REVIEW

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

Dr. Kanae Jennifer Nagao MBBS (Hons), FRACP, Neepa J Patel MD

Department of Neurology, Henry Ford Health System, West Bloomfield, Michigan, USA

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.

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.[1,2] 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.[3,4] 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.[5] 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.[6–8]

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.[9,10] 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.[11]

Up to 40% of PD patients experience motor fluctuations and more than one-third experience dyskinesias within 4–6 years of diagnosis.[8] Risk factors include young age of onset, longer disease duration, and greater disease severity.[8,12,13]

Motor fluctuations were initially believed to reflect variable striatal L-Dopa bioavailability in the context of declining dopamine storage in nigrostriatal terminals[14] and unpredictable oral L-Dopa absorption.[15,16] However, the occurrence of fluctuations with dopamine agonists suggests that post-synaptic pharmacodynamic factors may also play a role.[7,17] This is further supported by clinical observations of reduced dyskinesias and motor fluctuations with deep brain stimulation (DBS) and continuous infusion therapies,[18] 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.[6,10]

As PD progresses, motor complications become a major source of disability and reduced quality of life.[9,19,20] 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.

	$T_{1/2}$ (h)	C_{max} (ng/mL)	T_{max} (h)
DDI-LD immediate release			
25–100 mg			
Controls[22,50,140–142] (n=75–77)	1.53 [1.4–1.91][d]	1047 [850–1210][d]	0.94 [0.58–1.0][d]
Mild and moderate PD[143] (n=8)	1.51 (SEM 0.07)	2080 (SEM 354)	0.78 (SEM 0.22)
Mild–advanced PD[49] (n=10)	1.35 (CV 23.7)	1484 (CV 26)	1.00 [0.5–4] [d]
25–250 mg			
Controls[141] (n=14–16)	–	1760±690	1.02±0.80
Mild PD[144] (n=10)	–	1490±80	1.23±0.34
Moderate PD[144] (n=8)	–	1350±100	1.25±0.25
Advanced PD[144] (n=13)	–	1560±100	1.14±0.29
CD-LD-controlled release			
25–100 mg			
Controls[22] (n=23)	1.6±0.2	855±299	1.5 [1.0–2.0][d]
Mild PD[145] (n=9)	1.7±0.3	887±355	1.3±0.6
50–200 mg			
Mild PD[145] (n=9)	1.9±0.4	1282±454	1.8±0.9
Mild and moderate PD[146] (n=13)	–	263 (SEM 35.92)	2.82 (SEM 0.27)
Moderate–advanced PD[25] (n=17)	–	1840±889	2.4±1.02
DDI-LD-entacapone			
25–100–200 mg			
Controls[22,50,140,141] (n=64–66)	1.81 [1.6–2.11][d]	951.5 [720–1040][d]	1.22 [0.75–1.5][d]
Mild–moderate PD[143] (n=8)	2.00 (0.12 SEM)	1490 (SEM 110)	1.17 (SEM 0.24)
37.5–150–200 mg			
Controls[141] (n=14–16)	–	1090±310	0.90±0.5
Mild–moderate PD[146] (n=13)	–	257.2 (SEM 27.52)	2.33 (0.09 SEM)
Moderate–advanced PD[25] (n=17)	–	1926±760	2.03±0.98
DDI-LD-opicapone			
Controls[50] (n=16)			
25 mg	2.47 (CV 33.7)	1203 (CV 37.7)	1.00 [0.5–3.0][d]
50 mg	2.50 (CV 15.7)	1030 (CV 38.8)	0.75 [0.5–3.0][d]
75 mg	2.39 (CV 23.3)	1057 (CV 31.7)	1.50 [0.5–2.0][d]
Mild–advanced PD[49] (n=10)[a]			
5 mg	1.67 (CV 24.9)	1868 (CV 31.8)	1.00 [0.5–2.0][d]
15 mg	1.78 (CV 31.2)	1806 (CV 28.4)	0.75 [0.5–2.0][d]
30 mg	2.16 (CV 36.5)	2584 (CV 33.7)	0.50 [0.5–3.0][d]
CD-L-Dopa capsule			
Controls			
23.75–95 mg[26] (n=28)	1.5±0.3	317±90.3	2.8 [0.5–5][d]
36.25–145 mg[26] (n=28)	1.4±0.2	491±125	2.8 [0.5–5][d]
48.75–195 mg[26] (n=28)	1.5±0.6	630±187	4.0 [0.5–5][d]
61.25–245 mg[26] (n=28)	1.5±0.3	763±156	3.5 [0.5–5][d]
97.5–390 mg (n=22)[22]	1.9±0.7	1326±268	4.5 [0.5–8][d]
AP-CD-LD			
Controls[147] (n=12)[b]	5.15	1951	4.67
50–500 mg			
LCIG 16-hour infusion[58]			
Advanced PD (n=18)[e]			
mean CD 395±101 mg –			
LD 1580±403 mg daily	–	4210±1360	2.85±2.31

(Continued)

Table 1. **(Continued)**

This table summarizes the pharmacokinetic (PK) profiles of levodopa with adjuvant therapies and novel delivery mechanisms. Parkinson's disease (PD) patients were categorized by either the duration of disease (DD) or Hoehn and Yahr scores (H&Y). Study populations were grouped as healthy controls, mild PD (DD: 0–5 years; H&Y I–II), moderate PD (DD: 6–10 years; H&Y III), and advanced PD (DD: >10 years; H&Y IV–V). Parameters are expressed as mean ± standard deviation except where indicated.
[a]after 28 days of daily opicapone dosing to reach steady state; [b]no standard deviation available.
[d]Median values between multiple studies are reported with mean ranges listed in brackets.
[e]No details of the study population disease duration or H&Y stage were provided in this study. Subjects were labeled as advanced by the investigators.[58]
CD, carbidopa; CV, % coefficient variation; DDI, dopa decarboxylase inhibitor (carbidopa or benserazide); LCIG, levodopa carbidopa intestinal gel; LD, levodopa; SEM, standard error of mean.

---

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.[21] Immediate-release (IR) L-Dopa is the most readily available formulation worldwide; however, its short-acting pharmacokinetics results in unstable plasma L-Dopa concentrations.[22] Peak plasma concentrations are reached within 1 hour of oral administration but drop to less than 10% by 5 hours in healthy adults.[22] Another potential variable influencing L-Dopa bioavailability may be gastrointestinal hypomotility, a common nonmotor symptom of PD.[16,23]

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,[24] and both CLE and L-Dopa CR showed a large degree of intersubject variability in pharmacokinetics.[25] 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.[26] Furthermore, CD-L-Dopa capsule lasted 2.5 hours longer than the two other existing long-acting formulations (L-Dopa CR and CLE).[22]

CD-L-Dopa capsule provided greater *on* time without troublesome dyskinesias compared to IR L-Dopa reflective of a smoother pharmacokinetic profile (Figure 1).[27] 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.[27] 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.[27]

DM-1992

DM-1992 is a novel long-acting L-Dopa, currently under investigation.[28] 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.[29] One study crossing over PD patients from IR L-Dopa to DM-1992 demonstrated a reduction in "off" time by 1 hour.[28] 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.[28]

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.[30] In healthy controls and PD patients, AP-CD-LD provides less fluctuant plasma L-Dopa levels compared to IR L-Dopa.[31,32] 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).[32,33] Up to a 25% reduction in the total, daily L-Dopa dose was also reported.[33] A phase III randomized trial comparing AP-CD-LD with IR L-Dopa

was recently completed; however, results have not been published.[34]

