frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 19 February 2026
DOI 10.3389/fneur.2026.1738500

Check for updates

OPEN ACCESS

EDITED BY
Genko Oyama,
Saitama Medical University, Japan

REVIEWED BY
Ruggero Bacchin,
Azienda Provinciale per i Servizi Sanitari (APSS), Italy
Rani Priyanka Vasireddy,
University of Texas at Tyler, United States

*CORRESPONDENCE
María-Rosario Luquin
✉ rluquin@unav.es

RECEIVED 03 November 2025
REVISED 19 January 2026
ACCEPTED 22 January 2026
PUBLISHED 19 February 2026

CITATION
Luquin M-R, Lopez-Ariztegui N, Castrillo JCM, Manzanares LL, Bataller IS, Fernández AK, Pastor BV, Vila BS, Sauco MÁ, Mora JP, González JMA, Ruiz-Espiga PJG, de Fàbregues O, del Val JL, Arillo VC, Moreno C, Ameijeiras JB, Jiménez IP and Ayuela IT (2026) Real-world data of opicapone in patients with Parkinson's disease experiencing motor fluctuations: the OPTIMO study.
*Front. Neurol.* 17:1738500.
doi: 10.3389/fneur.2026.1738500

COPYRIGHT
© 2026 Luquin, Lopez-Ariztegui, Castrillo, Manzanares, Bataller, Fernández, Pastor, Vila, Sauco, Mora, González, Ruiz-Espiga, de Fàbregues, del Val, Arillo, Moreno, Ameijeiras, Jiménez and Ayuela. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

# Real-world data of opicapone in patients with Parkinson's disease experiencing motor fluctuations: the OPTIMO study

María-Rosario Luquin[1]*, Nuria Lopez-Ariztegui[2], Juan Carlos Martínez Castrillo[3], Lydia López Manzanares[4], Isabel Sastre Bataller[5], Antonio Koukoulis Fernández[6], Bárbara Vives Pastor[7], Berta Solano Vila[8], María Álvarez Sauco[9], Javier Pagonabarraga Mora[10], José Matías Arbelo González[11], Pedro José García Ruiz-Espiga[12], Oriol de Fàbregues[13], Javier López del Val[14], Víctor Campos Arillo[15], Clara Moreno[16], José Blanco Ameijeiras[16], Isabel Pijuan Jiménez[16] and Iciar Tegel Ayuela[16]

[1]Clínica Universidad de Navarra, Pamplona, Spain, [2]Hospital Universitario de Toledo, Toledo, Spain, [3]Servicio de Neurología, IRYCIS, Hospital Universitario Ramón y Cajal, Madrid, Spain, [4]Hospital Universitario La Princesa, Madrid, Spain, [5]Hospital Universitario y Politécnico La Fe, Valencia, Spain, [6]Hospital Álvaro Cunqueiro, Vigo, Spain, [7]Hospital Universitario Son Espases, Palma de Mallorca, Spain, [8]Hospital Josep Trueta, Girona y Hospital Santa Caterina Salt, Girona, Spain, [9]Hospital General Universitario de Elche, Elche, Spain, [10]Hospital de la Santa Creu i Sant Pau, Institut de Recerca, Barcelona, Spain, [11]Hospital Universitario San Roque, Las Palmas de Gran Canaria, Spain, [12]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain, [13]Hospital Universitario Vall d'Hebron, Barcelona, Spain, [14]Clínica HLA Montpellier, Zaragoza, Spain, [15]Hospital Vithas-Xanit, Benalmádena, Málaga, Spain, [16]Medical Department, Laboratorios Bial S.A, Madrid, Spain

**Purpose:** Evaluate the outcomes of opicapone as an add-on treatment to levodopa/DDCI in patients with Parkinson's disease (PD) and motor fluctuations (MF) in a real-world setting.

**Methods:** Observational, retrospective, and post-authorization study in patients with PD and MF treated with opicapone at 16 Spanish Movement Disorders centers.

**Results:** Of 245 patients included (55.9% men; mean [standard deviation] age: 67.7 [10.4] years), 41.9 and 33.6% presented rigid-akinetic and tremor-dominant phenotypes, respectively; 43.8% had a history of dyskinesias. Patients started treatment with 50 mg/day opicapone 8.3 (5.3) years after diagnosis. At initiation, the mean levodopa dose was 620.7 (313.7) mg/day. According to the PGI-C (available in 178 patients), 74.2% of patients reported clinical improvement in MF, without worsening of dykinesias in 64.6%. Clinical improvement of MF with stable/improved dyskinesias was similar between PD phenotypes ($p = 0.327$). Opicapone reduced the percentage of patients experiencing wearing-off phenomena (98.0% vs. 61.6%), delayed-on (10.2% vs. 5.3%; $p = 0.010$), no-on (6.5% vs. 2.9%; $p = 0.027$), and non-motor fluctuations (21.6% vs. 15.1%; $p = 0.010$). Furthermore, the off-time decreased (143.3 vs. 67.9 min/day; $p < 0.001$). After 4.8 (3.6) months of treatment, scores in UPDRS Parts II-IV significantly decreased, suggesting additional improvements in daily activities and motor function. The mean daily time with dyskinesias did not increase after initiating opicapone. Mild adverse events were observed in 21 (8.3%) patients.

**Conclusion:** This study demonstrates that opicapone added to levodopa improves motor function and reduces MF without significantly enhancing dyskinesia intensity, along with a tolerable profile. Moreover, there were no differences regarding clinical improvement among PD phenotypes.

KEYWORDS

catechol-o-methyltransferase inhibitors, motor fluctuations, opicapone, Parkinson's disease, real-world data, wearing-off

# 1 Introduction

Since the introduction of levodopa for the treatment of Parkinson's disease (PD), patients' quality of life has dramatically improved, and nowadays, levodopa associated with a decarboxylase inhibitor (levodopa/DDCI) remains the gold standard treatment for PD (1, 2). However, long-term levodopa therapy along with disease progression induces the appearance of motor and non-motor complications, including on/off motor fluctuations and dyskinesias, which negatively impact patients' quality of life (3–5). The most common motor complication is the "wearing-off" phenomenon, where PD symptoms reappear just before the next levodopa dose (6). Managing these fluctuations involves adjusting levodopa doses, using different levodopa formulations, or adding drugs that enhance the striatal dopamine tone, like dopamine agonists, monoamine oxidase B (MAO-B) inhibitors, and catechol-O-methyl transferase inhibitors (COMTi) (7, 8).

