

A microscopic image of a neuron, showing a central cell body with numerous branching processes extending outwards, set against a dark, glowing background.

The Need for Enhanced Strategies to Manage Levodopa-Induced Dyskinesia in Parkinson's Disease

Levodopa in the Treatment of Parkinson's Disease (PD)

PD affects an estimated 1 million people in the United States, with approximately 60,000 people newly diagnosed each year.¹ The prevalence increases with age, and because of the growing aging population, the number of patients with PD is expected to double by 2030.²

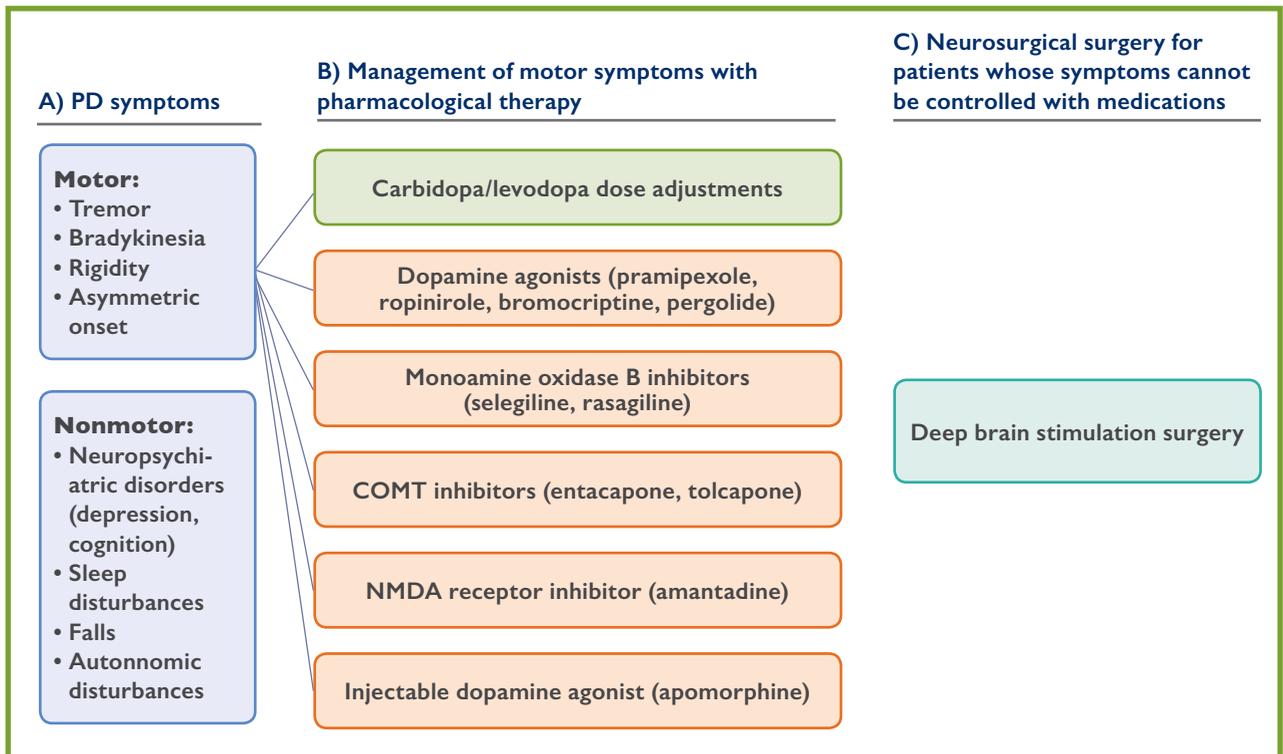
Neurodegenerative features of PD include the loss of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies in the residual dopaminergic neurons.^{3,4} Although pathologic changes can be detected up to 20 years before the onset of motor symptoms and other early nonspecific symptoms (Figure 1A),⁵ most patients are diagnosed only when symptoms appear in their 50s and 60s.⁶