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 peripherally[38] 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.[36] Selegiline and rasagiline are the two most commonly prescribed MAO-B inhibitors that are used as either mono- or adjunctive therapy to L-Dopa.[43–48] 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

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.
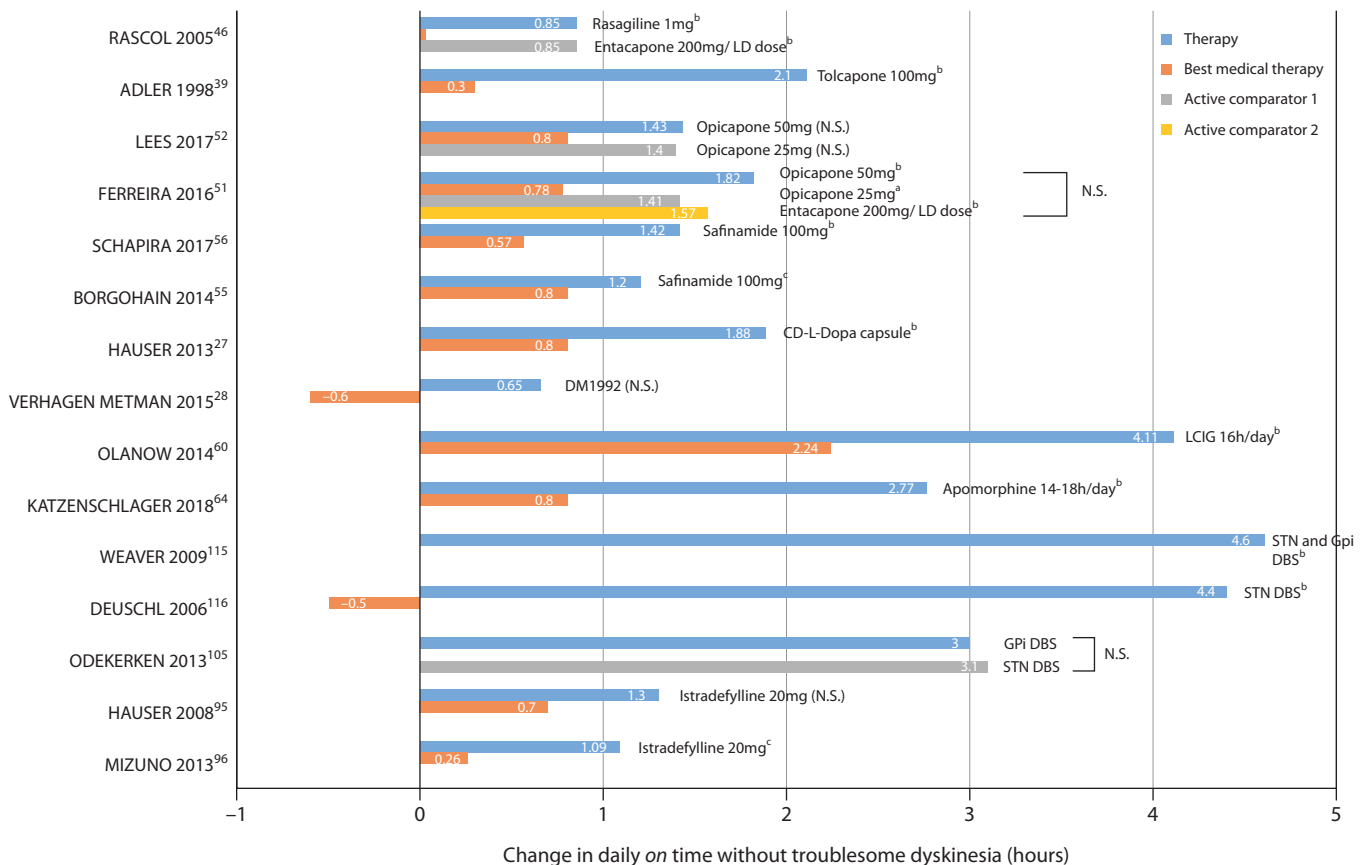
hypotension.[52] Treatment emergent dyskinesias were reported as an adverse effect more frequently with 50 mg opicapone compared to entacapone.[51] Other adverse effects included constipation and dry mouth.[51,52]

Safinamide

Safinamide is a highly selective, reversible MAO-B inhibitor[53] available in the US and select countries, with proposed antidyskinetic effects due to reduction in glutamate transmission.[54] 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 rasagiline (Figure 1).[46,55,56] 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 rasagiline and selegiline and had comparable efficacy to entacapone.[57] Furthermore, the antidyskinetic effects observed in primate models[54] were not replicated in human studies.[56]

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.[58,59] 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.[60] Significant improvements in quality of life, activities of daily living, and non-motor symptoms have been reported.[60] Additionally, more than one-third of patients were able to utilize LCIG as monotherapy.[61]

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.[62] Of note, most gastrointestinal and procedural adverse events occurred within the first 2 weeks postoperatively.[60] Finally, LCIG has an increased risk of polyneuropathy. Although the exact pathophysiology is unknown, vitamin B_{12} deficiency has

been implicated, warranting regular monitoring and B_{12} supplementation.[63]

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.[64,65] 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.[64] Skin nodules, nausea, and somnolence were the most commonly experienced adverse effects.[64] Uncommon but serious treatment-related adverse effects included severe hypotension, nonhemolytic anemia, leucopenia, hallucinations, confusion, and infusion-site cellulitis.[64] However, long-term apomorphine infusions may not be well tolerated.[66] 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.[67]

ND-0612

A subcutaneous CD-LD infusion is currently under investigation with promising results. Preliminary pharmacokinetic studies demonstrated stable plasma L-Dopa concentrations in healthy[68] and PD subjects,[69] with up to 2 hours reduction in "off" time compared to optimal oral therapy.[68,69] Oral L-Dopa intake was reduced by an average of 80% with 3 of 16 subjects achieving monotherapy.[69] 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.[70] Similar to subcutaneous apomorphine, subcutaneous nodules occurred.[68]

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%.[71,72] This medication is relatively fast acting with an onset of effect within 10–24 minutes.[71–73] However, its use is limited by intolerable side effects of nausea, somnolence, dizziness, and orthostatic hypotension,[71] with one-third of patients discontinuing this therapy by 12 months due to these.[74] 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.[75]

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.[76] Rapid absorption of L-Dopa through the pulmonary epithelium allows PD patients to achieve peak plasma L-Dopa concentration within 15 minutes of inhalation.[76] However, in clinical trials, significant improvements in motor symptoms only occurred at 30 minutes of using the highest studied dose of 84 mg.[77] The most common side effect was a non-dose-dependent cough, occurring within the first month of treatment.[77] 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.[77,78] Although infrequent but serious adverse effects of hypotension and atrial fibrillation occurred, LDIP was well tolerated in most patients.[77]

APL-130277

Sublingual apomorphine was first introduced in 1989 with comparable symptomatic effects to subcutaneous administration.[79] However, early sublingual preparations were impractical due to a prolonged dissolving time.[79] 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.[80,81] Similar to the subcutaneous formulation, common side effects were dizziness, somnolence, yawning, and nausea.[80,82] Although orthostatic hypotension, dyskinesias, and hallucinations rarely developed,[82] one-third of patients developed lip or oropharyngeal swelling and oral mucosal erythema, which lead to discontinuation.[82]

