Motor and Nonmotor Complications of Levodopa: Phenomenology, Risk Factors, and Imaging Features

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ABSTRACT: Despite enormous advances in our current understanding of PD since James Parkinson described the “shaking palsy” 200 years ago, L-dopa, in clinical use since the 1960s, remains the gold standard of treatment. Virtually every patient with PD requires varying doses of L-dopa to manage motor and some nonmotor symptoms and retain an acceptable quality of life. However, after a period of treatment with L-dopa, a number of problems emerge; the key ones are motor and nonmotor fluctuations, a range of dyskinesias, and a combination of both. Nonmotor complications can range from behavioral problems to sensory, autonomic, and cognitive issues. Even with a wealth of data, both in animal models and in vivo imaging that address the pathophysiology of L-dopa-related motor and nonmotor complications, the treatment remains challenging and is an unmet need. Although refinement in types of dopamine replacement therapy and delivery systems have improved the management of L-dopa-related complications, the search for the ideal treatment continues. © 2018 International Parkinson and Movement Disorder Society

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Even after more than 50 years of clinical use, L-dopa remains the gold standard for symptomatic treatment of the motor symptoms of Parkinson’s disease (PD).1 With the exception of apomorphine, which was used in PD even earlier than L-dopa,2 no other dopaminergic agent developed over the last decades has matched the effect size of L-dopa. Nevertheless, chronic oral L-dopa substitution in PD is associated with evolution of motor and nonmotor complications, including motor and nonmotor fluctuations (NMFs) and drug-induced dyskinesias in a majority of patients after more than 5 years of exposure. Up to 30% develop these problems within the first 2 years.3-5

Either class of motor complications can seriously compromise motor control and lead to increasing disability and loss in quality of life (QoL). Despite many advances over the past 20 years, their treatment remains challenging.

Here, we review the clinical spectrum of this complex facet of advancing PD as well as current concepts about the underlying mechanisms and risk factors.

Clinical Spectrum of Levodopa-Related Motor Complications

Motor Response Fluctuations

Fluctuations in motor improvement following oral doses of L-dopa that seemed to parallel dosing intervals was noted very early in the history of its use in PD. Cotzias commented on what he called a “short-lived effect” of L-dopa soon after his seminal work in the 1960s, and Muenter and colleagues coined the term “short-duration response” to L-dopa in the 1970s.6,7 In that period, the first clinical pharmacokinetic studies were performed to show parallel swings in L-dopa plasma levels and motor performance.8
Clinicopharmacological observations that followed have revealed different patterns of L-dopa-related motor fluctuations with different underlying mechanisms (Fig. 1).

The most common initial manifestation of a reduced response duration to chronic L-dopa is re-emergence of parkinsonian symptoms in the morning before the first daily dose of L-dopa. A recent survey involving 320 patients has found early morning OFFs (EMOs) in 44% of patients in early disease stages and an overall prevalence of 60%.9 Wearing-off of drug effects at the end of interdose intervals is the most common response oscillation pattern to L-dopa overall, but studies have shown that a significant proportion of daily OFF time in fluctuators is attributable to delays in switching on after oral doses (time-to-on), highlighting the role of therapies that will provide rapid onset of effect after dosing.10,11

Evidence from clinical trials investigating differential effects of dopaminergic treatments on development of motor complications have shown that even within the first year of treatment with L-dopa, up to 30% of patients in a dose-dependent fashion may develop wearing-off type motor fluctuations. This percentage may rise to almost 50% within 3 years of initiating therapy.4,5,12 Longer-term follow-up clinical trials and surveys of patients in routine clinical care have consistently found that motor fluctuations occur in 50% or more of PD subjects treated for longer than 5 years.5,13-15 The occurrence of the wearing-off phenomena early in the course of L-dopa therapy has been emphasized recently by a large, cross-sectional study in 667 PD patients, where treating neurologists detected wearing off in 22% of those with less than 2.5 years of treatment. Affirmative responses on the patient-based wearing-off questionnaire (WOQ) were obtained from more than 40% of subjects.5,15 Whereas L-dopa-induced dyskinesias and motor fluctuations often occur in close temporal association over the course of L-dopa therapy, there is some evidence that a greater proportion of patients first develop wearing-off or EMO problems before dyskinesias also become apparent.16

