

General

Opicapone, a Novel Catechol-O-methyl Transferase Inhibitor, for Treatment of Parkinson's Disease "Off" Episodes

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Parkinson's Disease (PD) is a common neurodegenerative disorder and the leading cause of disability. It causes significant morbidity and disability through a plethora of symptoms, including movement disorders, sleep disturbances, and cognitive and psychiatric symptoms. The traditional pathogenesis theory of PD involves the loss of dopaminergic neurons in the substantia nigra (SN). Classically, treatment is pursued with an assortment of medications that are directed at overcoming this deficiency with levodopa being central to most treatment plans. Patients taking levodopa tend to experience "off episodes" with decreasing medication levels, causing large fluctuations in their symptoms. These off episodes are disturbing and a source of morbidity for these patients. Opicapone is a novel, peripherally acting Catechol-O-methyl transferase (COMT) inhibitor that is used as adjunctive therapy to carbidopa/levodopa for treatment and prevention of "off episodes." It has been approved for use as an adjunct to levodopa since 2016 in Europe and has recently (April 2020) gained FDA approval for use in the USA. By inhibiting COMT, opicapone slows levodopa metabolism and increases its availability. Several clinical studies demonstrated significant improvement in treatment efficacy and reduction in duration of "off episodes." The main side effect demonstrated was dyskinesia, mostly with the 100mg dose, which is higher than the approved, effective dose of 50mg. Post-marketing surveillance and analysis are required to further elucidate its safety profile and contribute to patient selection. This paper reviews the seminal and latest evidence in the treatment of PD "off episodes" with the novel drug Opicapone, including efficacy, safety, and clinical indications.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease associated with the accumulation of α -synuclein protein in nuclei of the substantia nigra (SN) of the brainstem and the cortex. The clinical presentation includes stereotyped motor symptoms of tremor, rigidity, bradykinesia, and postural instability.¹ In addition, non-motor symptoms can manifest, including hyposmia or anosmia, genitourinary com-

plications, constipation, cognitive impairment, psychiatric issues, and rapid eye movement (REM) sleep behavior disorder.²

PD is a common disorder and the fastest-growing neurodegenerative disorder. In North America alone, the prevalence of PD in 2020 is estimated to be 572 individuals per 100,000, approximately 930,000 Americans.³ The mean age at diagnosis is 70.5 years.⁴ Starting from age 50, a higher prevalence has been cited in men.⁵

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Patients with PD taking long-term levodopa, the most common therapy, experience fluctuations throughout the day in the presence and intensity of symptoms. Typically, the recurrence of symptoms is mitigated after a new dose of medication.⁶ These end-of-dose deteriorations, or wearing “off” states, are classically described by motor complications such as rest tremor, bradykinesia, and rigidity.^{7,8} Non-motor fluctuations, such as anxiety, mood changes, hyperhidrosis, slowed cognition, fatigue, and akathisia, may also manifest.^{9,10} Off episodes have been traced as a key factor in health-related quality of life reporting.¹¹

There is a large variation in the time it takes for “off” episodes to develop in the patient throughout the course of PD treatment. These symptoms present in 30% of patients in as little as 40 weeks of treatment; in others (about 40% of patients), they only appear after 4-6 years of treatment.^{12,13} Another study showed that off episode frequency increased to 76.2% in patients living with the disease for 10-15 years.¹⁴ Typically, younger age of PD onset, female gender, and higher dose of levodopa predispose towards higher rates of motor fluctuations.^{15,16} Genetic variations, differences in comorbidities, and availability of adjunctive therapies can also influence the onset of the off episodes.¹⁷ About 75% of motor fluctuations also present with nonmotor symptoms.¹⁰ Some studies show up to 40% of all patients with PD report an experience of anxiety that disrupts daily life.¹⁸

Opicapone (Ongentys) is a novel Catechol-O-methyl transferase (COMT) inhibitor, used as adjunctive treatment with levodopa and the carbidopa/levodopa combination in patients with PD experiencing “off episodes.” The background, indications, and clinical data surrounding its use are reviewed in this paper.

METHODS

We conducted literature searches using PubMed and Google Scholar between 2020-2021. Articles were chosen based on relevance to Opicapone and its therapeutic effects on Parkinsonism. We selected primary literature as well as clinical trial studies to reflect the validity of the review. Older articles were included as well to refer to previous background information.

The PubMed and Google Scholar keywords searched were as follows: Parkinsonism, Parkinson’s disease, opicapone, neurodegenerative disease, and COMT inhibitor.

PARKINSON’S DISEASE

Parkinson’s disease (PD) is a vanguard among parkinsonism. It is a neurodegenerative disease associated with an accumulation of α -synuclein protein, or Lewy bodies, in nuclei of the substantia nigra (SN) of the brainstem and in the cortex. These aggregates can also be found in regions of the enteric and peripheral nervous system.¹⁹

EPIDEMIOLOGY

Per the 2016 Global Burden of Disease, neurological disorders have become the leading cause of disability, and PD is the fastest growing among them. Since PD prevalence increases with age, the burden of disease falls heavily on aging populations.^{20,21} The mean age at diagnosis is 70.5 years.⁴ Between 1990 and 2016, the global burden of PD has more than doubled from 2.5 million patients to 6.1 million patients.²⁰ In North America alone, the prevalence in 2020 is estimated to be 572 individuals per 100,000 or approximately 930,000 Americans.³ Starting from age 50, a higher prevalence of PD has been cited in men.⁵ However, this gender-based divergence remains poorly understood in light of multifactorial risk factors and emerging disease subtypes.²²

PATHOPHYSIOLOGY

The loss of dopaminergic neurons has been suggested to be the primary factor for motor symptoms, whereas the death of cholinergic, serotonergic, and noradrenergic neurons may be responsible for cognitive, psychiatric, and other prodromal changes.^{23,24} An oft-cited hypothesis of disease onset describes the course of PD over six stages with the earliest dysfunction beginning at the olfactory bulb and the medulla.²⁵ In the early stages, patients may experience hyposmia, gastrointestinal difficulties, such as constipation, and REM sleep disorders. The stereotyped motor function loss results from the decay of neurons in the pars compacta in SN and other components of the basal ganglia and midbrain over the course of stages 3 and 4. The late-stage disease presents with hallucinations and further cognitive decline due to widespread cortical progression. Alternative hypotheses have been proposed reconsidering the directionality of α -synuclein aggregation such that in some PD subtypes, nigrostriatal dopaminergic dysfunction precedes the involvement of the autonomic nervous system.²⁶

At the cellular level, the pathophysiology of PD overlaps with numerous molecular pathways associated with the management of misfolded proteins.²⁷ Gene involvement of α -synuclein (*SNCA*) and leucine-rich repeat kinase 2 (*LRRK2*) implicate the ubiquitin-proteasomal system and autophagy-lysosomal pathway, respectively.^{28,29} Mitochondrial dysfunction ranges from impaired mitochondrial maintenance, defective mitophagy, calcium imbalance, oxidative stress, and neuroinflammation.³⁰⁻³⁴ These are thought to be due to the downstream effects of the *LRRK2* scaffold upon Parkin (*PRKN*), PTEN induced putative kinase 1 (*PINK1*), β -glucocerebrosidase 1 (*GBA1*) proteins, among others.³⁵⁻³⁷ Definitive neuroanatomical models have not yet been determined to trace pathology up from the cellular level.³⁸ Recent studies have indicated further molecular-level gastroenterological associations involving toll-like receptors in the gut microbiome, reactive pleocytosis in the bowel, and absence of anti-inflammatory, butyrate-producing bacteria.³⁹⁻⁴³

RISK FACTORS

Genetic inheritance has been demonstrated for PD.⁴⁴ Multiple inheritance patterns have been shown, and several nuclear genes are linked to disease progression. While no conclusive direct relationships have been shown between environmental triggers, these continue to be a source of study. The strongest risk factors for late-stage diagnosis of PD include a family history of either PD or tremor, constipation, and absence of smoking (smoking has a protective role).⁴⁵ Caffeine may also be protective.¹ Other risk factors include depression, exposure to pesticides, herbicides, heavy metals, and high consumption of dairy products.⁴⁶ Further study of risk factors and the genetic basis of the disease could be useful to the development of disease-modifying therapies or preventative measures.

