Levodopa-Induced Dyskinesia: Medical and Surgical Management

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In the 1960s, the treatment of Parkinson disease (PD) was revolutionized by the introduction of levodopa. Soon after its discovery, however, it was observed that continuous treatment was complicated by the emergence of choreoathetoid movements and off episodes.¹

Although levodopa therapy remains the most effective symptomatic treatment for PD, its usefulness may be limited by these motor complications, which result in deterioration in quality of life. Levodopa-induced dyskinesia (LID) is characterized by a variety of hyperkinetic movements. Although chorea and dystonia are the most common manifestations of LID, stereotypes, tics, myoclonus, or ballism may occur. LID commonly starts in the lower extremity ipsilateral to the side first affected by PD, usually the most affected side. Early in LID, patients may not notice subtle hyperkinetic movements; however, as LID worsens it may interfere with activities of daily living, resulting in functional impairment, disability, and poor quality of life.²⁵

LID occurs in 3 temporal patterns related to timing of levodopa dosing.¹ Peak-dose dyskinesias are the most common and are characterized by the sequence of "improvement-dyskinesia-improvement." Diphasic dyskinesias are characterized by "dyskinesia-improvement-dyskinesia" and are often manifested clinically by dystonia and stereotypes.⁶

Diphasic dyskinesia accounts for 15% to 20% of LID.⁷ Some hyperkinetic movements occur in the functional off state in which patients may experience off dystonia characterized by painful sustained contractions. Off-dystonia occurs when plasma levodopa concentrations are low; therefore, off-dystonia frequently manifests itself before the first dose of levodopa is taken in the early morning on awakening, although it can occur during any off state.⁸

Epidemiology of DYSKINESIA

The risk of developing LID has been linked to disease severity, younger age at onset, female sex, duration of levodopa treatment, and total levodopa exposure.⁹¹⁰ The use of different methods to recognize LID has resulted in variations in the frequency rate reported in the literature. A literature survey of more than 2000 publications identified LID in almost 40% of patients with PD treated with levodopa for 4 to 6 years.¹¹ Another review found a prevalence of LID in up to 85% of patients with PD.³

In the DATATOP (Deprenyl and Tocopherol Antioxidative Therapy for Parkinson's Disease) study, LID was observed in almost 30% of patients after 20.5 months of levodopa therapy.¹² In a community study, LID was present in 28% of patients with PD, with a mean time to onset of 6.7 years.¹³

Pathogenesis of LID

In the dopamine-denervated state, striatal dopamine levels depend on exogenously administered levodopa. With the short half-life of levodopa, fluctuating plasma and striatal dopamine concentrations and nonphysiological pulsatile striatal stimulation occur.¹⁴ The pulsatile stimulation results in abnormal basal ganglia firing patterns,¹⁵ altered striatal neurotransmitter receptors,¹⁶ abnormalities in neuropeptide levels,¹⁶ and immediate early gene expression.¹⁷ These alterations lead to functional changes in the basal ganglia input and output pathways. The direct striatal output pathway provides g-aminobutyric acidergic inhibitory input to the globus pallidus interna (GPI) and substantia nigra pars reticulata. Overactivity of the direct pathway drives the development of LID.¹⁸ The direct pathway is modulated by excitatory glutaminergic corticostratial projections.¹⁹ In addition, serotonergic 5HT₁A 20 and 5HT₂A α-receptors,²¹ and α₂-adrenergic receptors nineteen influence the direct pathway. These provide potential targets for novel therapeutic discovery.
MEDICAL MANAGEMENT

When approaching the medical management of LID, it is important to recognize its clinical pattern; peak-dose and diphasic dyskinesia are managed differently. Treatment of peak-dose dyskinesia includes levodopa-based strategies or optimizing non-levodopa treatments.

Levodopa-based strategies are aimed at providing more constant dopaminergic delivery to the striatum while reducing peak plasma dopamine concentrations, including using smaller, more frequent doses of levodopa, reducing the individual doses, or changing formulations. Agents that might be considered in the management of dyskinesia include the following:

- **Adjunctive dopamine agonists.** A reduction in total levodopa dosage may be complicated by an increase in off time. The addition of dopamine agonists, which are less likely to result in LID, may allow for reduction in total levodopa dosage without inducing an off state. An example of this was illustrated by an open-label trial of 36 patients with advanced PD and severe dyskinesia who were treated with a high dose of the dopamine agonist ropinirole (Requip) to minimize levodopa use and reduce LID. At 12 months' follow-up, there was a reduction in total daily levodopa dosage (734.1 ± 254.8 mg/d to 502 ± 228.4 mg/d); the mean ropinirole dosage was 34.7 ± 5.5 mg/d. This correlated with improvements in LID during on and off time. Eleven patients withdrew from the study because of intolerable adverse effects or worsening motor function.