Patients tend to rank response fluctuations to their medication highly on their list of the most troublesome symptoms of PD,17 and several studies have shown their association with reductions in QoL scores.15,18 Subjects with both dyskinesias and motor fluctuations tend to prefer the ON state with dyskinesias over the OFF condition.19

Non Motor Fluctuations (NMF)

Motor fluctuations are usually characterized by several patterns of motor “off” periods, although a majority of fluctuators also experience a range of nonmotor symptoms (NMS) characterized as NMFs, first described by Hillen and Sage.20 The pattern of these NMS associated with motor fluctuations related to L-dopa have now been recognized, and a clinical observational study classified these symptoms as sensory, cognitive, and autonomic.21 These symptoms can also be classified within the spectrum of behavioral effects of L-dopa.102

A recent prospective, multicenter, cross-sectional study used quantification of clinical examination of 10 NMS using a visual analog scale, a modified version of the PD NMS scale, in a motor off and on state using self-ratings at home in 100 fluctuating L-dopa-treated PD patients.22 NMF was present in all, and patients (100%) had at least two nonmotor symptoms.
The researchers reported that the pattern of NMS fluctuations were heterogeneous and complex. Psychiatric symptoms and pain were the most fluctuating NMS (in frequency and severity), and no correlations with demographic parameters or motor function were reported. NMS were noted during L-Dopa-induced motor “on” and worsened during “off,” whereas some, such as concentration difficulties, fatigue, and depression and anxiety, were also observed during off alone periods (isolated NMF; Fig. 2).

The phenomenology of L-Dopa-induced NMF has been further categorized and involves the wearing-off phenomenon that occurs late at night or early morning, recognized as the EMO period (often manifested as an off-period–related dystonia). A multicenter study of 320 patients reported significant EMO in 59.7%, and 88% reported severe NMS on awakening, such as urinary frequency, anxiety, depression, pain, and dribbling of saliva. The association of depression and anxiety with motor fluctuations is also described by Brown and colleagues; they described depressed, anxious, and anxious-depressed subtypes of PD associated with a variety of motor fluctuations and dyskinesias. The anxious-depressed phenotype showed the most consistent association with off periods and dyskinesias (Fig. 2). This observation forms the basis of the recent description of Park-depression/anxiety (mixed pattern), one of the several nonmotor endophenotypes of PD. Apart from “off” periods, NMS such as anxiety, paresthesiae, pain, and fatigue can also complicate dyskinesias, particularly peak dose and diphasic dyskinesias. Apathy or panic attacks can be disabling aspects of severe NMFs, given that the symptoms sometimes overshadow the motor off period. There is often a mismatch between the phenomenology of motor fluctuations and NMFs, and patients may develop NMFs before or after the motor counterpart. The concept of such isolated NMF is less clear, but has been recognized by Storch and colleagues, and also forms a spectrum of L-Dopa-induced NMFs (Fig. 2). Such fluctuations are difficult to identify and have the potential for misdiagnosis. Severe anxiety-related states, for instance, could be misdiagnosed as dopamine dysregulation syndrome related to excessive L-Dopa intake and dyskinesias. Neurobehavioral syndromes can also masquerade as NMFs and can include the commonly recognized impulse control disorders (ICDs) or punding in addition to dopamine dysregulation syndrome, all of which occur with L-Dopa intake with varying severity. In particular, L-Dopa-induced dyskinesias may be associated with punding and impulsivity. A recently described phenomenon is “metacognitions,” where motor fluctuations induce anticipatory “thinking,” which, in turn, can worsen the severity of the fluctuations. Metacognitions refers to a perception of an impending off period (thinking about thinking), which could actually increase off period distress (Fig. 1). A central basis of NMFs is possible, as has been shown by changes in pain threshold activation studies during L-Dopa-related on and off state using PET studies.

