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Review Article

INCIDENCE OF ADVERSE AND SAFETY EVENTS IN INDIVIDUALS WITH PARKINSON'S DISEASE TREATED WITH CATECHOL-O-METHYLTRANSFERASE INHIBITOR OPICAPONE AS AN ADD-ON TO LEVODOPA TREATMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Opicapone, a once-daily catechol-O-methyltransferase (COMT) inhibitor, is used as an add-on to levodopa treatment to manage motor fluctuations in Parkinson's Disease (PD). Although its efficacy in extending ON time is established, the safety profile of opicapone, particularly regarding adverse events and dyskinesia, remains under investigation. A systematic review and meta-analysis were performed with randomized controlled trials (RCTs) and open-label trials that investigated the incidence of adverse events in individuals with PD treated with opicapone as an add-on to levodopa treatment. The systematic search was conducted in PubMed, Cochrane, and EBSCO Megafile databases. Random-effects meta-analyses calculated risk ratios (RR) for adverse events, serious adverse events, adverse events leading to discontinuation, and dyskinesia. Certainty of evidence was assessed using the Cochrane Grading Recommendations Assessment, Development and Evaluation approach. Six studies (n = 2705) were included, with four RCTs eligible for meta-analysis. Opicapone at both 25 mg and 50 mg doses was associated with a significantly increased risk of dyskinesia compared to placebo (25 mg: RR = 2.47; 50 mg: RR = 2.75). No statistically significant differences were found for overall adverse events, serious adverse events, or adverse events leading to discontinuation. Heterogeneity across studies was generally low. Opicapone, as an add-on to levodopa treatment, shows a favorable overall safety profile, with the primary concern being an increased incidence of dyskinesia. Clinicians should monitor for motor complications and adjust levodopa dosing as needed. Further research is needed to refine dyskinesia management strategies and evaluate long-term safety outcomes.

KEYWORDS: Parkinson's Disease, Opicapone, adverse events, safety events

1. Introduction

Opicapone is a once-daily, peripheral catechol-O-methyltransferase (COMT) inhibitor

manage limitations observed with earlier COMT inhibitors such as Tolcapone and Entacapone, specifically, the need for frequent dosing and concerns over hepatotoxicity [1]. Its longer half-life and high binding affinity allow for sustained COMT inhibition with a single daily dose, improving patient adherence and maintaining more stable levodopa plasma levels over time [1].

Following its approval in Europe in 2016 and later in other regions, opicapone has been developed to enhance the clinical effects of levodopa by reducing its enzymatic breakdown in the periphery [1]. As a third-generation COMT inhibitor, opicapone was designed to increasingly used as an add-on treatment for motor fluctuations in individuals receiving levodopa for Parkinson's Disease (PD) [2]. The rationale for its use is based on its ability to extend ON time (the time when medication is effectively controlling symptoms) and reduce OFF time (the time when medication effects wear off), which are common complications in the long-term management of PD [3]. While its efficacy in controlling motor symptoms is well documented, the safety profile of opicapone has been the subject of ongoing investigation,

particularly concerning dopaminergic side effects such as dyskinesia and the potential for serious adverse events [3].

Adverse and safety events have been reported in randomized controlled trials (RCTs) and open-label studies of opicapone, but the extent to which these events differ by dose or in comparison to placebo remains unclear [4-9]. Furthermore, serious adverse events, adverse events leading to treatment discontinuation, and dyskinesia associated with opicapone use vary across studies. Some studies suggest a tolerable safety profile [7-9], while others highlight higher study discontinuation rates or a significant increase in dyskinesia, especially at the 50 mg opicapone dose [4-6]. These inconsistencies highlight the need for a focused synthesis of safety data to guide clinical practice.

A recent meta-analysis by Xie et al.,2022 evaluated both short-term (less than 6 months) and long-term (more than 6 months) tolerability of opicapone as an adjunct to levodopa, reporting pooled incidence rates for general treatment-emergent adverse events, serious adverse events, and discontinuation across studies involving over two-thousand patients. In contrast, the present study focuses exclusively on controlled trials, distinguishing between placebo-controlled data and open-label extension data. We provide risk-ratio estimates for specific adverse outcomes, grouped by opicapone dose (25 mg vs. 50 mg), and apply an assessment of evidence certainty for each safety endpoint, a level of specificity and rigor not addressed previously. In contrast, this systematic review and meta-analysis was designed to evaluate safety outcomes as the primary focus, offering a detailed comparison of the incidence of adverse events, serious adverse events, adverse events leading to discontinuation, and dyskinesia between opicapone (25 mg and 50 mg) and placebo. Given the variability in trial designs and reporting standards, both RCTs with placebo as a comparator and open-label studies without a comparator providing long-term descriptive safety data were included.

