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From medications to surgery: advances in the treatment of motor complications in Parkinson's disease.

Kanae Nagao

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REVIEW

From medications to surgery: advances in the treatment of motor complications in Parkinson’s disease

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Abstract
Motor complications are responsible for the large burden of disability and poor quality of life in Parkinson’s disease (PD). The pulsatile nature of stimulation with oral dopaminergic therapies due to relatively short pharmacokinetic profiles and dysfunctional gastrointestinal absorption have been attributed to the development of PD motor complications. In this review, we will provide an overview of the pharmacologic and surgical therapies currently available and under investigation for the treatment of motor fluctuations and dyskinesia.

Keywords: Parkinson’s disease, levodopa, therapy, deep brain stimulation.

Citation

Introduction
Parkinson’s disease (PD) affects more than 6 million people worldwide with an increasing prevalence predicted to exceed 9 million by the year 2030. L-Dopa (3,4-dihydroxy-L-phenylalanine) has revolutionized the treatment of PD since its introduction in the 1960s, and it remains the gold standard for symptomatic management of the cardinal motor symptoms throughout the course of disease. L-Dopa crosses the blood–brain barrier, where it is converted to dopamine by the enzyme DOPA-decarboxylase. Reduction in the motor symptoms of PD is attributed to increasing dopamine concentrations in the central nervous system or stimulating dopamine receptors in the basal ganglia using dopamine agonists. However, the beneficial effects of dopaminergic agents will decline over time, resulting in an increasing frequency of rapid and, at times, unpredictable cycling between good therapeutic response (“on” phenomenon) and poorly controlled symptoms (“off” phenomenon) that are called motor fluctuations.

The various manifestations of L-Dopa-associated motor complications include early “wearing off” of symptom control between doses, prolonged latency to therapeutic effect, unpredictable abrupt loss of benefit (sudden “on-off” phenomena), unexpected dose failures, and/or troublesome dyskinesias. Dyskinesias are involuntary movements, often choreiform, that occur either at “peak-dose” concurrent with maximal therapeutic effect or are “diphasic,” occurring at the beginning or end of dose when plasma L-Dopa is within subtherapeutic ranges. Up to 40% of PD patients experience motor fluctuations and more than one-third experience dyskinesias within 4–6 years of diagnosis. Risk factors include young age of onset, longer disease duration, and greater disease severity. Motor fluctuations were initially believed to reflect variable striatal L-Dopa bioavailability in the context of declining dopamine storage in nigrostriatal terminals and unpredictable oral L-Dopa absorption. However, the occurrence of fluctuations with dopamine agonists suggests that post-synaptic pharmacodynamic factors may also play a role. This is further supported by clinical observations of reduced dyskinesias and motor fluctuations with deep brain stimulation (DBS) and continuous infusion therapies, suggesting that the pulsatile nature of dopaminergic stimulation from conventional oral therapies may alter the firing patterns within the neuronal networks of the basal ganglia.

As PD progresses, motor complications become a major source of disability and reduced quality of life. Thus, treatment of these has been a major focus of therapeutic advancements in PD over the past decade. This review will serve as a guide to understand the newer pharmacologic and surgical therapies that are currently available and in the pipeline for development to treat PD motor complications. Discussion will be focused...
Table 1. Pharmacokinetic profiles of levodopa therapies currently available in the US and Europe.