The overall clinical course of PD and the spectrum of signs and symptoms can vary considerably among patients.^{7,8} Because interventions that cure PD or at least modify its progression are not currently available, treatment for patients with PD focuses on improving functional disability due to motor and nonmotor symptomatology, which generally requires lifelong pharmacologic therapy.⁹ Surgical options, such as deep brain stimulation, are also available for symptomatic control, but tend to be reserved for patients with advanced disease in whom disabling symptoms progress despite optimal medical therapy.⁴

The primary aim of pharmacologic treatment is to restore striatal dopamine activity to the fullest extent possible. To this end, levodopa, the precursor of dopamine, has been the mainstay option for improving PD symptoms since becoming available in the 1960s. Despite the subsequent development and availability of other agents such as dopamine agonists, monoamine oxidase B inhibitors, catechol-O-methyltransferase (COMT) inhibitors, and N-methyl D-aspartate (NMDA) receptor inhibitors, levodopa remains the gold standard for treating parkinsonian symptoms, especially bradykinesia or rigidity (Figure 1B).^{4,9}

Levodopa improves disability and capacity to perform important activities of daily living (ADL). Approximately 85% of patients have some degree of benefit with this therapy.¹⁰ Although treatment with levodopa effectively reduces parkinsonian symptoms, it has also been associated with numerous adverse events.¹⁰ The most common and burdensome adverse events associated with long-term levodopa use are abnormal involuntary movements (dyskinesias), typically referred to as levodopa-induced dyskinesia (LID).⁴

Figure 1. Symptoms and management of motor complications as part of the PD patient journey⁴



Levodopa-induced dyskinesia (LID)

LID is characterized by involuntary movements during the waking hours that are nonrhythmic, purposeless, and unpredictable. In some cases, and especially for patients, it is difficult to recognize the occurrence of dyskinesias as a side-effect of levodopa and not a symptom of the underlying PD.¹⁰ An increased risk of developing LID has been associated with different factors, including:

- An early onset (<50 years) of PD^{11,12}
- A longer duration of PD¹²
- Longer periods of treatment with levodopa¹²
- Higher-daily levodopa dosages^{13,14}

Although the pathophysiologic changes are not completely understood, LID is most likely a consequence of progressive motor circuitry dysfunction in the parkinsonian brain and levodopa therapy.

In the non-disease state, purposeful movement is generated through the interplay of cortical and subcortical motor pathways. The motor cortex sends axonal projections to the subcortical structures collectively referred to as the basal ganglia. Cortical inputs to the basal ganglia are received in the area known as the striatum. Outputs from the basal ganglia are carried by way of 2 main pathways, the direct and indirect pathways. These 2 subcortical pathways work in opposing, but coordinated, fashion to regulate movement, the direct (or GO) pathway facilitating movement, and the indirect (or STOP) pathway inhibiting it.¹⁵

The direct (GO) and indirect (STOP) pathways both receive excitatory drive via glutamate, a neurotransmitter that is released from cortical axon terminals within the striatum. The responsiveness of these 2 pathways to glutamatergic excitation is, however, differentially modulated by dopamine. Dopamine acting on the neurons of the direct (GO) pathway (expressing D-1 type dopamine receptors) facilitates glutamate-mediated neuronal activity, whereas dopamine acting on the neurons of the indirect pathway (expressing D-2 type dopamine receptors) inhibits glutamate-mediated neuronal activity.^{15,16}

The striatum receives its dopaminergic innervation from axonal projections from the specialized neurons of the substantia nigra. In return, the activity of the substantia nigra is regulated by reciprocating pathways from the basal ganglia. Thus, it is the regulated release of dopamine from substantia nigra neurons that modulates the responsiveness of striatal neurons in both the direct (GO) and indirect (STOP) pathways to glutamatergic activation originating from the motor cortex.¹⁵

It is well-established that PD results from the progressive degeneration and loss of dopaminergic neurons in the substantia nigra. In PD, as dopamine is lost, the subcortical motor pathways become dysregulated, with the indirect (STOP) pathway becoming overactive and the direct (GO) pathway becoming under-active. Dopamine loss therefore shifts the balance of signaling in the key motor pathways of the basal ganglia in favor of STOP signals, leading to reduction and slowing of voluntary movement, cardinal symptoms of the disease.¹⁶

