



## Early DEtection of wEaring off in Parkinson disease: The DEEP study



F. Stocchi<sup>a,\*</sup>, A. Antonini<sup>b</sup>, P. Barone<sup>c</sup>, M. Tinazzi<sup>d</sup>, M. Zappia<sup>e</sup>, M. Onofrj<sup>f</sup>, S. Ruggieri<sup>g</sup>, L. Morgante<sup>h</sup>, U. Bonuccelli<sup>i</sup>, L. Lopiano<sup>j</sup>, P. Pramstaller<sup>k</sup>, A. Albanese<sup>l</sup>, M. Attar<sup>m</sup>, V. Posocco<sup>m</sup>, D. Colombo<sup>m</sup>, G. Abbruzzese<sup>n</sup>, on behalf of DEEP study group

<sup>a</sup> Department of Neurology, Institute of Research and Medical Care, IRCCS San Raffaele, Rome, Italy

<sup>b</sup> Department for Parkinson's disease, IRCCS San Camillo, Venice, Italy

<sup>c</sup> School of Medicine, University of Salerno, Salerno, Italy

<sup>d</sup> U.O. Neurologia Ospedale Civile Maggiore, Borgo Trento, Verona, Italy

<sup>e</sup> Clinica Neurologica I Policlinico Universitario, Catania, Italy

<sup>f</sup> CeSI-Centro Studi Invecchiamento Fondazione Università Gabriele D'Annunzio, Chieti, Italy

<sup>g</sup> Neurologia Istituto Mediterraneo Neuromed, Isernia, Italy

<sup>h</sup> Dipartimento di Neuroscienze Università di Messina, Messina, Italy

<sup>i</sup> U.O. Neurologia Ospedale Versilia, Lucca, Italy

<sup>j</sup> Neurologia 4 A.S.O. Molinette, Turin, Italy

<sup>k</sup> Neurologia Ospedale di Bolzano, Bolzano, Italy

<sup>l</sup> Neurologia I Istituto Nazionale Neurologico C. Besta, Università Cattolica del Sacro Cuore, Milan, Italy

<sup>m</sup> Novartis Pharma Italia, Medical Department, Origgio, Italy

<sup>n</sup> Department of Neurosciences, University of Genoa, Genoa, Italy

### ARTICLE INFO

#### Article history:

Received 12 March 2013

Received in revised form

23 October 2013

Accepted 25 October 2013

#### Keywords:

Parkinson's disease

Wearing-off

Wearing-off questionnaire

Quality of life

### ABSTRACT

**Objective:** Assessing the frequency of Wearing-Off (WO) in Parkinson's disease (PD) patients, and its impact on Quality of Life (QoL).

**Methods:** Consecutive ambulatory patients, who were on dopaminergic treatment for  $\geq 1$  year, were included in this multicentre, observational cross-sectional study. In a single visit, WO was diagnosed based on neurologist assessment as well as using the validated Italian version of a patient self-rated 19-question Wearing-Off Questionnaire (WOQ-19); WO was defined for scores  $\geq 2$ . QoL was evaluated by the 8-item Parkinson's Disease Questionnaire (PDQ-8).

**Results:** 617 subjects were included, with a mean anti-Parkinson treatment duration of  $6.6 \pm 4.6$  years, 87.2% were on levodopa treatment. Neurologists identified presence of WO in 351 subjects (56.9%), whereas 415 subjects (67.3%) were identified by the self-administered WOQ-19. In patients with a  $< 2.5$  years disease duration, WO was diagnosed in 12 subjects (21.8%) by neurologists and in 23 subjects (41.8%) by the WOQ-19. The most frequent WO symptoms, as identified by WOQ-19, were "slowness of movements" (55.8%) and "reduced dexterity" (48.8%). Younger age, female gender, Unified Parkinson's Disease Rating Scale (UPDRS) part II score and duration of anti-Parkinson treatment were found significantly associated with WO. The number of motor ( $p < 0.0001$ ) and non-motor ( $p < 0.0001$ ) WO symptoms correlated with PDQ-8 total score. **Conclusions:** WO is common already at the early stages of PD and is underestimated by routine neurological clinical evaluation. The number of WO symptoms, both motor and non motor, increases along with disease duration and has a negative impact on patients QoL.

© 2013 Elsevier Ltd. All rights reserved.

