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Motor Fluctuations and Dyskinesias in Parkinson's Disease: Clinical Manifestations

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Abstract: Fluctuations in the symptoms of Parkinson's disease (PD), such as wearing-off and *on–off* effects, and dyskinesias are related to a variety of factors, including duration and dosage of levodopa, age at onset, stress, sleep, food intake, and other pharmacokinetic and pharmacodynamic mechanisms. The majority of patients, particularly those with young onset of PD, experience these levodopa-related adverse effects after a few years of treatment. Assessment of these motor complications is difficult because of the marked clinical variability between and within patients. Daily diaries have been used in clinical trials designed to assess the effects of various pharmacological and surgical interventions on motor fluctuations and dyskinesias. The most common type of dyskinesia, called "peak-dose dyskinesia", usually consists of stereotypical choreic or ballistic movements involving the head, trunk, and limbs, and occasionally, the respiratory muscles, whereas tremor and punding are less-common complications. Dystonia is also typically seen in patients with diphasic dyskinesia and wearing-off effect. Recognition of the full spectrum of clinical phenomenology of levodopa-related motor complications is essential for their treatment and prevention. © 2005 Movement Disorder Society

Key words: motor complications; Parkinson's disease; dyskinesia; wearing off; levodopa

Introduced in the 1960s, levodopa revolutionized the treatment of Parkinson's disease (PD). Although L-dopa remains the most effective drug in the symptomatic treatment of PD, the emergence of side effects, particularly motor fluctuations and dyskinesias, limits its usefulness.[1] Several algorithms (decision trees), highlighting the need for L-dopa–sparing strategies and continuous dopaminergic stimulation have been offered as treatment guidelines.[2,3] A standard "cookbook" approach to management of PD is not generally recommended[4]; rather, the therapy of PD should be individualized and tailored to the specific needs of each patient. This review focuses on the assessment, risk factors, and clinical features of L-dopa–related motor complications. It is beyond the scope of this review to discuss pathophysiology and treatment. The reader is referred to other reviews on mechanisms of L-dopa–related complications[5–9] and their treatment.[10–12]

ASSESSMENT OF MOTOR FLUCTUATIONS

A variety of neurophysiological and computer-based techniques have been proposed as quantitative and objective methods of capturing the clinical features of PD and L-dopa–related complications but most studies still rely on clinical rating scales, particularly the Unified Parkinson's Disease Rating Scale (UPDRS).[13] This widely used instrument has been found to have excellent test–retest reliability[14] but is currently being revised by The *Movement* Disorder Society task force to further improve its sensitivity and consistency. The revised UPDRS Part IV contains items related to motor complications of L-dopa, based on historical information. Although the revised version of the UPDRS represents a major improvement in standardizing the assessment of the various parkinsonian symptoms and signs, it still does not attempt to quantitate dyskinesias based on examination. Indeed, the rating scale does not adequately address how the presence of dyskinesia masks the underlying parkinsonian features and how it interferes with

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TABLE 1. *Young- versus late-onset Parkinson's disease*

Symptom*	Young onset (%), n = 88	Late onset (%), n = 110	*P*
Tremor	59.1	65.5	NS
Bradykinesia	10.2	14.5	NS
Rigidity	18.2	8.2	0.051
Postural instability	3.4	13.6	0.013
Gait difficulty	14.8	28.2	0.026
Wearing-off	73.8	36.8	0.00001
Wearing-off dystonia	25.8	5.3	0.0003
L-Dopa dyskinesia	69.2	41.1	0.0007

*Presenting features and levodopa-related motor complications
Young onset, 20 to 40 years of age; late onset, 60 years of age or older.

the UPDRS assessment and examination (Part III). Rating scales specifically designed to assess L-dopa–induced dyskinesias, some based on patient's diaries,[15] increasingly are used in PD clinical trials[16,17] but have not yet been fully incorporated into quality of life instruments.[18,19]

RISK FACTORS FOR MOTOR COMPLICATIONS

The frequency of motor complications associated with L-dopa therapy is dependent on several variables, such as the age at onset of the disease and initiation of L-dopa therapy, duration of treatment, total daily dose, and other factors. To determine whether age at onset is a predictor of the future course and response to L-dopa, we compared 88 patients with young-onset PD patients (onset between 20 and 40 years) with 110 late-onset PD patients (onset at 60 years or older).[11,20] Similar to other studies,[21,22] young-onset PD patients responded to L-dopa better than the late-onset group but were more likely to develop dyskinesias and "wearing-off" (Table 1).