To offset the imbalance between the STOP and GO pathways, and thereby to reestablish voluntary movement, dopamine needs to be resupplied to the striatum of patients with PD. This is best achieved through the systemic (usually oral) administration of levodopa, a precursor of dopamine. When plasma levodopa levels are adequate to generate striatal dopamine levels capable of facilitating the GO and inhibiting the OFF pathways to the point where a PD patient can move voluntarily, the patient is said to be in the “ON” state; and when they are insufficient, and cardinal symptoms of PD return, the patient is said to be in the “OFF” state. Switching between ON states and OFF states is referred to as the “ON-OFF phenomenon.”¹⁷

Early in the course of PD, there is a sufficient number of surviving dopaminergic neurons (as many as 50%) to allow for the conversion of levodopa to dopamine by neurons that are still subject to physiologic regulation. When this is the case, OFF periods tend to occur predictably, as end-of-dose wearing-off, and ON periods are characterized by movement that approximate normal mobility.¹⁷

With continued loss of dopaminergic neurons, higher doses of levodopa are usually required to overcome the OFF state. Additionally, serotonergic neurons take over the processing of levodopa and release of dopamine, but they lack the appropriate regulatory mechanisms. This results in wide and often unpredictable fluctuations in striatal dopamine levels in response to levodopa admin-

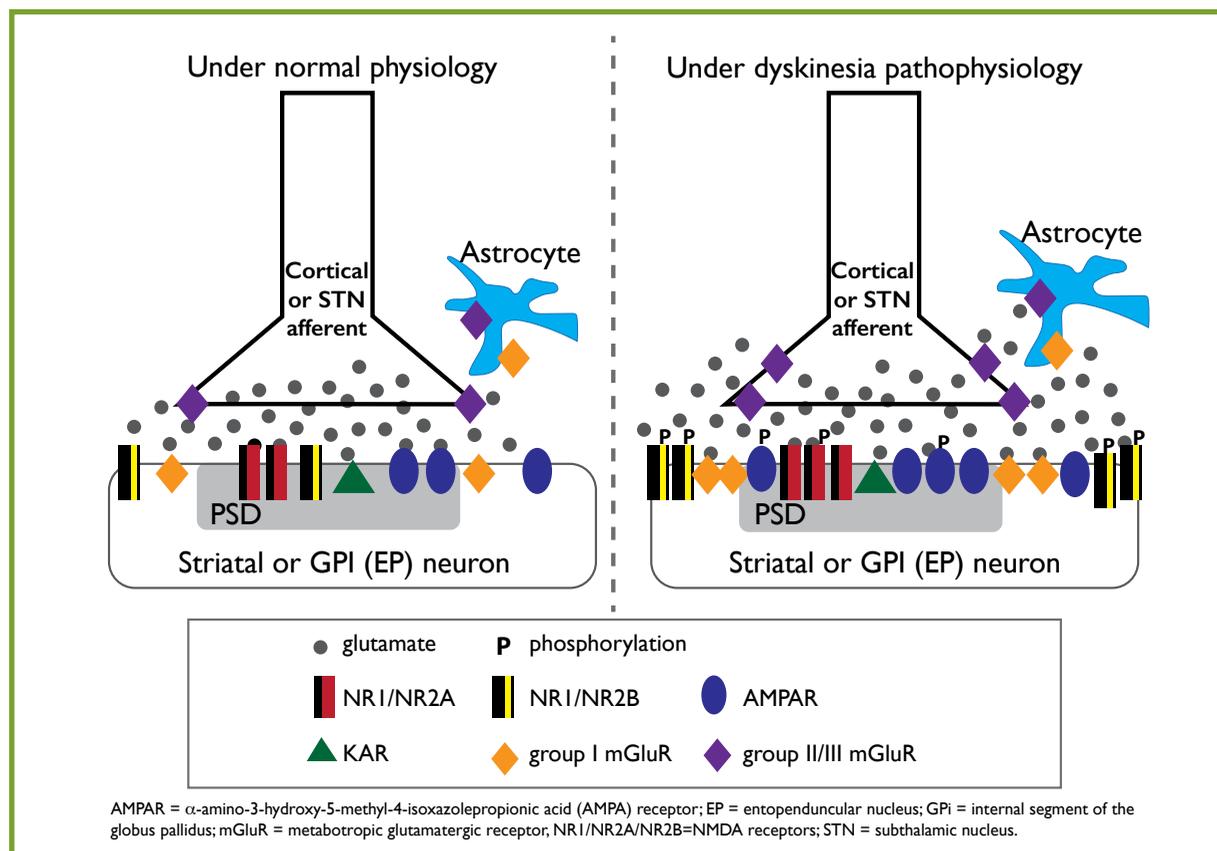
istration.¹⁷ As a consequence, OFF periods may occur more frequently and less predictably. Moreover, ON periods may occur less frequently and be accompanied by the abnormal movements of LID.