<table>
<thead>
<tr>
<th>Drug Formulation</th>
<th>T½ (h)</th>
<th>Cmax (ng/mL)</th>
<th>Tmax (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DDI-LD immediate release</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–100 mg Controls</td>
<td>1.53 [1.4–1.9]</td>
<td>1047 [850–1210]</td>
<td>0.94 [0.58–1.0]</td>
</tr>
<tr>
<td>Mild and moderate PD</td>
<td>1.51 (SEM 0.07)</td>
<td>2080 (SEM 354)</td>
<td>0.78 (SEM 0.22)</td>
</tr>
<tr>
<td>Mild–advanced PD</td>
<td>1.35 (CV 23.7)</td>
<td>1484 (CV 26)</td>
<td>1.00 [0.5–4]</td>
</tr>
<tr>
<td>25–250 mg Controls</td>
<td>–</td>
<td>1760±690</td>
<td>1.02±0.80</td>
</tr>
<tr>
<td>Mild PD</td>
<td>–</td>
<td>1490±80</td>
<td>1.23±0.34</td>
</tr>
<tr>
<td>Moderate PD</td>
<td>–</td>
<td>1350±100</td>
<td>1.25±0.25</td>
</tr>
<tr>
<td>Advanced PD</td>
<td>–</td>
<td>1560±100</td>
<td>1.14±0.29</td>
</tr>
<tr>
<td><strong>CD-LD-controlled release</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–100 mg Controls</td>
<td>1.6±0.2</td>
<td>855±299</td>
<td>1.5 [1.0–2.0]</td>
</tr>
<tr>
<td>Mild PD</td>
<td>1.7±0.3</td>
<td>887±355</td>
<td>1.3±0.6</td>
</tr>
<tr>
<td>50–200 mg Controls</td>
<td>1.9±0.4</td>
<td>1282±454</td>
<td>1.8±0.9</td>
</tr>
<tr>
<td>Mild PD</td>
<td>–</td>
<td>263 (SEM 35.92)</td>
<td>2.82 (SEM 0.27)</td>
</tr>
<tr>
<td><strong>DDI-LD-entacapone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–100–200 mg Controls</td>
<td>1.81 [1.6–2.1]</td>
<td>951.5 [720–1040]</td>
<td>1.22 [0.75–1.5]</td>
</tr>
<tr>
<td>Mild–moderate PD</td>
<td>2.00 (0.12 SEM)</td>
<td>1490 (SEM 110)</td>
<td>1.17 (SEM 0.24)</td>
</tr>
<tr>
<td>37.5–150–200 mg Controls</td>
<td>–</td>
<td>1090±310</td>
<td>0.90±0.5</td>
</tr>
<tr>
<td>Mild–moderate PD</td>
<td>–</td>
<td>257.2 (SEM 27.52)</td>
<td>2.33 (SEM 0.09)</td>
</tr>
<tr>
<td>Moderate–advanced PD</td>
<td>–</td>
<td>1926±760</td>
<td>2.03±0.98</td>
</tr>
<tr>
<td><strong>DDI-LD-opicapone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>2.47 (CV 33.7)</td>
<td>1203 (CV 37.7)</td>
<td>1.00 [0.5–3.0]</td>
</tr>
<tr>
<td>50 mg</td>
<td>2.50 (CV 15.7)</td>
<td>1030 (CV 38.8)</td>
<td>0.75 [0.5–3.0]</td>
</tr>
<tr>
<td>75 mg</td>
<td>2.39 (CV 23.3)</td>
<td>1057 (CV 31.7)</td>
<td>1.50 [0.5–2.0]</td>
</tr>
<tr>
<td>Mild–advanced PD</td>
<td>1.67 (CV 24.9)</td>
<td>1868 (CV 31.8)</td>
<td>1.00 [0.5–2.0]</td>
</tr>
<tr>
<td>5 mg</td>
<td>1.78 (CV 31.2)</td>
<td>1806 (CV 28.4)</td>
<td>0.75 [0.5–2.0]</td>
</tr>
<tr>
<td>30 mg</td>
<td>2.16 (CV 36.5)</td>
<td>2584 (CV 33.7)</td>
<td>0.50 [0.5–3.0]</td>
</tr>
<tr>
<td><strong>CD-L-Dopa capsule</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>1.5±0.3</td>
<td>317±90.3</td>
<td>2.8 [0.5–5]</td>
</tr>
<tr>
<td>23.75–95 mg</td>
<td>1.4±0.2</td>
<td>491±125</td>
<td>2.8 [0.5–5]</td>
</tr>
<tr>
<td>36.25–145 mg</td>
<td>1.5±0.6</td>
<td>630±187</td>
<td>4.0 [0.5–5]</td>
</tr>
<tr>
<td>48.75–195 mg</td>
<td>1.5±0.3</td>
<td>763±156</td>
<td>3.5 [0.5–5]</td>
</tr>
<tr>
<td>61.25–245 mg</td>
<td>1.9±0.7</td>
<td>1326±268</td>
<td>4.5 [0.5–8]</td>
</tr>
<tr>
<td>97.5–390 mg</td>
<td>–</td>
<td>4210±1360</td>
<td>2.85±2.31</td>
</tr>
<tr>
<td><strong>AP-CD-LD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>5.15</td>
<td>1951</td>
<td>4.67</td>
</tr>
<tr>
<td>50–500 mg</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>LCIG 16-hour infusion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced PD</td>
<td>5.15</td>
<td>1951</td>
<td>4.67</td>
</tr>
<tr>
<td>mean CD 395±101 mg</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>LD 1580±403 mg daily</td>
<td>–</td>
<td>4210±1360</td>
<td>2.85±2.31</td>
</tr>
</tbody>
</table>