L-Dopa–related complications occur at much earlier stages of dopaminergic therapy than previously thought. In a review of 74 publications with adequate data related to frequency of L-dopa–induced fluctuations and dyskinesias, Ahlskog and Muenter[23] concluded that, after 5 years of L-dopa therapy, approximately 40% of patients experience fluctuations and the same number experience dyskinesias. The limitations of such a survey, including marked heterogeneity of diagnostic criteria for L-dopa–related motor complications, doses, duration of follow-up, and other problems must be carefully considered when interpreting these, mostly retrospective, data. In a large, prospective study 352 de novo patients originally enrolled in the DATATOP protocol experienced the following complications after 20.5 ± 8.8 months of L-dopa therapy: wearing-off in approximately half, dyskinesia in one third, and severe *on–off* in approximately 10% of patients.[24] This finding is consistent with previous studies.[25] However, in a study of 618 patients enrolled in the CR First Study, in which standard and CR Sinemet were compared, only 22% of the patients developed fluctuations or dyskinesias during a 5-year prospective follow-up.[26] The difference may be explained in part by the more stringent criteria for the detection of the time to onset of motor fluctuations in the CR First Study: when more than 20% of the waking day was spent in the *off* state, or when more than 10% of the waking day was spent in the "*on* with dyskinesia" state. In a study of 41 patients with autopsy proven PD, with a mean duration of illness of 15.9 years and a mean duration of follow-up of 9.1 years, 62% experienced dyskinesias, 36% wearing-off and 17% *on–off* effect.[27] Dyskinesia, the earliest motor side effect, was seen in 31% of patients after 6.4 years on L-dopa. Nutt and coworkers[28] showed that, when patients are carefully observed, a majority of patients develop motor fluctuations and dyskinesias even during the first year of L-dopa therapy. There are many reasons for the apparent discrepancies in the frequency of motor complications between the different studies, perhaps the most important of which is a difference in definitions of the thresholds for recognizing motor complications.[29]

In addition to the duration of L-dopa exposure, the daily dosage of L-dopa is also a critical risk factor for the development of dyskinesias. Despite previous reports that L-dopa does not cause dyskinesia in normal animals or humans, L-dopa in high doses has been demonstrated to produce dyskinesias in normal monkeys.[30,31] A large, multicenter study, the ELLDOPA trial, evaluated the effects of L-dopa on progression of PD in 361 patients with no prior anti-PD treatment and not requiring symptomatic therapy who were randomly assigned to placebo or L-dopa at 150, 300, or 600 mg/day for 40 weeks, followed by a 2-week washout.[32,33] Wearing-off and dyskinesias were significantly more common in the highest-dose group.

Whether there is a genetic predisposition for the development of L-dopa–related complications has not been established, but this predisposition could explain the marked inter-subject heterogeneity of response to L-dopa. There are many patients exposed to large doses of L-dopa over long periods without ever developing dyskinesias, whereas others develop dyskinesias within a few days of exposure even using relatively small daily doses. Furthermore, L-dopa–induced dyskinesias usually do not occur in patients with atypical, postsynaptic, Parkinsonism, which suggests that this complication is mediated in PD patients by postsynaptic dopamine receptors.[34] In a case–control study of 136 patients with PD and 224 controls, Oliveri and associates[35] found that