While the progressive loss of levodopa to provide adequate and reliable levels of striatal dopamine is one of the major contributors to the development of levodopa-associated motor complications, another is the overactivation of glutamatergic motor pathways in response to dopamine dysregulation. This is particularly relevant to the development of LID.¹⁷

Evidence suggests that the overactivation of glutamatergic motor pathways involves excessive release of glutamate from the presynaptic terminals of cortical neurons projecting to the striatum. Further evidence suggests the involvement of postsynaptic mechanisms, including the up-regulation of glutamate receptors of the NMDA class on striatal neurons.¹⁷ Thus, in PD, levodopa administration can cause increased release of glutamate into the synaptic cleft, resulting in excessively high levels of glutamate receptor stimulation (Figure 2),¹⁵ and its clinical manifestation, LID.

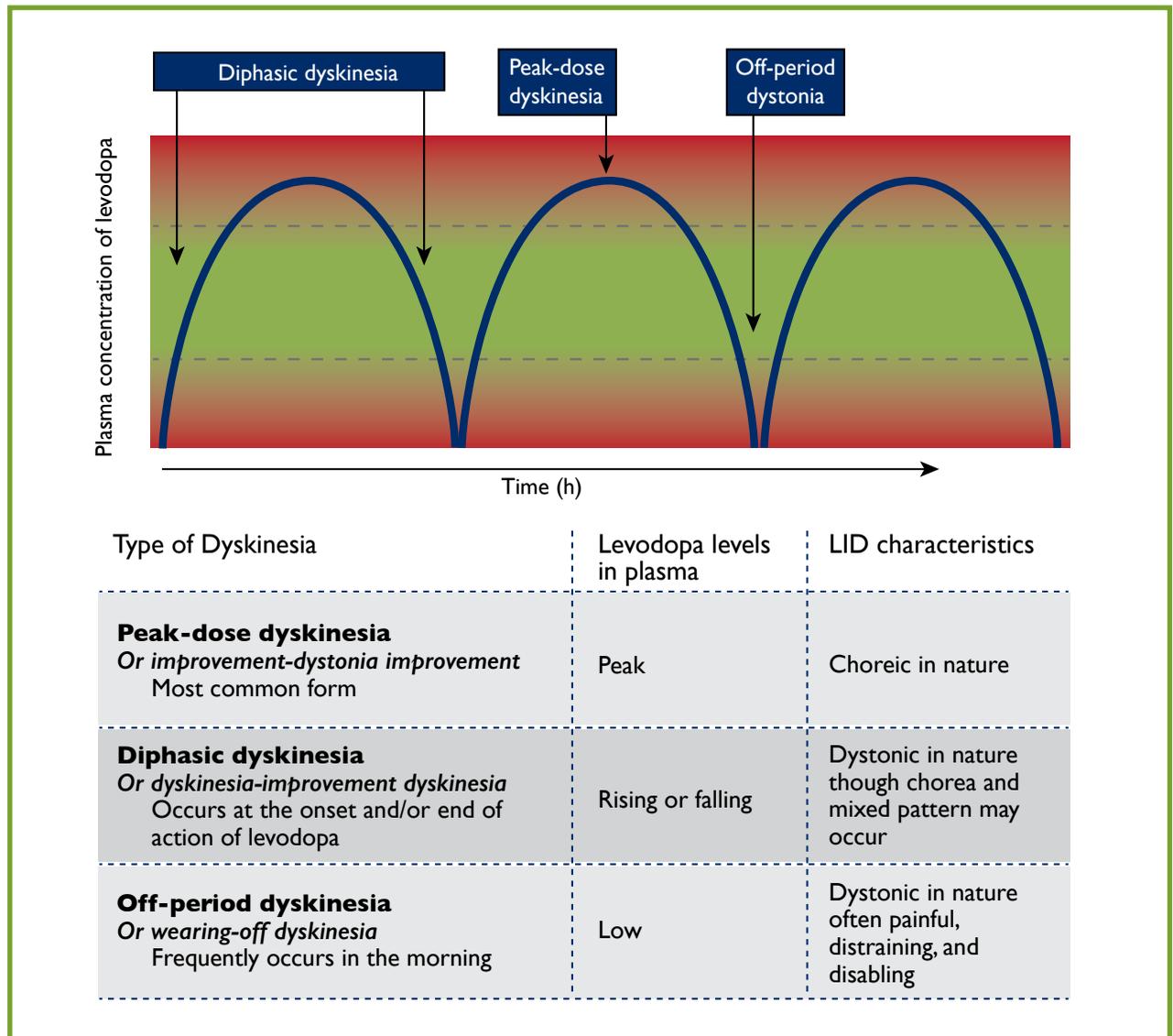
The clinical manifestations of LID can be heterogeneous and include rapid, dance-like (choreic) movements, as well as slow twisting or writhing (dystonic) movements. The occurrence of LID can be related to the levodopa plasma levels and classified on this basis. The most

