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Different Dyskinesias in Parkinson's Disease and Their Relationship to Levodopa

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ABSTRACT

Levodopa is the principal agent in the treatment of Parkinson's disease (PD). Unfortunately the therapeutic benefits are optimal only in the early stages of the disease, with long-term use associated with motor complications such as levodopa-induced dyskinesia (LID). Risk factors associated with the development of LID are generally accepted to involve the degree of dopamine (DA) denervation in the nigrostriatal pathway, levodopa dose, and duration of levodopa treatment. Little is known regarding the underlying mechanisms of LID, although it is known that levodopa plasma concentrations are closely associated with the onset of some types of LIDs (peak-dose and biphasic dyskinesias) and it appears that increased DA turnover plays a crucial role in LID development. Recent evidence suggests that other cell types such as serotonin neurons possess the ability to convert levodopa into DA, subsequently storing and releasing it thereby increasing the levels of extracellular DA, exacerbating LID. This review will highlight the evidence to date from *in vitro* and *in vivo* studies utilizing both animal models and patients, regarding the relationship between levodopa treatment and the development of LID. Understanding the pathogenesis of LID is a therapeutic priority in tackling motor complications related to levodopa treatment in PD.

Keywords: Parkinson's disease, dyskinesia, levodopa, dopamine, serotonin

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the motor features of bradykinesia, tremor, and rigidity due in part to a loss of dopamine (DA) neurons in the nigrostriatal pathway. However, there is established evidence that other neurotransmitter systems such as the serotonergic system also display reduced innervation that may be responsible for the appearance of nonmotor symptoms also commonly seen in the clinical course of the disease.[1–3] Nonetheless, the principal agents for treating PD are dopaminergic drugs (eg, levodopa and DA agonists), which are effective in relieving the motor symptoms of the disease. Unfortunately, long-term use of dopaminergic drugs often leads to motor complications such as on-off fluctuations and dyskinesia. The term levodopa-induced dyskinesia (LID) specifically refers to the motor complication arising from long-term use of levodopa.[4] It appears that DA agonists are less likely to induce dyskinesia in PD patients compared to levodopa.[5]

Little is known regarding the pathogenesis of LID in PD; however, it has been established in animal models[6,7] and patient[8] studies that risk factors associated with the emergence of LID include the disease severity, the extent of striatal DA denervation, as well as the dose and duration of levodopa treatment. Motor function is expected to be dependent upon DA levels in the nigrostriatal system, and in PD the loss of DA terminals is associated with a decrease in endogenous synaptic DA. Therefore, the nigrostriatal system in PD patients is reliant upon exogenous sources of DA (levodopa) in order to maintain DA levels at the synapse. However, recent evidence also suggests that other neurotransmitter systems may play a role in the development of LID in PD, including the serotonergic system.[9] Here, we aim to review the literature to date regarding the pharmocokinetics of levodopa in the development of dyskinesias in PD patients from both animal models and patient studies.

DIFFERENT DYSKINESIAS IN PARKINSON'S DISEASE (PD)

Dyskinesia is a common complication of dopaminergic pharmacotherapy in PD. Various studies have estimated between 30% and 90% of PD patients develop LID after 4–6 years and 9 years after initiation of levodopa treatment, respectively,[10] with its emergence occurring within a few years following initiation of levodopa treatment.[11] Studies observing LID report that they typically start in the foot, ipsilateral to the side most affected by PD.[12] This observation is interesting given early loss of dopaminegic innervation has been shown in the dorsolateral striatum, which correspond somatotopically to the foot area and is innervated by the ventrolateral portion of the substantia nigra.[13] The initial presentation of LID is often mild and many patients do not notice the development of the unusual choreic movements in the beginning. Furthermore, the majority of patients prefer to continue the levodopa therapy reaping the therapeutic

benefits while experiencing some form of dyskinesia, rather than reduce levodopa therapy with its associated decrease in mobility but attenuation of dyskinesia.

The most common form of dyskinesia is ''peak-dose'' dyskinesia, which consists of a combination of dystonic and choreiform movements and occur during the period in which levodopa reaches peak-plasma concentration (60–90 min after levodopa administration).[14,15] Peak-dose dyskinesias are characterized by a sequence of Improvement-Dyskinesia-Improvement (IDI) and are usually alleviated by reducing the dose of levodopa (for review see Nutt *et al*[14] and Fahn[16]). Biphasic dyskinesias occur when DA plasma concentration levels are rising or falling and typically consist of repetitive, stereotypic movements of the legs.[17] This is the less common form of LID, although no systematic epidemiological data has been reported. Conversely to peak-dose dyskinesias, biphasic dyskinesias are characterized by a sequence of Dyskinesia-Improvement-Dyskinesia (DID). Another form of LID, the so-called yo-yo dyskinesia does not appear to follow an Improvement-Dyskinesia sequence and does not appear to be clearly related to levodopa dosing[18] as the response to levodopa fluctuates from ''on'' to ''off'' and back again throughout the levodopa-dose cycle. An unusual form of dyskinesia termed ''off-phase dyskinesia'' occurs when patients are in the ''off'' state (ie, they are not taking any DA treatment). Off-phase dyskinesia has been observed both following deep brain stimulation surgery and neural transplantation with fetal tissue.[19] The later is termed graft-induced dyskinesias (GID) and it is unclear whether GID and LID share the same pathogenic mechanisms.