TABLE 2. *Levodopa-related motor complications*

Symptom	Description
Motor fluctuations	
Wearing off	Gradual or sudden
	Predictable (related to meals, exercise, rest)
	Unpredictable (random)
On–off effects	Random "yo-yo-ing"
Delayed *on*	
No *on*	Dose failure
Freezing	*Off* or *on*; may not be related to levodopa
Other fluctuations	Blood pressure, behavioral, sensory, sleep pattern

certain alleles of the short tandem repeat polymorphism of the D2 receptor gene reduce the risk of developing L-dopa–induced dyskinesias. In another study, the DRD2Taq1A polymorphism was associated with an increased risk for developing motor fluctuations.[36] Other studies showed no evidence of any association between L-dopa dyskinesias and genetic variations in the DRD2, DRD3, or DRD4 genes, but the nine-copy allele 40-bp variable numbers of tandem repeat of the DAT gene appears to predict the occurrence of psychosis or dyskinesia in L-dopa–treated patients.[37]

PHENOMENOLOGY OF L-DOPA–RELATED MOTOR FLUCTUATIONS

The phenomenology of different types of motor fluctuations and L-dopa–induced dyskinesias has been well characterized[1,10,38–42] (Table 2). The most common form of clinical fluctuation, the wearing-off effect, is characterized by end-of-dose deterioration and recurrence of parkinsonian symptoms as a result of shorter (sometimes only 1 to 2 hours) duration of benefit after a given dose of L-dopa. When the previous L-dopa dose wears off, the patient notices a return of parkinsonian symptoms and signs, such as bradykinesia, tremor, rigidity, difficulty arising from a chair or getting in and out of a car, freezing (also referred to as motor blocks). Although freezing is a common parkinsonian sign during the *off* state, it may occur even when the patient is *on* ("*on* freezing"). Besides the return of parkinsonian symptoms, some patients experience "*off* dyskinesias", most frequently *off* dystonia (discussed below). In addition to the motor *off* symptoms, many patients experience "sensory *off*s", "behavioral *off*s", or a combination of the two. The sensory *off*s typically consist of pain and paresthesias, whereas the behavioral *off*s usually include depression, anxiety, dysphoria, or panic. Akathisia, a combination of sensory phenomenon (inner restlessness and urge to move) and motor phenomenon (stereotypic movements), is typically present during *off* periods and may indeed be a symptom of PD but may also rarely occur during *on* times. These sensory and behavioral phenomena are often more troublesome for the patients than are the cardinal signs and drive the patient to increase L-dopa use, sometimes leading to L-dopa abuse, turning some patients into L-dopa addicts (the so-called dopamine dysregulation syndrome).[43]

L-DOPA–RELATED DYSKINESIAS

The most frequent forms of dyskinesia include stereotypies, chorea, ballism, dystonia, and myoclonus. Although these involuntary movements can be quite violent and disabling, many patients prefer being *on* with dyskinesia than being *off* without dyskinesia. Studies of the impact of dyskinesias on quality of life measures have reported conflicting results, some concluding that patients with dyskinesias have lower quality of life scores,[44] whereas others find that dyskinesias have a relatively minimal impact on quality of life of patients with PD.[18,39,45] Careful studies of patients during periods of dyskinesias suggest that L-dopa–induced dyskinesias usually start in the foot, ipsilateral to the side most affected by PD.[40,46] This finding is consistent with early loss of dopaminergic innervation in the dorsolateral striatum, which corresponds somatotopically to the foot area, innervated by the ventrolateral portion of the substantia nigra.[47]

The most common type of dyskinesia, called peak-dose dyskinesia, usually consists of stereotypic, choreic or ballistic movements involving the head, trunk, and limbs, and occasionally, the respiratory muscles.[10,48,49] A relatively rare form of stereotypic motor behavior related to L-dopa is punding, characterized by intense fascination with repetitive handling, examining, sorting, and arranging of objects.[50] Another form of L-dopa–related dyskinesia, occurring in approximately 15 to 20% of patients chronically treated with L-dopa, is the so-called "diphasic dyskinesia". In contrast to the more frequent peak-dose