(Continued)
on therapies that have completed phase II clinical trials in PD patients.

**Levodopa: old becomes new**

Carbidopa (CD) or benserazide is combined with L-Dopa to reduce its peripheral conversion to dopamine by inhibiting DOPA-decarboxylase, thereby improving L-Dopa bioavailability. Clinically, this reduces the side effects of L-Dopa-associated nausea and vomiting. Immediate-release (IR) L-Dopa is the most readily available formulation worldwide; however, its short-acting pharmacokinetics results in unstable plasma L-Dopa concentrations. Peak plasma concentrations are reached within 1 hour of oral administration but drop to less than 10% by 5 hours in healthy adults. Another potential variable influencing L-Dopa bioavailability may be gastrointestinal hypomotility, a common nonmotor symptom of PD.

Measures to overcome inconsistent L-Dopa bioavailability led to the early development of longer-acting formulations. Early formulations of controlled-release (CR) L-Dopa (Sinemet CR, Merck & Co, Whitehouse Station, NJ, USA) and a single tablet CD-L-Dopa combined with entacapone (CLE), a peripheral inhibitor of the catechol-O-methyltransferase (COMT) (marketed as Stalevo, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA), were developed to increase the duration of effect and peak plasma concentrations of L-Dopa, respectively. However, CLE only demonstrated a modest increase in L-Dopa half-life by 0.5–0.7 hours in PD patients, and both CLE and L-Dopa CR showed a large degree of intersubject variability in pharmacokinetics. Development of better, more consistent, and reliable long-acting formulations of L-Dopa remains a priority for drug development (Table 1).

**Carbidopa–levodopa capsule**

CD-L-Dopa Capsule (Rytary, Impax Laboratories, Hayward, CA, USA) is a dual-release formulation of immediate- and extended-release CD-L-Dopa beads in a single capsule that was recently approved for use in the United States (US) and select countries. Similar to IR L-Dopa, CD-L-Dopa capsule achieved initial peak plasma L-Dopa concentration within 1 hour; however, these concentrations were sustained for up to 4–5 hours in healthy volunteers. Furthermore, CD-L-Dopa capsule lasted 2.5 hours longer than the two other existing long-acting formulations (L-Dopa CR and CLE).

CD-L-Dopa capsule provided greater on time without troublesome dyskinesias compared to IR L-Dopa reflective of a smoother pharmacokinetic profile. In a phase III clinical trial, an average of 3.6 doses of CD-L-Dopa capsule was used per day compared to 5 doses in the IR group. However, anecdotally, this medication may need to be prescribed more frequently to achieve stable “on” time in advanced PD. Common adverse effects were insomnia, nausea, dizziness, falls, and dyskinesia with similar incidence to the IR L-Dopa cohort.

