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SHORT COMMUNICATION

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

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Abstract

Background Opicapone is a third-generation catechol-*O*-methyl-transferase inhibitor currently used for the treatment of motor fluctuations in Parkinson's disease. Its benefit and safety have been established by clinical trials; however, data about its use in a real-life context, and particularly in an Italian population of patients with Parkinson's disease, are missing.

Objectives We aimed to gather data about the real-life tolerability/safety of opicapone when used for the treatment of Parkinson's disease-related motor fluctuations.

Methods We enrolled 152 consecutive patients with Parkinson's disease and followed them for 2 years after opicapone introduction. We obtained baseline clinical and demographical information, including disease duration, stage, phenotype, as well as axial and non-motor symptoms. We collected the reasons for any treatment interruption and adverse events emerging after opicapone introduction.

Results Eighty-nine (58%) patients reported adverse events and 46 (30%) patients discontinued the treatment. Adverse events occurred less frequently in "earlier" patients accordingly to the disease course and L-Dopa treatment pathway; a motor fluctuation duration ≥12 months and Hoehn and Yahr scale score ≥2.5 were the main predictors of therapy withdrawal.

Conclusions This study confirms the good tolerability/safety profile of opicapone in a real-life setting and provides country-specific data for Italian patients with Parkinson's disease.

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Key Points

Data on the use of opicapone in daily clinical practice are limited and particularly lacking for an Italian population.

The results of the study are overall in line with those of clinical studies.

The tolerability and safety of opicapone in the real-life setting were better when therapy was initiated earlier based on the disease duration and L-dopa treatment pathway.

The strongest clinical predictor of discontinuing opicapone therapy because of any treatment-related side effect is the disease stage based on the Hoehn and Yahr scale score and the duration of motor fluctuations.

1 Introduction

The addition of catechol-*O*-methyl-transferase inhibitors to L-Dopa (LD) represents an established strategy for the management of end-of-dose motor fluctuations (MFs) in Parkinson's disease (PD), owing to their ability to reduce the peripheral metabolism of LD and increase its brain bioavailability [1]. Opicapone (OPC) is a third-generation, long-acting, peripherally selective catechol-*O*-methyl-transferase inhibitor, whose effectiveness and safety in patients with PD with MFs have been established through two phase II clinical trials [2, 3] and three phase III randomized controlled trials (RCTs) with open-label extensions [4–11]. An ongoing RCT is also currently evaluating the use of OPC before MF onset [12]. However, RCTs have several limitations owing to their controlled experimental context, eligibility criteria, and limited observational time, despite their leading role in the establishment of the drug's efficacy and tolerability/safety [13]. Post-marketing data gathered from everyday clinical practice are relevant to expand drug knowledge in terms of safety and comparative effectiveness and in the field of a cost-effectiveness analysis [14]. Available post-marketing data derive from one phase IV, open-label prospective trial conducted in Germany and the UK [9–11], a retrospective monocentric Portuguese real-life study involving 35 patients with PD [15], and a revision of 18 Spanish clinical reports, which overall included about 1000 patients [16]. Country-specific data about OPC use under real-life settings in an Italian population of patients with PD are still missing. This study aims to report the real-life experience of two Italian movement disorder outpatient clinics with the use of OPC for MF treatment in patients with PD, focusing on tolerability/safety and clinical characteristics associated with treatment discontinuation.