By synthesizing the available evidence, this systematic review and meta-analysis aims to provide a clear and comprehensive overview of the safety profile of opicapone when used as an add-on to levodopa treatment in individuals with PD experiencing motor fluctuations. The findings are intended to support informed decision-making in clinical settings, clarify potential risks associated with different dosages, and identify gaps for future research on opicapone's long-term tolerability.

2. Materials and Methods

2.1. Source of Data and Search Strategy

This systematic review followed the guidelines outlined in the 2020 update of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11]. The review protocol was registered in the PROSPERO database under the ID CRD420251042716 and was reviewed by a qualified research librarian. A comprehensive literature search was carried out across PubMed, the Cochrane Library, and EBSCO Megafile databases, supplemented by manual reference checks. The search spanned from database inception through May 27, 2025, and was limited to RCTs published in English. A full list of search terms is provided in Appendix 1.

2.2. Outcome Measures

Adverse events were defined as any unfavorable medical occurrences that took place after the administration of opicapone, regardless of whether a causal relationship was established [12]. Serious adverse events were those that resulted in death, posed a life-threatening risk, required initial hospitalization or extended an existing hospital stay, led to significant or lasting disability or incapacity, or involved a congenital anomaly or birth defect [12]. Adverse events leading to discontinuation referred to events that were severe or serious enough to result in the permanent discontinuation of the study drug [12]. Dyskinesia was defined as involuntary, excessive, and erratic movements [13]. Reports of adverse events, serious adverse events, adverse events leading to discontinuation, and dyskinesia were presented separately for participants in the 25 mg and/or 50 mg opicapone groups, either in comparison to placebo (in RCTs) or descriptively when no comparator was included (in open-label studies). All adverse events occurring from the time of informed consent (baseline) through the final study visit were included in the analysis.

2.3. Inclusion and Exclusion Criteria

Eligible studies met the following inclusion criteria: participants were male or female adults aged 18 years or older with a clinical diagnosis of PD based on the UK Brain Bank criteria [14], currently undergoing daily levodopa treatment, and experiencing motor fluctuations while on levodopa. The intervention of interest was opicapone, a COMT inhibitor, administered as an add-on to levodopa treatment. Studies were required to report on at least one of the following outcomes: adverse events, serious adverse events, adverse events leading to treatment discontinuation, and/or dyskinesia. Only RCTs published in English were considered (see Table 1). Studies were excluded if they involved participants with severe, disabling peak-dose or biphasic dyskinesia or with unpredictable or wide-ranging symptom fluctuations. Additional exclusion criteria included the absence of opicapone as the intervention, participants not receiving daily levodopa, studies not assessing the specified safety-related outcomes, or study designs such as expert opinions, editorials, case reports, abstracts without accessible full texts, or unpublished preprints.

2.4. Study Selection

Two reviewers (PA, GJ) independently screened the titles and abstracts of all retrieved records. Full-text articles were then obtained for studies considered potentially eligible based on the initial screening. Both reviewers independently assessed the full texts for inclusion. Any disagreements regarding study eligibility were resolved through discussion between the reviewers. Studies that fulfilled all predefined inclusion and exclusion criteria were included in the final review.

2.5. Data Extraction

Data extraction was performed by one reviewer (PA) using a standardized form, capturing key study characteristics including lead author, year of publication, country, study design, type of intervention, sample size,

participant age, and reported outcomes related to adverse events, serious adverse events, adverse events leading to treatment discontinuation, and dyskinesia. A second reviewer (GJ) independently verified the extracted data to ensure accuracy. No discrepancies were identified between the reviewers. In cases where essential data were missing, corresponding authors were contacted to request additional information.

2.6. Risk of Bias

The methodological quality of the included studies was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool [15]. This tool evaluates five domains of potential bias: (1) the randomization process, (2) deviations from intended interventions (including both the effect of assignment and adherence), (3) missing outcome data, (4) outcome measurement, and (5) selection of the reported result. Based on the domain-level assessments, an overall risk of bias judgment was assigned as either low risk, some concerns, or high risk. Two reviewers (PA, GJ) independently conducted the risk of bias assessments. Any disagreements regarding the risk of bias assessment were resolved through discussion between the reviewers.