Apathy may also coexist with ICD, which illustrates the psychostimulant potential of L-Dopa and dopamine replacement therapy.
fluctuation–related complications include behavioral- and addiction-linked symptoms, such as dopamine dysregulation syndrome and punding. In many, these symptoms are associated with dyskinesias. In some, these symptoms overlap with ICD, which is typically associated with dopamine agonist use. Certain genetic mutations can also influence l-dopa-induced dyskinesias. The proposed genes include dopamine-linked genes such as DRD3 p.Ser9Gly, DRD2 A1 allele, TaqIA (CT SNP), as well as the LL genotype of the catechol-O-methyl transferase. Future therapy may be driven by identification of such pharamacogenetic factors and delivery of precision medicine and forms the basis of personalized medicine for PD.

Quantification of NMF in the clinic is difficult. One can use the WOQ, and recently the PD NMS scale has been validated for NMF using selected items. Diary reporting of NMS coupled with ambulatory-sensor–based monitors to detect motor fluctuations may also provide a useful method to ascertain NMF in the future. NMF has an adverse effect on health-related QoL, and recognition is important so that inappropriate treatment (e.g., use of antidepressants) is not offered where management of fluctuations with suitable treatment strategies, such as continuous drug delivery, could be beneficial.

Levodopa-Induced Dyskinesias

L-dopa-induced dyskinesias (LIDs) often accompany the evolution of motor response fluctuations, although they are a later event in around 30% of patients and may, less commonly, also precede the appearance of motor fluctuations. They include a variety of abnormal movement patterns, most commonly chorea or mixed chorea and dystonia. Complex movement patterns, where many abnormal movements may be intermixed, occur during diphasic dyskinesias. Dystonia, though commonly complicating off periods, can also be observed occasionally as the patient “turns on” after l-dopa therapy as well as during “on”-related severe dyskinesias.

In a majority of patients, LIDs predominantly involve the limbs and are more marked on the side initially affected by parkinsonian signs, although crossed lateralities may also occur.30 Trunk involvement is also common, and dystonic patterns, like facial grimacing, torticollis, or, rarely, oculogyria or blepharospasm, may prevail when LIDs involve the craniocervical region. There is a curious and still poorly understood association between the l-dopa response cycle and the pattern and topographic distribution of LIDs. Limb chorea is the in contrast commonest related movement type in ON periods (whereas ON period craniocervical LIDs are usually dystonic) and painful dystonic cramping of the foot is the most common type of l-dopa-induced movement abnormality during OFF periods.

Biphasic (or diphasic) dyskinesias appearing at onset and wearing-off time points following a single dose of l-dopa are another set of phenomena that are poorly understood. In addition, sometimes these dyskinesias may occur at only one of these time points. They often comprise a mix of phasic and dystonic elements and can be violent in excursion of movements. Several clinical observational studies have furthermore shown onset in the foot of LIDs following a single-dose challenge proximal spread over the involved limbs as patients transition to full ON. Although this is likely related to the topographical organization of corticostriatal connectivity and regional patterns of striatal dopamine loss in PD, the exact mechanisms underlying these associations are not understood.

Freezing of gait (FOG) is a particular challenge in the management of PD and could at least be related, in part, to l-dopa-related motor complications, although the notion remains controversial. FOG has been described immediately after introduction of l-dopa therapy, and other workers have suggested that FOG correlates with advancing disease and length of l-dopa therapy. Thus, although FOG is thought to be a part of the PD symptom spectrum, it could also be considered to be a l-dopa-related motor complication.