Opicapone, a third-generation COMTi, was approved in 2016 by European regulatory agencies as an adjunctive therapy to levodopa/DDCI (9). Due to its high binding affinity and slow dissociation rate, opicapone provides long-lasting COMT inhibition with convenient once-daily administration (10, 11). Pharmacokinetic data showed that opicapone add-on levodopa provides higher levodopa bioavailability with avoidance of trough levels, resulting in reduced pulsatile dopaminergic stimulation produced by individual and repeated levodopa doses, thus allowing the use of lower doses of levodopa (12).

The efficacy and safety of opicapone have been consistently demonstrated in two phase III, randomized, placebo-controlled trials, BIPARK I and BIPARK II. These studies showed that opicapone significantly prolonged the clinical effects of levodopa, thereby improving motor function and reducing the daily "off" time while being generally well-tolerated (13, 14). These observations were later supported by some real-world data (RWD) studies (15, 16), such as the OPTIPARK trial that demonstrated the effectiveness of opicapone and improved quality of life in patients with PD after 3 months of routine treatment in clinical practice in Germany and the UK (15). More recently, new data have been published on the efficacy and safety of opicapone when administered with daily doses of levodopa of ≈400 mg in patients who suffered early motor fluctuations (<2 years of motor fluctuations). This randomized, open-label, phase IV clinical study proved that opicapone is more effective in reducing the daily off time than increasing 100 mg of levodopa (16).

Despite the robust clinical evidence supporting the efficacy and safety of opicapone (13, 14), and the availability of RWD on its use (15, 17–19), the present study provides a unique approach as the first comprehensive real-world evidence analysis in Spain, which aims to identify predictive factors for clinical response to opicapone in PD. The OPTIMO study evaluates the effectiveness of opicapone in reducing motor fluctuations in real-life patients with PD, as well as its tolerability and clinical management.

# 2 Methods

## 2.1 Study design and patients

OPTIMO was a multicenter, observational, retrospective, and post-authorization study designed to describe the clinical change derived from opicapone as an add-on treatment to levodopa/DDCI in patients with PD, conducted at outpatient consultations in 16 Spanish Movement Disorders centers.

Consecutive adult patients (≥18 years old) with PD, with an I-III Hoehn & Yahr stage during the ON periods (20), exhibiting levodopa-induced motor complications (motor fluctuations with and without dyskinesia), who were receiving opicapone at least during the preceding 3 months, were included in the study. This study encompassed a 12-month recruitment period. Patients attended a single visit in which they were informed and invited to participate in the study. Data on routine medical practice were retrospectively collected from patients' medical records. This included clinical data before the treatment initiation with opicapone and those reported after 3 to 7 months of therapy. Given the non-interventional nature of the study, treatment decisions were not altered by the participation in the study. Study variables were extracted from patients' medical records and recorded using a standardized case report form (CRF) to ensure consistency across centers. Only routinely documented variables were included, and ambiguous or inconsistently recorded data were excluded from the analyses.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice (GCP), and in compliance with European and national regulations. The Ethics Committee of Hospital Universitario de Navarra (Spain) approved the study, and written informed consent was obtained from all patients before their inclusion.

## 2.2 Study endpoints

The primary endpoint was the clinical change obtained in patients with PD after adding opicapone to the regular levodopa/DDCI regimen. The clinical change produced by opicapone was defined as the percentage of patients who reported motor fluctuations improvement without worsening dyskinesias (i.e., stable or improved dyskinesias) during the established period of treatment with opicapone. The change was evaluated using the Patient's Global Impression of Change (PGI-C) scale (21), in which patients indicated whether they felt better (improved)/no change (stable)/worsening in both motor fluctuations and dyskinesias.

Secondary endpoints included the identification of the PD clinical phenotype that benefits most from opicapone treatment; the description of the effect of opicapone on certain PD symptoms; the clinical management of opicapone concerning concomitant

10.3389/fneur.2026.1738500

treatments, the modification of levodopa doses after adding opicapone, the rate of opicapone therapy discontinuation; the evaluation of opicapone safety profile by collecting all adverse events (AEs) reported during opicapone treatment and treatment-related AEs; and the identification of demographic and clinical risk factors for developing dyskinesias after initiating treatment with opicapone.

## 2.3 Statistical analysis

We calculated that a sample size of 432 patients would be sufficient to estimate a percentage of 31.7% in the proportion of patients with PD experiencing improved clinical change during opicapone treatment as determined by PGI-C scores, with a 0.05 alpha and a precision of 4.5% in a bilateral contrast (assuming 5% data loss).

A descriptive statistical analysis was performed on the study variables. Measures of central tendency and dispersion (mean and standard deviation [SD], median and interquartile range [IQR]) were used to describe quantitative variables, while frequencies and valid percentages were used to describe qualitative variables; 95% confidence intervals (CI) were calculated. Data collected from medical records included patients' age, sex, body mass index (BMI), and PD-related data, such as its severity and symptoms, age at onset, time of evolution of the disease, time from diagnosis to opicapone initiation, prior treatments, and history of dyskinesias. Group comparisons for categorical variables were made using Fisher's exact, Wilcoxon-Mann–Whitney, or McNemar tests, as appropriate.

A logistic regression model was performed to study the association between the clinical change (PGI-C)/development of dyskinesias and each of the possible demographic or clinical factors (including prior treatments) of interest, starting with all variables that were significant in a first-step bivariate analysis ($p < 0.002$).

Missing data were not considered in the analyses, and no imputation was performed, reflecting the nature of routinely collected RWD. All hypothesis tests were bilateral; significance was considered at $p < 0.05$. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL).