Dyskinesias

Dyskinesias are another source of significant disability and reduced quality of life.[19] Up to 40% of patients treated with L-Dopa will develop dyskinesias within 5 years,[8] and all PD patients are expected to develop dyskinesias by 20 years if treated with dopaminergic medications.[83] Altered striatal glutamate receptor trafficking, secondary to nigrostriatal dopamine depletion and pulsatile exogenous L-Dopa stimulation, has been implicated in the development of dyskinesas.[84] Amantadine, a non-competitive NMDA receptor inhibitor, has been the primary medication used to treat dyskinesias[85–87]; however, dose-dependent side effects of hallucinations, dry eye, dry mouth, constipation, and cognitive dysfunction limits use.[86] 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.[88,89]

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.[90] 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.[91] 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.[92,93]

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.[94] However, only a modest 0.7-hour reduction in daily "off" time was observed in two randomized clinical trials,[95,96] while a third randomized placebo-controlled trial did not demonstrate statistically significant improvement over placebo.[97] Although only mild to moderate in severity, dyskinesias were more prevalent in the therapy arms.[95,96] 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.[98] The most commonly reported adverse effects were dyskinesias and hallucinations.[98]

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.[99,100] Open-label studies comparing DBS to LCIG and subcutaneous apomorphine infusions have demonstrated superior control of dyskinesia and less procedure or device-related complications.[18,66] 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.[101] A 1.3% risk of symptomatic intracerebral hemorrhage was found across pooled data from three large case series conducted between 1993 and 2010.[101–103]

The subthalamic nucleus (STN) and globus pallidus interna (GPi) are the most commonly targeted structures for PD.[99] Based on comparable safety and efficacy in multiple randomized studies in advanced PD, there is no consensus on the preferred target for stimulation.[104–109] The potential advantages of STN include an opportunity to reduce dopaminergic medications while utilizing relatively lower stimulation parameters, which prolongs battery life.[105,107] However, STN stimulation often amplifies dyskinesias during the initial phases of programming[110] and has been associated with increased risk of cognitive and psychiatric complications.[104,107] Conversely, GPi stimulation tends to have less negative impact on mood and cognitive processing[107,109] and greater reduction in dyskinesia.[105,106,111] 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.[105,107] 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.[112–114] Compared to best medical therapy, DBS improves "on" time without troublesome dyskinesias by a magnitude of 4.6–5 hours,[115,116] with more than two-thirds of advanced PD patients achieving meaningful improvements in motor fluctuations with either STN or GPi DBS by 6 months.[115] 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.[117–119] 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.[117] Although initially, patients' stimulation requirements have been shown to increase as the disease progresses,[118] 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.[119,120] 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.[101] 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).[121,122] 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.[121,123,124]

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").[125] It is hypothesized to provide better control of motor fluctuations than conventional high-frequency stimulation.[125] By interpretation of biomarkers, individualized and variable stimulation will be provided during times of poor symptom control through the use of algorithmic models.[112,125–127] Potential advantages of aDBS are minimization of stimulation-related side effects, reduction of long-term tolerance to stimulation, and prolongation of battery life.[125,127,128]

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.[127–129] Bradykinesia and rigidity in the "off" state have been correlated with excessive

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.**
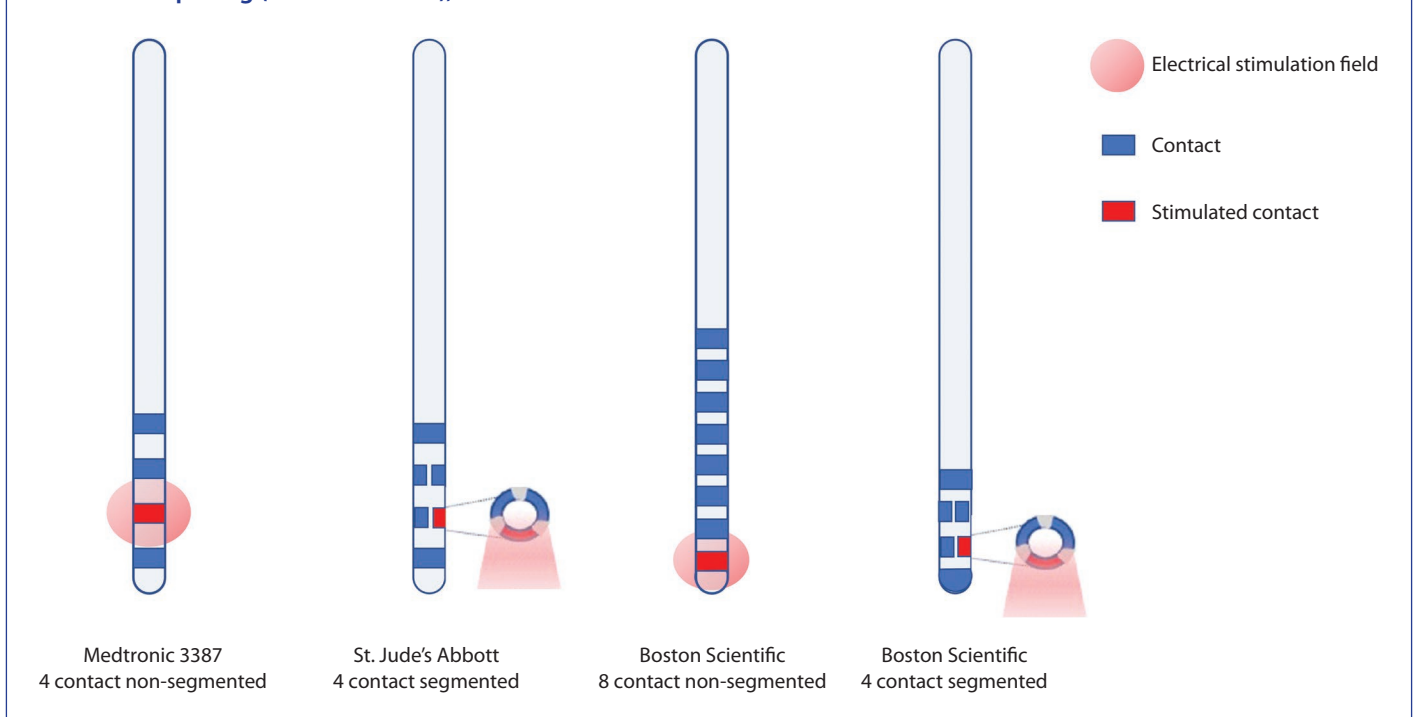
synchronization of beta frequency oscillations within corticobasal ganglia networks.[128–130] These oscillations are suppressed when a patient is treated with either L-Dopa or DBS.[114,129,131,132] Preliminary studies have correlated suppression of beta frequency oscillations with reduced bradykinesia, rigidity, and freezing of gait in PD patients.[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.[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.[136,137] Infusion of pluripotent and human embryonic stem cells for targeted regeneration of dopaminergic neurons are also being studied in small populations.[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.[139] Thus, studies targeting specific sub-populations of PD for individualized treatment are needed.[139] Although we eagerly await a breakthrough in disease modification, improved control of motor complications remains a priority for patient care.

References

1. GBD 2015 Neurological Disorders Collaborator Group. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the global burden of disease study 2015. *Lancet Neurol.* 2017;16(11):877-897. http://dx.doi.org/10.1016/S1474-4422(17)30299-5

2. Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology.* 2007;68(5):384-386. http://dx.doi.org/10.1212/01.wnl.0000247740.47667.03

3. Cotzias GC, Papavasiliou PS, Gellene R. Modification of Parkinsonism—chronic treatment with l-dopa. *N Engl J Med.* 1969;280(7):337-345. http://dx.doi.org/10.1056/NEJM196902132800701

4. Cotzias GC, Van Woert MH, Schiffer LM. Aromatic amino acids and modification of Parkinsonism. *N Engl J Med.* 1967; 276(7):374-379. http://dx.doi.org/10.1056/NEJM196702162760703

5. Tolosa E, Marti MJ, Valldeoriola F, Molinuevo JL. History of levodopa and dopamine agonists in Parkinson's disease treatment. *Neurology.* 1998;50(6 Suppl 6):S2-10; discussion S44-18. http://dx.doi.org/10.1212/wnl.50.6_suppl_6.s2

6. Obeso JA, Rodriguez-Oroz MC, Chana P, Lera G, Rodriguez M, Olanow CW. The evolution and origin of motor complications in Parkinson's disease. *Neurology.* 2000;55(11 Suppl 4):S13-20; discussion S21-13.