PATHOGENESIS OF LEVODOPA-INDUCED DYSKINESIA (LID) IN PARKINSON'S DISEASE (PD)

Evidence in animals

The most common animal models of LID pathogenesis primarily consist of the 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine (MPTP)-lesioned primate model and 6-hydroxydopamine (6-OHDA)-lesioned rat model. The MPTP is a lipophilic substance that can efficiently cross the blood-brain-barrier, whereby it is then taken up by the DA transporter to inhibit complex I of the mitrochondrial respiratory chain,[20] inducing Parkinsonian behavioral, neurochemical, and pathological effects.[21] Permanent DA depletion, specific to the nigrostriatal pathway can be achieved using the 6-OHDA-lesioned rat model. The 6-OHDA is a nonspecific catecholaminergic toxin and is administered via stereotaxial surgery to induce usually unilateral lesions at various points along the nigrostriatal pathway in order to achieve DA degeneration and subsequent Parkinsonian deficits. In both models, levodopa treatment will be administered in order to reproduce human LID (dyskinetic group) and at least one control group, which may or may not be lesioned, but will not have dyskinesia induced (nondyskinetic group).

The majority of animal studies corroborate what is observed clinically (ie, that degree of DA denervation is associated with the development of dyskinesia). One interesting finding is that MPTP-lesioned primates who did not develop Parkinson motor symptoms did go on to develop dyskinesia, which indicates that the threshold of DA denervation is lower for the production of LID compared to PD symptoms. Furthermore, there are findings that dyskinesia can be induced in normal, unlesioned primates.[22,23] However, it must be noted that levodopa doses administered in such animal studies are invariably much higher than those for PD patients within the clinical setting and, therefore, may account for the rapid development of involuntary movements.[24]

The pathogenesis of LID can be studies in animal models by reproducing risk factors associated with LID development in PD patients. The 6-OHDA-lesioned rats that have been subjected to daily administration of levodopa, during which abnormal movements not ascribed to the execution of purposeful behavior (ie, dyskinesia) are exhibited in the animals. These movements emerge 20–30 min after administration of levodopa reproducing peak-dose dyskinesia observed in PD patients.[25] It has been demonstrated that the levodopa dose has an effect on dyskinesia exhibited in 6-OHDA-lesioned rats.[26] When a therapeutic dose of levodopa was applied (6–10 mg/kg levodopa/day), nearly all developed dyskinesia within 2–3 weeks. Following an increase in a levodopa dose (50 mg/kg levodopa/day), latency was shortened and severity and incidence of dyskinesia increased.

It has also been reported that exposure to levodopa may lead to a priming effect as evidence in MPTP-treated primates who were administered levodopa but did not develop Parkinson symptoms. These primates also experienced a reoccurrence of dyskinesia more readily than the primates who have not received levodopa and those that were only partially lesioned. Indeed, primates severely lesioned developed dyskinesia following the first dose of levodopa compared to those that were only partially lesioned and requiring several doses before the involuntary movements are exhibited. The authors concluded that the degree of DA denervation correlated with the severity of dyskinesia experienced once primed for levodopa.[24] The extent of nigrostriatal lesions in 6-OHDA-lesioned rats (ie, injecting different amounts of 6-OHDA to create either partial or complete lesions) has revealed that a threshold value of 80% loss of nigrostriatal neurons was required for the animals to develop dyskinetic movements.[7] In addition, the same study demonstrated that some animals that had complete DA denervation did not go on to develop dyskinesia. This finding indicates that the complete DA denervation is not solely responsible for the induction of LID in rats, and likely not the only contributory factor for LID in PD patients. Although, it must be noted that complete DA denervation is never reached in PD patients and end-stage patients will not only have a great loss of presynaptic DA but also a reduction in autoregulatory feedback from DA transporters. It is not known whether these end-stage patients will experience less dyskinesia as a result and is an area warranting further research.

One proposed presynaptic mechanism contributing to LID is related to a dramatic increase in synaptic DA levels, which would lead to alterations in the degree of receptor stimulation, induced by levodopa administration. This suggestion is supported clinically by the demonstration that peak-dose LID are dose dependent with a reduction of the levodopa dose leading to an increased severity of dyskinetic movements.[27,28] It has been suggested that a decrease in the presynaptic ''buffering'' is not dependent upon the degree of presynaptic denervation.[23]

Postsynaptic changes have been suggested as leading to the development of LIDs. It is suggested that dysplastic changes occur following the destruction of dopaminergic input to the striatum and subsequent levodopa treatment.[29] It is thought that alterations at the receptor level (denervation supersensitivity)[30] create a downstream cascade of modifications, which include the second messenger and signaling pathways[31] ultimately leading to the emergence of LIDs.

