

Noninvasive options for 'wearing-off' in Parkinson's disease: a clinical consensus from a panel of UK Parkinson's disease specialists

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Practice points

- At each consultation, ask whether your patient is experiencing motor fluctuations, such as end-of-dose wearing-off and dyskinesia. Patient diaries or wearing-off questionnaires can be helpful here.
- Be aware that dopamine fluctuations can manifest in a range of nonmotor symptoms; these may include pain, problems swallowing, depression, anxiety and cognitive impairment.
- Consider the relative merits of adjusting your patient's existing regimen, for example, levodopa dose adjustments versus incorporating an adjuvant treatment into their polypharmacy regimen.
- Consider whether your patient exhibits any special features of Parkinson's disease (e.g., fatigue, psychosis), and how this affects the clinical decision in choice of agent.
- Be aware that, at some stage, your patient may need to be evaluated for advanced Parkinson's disease therapies.
- Monitor the outcome of any major change in prescription, for example, initiating adjuvant treatment.

In the past 4 years, two adjunctive treatment options to levodopa have been licensed for use in the UK in patients with Parkinson's disease (PD) and motor fluctuations: opicapone, a third-generation catechol-O-methyl transferase inhibitor, and safinamide, a monoamine oxidase B inhibitor. This clinical consensus outlines the practical considerations relating to motor fluctuations and managing wearing-off in patients with PD, and provides a clinical insight to adjunctive treatment options, including opicapone and safinamide. Practice-based opinion was provided from a multidisciplinary steering Group of eight UK-based movement disorder and PD specialists, including neurologists, geriatricians and a nurse specialist, from England, Scotland and Wales.

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Parkinson's disease (PD) is the second most common neurodegenerative disorder in the world after Alzheimer's [1]. The annual incidence of PD in the UK is 15–20 individuals per 100,000 [2], with a significantly higher incidence in males (1.5 times greater) compared with females [3]. With an increasing aging population, the estimated prevalence of PD in the UK is expected to rise by approximately 18% in the next 7 years; however, about 7% of people living with PD in 2018 will be under 60 years old [4].

This progressive disorder is characterized by motor symptoms (rigidity, bradykinesia, tremor, postural instability) [5] and a range of nonmotor symptoms (NMS) such as pain, constipation, problems with swallowing, depression, anxiety and cognitive impairment, which can occur from disease onset [6,7], and often before the onset of motor symptoms [8]. The gold standard treatment for PD is still considered to be levodopa (L-dopa) [9]. Initial

treatment with L-dopa allows for better symptom control and patient-related quality of life (QoL) for at least 7 years [10], compared with initial L-dopa sparing regimens (dopamine agonists [DAs] or monoamine oxidase B [MAO-B] inhibitors) [10]. There remains uncertainty about the optimum first drug class treatment choice in young onset PD, diagnosed at 45 years or younger, given the even greater long-term duration that these patients will require [10]. However, long-term use of L-dopa has its limitations: patients develop motor complications, such as motor fluctuations including end-of-dose wearing-off and L-dopa induced involuntary movements or dyskinesia [11] that impact on QoL [12]. Higher doses of L-dopa, which may be required in later disease, can also result in a greater frequency of dyskinesia as well as wearing-off symptoms [13]. Therefore, to improve motor fluctuations, ideally without exacerbating dyskinesia, many patients with PD will eventually require add-on therapies [2].

Although recent 2017 NICE guidance provides recommendations for first- and second-line adjunctive therapies for patients currently receiving L-dopa, the choice of drug class, treatment preference within a class, drug administration alone or in combination, when to prescribe and in what order to prescribe these treatments are personal decisions made jointly between physician and patient [2]. Furthermore, the fact that only two new oral treatments have been developed over the last 10 years has added to the challenge of individualizing and personalizing treatment for people living with PD; personalized medicine in PD is therefore a key unmet need [14].

Recently, however, two adjunctive treatment options have been licensed for use in the UK: opicapone is a third-generation catechol-O-methyl transferase (COMT) inhibitor [15] and safinamide has a main mechanism of action as a selective and reversible MAO-B inhibitor [16]. Safinamide is known to have additional activity as a selective sodium channel blocker and calcium modulator although the clinical utility of these properties is yet to be established [16,17]. To determine where these new therapies are to fit within the currently available treatment options requires expert advice and opinion from practical clinical experience.

A multidisciplinary steering group of eight UK-based experts (neurologists, geriatricians and a nurse specialist) who are all movement disorder and PD specialists from England, Scotland and Wales convened in November 2017 to put forward a clinical consensus of practical considerations for managing motor fluctuations in patients with PD that complement current national guidelines from NICE (England, Wales and Northern Ireland) [2] and SIGN (Scotland) [18]. The group had direct clinical experience of using PD therapies available in the UK, including the newer adjunctive therapies.

It is important to highlight that this article is not a review of the current literature, but practice-based opinion, including experience of using the two more recently available therapies, opicapone and safinamide. Differences in trial design have resulted in greater UK-wide clinical experience with opicapone within the Phase IV trial setting compared with safinamide, and this is reflected in the steering group's current clinical practice and experience. Also, with formulary applications for opicapone and safinamide still in progress across the UK, the ability to prescribe one or both agents is limited in some regions.

When considering a treatment regimen, key to the decision-making process is the agreement of a comprehensive care plan between the patient, family members/carer(s), specialist and secondary health providers [2].

Challenges to manage wearing-off in patients with PD on L-dopa

Although L-dopa is still the most effective antiparkinsonian drug [19], the development of a treatment strategy that provides the benefits of L-dopa with reduced motor complications, including wearing-off, remains a significant clinical challenge for patients with PD [20].

