VIEWPOINT

Dyskinesia Matters

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ABSTRACT: Levodopa-induced dyskinesia (LID) represents a significant source of discomfort for people with Parkinson's disease (PD). It negatively affects quality of life, it is associated with both motor and nonmotor fluctuations, and it brings an increased risk of disability, balance problems, and falls. Although the prevalence of severe LID appears to be lower than in previous eras (likely owing to a more conservative use of oral levodopa), we have not yet found a way to prevent the development of this complication. Advanced surgical therapies, such as deep brain stimulation, ameliorate LID, but only a minority of PD patients qualify for these interventions. Although some have argued that PD patients would rather be ON with dyskinesia than OFF, the deeper truth is that patients would very much prefer to be ON without dyskinesia. As researchers and clinicians, we should aspire to make that goal a reality. To this end, translational research on LID is to be encouraged and persistently pursued. © 2019 International Parkinson and Movement Disorder Society

Key Words: animal models; basal ganglia; drug development; pathophysiology; therapy complications

The dopamine (DA) precursor levodopa continues to be the most effective treatment for the motor features of Parkinson's disease (PD). Unfortunately, however, the response to this treatment changes during the progression of the disease. As the severity of clinical PD increases, larger daily levodopa dosages become necessary, which in turn entails a considerable risk of dyskinesia (abnormal involuntary movements). Over the years, the health-related burden of dyskinesia has been discussed in a number of publications, sometimes leading to discordant conclusions. The latest addition to this literature is the viewpoint article by Chaudhuri and colleagues[1] recently published in *Movement Disorders*. Although the authors acknowledge that levodopa–induced dyskinesia (LID) still occurs to a high degree in PD, the main thrust of the article is that troublesome involuntary movements are not so common as they used to be and therefore dyskinesia "should not be given much emphasis as a matter of clinical significance or priority for research."

We thank Chaudhuri and colleagues[1] for raising awareness that the prevalence of disabling dyskinesias has been gradually diminishing as the result of a more cautious use of levodopa. Indeed, it is now well established that high doses of levodopa are strongly associated with more frequent and more severe dyskinesias in both PD patients[2] and animal models of PD.[3] Other notions in the article, however, deserve a more analytical review or they may be subject to misinterpretation. This perception is supported by a debate that has recently arisen on the social media. Several people with PD have expressed concerns about the viewpoint by Chaudhuri and colleagues[1] via the online forum Parkinson Research Interest Group, which is a patient-driven discussion group aiming to promote a better understanding of the disease, foster informed communication, and motivate the PD community to be more involved in research. As the group's founder Martin Taylor puts it: "For those of us diagnosed today, the

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Relevant conflicts of interests/financial disclosures: Nothing to report.

Received: 23 August 2019; **Revised:** 18 November 2019; **Accepted:** 2 December 2019

Published online 00 Month 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27959

prospect of dyskinesia is either a bothersome reality or a deep concern for the future. It's only right that it should be better treated." Elaborate rebuttals have also been posted through other websites by patients with PD (see an eloquent example in ref. 4). Taken together, the ongoing discussions among people with PD contradict the authors' contention that levodopaphobia is a rare phenomenon and that dyskinesia "does not worry the patients affected."[1]

In the present article, we aim to provide additional perspective on the medical and scientific importance of dyskinesia, thus contributing to a balanced debate. We borrow 6 passages from the article by Chaudhuri and colleagues, which will serve as starting points for our considerations.

> (1) "Antidyskinesia management in PD (oral therapies, infusion therapies, DBS, and radioablation) have all focused on dyskinesia reduction (usually troublesome dyskinesia) as one of the key aims of the therapy along with improvement of off-time in PD. However, a large body of clinical trials data point otherwise, and suggest that cautious use of levodopa therapy in low-dose regimes or early use of longer-acting therapies may substantially reduce the risk of troublesome dyskinesia in PD."[1]

Although the development of dyskinesia can be delayed by attempting to maintain a low dosage of levodopa, increasing dosages often become necessary over time to maintain adequate function. As we have begun to monitor patients with wearable accelerometers and other objective measurements, we are realizing that patients may be paying the price for our efforts at avoiding higher levodopa dosages by suffering with increased bradykinesia and OFF periods.[5-7] The cautious use of levodopa and DA agonists will not obviate this residual motor disability, and increasing medication dosages may cause resurgent, severe dyskinesias. Given that more than 75% of people with PD will eventually experience LID,[1] a plan of specific "antidyskinesia management" is therefore necessary. Today, the most effective options in this regard are advanced surgical therapies, such as deep brain stimulation targeting the subthalamic nucleus or the internal globus pallidus. Less than 10% of PD patients, however, qualify for these interventions,[8] which have many contraindications, potential side effects of their own, and very high costs.