Investigating the mechanisms underlying LID in animal models typically involves the destruction of presynaptic DA terminals following the administration of a specific neurotoxin. It is generally thought that both presynaptic (production, storage, release, and reuptake of DA by dopaminergic neurons in the nigrostriatal pathway) and postsynaptic (receptor and second messenger signaling pathway status in striatal neurons) components are crucial in the development of LID.[31] However, dissociating changes induced by each compartment independently is complicated by the fact that following destruction of the presynaptic DA neurons, plastic changes of the postsynaptic neurons occur simultaneously.[32,33]

The pharmocokinetics of levodopa require intestinal or mucosal absorption and transportation from plasma to the brain across the blood-brain-barrier to reach the striatum where levodopa decarboxylation occurs for conversion to DA.[15] The duration of dyskinesia is closely related to plasma levodopa concentrations although severity of the LID experience does not appear to be influenced by levodopa dose or concentration.[14,34] It has been demonstrated that peripheral pharmocokinetics of levodopa (ie, before levodopa reaches the brain) do not differ between dyskinetic rats and nondyskinetic rats. This finding suggests that any differences in striatal levodopa levels between such groups are not caused by a differential absorption of the amino acid in the blood.[35] Considering the rate of levodopa decarboxylation is not influenced by extracellular levodopa concentrations[36] and that DA levels are greater in dyskinetic rats compared to nondyskinetic rats, the authors suggest that dyskinetic cases are able to transport levodopa from the blood to the brain more rapidly and that striatal levodopa levels are the most prominent risk factor for the development of LID.[35] However, several studies in patients have concluded that motor complications, including LID, after chronic levodopa therapy in PD patients correlate with fluctuating plasma concentrations of levodopa.[37–39]

Evidence in patients: imaging studies

Considering the role of DA denervation in the pathogenesis of PD, the use of PET techniques allows the assessment of presynaptic and postsynaptic dopaminergic systems in relation to LID in PD patients.

Fluorine-18-6-fluorodopa (^{18}F-Dopa) PET can be used to assess several monaminergic systems, including the presynaptic dopaminergic system by targeting l-aromatic-amino-acid-decarboxylase (AADC). An ^{18}F-Dopa PET study has reported a 28% decrease in presynaptic terminal function in the putamen in PD subjects who had a fluctuating motor response to levodopa (namely ''wearing-off'' effect) compared to patients who had a stable response to levodopa.[40] The authors suggested that the differences observed support the ''storage hypothesis'' ie, that loss of DA terminals in the nigrostriatal pathway is responsible for the motor fluctuations observed in PD patients. They also suggested that their results might reflect an altered ''buffering'' capacity of the DA terminals in response to differences in the degree of nigrostriatal damage between groups. However, there was considerable overlap between the two groups studied indicating that other factors may play a role. Another study of presynaptic mechanisms in relation to motor complications that utilized ^{11}C-methylphenidate (DA transporter [DAT] marker) demonstrated that greater DAT levels were directly related to lower DA turnover and lower changes in the synaptic DA concentration.[41] This is implicit of a crucial role of DAT in maintaining consistent levels of DA in the synapse and terminals. Therefore, a decrease in DAT may lead to an increase in DA turnover and higher oscillations in synaptic DA concentration, thereby possibly predisposing a patient to the occurrence of motor complications as disease processes. A more recent study assessing PD patients with motor fluctuations (27/36 patients presenting dyskinesia) using the presynaptic DA markers, ^{11}C-d-threo-methylphenidate (MP) and [11C]Dihydrotetrabenazine (DTBZ) PET demonstrated that putaminal MP/DTBZ was decreased in the motor fluctuation group compared to stable responders,[42] ie, that DA transporter levels per surviving nigrostrial DA nerve terminal were lower in the dyskinetic group. These findings are further support for presynaptic alterations playing a role in the appearance of dyskinesia due to continued DAT downregulation leading to increased levels of extracellular DA.

PET has also been used to assess the possible postsynaptic mechanisms of LID. The ^{11}C-SCH23390 (D1 receptor) and ^{11}C-raclopride (RAC) (D2 receptor) have been used in studies of PD patients with and without dyskinesia,[43,44] Findings from these demonstrate that the mean D1 receptor availability is within normal range in the caudate nucleus and putamen and mean D2 receptor availability in the putamen during the baseline condition in both dyskinetic and nondyskinetic PD patients. However, mean D2 receptor availability is reduced by around 15% in the caudate nucleus in both groups. From this, it may indicate that changes in postsynaptic receptor availability are possibly not involved in the pathophysiology

of LID in PD as the reductions in caudate may be a result of disease progression and not due to the development of LID.