Wearing-off occurs toward the end of the treatment interval between individual doses of L-dopa, and occurs earlier and becomes more severe with disease progression and duration of drug treatment [21]; it often consists not only of motor symptoms (e.g., recurrent tremor, walking impairment) but also NMS (e.g., anxiety) [22]. Wearing-off generally improves with the next dose of antiparkinsonian medication [22]. Wearing-off eventually affects the majority of patients with PD [13,20,23,24]. Observational data from the DEEP study have shown that for patients receiving L-dopa therapy, wearing-off was experienced by: 63.0–75.6% of patients (diagnosed by neurologist and 19-item Wearing-Off Questionnaire (WOQ-19), respectively) at 1–2 years, 55.1–66.3% at 3–5 years and 76.8–80.4% at > 10 years [24]. Wearing-off of motor symptom control (e.g., recurrent tremor, slowing of walking) is generally easier for patients and physicians to identify than NMS (e.g., anxiety, restlessness). Day-to-day variability in symptom severity can also be dependent on how well a patient has slept, their specific activity or particular mood. The wearing-off questionnaire can be used to help patients and clinicians identify and monitor wearing-off [25,26].

As well as wearing-off, long-term treatment with L-dopa is associated with the development of other 'off' episodes [27]. One of the most frequent motor fluctuations is early-morning off periods [28], with the re-emergence

of parkinsonian symptoms in the morning before the first L-dopa dose. Other motor fluctuations include dose failures (individual L-dopa doses that do not result in the patient achieving the 'on' state) or delayed on-periods; these motor fluctuations can either be predictable or unpredictable [27].

Considerations in managing wearing-off in patients with PD on L-dopa

Modifiable factors

Advice from a PD specialist with expertise in managing wearing-off is essential. Before making dose adjustments to the L-dopa regimen, or adding another class of drug, a number of modifiable factors that directly impact on wearing-off need to be considered. These include: therapy compliance (which is influenced by depression, cognitive function and apathy), dietary factors (such as quantity and timing of protein intake) and gastrointestinal (GI) absorption (including *Helicobacter pylori* status and constipation). Other associated factors, such as insomnia and depression, can influence overall function in patients with PD, although depression can be a nonmotor manifestation of wearing-off [22].

GI absorption of L-dopa

Constipation

Constipation is a frequent NMS and the most common GI symptom of PD [29], affecting 60–80% of patients with PD [30] and negatively impacting on QoL [31]. Constipation is characterized by infrequent bowel movements and hard stools that are difficult to pass, as well as straining and pain when passing stools [32]. Constipation may interfere with L-dopa absorption, worsening motor fluctuations [31]. Dietary intervention is recommended, including increasing fiber intake and drinking plenty of fluids throughout the day [30]. If diet, fluid intake and exercise do not alleviate constipation, use of osmotic laxatives may be necessary [32].

Delayed gastric emptying

Impaired mobility of the stomach results in gastroparesis that can impact on the absorption and action of L-dopa [33]. Dietary changes to help improve symptoms of delayed gastric emptying, such as multiple small meals limited in fat and fiber content [34], together with exercise and, if necessary, pharmacotherapy, are all management options [35].

Dietary protein intake

A large protein meal can delay gastric emptying and competes with the absorption of L-dopa; therefore, the timing of L-dopa dosing around mealtimes is an important consideration [30]. Best practice guidance on managing patients with PD suggests a 40-min delay between L-dopa dosing and protein intake to help reduce wearing-off symptoms [30]. Data on dietary protein intake and GI absorption of L-dopa show improvements in motor fluctuations with dietary modifications, such as low protein diets and daily dietary protein consumed at the final main meal of the day (protein redistribution diet). Improvements have been observed in clinical response ranging from 30% (protein redistribution diet) to 82% (low protein diet) [36–38]. Recent recommendations advise that clinicians should discuss the potential of a protein redistribution diet with patients who are beginning to fluctuate in their response to dopaminergic medication [2]. Specialist advice from a dietician should also be considered [2].

Helicobacter pylori

The gut microbiome is increasingly recognized as playing an important role in the etiology of PD [39]. A high prevalence of one such microbe in patients with PD, the Gram-negative *H. pylori* bacterium, is thought to affect the absorption of L-dopa with the potential to cause motor fluctuations [40]. There are conflicting views as to whether patients with PD should be tested for *H. pylori* status and treatment initiated to eradicate infection in positive cases [40]. Further studies are needed to fully elucidate the relationship of L-dopa absorption in the presence of *H. pylori* and its impact on clinical outcomes [40,41]. Currently, there is no direct guidance in this area, with NICE guidance simply stating that “antiparkinsonian medicines should not be allowed to fail suddenly due to poor absorption” [2].

Other modifiable factors that can influence overall function in patients with PD

Assessments are recommended to monitor unintentional weight loss or gain, bone health (reduced bone density may indicate low vitamin D levels), insufficient fluid intake (which may indicate potential swallowing problems or concerns about bladder urgency), postural hypotension (potential fluid/salt intake imbalance) and physical difficulties that impair eating, drinking and preparing meals [30].

