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Opicapone: A New FDA Approval to Reduce Pill Burden in Parkinson's Disease

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Abstract

Treatment developments for Parkinson's Disease patients have continued to grow since its first diagnosis as a neurological syndrome in 1817. The options for these patients has improved over that time and with it has come an increasing responsibility for pharmacists to know the most up to date guidelines and newer medications to treat Parkinson's Disease when one of these patients is presented to them. Future guidelines may incorporate opicapone, a newly developed once daily pill, as a viable treatment option for Parkinson's Disease patients.

Parkinson's Disease is a progressive and chronic neurodegenerative disorder that is characterized by motor symptoms such as resting tremor, bradykinesia, and rigidity, as well as non-motor symptoms such as mood disorders, sleep disturbances and cognitive impairment. In the United States each year an estimated 50,000 people are diagnosed with Parkinson's Disease and about one million Americans currently have the disease.[1] Progression of Parkinson's Disease and the emergence of worsening symptoms may differ from patient to patient following diagnosis.[1] There is no cure for Parkinson's Disease; the goals for treatment are to improve quality of life and manage symptoms of the disease.[2] The critical role of the pharmacist in the care of this patient population is utilizing their pharmacological knowledge to improve the quality of the lives of patients living with Parkinson's.

The Canadian guideline for Parkinson's Disease of 2019 reflects the substantial changes in the literature on the treatment of the disease over the last 10 years.[2] This guideline reflects the substantial changes in the literature on the treatment of the disease over the last 10 years, with the most up to date evidence. According to that guideline, the goals of treatment for Parkinson's includes maintaining activities of daily living, limiting adverse effects of pharmacological treatment, and most notably includes cultivating patient independence and quality of life.[2] The quality of life for Parkinson's patients, particularly those that are stages 3 and above, is considerably low due to the severe debilitation that comes with advanced disease.[2] These patients can no longer move as they normally would and subsequently require constant support and monitoring.[2] Both the stiffness in the legs that make it impossible to stand or walk and the hallucinations and delusions that could result make it necessary to use medications to manage the disease.[3]

The pathophysiology of Parkinson's Disease involves a loss of function of a number of neurotransmitters, but most notably a deficiency of the neurotransmitter dopamine. Dopamine is the essential coordination neurotransmitter and enables neurons in the brain to communicate and control movement; in Parkinson's patients this chemical imbalance causes loss of fine motor movement and motor symptoms as well as non-motor symptoms such as depression.[4] Because of this, pharmacological management of Parkinson's Disease includes dopamine replacement therapy or treatments that can increase the amount of dopamine in the brain. The formulation carbidopa and levodopa is the mainstay of treatment. While this therapy reduces symptoms, it tends to become less effective over time leading to the development of "off" periods where symptoms are not controlled effectively and the quality of life for patients rapidly decreases in correlation with disease progression.[4] Additionally, patients needing carbidopa and levodopa therapy may need to manage these periods by taking this medication every two to four hours in some cases, with a maximum dosage limit of 800 milligrams of levodopa per day.[4]

The later stages of Parkinson's Disease see more of these "off" periods, and as such medications have been developed to

manage these periods and prolong disease progression as much as possible.[4] One such dopamine preserving medication is the COMT (catechol-o-methyl transferase) inhibitor, which blocks the ability of enzymes that normally break down levodopa, thereby extending its effect in the body.[4] The problem, however, is that COMT inhibitors as they existed before the year 2020 had to be co-administered with carbidopa and levodopa in order to achieve clinical effect, sometimes every two to four hours. This, in turn, led to a higher pill burden for those patients that needed additional therapy to carbidopa and levodopa, with an added pill to take each time. A series of reports from the U.S. Food and Drug Administration published in 2016 in which Parkinson's Disease patients were surveyed for their perspectives and what is most critical to them in treatment considerations revealed the three biggest downsides of treatment were the pill burden of their daily lives, the periods of "off-time" that they experienced, and the limited treatment options that existed for their disease.[5] Some of these concerns were addressed in the recent FDA approval of a COMT inhibitor that patients take once daily at bedtime instead of up to six times daily with carbidopa and levodopa.

