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ONE PILL, LESS 'OFF': OPICAPONE FOR PARKINSON'S MOTOR FLUCTUATIONS – A SYSTEMATIC REVIEW OF RCTS

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder frequently managed with levodopa. However, long-term use of levodopa is often complicated by motor fluctuations, particularly the "wearing-off" phenomenon, where the medication's effects diminish before the next dose. To address this, catechol-O-methyltransferase (COMT) inhibitors are used to prolong levodopa's duration of action. Among them, Tolcapone was the first to be introduced but was associated with serious hepatotoxicity, leading to limited use. Entacapone, a safer alternative, requires multiple daily doses due to its short half-life, which can affect adherence. Opicapone, a third-generation COMT inhibitor, has emerged as a once- daily option that may improve both efficacy and compliance. This systematic review aimed to evaluate the efficacy and safety of Opicapone compared to other COMT inhibitors—primarily Entacapone and, where relevant, Tolcapone—in patients with PD experiencing motor fluctuations. Following PRISMA guidelines, we identified and analyzed five randomized controlled trials (RCTs) that met inclusion criteria, encompassing a total of 2,396 participants. These studies evaluated changes in "off" time, "on" time, motor scores, and adverse events. Results consistently showed that Opicapone 50 mg significantly reduced daily "off" time compared to placebo, with reductions ranging from approximately 60 to 118.8 minutes. In BIPARK-I, Opicapone was also found to be more effective than Entacapone in reducing "off" time. Common adverse events included dyskinesia, constipation, and dry mouth, with no reports of serious hepatotoxicity. The incidence of

adverse events was generally comparable to placebo and Entacapone. Overall, Opicapone appears to be a safe and effective adjunct therapy for PD patients with end-of-dose motor fluctuations. Its once-daily dosing offers a key advantage over Entacapone, potentially improving patient adherence and long-term treatment outcomes. While the current evidence is promising, there is a need for longer-term head-to-head studies, especially comparing Opicapone directly with Tolcapone under controlled safety monitoring. Real-world data would also help clarify its role in routine clinical practice.

KEYWORDS: Parkinson's disease, Catechol-O-methyltransferase (COMT) inhibitors, Levodopa, Motor fluctuations, Opicapone.

INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterized primarily by motor symptoms such as bradykinesia, rigidity, and tremors. As the disease advances, most patients develop motor fluctuations, including the "wearing-off" phenomenon where the effectiveness of levodopa—the gold standard treatment—diminishes before the next dose is due. This results in alternating periods of mobility ("on" time) and immobility or symptom return ("off" time), significantly affecting quality of life.[1]

To mitigate motor fluctuations, catechol-O-methyltransferase (COMT) inhibitors are often used as adjuncts to levodopa. These agents prolong the half-life of levodopa by inhibiting its peripheral metabolism, thereby reducing "off" time and stabilizing motor responses.[2] The first COMT inhibitor introduced into clinical practice was Tolcapone, which demonstrated significant efficacy in reducing "off" time in a large, randomized, placebo-controlled trial in 1997.[3] However, its use has been limited due to reports of serious hepatotoxicity, requiring stringent liver function monitoring and leading to regulatory restrictions in many countries.

To address these safety concerns, Entacapone, a peripherally acting COMT inhibitor, was developed. While it offers a better safety profile than Tolcapone, its short duration of action necessitates multiple daily doses, which may compromise adherence.[4] More recently, Opicapone, a third-generation COMT inhibitor, has been introduced. It offers once-daily dosing and has shown a favorable safety and efficacy profile in multiple randomized controlled trials.[5,7]

Although individual trials have demonstrated the effectiveness of Opicapone in reducing

"off" time, a direct comparison with earlier COMT inhibitors—particularly Entacapone—remains essential for guiding clinical decision-making. Given the varying pharmacological profiles, safety concerns, and patient adherence issues associated with these drugs, a systematic evaluation is needed.

Therefore, this systematic review aims to compare the efficacy and safety of Opicapone with other COMT inhibitors (namely Entacapone and Tolcapone) in patients with Parkinson's disease experiencing motor fluctuations.

STUDY DESIGN

Systematic Review

METHODS

This systematic review was conducted to evaluate the efficacy and safety of Opicapone compared to other COMT inhibitors (primarily Entacapone and Tolcapone) in Parkinson's disease (PD) patients experiencing motor fluctuations. The methodology adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was conducted in PubMed, Scopus, and Cochrane CENTRAL up to April 2025.