Similar to motor fluctuations, the prevalence of LIDs in PD increases with time of exposure. Rates observed in clinical trials range from 16% after less than 1 year of l-dopa treatment to between 33% and 54% after 3 to 6 years. Long-term follow-up of trial cohorts have reported rates between 58% and 78% after 10 to 14 years, but these observations are based on very small numbers of subjects. Some observational studies in routine care settings have shown somewhat lower figures of around 30% after 5 years of treatment. There is considerable variability depending on age and other risk factors in the populations studied with particularly high rates in young-onset cases (see below). Rates of disabling dyskinesias, however, seem to be lower and have been less than 10% in controlled l-dopa trials with up to 6 years of follow-up.

When dyskinesias are not disabling, many patients prefer being ON with LIDs, but these symptoms are nevertheless associated with poorer QoL scores and increased health care costs.

Mechanisms and Risk Factors

Levodopa-Induced Motor Fluctuations

The mechanisms underlying the late development of response fluctuations in PD include well-characterized peripheral factors related to l-dopa pharmacokinetics, absorption, and transport as well as central pharmacodynamic changes that are less well understood (see Fig. 2). The short half-life of l-dopa in plasma of
approximately 90 minutes is associated with peaks and troughs of blood levels, and it was already observed in the 1970s that these oscillations correspond to performance variations in motor tasks. In addition, absorption of l-dopa only begins in the duodenum and is thus dependent on gastric emptying, such that reduced gastric motility after a meal or as part of the gastrointestinal symptoms of PD can translate into a delayed onset of drug effect. Intestinal absorption of l-dopa occurs through active transport mediated by a specific transporter for large neutral amino acids, such that competition with neutral amino acids from the diet can reduce blood levels and the clinical effect from a dose. A similar competition can also occur at the blood–brain barrier, which has been shown by imaging studies using F-Dopa PET and amino acid loading.

Clinicopharmacological experiments in PD patients have provided direct evidence for this blood–brain barrier transport effect of amino-acid loading during constant rate infusions of l-dopa.

Risk factors for development of motor fluctuations specifically have been less robustly characterized compared to those for LIDs (see below), but higher l-dopa dose, longer disease duration, and younger age have all been associated with development of motor fluctuations.

**Imaging Studies**

Fluctuations in motor response following oral l-dopa administration are associated with reduced dopamine terminal function. However, there is no clear correlation between levels of striatal F-Dopa uptake or dopamine transporter (DAT) binding and severity of fluctuations, suggesting that postsynaptic mechanisms may also be relevant. 11C-raclopride binds to D2/D3 receptors with nanomolar affinity, but its binding is influenced by competition from levels of synaptic dopamine. By performing raclopride PET scans before and after giving oral l-dopa, one can estimate the induced rise in exogenous synaptic dopamine levels. PD patients with early disease and sustained therapeutic responses to l-dopa show a progressive reduction in striatal 11C-raclopride binding after oral l-dopa that is maintained for at least 4 hours, compatible with a sustained increase in their synaptic dopamine levels. In contrast, 11C-raclopride PET suggests that fluctuating cases show larger initial dopamine rises 1 hour after l-dopa which are short-lived and return to baseline by 4 hours. Such a profile confirms that nonphysiological pulsatile swings in dopamine levels are occurring.

As loss of dopamine terminals in PD becomes severe, the striatum fails to store dopamine in terminal vesicles and buffer synaptic levels after exogenous l-dopa is taken orally. This problem is magnified by a relatively greater loss of DATs from terminals, the mechanism for dopamine uptake from the synapse, compared with intraterminal dopa decarboxylase activity. Abnormal pulsatile swings in synaptic dopamine levels will promote internalization of dopamine receptors. They thus become temporarily unavailable and contribute to fluctuating treatment responses. Maintaining sustained synaptic dopamine levels in fluctuators by the use of duodenal infusions of l-dopa gel has been shown with 11C-raclopride PET to allow a stable population of external postsynaptic dopamine receptors to be maintained and promote a return of sustained relief of symptoms (Politis M, submitted).