2 Methods

The study included all the consecutive patients affected by idiopathic PD (according to 2015 movement disorders society (MDS) criteria) attending the Movement Disorders Outpatient Clinic of the University Hospital of Trieste and Trento, which introduced OPC for MFs between January 2017 and June 2021. Enrolled patients have been regularly followed for 2 years after treatment commenced. Each patient has been managed by one of the specialists in movement disorders involved in the study (RB, MC, MCM, LA). The minimum interval between follow-up visits was 6 months, but in the case of need (i.e., onset of a new symptom, unexpected worsening of the clinical condition), patients were promptly (within 1 day) interviewed by phone with an early follow-up visit. Parkinson's disease therapy (including LD treatment duration, LD daily dose amount, and percentage of reduction after OPC introduction) and all baseline clinical–demographic variables, including disease duration, Hoehn and Yahr scale score, MF duration, Unified Parkinson's Disease Rating Scale III score, PD phenotype, presence of axial symptoms, history of falls, and the presence of non-motor symptoms were collated [17]. Clinicians considered all adverse events (AEs) that emerged during the follow-up and if retained as probably related to OPC. Additionally, the reason for therapy withdrawal, if it occurred, was annotated. Patients were grouped as "earlier" and "later" accordingly to the PD duration (<6 vs ≥6, <7 vs ≥7, <8 vs ≥8, <9 vs ≥9 years), Hoehn and Yahr scale score (<2.5 vs ≥2.5), duration of MFs (<1 vs ≥1 and <2 vs ≥2 years), LD treatment duration (<4 vs ≥4, <5 vs ≥5, <6 vs ≥6, <7 vs ≥7, <8 vs ≥8 years), LD daily amount (<500 vs ≥500, <600 vs ≥600, <700 vs ≥700, <800 vs ≥800 mg), assumption of LD alone, LD plus dopamine agonist (DA), LD plus monoamine-oxidase-B inhibitor (iMAOB), LD plus DA and iMAOB, and if receiving advanced therapy (deep brain stimulation or continuous subcutaneous apomorphine infusion), with similar methodology proposed by Rocha et al. [18, 19]. Baseline characteristics of patients who withdrew OPC ("withdrawers") have been compared with those of patients who continued OPC ("continuers"), through a univariate and multivariate analysis. Statistical analysis has been performed using Stata/IC 11.2 (StataCorp LP, College Station, TX, USA). Quantitative variables were presented by mean ± standard deviation. Parametric (paired t-test and unpaired t-test), and non-parametric (Wilcoxon test or Mann–Whitney) tests have been used for between-group comparisons. Differences between categorical variables have been tested using Chi-square or Fisher's exact tests. A logistic regression analysis (forward conditional method) was performed entering categorical variables significantly associated with OPC withdrawal in an univariate analysis as independent variables while OPC withdrawals because of any AEs or dopamine-related AEs were dependent variables. Statistical significance was set at <0.05. The study has been approved by the local ethics committee and informed consent was obtained from all patients.

3 Results

We enrolled 152 (89 male individuals out of 152 patients, 58%) patients in the study. Table 1 lists the baseline clinical characteristics, study-specific variables concerning the use of OPC, incidence of AEs, and causes of withdrawal. The diagnosis of PD was confirmed for all patients who completed the follow-up period. Eighty-nine out of 152 (58%)

Table 1 Patient characteristics and study variables

Demographic characteristics	
Study population, *N*	152
Men, *N* (%); female, *N* (%)	89 (58%); 63 (42%)
Age, years (mean ± SD)	69.1 ± 9.3
Clinical characteristics	
Disease duration, years (mean ± SD)	9.7 ± 4.9
Hoehn and Yahr stage, *N* (± SD)	2.4 ± 0.7
MF duration, months (± SD)	23.1 ± 20.9
UPDRS III	
PD phenotype TD; AR; ET (%)	54 (35%); 67 (44%); 31 (21%)
Axial symptoms, *N* (%)	40 (26%)
Past history of hallucinations, *N* (%)	32 (21%)
MCI, *N* (%)	27 (18%)
Autonomic dysfunction, *N* (%)	25 (16%)
Past history of addictive behavior, *N* (%)	16 (10%)
History of falls (≥1 since PD onset), *N* (%)	15 (9%)
PD therapy at baseline	
Assuming LD, *N* (%)	148 (97%)
LD daily dose, mg (mean ± SD)	628.9 ± 225.8
LD therapy duration, years (mean ± SD)	8.1 ± 4.9
Assuming DA, *N* (%)	88 (58%)
Assuming iMAOB, *N* (%)	71 (47%)
Assuming amantadine, *N* (%)	9 (6%)
Assuming iCOMT, *N* (%)[a]	2 (1%)
Assuming LD only, *N* (%)	38 (25%)
Assuming LD + DA, *N* (%)	33 (22%)
Assuming LD + iMAOB, *N* (%)	22 (14%)
Assuming LD + iCOMT	2 (1%)
Assuming LD + DA + iMAOB, *N* (%)	48 (32%)
Advanced therapy (DBS/CSAI), *N* (%)	9 (6%)
LD therapy modifications	
LD daily dose amount reduction, yes/no	74 (49%)/78 (51%)
LD daily dose amount reduction, mg (mean ± SD)	195.0 ± 62.7
% of LD reduction (mean ± SD)	36.3 ± 19.6
Safety/tolerability	
AEs, *N* (%)	89 (58%)
Dyskinesias	23 (15%)
Gastrointestinal symptoms (nausea/vomiting)	18 (12%)
Hallucinations	11 (7%)
Orthostatic hypotension	8 (5%)
Tiredness/fatigue worsening	6 (4%)
Insomnia	5 (3%)
Confusional state	5 (3%)
Dizziness	4 (2.5%)
Dopamine-induced behavioral disorder	4 (2.5%)
Headache	3 (2%)
PD aggravated	2 (1%)
OPC discontinuation, *N* (%)	46 (30%)
Therapy withdrawals	
Due to AE, *N* (%)	41/46 (89%)
Dopaminergic-related AE, *N* (%)	35/46 (76%)
Disabling dyskinesia	17