DIAGNOSIS AND CLINICAL PRESENTATION

PD is best known for its characteristic movement abnormalities, such as resting tremor, bradykinesia, rigidity, decreased coordination, postural instability, and abnormal gait.¹ In addition to these classic symptoms, current clinical practice appreciates many non-motor symptoms, including hyposmia or anosmia, genitourinary complications, constipation, cognitive impairment, psychiatric issues, and rapid eye movement (REM) sleep behavior disorder.² The clinician must apply caution to distinguish resting tremors from essential tremors and re-emergent tremors. Resting tremors in PD occur while the body part is at rest and not engaged in purposeful action. Re-emergent tremors can be confused for essential tremors, thereby making PD subtyping more challenging.⁴⁷ Diagnosis of PD occurs with the identification of α -synuclein aggregates in the SN, basal ganglia, midbrain, and regions of the peripheral nervous system.⁴⁸ While the gold standard remains the identification of the Lewy bodies at post-mortem pathological examination, detection of prodromal symptoms in the pre-motor phase could prove useful for diagnosis at an earlier stage of the disease.^{49,50} Various phenomenological and systematic categorizations have been made to distinguish subtypes of PD. These categorizations focus on the rate of disease progression (malignant or mild) on either motor or non-motor axes, age at onset (below 50 vs. over 50), and responsiveness to medications, such as dopamine replacement therapies.⁵¹⁻⁵³ Molecular-level studies have become more popular in influencing the data-driven clustering of subtypes.²⁷ Some imaging techniques can aid as diagnostic tools in PD detection: dopamine transport single-photon emission computed tomography, to distinguish resting tremor in PD from essential tremor, and magnetic resonance imaging, to distinguish PD from other parkinsonism syndromes.² Responsiveness to dopaminergic therapy is a useful diagnostic marker alongside on-off fluctuations in concert with drug dosage. There are absolute exclusion criteria to rule out PD: lack of responsiveness of dopaminergic neurons to high-dose levodopa, the responsiveness of these neurons to dopamine receptor blockers, progressive degeneration in limb movement coordination, aphasia, or oculomotor abnormalities.²⁴ Red flags such as rapid gait impair-

ment, bulbar dysfunction, severe autonomic failure such as orthostatic hypotension, and severe urinary retention/incontinence would also exclude PD as the diagnosis.²⁴ Characteristics of advanced Parkinson's disease include severe off periods, excessive daytime sleepiness, difficulties in ambulation, impaired cognition and/or presence of psychiatric symptoms, dysphagia, dysarthria, and required assistance for mundane activities.⁵³ Often, the difficulties in ambulation manifest as freezing of gait, impairments in balance, dyskinesia, and recurrent falls.²⁴ These, along with psychiatric symptoms such as hallucinations, psychosis, depression, and apathy, predicate the need for a caregiver or placement at nursing homes.⁵⁴

CURRENT TREATMENT OPTIONS

Parkinson's Disease (PD) is usually the result of balancing treatment effects and disease impact on daily life.² There are both pharmacologic and nonpharmacologic treatment options for patients, and these may also be combined and tailored to disease severity and individual choice.²

CONSERVATIVE TREATMENT

Nonpharmacologic treatment, including aerobic exercise or physical therapy, is initiated at diagnosis and should be continued throughout the disease course. Moderate-intensity aerobic exercise, defined as achieving >60% maximum heart rate for four days per week for six months, has shown a positive impact on the clinical course of PD.⁵⁵ Although exercise does not slow the progression of akinesia or rigidity, it has been shown to alleviate secondary symptoms such as flexed posture and nonmotor symptoms, as well as ameliorate motor tasks.^{55,56} A recent study investigating the effects of high-intensity treadmill training found that motor function worsened significantly less over the span of 6 months in the exercise group when compared to the control group.⁵⁷

PHARMACOLOGICAL THERAPY

There are several pharmacologic classes of PD treatment, including monoamine oxidase type B (MAO-B) inhibitors, adamantanes (amantadine), dopamine agonists (DAs), levodopa, anticholinergics, and Catechol-O-methyl transferase (COMT) inhibitors. MAO-B inhibitors such as selegiline, rasagiline, and safinamide are beneficial in early PD and can be used in patients of any age. Among the MAO-B inhibitors, safinamide is used as adjunctive therapy for levodopa in advanced PD. When combined with levodopa, MAO-B inhibitors improve the long-term clinical course of PD as measured by the Unified Parkinson Disease Rating Scale over the span of 7 years.⁵⁸ Amantadine affects several neurotransmitter systems and is used as a monotherapy alternative to MAO-B inhibitors. Amantadine acts by increasing dopamine release, inhibiting dopamine reuptake and NMDA receptors, stimulating dopamine receptors, and exerting central anticholinergic effects.⁵⁹ Amantadine is preferentially utilized in tremor-prominent-PD and has been

shown to have greater efficacy in treating rigidity and bradykinesia than anticholinergic drugs used in PD treatment.⁶⁰ Non-ergot DAs are preferentially used when motor symptoms interfere with a patient's quality of life. They include the oral medications pramipexole and ropinirole, and the transdermal formulation rotigotine. They are most effective in early disease as monotherapy. Levodopa revolutionized PD treatment over half a century ago, relieving severely disabled PD patients from their symptoms.⁶¹ Levodopa provides a more effective improvement in motor function and quality of life when compared to Das.^{12,62-64} Formulations include carbidopa-levodopa (Sinemet) and benserazide-levodopa (Prolopa), both of which add peripheral decarboxylase inhibitor action, decreasing adverse effects.⁶⁵ Levodopa is initiated when motor symptoms interfere with the quality of life. Patients less than 65 years of age with clinically significant tremors and without bradykinesia or gait disturbance can be given anticholinergics. Anticholinergics such as trihexyphenidyl and benztropine can be useful in patients with persistent tremors already being treated with DAs or levodopa. COMT inhibitors such as entacapone, tolcapone, and opicapone, potentiate the effect of levodopa and reduce the 'off-time when Parkinson's symptoms return.⁶⁴ Levodopa dosage should be reduced by 10-30% when combined with COMT inhibitors to avoid dopaminergic side effects.⁶⁶

INTERVENTIONAL THERAPY

Deep brain stimulation and MRI-guided focused ultrasounds are surgical treatment options used in patients with complications and frequent off periods that are non-responsive to medication adjustments.⁶⁷ Deep brain stimulation requires surgical placement of unilateral/bilateral leads within the brain. MRI-guided focused ultrasound utilizes ultrasound beams in order to scar the thalamus while under MRI monitoring to interrupt the abnormal activity and decrease tremors.⁶⁷ These methods are useful for patients with medication-responsive motor symptoms but with complications such as dyskinesias. These tools can reduce medication refractory tremors by targeting the thalamus.

LINES AND HIERARCHY OF TREATMENT

Nonpharmacological treatment with or without MAO-B inhibitors is recommended for patients without the significant quality of life impairment.^{64,68} Patients with motor symptoms and cognitive impairment should be given levodopa, along with treatment for underlying neurobehavioral dysfunctions. These patients should not receive anticholinergics or amantadine. In patients with pure motor symptoms, initial therapy should include levodopa preparations, DAs, or MAO-B inhibitors if treating tremor and bradykinesia, or anticholinergic agents if treating only tremor. If symptoms continue to progress or the patient experiences "wearing off," increase the dosages of the previously mentioned medications and/or add amantadine or COMT inhibitors. Advanced treatment options include levodopa-carbidopa preparations. If the disease continues to

progress even with dose modifications, deep brain stimulation may be used. If the patient experiences tremors and bradykinesia, a unilateral/bilateral deep brain stimulation of the subthalamic nucleus or globus pallidus interna should be done. Otherwise, unilaterally focused ultrasound thalamotomy or deep brain stimulation of the thalamus may be used for patients experiencing tremors. Finally, exercise and physical therapy should be upheld throughout the course of the disease to prevent deterioration of the patient's condition.