- **Sustained-release levodopa.** Sustained-release levodopa can result in worsening dyskinesia at the end of the day because plasma levels of the drug accumulate. Substituting a sustained-release formulation of levodopa for an immediate-release formulation may be required. When converting from controlled-release levodopa to immediate-release, the dosage will need to be reduced to account for the relative reduction in controlled-release levodopa bioavailability.

- **Liquid levodopa.** Liquid levodopa may be required when immediate-release oral levodopa preparations, used with frequent dosing, fail to adequately control LID. Liquid levodopa allows for tailoring the doses when doses smaller than those achieved with standard oral preparations are required.

To prepare liquid levodopa at a concentration in which 1 mL is equivalent to 1 mg of levodopa, dissolve 10 tablets of 25/100 mg of carbidopa/levodopa and 2 g of ascorbic acid with 1 L of water. Continuous levodopa infusion delivered into the duodenum results in stable plasma levodopa levels and reduction in motor fluctuations and dyskinesia. Liquified levodopa has been shown to improve on time without increasing dyskinesia.

- **Amantadine.** Amantadine (Symmetrel) is a N-methyl-d-aspartic acid receptor antagonist. It was the only pharmacological agent found to be beneficial for the treatment of dyskinesia in a recent evidence-based review. An open-label study also showed that the agent has a small benefit in improving off time.

Several studies have documented the benefits of amantadine in controlling dyskinesia. A 45% reduction in total dyskinesia in patients with advanced PD and LID was reported in one randomized, placebo-controlled, double-blind study. A 60% reduction in dyskinesia without exacerbation of motor function was observed in another randomized placebo-controlled trial with crossover design. In the 1-year open-label follow-up, 13 of the 17 study participants continued taking amantadine. A sustained reduction in dyskinesia of 56% was seen, a finding that was in contrast to that of another study in which a shorter duration of benefit was reported. In another study, intravenous amantadine at a dose of 200 mg in patients with PD and LID resulted in a marked improvement of 50% without worsening motor function. (Rimantadine [Flumadine], an a-methyl derivative of amantadine, may be an alternative for patients who experience peripheral adverse effects [eg, lower extremity edema and livedo reticularis] from amantadine.)

- **Clozapine.** Clozapine, an atypical neuroleptic, has been associated with a reduction in LID without worsening of motor symptoms in patients with PD in open-label trials. In a double-blind, randomized, placebo-controlled study of 50 patients with PD and LID, the effectiveness of clozapine was assessed using self-evaluation and levodopa challenge. After 10 weeks, a significant reduction in total LID and a maximal LID score after levodopa challenge was seen. Rarely, clozapine is associated with agranulocytosis; nevertheless, its
Other agents have been tried as well. Two recently published randomized controlled trials failed to confirm the open-label antidyskinetic properties of the novel serotonin-5HT	extsubscript{1A} agonist sarizotan,	extsuperscript{45,46} Other agents reported to reduce LID in preclinical animal studies or open-label trials include riluzole (Rilutek),	extsuperscript{47} memantine (Namenda),	extsuperscript{48} dextromethorphan,	extsuperscript{36} propranolol (Inderal),	extsuperscript{49} levetira-cetam (Keppra),	extsuperscript{50-52} remacemide,	extsuperscript{53} and topiramate (Topamax).	extsuperscript{54}

Diphasic dyskinesia is more difficult to treat than peak-dose dyskinesia. Higher doses of levodopa may be successful in ameliorating diphasic dyskinesia.	extsuperscript{55} In addition, converting controlled-release levodopa to standard-release formulations may alleviate symptoms because controlled-release levodopa has lower bioavailability and reduced intestinal absorption. Patients may need to take frequent doses of levodopa to maintain adequate plasma dopamine concentrations; however, this may exacerbate peak-dose dyskinesia.

Apomorphine has been shown to be effective in temporarily reducing the duration of diphasic dyskinesias.	extsuperscript{56} The dose required was higher than needed to induce the on state. Although not available in the United States, lisuride, apomorphine infusion, and duodenal levodopa infusion may be future treatment options.