Table 1 (continued)

Gastrointestinal symptoms	11
Disabling hallucinations	9
Orthostatic hypotension	7
DDS	4
Non-dopaminergic related AE, *N* (%)	6/46 (13%)
Switch to advanced therapy (DBS, CSAI), *N* (%)	3/46 DBS; 1/46 CSAI (9%)
Other causes (unrelated to PD), *N* (%)	1/46 (2%)
Time under OPC treatment, months (mean ± SD)	24.6 ± 17.1

AE adverse events, *AR* Akineto-Rigid phenotype, *CSAI* continuous subcutaneous apomorphine infusion, *DA* dopamine agonist, *DBS* deep brain stimulation, *DDS* dopamine dysregulation syndrome, *ET* equivalent type phenotype, *iCOMT* catechol-*O*-methyl-transferase inhibitor, *iMAOB* monoamine-oxidase B inhibitor, *LD* levodopa, *MCI* mild cognitive impairment, *MF* motor fluctuations, *OPC* opicapone, *PD* Parkinson's disease, *SD* standard deviation, *TD* tremor dominant phenotype, *UPDRS III* Unified Parkinson's Disease Rating Scale III

[a]All patients were receiving entacapone prior to the switch to OPC

patients reported at least one AE during the 2-year follow-up, and 24 out of 152 (16%) reported two or more AEs. Dyskinesia was the most frequent AE reported (23 out of 152 patients, 15%). Sixty-four out of 152 (42%) patients reported dopamine-related AEs. Patients affected by dopamine-related AEs had a significantly longer disease duration compared with those who did not manifest side effects (11.1 ± 5.8 vs 9.0 ± 4.3 years, $p = 0.030$); furthermore, the prevalence of patients who reduced the LD daily amount at the moment of OPC introduction was lower compared with patients who did not manifest side effects (18 out of 64, 28% vs 56 out of 88, 63%; $p = 0.031$).

Forty-six out of 152 (30%) patients discontinued OPC, 41 out of 152 (27%) because of AEs, four because they switched to advanced therapy that required oral medication remodulation (three patients underwent deep brain stimulation surgery and one patient received a continuous subcutaneous apomorphine infusion), and one patient presented with severe dysphagia unrelated to PD. The leading cause of OPC discontinuation was dopamine-related AEs (35 out of 46 patients, 76%).