# 3 Results

## 3.1 Patient characteristics

Between August 2019 and May 2021, a total of 263 patients were enrolled in the study. Eighteen patients were excluded due to non-compliance with eligibility criteria; therefore, 245 patients were evaluable for statistical analyses. As shown in Table 1, the mean (SD) age was 67.7 (10.4) years, with a higher proportion of men (55.9%). The akinetic rigid phenotype was the most prevalent (41.9%), followed by the tremor-dominant (33.6%). Most patients with PD (63.9%) were in stage II of the Hoehn & Yahr scale. Concomitant clinical conditions unrelated to PD were reported in 62.4% of patients, the most frequent being hypertension (55.6%), dyslipidemia (39.9%), diabetes (21.6%), and neuropsychiatric history (13.1%; data not shown).

On average (SD), patients started treatment with opicapone 8.3 (5.3) years after PD diagnosis. Almost all (98%) patients reported wearing-off motor fluctuations (as per established selection criteria), with a mean (SD) duration of daily OFF time of 143.3 (126.4) minutes. A previous history of dyskinesias was present in 43.8% of patients. Non-troublesome dyskinesias were reported by 29.0% of patients at the time of opicapone initiation, while troublesome dyskinesias were described in 3.3% (Supplementary Table 1).

TABLE 1 General characteristics of study patients.

| Characteristics | Value |
|---|---|
| **Demographics** | |
| Age (years), mean (SD) [N] | 67.7 (10.4) [245] |
| Sex (male), n (%) [N] | 137 (55.9) [245] |
| BMI (kg/m$^2$), mean (SD) [N] | 26.9 (4.7) [105] |
| **Clinics of PD** | |
| Time from diagnosis to treatment with opicapone (years), mean (SD) [N] | 8.3 (5.3) [229] |
| **Clinical phenotype, n (%) [N]** | |
| Akinetic rigid | 96 (41.9) [229] |
| Predominance of tremors | 77 (33.6) [229] |
| Mixed or indeterminate | 45 (19.7) [229] |
| PIGD | 11 (4.8) [229] |
| **Hoehn & Yahr stage** | |
| I | 10 (4.3) [230] |
| II | 147 (63.9) [230] |
| III | 73 (31.7) [230] |
| **History of dyskinesias, n (%) [N]** | |
| Yes | 106 (43.8) [242] |
| No | 136 (56.2) [242] |

BMI, body mass index; PD, Parkinson's disease; PIGD, postural instability and gait difficulties; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

Before the treatment with opicapone, the average (SD) daily levodopa dose was 620.7 (313.7) mg. In addition, 69.4% of patients had been treated with MAO-B inhibitors, 64.5% with dopamine agonists, and 11% with COMTi other than opicapone (Supplementary Table 2).

## 3.2 Treatment management

During opicapone treatment, levodopa dose was maintained stable in 63% of patients, increased in 18%, and reduced in 19%; on average, this reduction was of 210.7 (176.8) mg/day.

While receiving opicapone, 5.6 and 8.7% of patients stopped the treatment with dopamine agonists and MAO-B inhibitors, respectively. Most patients treated with antidepressants continued the treatment (96.5%; 55 patients).

## 3.3 Effectiveness of opicapone

Data on the PGI-C was available for 178 patients (73% of 245 total patients). As shown in Figure 1, 74.2% (95% CI: 67.1–80.4%) of them reported improvements in motor fluctuations during the treatment with opicapone according to the PGI-C assessment. Indeed, 64.6%

(95% CI: 57.1–71.6%) of patients noted clinically improved motor fluctuations without worsening dyskinesias (improved or stable).

No changes in motor fluctuations (stable) during opicapone treatment were reported by 23.0% of patients, while only 2.8% reported worsening of motor fluctuations (Figure 1). Overall ($n = 178$), 60.7% of patients reported stable dyskinesias, 23.6% improved, and 15.7% experienced worsening (not shown).

Among patients with a previous history of dyskinesias ($n = 106$), 38.7% (41 patients) did not show dyskinesia during treatment. Meanwhile, 84.6% (115 patients) of patients without a previous history of dyskinesias ($n = 136$) did not develop abnormal movements during treatment.

We also assessed the clinical change perceived in motor fluctuations and dyskinesias among patients with different PD phenotypes. For that analysis, we considered data from 166 patients. We found that improvement of motor fluctuations with stable/improved dyskinesias was not associated with a particular PD phenotype ($p = 0.327$; data not shown).

Subgroup analyses of patients' demographic and clinical characteristics associated with PD clinical change are shown in Supplementary Table 3. Multivariate analyses revealed that the daily off time before opicapone treatment, the time with dyskinesias, and the complexity of motor fluctuations were independent predictive factors of clinical improvement in motor fluctuations with improved or stable dyskinesias. For instance, those patients with a lower daily off-time (in case of wearing-off motor fluctuations) before opicapone initiation, and those with a minimum time with dyskinesias or minimum complexity of motor fluctuations on the UPDRS, were more likely to perceive improvements in motor fluctuations without worsening dyskinesias.

The effect of opicapone on PD symptoms was evaluated in the entire study cohort (N = 245). During the treatment with opicapone, the percentage of patients suffering from wearing-off motor fluctuations decreased to 61.6% (Table 2). In accordance, the mean (SD) daily off-time duration decreased up to 67.9 (111.2) minutes during opicapone treatment, compared to that before treatment initiation (143.3 [126.4] minutes; $p < 0.001$; Figure 2A). Based on item 4 of UPDRS Part IV, we found that the functional impact of motor fluctuations was reduced after opicapone treatment. Before treatment initiation, 69.8% of patients reported it as mild (28.1%), moderate (34.5%), or serious (7.2%). In contrast, during opicapone treatment, 37.4% of patients reported the functional impact of motor fluctuations as mild (23.7%), moderate (12.2%), or serious (1.5%; Figure 2B).