**DM-1992**

DM-1992 is a novel long-acting L-Dopa, currently under investigation. It consists of an IR L-Dopa layer and a novel expanding core of extended-release L-Dopa that is retained in the stomach for 8–9 hours, resulting in a more stable pharmacokinetic profile. One study crossing over PD patients from IR L-Dopa to DM-1992 demonstrated a reduction in “off” time by 1 hour. Worsening Parkinsonian gait and dizziness were common in the DM-1992 arm, but there were no significant differences in types of adverse effects seen compared to IR L-Dopa.

**AP-CL-LD**

The Accordion Pill (AP-CD-LD; Intec Pharma, Inc, New York, NY, USA) is another novel slow-release preparation of L-Dopa that is currently under investigation. This medication comprises multiple layers of CD combined with both IR and CR L-Dopa that is retained in the stomach for 12–14 hours. In healthy controls and PD patients, AP-CD-LD provides less fluctuant plasma L-Dopa levels compared to IR L-Dopa. In phase II trials, there was significant clinician and patient-rated symptom improvement and greater non-troublesome “on” time compared to traditional oral L-Dopa therapy (IR or CR). Up to a 25% reduction in the total, daily L-Dopa dose was also reported. A phase III randomized trial comparing AP-CD-LD with IR L-Dopa was also reported.
was recently completed; however, results have not been published.24

**Levodopa adjuvant therapies**

Another strategy to increase the peak plasma concentrations and duration of action of L-Dopa is by slowing its metabolism. Adjunctive medications such as COMT inhibitors and monoamine oxidase B (MAO-B) inhibitors can be used to prolong L-Dopa’s therapeutic effects by interfering with dopamine and L-Dopa metabolism, respectively.35,36

As previously discussed, COMT inhibitors prolong L-Dopa bioavailability and can delay the increase in dose frequency. Although it only provides an average of 0.8 hours increase in on time, entacapone is currently the most commonly used COMT inhibitor (Figure 1).37 Although entacapone only acts peripherally, tolcapone is another COMT inhibitor that acts both centrally and peripherally38 and improves “on” time by 1.8 hours (Figure 1).39 Despite its superiority over entacapone, its use has been restricted in the US due to the adverse effects of fulminant hepatotoxicity.40–42

MAO-B inhibitors selectively decrease the metabolism of striatal dopamine without causing tyramine-induced hypertension response typical of MAO-A inhibitors.43 Selegiline and rasagiline are the two most commonly prescribed MAO-B inhibitors that are used as either mono- or adjunctive therapy to L-Dopa.44–48 In one study, utilizing rasagiline or entacapone as an adjunct to L-Dopa, comparable increases in “on” time without troublesome dyskinesias were observed at 0.85 hours (Figure 1).46 Thus, development for more potent therapies to augment L-Dopa metabolism is needed.

**Opicapone**

Opicapone is a third-generation, selective, peripherally acting, once-daily COMT inhibitor.49,50 It was approved for use in Europe in 2016 and is currently under investigation in the US. At the recommended dose of 50 mg daily of opicapone, L-Dopa bioavailability is significantly higher than that achieved by entacapone.50 Unfortunately, opicapone’s pharmacokinetic superiority was not mirrored in clinical trials. Two phase III studies demonstrated only modest increase in “on” time without troublesome dyskinesias when compared to placebo,51,52 and no significant difference when compared to entacapone (Figure 1).51 Opicapone was well tolerated with discontinuation primarily attributed to dopaminergic side effects of dyskinesias, hallucinations, and orthostatic

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**Figure 1.** Increase in daily “on” time without troublesome dyskinesia. This figure summarizes the data from randomized controlled trials, as it relates to improvement of “on” time without troublesome dyskinesias. Statistical analysis between investigational therapy and best medical therapy is designated by the following p-values: a: p<0.05; b: p<0.01; c: no p-value available. N.S. not significant.
hypotension. Treatment emergent dyskinesias were reported as an adverse effect more frequently with 50 mg opicapone compared to entacapone. Other adverse effects included constipation and dry mouth.