Comparing "earlier" versus "later" subgroups, the incidence of AEs was generally equal or lower in the former group (see Table 2). The only exceptions were subgroups of patients assuming LD plus DA and iMAOB, or receiving advanced therapy, which showed a lower incidence of AEs. "Withdrawers" were significantly older, with longer disease and MF durations, and a higher Hoehn and Yahr scale score compared with "continuers". Furthermore, "withdrawers" were more frequently affected at baseline by hallucinations, addictive behavior, mild cognitive impairment, and falls compared with "continuers" (see Table 3). Logistic regression models identified a MF duration ≥12 months and a Hoehn and Yahr scale score ≥2.5 as independent factors significantly associated with OPC withdrawal; a falls history showed only a trend of significance ($p < 0.055$) predicting withdrawal because of dopamine-related AEs (see Table 4A, B).

4 Discussion

We present results of the first Italian prospective real-world study on the tolerability/safety of OPC in PD. Opicapone showed an overall good level of tolerance/safety in the Italian PD population in daily clinical practice.

The incidence of AEs during the 2-year follow-up was in line with that reported by Xie and colleagues in a systematic review including all RCTs (58% vs 62.9%) [20] and lower compared with that reported by Portuguese and Spanish real-life studies (58% vs respectively 73% and 81%) [15, 16]. Dopamine-related AEs, particularly dyskinesia, represented the most frequent AEs, and the leading cause of OPC withdrawal, in line with clinical trials and previous real-life studies [15, 16, 20]. A lower incidence of AEs (related in 37% of cases to dyskinesia; see Table 1) in our cohort of patients could be related to the shorter duration of MFs (23.1 ± 20.9 months) compared with previous real-life studies (mean 33.6 ± 22.8 months) [15, 16].

We also found a rate of withdrawal because of AEs equal to 27%, which is higher compared with that reported by Xie et al. (8.4–9.3%), and similar to those of previous real-life studies (21% and 23%) [15, 16, 20]. Otherwise, the incidence of hallucinations (7%) was significantly higher compared with trials and the Portuguese real-life study (respectively 2.5–3.1% and 0.05%), but lower compared with Spanish reports (34.6%) [15, 16, 20].

We can suppose that these differences could be related to the higher patient age of our sample (69.1 ± 9.3 years) compared with BIPARK-I and BIPARK-II (63.6 ± 9.3 years) and the greater number of patients with cognitive decline (55% of those presenting with hallucinations had mild cognitive

Table 2 Comparisons of the AE incidence between "earlier" and "later" subgroups

Subgroup	*N*	Any AE, %	Any dopaminergic related AE, %	Any AE leading to treatment withdrawn, %
Disease related				
Disease duration (years)				
<6	40	**27.5**	**17.5**	**17.5**
≥6	112	40.2	25.0	30.4
<7	40	**27.5**	**17.5**	**17.5**
≥7	112	40.2	25.0%	30.4%
<8	56	**26.8**	**19.6%**	**21.7%**
≥8	96	42.7	25.0	31.3
<9	69	**27.5**	**20.3**	**21.7**
≥9	83	44.6	25.3	31.3
Hoehn and Yahr stage				
<2.5	95	**26.3**	**12.6**	**15.7**
≥2.5	57	54.4	40.4	45.6
MF duration (years)				
<1	69	**26.1**	**15.9**	**18.8**
≥1	83	45.8	28.9	35.0
<2	81	**27.2**	**18.5**	**23.2**
≥2	71	47.9	28.2	38.0
Therapy related				
Baseline LD daily dose amount				
<500	37	**35.1**	**21.6**	26.0
≥500	115	37.4	23.5	26.0
<600	73	**34.2**	**21.9**	**26.9**
≥600	79	39.2	24.0	27.0
<700	99	**36.4**	**22.6**	**24.5**
≥700	53	37.7	23.3	28.3
<800	118	**35.6**	**22.0**	**26.3**
≥800	34	41.2	26.5	29.4
LD therapy duration				
<4	21	**28.6**	**19.0**	**19.0**
≥4	131	38.2	23.7	28.2
<5	29	**27.6**	**20.7**	**20.7**
≥5	123	39.0	23.6	28.5
<6	54	**31.5**	**22.4**	**24.1**
≥6	98	39.8	24.4	28.6
<7	73	**26.0**	**19.2**	**19.2**
≥7	79	46.8	26.6	34.2
<8	84	**29.8**	**21.4**	**22.6**
≥8	68	45.6	25.0	32.4
LD only				
Yes	38	36.8%	26.3%	27.2%
No	114	36.8%	**21.9%**	**26.3%**
LD plus DA				
Yes	33	39.4	27.3	33.3
No	119	**36.1**	**21.8**	**25.2**
LD plus iMAOB				
Yes	22	50.0	36.4	40.9
No	130	**34.6**	**20.8**	**24.6**
LD plus DA plus iMAOB				
Yes	48	**27.0**	**10.4**	**16.7**
No	104	41.3	28.8	31.7
Advanced therapy				
Yes	9	**33.3**	**22.2**	**22.2**
No	143	37.0	23.1	27.3