7. Colosimo C, De Michele M. Motor fluctuations in Parkinson's disease: pathophysiology and treatment. *Eur J Neurol.* 1999; 6(1):1-21.

8. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord.* 2001;16(3):448-458.

9. Anthony J, Spears J, Van Lunen B. Implications of motor fluctuations in Parkinson's disease patients on chronic therapy (impact): results from an observational registry. *Mov Disord.* 2005;20(S10):S146.

10. Stocchi F. The hypothesis of the genesis of motor complications and continuous dopaminergic stimulation in the treatment of Parkinson's disease. *Parkinsonism Relat D.* 2009;15:S9-S15. http://dx.doi.org/10.1016/S1353-8020(09)70005-7

11. Luquin MR, Scipioni O, Vaamonde J, Gershanik O, Obeso JA. Levodopa-induced dyskinesias in Parkinson's disease: clinical and pharmacological classification. *Mov Disord.* 1992;7(2):117-124. http://dx.doi.org/10.1002/mds.870070204

12.   Cilia R, Akpalu A, Sarfo FS, et al. The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa. *Brain*. 2014;137(10):2731-2742. http://dx.doi.org/10.1093/brain/awu195

13.   Grandas F, Galiano ML, Tabernero C. Risk factors for levodopa-induced dyskinesias in Parkinson's disease. *J Neurol*. 1999;246(12):1127-1133.

14.   Fabbrini G, Mouradian MM, Juncos JL, Schlegel J, Mohr E, Chase TN. Motor fluctuations in Parkinson's disease: central pathophysiological mechanisms, part i. *Ann Neurol*. 1988;24(3):366-371. http://dx.doi.org/10.1002/ana.410240303

15.   Nyholm D, Lennernas H. Irregular gastrointestinal drug absorption in Parkinson's disease. *Expert Opin Drug Metab Toxicol*. 2008;4(2):193-203. http://dx.doi.org/10.1517/17425255.4.2.193

16.   Djaldetti R, Baron J, Ziv I, Melamed E. Gastric emptying in Parkinson's disease: patients with and without response fluctuations. *Neurology*. 1996;46(4):1051-1054. http://dx.doi.org/10.1212/wnl.46.4.1051

17.   Colosimo C, Merello M, Hughes AJ, Sieradzan K, Lees AJ. Motor response to acute dopaminergic challenge with apomorphine and levodopa in Parkinson's disease: implications for the pathogenesis of the on-off phenomenon. *J Neurol Neurosurg Psychiatry*. 1996;60(6):634-637. http://dx.doi.org/10.1136/jnnp.60.6.634

18.   Merola A, Espay AJ, Romagnolo A, et al. Advanced therapies in Parkinson's disease: long-term retrospective study. *Parkinsonism Relat Disord*. 2016;29:104-108. http://dx.doi.org/10.1016/j.parkreldis.2016.05.015

19.   Chapuis S, Ouchchane L, Metz O, Gerbaud L, Durif F. Impact of the motor complications of Parkinson's disease on the quality of life. *Mov Disord*. 2005;20(2):224-230. http://dx.doi.org/10.1002/mds.20279

20.   Wilson RE, Silver D, Spears JB, Van Lunen BE. Implications of motor fluctuations in Parkinson's patients on chronic therapy (impact) registry: quality of life (qol) data. *Mov Disord*. 2006;21:S151.

21.   Markham C, Diamond SG, Treciokas LJ. Carbidopa in Parkinson disease and in nausea and vomiting of levodopa. *Arch Neurol*. 1974;31(2):128-133.

22.   Hsu A, Yao HM, Gupta S, Modi NB. Comparison of the pharmacokinetics of an oral extended-release capsule formulation of carbidopa-levodopa (ipx066) with immediate-release carbidopa-levodopa (sinemet((r))), sustained-release carbidopa-levodopa (sinemet((r)) cr), and carbidopa-levodopa-entacapone (stalevo((r))). *J Clin Pharmacol*. 2015;55(9):995-1003. http://dx.doi.org/10.1002/jcph.514

23.   Goetze O, Wieczorek J, Mueller T, Przuntek H, Schmidt WE, Woitalla D. Impaired gastric emptying of a solid test meal in patients with Parkinson's disease using 13c-sodium octanoate breath test. *Neurosci Lett*. 2005;375(3):170-173. http://dx.doi.org/10.1016/j.neulet.2004.11.007

24.   Kuoppamaki M, Korpela K, Marttila R, et al. Comparison of pharmacokinetic profile of levodopa throughout the day between levodopa/carbidopa/entacapone and levodopa/carbidopa when administered four or five times daily. *Eur J Clin Pharmacol*. 2009;65(5):443-455. http://dx.doi.org/10.1007/s00228-009-0622-y

25.   LeWitt PA, Jennings D, Lyons KE, et al. Pharmacokinetic-pharmacodynamic crossover comparison of two levodopa extension strategies. *Mov Disord*. 2009;24(9):1319-1324. http://dx.doi.org/10.1002/mds.22587

26.   Yao HM, Hsu A, Gupta S, Modi NB. Clinical pharmacokinetics of ipx066: evaluation of dose proportionality and effect of food in healthy volunteers. *Clin Neuropharmacol*. 2016;39(1):10-17. http://dx.doi.org/10.1097/WNF.0000000000000126

27.   Hauser RA, Hsu A, Kell S, et al. Extended-release carbidopa-levodopa (ipx066) compared with immediate-release carbidopa-levodopa in patients with Parkinson's disease and motor fluctuations: a phase 3 randomised, double-blind trial. *Lancet Neurol*. 2013;12(4):346-356. http://dx.doi.org/10.1016/S1474-4422(13)70025-5

28.   Verhagen Metman L, Stover N, Chen C, Cowles VE, Sweeney M. Gastroretentive carbidopa/levodopa, dm-1992, for the treatment of advanced Parkinson's disease. *Mov Disord*. 2015;30(9):1222-1228. http://dx.doi.org/10.1002/mds.26219

29.   LeWitt PA. New levodopa therapeutic strategies. *Parkinsonism Relat Disord*. 2016;22 Suppl 1:S37-40. http://dx.doi.org/10.1016/j.parkreldis.2015.09.021

30.   Navon N, Gendreau R, Meckler J. Gastric retention of the accordion pill[tm]: results from MRI studies with Parkinson's disease patients and healthy volunteers. *Mov Disord*. 2018;33(S2):S113.

31.   Navon N, Weiss Z, Gendreau RM, Meckler J. Optimizing delivery of carbidopa/levodopa via the accordion pill™: comparative pk and safety from 2 randomized crossover studies in healthy volunteers (p2.040). *Neurology*. 2018;90(15 Supplement):P2.040.

32.   LeWitt P, Giladi N, Navon N. Pharmacokinetics and efficacy of a novel formulation of carbidopa-levodopa (accordion pill[tm]) in Parkinson's disease. *Parkinsonism Relat Disord*: 2019 May 22. http://dx.doi.org/10.1016/j.parkreldis.2019.05.032. Epub ahead of print.