Besides, opicapone was able to alleviate most of the PD symptoms evaluated, including morning akinesia (35.9% vs. 24.1%; $p < 0.001$), non-motor fluctuations (21.6% vs. 15.1%; $p = 0.010$), nocturnal akinesia (20.8% vs. 8.2%; $p < 0.001$), delayed-on (10.2% vs. 5.3%; $p = 0.010$), and no-on motor fluctuations (6.5% vs. 2.9%; $p = 0.027$). The percentage of patients with impulse control disorder did not increase after initiating opicapone (6.1% vs. 2.4%; $p = 0.016$; Table 2).

As shown in Table 2, 89 (36.3%) patients experienced dyskinesias (troublesome and/or non-troublesome) during opicapone treatment. Of note, 79 of them (88.8%) already suffered from dyskinesias before starting treatment with opicapone. The mean (SD) percentage of daily time with dyskinesias did not show significant differences during opicapone treatment (25.1 [11.6] % vs. 28.5 [18.3] %; $p = 0.454$) as compared with the baseline evaluation.

We compared UPDRS data ($n = 130$) before opicapone initiation with those obtained after a mean (SD) time of 4.8 (3.6) months after opicapone initiation to determine changes in the disease stage. The mean score in UPDRS Part I remained stable in more than half (52.0%) of patients compared to before opicapone initiation. In contrast, scores on Parts II and III decreased in most (58.0 and 62.7%) patients, indicating improvements in activities of daily living and motor function. The mean (SD) score on the UPDRS I-III was 34.7 (13.6), showing a statistically significant decrease ($p < 0.001$) in 70.0% of patients during treatment with opicapone, compared to the assessment completed before starting the treatment. The mean score in Part IV also decreased significantly, confirming the improvement in motor complications (Table 3).

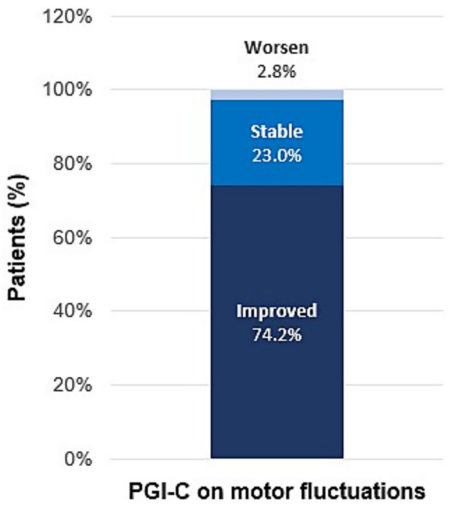


FIGURE 1
Clinical changes in motor fluctuations perceived by patients with PD treated with opicapone, according to the PGI-C scale. Percentage of patients who perceived the indicated clinical changes (improvement/stability/worsening) in motor fluctuations; PGI-C, Patient's Global Impression of Change.

## 3.4 Tolerability

Overall, 12.2% ($n = 30$) of patients experienced any AE during the treatment with opicapone. A total of 30 AEs were considered related to opicapone, affecting 8.6% ($n = 21$) of patients. Among them, the most frequent AEs were dyskinesias ($n = 9$; 3.7%), hallucinations ($n = 2$; 0.8%), loose stools ($n = 2$; 0.8%), constipation ($n = 2$; 0.8%), insomnia ($n = 2$; 0.8%), and dizziness ($n = 2$; 0.8%; Table 4).

Two (0.8%) patients reported severe AEs (SAEs). One of them reported hallucinations after 122 days from opicapone initiation, which was considered related to the treatment. The other patient developed acute respiratory failure, not related to opicapone.

# 4 Discussion

The present study provides evidence for the effectiveness and tolerability of opicapone as an add-on therapy in patients with mild

TABLE 2 Differences in the symptoms experienced by patients with PD after opicapone treatment initiation.

| Symptoms of PD* | Patients, *n* (%) | | *p*-value[a] |
|---|---|---|---|
| | Before opicapone | During opicapone | |
| Wearing-off motor fluctuations | 240 (98.0)** | 151 (61.6) | Not available*** |
| Morning akinesia | 88 (35.9) | 59 (24.1) | <0.001 |
| Non-troublesome dyskinesia | 71 (29.0) | 74 (30.2) | 0.787 |
| Non-motor fluctuations (pain, anxiety, distress) | 53 (21.6) | 37 (15.1) | 0.010 |
| Nocturnal akinesia | 51 (20.8) | 20 (8.2) | <0.001 |
| Freezing of the gait | 41 (16.7) | 40 (16.3) | >0.999 |
| Delayed-on motor fluctuations | 25 (10.2) | 13 (5.3) | 0.010 |
| Off dystonia | 21 (8.6) | 12 (4.9) | 0.081 |
| No-on motor fluctuations | 16 (6.5) | 7 (2.9) | 0.027 |
| Impulse control disorders | 15 (6.1) | 6 (2.4) | 0.016 |
| Falls | 11 (4.5) | 11 (4.5) | >0.999 |
| Troublesome dyskinesia | 8 (3.3) | 15 (6.1) | 0.146 |
| Cognitive impairment | 7 (2.9) | 6 (2.4) | >0.999 |
| Complex and unpredictable motor fluctuations | 6 (2.4) | 6 (2.4) | >0.999 |
| Hallucinations and delusions | 5 (2.0) | 7 (2.9) | 0.752 |

PD, Parkinson's disease; SD, standard deviation. *PD symptoms were collected as presence/absence. Percentages may add more than 100% as each patient could present more than one symptom (multiple choice variable). **Although 5 patients did not select wearing-off motor fluctuation as a symptom in this questionnaire, all patients presented wearing-off motor fluctuations as they met the following inclusion criterion: "Patient with PD treated with levodopa + DDCI who presents wearing-off motor fluctuations with or without dyskinesias". ***The *p*-value associated with this test could not be calculated because any patient (0%) had absence of wearing-off motor fluctuations before starting opicapone as per established selection criteria. [a]McNemar test.

to moderate PD in routine clinical practice in Spain and is in line with the results obtained in the randomized studies. A key finding of our study is that opicapone induces a similar motor benefit and safety profile across the different PD phenotypes.