TABLE 3. *Levodopa-induced motor complications*

Simultaneous dyskinesia-parkinsonism
Dyskinesia
Peak-dose dyskinesia (I-D-I)
Stereotypy, chorea, ballism
Dystonia
Limb, trunk, pharyngeal, oromandibular, multiple system atrophy
Diphasic dyskinesia (D-I-D)
Off dystonia
Wearing-off, early morning
Myoclonus
Awake, during sleep
Akathisia
Wearing-off, peak-dose
Respiratory dyskinesia/dysregulation
Punding

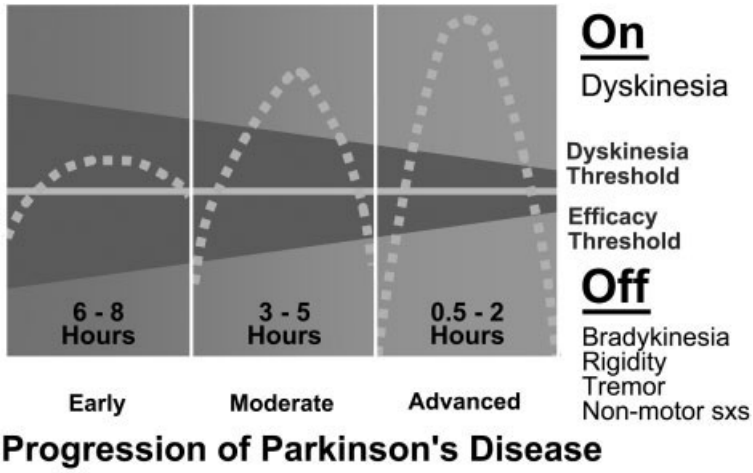

FIG. 1. In addition to shortening of response from each dose of levodopa, related to shortening of striatal half life of L-dopa, patients develop peak-dose dyskinesia, eventually leading to more unpredictable (*on–off*) response and narrowing of the therapeutic window.

dyskinesias, manifested by the sequence of Parkinsonism–improvement–dyskinesia–improvement–Parkinsonism (I-D-I), the diphasic response is characterized by Parkinsonism–dyskinesia–improvement–dyskinesia–Parkinsonism (D-I-D; Table 3).

Typically, the natural progression of PD is characterized by an insidious onset of symptoms, such as shoulder pain, decreased arm swing, rest tremor, shuffling gait, or bradykinesia, followed by improvement with initiation of dopaminergic therapy. This "honeymoon period", however, gradually comes to an end with the emergence of shortening of response to L-dopa, wearing-off effect, peak-dose dyskinesia, and more unpredictable response without obvious relationship to L-dopa dosing, the so-called *on–off* effect (Fig. 1).

In some cases, dystonia (especially of the foot) may be the presenting symptom of PD, especially in patients with young-onset disease, including those with the *Parkin* mutation.[22,51,52] However, dystonia can also be associated with atypical parkinsonian disorders such as corticobasal degeneration,[53] neurodegeneration with brain iron accumulation,[54] other neurodegenerative disorders, and after fetal cell transplants.[55,56] Dystonic postures (striatal hand and foot) and other skeletal deformities (scoliosis and bent spine, including camptocormia) may be also associated with PD and other parkinsonian disorders[57–59] (Table 4).

TABLE 4. *Other abnormal movement or postures in Parkinson's disease*

Blepharospasm
Oromandibular dystonia
Akathisia (overlap with)[a]
Sleep-related behavioral/motor disorders[a]
Skeletal deformity ("striatal" hand/foot)[a]
Scoliosis
Bent spine (anterocollis, camptocormia)[a]

[a]May not be related to levodopa.