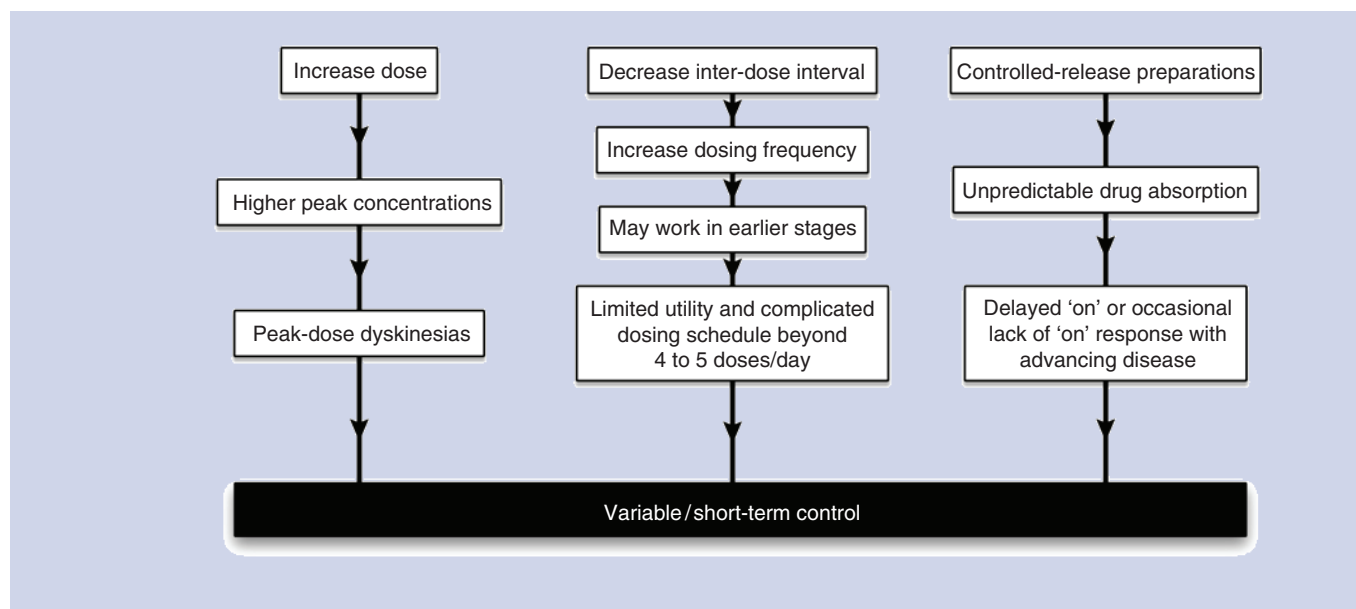


Figure 1. Traditional strategies to treat wearing-off. Adapted from Olanow, 2001 [42].

In patients with PD, other NMS including cognitive and mood dysfunction (e.g., anxiety, apathy, depression, cognitive impairment), postural hypotension, sleep disturbance and pain can impact on overall function. These NMS require appropriate investigation and individualized management with nonpharmacological strategies, followed by drug treatment, where appropriate [2].

Dose-adjusting strategies for L-dopa

Several strategies involving L-dopa alone are available to treat wearing-off, including increasing the dose of L-dopa, increasing the dosing frequency, using different formulations and adjusting dosing times (e.g., controlled-release preparations taken at bedtime) [42]. These traditional strategies, however, usually only offer variable, short-term control (Figure 1) [42].

Adjuvant treatment

Recent NICE guidelines recommend that patients with PD who have developed wearing-off or dyskinesia despite optimal L-dopa therapy should be offered a choice of COMT inhibitors, DAs or MAO-B inhibitors as adjunctive therapy to L-dopa (Figure 2) [2]. However, the decision regarding which adjunctive therapy to use or not to use, requires considerable clinical experience from the treating clinician.

First-line adjuvant treatment choice considerations

As part of the steering group's combined clinical experience, general factors influencing first-line adjunctive treatment choice of drug class and preparation within class, are summarized as checklists in Table 1. For example, for an elderly, frail patient with impaired cognition and difficulty swallowing, pill burden including complex daily regimens and potential swallowing difficulties are important factors in the choice of adjunctive treatment. Similarly, for a patient with recurring GI issues, tolerability and drug formulation with adequate absorption influence the choice of adjunctive treatment. Young patients with a history of impulsive behaviors should be cautioned about the risks of DAs.

Where do the opicapone & safinamide fit in the treatment of wearing-off?

Opicapone

Two Phase III randomized clinical trials have demonstrated efficacy of opicapone as an adjunctive therapy to L-dopa in patients with PD and end-of-dose motor fluctuations, with both studies meeting primary end point criteria. In the BIPARK-I trial, opicapone (50 mg) was superior to placebo and noninferior to entacapone. The primary end point was the change from baseline to end of study treatment in absolute off-time based on patient diaries [61]. In

Table 1. Factors influencing the choice of adjuvant treatment for wearing-off in patients with Parkinson's disease: clinical considerations from the Parkinson's disease steering group's experience.

What are the factors influencing adjuvant treatment choice?	Clinical considerations	Adjuvant drug class/drug considerations
<p>Symptoms:</p> <p>How symptomatic is the patient?</p> <p>Which are the patient's most troublesome motor symptoms?</p> <p>What are the patient's most troublesome NMS?</p> <p>Is the patient very elderly and frail?</p> <p>Does the patient have a history of impulsive behaviors?</p>	<p>Are there any motor symptoms that are refractory to L-dopa (e.g., tremor)? If so, consider referral for DBS (NB: none of the L-dopa augmenting strategies will improve symptoms that are truly L-dopa refractory)</p> <p>What potential is there for exacerbation of dyskinesia? (NB: background doses of L-dopa may need to be reviewed early after initiating any adjuvant treatment.)</p> <p>If adjustment unsuccessful, consider referral/initiating advanced therapies (i.e., apomorphine, DBS, DuoDopa)</p> <p>Does the patient have any of the following NMS: cognitive impairment, psychosis, low mood, apathy, fatigue, clouded thinking, excessive daytime somnolence, postural hypotension? These can be differentially affected by the different adjuvant drug classes</p>	<p>COMT inhibitors [43–45]:</p> <ul style="list-style-type: none"> • Potency: opicapone > tolcapone > entacapone [15] • Can exacerbate postural hypotension • Can exacerbate dyskinesia <p>DAs [46–48]:</p> <ul style="list-style-type: none"> • Can exacerbate dyskinesia • May cause or exacerbate postural hypotension • May result in, or exacerbate, cognitive impairment, impulsive behaviors or psychosis • Potential for use in RLS [46] <p>MAO-B inhibitors [16,49,50]:</p> <ul style="list-style-type: none"> • Can exacerbate postural hypotension • Can exacerbate confusion • Selegiline generally avoided in presence of postural hypotension, dementia, psychosis, cardiovascular disease and general frailty [51]
<p>Patient preference:</p> <p>What are the patient's priorities and treatment objectives?</p> <p>Are there influencers for patient's choice of treatment?</p>	<p>Consider adherence to treatment/compliance and contributory factors</p>	<p>Entacapone:</p> <ul style="list-style-type: none"> • Potential dark discoloration/staining of secretions with entacapone: urine, and to a lesser extent saliva and sweat (not harmful) [51,52]
<p>Tolerability:</p> <p>What are the tolerability issues with existing and previous PD medications?</p> <p>What are the tolerability considerations with adjunctive therapy?</p> <p>Is the patient very elderly and frail?</p>	<p>Directly consider co-existing conditions:</p> <ul style="list-style-type: none"> • GI tolerability • Neuropsychiatric problems, especially hallucinations, impulsive behaviors • Cardiovascular effects 	<p>COMT inhibitors:</p> <ul style="list-style-type: none"> • Hepatotoxicity with tolcapone requires monitoring [45] • Potential GI problems with entacapone: ~10% of patients develop diarrhea [53]; for prolonged/persistent diarrhea, entacapone should be discontinued [44]. <p>Approximately 1% of patients will discontinue treatment due to diarrhea [53]; it is not possible to predict which patients will experience diarrhea</p> <p>MAO-B inhibitors:</p> <ul style="list-style-type: none"> • Generally well tolerated [54] • Selegiline, specific caution: cardiovascular disease, especially arrhythmias [50] <p>DAs:</p> <ul style="list-style-type: none"> • May be poorly tolerated in frail, elderly patients [55]
<p>Polypharmacy:</p> <p>What other medications is the patient taking?</p>	<p>Consider drug interactions with common concomitant medications (e.g., antidepressants)</p>	<p>COMT inhibitors:</p> <ul style="list-style-type: none"> • Avoid treatment/concomitant use with nonselective MAO inhibitors (e.g., phenelzine, tranylcypromine) [44,45]; concomitant use of opicapone with MAO inhibitors used to treat PD is acceptable [43] <p>MAO-B inhibitors:</p> <ul style="list-style-type: none"> • For rasagiline and safinamide, avoid concomitant use with fluoxetine and fluvoxamine [16,49] • For selegiline, contraindicated with antidepressants in general [50] <p>DAs:</p> <ul style="list-style-type: none"> • For rotigotine patch, caution when taking CNS depressants (e.g., benzodiazepines, antipsychotics, antidepressants) [46]
<p>Pill burden:</p> <p>Can the patient manage the frequency of doses?</p> <p>What is the total number of tablets (including tablets for other conditions) that this patient is taking?</p>	<p>Complicated daily oral regimens may be a challenge for patients with impaired cognition</p> <p>Consider timing of adjuvant dose in relation to L-dopa dosing</p> <p>Consider nonoral drug preparations</p>	<p>COMT inhibitors:</p> <ul style="list-style-type: none"> • Opicapone is once-daily dosing taken at bedtime 1 h before/after L-dopa [43] • Tolcapone has a shorter duration of action versus opicapone and requires t.i.d. dosing [45] • Entacapone available in combination formulation with L-dopa/DDCI [52] <p>MAO-B inhibitors:</p> <ul style="list-style-type: none"> • Rasagiline, selegiline and safinamide available in once-daily formulations [16,49,50] <p>DAs:</p> <ul style="list-style-type: none"> • Newer (nonergot) DAs available in once-daily preparations: oral formulations – pramipexole [56] and ropinirole [57]; transdermal patch – rotigotine [46] • Transdermal skin patch formulations are less potent (24-h effect) [46]