**Levodopa Induced Dyskinesias**

The mechanisms involved in the pathogenesis of LIDs are complex and incompletely understood. Current evidence supports an interplay of pre- and postsynaptic events (see Fig. 3).

The most important presynaptic factor is discontinuous delivery of l-dopa to the brain as a consequence of intermittent oral dosing. Loss of dopaminergic nigrostriatal terminals with advancing disease leads to reduced presynaptic dopamine storage capacity, such that fluctuations in l-dopa plasma levels increasingly translate into oscillations of synaptic DA and result in pulsatile activation of postsynaptic DA receptors. In addition, serotonergic terminals projecting from the raphe nucleus to the striatum are an important source for conversion of l-dopa to DA in the parkinsonian striatum, but DA release from this ectopic source lacks the regulatory mechanisms of nigrostriatal terminals and adds to the occurrence of dysregulated surges of DA at synaptic levels. The role of striatal serotonergic terminals in the pathogenesis of LIDs is also supported by imaging studies in dyskinetic PD patients (see below).

Dysregulated striatal DA release is associated with multiple and complex postsynaptic changes, including a variety of effects on gene transcription and protein translation in striatal medium spiny neurons of the direct and indirect pathways as well as structural and molecular changes leading to altered signal processing in striatal neurons. Serotonergic maladaptive plasticity with sprouting of striatal serotonin terminals has been shown both in animal models of LID and postmortem striatal tissue from patients with LIDs, and ectopic DA release from transplanted 5-HT neurons contained in fetal mesencephalic grafts is considered a key mechanism in the development of graft-induced dyskinesias after fetal cell transplantation in PD. l-dopa has also been shown to affect spine morphology of striatal medium spiny neurons. These projection neurons of the direct and indirect pathway lose dendrites and spines in PD. In animal models, l-dopa has been shown to preferentially restore spine density in neurons of the indirect projection, and this has been linked to development of LIDs in the 6-OHDA rodent model.
Alterations in postsynaptic glutamate receptors are another facet of L-dopa-induced maladaptive neuronal plasticity that affect corticostriatal signaling with aberrant long-term potentiation (LTP) and depotentiation at the level of striatal projection neurons in LID models. Excessive glutamatergic activity in corticostriatal and subthalamopallidal projections contribute to altered activity patterns in basal ganglia thalamocortical networks that underlie LIDs and are the target of antiglutaminergic drugs like amantadine or DBS to modulate activity in these subcortico-cortical networks.

**Insights from Imaging Studies**

Severity of peak-dose dyskinesias following oral L-dopa administration to PD patients has been shown to correlate with the rises of synaptic dopamine it induces, as reflected by reductions in putaminal \(^{11}\)C-raclopride binding. Recently, striatal serotonergic terminals have been shown to play a role in generating peak dose dyskinesias after L-dopa administration. \(^{11}\)C-DASB PET, a marker of serotonin transporter availability, shows that only a mild 20% loss of SERT binding occurs in dyskinetic PD. These serotonin terminals can take up and decarboxylate L-dopa, but are unable to physiologically store dopamine, releasing it as it forms. If an HT1A agonist, such as buspirone, is given alongside levodopa to dyskinetic PD patients, \(^{11}\)C-raclopride PET shows that release of exogenous dopamine from serotonergic terminals is blocked by autoreceptors, resulting in less severe and prolonged dyskinesias.