2.7. Data Analysis

A random-effects meta-analysis was conducted using the restricted maximum likelihood (REML) method to estimate the log risk ratios and corresponding 95% confidence intervals (CIs) for adverse and safety outcomes associated with opicapone as an add-on to levodopa compared to placebo. A random-effects inverse-variance meta-analysis using the DerSimonian-Laird estimator for tau^2 was performed to calculate the risk ratios and 95% CIs for the same outcomes. These analyses were carried out separately for adverse events, serious adverse events, adverse events leading to discontinuation, and dyskinesia. Heterogeneity across studies was evaluated using the Q statistic, associated p-values, I^2 values, and the 95% prediction interval (PI). I^2 values were interpreted as follows: 0 - 40% indicating low heterogeneity, 30 - 60% moderate, 50 - 90% substantial, and 75 - 100% considerable heterogeneity [16]. PIs were reported when more than two studies were included in a given meta-analysis. Publication bias assessment was planned for outcomes with at least ten contributing studies, as per Cochrane recommendations [17]. However, as fewer than ten studies met the inclusion criteria for each outcome, publication bias could not be formally evaluated in this review. All statistical analyses were performed using STATA 18 (StataCorp. Stata statistical software: release 18. College Station, TX: StataCorp LP. 2023). For open-label studies lacking a placebo control group, findings related to adverse events, serious adverse events, adverse events leading to discontinuation, and dyskinesia were presented descriptively in narrative format.

Table 1: PICOS Criteria for Inclusion and Exclusion of Studies

Parameter	Inclusion Criteria	Exclusion Criteria
Population	Female and male individuals over the age of 18 with a clinical diagnosis of PD consistent with the UK Brain Bank criteria receiving daily levodopa treatment, and experiencing motor fluctuations while receiving levodopa treatment	individuals with severe disabling peak-dose or biphasic dyskinesia or with unpredictable or widely swinging symptom fluctuations
Intervention	COMT inhibitor opicapone	Other types of PD medication
Comparator	Placebo or no comparator	Comparator other than placebo or other than no comparator
Outcome	Adverse events, serious adverse events, adverse events leading to discontinuation and/or dyskinesia	Adverse events, serious adverse events, adverse events leading to discontinuation and/or dyskinesia not included as safety endpoints
Study Design	Randomized Controlled Trials published in English	Expert opinions, editorials, case reports, abstracts without full reports, and preprints. Published in any other language than English

2.8. Certainty of Evidence

The certainty of evidence for each meta-analysis was independently evaluated by two reviewers (PA, GJ) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (GRADEpro GDT: Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2022. Available from: gradepro.org) [18]. The quality of evidence was categorized as very low, low, moderate, or high, based on GRADE criteria. In line with GRADE guidance, suspected publication bias was considered when observed risk estimates were imprecise, effects were inconsistent with the broader literature, or small-study effects were likely. Although formal funnel plot assessment was not possible due to the limited number of studies, narrative indicators such as asymmetry in reported effect sizes and selective outcome reporting informed this downgrade.

3. Results

3.1. Study Selection

The electronic search of databases yielded 211 articles. Ten articles were found to be duplicates, leaving a total of 201 articles. One hundred and ninety-two articles were excluded after reviewing titles and abstracts. The remaining nine articles were retrieved and assessed for eligibility. Three articles were excluded because they did not meet the inclusion criteria. Six remaining articles were found eligible and included in the review [4-9]. Four of the included articles were utilized to perform meta-analyses [4-5,7,9], as the open-label studies did not include placebo as the comparator and could therefore not be used to calculate risk ratios (Figure 1).