We also point out that even if early use of longer acting therapies reduces the risk of LID, we have not yet found a way to easily and noninvasively achieve that goal. Initiating therapy with the combined administration of levodopa/carbidopa and entacapone (which prolongs the peripheral half-life of levodopa) has not been found to delay the time to LID onset nor to reduce its frequency.[9] In a study conducted in early de novo PD patients, initiating therapy with carbidopa/levodopa extended-release capsules (Rytary, IPX066, Impax Pharmaceuticals, Hayward, CA, USA) yielded a dyskinesia adverse event incidence of up to 5.1% after only 30 weeks.[10] Moreover, attempts to employ dopa–sparing strategies, such as starting therapy with a dopamine agonist, have shown that the cost of delaying the onset of dyskinesia may be worse motor function, more impairment in the activities of daily living, and a decreased quality of life.[11]

> (2) "Improvements in the delivery pattern of levodopa alone may reduce the prevalence of dyskinesia."

The notion that dyskinesia stems not from levodopa per se but from the pulsatile mode of levodopa delivery has been reiterated by many influential review articles during the past 3 decades. The theory builds on the assumption that a continuous supply of levodopa would be able to reproduce the physiological features of nigrostriatal DA transmission[12] by blunting deleterious fluctuations in striatal DA levels (as those described in dyskinetic PD patients shortly after drug administration[13]). In keeping with these notions, several small–medium scale studies have reported improvements in either severity or duration of dyskinesias after a switch from standard oral therapies to dopaminergic infusion therapies (reviewed in ref. 14). However, a recently published post hoc analysis of the GLORIA registry (a large multinational observational registry of patients receiving continuous intrajejunal infusion of levodopa–carbidopa intestinal gel [LCIG] for 24 months) reveals that dyskinesias are not eliminated by this therapy and that significant reductions in dyskinesia severity and durations are evident only in patients with high LID burden at baseline.[15] This is not totally surprising if one considers the complexity of PD dyskinesias and their underlying pathophysiology, which does not simply equate with surges of striatal DA release but involves persistent reorganization of brain cells and circuits mainly driven by the progression of PD[16] and its inherent nigrostriatal dopaminergic degeneration.[17-19] Accordingly, we have noted that it is not uncommon for patients on stable LCIG therapy to exhibit dyskinesia after an exciting or unexpected event during routine daily living. Although rarely acknowledged in the medical literature, these observations are consistent with reports communicated by the Swedish group who pioneered the development of LCIG.[20] Adding even more complexity to the picture, some recent studies have reported disabling diphasic-type dyskinesias in patients switched to LCIG treatment.[21,22] Here we do not intend to question the utility of LCIG or other infusion therapies for PD that provide well-documented benefits and improve the quality of life of many

patients. We rather point out that overestimating the curative possibilities of continuous dopaminergic stimulation may lead to the misconception that the problem of dyskinesia in PD has already been solved.

(3) "…only 5% of those (patients) with dyskinesia rated the movements as painful and 10% … rated them as mildly disabling—the remainder found dyskinesia not disabling. … Less than 1% rated their dyskinesia as severe and less than 2% as painful."

This and other passages (see later) refer to patient-reported assessments of dyskinesias, and it is therefore warranted to discuss the limitations intrinsic to such methodology. First, a significant proportion of PD patients are either partially or totally unaware of the presence of dyskinesia,[23-25] and overt denial of LID has been documented in some cases.[26] The limited self-awareness of LID among PD patients appears to depend on dopaminergic overstimulation of mesocorticolimbic circuits,[23,27] and not on patient ignorance of the phenomenon. In addition, specific deficits in the perception of trunk dyskinesias have been attributed to sensory proprioceptive dysfunction.[24] Finally, the burden of peak-dose dyskinesia tends to be underreported because patients usually prefer being *on* with dyskinesia than being *off*. Having firsthand experience of this disorder, one of us (S.R.) reports that LID has several nonmotor correlates, such as accelerations in heart rate, breathing, and thinking. S.R. explains that although the involuntary movements themselves are disruptive and socially embarrassing, the accelerated thinking may actually be perceived as pleasant. Accordingly, it has now been established that PD patients affected by motor complications often experience a state of euphoria in the *on* medication state[28] and that the high mood may be associated with poor judgment[28] and anosognosia.[24]

(4) "…in advanced PD patients with disabling fluctuations, only 23 of 71 had more than 1 hour of daily troublesome dyskinesia."