33.   LeWitt PA, Giladi N, Gurevich T, et al. Accordion pill carbidopa/levodopa (ap-cd/ld) for treatment of advanced pd. *Mov Disord*. 2014;29(S1):S248.

34.   LeWitt P, Gendreau R, Meckler J, Navon N. Design of a phase 3 efficacy and safety trial of accordion pill[tm] carbidopa/levodopa for Parkinson's disease (pd) patients. *Mov Disord*. 2018;33(S2):S154.

35.   Nutt JG. Catechol-o-methyltransferase inhibitors for treatment of Parkinson's disease. *Lancet*. 1998;351(9111):1221-1222. http://dx.doi.org/10.1016/S0140-6736(05)79311-9

36. Thebault JJ, Guillaume M, Levy R. Tolerability, safety, pharmacodynamics, and pharmacokinetics of rasagiline: a potent, selective, and irreversible monoamine oxidase type b inhibitor. *Pharmacotherapy.* 2004;24(10):1295-1305.

37. Kuoppamaki M, Vahteristo M, Ellmen J, Kieburtz K. Pooled analysis of phase iii with entacapone in Parkinson's disease. *Acta Neurol Scand.* 2014;130(4):239-247. http://dx.doi.org/10.1111/ane.12278

38. Ceravolo R, Piccini P, Bailey DL, Jorga KM, Bryson H, Brooks DJ. 18f-dopa pet evidence that tolcapone acts as a central comt inhibitor in Parkinson's disease. *Synapse.* 2002;43(3):201-207. http://dx.doi.org/10.1002/syn.10034

39. Adler CH, Singer C, O'Brien C, et al. Randomized, placebo-controlled study of tolcapone in patients with fluctuating Parkinson disease treated with levodopa-carbidopa. Tolcapone fluctuator study group iii. *Arch Neurol.* 1998;55(8):1089-1095.

40. Marsala SZ, Gioulis M, Ceravolo R, Tinazzi M. A systematic review of catechol-0-methyltransferase inhibitors: efficacy and safety in clinical practice. *Clin Neuropharmacol.* 2012;35(4):185-190. http://dx.doi.org/10.1097/WNF.0b013e31825c034a

41. Ferreira JJ, Katzenschlager R, Bloem BR, et al. Summary of the recommendations of the efns/mds-es review on therapeutic management of Parkinson's disease. *Eur J Neurol.* 2013;20(1):5-15. http://dx.doi.org/10.1111/j.1468-1331.2012.03866.x

42. Assal F, Spahr L, Hadengue A, Rubbia-Brandt L, Burkhard PR. Tolcapone and fulminant hepatitis. *Lancet.* 1998;352(9132):958. http://dx.doi.org/10.1016/s0140-6736(05)61511-5

43. Myllyla VV, Sotaniemi KA, Hakulinen P, Maki-Ikola O, Heinonen EH. Selegiline as the primary treatment of Parkinson's disease—a long-term double-blind study. *Acta Neurol Scand.* 1997;95(4):211-218.

44. Parkinson Study G. A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. *Arch Neurol.* 2004;61(4):561-566. http://dx.doi.org/10.1001/archneur.61.4.561

45. Parkinson Study G. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the presto study. *Arch Neurol.* 2005;62(2):241-248. http://dx.doi.org/10.1001/archneur.62.2.241

46. Rascol O, Brooks DJ, Melamed E, et al. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (largo, lasting effect in adjunct therapy with rasagiline given once daily, study): a randomised, double-blind, parallel-group trial. *Lancet.* 2005;365(9463):947-954. http://dx.doi.org/10.1016/S0140-6736(05)71083-7

47. Parkinson Study G. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med.* 1993;328(3):176-183. http://dx.doi.org/10.1056/NEJM199301213280305

48. Golbe LI, Lieberman AN, Muenter MD, et al. Deprenyl in the treatment of symptom fluctuations in advanced Parkinson's disease. *Clin Neuropharmacol.* 1988;11(1):45-55.

49. Ferreira JJ, Rocha JF, Falcao A, et al. Effect of opicapone on levodopa pharmacokinetics, catechol-o-methyltransferase activity and motor fluctuations in patients with Parkinson's disease. *Eur J Neurol.* 2015;22(5):815-825, e856. http://dx.doi.org/10.1111/ene.12666

50. Rocha JF, Falcao A, Santos A, et al. Effect of opicapone and entacapone upon levodopa pharmacokinetics during three daily levodopa administrations. *Eur J Clin Pharmacol.* 2014;70(9):1059-1071. http://dx.doi.org/10.1007/s00228-014-1701-2

51. Ferreira JJ, Lees A, Rocha JF, et al. Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomised, double-blind, controlled trial. *Lancet Neurol.* 2016;15(2):154-165. http://dx.doi.org/10.1016/S1474-4422(15)00336-1

52. Lees AJ, Ferreira J, Rascol O, et al. Opicapone as adjunct to levodopa therapy in patients with Parkinson disease and motor fluctuations: a randomized clinical trial. *JAMA Neurol.* 2017;74(2):197-206. http://dx.doi.org/10.1001/jamaneurol.2016.4703

53. Marzo A, Dal Bo L, Monti NC, et al. Pharmacokinetics and pharmacodynamics of safinamide, a neuroprotectant with antiparkinsonian and anticonvulsant activity. *Pharmacol Res.* 2004;50(1):77-85. http://dx.doi.org/10.1016/j.phrs.2003.12.004

54. Gregoire L, Jourdain VA, Townsend M, Roach A, Di Paolo T. Safinamide reduces dyskinesias and prolongs l-dopa antiparkinsonian effect in Parkinsonian monkeys. *Parkinsonism Relat Disord.* 2013;19(5):508-514. http://dx.doi.org/10.1016/j.parkreldis.2013.01.009

55. Borgohain R, Szasz J, Stanzione P, et al. Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. *Mov Disord.* 2014;29(2):229-237. http://dx.doi.org/10.1002/mds.25751

56. Schapira AH, Fox SH, Hauser RA, et al. Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson disease and motor fluctuations: a randomized clinical trial. *JAMA Neurol.* 2017;74(2):216-224. http://dx.doi.org/10.1001/jamaneurol.2016.4467

57. Binde CD, Tvete IF, Gasemyr J, Natvig B, Klemp M. A multiple treatment comparison meta-analysis of monoamine oxidase type b inhibitors for Parkinson's disease. *Br J Clin Pharmacol.* 2018;84(9):1917-1927. http://dx.doi.org/10.1111/bcp.13651

58. Nyholm D, Odin P, Johansson A, et al. Pharmacokinetics of levodopa, carbidopa, and 3-o-methyldopa following 16-hour jejunal infusion of levodopa-carbidopa intestinal gel in advanced Parkinson's disease patients. *AAPS J.* 2013;15(2):316-323. http://dx.doi.org/10.1208/s12248-012-9439-1

59. Othman AA, Rosebraugh M, Chatamra K, Locke C, Dutta S. Levodopa-carbidopa intestinal gel pharmacokinetics: lower variability than oral levodopa-carbidopa. *J Parkinsons Dis.* 2017;7(2):275-278. http://dx.doi.org/10.3233/JPD-161042

60. Olanow CW, Kieburtz K, Odin P, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. *Lancet Neurol.* 2014;13(2):141-149. http://dx.doi.org/10.1016/S1474-4422(13)70293-X

61. Antonini A, Poewe W, Chaudhuri KR, et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's: final results of the gloria registry. *Parkinsonism Relat Disord.* 2017;45:13-20. http://dx.doi.org/10.1016/j.parkreldis.2017.09.018