The RAC PET can be used in conjunction with levodopa challenge in order to assess *in vivo* increases in synaptic DA through the decrease of D2 receptor availability.[27,28,45,46] An early study found that RAC binding decreases in the putamen by 23% following a single intravenous injection of levodopa compared to 10% decrease in stable responders.[47] This is suggestive of exogenous levodopa provoking greater DA release in the putamen of fluctuating responders than stable responders. Moreover, Unified Parkinson's Disease Rating Scale (UPDRS) scores in the ''off'' medication state inversely correlated with the reduction of putaminal binding. Therefore, it seems that as the disease progresses, evidenced by the decline in motor function, the regulation of DA release following exogenous administration of levodopa is impaired. The authors speculate that the regulation of DA back in to the synapse is impaired following levodopa administration due to the remaining terminals increasing DA synthesis and DAT is unable to compensate by reuptaking the excess DA. Another RAC PET study performed a baseline scan on two groups of PD patients, with and without motor fluctuations following a levodopa challenge.[27] The authors reported that synaptic levels of DA in PD patients with motor fluctuations were three times higher than that in those with a stable response to levodopa 1 hour after administration, which provides an explanation for their rapid response to the medication. Moreover, stable responders maintained increased DA levels for 4 hours after levodopa administration, whereas the synaptic levels in patients with a fluctuating response dropped to baseline (''off'') state. A more recent study positively correlated the presence of dyskinesia with increased levels of DA in the synapse as measured by RAC PET.[48] More specifically, dyskinetics cases showed significantly decreased levels of putaminal RAC binding reflecting greater levels of synaptic DA, following levodopa administration compared to nondyskinetics. Furthermore, in the same study the author's correlated levodopa induced increases in synaptic DA with corresponding motor scores. It was found that rigidity and bradykinesia but not tremor correlated with DA release in the putamen.

Opioid neuropeptides are abundant in the basal ganglia[49] and are known that the opioid system is involved in the pathophysiology of PD.[50] However, the involvement of the opioid system in the genesis of LID is unknown. Altered opioid transmission has been investigated using ^{11}C-Diprenorphine PET in relation to the development of LID.[51] In this study, it was demonstrated that PD patients with LID had reduced binding in both striatal (caudate nucleus and putamen) and extra-striatal (thalamus and anterior cingulate) regions compared to stable responders, suggestive of a possible opioid system involvement in the underlying mechanisms of LID. Animal studies have also supported these findings, with 6-OHDA-lesioned rats displaying reduced kappa opioid receptor density in striatal and nigral sites.[52] Furthermore, the selective kappa opioid receptor agonist, U50,488 ((*trans*)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl] benzeneacetamide methanesulfonate), has been shown to abate LID in 6-OHDA-lesioned rats.[53] The ^{18}F-L829165 is a selective marker of Neurokinin 1 (NK1) receptor availability. The NK1 receptors belong to the family of neuropeptides called Tachykinins and can be found in both the central and peripheral nervous system. In a preliminary study, it has been demonstrated that thalamic NK1 availability is reduced in dyskinetic patients while remaining within the normal range in stable responders.[54] The latter two *in vivo* findings are suggestive of the presence of elevated levels of endogenous neuropeptides in the basal ganglia of dyskinetic PD and may be, in part, responsible for the appearance of LID in PD patients.

A therapeutic alternative to the standard oral levodopa therapy is continuous dopaminergic stimulation (CDS). The rational of such therapy is to overcome the pusitile stimulation of DA receptors, which may contribute to the fluctuating motor responses to levodopa due to disease progression and the loss of functioning DA terminals. The CDS treatment option to date includes the subcutaneous apomorphine infusion and intestinal infusion of levodopa. To date, the findings are somewhat encouraging with the reduction of ''off'' time and a better control of motor fluctuations as well as the improvement of dyskinesia.[55,56] The authors suggest that even following the use of levodopa equivalent doses dyskinesia experience is improved, suggesting that the levodopa dose is not solely responsible for the development of dyskinesia but the pusitile stimulation of DA receptors. Further studies should utilize *in vivo* imaging techniques to assess the CDS effect on attenuating LID.

LEVODOPA-INDUCED DYSKINESIA (LID) AND THE SEROTONERGIC SYSTEM

It is generally accepted that levodopa acts in the early stages of the disease by being taken up into the spared DA terminals, where it is converted to DA, stored in synaptic vesicles, and released in an activity-dependent manner. However, as the disease progresses, fewer DA terminals are available for this conversion and other cell types have been suggested to play a role in the decarboxylation of levodopa in the advanced disease. Serotonergic neurons express AADC, the enzyme that converts l-DOPA to DA, and vesicular monamine transporter 2 (VMAT-2),[57–59] which enables the vesicular storage of synthesized DA. Moreover, serotonin neurons in the dorsal and median raphe nuclei innervate the striatum.[60,61] Therefore, the presence of AACD and VMTA-2 in serotonin neurons provides the possibility for levodopa-derived DA to be formed, stored, and released thus acting as a ''false neurotransmitter'' in serotonergic terminals. However, serotonergic neurons are unable to regulate DA release in a normal way. Dopaminergic synapes maintain extracellular DA levels within a narrow physiological range via a combination of autoreceptor-mediated feedback control and reuptake via DAT. The process of DA reuptake allows effective elimination of excess DA from the synaptic cleft, with the D2 autoreceptor maintaining the release from DA terminals in response to changes in the extracellular DA levels[62,63] within the desired

range. Serotonin neurons do not possess this autoregulatory mechanism; therefore, DA released from serotonergic terminals is likely to generate excessive swings in extracellular levels of DA in response to levodopa administration.[64] To date, the possible role of serotonin in LID has been studied only in animal models in PD.[11,57–61,64–72]

