37% [IQR: 26%-57% $p < 0.001$]) after L-dopa (Table 2).

The intake of L-dopa had no significant effect on mean BP and fatigue. Four and five patients (according to criteria I and II, respectively) developed asymptomatic OH in MED ON (Table 2). L-dopa improved pain and anxiety ($p < 0.05$). The ΔVAS-p did not correlate with ΔMDS-UPDRS-III. On the other hand, the ΔSTAI had a moderate correlation with the magnitude of L-dopa response ($R = 0{,}427$; $p < 0.05$) but not with presence of "wearing-off" or "dyskinesias" (MDS-UPDRS-IV item 4.3 and 4.1). A moderate correlation was found between MDS-UPDRS part III (MED ON/STIM OFF) and the NMSS ($R = 0{,}427$; $p < 0.05$) but no correlation was found with neither the MDS-UPDRS part I nor the NPI-12.

**Discussion**

As previously reported, we found a high frequency and severity of NMS among LSPD patients, [3, 6, 19] which were correlated with motor disability. All domains of NMS were involved and most domains affected all patients. Frequency of NMS was similar among different scales, giving internal consistency to our results. We were able to perform a L-dopa challenge on these very disabled patients, although the difficulty of patients completing the self-reported scales has possibly hampered the assessment of the response of NMS. Despite this, the results showed no significant effect of an acute L-dopa challenge on pain, fatigue and anxiety, while SBP decreased

after L-dopa intake and OH emerged in about 25% of tested patients. Additionally, AEs occurred in one-third of patients after the intake of L-dopa, namely sleepiness. Furthermore we applied the same study protocol to a representative group of advanced stage PD patients that was used as an "active control group". The lack of data on acute L-dopa effect on NMS in LSPD patients suggested the need to adopt this group of advanced PD patients in order to validate the results and study tools.

We decided to restrict the assessment of NMS only to some symptoms, namely pain, fatigue, anxiety and BP, whose specific acute modifications could be evaluated during a L-dopa challenge in a LSPD population. Indeed the instruments available to assess NMS in PD may be inadequate in very disabled patients, similarly to other neurodegenerative conditions [20]. Such burden is a specific trait of LSPD patients, as we found no similar difficulties for our group of advanced PD patients. There is the additional risk of low reliability of LSPD patients' response to self-reported scales or questionnaires due to cognitive and speech impairment and the occurrence of AEs after L-dopa.

Nevertheless, we diagnosed probable dementia in 70% of LSPD patients, which is quite high compared to other case series (45%-50%) with similar disease duration [3, 4], whereas the frequency of psychosis was similar to previous reports (about 45%) [3, 4]. Depression was diagnosed in 88% of patients and the difficulty encountered in completing the GDS may have nevertheless resulted in an underestimation of its frequency and severity. Our frequency of mild depression (70%) is rather high but almost half of depressed patients were not taking antidepressants, which highlights how depressive symptoms may go unnoticed in such a late phase, or, alternatively, that antidepressants were discontinued in the past due to AEs. Dysautonomic symptoms were equally very frequent and bothersome to LSPD patients. The high frequency of daytime sleepiness, apathy and motor aberrant behavior in LSPD patients result in a severe clinical picture, in which patients spend most part of the day alternating between an "apathetic state" with eyes closed and periods of excessive sleepiness or purposeless motor behavior.

The acute L-dopa challenge induced a 23 mmHg drop in SBP and the occurrence of OH in one-fourth of patients. OH was symptomatic only in one, which contrasts with the high frequency of symptoms of orthostatism. Diagnosing and treating low BP in LSPD may prove beneficial in improving patients' handicap. Interestingly, L-dopa did not cause a significant decrease in BP in advanced PD patients, who had longer disease duration, suggesting that severity of dysautonomia may not be determined solely by disease duration.

The intake of L-dopa did not significantly change the severity or the frequency of pain, fatigue and anxiety. This contrasts with the significant improvement of both anxiety and pain among advanced PD patients, possibly linked in part to their better motor response to L-dopa.

Alternatively, the major source of pain in LSPD patients may be related to secondary causes such as radicular compression, musculoskeletal deformities and contractures, which do not respond to L-dopa and whose treatment is challenging [9]. In fact, the frequency of painful off-dystonia, highly responsive to L-dopa, was similar for LSPD and DBS patients, but two-thirds of patients reported some discomfort due to pain, suggesting that other causes of pain could have greater impact on patients [21, 22].

