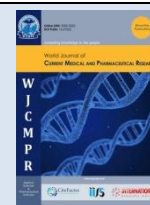




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SAFETY OF OPICAPONE USE IN PARKINSON'S DISEASE: REVIEW OF LITERATURE AND REAL-WORLD SAFETY DATA

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Article History	Abstract
Received on: 21-07-2023 Revised on: 14-08-2023 Accepted on: 26-09-2023	Parkinson's disease (PD) presents a significant global health concern with increasing prevalence and burden. This review article examines the safety data of drug Opicapone from literature and real-world sources of safety data, highlighting the need for vigilance over anti-parkinsonian drugs. For literature review, the PubMed database was mined which concluded that Opicapone, a selective COMT inhibitor for PD, demonstrated ADR like dyskinesia, nausea, vomiting, headache, and constipation where on the other hand real-world evidence showed no safety alerts or recalls initiated by regulatory authorities for Opicapone, but known risks like dyskinesia and hallucination were identified. However, clinical trial statistics revealed hypertension as the most probable ADR, alongside constipation, dizziness, dyskinesia, headache, somnolence, and hyperhidrosis. Whereas, unlisted events, such as somnolence, hyperhidrosis, pulmonary embolism, and abdominal pain, were also observed. Most ADRs belonged to the nervous system disorders and gastrointestinal disorders class which can be attributed to the pharmacological effect of Opicapone. It was concluded from this review that there is need for continuous safety vigilance for Opicapone use as despite the presence of well-structured safety guidance, new risks can emerge.
	Keywords: COMT inhibitor, Opicapone, Parkinson's disease, Real-World, Pharmacovigilance, Adverse drug reaction
	

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1. Introduction

Parkinson's disease (PD) is one of the most significant neurodegenerative conditions of high prevalence which manifests through progressive motor and non motor symptoms that worsen with time. In recent years, PD has emerged as a significant contributor to global disability, posing considerable challenges at both personal and societal levels [1]. PD has been a complex disorder with significant global impact [2]. Epidemiological studies have demonstrated a rapid increase in the prevalence of PD worldwide as it affects millions of individuals especially persons with age of 60 years and above [3]. Its prevalence has been projected to be doubled and intensify in coming years [4, 5].

The PD is basically managed through administration of anti-parkinsonian drugs. However, these medications can pose challenges due to their potential adverse effects. The safety

profiles of various classes of anti-parkinsonian drugs, such as COMT inhibitors, MAO-B inhibitors, dopamine agonists, and anticholinergics required to be assessed in order to understand the risks and benefits associated with these medications and minimize the potential harm.

Opicapone is a new-generation COMT inhibitor, used as adjunct therapy and works peripherally to increase the availability of levodopa (L-Dopa) [6]. To assess its safety in use for treatment of PD, the critical analysis of published literature as well as real-world safety data is pivotal. The health regulatory authorities report and alerts on drug safety as well as the ADR data posted by ongoing or completed clinical trials serves as real-world evidence of safety. This review analyzes data from literature sources like PubMed, safety alerts from regulatory authorities and ADR posted by clinical trials.

This comprehensive review focuses on the safety of new anti-parkinsonian drug Opicapone which is used as adjunct to levodopa. It also includes epidemiological trends, real-world evidence of risks, and insights from clinical trials. By synthesizing the latest evidence, an attempt is made to shed light on real-world safety data.

2. Introduction to Parkinson's Disease

PD is a debilitating disorder causing neurodegeneration which can be characterized by the progression in dopaminergic neuron loss in the substantia nigra region of the brain, leading to the hallmark motor symptoms of rigidity, postural instability, tremors, and bradykinesia.

2.1 Etiology

The genesis of PD is still unknown but modern experimental models of Parkinson's disease have attempted to reveal the precise disease status of PD by neuropathologic examinations, genetic research, and epidemiologic studies. Interestingly, researchers are focusing on genes associated to Parkinson's disease, which consists of ten unique loci that are important for the development of this illness condition [7]. The factors contributing in the PD etiology includes genetic factors (LRRK2, SNCA, Parkin, PINK1, and DJ-1), [8] environmental factors (Toxins like pesticides and head injuries) [9], oxidative stress and mitochondrial dysfunction [10], neuroinflammation [11], and lifestyle factors [12].