A more recent study using 6-OHDA-lesioned rats has demonstrated a near-complete suppression of the abnormal involuntary movements induced by chronic levodopa treatment by blocking DA release from the serotonin neurons using 5-HT1A and 5-HT1B autoreceptor agonists.[64] The same group reported that the content of serotonin in striatal tissue reduces by 50% one hour following administration of levodopa (dose at 6 mg/kg) as measured by high-performance liquid chromatography (HPLC)[64] An earlier study, utilizing microdialysis, reported a reduction of levodopa-derived extracellular levels of DA in the striatum by up to 80% following serotonin neuron lesions.[68] The same group also demonstrated a similar decrease of extracellular DA levels after coadministration of levodopa with the 5-HT1A receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OHDPAT), as well as inhibition of rotational behavior.[73] Furthermore, the partial 5-HT1A agonist, buspirone has been shown to reduce the expression and development of LID.[74] Taken together, these results are suggestive of a competition for storage at the serotonergic synapse between levodopa-derived DA and serotonin. This competition is suggested to cause a depletion in serotonin content resulting in an overactivation of serotonin terminals attempting to compensate for the reduced binding of neurotransmitter to the presynaptic serotonin autoreceptors. Subsequently there is an excessive release of DA from these neurons, triggering the LID.

The animal model considered the best to test the ability of drugs to reduce LID and most characteristic of PD in patients is the MPTP-lesioned monkey model. Iravani *et al*[75] demonstrated a decrease in dyskinesias in MPTP-treated marmosets following administration of the 5-HT1A agonist (+)-8-OHDPAT. In addition, the same group found a similar effect using 5-HT1B/1D receptor agonist.[76] However, the antidyskinetic effect was also accompanied by a reduction in the therapeutic effect of levodopa. These results raise the possibility that the therapeutic effect of levodopa in MPTP treated primates is dependent upon DA release from serotonergic neurons and that increased motor symptoms and a reduction of dyskinesias after administration of 5-HT1A agonists may be due to the reduced DA released from serotonin neurons.

CONCLUSIONS

The response to levodopa in PD patients is complex due to various factors including age, disease duration, disease severity (degree of DA denervation and motor dysfunction), levodopa dose, and duration of levodopa treatment. The occurrence of LID in PD patients is a troublesome side effect; therefore, delineating the underlying mechanisms is a therapeutic priority in the management of PD. However, evidence to date from both animal models and patient studies are revealing a much more complex pathophysiology than initially thought. It does not appear that the degree of DA denervation, which is the principal characteristic of PD, is the sole mediator in the emergence of LID. Indeed, other neurotransmitter systems such as the serotonergic system may play a crucial role in the development of LID.