MAO-B inhibitors are also licensed for early PD.

COMT: Catechol-O-methyl transferase; DA; Dopamine agonist; DBS: Deep-brain stimulation; DDCl: Dopa decarboxylase inhibitor; L-dopa: Levodopa; MAO-B: Monoamine oxidase B; NMS: Nonmotor symptom; PD: Parkinson's disease; RLS: Restless leg syndrome; t.i.d.: Three times daily.

Table 1. Factors influencing the choice of adjuvant treatment for wearing-off in patients with Parkinson’s disease: clinical considerations from the Parkinson’s disease steering group’s experience (cont.).

What are the factors influencing adjuvant treatment choice?	Clinical considerations	Adjuvant drug class/drug considerations
Swallowing: Does this patient have trouble swallowing? What are the swallowing considerations with adjunctive therapy?	Large tablet size may be an issue, especially with some combination formulations Consider nonoral drug preparations	<p>COMT inhibitors:</p> <ul style="list-style-type: none"> • Opicapone’s capsule form and size may offer a potential advantage for patients with swallowing difficulties (capsule 19 × 6.9 mm) [43,58], compared with L-dopa/carbidopa/entacapone (oval, round or ellipse-shaped tablets up to 16.2 × 10.2 mm) [59] <p>MAO-B inhibitors:</p> <ul style="list-style-type: none"> • Sublingual preparation available for selegiline [60] <p>DAs:</p> <ul style="list-style-type: none"> • DA patch formulation • Easier alternative for patients who have difficulties swallowing; however, as the patch needs to be applied to dry skin and pressed down firmly [46], difficulties may arise if skin is sweaty

MAO-B inhibitors are also licensed for early PD.
 COMT: Catechol-O-methyl transferase; DA: Dopamine agonist; DBS: Deep-brain stimulation; DDCl: Dopa decarboxylase inhibitor; L-dopa: Levodopa; MAO-B: Monoamine oxidase B; NMS: Nonmotor symptom; PD: Parkinson’s disease; RLS: Restless leg syndrome; t.i.d.: Three times daily.

the BIPARK-II trial, opicapone (50 mg) was associated with a significant reduction in mean daily off-time, with effect maintained for at least 1 year. Primary end point was the change from baseline in absolute off-time based on patient diaries during the double-blind phase [62]. Opicapone was well tolerated in both studies [61,62]. Marketing authorization in the EU was granted in June 2016 as an adjunctive therapy to L-dopa and decarboxylase inhibitors in adult patients with PD and end-of-dose motor fluctuations [15].

Clinical insights & scenarios for using opicapone

Opicapone is a long-acting, once-daily, purely peripheral COMT inhibitor [15], with more sustained COMT inhibition than tolcapone and entacapone. COMT inhibition at 1 h is 99, 82 and 68% with opicapone, tolcapone and entacapone, respectively, and at 9 h, 91, 16 and 0%, respectively [63,64]; the corresponding average treatment