SIDE-EFFECTS OF CURRENT TREATMENTS

Pharmacological treatments of PD cause numerous adverse effects. MAO-B inhibitors commonly cause nausea and headaches, but may also cause confusion and hallucinations in severe cases.⁶⁹ Amantadine may precipitate livedo reticularis and ankle edema.⁷⁰ Anticholinergics result in an array of adverse effects. Older patients and patients with cognitive impairments are particularly susceptible to hallucinations, confusion, and memory loss. These antimuscarinics may cause peripheral issues such as dry mouth, blurred vision, constipation, impaired sweating, and tachycardia.⁷¹ Side-effects of levodopa for older patients may include confusion, hallucinations, delusions, agitation, and psychosis. Adverse effects of DA agonists include hallucinations, hypotension, nausea, vomiting, pathological gambling, compulsive shopping, and hypersexuality.⁷² The side effects of COMT inhibitors are commonly due to dopaminergic overstimulation. This may lead to hallucinations, dyskinesia, or somnolence. Additionally, COMT inhibitors can cause a benign orange discoloration of urine or diarrhea which may require drug discontinuation if severe enough.^{73,74}

An important area where current treatments fall short, as described above, is the multitude of adverse effects. Additionally, with the progression of the disease, the efficacy of levodopa decreases and ceases to improve disabling motor and nonmotor features of PD.⁷⁵ Other interventions such as COMT inhibitors, MAO-B inhibitors, DAs, and deep brain stimulation have been used in combination with levodopa to alleviate some of these shortcomings; however, these drugs are associated with their own side effects as mentioned above. The drug classes each improve only one symptom type, making them inefficient.⁷⁶ Additionally, novel treatments such gene therapy or targeted molecular therapy tend to be expensive, complex for patients, or not available at their facility or in their country. Overall, there is still a lack of efficacious, cheap, neuroprotective, and restorative PD treatment, which has led to unmet medical needs in PD management.⁷⁵

OPICAPONE

Opicapone, otherwise known as Ongentys®, is a peripherally acting agent that selectively and reversibly binds to COMT enzymes. It is used as an adjunctive treatment to the carbidopa/levodopa combination in patients with PD, typ-

ically experiencing 'off periods,' as per the Food and Drug Administration guidelines.

Compounds such as the COMT inhibitors have been manufactured to increase the efficiency of central-acting levodopa, a dopamine precursor that is peripherally broken down by enzymes such as L-aminoacid decarboxylase (AADC) and COMT. Previously, the clinically available COMT inhibitors have demonstrated an increased risk of acute liver failure (tolcapone), liver safety concerns (necapone), and limited efficacy with frequent dosing (entacapone).⁷⁷⁻⁷⁹ These shortcomings necessitated the development of novel COMT inhibitors such as Opicapone.

PROPERTIES AND GUIDELINES

Opicapone is a hydrophilic oxadiazole analog with a pyridine N-oxide at the 3rd position, providing its strong inhibitory effect while also minimizing cell toxicity.⁸⁰ It is recommended as a 50mg once-daily oral capsule at bedtime. It is advised that patients do not have oral intake for the hour preceding or following opicapone. This is because peak and total drug exposure may decrease significantly following a meal when compared to fasting.⁸¹

Adjusted guidelines, utilizing the Child-Pugh scoring system (system for measuring chronic liver disease), were created for adult patients with hepatopathy. A patient with mild hepatopathy (Child-Pugh A) needs no adjustments. A patient with Child-Pugh B is recommended to have 25mg daily at bedtime, and finally, at Child-Pugh C, patients should avoid the use of opicapone, mainly due to lack of data on this population.⁸² Guidelines for the geriatric population are similar to that of the adult population. Contraindications for opicapone include concomitant use of MAO inhibitors, pheochromocytoma, paraganglioma, or any other catecholamine secreting neoplasms.⁸³

Opicapone is available in 25 or 50mg hard gelatin capsules. This drug is considered flammable and should be stored at a temperature below 30°C.⁸³

As of June 2016, The European Medicines Agency approved opicapone, originally developed by BIAL Pharmaceuticals, for marketing authorization throughout the European Union as an adjunct to levodopa and decarboxylase inhibitors in PD patients and end-of-dose motor fluctuations. In April 2020, the Food and Drug Administration approved opicapone as an adjunctive treatment for Sinemet in PD patients experiencing "off episodes."⁸⁴

MECHANISM OF ACTION

COMT is responsible for catalyzing the methyl group transfer of S-adenosyl-L-methionine to a substrate with a catechol group. When the degradation of levodopa is prevented by carbidopa or benserazide, COMT becomes the major metabolizing enzyme of levodopa.⁸⁵ As a COMT inhibitor, opicapone inhibits the O-methylation of levodopa to 3-O-methyldopa.⁸⁵ Opicapone has been found to act through reversible and selectively peripheral COMT inhibition, decreasing the degradation of levodopa. One of the major advantages of opicapone is its selective action in the periphery, setting it apart from other COMT inhibitors, which also

act in the central nervous system.⁸⁰ Finally, opicapone has a high binding affinity, resulting in a slow dissociation rate constant (K_d).⁸⁶

PHARMACODYNAMICS AND PHARMACOKINETICS

Oral administration of opicapone has been shown to have long-lasting COMT inhibitory action due to its slow, complex dissociation rate.^{87,88} This inhibitory action was found to last longer than other COMT inhibitory drugs such as entacapone.⁷⁸ A study conducted by Almeida *et al.* has shown that opicapone has a dose-dependent increase in peak serum concentration (C_{max}) and overall drug exposure within the bloodstream (AUC).⁸¹ Opicapone, when combined with Prolopa®, has been shown to increase the C_{max} of levodopa and benserazide; however, it has not shown similar effects when combined with DA agonists or MAO B inhibitors.^{82,89}

Studies have shown that opicapone inhibition of COMT may be dose-dependent. In such studies, a 10mg opicapone dose elicited 36.1% inhibition.⁹⁰ Total inhibition of 100% was elicited by 200mg or greater.⁹¹ Half-life was found to be between 0.8 (50mg) and 3.2 (1200mg) hours; however, as mentioned above, COMT inhibitory effect of opicapone can be detected even after 24 hours due to the compound's slow dissociation rate.⁹¹

Elimination of opicapone has been shown to be accomplished through sulfation at the hepato-biliary system by the BIA 9-1103 enzyme.⁹² This has been supported by the fact that opicapone levels have been shown to be elevated in patients with moderate liver impairment.⁹³ The maximum urinary excretion rate is said to occur within 4 hours of dose and continues to rise in a less than dose-proportional manner.⁸¹ Opicapone is primarily excreted through the feces (70%) and expired air (20%).⁹³

At 25mg, 50mg, and 75mg, the use of opicapone has demonstrated increased levodopa availability when compared to placebo or entacapone.⁹³ Finally, due to the long-lasting effects of opicapone, it is recommended that opicapone be taken only once daily. Further, since levodopa dosing may require several doses throughout the day, opicapone is recommended to be taken at bedtime, allowing for easily modifiable levodopa regimens without concern for potential absorption interactions.⁹⁴

According to a randomized, double-blind, placebo-controlled study comparing the pharmacokinetics of opicapone in Japanese and white subjects, neither ethnicity, age, nor sex influenced drug effects.⁹⁵ The FDA further elaborates that there were no clinically significant differences in the pharmacokinetics of opicapone when comparing Japanese, Caucasian, Asian, or Black populations.⁸³

SIDE EFFECTS AND ADVERSE EVENTS

The controlled, double-blind, randomized phase III study BIPARK-I investigated the effects of incremental dosages (5, 25, 50mg) of opicapone compared to placebo and entacapone.⁹⁶ This study found that all doses had the potential to elicit dyskinesia, with 50mg dose producing the most prominent signs.⁹⁶ Dyskinesia was the most common side

effect and generally occurred within the first three weeks.⁹⁶ It was unclear whether the dyskinesia was related to the increased levodopa levels or the direct effect of opicapone. A follow-up study BIPARK-II found similar results.⁹⁷ In a pooled analysis of these two similarly designed studies, adverse events such as insomnia, dry mouth, dizziness, constipation, and elevated creatine phosphokinase were all recorded. There is concern that adverse events may ensue in patients with hepatopathy due to the possibility of increased plasma concentration.⁹⁸