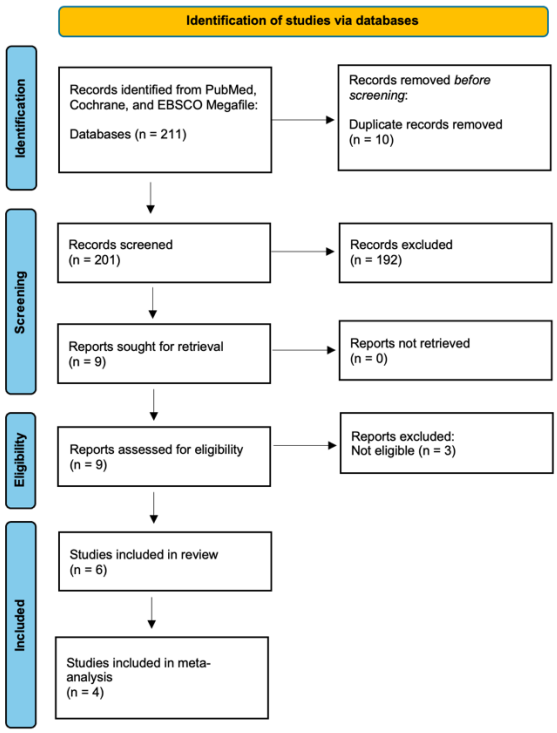


Figure 1: PRISMA Flow Diagram for Systematic Searches

3.2. Characteristics of Selected Studies

As summarized in Table 2, 2705 individuals were assessed in studies across Europe [4,6,9], Russia [4,5], United Kingdom [5], Israel [5], South Africa [5], Australia [5], South Korea [5], India [5], Argentina [5], Chile [5], and Japan [7,8]. The duration of the studies ranged between 14 to 52 weeks. One study included a 5 mg opicapone group [4], four studies included a 25 mg opicapone group [4-7], and five studies included a 50 mg opicapone group [4-5,7-9]. The studies reported adverse and safety events over 14-15 weeks [4-5,7], 24 weeks [9], and 52 weeks [6,8]. Four studies included a placebo as the comparator [4-5,7,9], and two studies were open-label and did not include a placebo as the comparator [6,8].

Table 2: Summary of the Studies on the COMT Inhibitor Opicapone Retrieved from the Literature

Authors	Number of Participants at Baseline	Gender Allocation	Mean Age of Participants in the opicapone Group	Group Allocation	Intervention Duration
Ferreira et al., 2016 [4]	600	59.1% male, 40.9% female	63.6 ± 9.3 in the 5 mg opicapone group, 64.4 ± 9.0 in the 25 mg opicapone group, 63.5 ± 9.2 in the 50 mg opicapone group	122 participants received 5 mg opicapone, 119 participants received 25 mg opicapone, 115 participants received 50 mg opicapone, 122 participants received Epicapone, 121 participants received the placebo	14-15 weeks
Lees et al., 2017 [5]	427	59.5% male, 40.5% female	62.5 ± 8.5 in the 25 mg opicapone group, 65.5 ± 8.4 in the 50 mg opicapone group	125 participants received 25 mg opicapone, 147 participants received 50 mg opicapone, 135 participants received the placebo	14-15 weeks
Ferreira et al., 2018 [6]	495	60.4% male, 39.6% female	63.7 ± 8.8 in the 25 mg opicapone group	495 participants received 25 mg opicapone (open-label)	52 weeks
Takeda et al., 2020 [7]	437	39.8% male, 60.2% female	67.9 ± 9.1 in the 25 mg opicapone group, 67.4 ± 7.8 in the 50 mg opicapone group	145 participants received 25 mg opicapone, 145 participants received 50 mg opicapone, 147 participants received placebo	14-15 weeks
Takeda et al., 2021 [8]	391	Not reported	Not reported	391 participants received 50 mg opicapone (open-label)	52 weeks
Ferreira et al.,	355	64.8% male, 35.2%	63.7 ± 9.5 in the 50 mg	177 participants	24 weeks

2025 [9]	female	opicapone group	received 50 mg opicapone, 178 participants received the placebo

There was an overlap of individuals between some of the included studies. Four hundred and ninety-five individuals from the Ferreira et al., 2016 study [4] rolled over to the Ferreira et al., 2018 open-label study [6]. Three hundred and ninety-one individuals from the Takeda et al., 2020 study [7] rolled over to the Takeda et al., 2021 open-label study [8]. Adverse and safety events in the open-label studies [6,8] were reported as newly emergent and independent of the adverse and safety events in the parent studies [4,7].

3.3. Characteristics of Participants

The mean age of participants ranged from 62.5 to 67.9 years in the opicapone groups and from 61.5 to 68.5 years in the placebo groups. The average daily levodopa dose administered ranged from 386.8 to 806 mg/day in the opicapone groups and from 391.4 to 714 mg/day in the placebo groups. The study by Takeda et al., 2021 [8] did not report separate baseline characteristics for participants continuing from the earlier Takeda et al., 2020 trial [7]. The proportion of female participants across studies ranged from 35.2% to 60.2%.

3.4. Study Quality

Risk of bias was judged as low in four studies [4-5,7,9], and high in two studies [6,8]. In the latter two, the high risk was attributed to lack of randomization and blinding due to the open-label design (Figure 2).

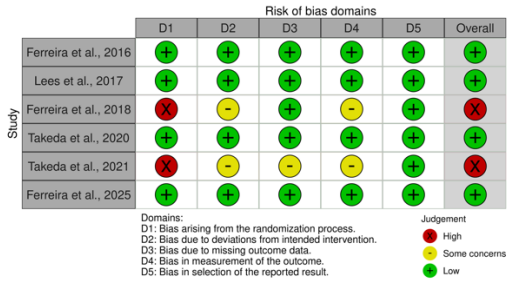


Figure 2: Traffic Light Plot of Risk of Bias

3.5. Study Outcomes

All included studies reported safety outcomes from informed consent (baseline) through the final study visit. Data on adverse events, serious adverse events, adverse events leading to discontinuation, and dyskinesia were available across all studies [4-9]. Outcomes for the 25 mg opicapone dose were reported in four studies [4-7], while five studies included data for the 50 mg dose [4-5,7-9]. Four studies provided placebo group data [4-5,7,9]. Adverse and safety events were assessed based on participant-reported symptoms, objective clinical findings, laboratory and physiological tests, and vital sign monitoring.