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REFERENCES

1. Leibowitz SF, Alexander JT. Hypothalamic serotonin in control of eating behavior, meal size, and body weight. *Biol Psychiatry*. 1998;1;44(9):851–864.
2. Wurtmann J. Depression and weight gain: the serotonin connection. *J Affect Dis*. 1993;29:183–192.
3. Politis M, Wu K, Loane C, *et al*. Staging of serotonergic dysfunction in Parkinson's disease: an in vivo 11C-DASB PET study. *Neurobiol Dis*. 2010;40(1):216–221.
4. Kumar A, Huang Z, de la Fuente-Fernández R. Mechanisms of motor complications in treatment of Parkinson's disease. *Adv Neurol*. 2003;91:193–201.
5. Rascol O, Brooks DJ, Korczyn AD, *et al*. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. *N Engl J Med*. 2000;342:1484–1491.
6. Jenner P. Factors influencing the onset and persistence of dyskinesia in MPTP-treated primates. *Ann Neurol*. 2000;47(4 suppl 1):S90–S99; discussion S99–S104.
7. Winkler C, Kirik D, Björklund A, *et al*. L-DOPA-induced dyskinesia in the intrastriatal 6-hydroxydopamine model of Parkinson's disease: Relation to motor and cellular parameters of nigrostriatal function. *Neurobiol Dis*. 2002;10(2):165–186.
8. Schrag A, Quinn N. Dyskinesias and motor fluctuations in Parkinson's disease. A community-based study. *Brain*. 2000;123(Pt 11):2297–2305.
9. Politis M, Wu K, Loane C, *et al*. Serotonergic involvement in L-DOPA-induced dyskinesia [abstract]. *Mov Disord*. 2010;25(suppl 3):S658.
10. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord*. 2001;16(3):448–458.
11. Obeso JA, Rodriguez-Oroz MC, Chana P, *et al*. The evolution and origin of motor complications in Parkinson's disease. *Neurology*. 2000;55(11 suppl 4):S13–S20.
12. Marconi R, Lefebvre-Caparros D, Bonnet AM, *et al*. Levodopa-induced dyskinesias in Parkinson's disease phenomenology and pathophysiology. *Mov Disord*. 1994;9(1):2–12.
13. Fearnley JM, Lees AJ. Striatonigral degeneration. A clinicopathological study. *Brain*. 1990;113(Pt 6):1823–1842.
14. Nutt JG, Woodward WR, Carter JH, *et al*. Effect of long-term therapy on the pharmacodynamics of levodopa. Relation to on-off phenomenon. *Arch Neurol*. 1992;49(11):1123–1130.
15. Contin M, Riva R, Martinelli P, *et al*. Pharmacodynamic modeling of oral levodopa: Clinical application in Parkinson's disease. *Neurology*. 1993;43(2):367–371.
16. Fahn S. The spectrum of levodopa-induced dyskinesias. *Ann Neurol*. 2000;47(4 suppl 1):S2–S9.
17. Luquin MR, Scipioni O, Vaamonde J, *et al*. Levodopa-induced dyskinesias in Parkinson's disease: Clinical and pharmacological classification. *Mov Disord*. 1992;7(2):117–124.
18. Nutt JG, Wooten GF. Clinical practice. Diagnosis and initial management of Parkinson's disease. *N Engl J Med*. 2005;353(10):1021–1027.
19. Hagell P, Piccini P, Björklund A, *et al*. Dyskinesias following neural transplantation in Parkinson's disease. *Nat Neurosci*. 2002;5(7):627–628.
20. Heikkila RE, Nicklas WJ, Vyas I, Duvoisin RC. Dopaminergic toxicity of rotenone and the 1-methyl-4-phenylpyridinium ion after their stereotaxic administration to rats: Implication for the mechanism of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine toxicity. *Neurosci Lett*. 1985;62(3):389–394.