AE adverse event, *DA* dopamine agonist, *iCOMT* catechol-*O*-methyl-transferase inhibitor, *iMAO* monoamine-oxidase inhibitor, *LD* levodopa (including LD/benserazide, LD/carbidopa (immediate or controlled release), *MF* motor fluctuation

Bold values indicate a lower incidence of AEs than that of the matched comparative row

impairment at baseline) and a previous history of hallucinations. Further, all patients presenting with hallucinations as AEs had already experienced hallucinations previously at baseline [4, 5].

The same considerations could also explain the higher incidence of behavioral symptoms (2.5%) belonging to dopamine-dysregulation-syndrome (DDS) in our cohort of patients when compared with trials and previous real-life studies (which have not mentioned any case of DDS induced by OPC). Disease duration, which is a known risk factor for DDS, is longer in our sample (9.7 ± 4.9 years) compared with those of RCTs and previous real-life studies (respectively 7.6 ± 4.3 and 7.9 ± 3.6 years), moreover, the 75% of our patients presenting with behavioral symptoms as AEs experienced addictive behavior in their past at baseline [15, 16, 20, 21].

The Rocha et al. post-hoc analysis of BIPARK-I and BIPARK-II clinical trials demonstrated an increased drug tolerability/safety in patients introducing OPC "earlier" versus "later", according to their disease course and LD treatment pathway [19]. Our study confirms the results of Rocha and colleagues that was also in a real-life context, although differences could be identified. Particularly, we found that the "later" subgroup of patients not assuming LD alone at baseline presented with a lower incidence of AEs compared with "earlier" patients assuming LD alone, as well as "later" subgroups of patients receiving LD plus DA and iMAOB, or receiving advanced therapy (deep brain stimulation), compared to their corresponding "earlier" patients.

To date, only Pons and colleagues identified the Schwab and England Activity of Daily Living scale scores and the Hoehn and Yahr scale scores as clinical variables associated with OPC therapy withdrawal, based on the data gathered

Table 3 Comparisons between patients who continued ("continuers") and withdrew ("withdrawers") opicapone treatment because of any dopaminergic-related AE