\* Corresponding author. IRCCS San Raffaele Pisana di Roma, Dipartimento di Neurologia, Via della Pisana 216, 00163 Rome, Italy. Tel.: +39 (0) 06 522 524 56; fax: +39 (0) 06 660 584 86.

E-mail addresses: [fabrizio.stocchi@tin.it](mailto:fabrizio.stocchi@tin.it), [deep@medidata.it](mailto:deep@medidata.it) (F. Stocchi), [angelo3000@yahoo.com](mailto:angelo3000@yahoo.com) (A. Antonini), [pbarone@unisa.it](mailto:pbarone@unisa.it) (P. Barone), [michele.tinazzi@ospedaleuniverona.it](mailto:michele.tinazzi@ospedaleuniverona.it) (M. Tinazzi), [m.zappia@unict.it](mailto:m.zappia@unict.it) (M. Zappia), [onofrj@unich.it](mailto:onofrj@unich.it) (M. Onofrj), [stefano.ruggieri@uniroma1.it](mailto:stefano.ruggieri@uniroma1.it) (S. Ruggieri), [morgante@unime.it](mailto:morgante@unime.it) (L. Morgante), [u.bonuccelli@med.unipi.it](mailto:u.bonuccelli@med.unipi.it) (U. Bonuccelli), [leonardo.lopiano@unito.it](mailto:leonardo.lopiano@unito.it) (L. Lopiano), [peter.pramstaller@eurac.edu](mailto:peter.pramstaller@eurac.edu) (P. Pramstaller), [alberto.albanese@unicatt.it](mailto:alberto.albanese@unicatt.it), [albanese@istituto-besta.it](mailto:albanese@istituto-besta.it) (A. Albanese), [mahmood.attar@novartis.com](mailto:mahmood.attar@novartis.com) (M. Attar), [valeria.posocco@novartis.com](mailto:valeria.posocco@novartis.com) (V. Posocco), [delia.colombo@novartis.com](mailto:delia.colombo@novartis.com) (D. Colombo), [giabbr@unige.it](mailto:giabbr@unige.it) (G. Abbruzzese).

### 1. Introduction

For over 40 years, levodopa has been the gold-standard of treatment of PD, and patients unavoidably will require it during the course of the disease. When patients are initially started on levodopa therapy they experience a sustained clinical response throughout the day. As the disease progresses, the therapeutic effect shortens and many patients experience benefit only for a few hours after ingestion of the drug; this step is otherwise known as

the WO. Despite several studies have been conducted in patients with fluctuations, it is difficult to infer from the available data a clear consensus on the prevalence, timing and characteristics of the WO phenomenon. For many years, doctors considered the WO as a late and even rare phenomenon. On the other hand, it is now widely recognized that the development of WO has a significant impact on patient's neurological disability and QoL [1–4].

The use of several patient self-assessed questionnaires proved to be an effective tool in the diagnosis of WO, showing higher sensitivity than the routine clinical evaluation [3,5,6]. Among them the WOQ-19 has recently been recognized by a task force of the Movement Disorders Society as "recommended diagnostic screening tool in PD" [7].

The current study was based on an observational, cross-sectional, multicentre study called *Early DETection of wEaring off in Parkinson disease* (DEEP Study). The primary goal was to look at the frequency of WO phenomena among a wide population of patients with PD, and secondarily to assess the impact of WO on patient's QoL.

## 2. Methods

### 2.1. Study design

The DEEP study included a preliminary phase, recently published [8], that had as objective the linguistic and the psychometric

validation as well as the diagnostic capacity assessment of the Italian version of the WOQ-19. In this manuscript we present the results of the core phase of the study, an epidemiological survey on WO symptoms and their associated phenomena, in a population of patients with PD.

From March to October 2010, we have prospectively recruited patients with PD to participate in the DEEP study, conducted at 37 movement disorder clinics in Italy. A total of 634 patients were evaluated, 207 have also participated to the WOQ-19 diagnostic capacity study [8]. The inclusion criteria were as follows: 1) age  $\geq 18$  years; 2) a diagnosis of PD [9]; 3) levodopa and/or dopamine agonists (DAs) therapy for  $\geq 1$  year before the study screening; 4) ability to understand and fill out the WOQ-19. The exclusion criteria included the following: 1) a Mini-Mental State Examination (MMSE) score  $\leq 23$  and/or a diagnosis of dementia according to DSM-IV; 2) any severe disabling conditions adversely affecting the patient's mental status; 3) Deep Brain Stimulation treatment; 4) any infusional therapy in the year before the study screening; 5) current inclusion in other clinical trials.