21. Jenner P, Rupniak NM, Rose S, *et al*. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism in the common marmoset. *Neurosci Lett*. 1984;50(1–3):85–90.
22. Mones RJ. Experimental dyskinesias in normal rhesus monkeys. In: Barbeau A, Chase TN, Paulson GW, eds. *Advances in Neurology* 1. New York, NY: Raven Press; 1973:665–669.
23. Sassin JF. Drug-induced dyskinesias in monkeys. In: Meldrum BS, Marsden CD, eds. *Advances in Neurology* 10. New York, NY: Raven Press; 1975:47–54.
24. Di Monte DA, McCormack A, Petzinger G, Janson AM, Quik M, Langston WJ. Relationship among nigrostriatal denervation, Parkinsonism, and dyskinesias in the MPTP primate model. *Mov Disord*. 2000;15(3):459–466.
25. Lundblad M, Andersson M, Winkler C, *et al*. Pharmacological validation of behavioural measures of akinesia and dyskinesia in a rat model of Parkinson's disease. *Eur J Neurosci*. 2002;15(1):120–132.
26. Lindgren HS, Andersson DR, Lagerkvist S, *et al*. L-DOPA-induced dopamine efflux in the striatum and the substantia nigra in a rat model of Parkinson's disease: Temporal and quantitative relationship to the expression of dyskinesia. *J Neurochem*. 2010;112(6):1465–1476.
27. de la Fuente-Fernández R, Lu JQ, Sossi V, *et al*. Biochemical variations in the synaptic level of dopamine precede motor fluctuations in Parkinson's disease: PET evidence of increased dopamine turnover. *Ann Neurol*. 2001;49(3):298–303.
28. de la Fuente-Fernández R, Sossi V, Huang Z, *et al*. Levodopa-induced changes in synaptic dopamine levels increase with progression of Parkinson's disease: Implications for dyskinesias. *Brain*. 2004;127(Pt 12): 2747–2754.
29. Hirsch EC. Nigrostriatal system plasticity in Parkinson's disease: Effect of dopaminergic denervation and treatment. *Ann Neurol*. 2000;47 (4 suppl 1):S115–S120; discussion S120–S121.
30. Antonini A, Schwarz J, Oertel WH, *et al*. [11C]raclopride and positron emission tomography in previously untreated patients with Parkinson's disease: Influence of L-dopa and lisuride therapy on striatal dopamine D2-receptors. *Neurology*. 1994;44(7):1325–1329.
31. Cenci MA, Lundblad M. Post- versus presynaptic plasticity in L-DOPA-induced dyskinesia. *J Neurochem*. 2006;99(2):381–392.
32. 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.
33. Ulusoy A, Sahin G, Kirik D. Presynaptic dopaminergic compartment determines the susceptibility to L-DOPA-induced dyskinesia in rats. *Proc Natl Acad Sci USA*. 2010;107(29):13159–13164.
34. Nutt JG, Woodward WR. Levodopa pharmacokinetics and pharmacodynamics in fluctuating Parkinsonian patients. *Neurology*. 1986;36(6): 739–744.
35. Carta M, Lindgren HS, Lundblad M, *et al*. Role of striatal L-DOPA in the production of dyskinesia in 6-hydroxydopamine lesioned rats. *J Neurochem*. 2006;96(6):1718–1727.
36. Wade LA, Katzman R. Synthetic amino acids and the nature of L-DOPA transport at the blood-brain barrier. *J Neurochem*. 1975;25(6):837–842.
37. Deleu D, Northway MG, Hanssens Y. Clinical pharmacokinetic and pharmacodynamic properties of drugs used in the treatment of Parkinson's disease. *Clin Pharmacokinet*. 2002;41(4):261–309.
38. Bhidayasiri R, Truong DD. Motor complications in Parkinson disease: Clinical manifestations and management. *J Neurol Sci*. 2008;266(1–2): 204–215.
39. Adamiak U, Kaldonska M, Klodowska-Duda G, *et al*. Pharmacokinetic-pharmacodynamic modeling of levodopa in patients with advanced Parkinson disease. *Clin Neuropharmacol*. 2010;33(3):135–141.
40. de la Fuente-Fernández R, Pal PK, Vingerhoets FJ, *et al*. Evidence for impaired presynaptic dopamine function in Parkinsonian patients with motor fluctuations. *J Neural Transm*. 2000;107(1):49–57.
41. Sossi V, de la Fuente-Fernández R, Schulzer M, *et al*. Dopamine transporter relation to dopamine turnover in Parkinson's disease: A positron emission tomography study. *Ann Neurol*. 2007;62(5):468–474.
42. Troiano AR, de la Fuente-Fernandez R, Sossi V, *et al*. PET demonstrates reduced dopamine transporter expression in PD with dyskinesias. *Neurology*. 2009;72(14):1211–1216.
43. Turjanski N, Lees AJ, Brooks DJ. In vivo studies on striatal dopamine D1 and D2 site binding in L-dopa-treated Parkinson's disease patients with and without dyskinesias. *Neurology*. 1997;49(3):717–723.
44. Kishore A, De la Fuente-Fernandez R, Snow BJ, *et al*. Levodopa-induced dyskinesias in idiopathic Parkinsonism (IP): A simultaneous PET study of dopamine D1 and D2 receptors. *Neurology*. 1997;48:A327.
45. Tedroff J, Pedersen M, Aquilonius SM, *et al*. Levodopa-induced changes in synaptic dopamine in patients with Parkinson's disease as measured by [11C]raclopride displacement and PET. *Neurology*. 1996;46(5): 1430–1436.
46. Endres CJ, Kolachana BS, Saunders RC, *et al*. Kinetic modeling of [11C]raclopride: Combined PET-microdialysis studies. *J Cereb Blood Flow Metab*. 1997;17(9):932–942.
47. Torstenson R, Hartvig P, Långström B, *et al*. Differential effects of levodopa on dopaminergic function in early and advanced Parkinson's disease. *Ann Neurol*. 1997;41(3):334–340.
48. Pavese N, Evans AH, Tai YF, *et al*. Clinical correlates of levodopa-induced dopamine release in Parkinson disease: A PET study. *Neurology*. 2006; 67(9):1612–1617.
49. Haber SN, Watson SJ. The comparative distribution of enkephalin, dynorphin and substance P in the human globus pallidus and basal forebrain. *Neuroscience*. 1985;14:1001–1024.
50. Fernandez A, De Ceballos ML, Jenner P, *et al*. Neurotensin, substance P, delta and mu opioid receptors are decreased in basal ganglia of Parkinson's disease patients. *Neuroscience*. 1994;61:73–79.
51. Piccini P, Weeks RA, Brooks DJ. Alterations in opioid receptor binding in Parkinson's disease patients with levodopa-induced dyskinesias. *Ann Neurol*. 1997;42(5):720–726.
52. Johansson PA, Andersson M, Andersson KE, Cenci MA. Alterations in cortical and basal ganglia levels of opioid receptor binding in a rat model of l-DOPA-induced dyskinesia. *Neurobiol Dis*. 2001;8(2):220–239.
53. Marin C, Bové J, Bonastre M, Tolosa E. Effect of acute and chronic administration of U50,488, a kappa opioid receptor agonist, in 6-OHDA-lesioned rats chronically treated with levodopa. *Exp Neurol*. 2003;183(1): 66–73.
54. Whone AL, Rabiner EA, Arahata Y, *et al*. Reduced substance P binding in Parkinson's disease complicated by dyskinesias: An F-18-L829165 PET study. *Neurology*. 2002;58:A488–A489.
55. Nyholm D, Askmark H, Gomes-Trolin C, *et al*. Optimizing levodopa pharmacokinetics: Intestinal infusion versus oral sustained-release tablets. *Clin Neuropharmacol*. 2003;26(3):156–163.
56. Nyholm D, Jansson R, Willows T, Remahl IN. Long-term 24-hour duodenal infusion of levodopa: outcome and dose requirements. *Neurology*. 2005;65(9):1506–1507.
57. Arai R, Karasawa N, Geffard M, *et al*. Immunohistochemical evidence that central serotonin neurons produce dopamine from exogenous L-DOPA in the rat, with reference to the involvement of aromatic L-amino acid decarboxylase. *Brain Res*. 1994;667(2):295–299.
58. Arai R, Karasawa N, Geffard M, *et al*. L-DOPA is converted to dopamine in serotonergic fibers of the striatum of the rat: A double-labeling immunofluorescence study. *Neurosci Lett*. 1995;195(3):195–198.
59. Arai R, Karasawa N, Nagatsu I. Dopamine produced from L-DOPA is degraded by endogenous monoamine oxidase in neurons of the dorsal raphe nucleus of the rat: an immunohistochemical study. *Brain Res*. 1996;722(1–2):181–184.
60. Lavoie B, Parent A. Immunohistochemical study of the serotoninergic innervation of the basal ganglia in the squirrel monkey. *J Comp Neurol*. 1990;299(1):1–16.
61. Nicholson SL, Brotchie JM. 5-hydroxytryptamine (5-HT, serotonin) and Parkinson's disease—opportunities for novel therapeutics to reduce the problems of levodopa therapy. *Eur J Neurol*. 2002;9(suppl 3):1–6.
62. Venton BJ, Michael DJ, Wightman RM. Correlation of local changes in extracellular oxygen and pH that accompany dopaminergic terminal activity in the rat caudate-putamen. *J Neurochem*. 2003;84(2):373–381.
63. Cragg SJ, Baufreton J, Xue Y, Bolam JP, Bevan MD. Synaptic release of dopamine in the subthalamic nucleus. *Eur J Neurosci*. 2004;20(7): 1788–1802.
64. Carta M, Carlsson T, Kirik D, *et al*. Dopamine released from 5-HT terminals is the cause of L-DOPA-induced dyskinesia in Parkinsonian rats. *Brain*. 2007;130(Pt 7):1819–1833.