2.2 Pathophysiology

The PD impairment results from the loss of dopaminergic neurons in the substantia nigra, disrupting signaling to the striatum and leading to nigrostriatal insufficiency. [13] PD is primarily characterized by dopamine deficiency in the basal ganglia, [14] which could be due to pathological factors like abnormal aggregation of alpha-synuclein protein, [15], mitochondrial dysfunction [16], chronic neuro inflammation [17], impaired protein clearance, [18] and the interaction between genetic mutations and environmental factors [19].

2.3 Clinical Presentation

PD primarily affects motor functions, characterized by range of motor and non-motor symptoms [20]. Motor symptoms due to PD, includes tremor (typically a resting tremor) [21], rigidity (stiffness or resistance to movement) [22], bradykinesia (slowness of movement) [23], and postural instability (difficulty maintaining balance and posture) [24] whereas non-motor symptoms include cognitive impairment can (affect memory, thinking, and decision-making abilities) [25], mood changes (depression, anxiety, and changes in motivation) [26], sleep disturbances (insomnia, excessive daytime sleepiness, and restless leg syndrome) [27], autonomic dysfunction (blood pressure regulation, digestion, and bladder control) [28], and sensory abnormalities (loss of smell, visual disturbances, and pain sensitivity) [29].

2.3 Drug Therapy

Drug-based treatments are essential for managing Parkinson's disease (PD) symptoms by enhancing dopamine function in the brain. Levodopa, a dopamine precursor, provides significant relief [32]. Dopamine agonists mimic dopamine effects [33], while MAO-B [34] and COMT [35] inhibitors prolong levodopa's effects. Anticholinergic drugs control tremors in some cases [36]. Individualized treatment depends on symptoms, disease stage, and health. Though not curative, drug therapy improves motor symptoms and quality of life. Close monitoring and dose adjustments are vital for managing side effects and optimizing symptom control [30-31].

3. The Need for Continuous Vigilance over Safety of Anti-Parkinsonian Drugs

The need for pharmacovigilance in the context of anti-parkinsonian drugs is evident when considering the adverse drug reactions (ADRs) experienced by patients, which not only pose risks to their health but also affect with a substantial financial burden. ADRs associated with anti-parkinsonian drugs impose a significant financial burden. In a prospective observational study (IATROSTAT) it was observed that the ADR due to anti-parkinsonian drug contributed around 1.3% of the total number of hospitalization due to ADR [37]. According to recent estimates, Parkinson's disease caused 5.8 million years of disability-adjusted life in 2019, an 81% rise from 2000 [38]. The burden of the disease has steadily risen worldwide, observed across various regions and 204 nations studied which indicated a frequency of 1 to 2 cases per 1,000 people. [39], another research revealed 90,000 PD cases every year in United States [40] and around 5.8 lakh people suffer from PD in India [41].

For such well-established drugs, it is often considered that the incidence of unanticipated adverse effects directly connected to pharmacological activity is extremely unlikely to be found [42]. However, the vigilance is required for newer drugs like Opicapone as its safety has not been established globally.

4. Safety Performance of Opicapone

Opicapone is a medication belonging to the class of selective catechol-O-methyltransferase (COMT) inhibitors. It is primarily used as an adjunctive treatment for Parkinson's disease in combination with levodopa/carbidopa. Opicapone works by inhibiting the enzyme COMT, which helps prolong the effects of levodopa therapy by preventing its breakdown which leads to improved motor control and reduced fluctuations in response to levodopa. Opicapone is generally well-tolerated and has been shown to be effective in extending the duration of the therapeutic effect of levodopa in patients with Parkinson's disease [43-44].

4.1 Review of Literature on safety of Opicapone

Opicapone, underwent multiple safety assessments and clinical investigations. The literature search for this review was performed in PubMed which yielded a total of 17 results from the year 2010 to 2023 with filtered search applied were "Clinical trials, Randomized clinical trials, Case reports, Clinical conference, Dataset and Meta-analysis". On critically evaluating these retrieved literatures some significant findings were observed.

Kwak, N. et al. (2022) conducted a meta-analysis for Opicapone to quantitatively synthesize its effectiveness which demonstrated significant reduction in off-time. However, the reporting ratio of ADRs such as dyskinesia was frequent [45].

Ferreira, J. J. et al. (2022) performed a study in which rise in blood glucose levels and an increase in gamma glutamyl transferase (GGT) levels were observed as treatment emerged ADR with Opicapone 50 mg regimen [46].