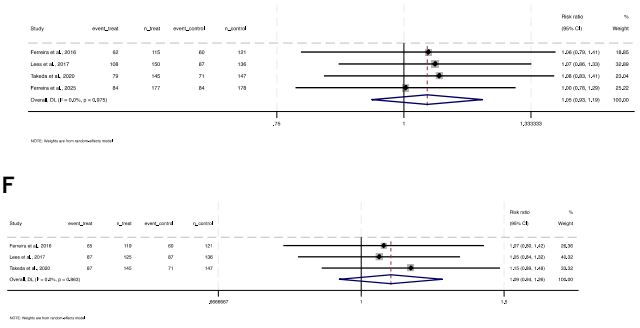
3.6. Meta-Analysis

3.6.1. Adverse Events

Three studies [4-5,7] (n = 1464) showed a statistically non-significant increase in the incidence of adverse events with 25 mg opicapone compared to placebo (RR = 1.09; 95% CI 0.94–1.26; p = 0.26). Heterogeneity was small and statistically non-significant (Q = 0.30, p = 0.86; I^2 = 0.00%; 95% PI –0.86 to 1.03) (Figure 3).

Figure 3: Forestplot Adverse Events 25 mg Opicapone Compared to Placebo

Four studies [4-5,7,9] (n = 1819) showed a statistically non-significant increase in adverse events with 50 mg opicapone compared to placebo (RR = 1.05; 95% CI: 0.93, 1.20; p = 0.41). Heterogeneity was small and statistically non-significant (Q = 0.21, p = 0.98; I^2 = 0.00%; 95% PI: 0.22, 0.33) (Figure 4).



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4: Forestplot Adverse Events 50 mg Opicapone Compared to Placebo

3.6.2. Serious Adverse Events

Three studies [4-5,7] (n = 1464) showed a statistically non-significant reduction in serious adverse events with 25 mg opicapone compared to placebo (RR = 0.96; 95% CI: 0.20, 4.57; p = 0.96). Heterogeneity was substantial and statistically non-significant (Q = 5.65, p = 0.06; I^2 = 64.6%; 95% PI: –18.19, 18.09) (Figure 5).

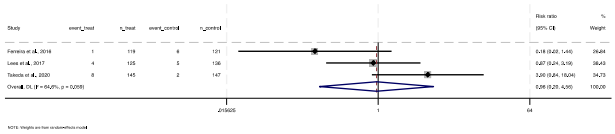

Figure 5: Forestplot Serious Adverse Events 25 mg Opicapone Compared to Placebo

Four studies [4-5,7,9] (n = 1819) showed a statistically non-significant increase in serious adverse events with 50 mg opicapone compared to placebo (RR = 1.35; 95% CI: 0.74,2.48; p = 0.33). Heterogeneity was small and statistically non-significant (Q = 1.38, p = 0.71; I^2 = 0.00%; 95% PI: –1.03, 1.63) (Figure 6).

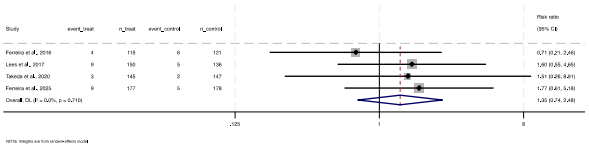

Figure 6: Forestplot Serious Adverse Events 50 mg Opicapone Compared to Placebo

3.6.3. Adverse Events Leading to Discontinuation

Three studies [4–5,7] (n = 1464) showed a statistically non-significant reduction in adverse events leading to discontinuation with 25 mg opicapone compared to placebo (RR = 0.95; 95% CI: 0.50, 1.81; p = 0.87). Heterogeneity was small and statistically non-significant (Q = 2.11, p = 0.35; I^2 = 5.0%; 95% PI: -4.11, 4.00) (Figure 7).

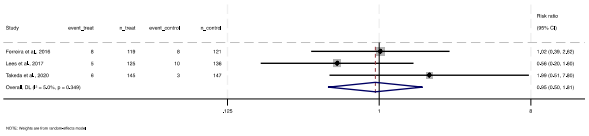

Figure 7: Forestplot Adverse Events Leading to Discontinuation 25 mg Opicapone Compared to Placebo

Four studies [4-5,7,9] (n = 1819) showed a statistically non-significant increase in adverse events leading to discontinuation with 50 mg opicapone compared to placebo (RR = 1.11; 95% CI: 0.48, 2.54; p = 0.81). Heterogeneity was moderate and statistically non-significant (Q = 6.11, p = 0.11; I^2 = 50.9%; 95% PI: -3.06, 3.26) (Figure 8).