**Safinamide**

Safinamide is a highly selective, reversible MAO-B inhibitor available in the US and select countries, with proposed antidyskinetic effects due to reduction in glutamate transmission. Safinamide was primarily studied as an adjunct to L-Dopa with only a slight increase in daily on time without troublesome dyskinesias, to a magnitude similar to rasagline (Figure 1). Although there are no head-to-head studies directly comparing the three MAO-B inhibitors and entacapone, Binde and colleagues performed a meta-analysis of 27 published trials demonstrating that safinamide was inferior to both rasagline and selegiline and had comparable efficacy to entacapone. Furthermore, the antidyskinetic effects observed in primate models were not replicated in human studies.

**Infusion therapies**

The goal to achieve stable plasma concentrations of L-Dopa prompted the development of infusion therapies. Several therapies discussed in this section have been utilized in Europe for many years and have only recently been investigated and approved in the US.

**Levodopa-carbidopa intestinal gel**

Levodopa-carbidopa intestinal gel (LCIG) infusion provides continuous jejunal infusion. Although it has been used for 15 years outside the US, it was approved in the US only in 2015. An external pump delivers L-Dopa continuously over 16 hours during the waking day via a percutaneous gastrojejunostomy tube (PEG-J). This provides more stable therapeutic plasma L-Dopa concentrations compared to oral IR preparations. LCIG increased “on” time without troublesome dyskinesias by almost 2 hours (Figure 1) and patients utilized less rescue doses of L-Dopa compared to the IR L-Dopa cohort at 12 weeks in a phase III trial. Significant improvements in quality of life, activities of daily living, and non-motor symptoms have been reported. Additionally, more than one-third of patients were able to utilize LCIG as monotherapy.

Despite these advantages, a barrier to widespread use is long-term device or procedure-related complications such as infection, tube dislocations, stoma complications, peritonitis, and pneumoperitoneum, which occurred in almost 70% of patients in an open-label prospective study. Of note, most gastrointestinal and procedural adverse events occurred within the first 2 weeks postoperatively. Finally, LCIG has an increased risk of polyneuropathy. Although the exact pathophysiology is unknown, vitamin B12 deficiency has been implicated, warranting regular monitoring and B12 supplementation.

**Subcutaneous apomorphine infusion**

Apomorphine is a dopamine agonist acting on postsynaptic dopamine receptors to improve the motor symptoms of PD. Subcutaneous apomorphine infusions have been used for more than a decade with good effect outside the US and is currently in clinical trials in the US. A randomized, double-blind study of 16-hour daily infusion demonstrated similar improvements in “on” time to LCIG (Figure 1), allowing patients to reduce their daily levodopa equivalent medication by more than 300 mg. Skin nodules, nausea, and somnolence were the most commonly experienced adverse effects. Uncommon but serious treatment-related adverse effects included severe hypotension, nonhemolytic anemia, leucopenia, hallucinations, confusion, and infusion-site cellulitis. However, long-term apomorphine infusions may not be well tolerated. In a 10-year observational study, two-thirds of patients ceased therapy after an average 17.9 months. Discontinuation was primarily attributed to neuropsychiatric complications such as hallucinations, impulse control disorder, and dopamine dysregulation.

**ND-0612**

A subcutaneous CD-DLD infusion is currently under investigation with promising results. Preliminary pharmacokinetic studies demonstrated stable plasma L-Dopa concentrations in healthy and PD subjects, with up to 2 hours reduction in “off” time compared to optimal oral therapy. Oral L-Dopa intake was reduced by an average of 80% with 3 of 16 subjects achieving monotherapy. A study comparing 24-hour versus 14-hour daytime infusions found that running the infusion overnight led to significant improvements in sleep quality and early-morning motor symptoms. Similar to subcutaneous apomorphine, subcutaneous nodules occurred.