Takeda, A. et al. (2021) indicated that when Japanese patients were given Opicapone 25 mg and 50 mg, their overall medication safety was good. However, the most common ADR found were mild to severe dyskinesia, nasopharyngitis, and hematoma. Changes in creatinine phosphokinase levels were also seen [47].

Takeda, A. et al. (2021) reported when 50 mg Opicapone was administered to patients, the most prevalent ADRs were dyskinesia, constipation, falls, back pain, nasopharyngitis, contusion, constipation, and weight loss. [48]

Nomoto, M. et al. (2021) reported nausea, vomiting, and dizziness as the most common ADR when the 50 mg Opicapone was provided in a phase 1 single dosage research on healthy Japanese volunteers [49].

Reichmann, H. et al. (2020) during an investigation, reported mild to moderate ADR like dyskinesia, dry mouth and nausea related with administration of 50 mg Opicapone usage [50].

Lopes, N. et al. (2019) in a post hoc pooled analysis observed that the patients using Opicapone suffered adverse events related with impulse control disorders (ICD) which included pathological gambling, hypersexuality, binge eating, and excessive shopping [51].

Ferreira, J. J. et al. (2018) In another Opicapone intervention, increase in the incidence of dopaminergic ADR such as dyskinesia, constipation, sleeplessness, dry mouth, dizziness, and elevated blood creatine phosphokinase appeared [52].

Rocha, J. F. et al. (2017) performed a study in which ADR like somnolence, headache, nausea, back discomfort, and diarrhea were observed when 5 mg, 15 mg, 30 mg, and 50 mg of Opicapone was administered. However, ADR such as asthenia, headache, sleeplessness, nausea, dizziness, pruritus, and orthostatic hypotension were seen, particularly at the 50 mg Opicapone dosage [53].

Lees, A. J. et al. (2017) In a randomized clinical study observed dyskinesia, constipation, and dry mouth more frequently with Opicapone 50 mg [54].

Rocha, J. F. et al. (2016) in another pharmacokinetic study focused on Opicapone, additional AEs were observed, including somnolence and an increase in eosinophil percentage. [55]

Ferreira, J. J. et al. (2016) In a study found dyskinesia, insomnia, and constipation as most commonly reported and dizziness, hallucination and nausea as less common ADR reported with administration of 25 mg and 50 mg opicapone [56].

Pinto, R. et al. (2015) in a study to evaluate effect of Opicapone on cardiac repolarization, headache and dizziness of mild intensity emerged as ADR after 50 mg dose [57].

Ferreira, J. J. et al. (2015) observed, dizziness and nausea after administration of 15 mg and 30 mg dose, whereas dyskinesia with 30 mg dose alone of opicapone in a study to determine pharmacokinetic effect of Opicapone on levodopa [58].

Rocha, J. F. et al. (2014) in another pharmacokinetic study involving Opicapone, AEs like nausea; vomiting, headache and dizziness were reported. Among this Nausea and vomiting presented as most frequently reported [59].

Rocha, J. F. et al. (2013) subjects experienced mild to moderate ADR like headache with Opicapone 5 mg, orthostatic hypotension with 20 mg, and muscular spasms with 30 mg in a study to assess the tolerance of Opicapone [60].

Almeida, L. et al. (2013) in another study with 50 mg opicapone intervention under fasting and feeding settings, somnolence, musculoskeletal stiffness, and headache were noted during the fasting phase, whereas somnolence, nasopharyngitis, attention disruption, and anemia was

observed during feeding phase. All of the adverse events were mild to moderate in severity [61].

4.2 Review of Real-world evidence for safety of Opicapone

Real-world evidence was obtained by analyzing data from real-world settings, such as observational studies, registries, clinical trials and electronic health records, researchers can evaluate the safety profiles of these medications in larger patient populations. This evidence provides insights into the occurrence and frequency of adverse events, helping to identify potential risks that may not have been apparent in controlled clinical trials.

4.2.1 Safety Data from regulatory authorities

A systematic search was conducted across multiple regulatory authority databases to get comprehensive overview of drug safety alerts and emerging ADR signals. These regulatory databases included World Health Organization-Uppsala Monitoring Centre (WHO-UMC), European Medicines Agency (EMA), Central Drugs Standard Control Organization (CDSCO), U.S. Food and Drug Administration (USFDA), Therapeutic Goods Administration (TGA, Australia), UK Medicines and Healthcare products Regulatory Agency (UKMHRA) and Health Canada.