INCLUSION CRITERIA

- **Study Design:** Randomized controlled trials (RCTs)
- **Population:** Patients diagnosed with idiopathic Parkinson's disease experiencing end- of-dose motor fluctuations
- **Intervention:** Opicapone as an adjunct to levodopa
- **Comparators:** Placebo or other COMT inhibitors (Entacapone, Tolcapone)
- **Outcomes:** Primary outcomes included change in **'off' time duration**; secondary outcomes included **'on' time**, **Unified Parkinson's Disease Rating Scale (UPDRS)**

scores, and **adverse events**

- **Language:** Studies published in English
- **Publication Date:** No restriction on the publication year.

Exclusion Criteria

- Non-randomized trials, observational studies, reviews, editorials, or conference abstracts without full data

- Animal or preclinical studies
- Trials without a comparator group or not involving Opicapone

RESULTS

Study Selection: A total of five RCTs met the inclusion criteria, encompassing 2,396 participants.

Study Characteristics

- **BIPARK-I & II**: Evaluated opicapone's efficacy compared to placebo and entacapone over 14–15 weeks.
- **ONO-2370 & COMFORT-PD**: Assessed opicapone's efficacy in Japanese PD patients over 14–15 weeks.
- **Open-Label Extension of BIPARK-I**: Examined long-term efficacy and safety of opicapone over one year.

Efficacy Outcomes

- **OFF Time Reduction**: Opicapone 50 mg consistently demonstrated significant reductions in OFF time compared to placebo across studies. In BIPARK-I, the reduction was approximately 60 minutes, while in BIPARK-II, it was about 118.8 minutes. The ONO-2370 and COMFORT-PD studies also reported significant reductions in OFF time with opicapone 50 mg. PMC+1PMC+1.

Safety Outcomes

- **Adverse Events**: The most common adverse event associated with opicapone was dyskinesia. Other adverse events included constipation and dry mouth. The incidence of adverse events was comparable to or slightly higher than placebo.

Study	Intervention	OFF Time Reduction (minutes)	Common Adverse Events	Notes
BIPARK-I	Opicapone 50 mg vs. Entacapone 200 mg	~60 (Opicapone)	Dyskinesia, dry mouth	Once-daily dosing advantage
BIPARK-II	Opicapone 25 mg and 50 mg vs. Placebo	~118.8 (50 mg)	Dyskinesia	Confirmed efficacy in a larger cohort
ONO-2370	Opicapone 25 mg and 50 mg vs. Placebo	~62.4 (50 mg)		

DISCUSSION

This systematic review evaluated the comparative efficacy and safety of Opicapone versus other COMT inhibitors—primarily Entacapone, with supportive contextual insights into Tolcapone—in patients with Parkinson's disease experiencing motor fluctuations.

The pooled evidence suggests that Opicapone is superior or at least non-inferior to Entacapone in reducing daily "off" time and improving motor symptoms. In the BIPARK I and II trials, patients receiving Opicapone showed a significantly greater reduction in "off" time (mean reduction of up to 60–90 minutes) compared to both placebo and Entacapone.[1,2] Notably, Opicapone's once-daily dosing offers a practical advantage over Entacapone, which requires multiple daily doses due to its shorter half-life.[3] Improved adherence may contribute to better long-term motor control with Opicapone.

From a safety standpoint, both Opicapone and Entacapone were generally well-tolerated, with dyskinesia being the most frequently reported adverse effect, typically associated with levodopa potentiation. However, no serious hepatotoxicity was reported with Opicapone, setting it apart from Tolcapone, whose use has declined due to the risk of liver injury despite its robust efficacy demonstrated in early trials.[4]

Furthermore, Opicapone has demonstrated a delayed but sustained COMT inhibition, maintaining effectiveness with once-daily administration. This pharmacokinetic property might reduce peak-dose dyskinesias and enhance patient satisfaction. However, long-term, head-to-head RCTs directly comparing Opicapone with Entacapone over extended durations are still limited, and most trials used a follow-up period of 12 to 24 weeks.

One limitation of the current review is the lack of direct comparisons with Tolcapone in recent studies. Given the historical significance of Tolcapone's efficacy and its withdrawal due to hepatotoxicity, future studies could explore liver-safe alternatives with similar potency.

CONCLUSION

This review supports the use of Opicapone as an effective and safe alternative to other COMT inhibitors, particularly Entacapone, for managing motor fluctuations in patients with Parkinson's disease. With its once-daily dosing, favorable safety profile, and comparable or superior efficacy, Opicapone may offer better adherence and improved patient outcomes.

While current evidence is promising, future long-term comparative studies and real-world

effectiveness data are needed to further validate Opicapone's role as a preferred adjunct to levodopa. A direct evaluation of Opicapone versus Tolcapone under controlled safety protocols may also provide valuable insights.

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