**Rapid-acting therapies**

Rapid-acting medications serve as a bridge for symptom control to address unpredictable “off” periods, dose failures, and prolonged latency to oral L-Dopa effectiveness. Subcutaneous apomorphine can be administered as a single-dose injection that improves early-morning akinesia and “off” periods by 95%. This medication is relatively fast acting with an onset of effect within 10–24 minutes. However, its use is limited by intolerable side effects of nausea, somnolence, dizziness, and orthostatic hypotension, with one-third of patients discontinuing this therapy by 12 months due to these. Another rapid-acting therapy available outside the US is dispersible benserazide-L-Dopa. Its clinical efficacy is limited, as it appears to take almost 20 minutes longer than subcutaneous apomorphine to take effect.
Levodopa inhaled powder

L-Dopa inhaled powder (LDIP) (Inbrija, Accorda Therapeutics, Ardsley, NY, USA) is a dry powder formulation administered by a breath-actuated device recently approved in the US. Rapid absorption of L-Dopa through the pulmonary epithelium allows PD patients to achieve peak plasma L-Dopa concentration within 15 minutes of inhalation. However, in clinical trials, significant improvements in motor symptoms only occurred at 30 minutes of using the highest studied dose of 84 mg. The most common side effect was a non-dose-dependent cough, occurring within the first month of treatment. Other respiratory side effects include upper respiratory tract infections, discolored sputum, and throat irritation; however, no short-term detrimental effects on lung function were noted in patients using up to 5 doses per day. Although infrequent but serious adverse effects of hypotension and atrial fibrillation occurred, LDIP was well tolerated in most patients.

APL-130277

Sublingual apomorphine was first introduced in 1989 with comparable symptomatic effects to subcutaneous administration. However, early sublingual preparations were impractical due to a prolonged dissolving time. APL-130277 is a novel bilayer film that achieves a full on state within 15–30 minutes of administration with an average duration of 50 minutes. Similar to the subcutaneous formulation, common side effects were dizziness, somnolence, yawning, and nausea. Although orthostatic hypotension, dyskinesias, and hallucinations rarely developed, one-third of patients developed lip or oropharyngeal swelling and oral mucosal erythema, which lead to discontinuation.

Dyskinesias

Dyskinesias are another source of significant disability and reduced quality of life. Up to 40% of patients treated with L-Dopa will develop dyskinesias within 5 years, and all PD patients are expected to develop dyskinesias by 20 years if treated with dopaminergic medications. Altered striatal glutamate receptor trafficking, secondary to nigrostriatal dopamine depletion and pulsatile exogenous L-Dopa stimulation, has been implicated in the development of dyskinesias. Amantadine, a non-competitive NMDA receptor inhibitor, has been the primary medication used to treat dyskinesias; however, dose-dependent side effects of hallucinations, dry eye, dry mouth, constipation, and cognitive dysfunction limits use. Furthermore, the long-term effectiveness of dyskinesia suppression by amantadine has been inconsistent in randomized, double-blind studies, which warrants further drug development targeting this symptom of PD.

Amantadine ER

Amantadine ER (Gocovri, Adams Pharmaceuticals, Inc, Emeryville, CA, USA) is an extended-release once-daily formulation that is currently available in the US and select countries. At the recommended dosage of 274 mg nightly, average daytime plasma amantadine concentrations are 1.4–2.0-fold higher than IR and slowly reach peak plasma concentration by 12–16 hours. In a 12-week clinical trial, Amantadine ER achieved an 18% reduction in dyskinesias resulting in 2.8 hours of increased “on” time without troublesome dyskinesia compared to placebo. However, similar to IR amantadine, side effects of hallucinations, confusion, peripheral edema, constipation, dry mouth, and dizziness occurred, of which hallucinations were the most common reason for discontinuation.

Istradefylline

Istradefylline is a selective adenosine A2A receptor antagonist approved for adjunctive treatment of motor fluctuations in PD in Japan. It was hoped that this therapy would control motor fluctuations without worsening dyskinesias, as it has no direct dopaminergic action, and it acts by modulating striatopallidal GABAergic output neurons. However, only a modest 0.7-hour reduction in daily “off” time was observed in two randomized clinical trials, while a third randomized placebo-controlled trial did not demonstrate statistically significant improvement over placebo. Although only mild to moderate in severity, dyskinesias were more prevalent in the therapy arms. Despite these equivocal results in clinical trials, a post-marketing surveillance study of 476 Japanese patients reported improvements in “off” time in approximately 40% of patients. The most commonly reported adverse effects were dyskinesias and hallucinations.