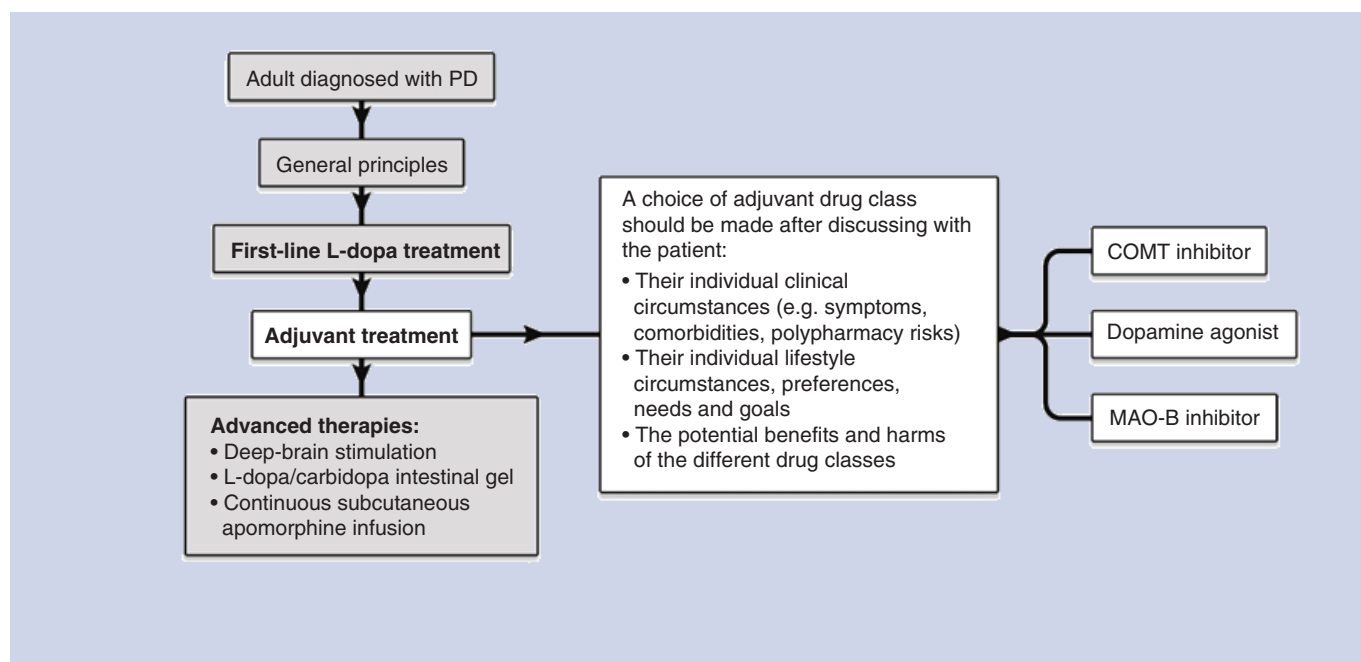


Figure 2. Managing motor symptoms in Parkinson’s disease: patient choice in adjuvant treatment.
 COMT: Catechol-O-methyl transferase; L-dopa: Levodopa; MAO-B: Monoamine oxidase B; PD: Parkinson’s disease.

Box 1. Clinical scenario – switching from levodopa/carbidopa/entacapone combination to opicapone plus levodopa/decarboxylase inhibitor.

1. Patients to continue on the L-dopa/carbidopa/entacapone combination until the penultimate dose of that day
2. For the last dose of that day:
 - Take L-dopa without entacapone, as either L-dopa/carbidopa (Sinemet), or L-dopa/benserazide (Madopar)
 - Take opicapone, either 1 h before or 1 h after L-dopa/carbidopa or L-dopa/benserazide
3. For the next 5–7 days:
 - Keep the L-dopa dose the same at each dose intake
 - Continue once-daily dosing with opicapone
4. Phone the patient to check for any adverse effects, including peak L-dopa effects (e.g., postural hypotension, psychosis, dyskinesia)
5. If peak L-dopa effects have occurred, then advise appropriate reductions in the dose of L-dopa/carbidopa or L-dopa/benserazide preparation (possibly by increasing the dose interval in the first instance)

L-dopa: Levodopa.

effect (off-time reduction vs placebo) is 60 min for opicapone [61], 90 min for tolcapone [65] and 40 min for entacapone [65].

Furthermore, opicapone has a favorable tolerability profile with a lack of hepatotoxicity in clinical trials and no severe diarrhea issues [43]. Opicapone does not produce the harmless, but often troublesome, reddish brown discoloration/staining of secretions (urine, sweat, saliva, semen) sometimes observed with entacapone [51,52]. The capsule formulation of opicapone, together with its size (19 mm in length and 6.91 mm in width) [43,58] offers a potential advantage for patients with swallowing difficulties, when compared with the tablet formulations of L-dopa/carbidopa/entacapone which have sizes ranging from a round tablet of 11.3 mm diameter at the lowest dose to an elongated ellipse-shaped tablet of 16.2 mm by 10.2 mm at the highest dose [59]. A benefit of once-daily dosing of opicapone is that it allows titration, where necessary, of L-dopa dosing independently of opicapone [43]. It is dosed at bedtime, 1 h before or 1 h after the last L-dopa dose of the day [43].

The steering group's combined clinical experience suggests that there are particular patients with PD where there are important clinical drivers for switching from entacapone to opicapone. It is the group's opinion that opicapone may be especially suited for patients who experience intermittent dose failures (individual L-dopa doses where the clinical effect is either none or negligible), who fail to reliably achieve good quality on time and who experience persistent wearing-off despite entacapone. The reason for switching in these scenarios is that COMT inhibition is both more complete and more prolonged with opicapone compared with entacapone [15]; this has been shown to translate to additional clinical benefit [66], and is consistent with the clinical experience of the group. Diarrhea is a common side effect (8–10%) for patients using entacapone [44,53] and the L-dopa/carbidopa/entacapone (Stalevo) combination tablet (12%) [52]. In cases where the severity of diarrhea leads to discontinuation of treatment, switching to opicapone is also an option. Moreover, entacapone nonresponders may be potential candidates for opicapone.

In these switching scenarios, the last entacapone dose of the day can be directly replaced by once-daily opicapone. Where entacapone is part of a combination tablet, for example, L-dopa/carbidopa/entacapone (Stalevo), in addition to replacing the entacapone component with opicapone, the L-dopa/decarboxylase inhibitor component must be substituted by either L-dopa/carbidopa (Sinemet) or L-dopa/benserazide (Madopar). Adjustment of the L-dopa dose is not usually required with the initial switch, but may need to be adjusted at a later stage depending on response; for instance, to avoid excessive L-dopa peaks that may cause peak dose dyskinesia, other hyperdopaminergic CNS effects, or to optimize L-dopa levels by a reduction in L-dopa dose and/or dose frequency to give further options as the disease progresses. The clinical team needs to make certain that patients do not inadvertently add opicapone to entacapone (resulting in a double dosage of COMT inhibitor) or, in the case of entacapone combination drugs, substitute this with opicapone but without L-dopa/carbidopa (Sinemet) or L-dopa/benserazide (Madopar), which would result in no L-dopa component. For patients currently using entacapone combination preparations, clear guidance needs to be given explaining that they are being switched from a combination tablet (entacapone/L-dopa/carbidopa) to an individual drug regimen (see **Box 1**).