	"Continuers"	"Withdrawers"	
		Any AE[a]	Dopaminergic related AE[a]
Demographic characteristics			
Study population, *N*	106	41	35
Male, *N* (%); female, *N* (%)	59 (56%); 47 (44%)	27 (66%); 14 (34%)	23 (66%); 12 (34%)
Age, years (mean ± SD)	68.3 ± 9.3	71.8 ± 9.0*	71.4 ± 9.2*
Clinical characteristics			
Disease duration, years (mean ± SD)	9.2 ± 4.3	11.3 ± 5.8*	10.9 ± 6.2*
MF duration, months (mean ± SD)	18.4 ± 14.8	35.5 ± 28.7***	33.3 ± 28.3**
MF duration ≥12 months, *N* (%)	52 (49%)	29 (71%)*	24 (69%)*
Hoehn and Yahr stage, *N* (mean ± SD)	2.3 ± 0.6	2.8 ± 0.7***	2.8 ± 0.7***
Hoehn and Yahr stage score ≥2.5, *N* (%)	30 (28%)	29 (71%)***	23 (66%)***
PD phenotype, TD; AR; ET (%)	40; 43; 23 (38; 40; 22%)	10; 23; 8 (24; 56; 20%)	10;20;5 (29; 57; 14%)
Axial symptoms, *N* (%)	25 (24%)	15 (37%)	13 (37%)
Past history of hallucinations, *N* (%)	18 (17%)	13 (32%)*	11 (31%)*
MCI, *N* (%)	14 (13%)	12 (29%)*	12 (34%)**
Autonomic dysfunction, *N* (%)	18 (17%)	7 (17%)	6 (17%)
Past history of addictive behavior, *N* (%)	7 (7%)	9 (22%)**	7 (20%)**
History of falls (≥1 since PD onset), *N* (%)	5 (5%)	9 (24%)***	9 (26%)***
PD therapy at baseline			
Assuming LD, *N* (%)	104 (99%)	43 (97%)	35 (97%)
LD daily dose, mg (mean ± SD)	634.1 ± 223.3	618.0 ± 231.9	634.7 ± 236.9
LD therapy duration, years (mean ± SD)	7.8 ± 4.5	9.6 ± 5.7	9.1 ± 5.9
Assuming DA, *N* (%)	64 (60%)	21 (51%)	16 (46%)
Assuming iMAOB, *N* (%)	52 (49%)	18 (41%)	14 (37%)
Assuming amantadine, *N* (%)	5 (5%)	3 (7%)	1 (3%)
Assuming iCOMT, *N* (%)	1 (1%)	1 (1%)	1 (3%)
Assuming LD only, *N* (%)	27 (25%)	10 (24%)	10 (29%)
Assuming LD + DA, *N* (%)	22 (21%)	11 (27%)	9 (26%)
Assuming LD + iMAOB, *N* (%)	13 (12%)	9 (22%)	8 (23%)
Assuming LD + DA + iMAOB, *N* (%)	37 (35%)	8 (19%)	5 (12%)
DBS, *N* (%)	6 (6%)	2 (5%)	2 (6%)
LD therapy modifications			
LD daily dose amount reduction, yes/no	53 (50%)	17 (41%)	12 (34%)
LD daily dose amount reduction, mg (mean ± SD)	200.6 ± 59.3	163.5 ± 67.7	172.9 ± 71.9
% of LD reduction (mean ± SD)	30.4 ± 13.4	25.8 ± 7.8	27.0 ± 7.4

AE adverse event, *AR* Akineto-rigid phenotype, *DA* dopamine agonist, *DBS* deep brain stimulation, *ET* equivalent type phenotype, *ICD* impulsive control disorder, *iCOMT* catechol-O-methyl-transferase inhibitor, *iMAO* monoamine-oxidase inhibitor, *LD* levodopa, *MCI* mild cognitive impairment, *MF* motor fluctuations, *PD* Parkinson's disease, *SD* standard deviation, *TD* tremor dominant phenotype

p-Values of between-group comparisons are reported, if less than 0.05, as ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$

[a]Significance is reported relative to the "continuers" subgroup

by a Spanish single-center study enrolling 126 patients with PD [16].

In the present study, although a univariate analysis recognized several clinical variables significantly associated with OPC therapy withdrawal (age at baseline, disease, and MF duration, Hoehn and Yahr scale score, history of hallucinations, addictive behavior and falls, and mild cognitive impairment), the multivariate model identified the Hoehn and Yahr scale score ≥2.5 and an MF duration ≥12 months as the most relevant independent factors significantly associated with OPC withdrawal because of any dopamine-related AE (see Table 4A, B).

The strengths of the present study are represented by the prospective design, long duration of follow-up (2 years vs a

Table 4 (A) Logistic regression analysis (forward conditional method) with the dependent variable opicapone withdrawal because of any adverse event. (B) Logistic regression analysis (forward conditional method) with the dependent variable opicapone withdrawal because of a dopaminergic-related adverse event