**SURGICAL INTERVENTION FOR LID**

Despite extensive research, pharmacological interventions offer transient and often limited improvement of LID. Fortunately, surgical options have expanded and provide benefit when performed properly in the appropriate candidate. Deep brain stimulation (DBS) has largely supplanted ablative surgeries in many countries, but many questions persist about optimizing patient and target selection. Furthermore, most reports in the literature focus on improvement in motor features but fail to emphasize the systematic assessment of motor complications.

**Ablative procedures.** Meyers	extsuperscript{58} introduced surgical intervention targeted to the basal ganglia in the 1940s. In 1955, Hassler introduced thalamotomy as a treatment for PD tremor; 3 decades later, Narabayashi and colleagues	extsuperscript{59} reported that thalamotomy ameliorated LID best when targeted to the ventralis oralis anterior and the posterior thalamic nuclei rather than the ventrals intermedius nucleus. Since then, most experts have advocated ablation of the GPI or the subthalamic nucleus (STN) rather than the thalamus, but recent reports of using thalamotomy for LID exist in the literature.

Increasing reports of pallidotomy over the past 12 years have signaled the reemergence of interest in surgical intervention for medically refractory PD. Investigators from various groups concluded that pallidotomy improved parkinsonian features, particularly LID, with improvement ranging from 50% to 100% (Table).

These studies, most of which were open-label,	extsuperscript{61-72} revealed a robust effect on contralateral LID (70% to 100%) with less pronounced improvement of ipsilateral LID (20% to 40%). No controlled studies have been completed to date on bilateral pallidotomy or on comparing unilateral with bilateral pallidotomy.

Safety concerns related to higher incidence of dysphagia, dysarthria, disequilibrium, and cognitive dysfunction have limited the use of bilateral pallidotomy despite evidence that it improves LID to a greater degree than unilateral pallidotomy.	extsuperscript{73-76} Experience with subthalamotomy is limited relative to pallidotomy, but both unilateral and bilateral ablation of the STN appear to ameliorate LID by 50% to 85%.	extsuperscript{76-78} Additional investigation of subthalamotomy is needed, but this research is unlikely given the current trend favoring DBS.

Among the controlled ablative studies completed to date is one by de Bie and colleagues	extsuperscript{79} who enrolled 37 patients and performed unilateral pallidotomy immediately in 19. These patients, who were randomly selected, were compared with the remaining 18 patients, who received the same surgical intervention after a 6-month delay. The Unified Parkinson's Disease Rating Scale (UPDRS) motor score improved in the immediate surgical group by 32% and worsened slightly in the delayed group (P < .001). LID was reduced by 50% in the treatment group; no change occurred in the control (delayed surgery) group (P = .02). Nine patients in the treatment group experienced adverse events, including dysarthria, reduced consciousness, pseudobulbar affect, confusion, hypophonia, hiccups, urinary incontinence, facial weakness, dysarthria, headache, dysphasia, postural instability, and sialorrhea.

In a study by Vitek and colleagues,	extsuperscript{80} 36 patients were randomly selected to receive medical therapy (n = 18) or unilateral pallidotomy (n = 18). After 6 months' follow-up, patients who received pallidotomy had a significant reduction (32%) in total UPDRS scores compared with those in the medical treatment group, whose scores slightly increased. LID was reduced by 75% contralateral and...
by 36% ipsilateral to the ablative lesion in patients who underwent pallidotomy; LID increased slightly in the control group.

Complications occurred in 3 patients: 1 experienced definite focal motor seizures, a second had possible complex partial seizures, and a third had a subcortical hemorrhage causing dysarthria that resolved by the 6-month follow-up visit. Three other patients had small asymptomatic hemorrhages detected on postoperative MRI.

Deep brain stimulation. DBS was first introduced in 1987 by Benabid and colleagues, who targeted the thalamic nucleus ventralis intermedius to treat PD. Since that time, DBS has largely replaced ablative procedures for the treatment of movement disorders, including PD, essential tremor, dystonia, and Tourette syndrome. The dramatic shift in the surgical management of movement disorders has led to a proliferation of centers offering DBS and brought with it concerns about the safety of DBS surgery. At Baylor College of Medicine, we reviewed medical records of 319 patients who underwent DBS for a variety of movement disorders to provide information about short-term and long-term complications.