OPICAPONE IN PARKINSON'S TREATMENT – CLINICAL DATA

EFFICACY

Data on the efficacy of opicapone in PD patients with motor fluctuations come from the results of several clinical trials to date, including BIPARK-I, BIPARK-II, their open-label extensions, and the OPTIPARK open-label study (Table 1 & 2).^{82,88,96,99-102} For Phase II trials, two double-blind studies were conducted involving a total of 45 PD patients with motor fluctuations.^{82,88,102} The first study was a multi-center, double-blind, randomized, placebo-controlled study of opicapone in 40 patients (20 female) with diagnosed idiopathic PD.⁸⁸ Data were evaluated from 35 subjects. Patients had a modified Hoen and Yahr stage of less than 5 in the OFF state, and the mean age was 67.5 years.¹⁰³ Efficacy measures were reported following administration of 5, 15, and 30 mg doses of opicapone compared to placebo. Following the 4-week double-blind treatment period, significant changes from baseline were found in motor responses as recorded in patient diaries, including absolute OFF time and ON time without dyskinesia.⁸⁸ A significant change in absolute OFF time of -145.0 minutes was reported for the 30 mg dose compared to placebo. Treatment with opicapone was also found to decrease the 'time to ON' and 'time to best-ON' compared to placebo, but these changes were not significantly different from the placebo.⁸⁸ The next Phase II trial was a 3-center, double-blind, randomized, placebo-controlled crossover study of opicapone in 10 patients (4 f) with diagnosed idiopathic PD.¹⁰² Patients had a modified Hoen and Yahr stage of less than 5 in the OFF state, and the mean age was 58.4 years.¹⁰³ On day 3 of the study, several significant efficacy measures were reported following the administration of 25, 50, and 100 mg doses of opicapone compared to placebo. The ON-time duration was found to have increased 18% with the 25 mg dose, and 25% with the 50 mg dose.¹⁰² The duration of ON time without dyskinesias also increased more than 100% following administration of the 25mg dose, and 73% with the 50mg dose. In addition, there was a notable 49% increase in ON time with dyskinesias with the 100mg dose.¹⁰²

Two Phase III trials to date plus their open-label extensions have yielded efficacy results for opicapone.^{82,96,100,101} The first was BIPARK-1, a randomized, double-blind, placebo-controlled, and active-controlled trial of opicapone in 600 PD patients with end-of-dose motor fluctuations.⁹⁶ Repeated oral doses of 5, 25, and 50 mg were investigated alongside an active comparator entaco-

pone 200mg and placebo over 14-15 weeks. The 50 mg opicapone dose was found to be superior to placebo and non-inferior to entacapone 200mg for reducing OFF symptoms. The mean change in 'time in the OFF state' was -116.8 minutes with 50 mg opicapone and -56 min with placebo. In addition, the mean change in OFF state with 5 and 25 mg doses did not differ from placebo.⁹⁶ The next study was BIPARK-2, a randomized clinical double-blind placebo-controlled study of opicapone in 427 patients (169 f) with diagnosed PD for at least 3 years.¹⁰⁰ Patients had a modified Hoen and Yahr stage of 1 to 3, and the mean age was 63.1 years. Either a 25 or 50 mg dose of opicapone or placebo was taken in the evening, at least 1 hour after the last dose of levodopa. Primary efficacy analysis showed that 50 mg opicapone was superior for the reduction of OFF-time compared to placebo (-54 min).¹⁰⁰ In addition, the 25 and 50 mg doses showed no significant increase 'ON time without dyskinesia' compared to placebo. The double-blind phase of the study lasted 14-15 weeks, followed by an open-label period lasting one year that was completed by 286 patients. At the end of the open-label period, the 50 mg once-daily dose was found to be associated with a significant reduction in mean daily OFF-time maintained for at least one year.¹⁰⁰

A subsequent pooled analysis of combined patient data from both the double-blind and open-label portions of BIPARK-I and BIPARK-2 yielded further information about the efficacy of opicapone.¹⁰¹ From the analysis of the double-blind phase, the mean treatment effect versus placebo was -35.1 minutes and -58.1 minutes in absolute daily OFF time for 25 mg and 50 mg doses, respectively. Significant reductions in OFF time were found, as were significant increases in ON time.¹⁰¹ From the analysis of the open-label phase, 341 patients switched doses from 25mg to 50mg opicapone, and 12 patients reduced the dose to 5 mg. The patient diary results of patients assigned to 50 mg in the double-blind phase indicated maintenance of treatment effects throughout the open-label phase. Patients and providers both noted qualitative improvements in motor fluctuations during the open-label phase, indicating maintenance of treatment effects via questionnaires and rating scales (i.e., PGI-C: Patient Global Impression of Change; UPDRS: Unified Parkinson's Disease Rating Scale; PDQ-8: Parkinson's Disease Questionnaire; CGI-C: Clinician's Global Impression of Change).¹⁰¹ Remarks have also been published regarding the methodologies of the opicapone Phase III studies.^{104,105}

The most recent clinical trial of opicapone was OPTIPARK, a prospective open-label, single-arm, multi-center study of opicapone in 502 patients with diagnosed PD and Hoehn and Yahr stage I-IV during ON periods.⁹⁹ Of the 495 treated patients (179 females) the mean age was 67.7 years. All patients were undergoing treatment with 3-7 daily doses of levodopa, and none were currently or previously taking tolcapone or entacapone. After 3 months, 71.3% of patients experienced an improvement in the Clinician's Global Impression of Change (CGI-C), and 76.9% experienced an improvement after 6 months. The primary endpoint of the OPTIPARK study was CGI-C, but significant improvements in secondary assessments included the UD-

PRS parameter 'activities of daily living during OFF' (mean \pm SD: -3.0 ± 4.6) and 'motor scores during ON' (-4.6 ± 8.1), as well as PDQ-8 score (-3.4 ± 12.8) and NMSS score (-6.8 ± 19.7).⁹⁹ Opicapone was generally well-tolerated, and the most frequent side effect was dyskinesia (11.5%).⁹⁹

SAFETY AND ADVERSE EVENTS

No remarkable side effects were reported in Phase I studies of single or repeated doses of opicapone.^{81,92} In patients with moderate chronic hepatic impairment (Child-Pugh category B, score 7-9), the bioavailability of a single 50mg dose of opicapone was found to be significantly higher at 72 hours compared to healthy controls.⁹² This finding supports the hypothesis that opicapone undergoes hepatobiliary excretion and may be subject to first-pass effects. No dose adjustment was recommended for patients with mild to moderate chronic hepatic impairment as a result of this finding.⁹² It was noted, however, that levodopa and/or opicapone dosage may require adjustment in select patients due to the potential for enhanced levodopa dopaminergic responses.⁹² No serious cases of hepatotoxicity were reported in the BIPARK-I or BIPARK-II clinical trials, or their open-label extensions.^{96,101,106,107} Regarding cardiac effects, Holter monitoring before and after single oral doses of opicapone found that neither 50 mg nor 800 mg caused significant QTc prolongation.¹⁰⁸

Pooled analysis of the BIPARK-I and BIPARK-II studies showed that the adverse effects of opicapone treatment included dyskinesia, insomnia, dry mouth, dizziness, constipation, and blood creatine phosphokinase elevation.^{82,101,109} No serious adverse events were reported in the open-label extension periods of these trials. Dyskinesia was the most commonly reported side effect across both BIPARK study double-blind phases, with 17.7% in the combined opicapone groups versus 6.2% with placebo.¹⁰¹ Dyskinesia was also the most frequently reported side effect in the OPTIPARK open-label study, occurring in 11.5% patients.⁹⁹ Among the total treatment-emergent adverse effects (TEAEs) reported in the results of the OPTIPARK study, the most common TEAE was also dyskinesia ($n=57$), followed by dry mouth ($n=32$), dizziness ($n=24$), nausea ($n=22$), and constipation ($n=20$).⁹⁹ The TEAE most frequently leading to discontinuation in OPTIPARK was nausea ($n=10$). A total of 34 serious TEAEs occurred in OPTIPARK, and 7 of these were treatment-related. In addition, total of 84 TEAEs leading to discontinuation were reported, and 66 of these were treatment-related.⁹⁹

Current prescribing information indicates that opicapone (Ongentys®) is absolutely contraindicated in patients taking non-selective monoamine oxidase (MAO) inhibitors, or in patients with pheochromocytoma paraganglioma, or other catecholamine secreting neoplasms.^{83,110} A summary of clinical efficacy and comparative studies can be seen in Tables 1 and 2.

CONCLUSION

PD is a common neurodegenerative disease with an increasing prevalence in increasing age. It is a common source of disability and morbidity and the fastest-growing neurodegenerative disorder today. The leading pathophysiological theory involves the loss of dopaminergic neurons, mostly in the basal ganglia, as well as the death of cholinergic, serotonergic, and noradrenergic neurons. These neuronal losses are not limited to the central nervous system, but also occur in the gut. Several molecular factors have been identified that may contribute to the pathogenesis, and studies are underway.