L-Dopa–related dystonia tends to occur when plasma, and presumably brain, levels are either rising or falling. Probably the most common form of dystonia in L-dopa–treated PD patients consists of wearing-off, including morning or nocturnal, painful foot cramps. In some patients, during the course of the disease and even during the *on* dyskinesia, chorea may evolve into athetosis and dystonia. If dystonia, particularly involving the oromandibular area, occurs early in the course of L-dopa therapy or as the chief manifestation of peak-dose dyskinesia, the diagnosis of multiple system atrophy should be considered.[60] While the mechanisms of the various forms of L-dopa–related dyskinesias are not well understood, the *off* dystonia appears to have the same physiological signature as seen in primary dystonia, i.e., abnormal irregular firing of globus pallidus interna neurons.[61,62]

The recognition of the full scope of phenomenology of L-dopa–related complications is essential for the selection of most appropriate therapeutic strategy. It is beyond the scope of this review to discuss nonmotor complications of L-dopa therapy such as sedation and psychiatric reactions, including depression, anxiety, agitation, panic, hallucination, psychosis, paranoia, hypersexuality,[63] and an addictive behavior ("hedonistic homeostatic dysregulation") similar to substance abuse.[43,64] These non-motor symptoms, whether they are complications of levodopa therapy or a part of the natural history of the disease, may adversely impact the quality of life more than the typical motor symptoms.[66]