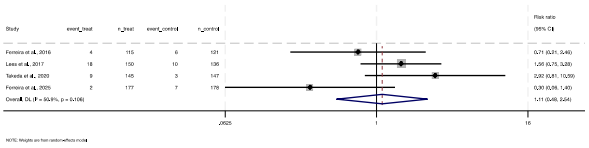

Figure 8: Forestplot Adverse Events Leading to Discontinuation 50 mg Opicapone Compared to Placebo

3.6.4. Dyskinesia

Three studies [4-5,7] (n = 1464) showed a statistically significant increase in dyskinesia with 25 mg opicapone compared to placebo (RR = 2.47; 95% CI: 1.51, 4.06; p < 0.001). Heterogeneity was small and statistically non-significant (Q = 0.56, p = 0.76; I^2 = 0.00%; 95% PI: -2.31, 4.13) (Figure 9).

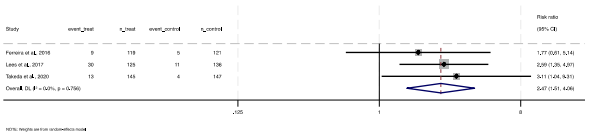

Figure 9: Forestplot Dyskinesia 25 mg Opicapone Compared to Placebo

Four studies [4-5,7,9] (n = 1819) showed a statistically significant increase in dyskinesia with 50 mg opicapone compared to placebo (RR = 2.75; 95% CI: 1.69, 4.48; p < 0.001). Heterogeneity was small and statistically non-significant (Q = 3.22, p = 0.36; I^2 = 6.9%; 95% PI: 0.00, 2.02) (Figure 10).

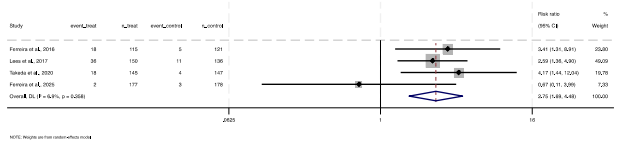

Figure 10: Forestplot Dyskinesia 50 mg Opicapone Compared to Placebo

3.7. Descriptive

3.7.1. Adverse Events

Two open-label studies [6,8] investigated the incidence of adverse events. One study [6] investigated the incidence of adverse events for several doses of opicapone, ranging from 5 mg to 50 mg, and found that 337 out of 495 individuals (68.1%) experienced at least one adverse event. One study [8] investigated the incidence of adverse events for 50 mg opicapone and found that 338 out of 391 individuals (86.4%) experienced at least one adverse event.

3.7.2. Serious Adverse Events

Two open-label studies [6,8] investigated the incidence of serious adverse events. One study [6] investigated the incidence of serious adverse events for several doses of opicapone, ranging from 5 mg to 50 mg, and found that 48 out of 495 individuals (9.7%) experienced at least one serious adverse event. One study [8] investigated the incidence of serious adverse events for 50 mg opicapone and found that 57 out of 391 individuals (14.6%) experienced at least one serious adverse event.

3.7.3. Adverse Events Leading to Discontinuation

Two open-label studies [6,8] reported the incidence of adverse events leading to discontinuation. One study [6] reported the incidence of adverse events leading to discontinuation for several doses of opicapone, ranging from 5 mg to 50 mg, which was 30 out of 495 individuals (6.1%). One study [8] reported the incidence of adverse events leading to discontinuation for 50 mg opicapone, which was 23 out of 391 individuals (5.9%).

3.7.4. Dyskinesia

Two open-label studies [6,8] investigated the incidence of dyskinesia. One study [6] investigated the incidence of dyskinesia for several doses of opicapone, ranging from 5 mg to 50 mg, and found that 72 out of 495 individuals (14.5%) experienced dyskinesia. One study [8] investigated the incidence of dyskinesia for 50 mg opicapone and found that 47 out of 391 individuals (12.0%) experienced dyskinesia.