Though no definite inheritance pattern for PD has been determined, family history remains the strongest risk factor. Other risk factors include depression, dairy consumption, and exposure to environmental toxins, whereas caffeine and smoking may have a protective role. The clinical presentation of PD includes stereotypical movement disorders, bradykinesia, rigidity gait disturbances, and postural instability. It also spans genitourinary symptoms, constipation, and sleep disorders, as well as cognitive and psychiatric deterioration. While official diagnosis can only be made post-mortem with the detection of Lewy Bodies in an autopsy, diagnoses are usually made based on clinical presentation with the aid of imaging and the response to levodopa treatment.

Traditional pharmacotherapy is based on increasing dopamine and acetylcholine effect to overcome the loss of neuronal activity and includes a central role for levodopa. Unfortunately, as the natural course of PD progresses, patients being to experience periods of return of symptoms, despite therapy; these symptoms, referred to as "off episodes," usually correlate with decreased medication activity and are alleviated with the next medication dose. Such "off episodes" are a source of great discomfort and morbidity in PD patients. Opicapone is a novel peripheral COMT inhibitor that is used in combination with standard treatment to prevent and alleviate these episodes. It acts by decreasing the metabolism of levodopa and has a synergistic effect. It was mainly developed to increase efficacy and avoid common side effects with previous generation COMT inhibitors. It has been approved as an adjunct therapy for PD treatment since 2016, and recently gained FDA approval for use in the USA.

Opicapone is approved for use with a single nightly 50mg dose, or a reduced 25mg dose in hepatic dysfunction (Child-Pugh B); due to lack of evidence, it should be avoided in patients classified as Child-Pugh C. Opicapone has been studied in several clinical trials, both versus placebo and entacapone, and found to be effective and safe. It was able to significantly extend the activity of levodopa, and decrease the duration of "off episodes" by about 50 daily minutes on average with a single 50mg nightly dose. The more recent OPTIPARK study also demonstrated significant improvement in the quality of life of patients taking opicapone, along with improvement in objective indices.

Opicapone use is not without risk, and the leading side effect is dyskinesia. Though it is considered safe for use in

Table 1. Clinical Efficacy and Safety

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Almeida et al. 2013 ⁸¹ Phase I	64 young healthy male volunteers; single rising oral doses (10, 25, 50, 100, 200, 400, 800 and 1200 mg).	Well tolerated at all doses tested; dose-dependent maximum COMT inhibition, 36.1 - 100% (10 to ≥ 200 mg); 72hrs post-dose COMT inhibition, 5.9 to 54.6% (10 – 800 mg).	Opicapone appears to be well tolerated at doses higher than 50 mg; systemic exposure to opicapone and its metabolites may increase proportional to dose. Dosage may safely be increased in select patients if poor response to starting 50 mg dose.
Almeida et al. 2013 ⁸¹ Phase I	12 young healthy male volunteers; single oral doses (50 mg).	Significantly lower drug concentration (238-635ng/mL) after standard breakfast compared to fasting.	Systemic exposure to opicapone and its metabolites may decrease after a meal. Be aware of the current clinical recommendation to take opicapone at bedtime.
Rocha et al. 2016 ¹⁰² Phase II	10 PD patients with motor fluctuations; single oral doses (25, 50, 100 mg)	Dose-dependent increase in levodopa plasma concentration; well tolerated with standard-release 100/25 mg levodopa+carbidopa or benserazide. Decreased 'time to best ON' and increased 'ON duration.'	In select patients with poor response to 50 mg, consider increasing opicapone dose with the aim of increasing circulating levodopa.
Ferreira et al. 2015 ⁸⁸ Phase II	35 PD patients with motor fluctuations; repeated oral doses (5, 15, 30 mg)	Dose-dependent increase in levodopa plasma concentration; decrease in absolute 'OFF' time with 30 mg (-145 min), increased 'ON time without dyskinesia.'	Lower doses of opicapone may have less impact on motor fluctuations in PD patients. Expect longer 'OFF' and shorter 'ON' periods if opicapone dose is reduced below 30 mg.
Lees et al. 2017 (BIPARK 2) ¹⁰⁶ Phase III	427 PD patients with end-of-dose motor fluctuations; repeated oral doses (25, 50 mg) compared to placebo over 14-15 weeks.	50 mg opicapone was superior for reduction of OFF time compared to placebo (-54 min); 25 and 50 mg opicapone did not significant increase 'ON time without dyskinesia' compared to placebo.	Opicapone 50mg once daily reduces OFF time in PD patients with motor fluctuations taking levodopa. Opicapone may be considered as a once daily COMT inhibitor, as it appears safe and well tolerated up to 1 year.
Ferreira et al. 2019 (BIPARK-1 and BIPARK-2 open-label extension) ¹⁰¹ Phase III	662 PD patients with end-of-dose motor fluctuations; repeated oral doses (25, 50 mg) compared to placebo over a 1 year open-label study period.	Mean treatment effect versus placebo was - 35.1 min and -58.1 min reduction in absolute daily OFF time for 25 mg and 50 mg, respectively. Switching 25mg to 50gm or placebo to opicapone improved motor fluctuations. Patients and providers noted maintenance of effect.	Opicapone was found to be safe and efficacious for up to 1 year, and may be a viable long-term option for PD patients with end-of-dose motor fluctuations. Data suggest that patients may respond positively to the new drug regimen.
Reichmann et al. 2020 (OPTIPARK open-label) ⁹⁹ Phase IV	495 treated patients with PD and motor fluctuations; 50 mg once daily at bedtime added to existing PD treatment for 3 or 6 months.	After 3 months, 71.3% of patients experienced any improvement in Clinician's Global Impression of Change (CGI-C), 76.9% after 6 months. Significant improvements also reported in PGI-C, UPDRS, and PDQ-8.* Generally well-tolerated; most frequent side effect dyskinesia (11.5%).	Addition of opicapone to levodopa treatment may improve patient perceptions of their global PD condition. Clinicians also may notice improvement. Consider opicapone in patients not already taking a COMT inhibitor.

* PGI-C: Patient Global Impression of Change, UPDRS: Unified Parkinson's Disease Rating Scale PDQ-8: Parkinson's Disease Questionnaire CGI-C: Clinician's Global Impression of Change

hepatic dysfunction, more evidence is likely needed to support this claim, and after-marketing studies will be required to elucidate safety in this and the general population.

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AUTHOR RESPONSIBILITIES

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- Ariel W, (study design, manuscript preparation)
- Jonathan I, (study design, manuscript preparation)
- Binil J, (study design, manuscript preparation)
- Jessica K, (study design, manuscript preparation)
- Rachel K, (study design, manuscript preparation)

Table 2. Comparative Studies

<p>Ferreira et al. 2016 (BIPARK-1)⁹⁶ Phase III</p>	<p>600 PD patients with end-of-dose motor fluctuations; repeated oral doses (5, 25, 50 mg) with active comparator entacapone 200mg over 14-15 weeks.</p>	<p>50 mg opicapone was superior to placebo and non-inferior to entacapone 200mg for reducing OFF symptoms. Mean change in 'time in the OFF state' was -116.8 minutes with 50 mg opicapone and -56 min with placebo. Mean change in OFF state with 5 and 25 mg did not differ from placebo.</p>	<p>50mg opicapone treatment was non-inferior to entacapone with a similar safety profile. Consider adding opicapone at bedtime for patients with PD and end-of-dose motor fluctuations.</p>
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REFERENCES