REFERENCES

1. Jankovic J. Complications and limitations of drug therapy for movement disorders. Neurology 2000;55(Suppl. 6):S2–S6.

2. Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. Neurology 2001;56(Suppl. 5):S1–S88.
3. Rascol O, Goetz C, Koller W, Poewe W, Sampaio C. Treatment interventions for Parkinson's disease: an evidence based assessment. Lancet 2002;359:1589–1598.
4. Ahlskog JE. Slowing Parkinson's disease progression. Recent dopamine agonist trials. Neurology 2003;60:381–389.
5. Bedard PJ, Blanchet PJ, Levesque D, et al. Pathophysiology of L-dopa-induced dyskinesias. Mov Disord 1999;14(Suppl. 1):4–8.
6. Jenner P. Factors influencing the onset and persistence of dyskinesia in MPTP-treated primates. Ann Neurol 2000;47(Suppl. 1): S90–S104.
7. Obeso JA, Rodriguez-Oroz MAC, Rodriguez M, et al. Pathophysiology of levodopa-induced dyskinesias in Parkinson's disease: problems with the current model. Ann Neurol 2000;47(Suppl. 1):S22–S34.
8. Verhagen Metman L, Konitsiotis S, Chase TN. Pathophysiology of motor response complications in Parkinson's disease: hypotheses on the why, where, and what. Mov Disord 2000;15:3–8.
9. Jankovic J. Therapeutic strategies in Parkinson's disease. In: Jankovic J, Tolosa E, editors. Parkinson's disease and movement disorders. 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2002. p 116–151.
10. Rascol O. L-Dopa-induced peak-dose dyskinesias in patients with Parkinson's disease: a clinical pharmacologic approach. Mov Disord 1999;14(Suppl. 1):19–32.
11. Jankovic J. Parkinson's disease therapy: tailoring choices for early and late disease, young and old patients. Clin Neuropharmacol 2000;23:252–261.
12. Rascol O. Medical treatment of levodopa-induced dyskinesias. Ann Neurol 2000;47(Suppl. 1):S179–S188.
13. Fahn S, Elton RL, members of the UPDRS Development Committee. The Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, editors. Recent developments in Parkinson's disease. Vol 2. Florham Park, New Jersey: Macmillan Healthcare Information; 1987. p 153–163, 293–304.
14. Siderowf A, McDermott M, Kieburtz K, et al. Test-retest reliability of the unified Parkinson's disease rating scale in patients with early Parkinson's disease: results from a multicenter clinical trial. Mov Disord 2002;17:758–763.
15. 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;2: 75–81.
16. Goetz CG. Rating scales for dyskinesias in Parkinson's disease. Mov Disord 1999;14(Suppl. 1):48–53.
17. Manson AJ, Brown P, O'Sullivan JD, et al. An ambulatory dyskinesia monitor. J Neurol Neurosurg Psychiatry 2000;68:196–201.
18. Schrag A, Selai C, Jahanshahi M, Quinn NP. He Q-5D - generic quality of life measure - is a useful instrument to measure quality of life in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2000;69:67–73.
19. Welsh M, McDermott MP, Holloway RG, Plumb S, Pfeiffer R, Hubble J. Development and testing of the Parkinson's disease quality of life scale. Mov Disord 2003;18:637–645.
20. Silver GA, Vuong K, Jankovic J. Young-onset versus late-onset Parkinson's disease: clinical features and disease progression. Mov Disord 2004;19(Suppl. 9):S264.
21. Schrag AS, Quinn N. Dyskinesias and motor fluctuations in Parkinson's disease. A community-based study. Brain 2000; 123:2297–2305.
22. Schrag A, Hovris A, Morley D, Quinn N, Jahanshahi M. Young-versus older-onset Parkinson's disease: impact of disease and psychosocial consequences. Mov Disord 2003;18:1250–1256.
23. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord 2001;16:448–458.
24. Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa. Ann Neurol 1996;39:37–45.
25. Poewe WH, Lees AJ, Stern GM. Low-dose L-dopa therapy in Parkinson's disease: a 6-year follow-up study. Neurology 1986; 36:1528–1530.
26. Block G, Liss C, Reines S, et al. Comparison of immediate-release and controlled release carbidopa/levodopa in Parkinson's disease. A multicenter 5-year study. Eur Neurol 1997;37:23–27.
27. Rajput AH, Fenton MA, Birdi S, et al. Clinical-pathological study of levodopa complications. Mov Disord 2002;17:289–296.
28. Nutt JG, Carter JH, Van Houten L, Woodward WR. Short- and long-duration responses to levodopa during the first year of levodopa therapy. Ann Neurol 1997;42:349–355.
29. Marras C, Lang AE. Measuring motor complications in clinical trials for early Parkinson's disease. J Neurol Neurosurg Psychiatry 2003;74:143–146.
30. Pearce RKB, Heikkila M, Linden IB, Jenner P. L-Dopa induces dyskinesia in normal monkeys: behavioural and pharmacokinetic observations. Psychopharmacology 2001;156:402–409.
31. Togasaki DM, Tan L, Protell P, et al. Levodopa induces dyskinesias in normal squirrel monkeys. Ann Neurol 2001;50:254–257.
32. Fahn S. Parkinson's disease, the effect of levodopa, and the ELLDOPA trial. Arch Neurol 1999;56:529–535.
33. Fahn S. Results of the ELLDOPA (earlier vs. later levodopa) study. Mov Disord 2002;17(Suppl. 5):S13.
34. Bravi D, Mouradian MM, Roberts JW, et al. Wearing-off fluctuations in Parkinson's disease: contribution of postsynaptic mechanisms. Ann Neurol 1994;36:27–31.
35. Oliveri RL, Annesi G, Zappia M, et al. Dopamine D_2 receptor gene polymorphism and the risk of levodopa-induced dyskinesias in PD. Neurology 1999;53:1425–1430.
36. Wang J, Liu Z-L, Chen B. Association study of dopamine D2, D3 receptor gene polymorphisms with motor fluctuations in PD. Neurology 2001;56:1757–1759.
37. Kaiser R, Hofer A, Grapengiesser A, et al. L-Dopa–induced adverse effects in PD and dopamine transporter gene polymorphism. Neurology 2003;60:1750–1755.
38. Riley DE, Lang AE. The spectrum of levodopa-related fluctuations in Parkinson's disease. Neurology 1993;43:1459–1464.
39. Marras C, Lang A, Krahn M, Tomlinson G, Naglie G. Quality of life in early Parkinson's disease: impact of dyskinesias and motor fluctuations. Mov Disord 2004;19:22–28.
40. Vidailhet M, Bonnet AM, Marconi N. The phenomenology of L-dopa–induced dyskinesias in Parkinson's disease. Mov Disord 1999;14(Suppl. 1):13–18.
41. Fahn S. The spectrum of levodopa-induced dyskinesias. Ann Neurol 2000;47(Suppl. 1):S2–S11.
42. Jankovic J. Levodopa strengths and weaknesses. Neurology 2002; 58(Suppl. 1):S19–S32.
43. Evans AH, Lees AJ. Dopamine dysregulation syndrome in Parkinson's disease. Curr Opin Neurol 2004;17:393–398.
44. Karlsen KH, Tandberg E, Arsland D, Larsen JP. Health related quality of life in Parkinson's disease: a prospective longitudinal study. J Neurol Neurosurg Psychiatry 2000;69:584–589.
45. Lees AJ, Katzenschlager R, Head J, Ben-Shlomo Y. Ten-year follow-up of three different initial treatments in de-novo PD: a randomized trial. Neurology 2001;57:1687–1694.
46. Marconi R, Lefebvre-Caparros D, Bonnet A-M, et al. Levodopa-induced dyskinesia in Parkinson's disease: phenomenology and pathophysiology. Mov Disord 1994;9:2–12.
47. Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 1991;114:2283–2301.
48. Jankovic J, Nour F. Respiratory dyskinesia in Parkinson's disease. Neurology 1986;36:303–304.
49. Rice JE, Antic R, Thompson PD. Disordered respiration as a levodopa-induced dyskinesia in Parkinson's disease. Mov Disord 2002;17:524–527.