Box 2. Clinical scenario – considerations in the ‘tailoring’ of adjunct therapies (catechol-O-methyl transferase inhibitors, monoamine oxidase inhibitors, dopamine agonists).

- A 64-year-old lady receiving:
 - L-dopa/carbidopa/entacapone 125 mg taken five times a day (7 am, 10 am, 1 pm, 4 pm, 7 pm)
 - Rasagiline 1 mg once-daily
 - Ropinirole XL 8 mg (amantadine was not tolerated)
- The patient developed significant motor and nonmotor wearing-off, and experienced pain 30–40 min before her next dose. Peak dose dyskinesia was also becoming socially embarrassing for her
- The L-dopa/carbidopa/entacapone dose was reduced, but taken more frequently (100 mg six times a day). At this dose the patient felt undertreated; reducing the ropinirole dose caused excessive mood disturbance. She also reported that she had never been convinced regarding the efficacy of rasagiline and thus a decision was made to see if safinamide would be more effective
- Rasagiline was discontinued. After a washout period of 14 days (as advised in the safinamide summary of product characteristics) [49], she was started on safinamide 50 mg
- Safinamide 50 mg had a positive impact on improving wearing-off, and when the dose was increased to 100 mg, the patient felt generally better, with a good reduction in nonmotor symptoms, and without noticeably worsening dyskinesia

L-dopa: Levodopa.

Safinamide

Two Phase III randomized clinical trials have demonstrated efficacy of safinamide as an adjunctive therapy to L-dopa in patients with mid- to late-stage PD with motor fluctuations. In the 24-week, double-blind, placebo-controlled SETTLE study, safinamide (50 mg/100 mg) significantly increased on-time without troublesome dyskinesia compared with placebo [67]. In study 016/018, a 24-week/2-year, double-blind, placebo-controlled study, safinamide (50 mg/100 mg) also significantly increased on-time without increasing dyskinesia compared with placebo. However, the primary end point, mean change from baseline to end point of the total score of the dyskinesia rating scale during on-time, was not met [68]. Both safinamide doses were well tolerated [67,68]. Marketing authorization in the EU was granted in December 2014 as an add-on therapy to stable dose L-dopa, alone or in combination with other PD therapies in mid- to late-stage fluctuating PD patients [17].

Clinical insights & scenarios for using safinamide

Safinamide is an α -aminoamide derivative that acts as a highly selective and reversible MAO-B inhibitor [17]. Safinamide has a favorable tolerability profile, but like rasagiline in this class, caution is needed with the concomitant antidepressant medications, fluoxetine and fluvoxamine [16].

As part of the steering group’s combined clinical experience, there are particular patients with PD where clinical drivers for using safinamide instead of rasagiline are warranted. Safinamide could be considered where patients have been unable to tolerate rasagiline or in cases of worsening dyskinesia associated with rasagiline. Safinamide could also be considered where patients continue to have wearing-off symptoms that have failed to respond to rasagiline or COMT inhibitors. However, robust data are currently lacking in terms of a head-to-head clinical trial comparison between safinamide and rasagiline. Clinical trial data have shown that safinamide reduces off-time by about 0.62 h/day versus placebo [53], and a Cochrane review reports reduction in off-time by about 0.93 h/day for rasagiline and selegiline [69], although comparisons of noncontemporaneous data can be misleading. Box 2 outlines considerations in the ‘tailoring’ of these adjunct therapies.

Conclusion

This clinical consensus is not intended to provide formal guidance on managing wearing-off, but to complement existing guidance and highlight areas of clinical practice that warrant further recognition in light of opicapone and safinamide becoming available for patients with PD on L-dopa therapy. Individual clinical experience is incorporated; while this experience is inevitably only anecdotal, it provides useful insights into current clinical practice based on the experience of this steering group. It is important to note that there has been more opportunity to gain clinical experience, including in Phase IV trials, with opicapone compared with safinamide in the UK, and this is reflected in the greater anecdotal experiences provided by the assembled steering group.

Although both opicapone and safinamide are available in the UK, these agents are not universally available on all formularies, and barriers exist in prescribing, more so in the community than the hospital setting. However, locally conducted evaluations on the use of PD medications will help to inform local clinical practice. The sharing of these methodologies will also be useful in facilitating the collection of data pertinent to UK clinical practice, and to consolidate the position of new treatments in current treatment algorithms for patients with PD experiencing wearing-off.

After more than 10 years without the development of new treatments for PD, opicapone and safinamide have now widened the armamentarium, providing greater choice to individualize treatment for patients with PD on L-dopa who have developed motor fluctuations.

Future perspective

The role of opicapone and safinamide alongside therapies for advanced PD in patients with wearing-off is an area that warrants future investigation. There is a possibility that these new treatments could eventually be used in combination with advanced PD therapies. In theory, opicapone could be used as an adjunctive therapy to carbidopa and L-dopa gel (DuoDopa), as opicapone has the potential to increase the bioavailability of DuoDopa, thereby reducing dosing/cassette requirements. Currently, there is no clinical evidence to support this strategy, but it represents an example of the versatility of once-daily adjunctive therapies. Other areas that warrant future investigation are the roles of opicapone and safinamide in early disease, the concomitant use of opicapone and safinamide with deep-brain stimulation and the routine genotyping of patients with PD for COMT polymorphisms to assess this as a predictor of opicapone response.