1. Kouli A, Torsney KM, Kuan WL. Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis. In: *Parkinson's Disease: Pathogenesis and Clinical Aspects*. Codon Publications; 2018:3-26. <https://doi.org/10.15586/codonpublications.parkinsonsdisease.2018.ch1>
2. Armstrong MJ, Okun MS. Diagnosis and Treatment of Parkinson Disease: A Review. *JAMA*. 2020;323(6):548-560. [doi:10.1001/jama.2019.22360](https://doi.org/10.1001/jama.2019.22360)
3. Marras C, Beck JC, Bower JH, et al. Prevalence of Parkinson's disease across North America. *npj Parkinson's Disease*. 2018;4(1):21. [doi:10.1038/s41531-018-0058-0](https://doi.org/10.1038/s41531-018-0058-0)
4. Van Den Eeden SK, Tanner CM, Bernstein AL, et al. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. *American Journal of Epidemiology*. 2003;157(11):1015-1022. [doi:10.1093/aje/kwg068](https://doi.org/10.1093/aje/kwg068)
5. Elbaz A, Bower JH, Maraganore DM, et al. Risk tables for parkinsonism and Parkinson's disease. *Journal of Clinical Epidemiology*. 2002;55(1):25-31. [doi:10.1016/s0895-4356\(01\)00425-5](https://doi.org/10.1016/s0895-4356(01)00425-5)
6. Stocchi F. The levodopa wearing-off phenomenon in Parkinson's disease: Pharmacokinetic considerations. *Expert Opinion on Pharmacotherapy*. 2006;7(10):1399-1407. [doi:10.1517/14656566.7.10.1399](https://doi.org/10.1517/14656566.7.10.1399)
7. Marsden CD, Parkes JD. "ON-OFF" EFFECTS IN PATIENTS WITH PARKINSON'S DISEASE ON CHRONIC LEVODOPA THERAPY. *The Lancet*. 1976;307(7954):292-296. [doi:10.1016/s0140-6736\(76\)91416-1](https://doi.org/10.1016/s0140-6736(76)91416-1)
8. Chou KL, Stacy M, Simuni T, et al. The spectrum of "off" in Parkinson's disease: What have we learned over 40 years? *Parkinsonism & Related Disorders*. 2018;51:9-16. [doi:10.1016/j.parkreldis.2018.02.001](https://doi.org/10.1016/j.parkreldis.2018.02.001)
9. Witjas T, Kaphan E, Azulay JP, et al. Nonmotor fluctuations in Parkinson's disease: Frequent and disabling. *Neurology*. 2002;59(3):408-413. [doi:10.1212/wnl.59.3.408](https://doi.org/10.1212/wnl.59.3.408)
10. Richard IH, Frank S, McDermott MP, et al. The ups and downs of Parkinson disease: A prospective study of mood and anxiety fluctuations. *Cognitive and Behavioral Neurology*. 2004;17(4):201-207.
11. Kerr C, Lloyd EJ, Kosmas CE, et al. Health-related quality of life in Parkinson's: impact of 'off' time and stated treatment preferences. *Qual Life Res*. 2016;25(6):1505-1515. [doi:10.1007/s11136-015-1187-0](https://doi.org/10.1007/s11136-015-1187-0)
12. Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson's Disease. *N Engl J Med*. 2004;351(24):2498-2508. [doi:10.1056/nejmoa033447](https://doi.org/10.1056/nejmoa033447)
13. Ahlskog JE, Muentner MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord*. 2001;16(3):448-458. [doi:10.1002/mds.1090](https://doi.org/10.1002/mds.1090)
14. Wan Y, Yuan C, Hou X, et al. Wearing-off Identification in Parkinson's Disease: The shapd-woq Study. *Front Neurol*. 2020;11. [doi:10.3389/fneur.2020.00116](https://doi.org/10.3389/fneur.2020.00116)
15. Kostic V, Przedborski S, Flaster E, Sternic N. Early development of levodopa-induced dyskinesias and response fluctuations in young-onset Parkinson's disease. *Neurology*. 1991;41(2):202-205. [doi:10.1212/wnl.41.2_part_1.202](https://doi.org/10.1212/wnl.41.2_part_1.202)
16. Schrag A, Ben-Shlomo Y, Brown R, Marsden CD, Quinn N. Young-onset Parkinson's disease revisited—clinical features, natural history, and mortality. *Mov Disord*. 1998;13(6):885-894. [doi:10.1002/mds.870130605](https://doi.org/10.1002/mds.870130605)
17. Bhidayasiri R, Hattori N, Jeon B, et al. Asian perspectives on the recognition and management of levodopa 'wearing-off' in Parkinson's disease. *Expert Review of Neurotherapeutics*. 2015;15(11):1285-1297. [doi:10.1586/14737175.2015.1088783](https://doi.org/10.1586/14737175.2015.1088783)
18. Lutz SG, Holmes JD, Ready EA, Jenkins ME, Johnson AM. Clinical presentation of anxiety in Parkinson's disease: A scoping review. *OTJR: Occupation, Participation and Health*. 2016;36(3):134-147. [doi:10.1177/1539449216661714](https://doi.org/10.1177/1539449216661714)
19. Breen DP, Halliday GM, Lang AE. Gut-brain axis and the spread of α -synuclein pathology: Vagal highway or dead end? *Mov Disord*. 2019;34(3):307-316. [doi:10.1002/mds.27556](https://doi.org/10.1002/mds.27556)
20. Ray Dorsey E, Elbaz A, Nichols E, et al. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*. 2018;17(11):939-953. [doi:10.1016/s1474-4422\(18\)30295-3](https://doi.org/10.1016/s1474-4422(18)30295-3)

21. Pringsheim T, Jette N, Frolkis A, Steeves TDL. The prevalence of Parkinson's disease: A systematic review and meta-analysis. *Mov Disord*. 2014;29(13):1583-1590. doi:10.1002/mds.25945
22. Meoni S, Macerollo A, Moro E. Sex differences in movement disorders. *Nat Rev Neurol*. 2020;16(2):84-96. doi:10.1038/s41582-019-0294-x
23. Factor SA, McDonald WM, Goldstein FC. The role of neurotransmitters in the development of Parkinson's disease-related psychosis. *Eur J Neurol*. 2017;24(10):1244-1254. doi:10.1111/ene.13376
24. Berg D, Postuma RB, Adler CH, et al. MDS research criteria for prodromal Parkinson's disease. *Mov Disord*. 2015;30(12):1600-1611. doi:10.1002/mds.26431
25. Braak H, Del Tredici K, Rüb U, De Vos RAI, Jansen Steur ENH, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging*. 2003;24(2):197-211. doi:10.1016/s0197-4580(02)00065-9
26. Borghammer P, Van Den Berge N. Brain-First versus Gut-First Parkinson's Disease: A Hypothesis. *JPD*. 2019;9(s2):S281-S295. doi:10.3233/jpd-191721
27. Li D, Mastaglia FL, Fletcher S, Wilton SD. Progress in the molecular pathogenesis and nucleic acid therapeutics for Parkinson's disease in the precision medicine era. *Med Res Rev*. 2020;40(6):2650-2681. doi:10.1002/med.21718
28. Chen ML, Wu RM. LRRK 2 gene mutations in the pathophysiology of the ROCO domain and therapeutic targets for Parkinson's disease: A review. *J Biomed Sci*. 2018;25(1). doi:10.1186/s12929-018-0454-0
29. Walden H, Muqit MMK. Ubiquitin and Parkinson's disease through the looking glass of genetics. *Biochemical Journal*. 2017;474(9):1439-1451. doi:10.1042/bcj20160498
30. Manecka DL, Vanderperre B, Fon EA, Durcan TM. The neuroprotective role of protein quality control in halting the development of alpha-synuclein pathology. *Front Mol Neurosci*. 2017;10. doi:10.3389/fnmol.2017.00311
31. Park JS, Davis RL, Sue CM. Mitochondrial Dysfunction in Parkinson's Disease: New Mechanistic Insights and Therapeutic Perspectives. *Curr Neurol Neurosci Rep*. 2018;18(5). doi:10.1007/s11910-018-0829-3
32. Xilouri M, Brekk OR, Stefanis L. Autophagy and Alpha-Synuclein: Relevance to Parkinson's Disease and Related Synucleopathies. *Mov Disord*. 2016;31(2):178-192. doi:10.1002/mds.26477
33. Gao F, Yang J, Wang D, et al. Mitophagy in Parkinson's disease: Pathogenic and therapeutic implications. *Front Neurol*. 2017;8(OCT). doi:10.3389/fneur.2017.00527
34. Ryan BJ, Hoek S, Fon EA, Wade-Martins R. Mitochondrial dysfunction and mitophagy in Parkinson's: From familial to sporadic disease. *Trends in Biochemical Sciences*. 2015;40(4):200-210. doi:10.1016/j.tibs.2015.02.003
35. Manzoni C. The LRRK2-macroautophagy axis and its relevance to Parkinson's disease. *Biochemical Society Transactions*. 2017;45(1):155-162. doi:10.1042/bst20160265
36. Nguyen TN, Padman BS, Lazarou M. Deciphering the Molecular Signals of PINK1/Parkin Mitophagy. *Trends in Cell Biology*. 2016;26(10):733-744. doi:10.1016/j.tcb.2016.05.008
37. Narendra D, Tanaka A, Suen DF, Youle RJ. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. *Journal of Cell Biology*. 2008;183(5):795-803. doi:10.1083/jcb.200809125
38. Cacabelos R. Parkinson's disease: From pathogenesis to pharmacogenomics. *IJMS*. 2017;18(3):551. doi:10.3390/ijms18030551
39. Caputi V, Giron M. Microbiome-gut-brain axis and toll-like receptors in parkinson's disease. *IJMS*. 2018;19(6):1689. doi:10.3390/ijms19061689
40. Chiang HL, Lin CH. Altered Gut Microbiome and Intestinal Pathology in Parkinson's Disease. *JMD*. 2019;12(2):67-85. doi:10.14802/jmd.18067
41. Bullich C, Keshavarzian A, Garssen J, Kraneveld A, Perez-Pardo P. Gut Vibes in Parkinson's Disease: The Microbiota-Gut-Brain Axis. *Mov Disord Clin Pract*. 2019;6(8):639-651. doi:10.1002/mdc3.12840
42. Devos D, Lebouvier T, Lardeux B, et al. Colonic inflammation in Parkinson's disease. *Neurobiology of Disease*. 2013;50(1):42-48. doi:10.1016/j.nbd.2012.09.007
43. Clairembault T, Kamphuis W, Leclair-Visonneau L, et al. Enteric GFAP expression and phosphorylation in Parkinson's disease. *J Neurochem*. 2014;130(6):805-815. doi:10.1111/jnc.12742