62. Fernandez HH, Standaert DG, Hauser RA, et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results. *Mov Disord.* 2015;30(4):500-509. http://dx.doi.org/10.1002/mds.26123

63. Uncini A, Eleopra R, Onofrj M. Polyneuropathy associated with duodenal infusion of levodopa in Parkinson's disease: features, pathogenesis and management. *J Neurol Neurosurg Psychiatry.* 2015;86(5):490-495. http://dx.doi.org/10.1136/jnnp-2014-308586

64. Katzenschlager R, Poewe W, Rascol O, et al. Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (toledo): a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Neurol.* 2018;17(9):749-759. http://dx.doi.org/10.1016/S1474-4422(18)30239-4

65. Sesar A, Fernandez-Pajarin G, Ares B, Rivas MT, Castro A. Continuous subcutaneous apomorphine infusion in advanced Parkinson's disease: 10-year experience with 230 patients. *J Neurol.* 2017;264(5):946-954. http://dx.doi.org/10.1007/s00415-017-8477-0

66. Antonini A, Isaias IU, Rodolfi G, et al. A 5-year prospective assessment of advanced Parkinson disease patients treated with subcutaneous apomorphine infusion or deep brain stimulation. *J Neurol.* 2011;258(4):579-585. http://dx.doi.org/10.1007/s00415-010-5793-z

67. Kimber TE, Fang J, Huddy LJ, Thompson PD. Long-term adherence to apomorphine infusion in patients with Parkinson disease: a 10-year observational study. *Intern Med J.* 2017;47(5):570-573. http://dx.doi.org/10.1111/imj.13378

68. Caraco Y, Oren S, LeWitt P. Constant therapeutic levodopa (ld) plasma concentrations maintained by continuous subcutaneous (sc) administration of nd-0612, a novel formulation of ld/carbidopa (cd). *Mov Disord.* 2013;28(S1):S162.

69. Giladi N, Caraco Y, Gurevich T, et al. Pharmacokinetic profile of nd0612l (levodopa/carbidopa for subcutaneous infusion) in patients with moderate to severe Parkinson's disease. *Mov Disord.* 2015;30(S87).

70. Stocchi F, Poewe W, Rachmilewitz Minei T, et al. Efficacy of nd0612 for nocturnal problems and early morning off. *Mov Disord.* 2018;33(S2):S102.

71. Isaacson S, Lew M, Ondo W, Hubble J, Clinch T, Pagan F. Apomorphine subcutaneous injection for the management of morning akinesia in Parkinson's disease. *Mov Disord Clin Pract.* 2017;4(1):78-83. http://dx.doi.org/10.1002/mdc3.12350

72. Dewey RB, Jr., Hutton JT, LeWitt PA, Factor SA. A randomized, double-blind, placebo-controlled trial of subcutaneously injected apomorphine for Parkinsonian off-state events. *Arch Neurol.* 2001;58(9):1385-1392.

73. Pfeiffer RF, Gutmann L, Hull KL, Jr., Bottini PB, Sherry JH, Investigators APOS. Continued efficacy and safety of subcutaneous apomorphine in patients with advanced Parkinson's disease. *Parkinsonism Relat Disord.* 2007;13(2):93-100. http://dx.doi.org/10.1016/j.parkreldis.2006.06.012

74. LeWitt PA, Ondo WG, Van Lunen B, Bottini PB. Open-label study assessment of safety and adverse effects of subcutaneous apomorphine injections in treating "off" episodes in advanced Parkinson disease. *Clin Neuropharmacol.* 2009;32(2):89-93. http://dx.doi.org/10.1097/WNF.0B013E31816D91F9

75. Merello M, Pikielny R, Cammarota A, Leiguarda R. Comparison of subcutaneous apomorphine versus dispersible madopar latency and effect duration in Parkinson's disease patients: a double-blind single-dose study. *Clin Neuropharmacol.* 1997;20(2):165-167.

76. Lipp MM, Batycky R, Moore J, Leinonen M, Freed MI. Preclinical and clinical assessment of inhaled levodopa for off episodes in Parkinson's disease. *Sci Transl Med.* 2016;8(360):360ra136. http://dx.doi.org/10.1126/scitranslmed.aad8858

77. LeWitt PA, Hauser RA, Pahwa R, et al. Safety and efficacy of cvt-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Neurol.* 2019;18(2):145-154. http://dx.doi.org/10.1016/S1474-4422(18)30405-8

78. LeWitt PA, Pahwa R, Sedkov A, Corbin A, Batycky R, Murck H. Pulmonary safety and tolerability of inhaled levodopa (cvt-301) administered to patients with Parkinson's disease. *J Aerosol Med Pulm Drug Deliv.* 2018;31(3):155-161. http://dx.doi.org/10.1089/jamp.2016.1354

79. Lees AJ, Montastruc JL, Turjanski N, et al. Sublingual apomorphine and Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 1989;52(12):1440. http://dx.doi.org/10.1136/jnnp.52.12.1440

80. Hauser RA, Olanow CW, Dzyngel B, et al. Sublingual apomorphine (apl-130277) for the acute conversion of off to on in Parkinson's disease. *Mov Disord.* 2016;31(9):1366-1372. http://dx.doi.org/10.1002/mds.26697

81. Factor S, Isaacson S, Sciarappa K, et al. Efficacy of sublingual apomorphine film (apl-130277) for the treatment of off episodes in patients with Parkinson's disease: results from the phase 3 double-blind, placebo-controlled trial. *Mov Disord.* 2018;33(S2):S107.

82. Pahwa R, Hauser R, Worden R, et al. Safety of sublingual apomorphine film (apl-130277) for the treatment of off episodes in patients with Parkinson's disease: results from a phase 3 double-blind, placebo-controlled trial. *Mov Disord.* 2018;33(S2):S165.

83.   Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov Disord*. 2008;23(6):837-844. http://dx.doi.org/10.1002/mds.21956

84.   Mellone M, Gardoni F. Glutamatergic mechanisms in l-dopa-induced dyskinesia and therapeutic implications. *J Neural Transm (Vienna)*. 2018;125(8):1225-1236. http://dx.doi.org/10.1007/s00702-018-1846-8

85.   Luginger E, Wenning GK, Bosch S, Poewe W. Beneficial effects of amantadine on l-dopa-induced dyskinesias in Parkinson's disease. *Mov Disord*. 2000;15(5):873-878.

86.   Verhagen Metman L, Del Dotto P, van den Munckhof P, Fang J, Mouradian MM, Chase TN. Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. *Neurology*. 1998;50(5):1323-1326. http://dx.doi.org/10.1212/wnl.50.5.1323

87.   Rajput AH, Rajput A, Lang AE, Kumar R, Uitti RJ, Galvez-Jimenez N. New use for an old drug: amantadine benefits levodopa-induced dyskinesia. *Mov Disord*. 1998;13(5):851. http://dx.doi.org/10.1002/mds.870130520

88.   Thomas A, Iacono D, Luciano AL, Armellino K, Di Iorio A, Onofrj M. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2004;75(1):141-143.