50. Fernandez HH, Friedman JH. Punding on L-dopa. Mov Disord 1999;14:836–838.
51. Hedrich K, Marder K, Harris J, et al. Evaluation of 50 probands with early-onset Parkinson's disease for Parkin mutations. Neurology 2002;58:1239–1246.
52. Khan NL, Graham E, Critchley P, et al. Parkin disease: a phenotypic study of a large case series. Brain 2003;126:1279–1292.
53. Vanek Z, Jankovic J. Dystonia in corticobasal degeneration. Mov Disord 2001;16:252–257.
54. Thomas M, Hayflick SJ, Jankovic J. Clinical heterogeneity of neurodegeneration with iron accumulation-1 (Hallervorden-Spatz Syndrome) and Pantothenate Kinase Associated Neurodegeneration (PKAN). Mov Disord 2004;19:36–42.
55. Ma Y, Feigin A, Dhawan V, et al. Dyskinesia after fetal cell transplantation for parkinsonism: a PET study. Ann Neurol 2002; 52:628–634.
56. Olanow CW, Goetz CG, Kordower JH, et al. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Ann Neurol 2003;54:403–414.
57. Poewe WH, Lees AJ, Stern GM. Dystonia in Parkinson's disease: clinical and pharmacologic features. Ann Neurol 1988;23:73–78.
58. Jankovic J, Tintner R. Dystonia and Parkinsonism. Parkinsonism Relat Disord 2001;8:109–121.
59. Umapathi T, Chaudry V, Cornblath D, et al. Head drop and camptocormia. J Neurol Neurosurg Psychiatry 2002;73:1–7.
60. Wenning GK, Geser F, Stampfer-Kountchev M, Tison F. Multiple system atrophy: an update. Mov Disord 2003;18(Suppl. 6):S34–S42.
61. Hashimoto T, Tada T, Nakazato F, et al. Abnormal activity in the globus pallidus in off-period dystonia. Ann Neurol 2001;49:242–245.
62. Sanghera M, Grossman RG, Kalhorn CG, Hamilton WJ, Ondo W, Jankovic J. Basal ganglia neuronal discharge in primary and secondary dystonia in patients undergoing pallidotomy. Neurosurgery 2003;52:1358–1373.
63. Fenelon G, Mahieux F, Huon R, Ziegler M. Hallucinations in Parkinson's disease. Prevalence, phenomenology and risk factors. Brain 2000;123:733–745.
64. Giovannoni G, O'Sullivan JD, Turner K, et al. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. J Neurol Neurosurg Psychiatry 2000; 68:423–428.
65. Pezzella FR, Colosimo C, Vanacore N, Di Rezze S, Chianese M, Fabbrini G, Meco G. Prevalence and clinical features of hedonistic homeostatic dysregulation in Parkinson's disease. Mov Disord 2005;20:77–81.
66. Jankovic J. Progression of Parkinson disease: are we making progress in charting the course? Arch Neurol 2005;62:351–352.