Figure 2. Hypothesized mechanisms that are associated with the development of LID¹⁵



common form of LID occurs when levodopa plasma levels are at their highest, ie, peak-dose dyskinesia. Manifestations of LID can, however, also occur between “on” and “off states,” so-called diphasic dyskinesia, the second most common form of LID. The least common manifestation of LID is the off-period form, which tends to be dystonic. (Figure 3)¹⁷⁻¹⁹

Figure 3. Common types of LID and levodopa pharmacodynamics¹⁷⁻¹⁹



Impact of LID on the Patient with PD

LID and other complications that arise from the long-term management of PD with levodopa have become a major concern for clinicians, patients, and payers.¹⁰ The prevalence of LID ranges from 30% to 45%²⁰⁻²²; however, the lack of a universally agreed-upon assessment method for LID and the various factors associated with its development contribute to varying prevalence estimates.²³ Nevertheless, reviews of observational studies and clinical trials agree that on average, LID affects 40% of PD patients after 5 years of treatment, and 90% of patients by 9 to 15 years of treatment.²³

The development of LID is a pivotal point in the journey of PD patients. Patients often suffer from one type or a combination of different types of dyskinesias associated with the long-term treatment of levodopa, and the impact they exert on a patient’s health-related quality of life (HR-QoL) increases as dyskinesias become more severe and frequent.^{18,24} LID has been associated with exhaustion, fatigue, and weight loss due to the excessive involuntary movement in patients, and it has been suggested to limit the PD patient’s social life, causing feelings of isolation, frustration, and depression.¹⁸ Several studies have evaluated the impact of LID in the PD patient’s

HR-QoL. Overall, these studies report that the “on-off” phenomenon negatively affects patients’ bodily comfort,^{24,25} that LID decreases patients’ mobility and their ability to perform ADL and communicate, and that LID has a detrimental effect upon patients’ stigma, as reflected by elements of the Parkinson’s Disease Questionnaire (PDQ-39; eg, items 23 to 26).²⁴⁻²⁶ A higher prevalence of falls in PD patients²⁷ and a higher risk of injuries in PD patients and their caregivers have been correlated with the presence of LID.¹⁸ Key studies are summarized in Table 1.