As the disease progresses, PD patients will frequently require adjustments of their medication regimen, often using multiple agents in combination. Maintenance of stable on time without troublesome dyskinesia will become more challenging over time, often limited by the development of intolerable side effects. Consideration of the mechanisms of action, pharmacokinetic profiles, and common adverse effects can guide the physician to adjust therapies to optimize PD symptom control. Selection of the appropriate agent(s) to address motor fluctuations should also include evaluation of the patient’s medical comorbidities and goals of care to avoid exacerbation of neuropsychiatric and cognitive complications.

Neurosurgical interventions

Deep brain stimulation

DBS is a surgically implanted device, which significantly reduces L-Dopa-associated motor complications by delivering continuous stimulation to deep structures of the brain through surgically implanted intracranial electrodes. It is indicated in PD patients who cannot achieve satisfactory control of L-Dopa responsive motor symptoms using medical therapy.
Motor fluctuations, dyskinesias, and classic PD tremor are the symptoms most responsive to DBS. Open-label studies comparing DBS to L-Dopa and subcutaneous apomorphine infusions have demonstrated superior control of dyskinesia and less procedure or device-related complications. DBS is a relatively low-risk procedure given the potential benefit. Common complications are associated with the surgical procedure and/or hardware and include wound infections or erosions, lead migration/malposition, lead or extension fractures and component malfunction. A 1.3% risk of symptomatic intracerebral hemorrhage was found across pooled data from three large case series conducted between 1993 and 2010. However, STN stimulation often amplifies dyskinesias during the initial phases of programming and has been associated with increased risk of cognitive and psychiatric complications. Conversely, GPI stimulation tends to have less negative impact on mood and cognitive processing and greater reduction in dyskinesia. The disadvantage of GPI is that it often requires higher stimulation parameters to achieve comparable therapeutic response and rarely allows for reduction in dopaminergic therapies. Therefore, target selection is individualized to features of the PD phenotype, patient-specific goals for treatment, and careful consideration of comorbidities.

The exact mechanism of action for DBS in the treatment of PD motor fluctuations is unknown. Modulation of pathological neuronal firing patterns within the corticobasal ganglia networks is hypothesized to improve PD motor symptoms. Compared to best medical therapy, DBS improves “on” time without troublesome dyskinesias by a magnitude of 4.6–5 hours, with more than two-thirds of advanced PD patients achieving meaningful improvements in motor fluctuations with either STN or GPI DBS by 6 months. Although the magnitude of benefit declines over time, these positive effects on PD motor symptoms and fluctuations have been reported to last greater than 10 years in several long-term studies. This is far beyond the clinical responses achieved by oral pharmacologic and infusion therapies.

Unfortunately, the beneficial effects of DBS begin to wane beyond 5 years. Although initially, patients’ stimulation requirements have been shown to increase as the disease progresses, there are limited studies reporting on motor outcomes beyond 10 years. Anecdotally, patients continue to require incremental increases in stimulation in combination with adjustment of medications. Although dyskinesias often remain controlled with DBS, the cycling between “on” and “off” motor states and decline in motor function begin to recur with time. This has been attributed to disease progression and development of stimulation and L-Dopa resistant symptoms such as postural instability and non-motor symptoms. This warrants the additional utilization of longer-acting formulations or continuous infusions as discussed earlier to provide additional benefits for the treatment of motor complications in advanced PD patients with DBS.

There are limitations to the therapeutic effects of DBS. The beneficial effects of DBS are dependent on the accurate placement of electrodes within the targeted structure. Simulation of unintended neighboring regions induces side effects such as speech disturbance, gait impairment, paraesthesia, and diplopia that may limit therapy optimization. Novel mechanisms for stimulation delivery are being developed to improve the clinical benefit of DBS.