(A)					
Variable	OR (SE)	95% CI	B (SE)	95% CI	*p*-Value
MF duration ≥12 months	1.04 (0.11)	1.016, 1.06	0.04 (0.01)	0.016, 0.06	0.000
Hoehn and Yahr scale score ≥2.5	2.63 (0.79)	1.455, 4.75	0.97 (0.30)	0.375, 1.56	0.001
Constant	0.01 (0.01)	0.002, 0.07	−4.30 (0.86)	−6.00, −2.61	0.000
(B)					
Variable	OR (SE)	95% CI	B (SE)	95% CI	*p*-Value
MF duration ≥12 months	1.02 (0.01)	1.005, 1.05	0.03 (0.01)	0.005, 0.05	0.015
Hoehn and Yahr scale score ≥2.5	2.54 (0.79)	1.376, 4.71	0.93 (0.31)	0.319, 1.54	0.003
History of falls (≥1 since Parkinson's disease onset)	3.16 (2.11)	0.854, 11.70	1.15 (0.67)	−0.157, 2.46	0.055
Constant	0.01 (0.01)	0.002, 0.08	−4.28 (0.89)	−6.038, −2.52	0.000

B beta, *CI* confidence interval, *MF* motor fluctuation, *OR* odds ratio, *SE* standard error

maximum of 1 year in previous studies), and large sample size. Furthermore, several characteristics of patients have been considered at baseline and entered into the statistical analysis, including axial symptoms and non-motor symptoms. We also believe that the clinical heterogeneity of the cohort of patients with PD enrolled, which included patients also with mild cognitive impairment and a previous history of DDS, represents a further strength of the study.

Limitations of the present study are represented by the interdependence of clinical variables such as disease duration, Hoehn and Yahr scale score, MF duration, and LD daily dosage amount, the higher prevalence of male patients than female patients in the cohort, and the small size of certain subgroups (i.e., patients receiving advanced therapy). Moreover, we can suppose that the long interval between follow-up visits (6 months less of particular patient needs) may have led to an underestimation of mild and transitory potential side effects, particularly when the patient did not report symptoms occurring for a long period before the interview.

5 Conclusions

The present real-life prospective study reinforces evidence about the increased tolerability/safety of OPC when introduced earlier accordingly to the disease course and LD treatment pathway, and the trend towards early combination in the management of PD therapy [22]. The Hoehn and Yahr scale score and MF duration have shown to be the most relevant variables in predicting OPC therapy withdrawal over 2 years. Although data need to be validated on larger samples and prospective studies, this evidence could represent useful elements to help clinicians in the tailoring of PD therapy.

Abbreviations PD: Parkinson's Disease; iCOMT: Catechol-O-Methyl-Transferase Inhibitors; MFs: Motor Fluctuations; LD: L-Dopa; AEs: Adverse Events; OPC: Opicapone; RCTs: Randomized Controlled Clinical Studies; UPDRSIII: Unified Parkinson Disease Rating Scale Part III; DA: Dopamine Agonist; iMAOB: Monoamine Oxidase B inhibitor; DBS: Deep Brain Stimulation; CSAI: Continuous Subcutaneously Apomorphine Infusion; ICD: Impulsive Control Disorder; MCI: Mild Cognitive Impairment; DDS: Dopamine-dysregulation-syndrome

Declarations

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Conflicts of Interest/Competing Interests Ruggero Bacchin, Marco Liccari, Mauro Catalan, Lucia Antonutti, Paolo Manganotti, Maria Chiara Malaguti, and Bruno Giometto have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval This study was approved by the local ethics committee (Azienda Provinciale per i Servizi Sanitari [APSS] and Azienda Sanitaria Universitaria Giuliano-Isontina [ASUGI]) and was conducted in accordance with the regulations of the Helsinki Declaration. We confirm that all authors have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Consent to participate All participants provided written informed consent before participation, as well as an opt-out consent.

Consent for Publication Not applicable.

Availability of Data and Material The data that support the findings of this study are available from the corresponding author (RB) upon reasonable request.

Code Availability Not applicable.

Authors' Contributions (1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript preparation: A. Writing of the first draft, B. Review and critique; RB: 1A, 1B, 2A, 2B, 2C, 3A, 3B; ML: 1C, 1B, 3A; MC: 1A, 2C, 3B; MCM: 2C, 3B; LA: 1C; BG: 2C, 3B; PM: 1A, 2C, 3B. All authors read and approved the final version.

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