The term "troublesome dyskinesia" was coined by Hauser and colleagues[29] for use in PD patient diaries and is defined as dyskinesia that interferes with function or causes meaningful discomfort. It was specifically chosen to allow patients to differentiate unwanted dyskinesia, which they perceive as having a negative impact, from nontroublesome dyskinesia, which they do not perceive as having a negative impact. A conscious decision was made to emphasize patient perception and recognize that dyskinesia does not need to be disabling to be unwanted or have a negative impact. In the cited passage, the authors refer to a trial of LCIG in advanced PD patients with disabling fluctuations[30] wherein "only" 23 of 71 patients had more than 1 hour of daily troublesome dyskinesia. Our interpretation of these data would be that 32% of these 71 patients had at least 1 hour per day of unwanted, clinically relevant dyskinesia.

To further support the notion that severe LID is infrequent, Chaudhuri and colleagues comment on a community-based study evaluating an incident PD cohort for approximately 5 years.[31] They indicated that 28% of 183 people with PD developed LID after 5 years, but only 10% of those with dyskinesia rated it as mildly disabling. Notably, we do not know how many patients in this study found their dyskinesia troublesome or unwanted. Furthermore, 15% of those with dyskinesia underwent a reduction of levodopa dosage or introduction of amantadine. To us, this suggests that LID was sufficiently clinically relevant to require a change in therapeutic regimen in this 15%. Importantly, we do not know the price that was paid by these patients. For those who underwent levodopa reduction, did bradykinesia or *off* time become worse? For those who received amantadine, how many experienced adverse events?

(5) "…the apparent high incidence of dyskinesia (mild to troublesome) still leads to a plethora of investigations at the preclinical level"; "…the commonly used animal models do not reflect dyskinesia as it occurs in PD because they require extreme levels of nigrostriatal denervation coupled to the use of high levodopa dosages that are now out of line with those used clinically to treat PD."

Possibly reflecting the attitude of many clinical investigators, Chaudhuri and colleagues here criticized the validity of current animal models of LID, revealing a need for clarifications. First, it should be understood that all models are necessarily a simplification of a more complex reality. Yet, even acknowledging this fundamental tenet, one can reasonably state that animal models of LID are among the best validated models within the landscape of preclinical PD research. Unlike other features of PD, LID can be modeled in animals with a high degree of face validity and construct validity. All of the main risk factors for LID (young age at disease onset, severe putaminal dopamine denervation, high levodopa doses) can easily be reproduced in laboratory animals. Both nonhuman primate and rodent models of LID respond to medications having proven antidyskinetic efficacy in people with PD, such as amantadine and clozapine.[32] The methodologies for inducing nigrostriatal lesions, administering levodopa, quantifying the abnormal involuntary movements and their functional impact are very well grounded on the clinical literature. The specific methodological aspects mentioned by Chaudhuri and colleagues have been

extensively discussed and justified in recent review articles, to which we refer.[3,32] Moreover, there are many commonalities between the available animal models and human LID regarding pathophysiological mechanisms and biomarkers thereof.[32,33] One recent example of mechanistic similarity has emerged from studies of levodopa–induced neurovascular dysregulation, which have demonstrated localized vasoregulatory changes in both rats and humans during LID.[34-36] In addition to providing novel information regarding the neurovascular unit in PD,[34] the demonstration of analogous changes in the rodent model is facilitating the discovery of completely novel therapeutic avenues.[37]

We thank Chaudhuri and colleagues for acknowledging that investigations in animal models of LID can significantly advance our understanding of basal ganglia pathophysiology. In this vein, it is worth mentioning that recent studies in rodent models of LID have provided major insights into the role and plasticity of striatal output pathways in hyperkinetic versus hypokinetic disorders.[38-40] In addition, one should consider that the mechanisms of LID have significant commonalities with those underlying other complications of PD therapy, such as motor and nonmotor fluctuations, dopamine dysregulation syndrome, and impulsive–compulsive behaviors. Therefore, mechanism-oriented studies in animal models of LID can provide scientific benefit to all of these areas.