44. Iwaki H, Blauwendraat C, Leonard HL, et al. Genomewide association study of Parkinson's disease clinical biomarkers in 12 longitudinal patients' cohorts. *Mov Disord*. 2019;34(12):1839-1850. doi:10.1002/mds.27845
45. Noyce AJ, Bestwick JP, Silveira-Moriyama L, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. *Ann Neurol*. 2012;72(6):893-901. doi:10.1002/ana.23687
46. Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JPA. Environmental risk factors and Parkinson's disease: An umbrella review of meta-analyses. *Parkinsonism & Related Disorders*. 2016;23:1-9. doi:10.1016/j.parkreldis.2015.12.008
47. Dirkx MF, Zach H, Bloem BR, Hallett M, Helmich RC. The nature of postural tremor in Parkinson disease. *Neurology*. 2018;90(13):e1095-e1102. doi:10.1212/wnl.0000000000005215
48. Marinus J, Zhu K, Marras C, Aarsland D, van Hilten JJ. Risk factors for non-motor symptoms in Parkinson's disease. *The Lancet Neurology*. 2018;17(6):559-568. doi:10.1016/s1474-4422(18)30127-3
49. Kalia LV, Lang AE. Parkinson's disease. *The Lancet*. 2015;386(9996):896-912. doi:10.1016/s0140-6736(14)61393-3
50. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. *Nat Rev Neurosci*. 2017;18(7):435-450. doi:10.1038/nrn.2017.62
51. Hess CW, Hallett M. The Phenomenology of Parkinson's Disease. *Semin Neurol*. 2017;37(2):109-117. doi:10.1055/s-0037-1601869
52. Marras C, Lang A. Parkinson's disease subtypes: Lost in translation? *Journal of Neurology, Neurosurgery & Psychiatry*. 2013;84(4):409-415. doi:10.1136/jnnp-2012-303455
53. Fereshtehnejad SM, Zeighami Y, Dagher A, Postuma RB. Clinical criteria for subtyping Parkinson's disease: Biomarkers and longitudinal progression. *Brain*. 2017;140(7):1959-1976. doi:10.1093/brain/awx118
54. Bjornestad A, Pedersen KF, Tysnes OB, Alves G. Clinical milestones in Parkinson's disease: A 7-year population-based incident cohort study. *Parkinsonism & Related Disorders*. 2017;42:28-33. doi:10.1016/j.parkreldis.2017.05.025
55. Shulman LM, Katzel LI, Ivey FM, et al. Randomized clinical trial of 3 types of physical exercise for patients with parkinson disease. *JAMA Neurol*. 2013;70(2):183-190. doi:10.1001/jamaneuro.1.2013.646
56. Amara AW, Memon AA. Effects of Exercise on Non-motor Symptoms in Parkinson's Disease. *Clinical Therapeutics*. 2018;40(1):8-15. doi:10.1016/j.clinthera.2017.11.004
57. Schenkman M, Moore CG, Kohrt WM, et al. Effect of high-intensity treadmill exercise on motor symptoms in patients with De Novo Parkinson disease a phase 2 randomized clinical trial. *JAMA Neurol*. 2018;75(2):219-226. doi:10.1001/jamaneuro.1.2017.3517
58. Ives NJ, Stowe RL, Marro J, et al. Monoamine oxidase type B inhibitors in early Parkinson's disease: Meta-analysis of 17 randomised trials involving 3525 patients. *BMJ*. 2004;329(7466):593-596. doi:10.1136/bmj.38184.606169.ae
59. Goetz CG, Koller WC, Poewe W, et al. Amantadine and other antiglutamate agents. *Mov Disord*. 2002;17(S4):S13-S22. doi:10.1002/mds.5557
60. Schwab RS. Amantadine in Parkinson's disease. Review of more than two years' experience. *JAMA: The Journal of the American Medical Association*. 1972;222(7):792-795. doi:10.1001/jama.222.7.792
61. Cotzias GC, Van Woert MH, Schiffer LM. Aromatic amino acids and modification of parkinsonism. *N Engl J Med*. 1967;276(7):374-379. doi:10.1056/nejm196702162760703
62. Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE. Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review: Report of the quality standards subcommittee of the American Academy of Neurology. *Neurology*. 2002;58(1):11-17. doi:10.1212/wnl.58.1.11
63. Stowe RL, Ives NJ, Clarke C, et al. Dopamine agonist therapy in early Parkinson's disease. *Cochrane Database of Systematic Reviews*. 2008;(2). doi:10.1002/14651858.cd006564.pub2
64. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease: A review. *JAMA*. 2014;311(16):1670-1683. doi:10.1001/jama.2014.3654
65. Dhall R, Kreitzman DL. Advances in levodopa therapy for Parkinson disease: Review of RYTARY (carbidopa and levodopa) clinical efficacy and safety. *Neurology*. 2016;86(14):S13-S24. doi:10.1212/wnl.0000000000002510