Table 1. Clinical studies that demonstrate the impact of LID on HR-QoL and other aspects in PD patients^{a,b}

	Study	PD patients (N)	HR-QoL results	Conclusion
	Pechevis M, et al. <i>Eur J Neurol</i> . 2005.	60 patients with idiopathic PD of at least 3 years’ duration, at a Hoehn and Yahr stages II-IV during “on” states	Increasing dyskinesia severity as measured by UPDRS and GDRS scores was associated with: <i>Significant reductions in QoL scores on the following scales:</i> • SF-36 ($P<0.001$) • PDQL Scale ($P<0.001$) <i>Significant increased depression scores on the following scale:</i> • Montgomery-Asberg Depression Rating Scale (all dimensions $P<0.001$, except for role emotion $P<0.005$, and the mental component summary $P=0.004$)	Increasing dyskinesia severity may adversely affect QoL and increase depression in patients with PD
	Chapuis S, et al. <i>Mov Disord</i> . 2005.	143 patients with PD and a Hoehn and Yahr stage II	LID affected PDQ-39 dimensions as follows: <i>Peak-dose dyskinesia was associated with a decrease in:</i> • Mobility ($P=0.0356$) • Emotional well-being ($P=0.0353$) • Cognition ($P=0.0186$) <i>Diphasic dyskinesia was associated with a decrease in:</i> • Mobility ($P<0.0237$) • Ability to conduct ADL ($P<0.02$) • Ability communication ($P=0.005$) <i>Diphasic dyskinesia was associated with an increase in:</i> • Stigma ($P=0.0171$) <i>Morning dystonias were associated with an increase in:</i> • Stigma ($P=0.0275$)	LID significantly decrease mobility, ability to ADL, and communication; and increase stigma in patients with PD
	Hechtner MC, et al. <i>Parkinsonism Relat Disord</i> . 2014.	817 patients with PD and a Hoehn and Yahr stage II	LID affected PDQ-39 dimensions as follows: <i>Peak-dose dyskinesia was associated with a decrease in:</i> • Ability to conduct ADL ($P=0.01$) • Cognitions ($P=0.03$) <i>Biphasic dyskinesias were associated with an increase in:</i> • Stigma ($P=0.01$) <i>Off dystonias was associated with an increase in:</i> • Bodily discomfort ($P=0.02$)	LID was not seen to affect global QoL scores, but had detrimental effects on the ability to conduct activities of daily living, cognitions, bodily discomfort, and stigma in patients with PD
	Rascol O, et al. <i>J Neural Transm (Vienna)</i> . 2015.	672 patients with PD (27.2% of patients suffered from LID)	<i>The probability of falling due dyskinesia is comparable to that of falling due to bradykinesia or due to difficulty rising from the chair, as indicated by the odd ratios (95% CI):</i> • Dyskinesia=1.83 (1.11–2.99) • Bradykinesia=1.83 (1.08–3.12) • Difficulty rising from the chair=1.69 (1.01–2.85) <i>In the 27.2% of patients who suffered from LID, a significant difference was observed in those who had falls and those who did not fall while on “on” state</i> • 24.1% of these patients had no falls on “on” state, and 43.5% had falls ($P<0.01$)	Falls in PD patients was associated with the presence of LID

^aThe qualification of dyskinesias and motor fluctuations in these studies was performed by using the Unified Parkinson’s Disease Rating Scale (UPDRS) part IV (which measures time spent with dyskinesias, functional impact of dyskinesias, painful off-state dystonia; and time spent in the off-state, functional impact of on-off fluctuations, and the complexity of motor fluctuations); the Hoehn and Yahr scale, which is a commonly used system for describing how the symptoms of Parkinson’s disease progress, and/or the Goetz Dyskinesia Rating Scale (GDRS).

^bIn these studies, HR-QoL was assessed using standard measurements such as the 36-item Short-Form health survey (SF-36), the Montgomery-Asberg Depression Rating Scale used to measure severity of depressive episodes; utility measurements such as the Euro-Qol (EQ-5D); and specific measurements for PD patients such as the Parkinson’s Disease Questionnaire (PDQ-39), which includes 39 items in 8 dimensions (mobility, ADL, emotional well-being, stigma, social support, cognitions, communication, and bodily discomfort), and the Parkinson’s Disease Quality of Life (PDQL) Scale, which consist of 37 health-related questions that are converted into 4 subscales (Parkinson symptoms, systemic symptoms, social functioning, and emotional functioning).