> (6) "…it is therefore timely that we pay attention to more appropriate allocation of funding for key unmet needs in PD rather than use much of our resource in dyskinesia-orientated clinical trials."

This passage refers to resources allocated to clinical trials by the private sector. Decisions taken within this sector are dictated by a number of practical and economical considerations. In this regard, it is worth highlighting a few aspects that may make LID an attractive area for pharmaceutical and biotech companies. For example, LID has been given orphan disease designation by the U.S. Food and Drug Administration, and drug development for orphan indications enjoys several financial incentives. On a more general level, other types of incentives can be envisaged. First, the translational roadmap for antidyskinetic drug development is relatively straightforward.[33,41] Second, in this area, even small trials of short duration can be highly informative to guide subsequent investments (see an example in ref. 42). Third, relevant therapeutic targets for LID have already been identified through extensive preclinical investigations and sometimes validated through positive proof-of-concept clinical studies.[18,33,41] The number of medications that have undergone phase III clinical trials is limited to amantadine extended release and sarizotan, and the latter has failed to produce significant antidyskinetic effects.[43] However, negative results in clinical trials do not necessarily invalidate the corresponding preclinical data because many technical reasons may underlie a failure to meet trial endpoints. In the case of LID, potential caveats of past clinical trials, and general challenges facing the translation of preclinical results, have been constructively discussed in several recent publications.[3,18,33,41] In fact, the awareness and experience gained from past trials of antidyskinetic treatments may increase the likelihood of successful outcomes in future studies.[41] Finally, there is no doubt that good antidyskinetic medications are needed. Given that the prevalence of PD is bound to rise because of population aging and that approximately 80% of levodopa–treated PD patients develop LID within 10 years,[2] it is anticipated that an increasing number of PD patients will require expensive invasive treatments for the management of motor complications. Yet, many patients with LID are not candidates for deep brain stimulation or LCIG therapy, and amantadine provides only partial relief. If we had an easily administered, well tolerated, highly effective antidyskinetic agent, we would be free to use oral levodopa more liberally to improve the management of bradykinesia and *off* periods throughout the course of the disease.

Concluding Remarks

LID represents a significant source of discomfort that ultimately affects a majority of PD patients. It negatively affects quality of life,[44,45] it is associated with both motor and nonmotor fluctuations,[28,46] and it brings an increased risk of disability, balance problems, and falls.[47,48] Although some have argued that if given the choice patients would rather be dyskinetic than *off*, the deeper truth is that patients would prefer to be *on* without dyskinesia through the day. As researchers and clinicians, we should aspire to make that goal a reality. To this end, translational research on LID is to be encouraged and persistently pursued. ■

References

1. Chaudhuri KR, Jenner P, Antonini A. Should there be less emphasis on levodopa-induced dyskinesia in Parkinson's disease? Mov Disord 2019;34(6):816–819.
2. Manson A, Stirpe P, Schrag A. Levodopa-induced-dyskinesias clinical features, incidence, risk factors, management and impact on quality of life. J Parkinsons Dis 2012;2(3):189–198.
3. Cenci MA. Presynaptic Mechanisms of l-DOPA-Induced Dyskinesia: The Findings, the Debate, and the Therapeutic Implications. Front Neurol 2014;5:242.
4. Granderouge. "Dear Prof. Chaudhuri… 2019." https://granderouge.wordpress.com/2019/05/01/dear-mr-chaudhuri/?fbclid=IwAR17AQ-h4ymWNaTtjqtYiS71eOA8QBuOzbS30bVEAfJFn7MP0-pWMJImLsw2019. Accessed on December 12th, 2019
5. Goubault E, Nguyen HP, Bogard S, et al. Cardinal motor features of Parkinson's disease coexist with peak-dose choreic-type drug-induced dyskinesia. J Parkinsons Dis 2018;8(2):323–331.