66. Schrag A. Entacapone in the treatment of Parkinson's disease. *Lancet Neurology*. 2005;4(6):366-370. doi:10.1016/s1474-4422(05)70098-3
67. Limousin P, Foltynie T. Long-term outcomes of deep brain stimulation in Parkinson disease. *Nat Rev Neurol*. 2019;15(4):234-242. doi:10.1038/s41582-019-0145-9
68. Jankovic J, Aguilar LG. Current approaches to the treatment of Parkinson's disease. *NDT*. 2008;4(4):743-757. doi:10.2147/ndt.s2006
69. Horn S, Stern MB. The comparative effects of medical therapies for Parkinson's disease. *Neurology*. 2004;63(7 Suppl 2):S7-S12. doi:10.1212/wnl.63.7_suppl_2.s7
70. Vollum DI, Parkes JD, Doyle D. Livedo Reticularis during Amantadine Treatment. *BMJ*. 1971;2(5762):627-628. doi:10.1136/bmj.2.5762.627
71. Dong J, Cui Y, Li S, Le W. Current Pharmaceutical Treatments and Alternative Therapies of Parkinson's Disease. *CN*. 2016;14(4):339-355. doi:10.2174/1570159x14666151120123025
72. Moore TJ, Glenmullen J, Mattison DR. Reports of pathological gambling, hypersexuality, and compulsive shopping associated with dopamine receptor agonist drugs. *JAMA Intern Med*. 2014;174(12):1930. doi:10.1001/jamainternmed.2014.5262
73. Nomoto M, Takeda A, Iwai K, Nishimura A, Hattori N. Effect of Opicapone Tablets on Levodopa and 3-O-Methyl-dopa Pharmacokinetics in Healthy Japanese Subjects: Phase 1 Study. *Clinical Pharmacology in Drug Development*. 2020;10(2):180-189. doi:10.1002/cpdd.799
74. Kiss LE, Ferreira HS, Torráo L, et al. Discovery of a long-acting, peripherally selective inhibitor of catechol- O -methyltransferase. *J Med Chem*. 2010;53(8):3396-3411. doi:10.1021/jm1001524
75. Rascol O, Payoux P, Ory F, Ferreira JJ, Brefel-Courbon C, Montastruc JL. Limitations of current Parkinson's disease therapy. *Ann Neurol*. 2003;53(S3):S3-S15. doi:10.1002/ana.10513
76. Lang AE, Lees A. Management of Parkinson's disease: An evidence-based review. *Mov Disord*. 2002;17(S4):i-i. doi:10.1002/mds.5554
77. Brooks DJ. Safety and tolerability of COMT inhibitors. *Neurology*. 2004;62(1 Suppl 1):S39-S46. doi:10.1212/wnl.62.1_suppl_1.s39
78. Dingemans J, Jorga KM, Schmitt M, et al. Integrated pharmacokinetics and pharmacodynamics of the novel catechol-O-methyltransferase inhibitor tolcapone during first administration to humans. *Clin Pharmacol Ther*. 1995;57(5):508-517. doi:10.1016/0009-9236(95)90035-7
79. Nissinen H, Kuoppamäki M, Leinonen M, Schapira AH. Early versus delayed initiation of entacapone in levodopa-treated patients with Parkinson's disease: A long-term, retrospective analysis. *European Journal of Neurology*. 2009;16(12):1305-1311. doi:10.1111/j.1468-1331.2009.02726.x
80. Kiss LE, Ferreira HS, Torráo L, et al. Discovery of a long-acting, peripherally selective inhibitor of catechol- O -methyltransferase. *J Med Chem*. 2010;53(8):3396-3411. doi:10.1021/jm1001524
81. Almeida L, Rocha JF, Falcão A, et al. Pharmacokinetics, pharmacodynamics and tolerability of opicapone, a novel catechol-o-methyltransferase inhibitor, in healthy subjects: Prediction of slow enzyme-inhibitor complex dissociation of a short-living and very long-acting inhibitor. *Clin Pharmacokinet*. 2013;52(2):139-151. doi:10.1007/s40262-012-0024-7
82. Salamon A, Zádori D, Szpisjak L, Klivényi P, Vécsei L. Opicapone for the treatment of Parkinson's disease: an update. *Expert Opinion on Pharmacotherapy*. 2019;20(18):2201-2207. doi:10.1080/14656566.2019.1681971
83. FDA, CDER. HIGHLIGHTS OF PRESCRIBING INFORMATION
84. Opicapone | C15H10Cl2N4O6 - PubChem. <http://pubchem.ncbi.nlm.nih.gov/compound/Opicapone>
85. Keränen T, Gordin A, Karlsson M, et al. Inhibition of soluble catechol-O-methyltransferase and single-dose pharmacokinetics after oral and intravenous administration of entacapone. *Eur J Clin Pharmacol*. 1994;46(2):151-157. doi:10.1007/bf00199880
86. Ongentys | European Medicines Agency. <https://www.ema.europa.eu/en/medicines/human/EPAR/ongentys>
87. Rocha JF, Almeida L, Falcão A, et al. Opicapone: a short lived and very long acting novel catechol-O-methyltransferase inhibitor following multiple dose administration in healthy subjects. *Br J Clin Pharmacol*. 2013;76(5):763-775. doi:10.1111/bcp.12081

88. Ferreira JJ, Rocha JF, Falcão 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-e56. doi:10.1111/ene.12666
89. Lopes N, Ferreira J, Lees A, Costa R, Disorders ASM. Exploratory efficacy of opicapone in combination with dopamine agonists or MAO-B inhibitors on the treatment of motor fluctuations in Parkinson's disease. Published online 2015.
90. Almeida L, Rocha JF, Falcão A, et al. Pharmacokinetics, pharmacodynamics and tolerability of opicapone, a novel catechol-o-methyltransferase inhibitor, in healthy subjects: Prediction of slow enzyme-inhibitor complex dissociation of a short-living and very long-acting inhibitor. *Clin Pharmacokinet*. 2013;52(2):139-151. doi:10.1007/s40262-012-0024-7
91. Almeida L, Rocha JF, Falcão A, et al. Pharmacokinetics, pharmacodynamics and tolerability of opicapone, a novel catechol-O-methyltransferase inhibitor, in healthy subjects: prediction of slow enzyme-inhibitor complex dissociation of a short-living and very long-acting inhibitor. *Clin Pharmacokinet*. 2013;52(2):139-151. doi:10.1007/s40262-012-0024-7
92. Rocha JF, Santos A, Falcão A, et al. Effect of moderate liver impairment on the pharmacokinetics of opicapone. *Eur J Clin Pharmacol*. 2014;70(3):279-286. doi:10.1007/s00228-013-1602-9
93. Rocha JF, Santos A, Falcão A, et al. Effect of moderate liver impairment on the pharmacokinetics of opicapone. *Eur J Clin Pharmacol*. 2014;70(3):279-286. doi:10.1007/s00228-013-1602-9
94. Svetel M, Tomić A, Kresojević N, Kostić V. Pharmacokinetic drug evaluation of opicapone for the treatment of Parkinson's disease. *Expert Opinion on Drug Metabolism & Toxicology*. 2018;14(3):353-360. doi:10.1080/17425255.2018.1430138
95. Falcão A, Rocha JF, Santos A, Nunes T, Soares-da-Silva P. Opicapone pharmacokinetics and pharmacodynamics comparison between healthy Japanese and matched white subjects. *Clinical Pharmacology in Drug Development*. 2016;5(2):150-161. doi:10.1002/cpdd.213
96. Ferreira JJ, Lees A, Rocha JF, Poewe W, Rascol O, Soares-da-Silva P. Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: A randomised, double-blind, controlled trial. *The Lancet Neurology*. 2016;15(2):154-165. doi:10.1016/s1474-4422(15)00336-1
97. 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. doi:10.1001/jamaneuro.2016.4703
98. Ferreira JJ, Lees A, Rocha JF, Poewe W, Rascol O, Soares-da-Silva P. Long-term efficacy of opicapone in fluctuating Parkinson's disease patients: a pooled analysis of data from two phase 3 clinical trials and their open-label extensions. *Eur J Neurol*. 2019;26(7):953-960. doi:10.1111/ene.13914
99. Reichmann H, Lees A, Rocha JF, et al. Effectiveness and safety of opicapone in Parkinson's disease patients with motor fluctuations: The OPTIPARK open-label study. *Transl Neurodegener*. 2020;9(1):9. doi:10.1186/s40035-020-00187-1
100. 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. doi:10.1001/jamaneuro.2016.4703
101. Ferreira JJ, Lees A, Rocha JF, Poewe W, Rascol O, Soares-da-Silva P. Long-term efficacy of opicapone in fluctuating Parkinson's disease patients: a pooled analysis of data from two phase 3 clinical trials and their open-label extensions. *Eur J Neurol*. 2019;26(7):953-960. doi:10.1111/ene.13914
102. Rocha JF, Ferreira JJ, Falcão A, et al. Effect of 3 Single-Dose Regimens of Opicapone on Levodopa Pharmacokinetics, Catechol-O-Methyltransferase Activity and Motor Response in Patients With Parkinson Disease. *Clinical Pharmacology in Drug Development*. 2016;5(3):232-240. doi:10.1002/cpdd.217
103. Goetz CG, Poewe W, Rascol O, et al. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: Status and recommendations. *Mov Disord*. 2004;19(9):1020-1028. doi:10.1002/mds.20213
104. Zhang Y, Huang X. Concerns Regarding Opicapone as Adjunct to Levodopa Therapy. *JAMA Neurol*. 2017;74(7):872-873. doi:10.1001/jamaneuro.1.2017.0723
105. Committee for Medicinal Products for Human Use (CHMP). *EMA Assessment Report - Ongentys*. 2016;44(April).

106. 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. [doi:10.1001/jamaneurol.2016.4703](https://doi.org/10.1001/jamaneurol.2016.4703)

107. Annus Á, Vécsei L. Spotlight on opicapone as an adjunct to levodopa in parkinson's disease: design, development and potential place in therapy. *DDDT.* 2017;11:143-151. [doi:10.2147/dddt.s104227](https://doi.org/10.2147/dddt.s104227)

108. Pinto R, l'Hostis P, Patat A, et al. Evaluation of opicapone on cardiac repolarization in a thorough QT/QTc study. *Clinical Pharmacology in Drug Development.* 2015;4(6):454-462. [doi:10.1002/cpdd.188](https://doi.org/10.1002/cpdd.188)

109. Fabbri M, Ferreira JJ, Lees A, et al. Opicapone for the treatment of Parkinson's disease: A review of a new licensed medicine. *Mov Disord.* 2018;33(10):1528-1539. [doi:10.1002/mds.27475](https://doi.org/10.1002/mds.27475)

110. Opicapone: Drug information - UpToDate. https://www.uptodate.com/contents/opicapone-drug-information?search=opicapone&source=panel_search_result&selectedTitle=1~2&usage_type=panel&kp_tab=drug_general&display_rank=1#F54346825