Neurologists experienced in movement disorders collected, following a specific training and during a single visit, standard demographic and clinical information on all participants who met the criteria, via a structured interview and by examination. This included but was not limited to age, sex, educational level,

**Table 1**  
Demographic and clinical data of patients with and without WO, according to the WOQ-19: the DEEP Study.

	Patients total (n = 617)	Patients WOQ-19 $\geq 2$ (n = 415)	Patients WOQ < 2 (n = 202)	p value
M:F (n)	381:236	244:171	137:65	0.0304
Age, mean $\pm$ SD (range)	66.8 $\pm$ 9.2 (29.1–88.5)	65.9 $\pm$ 9.1 (29.1–87.3)	68.6 $\pm$ 9.3 (31.4–88.5)	0.0005*
Disease duration, mean $\pm$ SD (range)	8.0 $\pm$ 4.7 (0.9–25.1)	8.97 $\pm$ 4.9 (0.9–25.1)	6.21 $\pm$ 3.9 (1.0–20.4)	<0.001*
Disease duration, n (%)				<0.001*
<2.5 y	55 (8.9%)	23 (41.8%)	32 (58.2%)	
2.5–5 y	130 (21.1%)	71 (54.6%)	59 (45.4%)	
5–10 y	238 (38.6%)	165 (69.3%)	73 (30.7%)	
>10 y	194 (31.4%)	156 (80.4%)	38 (19.6%)	
H&Y staging, n (%)				<0.0001*
Stage 1	60 (9.6%)	25 (41.7%)	35 (58.3%)	
Stage 1.5	88 (14.3%)	48 (54.5%)	40 (45.4%)	
Stage 2	220 (35.7%)	137 (62.3%)	83 (37.7%)	
Stage 2.5	139 (22.5%)	110 (79.1%)	29 (20.8%)	
Stage 3	88 (14.3%)	74 (84.1%)	14 (15.9%)	
Stage 4	20 (3.2%)	19 (95.0%)	1 (5.0%)	
Stage 5	2 (0.3%)	2 (100%)	0 (0%)	
UPDRS total score, mean $\pm$ SD (range)	37.4 $\pm$ 17.5 (5.0–111.0)	39.6 $\pm$ 18.1 (5.0–111.0)	32.8 $\pm$ 15.4 (10.0–81.0)	<0.0001*
Part I	2.2 $\pm$ 1.9 (0–11)	2.3 $\pm$ 2.1(0–11)	1.9 $\pm$ 1.6 (0–6)	0.0087
Part II	11.2 $\pm$ 6.2 (0–35)	12.3 $\pm$ 6.3 (0–35)	9.1 $\pm$ 5.2 (0–25)	<0.0001*
Part III	24.0 $\pm$ 11.7 (3–73)	25.1 $\pm$ 12.3 (3–73)	21.6 $\pm$ 10.1 (6–60)	0.0007*
Anti-Parkinson therapy duration (years), mean $\pm$ SD (range)	6.6 $\pm$ 4.6 (0–25)	7.4 $\pm$ 4.8 (1–25)	4.8 $\pm$ 3.7 (0–20)	<0.0001*
Levodopa therapy duration, (years), mean $\pm$ SD (range; n)	3.62 $\pm$ 3.32 (0.22–23.39, n = 525)	3.70 $\pm$ 3.58 (0.22–23.39; n = 377)	3.42 $\pm$ 2.55 (0.47–13.42; n = 148)	0.3104
Levodopa daily dosage, (mg), mean $\pm$ SD (range; n)	420.4 $\pm$ 209.3 (50–1500; n = 534)	439.4 $\pm$ 217.0 (50–1500; n = 386)	370.6 $\pm$ 179.3 (100–1200; n = 148)	0.0002*
Education (years), n				0.3199
None	17	8	9	
3–5	205	143	62	
6–8	176	119	57	
9–13	148	95	53	
>13	71	50	21	
Employment status, n (%)				0.0105
employed	92 (14.9%)	65 (15.7%)	27 (13.4%)	
unemployed	107 (17.3%)	84 (20.2%)	23 (11.4%)	
retired	418 (67.7%)	266 (64.1%)	202 (75.2%)	
Caregiver assistance, n (%)	112 (18.2%)	92 (22.2%)	20 (9.9%)	0.0002*
Smoking habits, n (%)	233 (38.5%)	154 (37.8%)	79 (39.9%)	0.6250
Alcohol consumption, n (%)	324 (54.5%)	209 (52.6%)	115 (58.4%)	0.1866
Physical activity, n (%)	195 (31.6%)	126 (30.4%)	69 (34.1%)	0.6658
MMSE	28.1 $\pm$ 1.7 (24–30)	28.1 $\pm$ 1.6 (24–30)	28.1 $\pm$ 1.7 (24–30)	0.9507