The absent effect of L-dopa on fatigue in both populations is not surprising. Indeed, even if L-dopa has been proposed to induce a slower progression of fatigue compared with placebo [23], currently no treatment is considered effective for this NMS [24] and dopaminergic pathways seem to be only partially involved in the pathogenesis of fatigue in PD [23]. Even though the same seems true for anxiety, the rate of missing data among LSPD patients is too high to draw any firm conclusion. In fact, severity of anxiety moderately correlated with the motor improvement with L-dopa in both groups of patients. The acute effect of L-dopa on anxiety has been investigated in a few studies with small and heterogeneous samples of non-demented PD patients in intermediate/advanced stages. The findings suggest that L-dopa improves anxiety that fluctuates with L-dopa intake, whose magnitude is stronger in patients with motor "wearing-off" and that the fluctuation of anxiety correlates with the magnitude of motor response [25, 26]. Accordingly, anxiety significantly improved after L-dopa in our advanced patients whose motor response to L-dopa was greater than in the LSPD group. The absent effect of L-dopa on anxiety among LSPD patients could be additionally explained due to a wider neurodegeneration of locus coeruleus in the latest disease phase, which has been implicated in the pathogenesis of anxiety in PD [27, 28]. Moreover, the lack of effect of L-dopa on anxiety in LSPD patients could be also related to the presence of Alzheimer's disease-type pathology among LSPD patients, in which the presence of depression and anxiety may be mainly related to the presence of dementia [29, 30]. Despite a lower L-dopa dose, the frequency of L-dopa-related AEs is slightly higher among LSPD patients than advanced ones. We may speculate that these AEs increase progressively with disease progression and the presence of dementia. Nevertheless, we did not find any correlation between frequency of AEs and disease duration, age, age at PD onset, PDD or disease severity of LSPD patients. The presence of these AEs, such as symptomatic OH, daytime sleepiness or hallucinations, frequently implies L-dopa dose reduction, making it even more difficult to manage PD in this late stage.

It could be interesting to investigate the acute effect on NMS of levodopa-carbidopa intestinal gel (LCIG) among LSPD patients. In fact, some recent reports suggest an improvement of some NMS such as sleep/fatigue, pain, gastrointestinal and urinary symptoms, as assessed by the NMSS,

during a chronic treatment with LCIG [31-33], the quality of evidence for reduction of NMS is still considered low [34] and no study have been specifically addressed to LSPD patients.

*Study limitations*

The sample size of the LSPD group was small, although these patients are very difficult to recruit [4]. The washout period for the STIM OFF condition in the advanced group was short, but many patients could not tolerate longer time without stimulation.

On the other hand, we could have investigated more NMS and also the several causes of pain in PD [35] and how they might respond differently to a L-dopa acute challenge. Importantly, our results concern the response of NMS to an acute intake of L-dopa and thus it may not indicate how these NMS respond to a chronic intake of L-dopa.

**Conclusions**

To our knowledge, this is the first study that explores the response of NM variable to an acute L-dopa challenge in LSPD. Our exploratory study confirms the high severity and frequency of NMS among LSPD patients, and highlights the need for assessment tools adapted to these very disabled PD patients.

Some NMS such as pain, fatigue and anxiety do not benefit from the acute action of a supra-threshold dose of L-dopa, which is in line with our recent findings for motor symptoms [10] and suggests an overall decrease of the effect of L-dopa with disease progression, at least its acute effect. Thus we could speculate that clinicians should not expect to have any gain for those NMS increasing the dose of L-dopa among LSPD patients. Despite this, L-dopa keeps the ability to induce AEs in LSPD patients; these AEs may possibly not occur if L-dopa dose is slowly increased. We acknowledge, however, that the benefit from an acute L-dopa challenge for pain, fatigue and anxiety in earlier stages of PD is not well established, in contrast to the amount of evidence of its effect on motor symptoms.

The expected increase in the prevalence of this orphan population, the limitation of current assessment scales and the apparent lack of response of certain NMS to L-dopa call for the need of larger studies of LSPD in order to optimize the assessment of these patients and the treatment of NMS, which are a major source of disability in later PD stages.

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**LEGEND FOR TABLES**

**Table 1.** Demographic and clinical characteristics of LSPD and DBS patients. Values are presented as median [IQR, 25th–75th percentile] if no otherwise specified. GDS: Geriatric Depression Scale. MMSE: Mini Mental State Examination. NMSS: Non-motor symptoms scale; NPI: Neuropsychiatric Inventory Scale; Missing data: (*) → GDS 3/20; the NPI was applied only to 16 LSPD patients and 18 DBS patients.

**Table 2**. NMS response to L-dopa. Values are presented as median [IQR, 25th–75th percentile]. STAI: State Trait of Anxiety Inventory (only the 20 items of state anxiety have been applied); VAS-p: visual analogue scale for pain; VAS-f: visual analogue scale for fatigue; BP_supine: blood pressure in supine position: BP_orto: blood pressure after 3 minutes of standing; OT: orthostatic hypotension HY: Hoehn Yahr; S&E: Schwab and England score; p*: MED OFF versus MEN ON; p°: MED OFF/STIM OFF versus MED ON/STIM OFF. **Missing values**→STAI: ^13 over 20; VAS: * 8 over 20; BP: ° 4 over 20; 1-OH: defined as decrease in systolic pressure >30 mmHg and in diastolic pressure>15 mmHg, within 3 minutes of standing; 2-OH: defines as decrease in systolic pressure >20 mmHg and in diastolic pressure>10 mmHg, within 3 minutes of standing.