3.8. Overall Quality of Evidence

The certainty of evidence for adverse events was rated as moderate for the 25 mg dose and low for the 50 mg dose, with both downgraded for imprecision due to CIs crossing the line of no effect. The 50 mg group was

further downgraded for suspected publication bias. For serious adverse events, the 25 mg dose was rated very low certainty due to serious inconsistency (I^2 = 64.6%) and very serious imprecision, reflected in the extremely wide CIs. The 50 mg group was rated low certainty, also downgraded for imprecision and suspected publication bias. Regarding adverse events leading to discontinuation, the certainty was moderate for the 25 mg dose due to imprecision, and very low for the 50 mg dose due to serious inconsistency, very serious imprecision, and suspected publication bias. In contrast, the evidence for dyskinesia was of high certainty for the 25 mg dose, and moderate certainty for the 50 mg dose. The 50 mg group was downgraded one level for suspected publication bias, despite showing a statistically significant increase in dyskinesia risk with minimal heterogeneity. No downgrades were applied for indirectness in any outcome. The overall quality of evidence was deemed very low to high for all meta-analyses (Appendix 2).

4. Discussion

This systematic review and meta-analysis found that opicapone, administered at both 25 mg and 50 mg doses as an add-on to levodopa, was generally well-tolerated in individuals with PD. The risk of adverse events, serious adverse events, and adverse events leading to treatment discontinuation was comparable to those seen in placebo groups, suggesting that opicapone does not introduce significant new safety concerns beyond those already inherent to dopaminergic treatments. However, both doses were associated with a significantly increased risk of dyskinesia, highlighting a key safety consideration when integrating opicapone into clinical practice.

Our findings align closely with prior reports [3,10], particularly pooled analyses or meta-analyses that noted improved motor function but emphasized the emergence of dyskinesia as a common side effect. levodopa-induced dyskinesia is a well-recognized phenomenon, and medication such as opicapone may increase dopaminergic stimulation by extending levodopa's efficacy, thus triggering these involuntary movements [13]. Dyskinesia rarely led to treatment discontinuation, which suggests that its severity was often manageable through dose adjustments, a strategy supported by previous clinical recommendations [1,2].

4.1. Safety and Tolerability Compared to Existing Treatments

In the broader context of COMT inhibitors, opicapone offers an improved safety and convenience profile relative to earlier medications such as Tolcapone and Entacapone. Unlike Tolcapone, which carries a risk of hepatotoxicity requiring intensive liver monitoring [1], opicapone has not been associated with significant hepatic adverse effects in clinical trials or long-term extensions [4-9]. Compared to Entacapone, which requires multiple daily doses and has been linked to diarrhea and orange-colored urine [1], opicapone's once-daily regimen and minimal non-dopaminergic side effects present an advantage in terms of adherence and patient satisfaction. Notably, no new or unexpected safety events emerged during longer-term follow-up in the randomized and open-label studies included in this systematic review [6,8-9]. This supports findings from a pooled analysis that reported sustained tolerability beyond initial trial periods [3]. However, the increased frequency of adverse events in open-label settings, where up to 86% of participants reported at least one adverse event [8], emphasizes the need for proactive patient monitoring in clinical practice.

4.2. Dyskinesia as a Clinical Challenge

The most consistent safety event across studies was the increased incidence of dyskinesia. This is not surprising given opicapone's mechanism of action, which prolongs levodopa's half-life and availability, intensifying both therapeutic and side effects of dopaminergic stimulation [13]. Similar findings have been reported with other dopaminergic add-on treatments, such as dopamine agonists and monoamine oxidase-B (MAO-B) inhibitors, where clinical benefits are frequently offset by increased motor complications [2]. Although the dyskinesias observed were generally mild and manageable, their presence has significant implications for patient quality of life and long-term treatment planning.

Strategies to reduce dyskinesia, including levodopa dose reduction or more refined timing of add-on treatment initiation, warrant further investigation. Emerging data from clinical practice suggest that initiating COMT inhibition earlier in the disease course, before dyskinesia becomes severe, may offer a therapeutic window where benefits outweigh risks [19]. Nonetheless, further randomized studies specifically targeting these strategies are needed.

4.3. Study Limitations

Several limitations should be considered when interpreting our findings. First, the number of available randomized studies was limited, restricting the statistical power to detect rare adverse and safety events. Additionally, while heterogeneity in meta-analyses was generally low, variability in study design, dosing regimens, and adverse event reporting methods may have influenced pooled estimates. Second, publication bias could not be formally assessed for all outcomes due to the limited number of included studies. Third, open-label studies, while valuable for understanding longer-term outcomes, inherently carry a high risk of bias due to lack of blinding and the potential for selective reporting. Finally, most included studies were conducted in relatively homogeneous populations, primarily from Europe and Asia, which may limit the generalizability of findings to more diverse clinical settings and patient populations.