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References

Papers of special note have been highlighted as: ●● of considerable interest

1. Lebouvier T, Chaumette T, Paillusson S *et al.* The second brain and Parkinson's disease. *Eur. J. Neurosci.* 30(5), 735–741 (2009).
2. National Institute for Health and Care Excellence. Parkinson's disease in adults: diagnosis and management (2017). www.nice.org.uk/guidance/ng71/evidence/full-guideline-pdf-4538466253
- **Provides current guidance on the management of Parkinson's disease in England.**
3. Wooten GF, Currie LJ, Bovbjerg VE, Lee JK, Patrie J. Are men at greater risk for Parkinson's disease than women? *J. Neurol. Neurosurg. Psychiatry* 75(4), 637–639 (2004).
4. Parkinson's UK. The incidence and prevalence of Parkinson's in the UK (2018). www.parkinsons.org.uk/sites/default/files/2018-01/CS2960Incidenceandprevalenceportbrandingsummaryreport.pdf
5. Odin P, Ray Chaudhuri K, Slevin JT *et al.* Collective physician perspectives on non-oral medication approaches for the management of clinically relevant unresolved issues in Parkinson's disease: consensus from an international survey and discussion program. *Parkinsonism Relat. Disord.* 21(10), 1133–1144 (2015).
6. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol.* 5(3), 235–245 (2006).
7. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. *Nat. Rev. Neurosci.* 18(8), 509 (2017).
8. Sauerbier A, Qamar MA, Rajah T, Chaudhuri KR. New concepts in the pathogenesis and presentation of Parkinson's disease. *Clin. Med. (Lond).* 16(4), 365–370 (2016).
9. LeWitt PA. Levodopa therapy for Parkinson's disease: pharmacokinetics and pharmacodynamics. *Mov. Disord.* 30(1), 64–72 (2015).
10. PD MED Collaborative Group, Gray R, Ives N *et al.* Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial. *Lancet* 384(9949), 1196–1205 (2014).
11. Aquino CC, Fox SH. Clinical spectrum of levodopa-induced complications. *Mov. Disord.* 30(1), 80–89 (2015).
12. 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.* 20(2), 224–230 (2005).
13. Fahn S, Oakes D, Shoulson I *et al.* Levodopa and the progression of Parkinson's Disease. *N. Engl. J. Med.* 351(24), 2498–2508 (2004).
14. Titova N, Chaudhuri KR. Personalized medicine in Parkinson's disease: time to be precise. *Mov. Disord.* 32(8), 1147–1154 (2017).
15. Fabbri M, Rosa MM, Ferreira JJ. Clinical pharmacology review of opicapone for the treatment of Parkinson's disease. *Neurodegener. Dis. Manag.* 6(5), 349–362 (2016).
16. Profile Pharma Ltd. Xadago (safinamide) 50mg film-coated tablets Xadago 100mg film-coated tablets – summary of product characteristics (2018). www.medicines.org.uk/emc/product/2159
17. Fabbri M, Rosa MM, Abreu D, Ferreira JJ. Clinical pharmacology review of safinamide for the treatment of Parkinson's disease. *Neurodegener. Dis. Manag.* 5(6), 481–496 (2015).
18. Scottish Intercollegiate Guidelines Network. Diagnosis and pharmacological management of Parkinson's disease. *SIGN 113* (2010). www.sign.ac.uk/sign-113-diagnosis-and-pharmacological-management-of-parkinson-s-disease.html
19. Chaudhuri KR, Jenner P. Two hundred years since James Parkinson's essay on the shaking palsy – have we made progress? Insights from the James Parkinson's 200 years course held in London, March 2017. *Mov. Disord.* 32(9), 1311–1315 (2017).
20. Stocchi F, Rascol O, Kieburtz K *et al.* Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: the STRIDE-PD study. *Ann. Neurol.* 68(1), 18–27 (2010).
21. Cenci MA. Presynaptic mechanisms of L-DOPA-induced dyskinesia: the findings, the debate, and the therapeutic implications. *Front. Neurol.* 5, 242 (2014).
22. Varanese S, Birnbaum Z, Rossi R, Di Rocco A. Treatment of advanced Parkinson's disease. *Parkinsons Dis.* 2010, 480260 (2010).
23. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov. Disord.* 16(3), 448–458 (2001).
24. Stocchi F, Antonini A, Barone P *et al.* Early Detection of wearing-off in Parkinson disease: the DEEP study. *Parkinsonism Relat. Disord.* 20(2), 204–211 (2014).
25. Stacy M, Hauser R, Oertel W *et al.* End-of-dose wearing-off in Parkinson disease: a 9-question survey assessment. *Clin. Neuropharmacol.* 29(6), 312–321 (2006).
- **The wearing-off questionnaire (WOQ-9) can be used to help patients and clinicians identify and monitor wearing-off.**
26. Stacy M, Bowron A, Guttman M *et al.* Identification of motor and nonmotor wearing-off in Parkinson's disease: comparison of a patient questionnaire versus a clinician assessment. *Mov. Disord.* 20(6), 726–733 (2005).
27. 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.* 31(9), 1366–1372 (2016).