The striatum contains high densities of transmitters other than dopamine. Adenosine A2A sites are found on striatal neurons of the indirect pathway and regulate its activity. Uptake of \(^{11}\)C-SCH442416 and \(^{11}\)C-TSMX, both markers of A2A receptor availability, is normal in the striatum of nondyskinetic, but significantly raised in dyskinetic, patients. N-methyl-D-
aspartate (NMDA) receptors are a subclass of glutamate receptors that contain a voltage-gated ion channel, which is open during learning and memory tasks. 11C-CNS5161 PET is a use-dependent marker of NMDA ion channel activity. Striatal 11C-CNS5161 uptake increases when PD patients are experiencing L-dopa-induced limb dyskinesias during PET. The presence of increased NMDA ion channel activation during dyskinesias may help to explain the beneficial mode of action of amantadine, an NMDA channel blocker. The opioid peptides, dynorphin and enkephalin, are also known to be abnormally raised in the striatum of animal lesion models of PD, which have been made dyskinetic by levodopa exposure. 11C-diprenorphine is a radioligand that binds to all opioid receptor subtypes and competes with natural opioid peptides (dynorphine and enkephalin) for those sites. It has been reported that striatal 11C-diprenorphine binding is reduced in untreated dyskinetic PD patients compatible with raised basal opioid peptide levels being present. Levels of putamen 11C-diprenorphine uptake correlated inversely with the severity of dyskinesias induced by L-dopa. Finally, 11C-IMA107 PET has shown that severity of parkinsonism and its motor complications has been reported to correlate with loss of phosphodiesterase 10A (PDE10A) from the striatum. PDE10A regulates cGMP and cAMP signaling pathways in the striatum, which, in turn, regulate dopamine signaling.

### Nonmotor Complications of PD

#### Cognitive Dysfunction

Eighty percent of PD patients will develop dementia if they survive for 20 years with their illness, and this complication can be more disabling than the locomotor problems. The dementia may reflect the presence of cortical Lewy body disease (LBD), coexistent vascular and/or Alzheimer’s pathology, and degeneration of dopaminergic and cholinergic projections to cortical areas. Volumetric magnetic resonance imaging (MRI) studies have shown the presence of posterior cortical thinning even in noncognitively impaired patients, which progresses in those with either PD-mild cognitive impairment (MCI) or frank dementia. Diffusion tensor imaging (DTI) can detect changes in white matter connectivity early in PD, which worsen with onset of cognitive deficits. Resting functional MRI performed using blood-oxygen-level–dependent (BOLD) sequence acquisition can detect slow oscillations in venous oxygenation in different brain regions. Independent component analysis (ICA) detects synchronization of these oscillations in functionally connected brain areas and can reveal resting networks of connected regions that subserve attention, motor activity, visual perception, and other functions. ICA has also revealed that a default mode network (DMN) exists, which is expressed at rest with eyes closed and connects medial frontal and lateral parietotemporal areas. An alternative approach is graph theory modeling of resting BOLD signals, which represents resting connectivity as nodes and hubs linked by short and long pathways. The small worlds are clusters of nodes and hubs linked by short paths. In PD, executive task performance has been shown to correlate with connectivity of the dorsal attentional network, whereas visual perception correlates negatively with DMN connectivity. PD patients show abnormal clustering of nodes and hubs, with disruption of longer pathways, and this worsens with cognitive deterioration.

Levels of 18F-2-fluoro-2-deoxyglucose (18FDG) uptake reflect neuronal synaptic activity. In nondemented PD patients, cortical 18FDG uptake is generally within normal limits, but covariance analysis reveals an abnormal profile of relatively increased lentiform nucleus and reduced frontoparietal metabolism. This has been labeled the PD-related profile (PDRP), and its degree of expression correlates with degree of motor disability. The PDRP normalizes after successful treatment with both dopaminergic drugs or DBS. Frankly demented PD patients show an Alzheimer’s disease (AD) pattern of impaired brain glucose utilization, where posterior cingulate, parietal, and temporal association areas are most affected. PD patients with MCI show a similar pattern of glucose hypometabolism, though to a lesser extent. This pattern of glucose hypometabolism in demented PD patients may reflect cortical LBD, coincidental AD, or some other degenerative process. In cases later pathologically proven to have cortical LBD, there tend to be greater occipital hypometabolism than that observed in Alzheimer’s patients. The PET ligand, 11C-PIB, a neutral thioflavin-T analogue marker of β-amyloid plaques in AD, has been used recently to assess the prevalence of amyloid in PD patients with dementia. Only a minority showed increased 11C-PIB uptake, suggesting that amyloid pathology is not a major contributor to their cognitive problems. However, what has emerged is that the presence of amyloid in PD predicts a more rapid cognitive decline even in the absence of cognitive deficits at baseline.