4.4. Implications for Future Research

Future studies should address several important gaps. Comparative studies directly evaluating opicapone against other add-on treatments, such as Entacapone, Tolcapone, and newer medications such as Safinamide, would provide a more specific understanding of its relative safety and tolerability. Research into patient-specific predictors of dyskinesia following opicapone initiation, such as age, disease duration, baseline levodopa dose, or genetic markers, could enable more personalized treatment strategies. Moreover, randomized studies exploring levodopa dose reduction strategies concomitant with opicapone initiation could help optimize motor control while minimizing dyskinesia risk. Longer-term observational studies, including more diverse patient populations and broader comorbidity profiles, are also needed to better assess opicapone's safety in clinical

practice over periods extending beyond one year.

5. Conclusions

This systematic review and meta-analysis found that opicapone is associated with a good overall safety profile when used as an add-on to levodopa treatment, without significantly increasing adverse events, serious adverse events, or study discontinuations compared to placebo. However, the use of opicapone, at both 25 mg and 50 mg doses, was associated with a significantly increased risk of dyskinesia. Clinicians should carefully monitor patients, particularly those at higher risk for motor complications, and adjust levodopa dosing to manage these effects. opicapone remains a valuable option for managing motor fluctuations in PD. However, further research is needed to refine strategies for minimizing dyskinesia and evaluate its long-term safety across diverse clinical settings and patient populations.

Appendix

Appendix 1: Search Terms

The search terms for the PubMed database were: ("Parkinson's disease" OR "Parkinson" OR "Parkinson disease") AND ("opicapone" OR "Ongentys") AND ("placebo") AND ("levodopa" OR "add-on" OR "adjunctive") AND ("adverse events" OR “serious adverse events” OR “safety events” OR “safety concerns”), Filters: Randomized Controlled Trials (RCTs)

The search terms for the Cochrane database were: ("Parkinson's disease" OR "Parkinson" OR "Parkinson disease") AND ("opicapone" OR "Ongentys") AND ("placebo") AND ("levodopa" OR "add-on" OR "adjunctive") AND ("adverse events" OR “serious adverse events” OR “safety events” OR “safety concerns”), Filters: Trials, English

The search terms for the EBSCO Megafile database were: ("Parkinson's disease" OR "Parkinson" OR "Parkinson disease") AND ("opicapone" OR "Ongentys") AND ("placebo") AND ("levodopa" OR "add-on" OR "adjunctive") AND ("adverse events" OR “serious adverse events” OR “safety events” OR “safety concerns”), Filters: Full Text

Appendix 2: GRADE Approach for Adverse and Safety Event Outcomes

Opicapone as an Add-On to levodopa Treatment Compared to Placebo for Parkinson's Disease

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**opicapone**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
3	randomised trials	not serious	not serious	not serious	serious	none	239/389 (61.4%)	218/403 (54.1%)	**RR 1.09** (0.94 to 1.26)	**49 more per 1,000** (from 32 fewer to 141 more)	⨁⨁⨁◯ Moderate
4	randomised trials	not serious	not serious	not serious	serious	publication bias strongly suspected	333/584 (57.0%)	302/581 (52.0%)	**RR 1.05** (0.93 to 1.20)	**26 more per 1,000** (from 36 fewer to 104 more)	⨁⨁◯◯ Low
3	randomised trials	not serious	serious	not serious	very serious	none	13/389 (3.3%)	13/403 (3.2%)	**RR 0.96** (0.20 to 4.57)	**1 fewer per 1,000** (from 26 fewer to 115 more)	⨁◯◯◯ Very low
4	randomised trials	not serious	not serious	not serious	serious	publication bias strongly suspected	25/584 (4.3%)	18/581 (3.1%)	**RR 1.35** (0.74 to 2.48)	**11 more per 1,000** (from 8 fewer to	⨁⨁◯◯ Low

										46 more)	
3	randomised trials	not serious	not serious	not serious	serious	none	19/389 (4.9%)	21/403 (5.2%)	**RR 0.95** (0.50 to 1.81)	**3 fewer per 1,000** (from 26 fewer to 42 more)	⊕⊕⊕◯ Moderate
4	randomised trials	not serious	serious	not serious	very serious	publication bias strongly suspected	33/584 (5.7%)	26/581 (4.5%)	**RR 1.11** (0.48 to 2.54)	**5 more per 1,000** (from 23 fewer to 69 more)	⊕◯◯◯ Very low
3	randomised trials	not serious	not serious	not serious	not serious	none	52/389 (13.4%)	20/403 (5.0%)	**RR 2.47** (1.51 to 4.06)	**73 more per 1,000** (from 25 more to 152 more)	⊕⊕⊕⊕ High
4	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected	74/584 (12.7%)	23/581 (4.0%)	**RR 2.75** (1.69 to 4.48)	**69 more per 1,000** (from 27 more to 138 more)	⊕⊕⊕◯ Moderate

CI: confidence interval; **RR:** risk ratio

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