Abbreviations: H&Y = Hoehn & Yahr scale; UPDRS = Unified Parkinson's Disease Rating Scale; MMSE = Mini Mental State Examination.

\*Shows statistically significant p-values after Bonferroni's correction (critical p-value = 0.0026).

employment status, need for care, life style habits. Specifically disease related data were collected on age at disease onset, disease duration, UPDRS scores, Hoehn & Yahr scale (H&Y), current and previous therapy information, concomitant diseases. Cognitive abilities and QoL were respectively investigated with the MMSE and the 8-item Parkinson's Disease Questionnaire (PDQ-8) [10].

## 2.2. Diagnosis of WO

The diagnosis of WO was made both on the neurologist evaluation as well as on the basis of the patient self-assessment using the Italian version of the WOQ-19. Neurologists used a trace of structured interview to patients, which investigated the periodic reappearance of symptoms during the day, the temporal relationship with the intake of at least one scheduled dose of medication in a consistent and predictable modality, and the improvement after intake of the drug. The interview was completed at discretion of the neurologists and the final diagnosis based on the overall impression. The WOQ-19 was filled in by participants in conjunction with the visit, but neurologists were instructed to not interfere with the compilation and were not aware of the questionnaire responses. The questionnaire consists of 9 items assessing fluctuations of motor symptoms, including tremor, difficulty in speech, weakness, problems with balance, slowness, reduced dexterity, general stiffness, muscle cramps, difficulty getting out of the chair; and 10 items assessing fluctuations of non-motor symptoms, including anxiety, sweating, mood changes, numbness, panic attacks, cloudy mind/dullness of thinking, abdominal discomfort, experience hot and cold, pain, aching [8]. For each item, patients were asked to tick whether symptoms were present and whether they improved after the following dose of anti-Parkinson treatment: a cutoff of  $\geq 2$  improved symptoms indicated diagnosis of WO [8].

## 2.3. Standard protocol approvals, registrations and patient consents

The study was approved by the Ethical Committees of each participating institution and written informed consent and processing personal data authorization were obtained from each participant.

## 2.4. Statistical analysis

Descriptive analyses were mean and standard deviation (SD), or median and interquartile range (IQR). Comparisons were performed either by analysis of variance and Chi-square or Fisher exact test. The significance threshold was set to 0.05 with Bonferroni's correction in case of multiple comparisons.

In order to identify the variables associated with WO, logistic regression analysis was performed, considering WOQ score  $\geq 2$  as outcome of the dependent variable and as regressors: disease duration, gender, age, education, UPDRS part I, II, III scores, treatment duration, smoking habit, need for care (treatment duration and dose were not considered for the model because available for a lower portion of patients). The effect exerted by these variables on QoL was also tested using linear models with PDQ8 as the continuous dependent variable. Project management including data banking, quality control and statistical analysis, was performed by MEDIDATA (Modena, Italy).

## 3. Results

Of the 634 patients screened, 617 (97.3%) met the inclusion criteria (Table 1); the excluded patients did not differ significantly on demographic and clinical parameters with respect to the study population. Fifty hundred thirty eight (87.2%) patients were taking

levodopa, 64 (10.4%) as monotherapy, 465 (75.3%) were on DAs. Additional medications were as follows: catechol O-methyltransferase (COMT) inhibitors in 211 (34.2%) subjects, MAO-B inhibitors in 241 (39.1%), anticholinergics in 22 (3.6%). Patients receiving psychotropic drugs were 185 (30.0%). The most frequent concomitant non-neurological disorders were: hypertension in 184 patients (29.8%), heart diseases in 75 (12.2%), diabetes in 54 (8.8%).