In this real-world analysis, we observed clinical improvements in motor fluctuations in 74.2% of patients, and 64.6% reported improvements in motor fluctuations with stability/improvement on dyskinesias according to the PGI-C. These results are similar to those observed in the BIPARK I (13) and ADOPTION (16) clinical trials, RWD from the OPTIPARK study (15), and data reported in a review from 18 Spanish real-life studies with small patient cohorts (17). In these analyses, 72.1, 77.0, 76.9%, and 66–77% of patients, respectively, presented clinical improvement, according to their perceptions.

Together with clinical improvements in motor fluctuations, we demonstrated a 75.4-min daily off-time reduction during treatment with opicapone, which is consistent with the results observed in the BIPARK trials where opicapone was compared to placebo (13, 14). These results are also aligned with the available RWD of ≈200 patients from 18 patient series in Spain, in which the off time decreased between 72 and 84 min (17). The ADOPTION trial recently showed a reduction in absolute off time of 62.1 min in patients receiving opicapone 50 mg, which was significantly superior to the group receiving additional 100 mg of levodopa (−16.7 min) (16).

Furthermore, our study patients with PD reported a significant improvement in non-motor fluctuations, including pain, anxiety, and distress, during opicapone treatment. Similarly, the OPEN-PD, a study specifically designed to explore the effect of opicapone on non-motor symptoms, demonstrated an overall improvement in non-motor symptoms of the disease. In this study, significant enhancements in the mood/apathy, sleep/fatigue, gastrointestinal symptoms, and miscellaneous (that also assess pain) domains were observed (22). Likewise, the clinical practice OPTIPARK trial showed a reduction in non-motor symptoms, according to the Non-Motor Symptom Scale (NMSS), after 3 months of treatment with opicapone (15). More recently, the OASIS study provided further proof of the effect of opicapone on reducing PD-related sleep disorders and fatigue (23). A real-life observational analysis of data from 50 patients with PD from the King's College Hospital Dubai also found improvement in non-motor burden as measured by the NMSS after 6 and 12 months of treatment with opicapone (24).

Besides the reduction of daily off time, an improvement in the severity of the "off" periods may affect the benefit registered in the PGI-C on motor fluctuations. Unfortunately, quantitative data (such as UPDRS III during off time) about off severity was not available as the UPDRS in ON and OFF conditions is not routinely recorded in clinical practice. However, item 4 of the UPDRS IV showed a qualitative improvement on this parameter, where 37.4% of patients qualified the functional impact of motor fluctuations as mild, moderate, or serious during opicapone treatment, as compared to 69.8% of patients before treatment initiation. Improvements in the UPDRS Part IV were also reported in the OPTI-ON study, in patients with PD experiencing OFF episodes who received opicapone and were followed up for 6 months (25). Although the off-period severity has been largely disregarded in PD treatment efficacy assessments, its impact on patients' quality of life may be as relevant as the daily off time. The OPTIMO study's data support the positive effect of opicapone on both parameters.

Of note, we found that the daily off time before opicapone treatment, the time with dyskinesias, and the complexity of motor

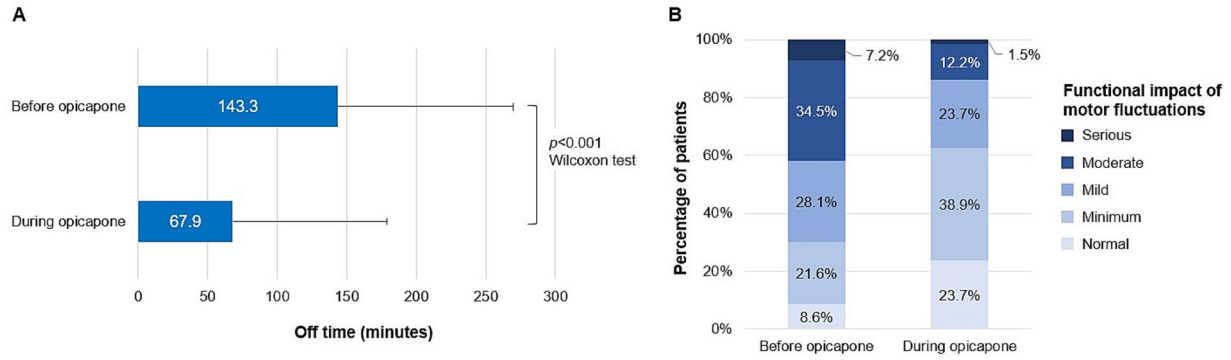


FIGURE 2
Impact of opicapone on motor fluctuations. **(A)** The daily off time (minutes), in case of wearing-off motor fluctuations, is shown as mean + standard deviation before starting treatment with opicapone and during treatment with opicapone. **(B)** Percentage of patients grading the functional impact of motor fluctuations according to the UPDRS part IV, before opicapone and during treatment with opicapone.

TABLE 3 Clinical change in the UPDRS after treatment with opicapone.

| UPDRS | Total score mean (SD) | | Change mean (SD) | *p*-value[a] |
|---|---|---|---|---|
| | Before opicapone | During opicapone | | |
| Part I (*N* = 50) | 2.9 (2.2) | 2.5 (2.3) | −0.4 (1.5) | 0.072 |
| Part II (*N* = 50) | 10.1 (6.4) | 8.2 (5.4) | −2.0 (3.6) | <0.001 |
| Part III (*N* = 110) | 22.4 (9.5) | 19.0 (10.7) | −3.4 (6.0) | <0.001 |
| UPDRS I-III (*N* = 50) | 34.7 (13.6) | 28.3 (14.8) | −6.4 (11.1) | <0.001 |
| Part IV (*N* = 107) | 6.7 (3.8) | 4.5 (3.3) | −2.2 (3.0) | <0.001 |

N, total of patients with available information of both UPDRS values (before and during opicapone) in medical records; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.
[a]Wilcoxon test.

fluctuations were predictive factors for the perception of clinical improvement in motor fluctuations without worsening dyskinesias. This observation is in line with the results of a post-hoc analysis of the BIPARK I/II studies in which patients with a shorter disease evolution (duration), lower PD severity, and shorter onset time of the motor fluctuations showed a trend for greater efficacy of opicapone (26). Moreover, an independent study identified longer disease duration and off time at baseline as predictive factors for opicapone treatment discontinuation (27). Accordingly, another post-hoc analysis of the BIPARK I/II studies and an Italian RWD study in 152 patients with PD showed that earlier patients, as opposed to later in their disease course, presented an even more favorable tolerability profile (28, 29). Even though opicapone is effective and safe at all stages and phenotypes of PD, these observations suggest that patients may benefit the most from introducing opicapone earlier in the course of the disease.