89.   Ory-Magne F, Corvol JC, Azulay JP, et al. Withdrawing amantadine in dyskinetic patients with Parkinson disease: the amandysk trial. *Neurology*. 2014;82(4):300-307. http://dx.doi.org/10.1212/WNL.0000000000000050

90.   Hauser RA, Pahwa R, Wargin WA, et al. Pharmacokinetics of ads-5102 (amantadine) extended release capsules administered once daily at bedtime for the treatment of dyskinesia. *Clin Pharmacokinet*. 2019;58(1):77-88. http://dx.doi.org/10.1007/s40262-018-0663-4

91.   Pahwa R, Tanner CM, Hauser RA, et al. Ads-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson disease (ease lid study): a randomized clinical trial. *JAMA Neurol*. 2017;74(8):941-949. http://dx.doi.org/10.1001/jamaneurol.2017.0943

92.   Oertel W, Eggert K, Pahwa R, et al. Randomized, placebo-controlled trial of ads-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson's disease (ease lid 3). *Mov Disord*. 2017;32(12):1701-1709. http://dx.doi.org/10.1002/mds.27131

93.   Pahwa R, Tanner CM, Hauser RA, et al. Amantadine extended release for levodopa-induced dyskinesia in Parkinson's disease (eased study). *Mov Disord*. 2015;30(6):788-795. http://dx.doi.org/10.1002/mds.26159

94.   Kase H, Aoyama S, Ichimura M, et al. Progress in pursuit of therapeutic a2a antagonists: the adenosine a2a receptor selective antagonist kw6002: research and development toward a novel nondopaminergic therapy for Parkinson's disease. *Neurology*. 2003;61(11 Suppl 6):S97-100. http://dx.doi.org/10.1212/01.wnl.0000095219.22086.31

95.   Hauser RA, Shulman LM, Trugman JM, et al. Study of istradefylline in patients with Parkinson's disease on levodopa with motor fluctuations. *Mov Disord*. 2008;23(15):2177-2185. http://dx.doi.org/10.1002/mds.22095

96.   Mizuno Y, Kondo T, Japanese Istradefylline Study G. Adenosine a2a receptor antagonist istradefylline reduces daily off time in Parkinson's disease. *Mov Disord*. 2013;28(8):1138-1141. http://dx.doi.org/10.1002/mds.25418

97.   Pourcher E, Fernandez HH, Stacy M, Mori A, Ballerini R, Chaikin P. Istradefylline for Parkinson's disease patients experiencing motor fluctuations: results of the kw-6002-us-018 study. *Parkinsonism Relat Disord*. 2012;18(2):178-184. http://dx.doi.org/10.1016/j.parkreldis.2011.09.023

98.   Takahashi M, Fujita M, Asai N, Saki M, Mori A. Safety and effectiveness of istradefylline in patients with Parkinson's disease: interim analysis of a post-marketing surveillance study in japan. *Expert Opin Pharmacother*. 2018;19(15):1635-1642. http://dx.doi.org/10.1080/14656566.2018.1518433

99.   Deep-Brain Stimulation for Parkinson's Disease Study G, Obeso JA, Olanow CW, et al. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. *N Engl J Med*. 2001;345(13):956-963. http://dx.doi.org/10.1056/NEJMoa000827

100.   Deuschl G, Fogel W, Hahne M, et al. Deep-brain stimulation for Parkinson's disease. *J Neurol*. 2002;249 Suppl 3:III/36-39. http://dx.doi.org/10.1007/s00415-002-1308-x

101.   Fenoy AJ, Simpson RK, Jr. Risks of common complications in deep brain stimulation surgery: management and avoidance. *J Neurosurg*. 2014;120(1):132-139. http://dx.doi.org/10.3171/2013.10.JNS131225

102.   Lyons KE, Wilkinson SB, Overman J, Pahwa R. Surgical and hardware complications of subthalamic stimulation: a series of 160 procedures. *Neurology*. 2004;63(4):612-616. http://dx.doi.org/10.1212/01.wnl.0000134650.91974.1a

103.   Oh MY, Abosch A, Kim SH, Lang AE, Lozano AM. Long-term hardware-related complications of deep brain stimulation. *Neurosurgery*. 2002;50(6):1268-1274; discussion 1274-1266. http://dx.doi.org/10.1097/00006123-200206000-00017

104.   Anderson VC, Burchiel KJ, Hogarth P, Favre J, Hammerstad JP. Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease. *Arch Neurol*. 2005;62(4):554-560. http://dx.doi.org/10.1001/archneur.62.4.554

105.   Odekerken VJ, van Laar T, Staal MJ, et al. Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (nstaps study): a randomised controlled trial. *Lancet Neurol*. 2013;12(1):37-44. http://dx.doi.org/10.1016/S1474-4422(12)70264-8

106. Ramirez-Zamora A, Ostrem JL. Globus pallidus interna or subthalamic nucleus deep brain stimulation for Parkinson disease: a review. *JAMA Neurol.* 2018;75(3):367-372. http://dx.doi.org/10.1001/jamaneurol.2017.4321

107. Follett KA, Weaver FM, Stern M, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med.* 2010;362(22):2077-2091. http://dx.doi.org/10.1056/NEJMoa0907083

108. Weaver FM, Follett KA, Stern M, et al. Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. *Neurology.* 2012;79(1):55-65. http://dx.doi.org/10.1212/WNL.0b013e31825dcdc1

109. Liu Y, Li W, Tan C, et al. Meta-analysis comparing deep brain stimulation of the globus pallidus and subthalamic nucleus to treat advanced Parkinson disease. *J Neurosurg.* 2014;121(3):709-718. http://dx.doi.org/10.3171/2014.4.JNS131711

110. Limousin P, Martinez-Torres I. Deep brain stimulation for Parkinson's disease. *Neurotherapeutics.* 2008;5(2):309-319. http://dx.doi.org/10.1016/j.nurt.2008.01.006

111. Oyama G, Foote KD, Jacobson CEt, et al. GPi and STN deep brain stimulation can suppress dyskinesia in Parkinson's disease. *Parkinsonism Relat Disord.* 2012;18(7):814-818. http://dx.doi.org/10.1016/j.parkreldis.2012.03.022

112. Rosin B, Slovik M, Mitelman R, et al. Closed-loop deep brain stimulation is superior in ameliorating Parkinsonism. *Neuron.* 2011;72(2):370-384. http://dx.doi.org/10.1016/j.neuron.2011.08.023

113. Herrington T, Cheng J, Eskandar E. Mechanisms of deep brain stimulation. *J Neurophysiol.* 2016;115:19-38. http://dx.doi.org/doi:10.1152/jn.00281.2015

114. Eusebio A, Thevathasan W, Doyle Gaynor L, et al. Deep brain stimulation can suppress pathological synchronisation in Parkinsonian patients. *J Neurol Neurosurg Psychiatry.* 2011;82(5):569-573. http://dx.doi.org/10.1136/jnnp.2010.217489

115. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA.* 2009;301(1):63-73. http://dx.doi.org/10.1001/jama.2008.929

116. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med.* 2006;355(9):896-908. http://dx.doi.org/10.1056/NEJMoa060281

117. Lachenmayer ML, Bettschen C, Bernasconi C, et al. Stimulation of the globus pallidus internus in the treatment of Parkinson's disease: long-term results of a monocentric cohort. *Parkinsonism Relat Disord.* 2019. http://dx.doi.org/10.1016/j.parkreldis.2019.03.009

118. Zibetti M, Merola A, Rizzi L, et al. Beyond nine years of continuous subthalamic nucleus deep brain stimulation in Parkinson's disease. *Mov Disord.* 2011;26(13):2327-2334. http://dx.doi.org/10.1002/mds.23903

119. Constantinescu R, Eriksson B, Jansson Y, et al. Key clinical milestones 15 years and onwards after DBS-STN surgery-a retrospective analysis of patients that underwent surgery between 1993 and 2001. *Clin Neurol Neurosurg.* 2017;154:43-48. http://dx.doi.org/10.1016/j.clineuro.2017.01.010