Impact of LID on the Cost of Healthcare

Extending beyond the clinical implications, the emergence of LID in patients with PD also imparts a considerable economic impact. The direct costs associated with overall PD treatment are estimated to be \$14 billion per year in the United States²⁸; however, it has been reported that these costs increase 3- to 5-fold for patients with advanced disease.⁹ Patients with more advanced PD, many of whom have LID, require more adjunctive pharmacological and surgical therapies and more frequent office visits; hence, incurring higher health-related costs.²⁶ In addition, while nursing home placement should be delayed as long as possible (because of negative effects on QoL and mortality),²⁹ this type of living arrangement is often necessary (25% of Medicare beneficiaries with PD received nursing home care in 1 study), thus adding significantly to the overall costs of care (~\$80,000 per year).³⁰

Suh et al evaluated the treatment patterns, direct healthcare costs, and predictors of treatment costs associated with LID in the United States. The total treatment costs increased from \$18,645 during the 12 months before LID onset to \$26,439 during the 12-month period after LID development, an incremental cost of \$7795 ($P<0.001$). The total outpatient costs also increased from \$6877 to \$9441 ($P<0.001$). The presence of LID resulted in an increase in total treatment costs of 29%, and of PD-related treatment costs of 78% when compared with costs incurred among those patients without LID. Other factors influencing treatment costs were the use of other PD medications and the presence of select comorbidities (psychiatric, cardiovascular, chronic renal disease, injury, and fracture).³¹

In Europe, the annual direct medical costs for PD patients with LID have been reported to be higher by \$2605 to \$3144, compared with patients without LID.³¹ Pechevis et al reported that each unit increase in dyskinesia score, measured by the UPDRS IV scale, resulted in additional total costs of \$664 per patient over a 6-month period ($P<0.0002$), which represented an 11% increase in total costs ($P<0.0003$).²⁶ This increase of \$664 per patient in the total cost was due to an indirect cost increase of \$532 and to a direct cost increase of \$131, which suggests that the effect of LID is greater on nonmedical-related costs (such as social and care services) than on medical costs.²⁶

Davis et al analyzed insurance claims data from 30 managed care plans (using the Integrated Health Care Information Services Database) and reported that over a 1-year period, approximately 61% of PD patients were nonadherent to different PD medications, including levodopa. Nonadherers obtained roughly 5 fewer levodopa prescriptions during follow-up compared with adherers ($P<0.001$). Mean total medical costs were significantly higher by \$6598 among nonadherers compared with adherers ($P<0.0001$). Total mean healthcare costs,

including both medical and pharmacy utilization, were \$18,511 and \$13,082 among nonadherers and adherers, respectively ($P<0.0001$). Compared with subjects who remained on PD therapy continuously, those with discontinuous medication use had a significant higher mean number of hospitalizations (2.4 vs 2.1, $P<0.05$) and other additional care visits (13.5 vs 10.8, $P<0.05$).³² Consistently, Delea et al assessed data from a retrospective cohort study using health insurance claims from a 5-year period, and reported that satisfactory adherence to oral levodopa/carbidopa/entacapone treatment was associated with 39% fewer PD-related hospitalizations ($P<0.0001$), 47% lower inpatient costs ($P=0.004$), and 18% lower total costs ($P<0.001$).³³ Complications that arise with the long-term use of levodopa may exert an effect on therapeutic adherence, and low treatment adherence due to these complications has been associated with increased medical costs and poor outcomes in PD patients.³⁴

Clinical Management of LID

Once a patient with PD has developed LID, the condition becomes increasingly more severe, and will not typically improve unless levodopa is tapered.¹⁰ However, reports indicate that patients prefer to be mobile and have treatment-related dyskinesias.¹⁸ Because levodopa continues to be the gold standard pharmacologic treatment available for PD, managing LID through additional measures (such as those noted below) is important:

- **Levodopa dose adjustments:** Levodopa dosages can be adjusted to manage the different types of dyskinesias; nevertheless, changes in frequency and doses often do not control LID successfully and may result in the worsening of parkinsonian symptoms and more OFF time.¹⁸ Strategies that are often considered include using extended release levodopa formulations, fractionating the levodopa dose, and decreasing the overall dose of levodopa.²² When levodopa doses are decreased, adjuvant therapies such as COMT inhibitors, monoamine oxidase-B (MAO-B) inhibitors, or dopamine agonists are commonly added:
 - The inhibitors of the enzyme COMT, such as entacapone and tolcapone, extend the half-life of levodopa.
 - MAO-B inhibitors are used to extend the duration of action of L-DOPA by decreasing the metabolic degradation of dopamine in the synaptic cleft.³⁵ Dopamine receptor agonists, such as pramipexole, ropinirole, bromocriptine, and pergolide can be used as they bind to dopaminergic receptors, mimicking the action of dopamine.^{22,35} These strategies could lead to other potential side effects such as peripheral edema, somnolence, hallucinations, compulsive disorders and cardiac effects.³⁶⁻³⁸

- **Adjunct therapy with amantadine immediate release (IR):** Due to the known underlying mechanisms of LID, which includes the overexpression of NMDA receptors, amantadine, an NMDA antagonist, is used off-label to treat dyskinesia. Small studies have shown that amantadine reduces dyskinesias associated with long-term treatment of levodopa.^{18,39,40} Amantadine IR administered with oral levodopa has reduced the duration and severity of dyskinesias, the severity of motor fluctuations, and the duration of wearing-off dyskinesias compared with placebo⁴¹; and has been suggested to improve apathy and fatigue in patients with LID.⁴¹ The efficacy of amantadine IR is related to its plasma concentration.³⁹ However, due to the lack of well-controlled clinical trials that meet evidence-based clinical and regulatory standards and that provide strong evidence that amantadine IR effectively controls LID, the 2006 American Academy of Neurology Treatment Guidelines give a Level C recommendation for the use of amantadine IR for the management of LID.⁴² Furthermore, amantadine is an uncompetitive, low-affinity NMDA receptor antagonist that only binds to the activated NMDA receptor³⁹; hence, higher local concentrations are required to sufficiently suppress receptor activity.⁴³ Additionally, while higher doses of amantadine IR have been shown to produce a greater

reduction in LID symptoms, an increased frequency of adverse events (particularly sleep and central nervous system [CNS] events) was also observed at these higher doses, which limits the routine use of amantadine HCl IR at doses of 300 mg/day or higher.⁴³ Amantadine IR is absorbed rapidly by the body, and the most commonly reported side effects include dizziness (lightheadedness), agitation, hallucinations, dry mouth, nausea, edema, and insomnia.⁴⁴

- **Neurosurgical procedures:** Neurosurgical procedures, such as pallidotomy, a procedure where an electrical probe is placed in the globus pallidum, have provided deep brain stimulation targeting the internal globus pallidum or subthalamic nucleus and have been shown to improve motor symptoms and reduce dyskinesia in advanced PD. Deep brain stimulation surgery has been an effective surgical treatment for LID in younger and older patients; however, it is only indicated for patients whose symptoms cannot be controlled with medications. (Figure 1C) Additionally, there is a loss of its effect after 5 years, and major risks (eg, infection) and high costs are associated with this procedure. Therefore, physicians should evaluate each individual patient and account for the risks involved.¹⁸

The Future of Clinical Management of LID

With a growing elderly population, the prevalence of PD is increasing in the United States and worldwide; thus, it is important that clinicians and payers take a critical look at the short- and long-term efficacy and adverse events of available therapies for this progressive disease in the current therapeutic landscape. A clear need exists for clinical strategies for levodopa therapy to optimally manage PD symptoms and address adverse effects associated with its long-term use, including LID.

As we better understand the underlying mechanisms of LID, the potential role of new levodopa formulations and of adjuvant therapies to relieve LID complications, and lessen the burden of LID on patients and the healthcare system becomes evident. The involvement of a nondopaminergic system in the pathogenesis of LID suggests that the modulation of glutamate, serotonin, and adenosine could serve as new drug targets.

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