In addition to the clinical improvements reported for motor and non-motor fluctuations, upon opicapone treatment, patients showed a statistically significant reduction of 3.4 points in the UPDRS III (during on time), which reached the threshold of 2.3–2.7 points accepted as a clinically important difference (30). This suggests that the reduction in the daily off time induced by opicapone treatment may be accompanied by an improvement in the motor condition of the patient during on time. Overall, this ultimately contributes to patients' experiences of daily living as assessed by the UPDRS Part II, where 58.0% of study patients showed an improvement upon opicapone treatment.

Adjuvant administration of opicapone increases levodopa bioavailability by 65% (31) and significantly prolongs its clinical effects (13, 14), which allows, in some cases, a reduction of the levodopa doses (18). The present study showed that the dose of levodopa was reduced in 19% of patients, and 82% did not require up-titration, suggesting a positive effect of opicapone on maintaining low levodopa doses.

The most common AE of opicapone is dyskinesia (32), which has often been associated with excessive dopaminergic stimulation during on periods due to enhanced levodopa exposure (33). In our study, opicapone did not significantly increase dyskinesias. Despite 36.3% of patients experiencing dyskinesia during opicapone treatment, most of them already suffered from it before starting the treatment, possibly due to the chronic nature of PD (with an evolution time of >8 years). Although data collected from medical records resulted in inconsistent reporting of dyskinesias as an AE, based on symptom reports, 15.4% (21 patients) of patients with no previous history of dyskinesias developed them during treatment. Aside from dyskinesias, other side effects reported were hallucinations, loose stools, constipation, insomnia, and dizziness. This tolerability profile is in harmony with the Spanish clinical

TABLE 4 Reported adverse events related to treatment with opicapone (*N* = 245).

| Adverse events | Patients *n* (%) |
|---|---|
| Dyskinesia[a] | 9 (3.7) |
| Constipation | 2 (0.8) |
| Dizziness | 2 (0.8) |
| Hallucinations | 2 (0.8) |
| Insomnia | 2 (0.8) |
| Loose stools | 2 (0.8) |
| Anorexia | 1 (0.4) |
| Asthenia | 1 (0.4) |
| Cramps | 1 (0.4) |
| Dopamine-dysregulation syndrome | 1 (0.4) |
| Edema in the legs | 1 (0.4) |
| Episodic confusional state | 1 (0.4) |
| Gait unsteadiness | 1 (0.4) |
| Nausea | 1 (0.4) |
| Nightmares at opicapone initiation | 1 (0.4) |
| Off-cervical dystonia | 1 (0.4) |
| Psychiatric AEs: excitation | 1 (0.4) |

AEs, adverse events.
[a]Indicated as: dyskinesia ($n$ = 2), increased dyskinesia ($n$ = 1), disabling generalized choreic dyskinesias ($n$ = 1), buccolingual dyskinesias ($n$ = 1), choreic dyskinesias ($n$ = 1), peak dyskinesias ($n$ = 1), worsening of peak dyskinesias ($n$ = 1), mild worsening of dyskinesias ($n$ = 1).

practice series (17), a Portuguese RWD monocentric study (18), as well as with phase III BIPARK studies (13, 14, 34), in which treatment-related AEs mostly occurred within the first 2 months. Therefore, our results confirm that opicapone is generally well tolerated, with a low risk of AEs, even in a population with a long disease duration and prior medium-high doses of levodopa. Adding to our data, a meta-analysis by Xie L. and collaborators suggested that a brief course of opicapone led to an increased incidence of dyskinesia, whereas long-term treatment may not be associated with a higher risk in patients with PD (32), supporting its usefulness in managing PD motor fluctuations.

Limitations of this study include the absence of a control group and missing information on some variables due to the observational nature of the study and the fact that electronic medical records were originally designed for clinical care rather than research purposes. Another limitation is the reliance on patient-reported outcomes such as the PGI-C, which, although widely used in RWD studies, is inherently subjective and may be influenced by patient expectations or the physician-patient relationship. In addition, we could not include the estimated number of patients, and this may limit the traceability of the results obtained. Despite these limitations, to our knowledge, this is the most extensive study conducted to date in the real-world setting in Spain describing the effectiveness and tolerability of opicapone as adjuvant therapy to levodopa/DDCI for the treatment of PD. As this was a real-world study conducted within the Spanish healthcare system, the generalizability of these findings to other countries should consider differences in healthcare organization, clinical practice patterns, and patient management approaches.

In conclusion, this study expands the knowledge on the effectiveness and safety of opicapone in real-life patients with PD and complements clinical trial data. Our findings demonstrate that opicapone improves both motor and non-motor symptoms of the disease, thus enhancing patients' perception of their PD condition. Additionally, the identified predictive factors for the improvement of motor fluctuations suggest that PD patients may benefit the most from the earlier introduction of opicapone. Opicapone also decreased the daily off time without significantly increasing dyskinesia, and reduced the functional impact during off time, making it an excellent adjunct treatment for PD motor fluctuations.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by the Ethics Committee of the Hospital Universitario de Navarra (Spain). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

## Author contributions

ML: Writing – review & editing, Writing – original draft, Conceptualization, Methodology, Investigation. NA: Writing – review & editing, Writing – original draft, Investigation. JC: Writing – original draft, Writing – review & editing, Investigation. LM: Writing – review & editing, Investigation, Writing – original draft. IB: Writing – review & editing, Investigation, Writing – original draft. AF: Writing – review & editing, Writing – original draft, Investigation. BP: Writing – review & editing, Investigation, Writing – original draft. BV: Writing – review & editing, Investigation, Writing – original draft. MS: Investigation, Writing – review & editing, Writing – original draft. JM: Investigation, Writing – review & editing, Writing – original draft. JG: Writing – original draft, Writing – review & editing, Investigation. PR-E: Writing – original draft, Investigation, Writing – review & editing. OF: Investigation, Writing – review & editing, Writing – original draft. JV: Writing – review & editing, Investigation, Writing – original draft. VA: Investigation, Writing – review & editing, Writing – original draft. CM: Writing – review & editing, Project administration. JA: Project administration, Writing – review & editing. IJ: Project administration, Writing – review & editing, Supervision. IA: Project administration, Supervision, Methodology, Writing – review & editing, Conceptualization.