Postmortem studies have shown that significant loss of cholinergic neurons in the nucleus basalis is an early phenomenon in PD, and surviving cells contained Lewy inclusion bodies. Acetylcholinesterase activity, a presynaptic cholinergic marker, is also decreased significantly in the frontal cortex of both demented and nondemented parkinsonian subjects compared to controls. Cholinergic terminal function in PD has been assessed with 11C-NMP4A and 11C-PMP PET, markers of acetylcholinesterase activity. Nondemented PD patients showed posteriorly reduced cholinergic function in parietal and occipital cortex. When dementia
was present, the PD patients had more severe and global reduction of cortical $^{11}$C-NMP4A binding. Levels of cortical acetylcholinesterase activity correlated with Mini-Mental State Examination (MMSE) scores and performance on executive tests such as card sorting and trail making in PD. These results suggest that progressive cognitive impairment in PD, in part, results from the cholinergic deficit.

**Depression**

A majority of PD patients experience depressive symptoms. Weintraub and colleagues$^{83}$ found an association between depressive symptoms and anxiety in PD and DAT availability measured with $^{99m}$Tc-TRODAT-1 single-photon emission computed tomography (SPECT) in the left anterior putamen. This finding suggests that disruption of association basal ganglia circuits projecting to the frontal and limbic areas may affect mood regulation. MRI studies with voxel based morphometry (VBM) and DTI largely support this view. Feldmann and colleagues$^{84}$ reported gray matter decrease in the bilateral orbitofrontal cortex, right superior temporal pole, and limbic system of depressed PD patients compared to those without depression. More severe white matter loss in the right frontal lobe, including the anterior cingulate bundle and the inferior orbitofrontal region in depressed PD patients compared to nondepressed patients, has also been reported.$^{85}$

It has been suggested that serotonergic loss might contribute to depression in PD; however, the findings from neuroimaging studies have been inconsistent. An $^{11}$C-DASB PET study reported that depressive symptoms in PD were associated with higher availability of serotonin transporters in amygdala, hypothalamus, caudal raphe nuclei, and posterior cingulate cortex.$^{86}$ The researchers suggested that this finding equated with reduced levels of synaptic serotonin in limbic areas and hypothalamus. However, in another study, midbrain uptake of $^{123}$I-β-CIT, also reflecting serotonin transporter availability, did not differ between PD patients with and without depression or correlate with Hamilton Depression Rating Scale scores.$^{87}$ Remy and coworkers used $^{11}$C-RT132 PET, a marker of dopamine and noradrenaline transporters, to assess PD patients with and without depression.$^{88}$ The depressed PD patients had lower $^{11}$C-RT132 binding in locus coeruleus and areas of the limbic system than nondepressed PD patients. This finding suggests that loss of limbic dopamine and noradrenaline may be relevant to the pathogenesis of depression in patients with PD.

**Sleep Disorders**

Sleep disorders are very common in PD and can be categorized as insomnia, excessive daytime somnolence (EDS), and parasomnias, including dreams, somnambulism, and rapid eye movement (REM) sleep behavior disorder (RBD). A significant inverse correlation between EDS severity rated with the Epworth Sleepiness Scale (ESS) and caudate and putamen $^{123}$I-FP-CIT binding in early (H & Y stage 2) PD has been reported.$^{89}$ No correlation of the ESS score with age, disease duration, UPDRS motor score, or depression score was found. Pavese and colleagues studied PD patients with and without EDS with $^{18}$F-dopa and $^{11}$C-DASB PET to assess integrity of monoaminergic terminal function and serotonin transport availability in the main sleep regulatory centers.$^{90}$ Compared to healthy volunteers, EDS patients had significant decreases in $^{11}$C-DASB binding in thalamus, locus coeruleus, rostral raphe, and hypothalamus and significantly reduced $^{18}$F-dopa uptake in locus coeruleus, rostral raphe, and ventral tegmental area. The same structures, except locus coeruleus, were preserved in the PD group without EDS. A direct comparison between patients with and without EDS showed significant reductions in $^{11}$C-DASB binding in thalamus, rostral raphe, frontal, and insular cortices in EDS. These findings provide evidence of serotonergic and potentially noradrenergic dysfunction in the neuronal networks responsible for daytime arousal in PD.