Although a sizable number (43.3%) of patients experienced some type of adverse effect, most DBS-related adverse effects (such as headache or confusion) were benign and transient. Some patients, however, developed more serious adverse effects, such as dysarthria, worsening gait, or cognitive dysfunction. In the patient population whose medical records we studied, serious vascular events were uncommon, occurring in 5 patients (1.6%): 2 intracerebral hemorrhages, 2 intraventricular hemorrhages, and 1 subdural hematoma.

In large DBS patient populations, seizures are reported in 0.9% to 9.1% and infection in 3.7% to 6.5%.

Our complication rates for these 2 adverse events compare favorably—1.2% and 4.4%, respectively; 42.8% of infections were minor and easily eradicated with antibiotics. One patient (0.3%) committed suicide, a complication reported to be as frequent as 4.3% in this population.

Investigators have reported a hardware-related complication (lead fracture, lead migration, electrode dysfunction, and infections) rate of 4.3% to 8.4% per electrode-year. Using a similar method, our hardware-related complication rate was lower than average: 2.5% per electrode-year.

As with ablation, most published studies of DBS are open-label. This literature supports the idea that DBS improves LID by 30% to 90%, with most reports in the 60% to 70% range. In a review article on STN DBS, Kleiner-Fisman and colleagues found the average reduction of LID to be 69.1% (95% confidence interval, 62.0% to 76.2%). Bilateral stimulation appears to be superior to unilateral stimulation, but not twice as effective.

Some reports indicate that DBS of the STN improves dyskinesia better than that of the GPi, while others indicate that DBS of the GPi may be slightly more effective.

Despite the fact that fewer publications deal with DBS of the GPi, certain investigators favor GPi specifically for patients with more severe dyskinesia. DBS of the STN typically allows for a 50% reduction in the use of levodopa equivalents, a phenomenon not associated with DBS of the GPi. On the other hand, adverse effects, including cognitive deterioration, are reported less frequently with DBS of the GPi.

Among the controlled studies of DBS completed to date are those of Limousin and colleagues, Burchiel and colleagues, the Parkinson's Disease Study Group, and Deuschl and colleagues. Limousin and colleagues used a randomized stimulation design in patients with PD that focused on STN DBS. Patients, but not examiners, were blind to the treatment. In contrast to all other studies in the literature, this study found no significant change (30%) in dyskinesia before or after surgery. Burchiel and colleagues selected 9 patients at random to undergo GPi (n = 4) or STN (n = 5) and found that STN improved LID by 67% and GPi by 47%. The DBS for Parkinson's Disease Study Group performed a prospective, double-blind, crossover (stimulation off/on) study with 134 patients (STN DBS, 96; GPi DBS, 38). STN stimulation reduced on-state dyskinesia by 70%; GPi stimulation reduced on-state dyskinesia by 66%.

Deuschl and colleagues randomly selected 156 patients with advanced PD to receive either STN DBS or medical management in an unblinded fashion. LID did not change appreciably in the medical management but decreased 54% in the STN DBS cohort.

Ablation versus DBS. Only a limited number of studies have attempted to systematically compare DBS with ablation. Merello and colleagues prospectively selected 13 patients at random to receive either unilateral pallidotomy or unilateral GPi DBS. UPDRS scores and activities of daily living improved equally, but pallidotomy reduced LID to a greater degree (P < .05). Esselink and colleagues compared unilateral pallidotomy with bilateral STN DBS in a randomized, observer-blind, multicenter trial. The improvement in UPDRS scores and the duration of dyskinesia were greater in patients receiving STN DBS than in those receiving pallidotomy, but an equal

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improvement in the severity of dyskinesia was seen in both groups. The number of adverse effects was approximately the same in both groups.

In another study, Esselink and collaborators\textsuperscript{114} randomly assigned 34 patients to unilateral pallidotomy or bilateral STN stimulation. Patients receiving STN DBS responded better as reflected in the UPDRS motor score and Schwab and England functional scale measurements. LID improved equally in both groups, with 1 severe adverse event in each.

Blomstedt and colleagues\textsuperscript{115} recently argued that pallidotomy should be considered first-line treatment in patients in whom dyskinesia or dystonia is the dominant symptom, but they base this conclusion on a report of a small study cohort (n = 5). Overall, the effectiveness of the DBS and pallidotomy is similar, but the safety of DBS is generally considered to be superior. Treatment decisions must be based on individual patient needs while taking into consideration availability of resources and the experience of the surgical staff.

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