120. Fasano A, Romito LM, Daniele A, et al. Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. *Brain.* 2010;133(9):2664-2676. http://dx.doi.org/10.1093/brain/awq221

121. Contarino MF, Bour LJ, Verhagen R, et al. Directional steering: a novel approach to deep brain stimulation. *Neurology.* 2014;83(13):1163-1169. http://dx.doi.org/10.1212/WNL.0000000000000823

122. Wagle Shukla A, Zeilman P, Fernandez H, Bajwa JA, Mehanna R. DBS programming: an evolving approach for patients with Parkinson's disease. *Parkinsons Dis.* 2017;2017:8492619. http://dx.doi.org/10.1155/2017/8492619

123. Pollo C, Kaelin-Lang A, Oertel MF, et al. Directional deep brain stimulation: an intraoperative double-blind pilot study. *Brain.* 2014;137(Pt 7):2015-2026. http://dx.doi.org/10.1093/brain/awu102

124. Dembek TA, Reker P, Visser-Vandewalle V, et al. Directional DBS increases side-effect thresholds-a prospective, double-blind trial. *Mov Disord.* 2017;32(10):1380-1388. http://dx.doi.org/10.1002/mds.27093

125. Habets JGV, Heijmans M, Kuijf ML, Janssen MLF, Temel Y, Kubben PL. An update on adaptive deep brain stimulation in Parkinson's disease. *Mov Disord.* 2018;33(12):1834-1843. http://dx.doi.org/10.1002/mds.115

126. Little S, Pogosyan A, Neal S, et al. Adaptive deep brain stimulation in advanced Parkinson disease. *Ann Neurol.* 2013; 74(3):449-457. http://dx.doi.org/10.1002/ana.23951

127. Priori A, Foffani G, Rossi L, Marceglia S. Adaptive deep brain stimulation (aDBS) controlled by local field potential oscillations. *Exp Neurol.* 2013;245:77-86. http://dx.doi.org/10.1016/j.expneurol.2012.09.013

128. Little S, Brown P. What brain signals are suitable for feedback control of deep brain stimulation in Parkinson's disease? *Ann N Y Acad Sci.* 2012;1265:9-24. http://dx.doi.org/10.1111/j.1749-6632.2012.06650.x

129. Bronte-Stewart H, Barberini C, Koop MM, Hill BC, Henderson JM, Wingeier B. The STN beta-band profile in Parkinson's disease is stationary and shows prolonged attenuation after deep brain stimulation. *Exp Neurol.* 2009;215(1):20-28. http://dx.doi.org/10.1016/j.expneurol.2008.09.008

130. Hammond C, Bergman H, Brown P. Pathological synchronization in Parkinson's disease: networks, models and treatments. *Trends Neurosci.* 2007;30(7):357-364. http://dx.doi.org/10.1016/j.tins.2007.05.004

131. Quinn EJ, Blumenfeld Z, Velisar A, et al. Beta oscillations in freely moving Parkinson's subjects are attenuated during deep brain stimulation. *Mov Disord.* 2015;30(13):1750-1758. http://dx.doi.org/10.1002/mds.26376

132. Kuhn AA, Kupsch A, Schneider GH, Brown P. Reduction in subthalamic 8-35 hz oscillatory activity correlates with clinical improvement in Parkinson's disease. *Eur J Neurosci.* 2006;23(7):1956-1960. http://dx.doi.org/10.1111/j.1460-9568.2006.04717.x

133. Toledo JB, Lopez-Azcarate J, Garcia-Garcia D, et al. High beta activity in the subthalamic nucleus and freezing of gait in Parkinson's disease. *Neurobiol Dis.* 2014;64:60-65. http://dx.doi.org/10.1016/j.nbd.2013.12.005

134. Kuhn AA, Kempf F, Brucke C, et al. High-frequency stimulation of the subthalamic nucleus suppresses oscillatory beta activity in patients with Parkinson's disease in parallel with improvement in motor performance. *J Neurosci.* 2008;28(24):6165-6173. http://dx.doi.org/10.1523/JNEUROSCI.0282-08.2008

135. Kuhn AA, Tsui A, Aziz T, et al. Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. *Exp Neurol.* 2009;215(2):380-387. http://dx.doi.org/10.1016/j.expneurol.2008.11.008

136. Jankovic J. Pathogenesis-targeted therapeutic strategies in Parkinson's disease. *Mov Disord.* 2019;34(1):41-44. http://dx.doi.org/10.1002/mds.27534

137. Lang AE, Espay AJ. Disease modification in Parkinson's disease: current approaches, challenges, and future considerations. *Mov Disord.* 2018;33(5):660-677. http://dx.doi.org/10.1002/mds.27360

138. Barker RA, Parmar M, Studer L, Takahashi J. Human trials of stem cell-derived dopamine neurons for Parkinson's disease: dawn of a new era. *Cell Stem Cell.* 2017;21(5):569-573. http://dx.doi.org/10.1016/j.stem.2017.09.014

139. Espay AJ, Lang AE. Parkinson diseases in the 2020s and beyond: replacing clinico-pathologic convergence with systems biology divergence. *J Parkinsons Dis.* 2018;8(s1):S59-S64. http://dx.doi.org/10.3233/JPD-181465

140. Keranen T, Gordin A, Harjola VP, et al. The effect of catechol-o-methyl transferase inhibition by entacapone on the pharmacokinetics and metabolism of levodopa in healthy volunteers. *Clin Neuropharmacol.* 1993;16(2):145-156.

141. Heikkinen H, Varhe A, Laine T, et al. Entacapone improves the availability of l-dopa in plasma by decreasing its peripheral metabolism independent of l-dopa/carbidopa dose. *Br J Clin Pharmacol.* 2002;54(4):363-371. http://dx.doi.org/10.1046/j.1365-2125.2002.01654.x

142. Kaakkola S, Mannisto PT, Nissinen E, Vuorela A, Mantyla R. The effect of an increased ratio of carbidopa to levodopa on the pharmacokinetics of levodopa. *Acta Neurol Scand.* 1985;72(4):385-391.

143. Myllyla VV, Sotaniemi KA, Illi A, Suominen K, Keranen T. Effect of entacapone, a comt inhibitor, on the pharmacokinetics of levodopa and on cardiovascular responses in patients with Parkinson's disease. *Eur J Clin Pharmacol.* 1993;45(5):419-423.

144. Kempster PA, Frankel JP, Bovingdon M, Webster R, Lees AJ, Stern GM. Levodopa peripheral pharmacokinetics and duration of motor response in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 1989;52(6):718-723. http://dx.doi.org/10.1136/jnnp.52.6.718

145. Hammerstad JP, Woodward WR, Nutt JG, Gancher ST, Block GA, Cyhan G. Controlled release levodopa/carbidopa 25/100 (sinemet cr 25/100): pharmacokinetics and clinical efficacy in untreated Parkinsonian patients. *Clin Neuropharmacol.* 1994;17(5):429-434.

146. Muller T, Ander L, Kolf K, Woitalla D, Muhlack S. Comparison of 200 mg retarded release levodopa/carbidopa - with 150 mg levodopa/carbidopa/entacapone application: pharmacokinetics and efficacy in patients with Parkinson's disease. *J Neural Transm (Vienna).* 2007;114(11):1457-1462. http://dx.doi.org/10.1007/s00702-007-0773-x

147. Navon N, Weiss Z, Gendreau M, Meckler J. Optimizing delivery of carbidopa/levodopa via the accordion pill[tm]: comparative pharmacokinetics and safety from 2 randomized studies in healthy volunteers. *Neurology.* 2018;90.