65. Ng KY, Chase TN, Colburn RW, *et al*. L-Dopa-induced release of cerebral monoamines. *Science*. 1970;170(953):76–77.
66. Ng KY, Colburn RW, Kopin IJ. Effects of L-dopa on efflux of cerebral monoamines from synaptosomes. *Nature*. 1971;230(5292):331e2.
67. Hollister AS, Breese GR, Mueller RA. Role of monoamine neural systems in L-dihydroxyphenylalanine-stimulated activity. *J Pharmacol Exp Ther*. 1979;208(1):37–43.
68. Tanaka H, Kannari K, Maeda T, *et al*. Role of serotonergic neurons in L-DOPA-derived extracellular dopamine in the striatum of 6-OHDA-lesioned rats. *Neuroreport*. 1999;10(3):631–634.
69. Brotchie JM. The neural mechanisms underlying levodopa-induced dyskinesia in Parkinson's disease. *Ann Neurol* 2000;47(4 suppl. 1): S105e12. Discussion S12e4.
70. Luginger E, Wenning GK, Bosch S, *et al*. Beneficial effects of amantadine on L-dopa-induced dyskinesias in Parkinson's disease. *Mov Disord*. 2000;15(5):873–888.
71. Crosby NJ, Deane KH, Clarke CE. Amantadine for dyskinesia in Parkinson's disease. *Cochrane Database Syst Rev*. 2003;2:CD003467.
72. Maeda T, Nagata K, Yoshida Y, *et al*. Serotonergic hyperinnervation into the dopaminergic denervated striatum compensates for dopamine conversion from exogenously administered L-DOPA. *Brain Res*. 2005;1046 (1–2):230–233.
73. Tomiyama M, Kimura T, Maeda T, *et al*. A serotonin 5-HT1A receptor agonist prevents behavioral sensitization to L-DOPA in a rodent model of Parkinson's disease. *Neurosci Res*. 2005;52(2):185–194.
74. Eskow KL, Gupta V, Alam S, *et al*. The partial 5-HT(1A) agonist buspirone reduces the expression and development of l-DOPA-induced dyskinesia in rats and improves l-DOPA efficacy. *Pharmacol Biochem Behav*. 2007;87 (3):306–314.
75. Iravani MM, Tayarani-Binazir K, Chu WB, *et al*. In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated primates, the selective 5-hydroxytryptamine 1a agonist (R)-(+)-8-OHDPAT inhibits levodopa-induced dyskinesia but only with increased motor disability. *J Pharmacol Exp Ther*. 2006;319(3):1225–1234.
76. Jackson MJ, Al-Barghouthy G, Pearce RK, *et al*. Effect of 5-HT1B/D receptor agonist and antagonist administration on motor function in haloperidol and MPTP-treated common marmosets. *Pharmacol Biochem Behav*. 2004;79(3):391–400.