On April 24th, 2020, opicapone (brand name: Ogentys) was approved for use by the Food and Drug Administration (FDA) in the United States.[6] Previously, this medication had been approved and used in Europe and Japan, after first being synthesized in 2017.[4] The medication comes in 50 and 25 milligram capsules, with a recommended dosage of 50 mg given once daily at bedtime. A dose adjustment to 25 mg once daily at bedtime should be recommended only in cases of patients with moderate hepatic impairment.[6] The medication should be taken at bedtime due to the reported side effect of sedation that is uncharacteristic of the traditional COMT inhibitors.[6] Potential advantages of opicapone may include no dose adjustments for renal deficiency and no geriatric dose considerations.[6]

Opicapone does show promise as a potential therapy for Parkinson's, but it is not without its limitations and side effects. This medication, like other existing COMT inhibitors, is contraindicated in patients already taking monoamine oxidase (MAO) inhibitors or in patients experiencing pheochromocytoma, paraganglioma, or a catecholamine secreting neoplasm.[6] Furthermore, opicapone contains additional precautions for cardiovascular effects, somnolence, hypotension, and dyskinesia.[7] Dyskinesia, the involuntary movements that often occur with Parkinson's Disease medications, is the most common adverse reaction leading to discontinuation of opicapone.[6] Opicapone, like other COMT inhibitors, must be added to existing regimens of carbidopa and levodopa, because it functions chiefly to enhance the effect of levodopa in the body. Futhermore, data has indicated that the incidence of dyskinesia is less than that with the other COMT inhibitors. According to the BIPARK-1 trial, the most common side effect reported with this medication is dyskinesia, with 20% of patients reporting the effect.[8] This was seen to be less than its predecessor entacapone in BIPARK-1, in which 25% reported tardive dyskinesia.[8]

Two twelve-week multinational phase 3 clinical trials testing the safety and effectiveness of opicapone as compared to placebo and to another COMT inhibitor entacapone (Comtan) was the basis for FDA approval.[9] These two trials, known as BIPARK-1 and BIPARK-2, demonstrated that individuals treated with opicapone had a significantly greater reduction in the time that they spend in "off" periods.[8] In BIPARK-1, a patient population receiving opicapone was compared to a patient population receiving entacapone, in which a COMT inhibitor was given each time levodopa was given.[8] Specifically, researchers aimed to assess the percentage of people that woke up in the morning without pain and assessed the time to first period of no pain as a UPDRS III score.[8] Data reported that the patient population receiving opicapone had less pain and less waking up in the morning with pain, and was overall statistically non-inferior to entacapone; opicapone treatment resulted in a numerically greater reduction in off-time (opicapone, −121.9±17.0; entacapone, −105.7±16.3 minutes; P = 0.46) and a significant reduction in UPDRS III score (opicapone, −4.6±0.8; entacapone, −2.4±0.8; P=0.04 versus entacapone).[8]

In the subsequent study BIPARK-2, the primary endpoint was a change from the "off" state of pain to the "on" state of no pain in comparing opicapone to placebo.[9] The results indicated that patients receiving opicapone had a statistically significant time decrease from pain to no pain.[9] The adjusted treatment difference vs. placebo was significant for the 50-mg/d opicapone group (treatment effect, -54.3 [95% CI, -96.2 to -12.4] minutes; P = 0.008), but was not statistically significant for the 25-mg/d opicapone group (treatment effect, -37.2 [95% CI, -80.8 to 6.4] minutes; P = 0.11).[9] The data from these trials was presented at the American Neurological Association's 2020 Virtual Meeting and might be a starting point for new guidelines for Parkinson's Disease being created with opicapone listed as a viable treatment option.[10]

As mentioned earlier, it is important to note that opicapone, like the classical COMT inhibitors, does not replace carbidopa and levodopa therapy, and must be added to existing medication regimens containing this medication.[11] It is critical for the pharmacist to be able to understand how to be able to apply this clinical knowledge to improve the care of a Parkinson's patient, and to put the role of new medications like opicapone into perspective. In this way, opicapone's use or future function in the guidelines is add-on therapy to patients having "off" periods of pain with maximized or near maximized carbidopa and levodopa.[12] A major advantage of opicapone is its propensity to be given once daily at bedtime. In the future, for patients not adequately controlled on carbidopa and levodopa, clinicians may choose to add on opicapone once daily instead of a different COMT inhibitor to be given each time levodopa is given.[13] The pharmacist's potential role of being able to help reduce the pill burden with once daily opicapone may help improve the quality of life of Parkinson's patients in the United States.

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