6. Goubault E, Nguyen HP, Bogard S, et al. Remnants of cardinal symptoms of Parkinson's disease, not dyskinesia, are problematic for dyskinetic patients performing activities of daily living. Front Neurol 2019;10:256.
7. Pahwa R, Isaacson SH, Torres-Russotto D, Nahab FB, Lynch PM, Kotschet KE. Role of the Personal KinetiGraph in the routine clinical assessment of Parkinson's disease: recommendations from an expert panel. Expert Rev Neurother 2018;18(8):669–680.
8. Morgante L, Morgante F, Moro E, et al. How many parkinsonian patients are suitable candidates for deep brain stimulation of subthalamic nucleus? Results of a questionnaire. Parkinsonism Relat Disord 2007;13(8):528–531.
9. Stocchi F, Rascol O, Kieburtz K, et al. Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: the STRIDE-PD study. Ann Neurol 2010;68(1):18–27.
10. Pahwa R, Lyons KE, Hauser RA, et al. Randomized trial of IPX066, carbidopa/levodopa extended release, in early Parkinson's disease. Parkinsonism Relat Disord 2014;20(2):142–148.
11. Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomized controlled trial. JAMA 2000;284(15):1931–1938.
12. Chase TN. Levodopa therapy: consequences of the nonphysiologic replacement of dopamine. Neurology 1998;50(5 suppl. 5):S17–S25.
13. de la Fuente-Fernandez R, Schulzer M, Mak E, Calne DB, Stoessl AJ. Presynaptic mechanisms of motor fluctuations in Parkinson's disease: a probabilistic model. Brain 2004;127(Pt 4):888–899.
14. Cenci MA, Ohlin KE, Odin P. Current options and future possibilities for the treatment of dyskinesia and motor fluctuations in Parkinson's disease. CNS Neurol Disord Drug Targets 2011;10(6):670–684.
15. Poewe W, Chaudhuri KR, Bergmann L, Antonini A. Levodopa-carbidopa intestinal gel in a subgroup of patients with dyskinesia at baseline from the GLORIA Registry. Neurodegener Dis Manag 2019;9(1):39–46.
16. Cilia R, Akpalu A, Sarfo FS, et al. The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa. Brain 2014;137(Pt 10):2731–2742.
17. Cenci MA, Lundblad M. Post- versus presynaptic plasticity in L-DOPA-induced dyskinesia. J Neurochem 2006;99(2):381–392.
18. Cerri S, Siani F, Blandini F. Investigational drugs in phase I and phase II for levodopa-induced dyskinesias. Expert Opin Inv Drugs 2017;26(7):777–791.
19. Nadjar A, Gerfen CR, Bezard E. Priming for l-dopa-induced dyskinesia in Parkinson's disease: a feature inherent to the treatment or the disease? Prog Neurobiol 2009;87(1):1–9.
20. Nyholm D, Johansson A, Aquilonius SM, Hellquist E, Lennernas H, Askmark H. Complexity of motor response to different doses of duodenal levodopa infusion in Parkinson disease. Clin Neuropharmacol 2012;35(1):6–14.
21. Melgari JM, Salomone G, di Biase L, Marano M, Scrascia F, Di Lazzaro V. Dyskinesias during levodopa-carbidopa intestinal gel (LCIG) infusion: management inclinical practice. Parkinsonism Relat Disord 2015;21(3):327–328.
22. Meloni M, Solla P, Mascia MM, Marrosu F, Cannas A. Diphasic dyskinesias during levodopa-carbidopa intestinal gel (LCIG) infusion in Parkinson's disease. Parkinsonism Relat Disord 2017;37:92–96.
23. Amanzio M, Palermo S, Zibetti M, et al. Self-unawareness of levodopa induced dyskinesias in patients with Parkinson's disease. Brain Cogn 2014;90:135–141.
24. Pietracupa S, Fasano A, Fabbrini G, et al. Poor self-awareness of levodopa-induced dyskinesias in Parkinson's disease: clinical features and mechanisms. Parkinsonism Relat Disord 2013;19(11):1004–1008.
25. Vitale C, Pellecchia MT, Grossi D, et al. Unawareness of dyskinesias in Parkinson's and Huntington's diseases. Neurol Sci 2001;22(1):105–106.
26. Sitek EJ, Soltan W, Wieczorek D, Robowski P, Schinwelski M, Slawek J. Assessing self-awareness of dyskinesias in Parkinson's disease through movie materials. Funct Neurol 2011;26(3):121–126.