Drug safety alerts

Drug safety alerts inform healthcare professionals and the public about potential risks associated with specific medications. Extensive searches conducted in the regulatory authority databases, including the USFDA, EMA, CDSCO, TGA, UKMHRA, Health Canada, and WHO, revealed no drug safety alerts.

CMDH list of safety concerns

In the list of safety concerns summarized from harmonized data gathered from diverse databases and studies by CMDH (Co-ordination group for mutual recognition and decentralized procedures), an extension of HMA (The Heads of Medicines Agencies), no risks were found for the drug Opicapone [62].

Product recalls

During the search of all databases of national and global regulatory authorities, no event of product recall or any associated safety issue was observed for the drug Opicapone.

Risk Management Plans

A Risk Management Plan (RMP) is a systematic approach designed to identify, assess, and mitigate the risk of ADRs associated with a pharmaceutical product which is submitted to national authorities by manufacturers and marketing authorization holders which was concluded from the data gathered during post-marketing surveillance. [63] While conducting the search, RMP report was identified from regulatory authority of Switzerland called Swiss medic. [64] Which provided information on important identified and potential risks observed during post-marketing period of Opicapone (Table 1).-

Table 1: Summary of safety concerns listed in the RMP for Opicapone published by Swiss medic [64].

Category of Risk	Risks	Listed/ Unlisted
Important identified risks	- Dyskinesia - Hallucinations	Listed as ADR

Important potential risks	- Ischaemic heart disease - Neuroleptic malignant syndrome - Impulse control disorders and other related behaviours	Listed as warning & Precaution
	Drug-related hepatic injury	
	Interactions with drugs metabolised by CYP2C8 (e.g. hypoglycaemia risk with repaglinide)	

After thorough review of RMP report Important identified and potential risks was gathered and compared with the SmPC (Summary of product characteristics) of Opicapone to interpret the listedness of ADR i.e. listed or unlisted. [65] In this report, all of the important identified risks like dyskinesia and hallucination are listed as. Whereas, the important potential risks (Table 1) are not mentioned as the designated ADR but the warnings and precautions have been provided for the same [65]. These same risks have been listed in Public Assessment Report (PAR) published by EMA [66] and TGA [67].

4.2.2 Data from clinical trials

To derive some valuable insights on safety of Opicapone with aim to extract data specifically related to the tolerability and safety of Opicapone, the clinical trial database of the National Library of Medicine (NLM) was mined.[68] A comprehensive procedure conducted to extract the list of clinical trials with primary objective of assessing the safety and tolerability of Opicapone and results posted yielded 4 clinical trials in which 2 each were in Phase 2 and Phase 3 (Table 2).

Table 2: Description of the clinical trials selected [68]

NCT Number	Study Title	Drug Intervention	Phase of clinical trial
NCT01227655	Efficacy and Safety of BIA 9-1067 in Idiopathic Parkinson's Disease Patients.	BIA 9-1067 Placebo	3
	A Study to Investigate the Tolerability and Effect of Three Single-dose Regimens of BIA 9-1067	Levodopa/Carbidopa Benserazide	
NCT01568034	Efficacy and Safety of BIA 9-1067 in Idiopathic Parkinson's Disease Patients With "Wearing-off"	BIA 9-1067 Placebo	2
		Levodopa/Carbidopa Benserazide	
NCT01568073			3

NCT01568047	Phenomenon	BIA 9-1067	2
	Multicentre Study in Four Parallel Groups of Parkinson's Disease (PD) Patients	Placebo	
		Levodopa/Carbidopa	
		Levodopa/Benserazide	

After thorough observation of ADR in these trials, it was found that some of the ADR appeared in more than one clinical trial. Hence, the effort was made to determine the frequency of appearance of an ADR among selected trials.

Table 3: List of ADR found common in the results posted by selected clinical trial

Adverse events	Clinical Trials			
	NCT01227655	NCT01568034	NCT01568073	NCT01568047
Abdominal pain upper	-	Y	-	Y
Constipation	Y	Y	Y	-
Dizziness	Y	-	Y	Y
Dyskinesia	Y	-	Y	Y
Fall	Y	-	Y	-
Hallucination	-	Y	Y	-
Headache	Y	Y	Y	-
Hyperhidrosis	-	Y	Y	Y
Hypertension	Y	Y	Y	Y
Hypotension	-	Y	Y	-
Insomnia	Y	Y	Y	-
Nausea	Y	-	Y	Y
Parkinson's Disease	Y	-	-	Y
Pulmonary embolism	Y	-	Y	-
Somnolence	Y	Y	Y	-