A majority of RBD patients are now known to progress to neurodegenerative diseases associated with alpha-synuclein aggregation such as PD and LBD (Lewy pathology) and MSA (glial inclusions). RBD may therefore represent a prodromal phenotype of these disorders. Serial FP-CIT SPECT scans have now shown progressive nigrostriatal dysfunction before the onset of parkinsonism in RBD patients.$^{91}$ Hilker and colleagues measured striatal and upper brainstem $^{18}$F-dopa uptake in PD patients with a history of sleep disorders. They found a significant inverse correlation between mesopontine $^{18}$F-dopa uptake and REM sleep duration measured with polysomnography, which suggests that brainstem dopamine has an inhibitory effect on REM sleep duration. $^{11}$C-PMP PET has shown that RBD in PD patients is also associated with cholinergic system degeneration in neocortical, limbic cortical, and thalamic areas.$^{92}$

**Dysautonomia**

PD patients show decreased myocardial uptake of markers of sympathetic terminal function, such as $^{123}$I-metaiodobenzylguanidine (MIBG) and $^{18}$F-fluorodopamine, even when cardiovascular reflexes are still intact. It has been reported in PD patients, even at early stages of the disease when cardiovascular reflexes are still intact.$^{94,95}$ However, MIBG SPECT is not a sensitive marker of early PD, given that 50% of H & Y stage I patients may still show normal tracer binding.$^{96}$ Oka and colleagues examined the association between myocardial $^{123}$I-MIBG uptake and
cardiovascular reflexes in PD patients and reported that mean myocardial $^{125}$I-MIBG uptake was significantly lower in those PD patients with orthostatic hypotension and an abnormal Valsalva response.

Recently, the development of $^{11}$C-donepezil has allowed PET to assess the integrity of parasympathetic cholinergic innervation of peripheral organs. Significantly decreased $^{11}$C-donepezil uptake in the small intestine and pancreas was found in 12 PD patients with established disease. There was also a trend toward reduced myocardial signal. No correlations were found between levels of $^{11}$C-donepezil uptake and disease duration, severity of constipation, gastric emptying time, or heart rate variability. Given that the dorsal motor nucleus of the vagus undergoes severe degeneration in PD but the enteric nervous system displays little or no loss of cholinergic neurons, the researchers concluded that decreases in enteric $^{11}$C-donepezil binding represented parasympathetic denervation.

Conclusion

Although l-dopa, after decades of clinical drug development in PD, still is the gold standard for symptomatic efficacy, motor and nonmotor complications associated with its chronic use pose significant therapeutic challenges. l-dopa-related motor response fluctuations are a source of major disability, not least attributed to their association with a variety of troublesome nonmotor symptoms. The same is true for l-dopa-induced dyskinesias, although many patients prefer an ON-state with nondisabling dyskinesias to an OFF-condition with reduced mobility, tremor, and additional nonmotor complaints. The mechanisms underlying these problems include peripheral pharmacokinetic factors as well as complex central mechanisms of maladaptive neuronal plasticity in response to discontinuous drug delivery and nonphysiological dopamine release. Whereas multiple strategies to modify l-dopa pharmacokinetics and dopaminergic drug delivery can alleviate motor and nonmotor fluctuations, amantadine and DBS remain the only approaches with proven efficacy to reduce LIDs.

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