**Advances in deep brain stimulation technology**

**Directional stimulation**

Conventional DBS electrodes use cylindrical contacts to generate a spherical electrical field that activates a large region of brain tissue. Devices utilizing segmented electrodes, more electrode contacts, and independent current sources enable programmers to shape the electric field toward therapeutic regions and away from regions causing side effects (Figure 2). In this manner, a wider therapeutic window can be achieved compared to traditional DBS electrodes by reducing stimulation-related adverse effects that often limit programming.

**Adaptive/closed-loop DBS**

The fluctuant nature of PD motor symptoms is challenging to treat, especially as the disease advances. To address this variability, adaptive DBS (aDBS) is being developed to provide more precise stimulation delivery when needed. This closed-loop system integrates real-time feedback, as it relates to the patient’s clinical state ("on" versus "off"). It is hypothesized to provide better control of motor fluctuations than conventional high-frequency stimulation. By interpretation of biomarkers, individualized and variable stimulation will be provided during times of poor symptom control through the use of algorithmic models. Potential advantages of aDBS are minimization of stimulation-related side effects, reduction of long-term tolerance to stimulation, and prolongation of battery life. Several potential biomarker signals are being considered for aDBS. The most promising are local field potentials (LFP), which reflect synchronous neuronal network activity and are collected through the DBS electrode. Bradykinesia and rigidity in the “off” state have been correlated with excessive
synchronization of beta frequency oscillations within
corticobasal ganglia networks.\textsuperscript{138-140} These oscillations are
suppressed when a patient is treated with either L-Dopa or
DBS.\textsuperscript{114,129,131,132} Preliminary studies have correlated suppression
of beta frequency oscillations with reduced bradykinesia,
rigidity, and freezing of gait in PD patients.\textsuperscript{132-135}

Initial aDBS models have proved promising and warrant
further investigation. A proof-of-concept study using LFP
beta band activity coupled with adaptable stimulation
showed a 27% greater mean improvement in motor
symptoms using aDBS compared to conventional DBS in
eight PD patients.\textsuperscript{126}

**Conclusions**

In summary, there are several exciting developments for the
treatment of PD motor complications. Treatment of PD is
individualized, taking into consideration factors such as the
nature of motor complications (fluctuations between “on” and
“off” versus dyskinesias), comorbidities, and cost to patient when
optimizing a patient’s motor symptom control. Strategies such
as infusion therapies and DBS may be cost effective for the
treatment of long-term PD motor complications. Nonetheless,
there remains a significant portion of “off” time and dyskinesias
in patients treated with continuous therapies including DBS,
suggesting alternate non-dopaminergic mechanisms that
require further investigation.

Development of disease-modifying therapies that either slow or arrest disease progression before the onset of motor
complications will be the ultimate therapeutic strategy for the
treatment of PD. In the last few years, several disease-modifying
agents have entered into phase I and phase II clinical trials. The
therapeutic targets being investigated include gene-specific
enzymatic dysfunction such as glucocerebrosidase and LRRK
2 kinase, alpha synuclein toxicity, mitochondrial dysfunction,
and neuroinflammation.\textsuperscript{156,157} Infusion of pluripotent and
human embryonic stem cells for targeted regeneration
dopaminergic neurons are also being studied in small
populations.\textsuperscript{138}

It is becoming apparent that a single panacea treatment of
PD is unlikely and that past failures in disease-modifying
studies may be attributed to the heterogeneous nature of
PD.\textsuperscript{139} Thus, studies targeting specific sub-populations of
PD for individualized treatment are needed.\textsuperscript{139} Although
we eagerly await a breakthrough in disease modification,
Improved control of motor complications remains a priority
for patient care.

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**Figure 2.** Comparison of commercially available deep brain stimulation electrodes. This figure shows the four
electrodes commercially available for implantation with representation of the electrical fields generated
by utilizing the conventional cylindrical contacts compared to segmented contacts. All electrode
contacts are 1.5 mm in width. St Jude’s Abbott utilizes 1.5 mm spacing between contacts, whereas Boston
Scientific utilizes 0.5 mm spacing. Medtronic offers both 0.5 mm spacing (3389 electrode) and 1.5 mm
spacing (3387 electrode), which is shown below.
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