After statistical evaluation it was observed that adverse events such as constipation, dizziness, dyskinesia, headache, somnolence and hyperhidrosis, were reported in three trials, indicating a higher probability of their occurrence. On the other hand, adverse events like abdominal pain upper, fall, hallucination, insomnia, pulmonary embolism, and hypotension were reported in two trials. Whereas, Hypertension was the only ADR that was reported in each of these trials (Table 3). Considering the fact that the frequency of occurrence of ADRs is crucial for assessing potential risks and safety profiles of medications or interventions in clinical trials [69], it can be concluded that the probability of occurrence of hypertension was highest. Whereas, ADR like constipation, dizziness, dyskinesia, headache, somnolence and hyperhidrosis also had good probability of occurrence.

5. Discussion

One of the key aspects discussed in this review is the safety data received for drug Opicapone from literature and real-world sources. It also indicated the need for continued vigilance over anti-parkinsonian drugs. ADRs associated with these medications can have a substantial impact on patients' well-being and impose a significant financial burden.

The safety and tolerability of Opicapone, have been extensively studied. While the drug's safety and efficacy were confirmed in clinical trials, multiple investigations highlighted dyskinesia as a common ADR, along with other AEs like nausea, vomiting, headache, dizziness, dry mouth, somnolence, and constipation. It could be concluded from the literature review that most of the ADR belonged to system organ class (SOC) of Nervous system disorders followed by SOC of Gastrointestinal disorders. While these literature evaluations highlighted few safety concerns and ensured overall drug safety, a comprehensive assessment of real-world safety data remains crucial for a better understanding of Opicapone risk-benefit profile.

In the thorough review of real-world evidence for safety of Opicapone safety data released by health/ drug regulatory authorities (USFDA, EMA, CDSCO, TGA, UKMHRA, Health Canada, and WHO) and data collected from clinical trial, no drug safety alerts or product recalls related to Opicapone were found. However, RMP for Opicapone revealed the already listed significant identified risks like Dyskinesia and hallucination with already known warnings and precautions like Ischemic heart disease, Neuroleptic malignant syndrome, and Impulse control disorders. These safety concerns were found to be consistent with the PAR published by EMA and TGA as well highlighting the need for comprehensive risk assessment and monitoring of Opicapone use in Parkinson's disease patients.

Whereas, considering the statistics presented by ADR results posted in clinical trials, it was noted that the probability of occurrence of hypertension was highest. Whereas, ADR like constipation, dizziness, dyskinesia, headache, somnolence and hyperhidrosis also had good probability of occurrence.

Summarizing all the evidences found from the literature and real-world safety data review, it can be noted that apart from the expected listed events (dyskinesia, dizziness, hypertension, headache, hallucination, constipation, and dry mouth), many unlisted events (somnolence, hyperhidrosis, pulmonary embolism, abdominal pain) were also observed which warrants the need for continuous vigilance of safety of Opicapone.

6. Conclusion

In conclusion, this review has given a comprehensive review and analysis of various aspects of safety of Opicapone in treatment of PD. The safety performance of Opicapone, a newer anti-parkinsonian drug, has been assessed by thorough review of safety data extracted from literature as well as real-world safety data (regulatory authorities and clinical trials). No significant safety alerts or product recalls were found for Opicapone in the regulatory authority databases, suggesting its overall tolerability. However, literature review, and reports from clinical trials highlighted the occurrence of specific adverse events including unlisted events, providing valuable

insights for healthcare professionals to guide patient management.

Overall, this review underscores the importance of a multidisciplinary approach, continuous monitoring, and evidence-based decision-making in the management of Parkinson's disease. By addressing the challenges associated with anti-parkinsonian drugs and optimizing patient safety, healthcare providers can enhance the quality of care and improve outcomes for individuals living with Parkinson's disease.

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9. Conflict of Interest

The authors Mr. Anuj Kumar Burakoti (AKB), Dr. Ram Kumar Roy (RKR) and Dr. Harikesh Dubey (HD) have no competing Interests.

10. Informed Consent & Ethical Statement

Not applicable

11. Author Contribution

AKB conceived and designed the study, processed the data and performed the statistical analyses. All authors interpreted the data. Mr. Anuj Kumar Burakoti drafted the work under the guidance of RKR and HD. All authors approved the final submitted version of the manuscript.

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