## Funding

The author(s) declared that financial support was received for this work and/or its publication. This study was sponsored by Laboratorios Bial S. A.

## Acknowledgments

Scientific advisory and medical writing assistance were provided by Carla Martín Cortázar from Evidenze Health España S. L. U. during the preparation of the clinical study report of the OPTIMO study and this manuscript, according to Good Publication Practice guidelines. Responsibility for opinions, conclusions, and interpretation of data lies with the authors.

## Conflict of interest

ML has received speaker, consultant honoraria, and support for attending meetings from Zambon, Esteve, and Bial; NA has received speaker honoraria and support for attending meetings from AbbVie, Stada, Italfarmaco, Zambon, KRKA, Orion, UCB, Bial, Lundbeck, Esteve; JC has received speaker, consultant honoraria and support for attending meetings from AbbVie, Bial, Stada, Italfarmaco; LM has received speaker honoraria from Abbott, AbbVie, Bial, Biogen, Esteve, Italfarmaco, Orion, STADA and Zambon. BV has received grants, speakers honoraria and support for attending meetings from AbbVie, Zambon, Esteve and Bial; MS has received consultant and speakers honoraria and support for attending meetings from Stada, Esteve, Bial, Zambon and Orphalan; JM has received consultant and speakers honoraria and participation in AB from Zambon, AbbVie, Bial, Ipsen, UCB and Esteve; PR-E has received speaker, consultant honoraria from Italfarmaco, Bial, Esteve, AbbVie, Britannia, Merz and Stada; OF has received speaker honoraria from AbbVie, Bial, Esteve and Orphalan; VA has received support for attending meetings and participation in AB from Zambon and Bial; CM, JA, IJ and IA are employees of Bial.

The authors declare that financial support was received for the research and/or publication of this article. This study was sponsored by Laboratorios Bial S.A. The funder participated in the study design and contributed to the writing and editing of the manuscript. The funder was not involved in data collection, analysis, interpretation of data, or the decision to submit the article for publication.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

## Generative AI statement

The author(s) declared that Generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2026.1738500/full#supplementary-material

## References

1. Olanow CW, Stocchi F. Levodopa: a new look at an old friend. *Mov Disord*. (2018) 33:859–66. doi: 10.1002/mds.27216

2. Tambasco N, Romoli M, Calabresi P. Levodopa in Parkinson's disease: current status and future developments. *Curr Neuropharmacol*. (2018) 16:1239–52. doi: 10.2174/1570159X15666170510143821

3. Hely MA, Morris JG, Reid WG, Trafficante R. Sydney Multicenter study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. *Mov Disord*. (2005) 20:190–9. doi: 10.1002/mds.20324

4. Chapuis S, Ouchchane L, Metz O, Gerbaud L, Durif F. Impact of the motor complications of Parkinson's disease on the quality of life. *Mov Disord*. (2005) 20:224–30. doi: 10.1002/mds.20279

5. Warren Olanow C, Kieburtz K, Rascol O, Poewe W, Schapira AH, Emre M, et al. Factors predictive of the development of levodopa-induced dyskinesia and wearing-off in Parkinson's disease. *Mov Disord*. (2013) 28:1064–71. doi: 10.1002/mds.25364

6. Pahwa R, Lyons KE. Levodopa-related wearing-off in Parkinson's disease: identification and management. *Curr Med Res Opin*. (2009) 25:841–9. doi: 10.1185/03007990902779319

7. Stocchi F, Oliveira R, Rocha F. Motor fluctuations in Parkinson's disease: perceptions and treatment. *Dialog Clin Neurosci Mental Health*. (2023) 6:11–24. doi: 10.26386/obrela.v6i1.261

8. Hayes MT. Parkinson's disease and parkinsonism. *Am J Med*. (2019) 132:802–7. doi: 10.1016/j.amjmed.2019.03.001

9. European Medicines Agency (EMA). Summary of Product Characteristics Ongentys (2023). Available online at: https://www.ema.europa.eu/en/documents/product-information/ongentys-epar-product-information_es.pdf.

10. Jost WH. Evaluating Opicapone as add-on treatment to levodopa/Ddci in patients with Parkinson's disease. *Neuropsychiatr Dis Treat*. (2022) 18:1603–18. doi: 10.2147/NDT.S279362

11. Song Z, Zhang J, Xue T, Yang Y, Wu D, Chen Z, et al. Different catechol-O-methyl transferase inhibitors in Parkinson's disease: a Bayesian network Meta-analysis. *Front Neurol*. (2021) 12:707723. doi: 10.3389/fneur.2021.707723

12. Ferreira JJ, Poewe W, Rascol O, Stocchi F, Antonini A, Moreira J, et al. Effect of Opicapone on levodopa pharmacokinetics in patients with fluctuating Parkinson's disease. *Mov Disord*. (2022) 37:2272–83. doi: 10.1002/mds.29193

13. 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. *Lancet Neurol*. (2016) 15:154–65. doi: 10.1016/S1474-4422(15)00336-1

14. Lees AJ, Ferreira J, Rascol O, Poewe W, Rocha JF, McCrory M, et al. Opicapone as adjunct to levodopa therapy in patients with Parkinson disease and motor fluctuations: a randomized clinical trial. *JAMA Neurol*. (2017) 74:197–206. doi: 10.1001/jamaneurol.2016.4703