28. Rizos A, Martinez-Martin P, Odin P *et al.* Characterizing motor and non-motor aspects of early-morning off periods in Parkinson's disease: an international multicenter study. *Parkinsonism Relat. Disord.* 20(11), 1231–1235 (2014).
29. Rossi M, Merello M, Perez-Lloret S. Management of constipation in Parkinson's disease. *Expert Opin. Pharmacother.* 16(4), 547–557 (2015).
30. Parkinson's UK. Best practice guideline for dietitians on the management of Parkinson's (2015). www.parkinsons.org.uk/sites/default/files/2017-12/dietitians-bestpracticeguideline.pdf
31. Sakakibara R, Kishi M, Ogawa E *et al.* Bladder, bowel, and sexual dysfunction in Parkinson's disease. *Parkinsons Dis.* 2011, 924605 (2011).
32. European Parkinson's Disease Association (EPDA). Bowel problems (2017). www.epda.eu.com/about-parkinsons/symptoms/non-motor-symptoms/bowel-problems/
33. Marrinan S, Emmanuel AV, Burn DJ. Delayed gastric emptying in Parkinson's disease. *Mov. Disord.* 29(1), 23–32 (2014).
34. Liu N, Abell T. Gastroparesis updates on pathogenesis and management. *Gut Liver* 11(5), 579–589 (2017).
35. Mukherjee A, Biswas A, Das SK. Gut dysfunction in Parkinson's disease. *World J. Gastroenterol.* 22(25), 5742–5754 (2016).
36. Virmani T, Tazan S, Mazzoni P, Ford B, Greene PE. Motor fluctuations due to interaction between dietary protein and levodopa in Parkinson's disease. *J. Clin. Mov. Disord.* 3, 8 (2016).
37. Bracco F, Malesani R, Saladini M, Battistin L. Protein redistribution diet and antiparkinsonian response to levodopa. *Eur. Neurol.* 31(2), 68–71 (1991).
38. Pincus JH, Barry K. Influence of dietary protein on motor fluctuations in Parkinson's disease. *Arch. Neurol.* 44(3), 270–272 (1987).
39. Sampson TR, Debelius JW, Thron T *et al.* Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. *Cell* 167(6), 1469–1480 (2016).
40. Çamcı G, Oğuz S. Association between Parkinson's disease and *Helicobacter pylori*. *J. Clin. Neurol.* 12(2), 147–150 (2016).
41. Liu H, Su W, Li S *et al.* Eradication of *Helicobacter pylori* infection might improve clinical status of patients with Parkinson's disease, especially on bradykinesia. *Clin. Neurol. Neurosurg.* 160, 101–104 (2017).
42. Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. *Neurology* 56(5), S1–S86 (2001).
43. Bial Pharma UK Ltd. Ongentys (opicapone) 50mg hard capsules – summary of product characteristics (2016). www.medicines.org.uk/emc/product/7386
44. Orion Pharma (UK) Ltd. Comtess (entacapone) 200 mg film-coated tablets – summary of product characteristics (2017). www.medicines.org.uk/emc/product/1632
45. Meda Pharmaceuticals. Tasmartol (tolcapone) 100mg tablets – summary of product characteristics (2014). www.medicines.org.uk/emc/medicine/15900
46. UCB Pharma Ltd. Neupro (rotigotine) 4mg/24h transdermal patch – summary of product characteristics (2017). www.medicines.org.uk/emc/product/1996
47. GlaxoSmithKline UK. Requip (ropinirole) 0.25mg tablets – summary of product characteristics (2017). www.medicines.org.uk/emc/product/1160/smpc
48. Boehringer Ingelheim Ltd. MIRAPEXIN (pramipexole) – summary of product characteristics (2018). www.medicines.org.uk/emc/product/7694
49. Teva Pharmaceuticals Ltd. Azilect (rasagiline) 1mg tablets – summary of product characteristics (2017). www.medicines.org.uk/emc/product/74/smpc
50. Orion Pharma (UK) Ltd. Eldepryl (selegiline) 5mg tablets – summary of product characteristics (2015). www.medicines.org.uk/emc/product/2251/smpc
51. Macmahon DG. The initial drug treatment of older patients with Parkinson's disease – consider an agonist, but don't demonise dopa. *Age Ageing* 32, 244–245 (2003).
52. Orion Pharma (UK) Ltd. Stalevo 100/25/200mg – summary of product characteristics (2018). www.medicines.org.uk/emc/product/6518/smpc
53. Novartis Pharmaceuticals Corporation. COMTAN (entacapone) prescribing information (2016). www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/comtan.pdf
54. Riederer P, Laux G. MAO-inhibitors in Parkinson's Disease. *Exp. Neurobiol.* 20(1), 1–17 (2011).
55. Thanvi BR, Lo TCN. Long term motor complications of levodopa: clinical features, mechanisms, and management strategies. *Postgrad. Med. J.* 80(946), 452–458 (2004).
56. Boehringer Ingelheim Ltd. MIRAPEXIN (Pramipexole) prolonged-release tablets – summary of product characteristics (2018). www.medicines.org.uk/emc/product/4455/smpc

57. Zentiva. Aimpart XL (Ropinirole prolonged-release) 2 mg prolonged-release tablets – summary of product characteristics (2013). www.medicines.org.uk/emc/product/2830
58. Capsugel. Coni-Snap[®] capsule size information (2013). www.capsugel.com/knowledge-center/coni-snap-capsule-size-information
59. Accord Healthcare Ltd. Levodopa, carbidopa, entacapone accord film-coated tablets public assessment report (2016). www.mhra.gov.uk/home/groups/par/documents/websiteresources/con658452.pdf
60. Cephalon (UK) Ltd. Zelapar (selegiline oral lyophilisate) – summary of product characteristics (2015). www.medicines.org.uk/emc/product/884/smpc
61. 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.* 15(2), 154–165 (2016).
 - **Provides data from the pivotal Phase III study (BIPARK 1) for opicapone.**
62. Lees AJ, Ferreira J, Rascol O *et al.* Opicapone as adjunct to levodopa therapy in patients with Parkinson disease and motor fluctuations. *JAMA Neurol.* 74(2), 197–206 (2017).
 - **Provides data from the pivotal Phase III study (BIPARK 2) for opicapone.**
63. Almeida L, Rocha JF, Falcão A *et al.* Pharmacokinetics, pharmacodynamics and tolerability of opicapone, a novel catechol-o-methyltransferase inhibitor, in healthy subjects. *Clin. Pharmacokinet.* 52(2), 139–151 (2013).
64. Bonifacio MJ, Torrão L, Loureiro AI, Wright LC, Soares-da-Silva P. 2.243 Opicapone: characterization of a novel peripheral long-acting catechol-o-methyltransferase inhibitor. *Parkinsonism Relat. Disord.* 18, S125 (2012).
65. Deane K, Spieker S, Clarke CE. Catechol-O-methyltransferase inhibitors for levodopa-induced complications in Parkinson's disease. *Cochrane Database Syst. Rev.*(4), CD004554 (2004).
66. Ferreira JJ, Lees AJ, Poewe W *et al.* Effectiveness of opicapone and switching from entacapone in fluctuating Parkinson disease. *Neurology* 90(21), e1849–e1857 (2018).
67. 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.* 74(2), 216–224 (2017).
 - **Provides data from the pivotal Phase III study for safinamide.**
68. Borgohain R, Szasz J, Stanzione P *et al.* Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease. *Mov. Disord.* 29(10), 1273–1280 (2014).
 - **Provides 2-year clinical trial data for safinamide.**
69. Stowe R, Ives N, Clarke CE *et al.* Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson's disease patients with motor complications. *Cochrane Database Syst. Rev.* (7), CD007166 (2010).