27. Palermo S, Lopiano L, Morese R, et al. Role of the cingulate cortex in dyskinesias-reduced-self-awareness: an fMRI study on Parkinson's disease patients. Front Psychol 2018;9:1765.
28. Delpont B, Lhommee E, Klinger H, et al. Psychostimulant effect of dopaminergic treatment and addictions in Parkinson's disease. Mov Disord 2017;32(11):1566–1573.
29. Hauser RA, Friedlander J, Zesiewicz TA, et al. A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia. Clin Neuropharmacol 2000;23(2):75–81.
30. Antonini A, Fung VS, Boyd JT, et al. Effect of levodopa-carbidopa intestinal gel on dyskinesia in advanced Parkinson's disease patients. Mov Disord 2016;31(4):530–537.
31. Scott NW, Macleod AD, Counsell CE. Motor complications in an incident Parkinson's disease cohort. Eur J Neurol 2016;23(2):304–312.
32. Cenci MA, Crossman AR. Animal models of l-dopa-induced dyskinesia in Parkinson's disease. Mov Disord 2018;33(6):889–899.
33. Bastide MF, Meissner WG, Picconi B, et al. Pathophysiology of L-dopa-induced motor and non-motor complications in Parkinson's disease. Prog Neurobiol 2015;132:96–168.
34. Jourdain VA, Tang CC, Holtbernd F, et al. Flow-metabolism dissociation in the pathogenesis of levodopa-induced dyskinesia. JCI Insight 2016;1(15):e86615.
35. Lerner RP, Francardo V, Fujita K, et al. Levodopa-induced abnormal involuntary movements correlate with altered permeability of the blood-brain-barrier in the basal ganglia. Sci Rep 2017;7(1):16005.
36. Ohlin KE, Sebastianutto I, Adkins CE, Lundblad C, Lockman PR, Cenci MA. Impact of L-DOPA treatment on regional cerebral blood flow and metabolism in the basal ganglia in a rat model of Parkinson's disease. NeuroImage 2012;61(1):228–239.
37. Boi L, Pisanu A, Greig NH, et al. Immunomodulatory drugs alleviate l-dopa-induced dyskinesia in a rat model of Parkinson's disease [published online ahead of print July 23, 2019]. Mov Disord. https://doi.org/10.1002/mds.27799
38. Alcacer C, Andreoli L, Sebastianutto I, Jakobsson J, Fieblinger T, Cenci MA. Chemogenetic stimulation of striatal projection neurons modulates responses to Parkinson's disease therapy. J Clin Invest 2017;127(2):720–734.
39. Parker JG, Marshall JD, Ahanonu B, et al. Diametric neural ensemble dynamics in parkinsonian and dyskinetic states. Nature 2018;557(7704):177–182.
40. Ryan MB, Bair-Marshall C, Nelson AB. Aberrant striatal activity in parkinsonism and levodopa-induced dyskinesia. Cell Rep 2018;23(12):3438–3446 e3435.
41. Fox SH, Brotchie JM. Viewpoint: developing drugs for levodopa-induced dyskinesia in PD: lessons learnt, what does the future hold? Eur J Neurosci 2019;49(3):399–409.
42. Svenningsson P, Rosenblad C, Af Edholm Arvidsson K, et al. Eltoprazine counteracts l-DOPA-induced dyskinesias in Parkinson's disease: a dose-finding study. Brain 2015;138(Pt 4):963–973.
43. Goetz CG, Damier P, Hicking C, et al. Sarizotan as a treatment for dyskinesias in Parkinson's disease: a double-blind placebo-controlled trial. Mov Disord 2007;22(2):179–186.
44. Damiano AM, McGrath MM, Willian MK, et al. Evaluation of a measurement strategy for Parkinson's disease: assessing patient health-related quality of life. Qual Life Res 2000;9(1):87–100.
45. Perez-Lloret S, Negre-Pages L, Damier P, et al. L-DOPA-induced dyskinesias, motor fluctuations and health-related quality of life: the COPARK survey. Eur J Neurol 2017;24(12):1532–1538.
46. Hauser RA, McDermott MP, Messing S. Factors associated with the development of motor fluctuations and dyskinesias in Parkinson disease. Arch Neurol 2006;63(12):1756–1760.
47. Curtze C, Nutt JG, Carlson-Kuhta P, Mancini M, Horak FB. Levodopa is a double-edged sword for balance and gait in people with Parkinson's disease. Mov Disord 2015;30(10):1361–1370.
48. Rascol O, Perez-Lloret S, Damier P, et al. Falls in ambulatory non-demented patients with Parkinson's disease. J Neural Transm (Vienna) 2015;122(10):1447–1455.