15. Reichmann H, Lees A, Rocha JF, Magalhaes D, Soares-da-Silva P. Effectiveness and safety of opicapone in Parkinson's disease patients with motor fluctuations: the Optipark open-label study. *Transl Neurodegener*. (2020) 9:9. doi: 10.1186/s40035-020-00187-1

16. Lee JY, Ma HI, Ferreira JJ, Rocha JF, Sung YH, Song IU, et al. Opicapone to treat early wearing-off in Parkinson's disease patients: the Korean Adoption trial. *Mov Disord Clin Pract*. (2024) 11:655–65. doi: 10.1002/mdc3.14030

17. Lopez-Ariztegui N, Mata-Alvarez Santullano M, Tegel I, Almeida F, Sarasa P, Rojo R, et al. Opicapone for the treatment of Parkinson's disease: real-life data in Spain. *Rev Neurol*. (2021) 73:S01–14. doi: 10.33588/rn.73s02.2021461

18. Meira-Carvalho F, Da Silva JD, Rodrigues M. Opicapone in Parkinson's disease: real-world data from a Portuguese Center. *Eur Neurol*. (2021) 84:129–31. doi: 10.1159/000514544

19. Reichmann H, Eggert K, Oehlwein C, Warnecke T, Lees AJ, Kemmer M, et al. Opicapone use in clinical practice across Germany: a sub-analysis of the Optipark study in Parkinson's disease patients with motor fluctuations. *Eur Neurol*. (2022) 85:389–97. doi: 10.1159/000523771

20. Bhidayasiri R, Tarsy D. Parkinson's disease: Hoehn and Yahr scale In: Movement disorders: A video atlas (2012)

21. Eremenco S, Chen WH, Blum SI, Bush EN, Bushnell DM, DeBusk K, et al. Comparing patient global impression of severity and patient global impression of change to evaluate test-retest reliability of depression, non-small cell lung Cancer, and asthma measures. *Qual Life Res*. (2022) 31:3501–12. doi: 10.1007/s11136-022-03180-5

22. Santos Garcia D, Fernandez Pajarin G, Oropesa-Ruiz JM, Escamilla Sevilla F, Rahim Lopez RRA, Munoz Enriquez JG. Opicapone improves global non-motor symptoms burden in Parkinson's disease: an open-label prospective study. *Brain Sci*. (2022) 12. doi: 10.3390/brainsci12030383

23. Ferreira J, Gago M, Costa R, Fonseca M, Almeida J, Rocha J, et al. Opicapone effect on sleep disorders in fluctuating Parkinson's disease patients: findings from the oasis trial. *Parkinsonism Relat Disord*. (2024) 122. doi: 10.1016/j.parkreldis.2024.106130

24. Metta V, Ibrahim H, Muralidharan N, Rodriguez K, Masagnay T, Mohan J, et al. A 12-month prospective real-life study of Opicapone efficacy and tolerability in Emirati and non-white subjects with Parkinson's disease based in United Arab Emirates. *J Neural Transm (Vienna)*. (2024) 131:25–30. doi: 10.1007/s00702-023-02700-y

25. Kilbane C, Drake R, Klepitskaya O, Serbin M, Jen E, Rattana S, et al. Improvements in Parkinson's disease motor complications after treatment with opicapone: results from the Opti-on study (abstract). *Mov Disord*. (2023) 38

26. Rocha JF, Ebersbach G, Lees A, Tolosa E, Ferreira JJ, Poewe W, et al. The added benefit of Opicapone when used early in Parkinson's disease patients with levodopa-induced motor fluctuations: a post-hoc analysis of Bipark-I and -ii. *Front Neurol*. (2021) 12:754016. doi: 10.3389/fneur.2021.754016

27. Vokurka P, Barron A, Sumaria S, Stockford L, Jarman P, Bhatia K, et al. Opicapone efficacy and tolerability in Parkinson's disease patients reporting insufficient benefit/failure of entacapone. *Mov Disord Clin Pract*. (2020) 7:955–60. doi: 10.1002/mdc3.13094

28. Rocha JF, Ebersbach G, Lees A, Tolosa E, Ferreira JJ, Poewe W, et al. The safety/tolerability of Opicapone when used early in Parkinson's disease patients with levodopa-induced motor fluctuations: a post-hoc analysis of Bipark-I and ii. *Front Neurol*. (2022) 13:994114. doi: 10.3389/fneur.2022.994114

29. Bacchin R, Liccari M, Catalan M, Antonutti L, Manganotti P, Malaguti MC, et al. Disease stage and motor fluctuation duration predict drug tolerability: a real-life, prospective Italian Multicenter study on the use of Opicapone in Parkinson's disease. *Drugs Real World Outcomes*. (2024) 11:361–8. doi: 10.1007/s40801-024-00442-1

30. Shulman LM, Gruber-Baldini AL, Anderson KE, Fishman PS, Reich SG, Weiner WJ. The clinically important difference on the unified Parkinson's disease rating scale. *Arch Neurol*. (2010) 67:64–70. doi: 10.1001/archneurol.2009.295

31. Rocha JF, Sicard E, Fauchoux N, Falcao A, Santos A, Loureiro AI, et al. Effect of opicapone multiple-dose regimens on levodopa pharmacokinetics. *Br J Clin Pharmacol*. (2017) 83:540–53. doi: 10.1111/bcp.13156

32. Xie L, Qi X, Wang X, He B, Wang Y, Zhang W, et al. Adverse event profiles of adjuvant treatment with Opicapone in Parkinson's disease: a systematic review and Meta-analysis. *Front Pharmacol*. (2022) 13:1042992. doi: 10.3389/fphar.2022.1042992

33. Espay AJ, Morgante F, Merola A, Fasano A, Marsili L, Fox SH, et al. Levodopa-induced dyskinesia in Parkinson disease: current and evolving concepts. *Ann Neurol*. (2018) 84:797–811. doi: 10.1002/ana.25364

34. Lees A, Ferreira JJ, Rocha JF, Rascol O, Poewe W, Gama H, et al. Safety profile of Opicapone in the Management of Parkinson's disease. *J Parkinsons Dis*. (2019) 9:733–40. doi: 10.3233/JPD-191593