## 3.1. Diagnosis of WO

Neurologists identified 351 subjects (56.9%) with WO symptoms while 415 subjects (67.3%) were identified by the WOQ-19. The WOQ-19 was more sensitive particularly in subjects with  $< 2.5$  years disease duration, with 23 (41.8%) patients indicating  $\geq 2$  WO symptoms compared with 12 (21.8%) patients identified by neurologists, similarly for subjects with 2.5–5 years (54.6% vs. 36.2%), 5–10 years (69.3% vs. 60.1%), and  $> 10$  years disease duration (76.8% vs. 80.4%; Fig. 1). For 489 (79.3%) patients there was agreement between neurologists and WOQ-19 for the absence in 170 (27.6%) or presence in 319 (51.7%) of WO. For 128 (20.8%) patients there was disagreement; 32 (5.2%) those in whom WO diagnosis by neurologists was not confirmed by WOQ-19, and 96 (15.6%) endorsed WO symptoms through WOQ-19, which their neurologists did not diagnose. When considering levodopa therapy duration, among patients under treatment for  $\leq 1$  year, 61 (77.2%) were diagnosed as having WO by WOQ-19 vs. 47 (59.5%) by neurologists, in subjects treated for 1–2 years, 96 (75.6%) vs. 80 (63.0%), for 2–3 years 71 (66.4%) vs. 62 (57.9%), for 3–5 years 65 (66.3%) vs. 54 (55.1%), 84 (73.7%) vs. 85 (74.6%) subjects under levodopa treatment for  $> 5$  years.

Given the well-established reliability and higher sensitivity of WOQ-19 in respect to the clinical evaluation, and considering also the low degree of disagreement among subjects diagnosed by neurologists and not through WOQ-19, from now on we will only focus on the results based on WOQ-19 data. Overall, the mean number of reported symptoms experienced in a normal day was  $8.7 \pm 3.8$ , of which  $5.6 \pm 2.1$  were motor and  $3.1 \pm 2.3$  were non-motor. Taking into account the symptoms reported as usually improving after the following dose of anti-Parkinson medications (otherwise defined as WO symptoms) they were equal to a total of  $4.1 \pm 3.8$ ,  $3.1 \pm 2.6$  were motor and  $1.0 \pm 1.6$  were non motor. The frequency of symptoms reported by patients through the WOQ-19 is listed in Table 2.

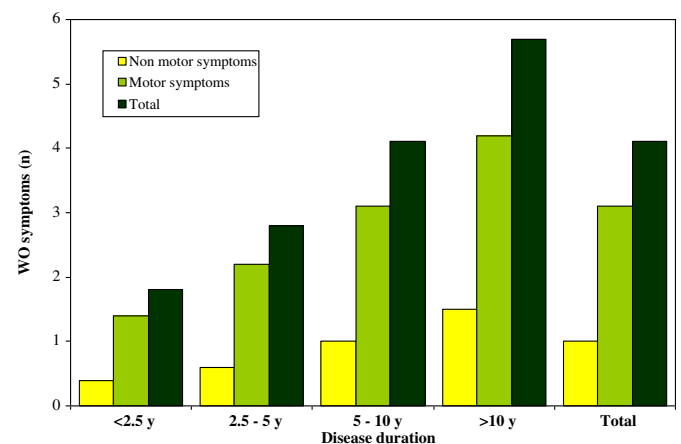


Fig. 1. Mean number of WO symptoms reported through the WOQ-19 by patients with PD, stratified by disease duration: the DEEP study.

### 3.2. Subjects with WO

Subjects with WO were significantly younger ( $65.9 \pm 9.1$  vs.  $68.6 \pm 9.3$  y;  $p = 0.0005$ ). Patients with WO had significantly longer disease duration ( $8.97 \pm 4.9$  vs.  $6.21 \pm 3.9$  y;  $p < 0.001$ ), longer anti-Parkinson treatment ( $7.4 \pm 4.8$  vs.  $4.8 \pm 3.7$  y;  $p < 0.0001$ ), greater disability, as measured by the UPDRS total score ( $39.6 \pm 18.1$  vs.  $32.8 \pm 15.4$ ;  $p < 0.0001$ ), and greater disease severity, as measured by the H&Y scale ( $p < 0.0001$ , Table 2), compared to subjects without WO. Three hundred and ninety (94.0%) subjects diagnosed with WO were being treated with levodopa, of whom 246 (84.8%) in polytherapy, 6 (1.4%) were treated with DAs in monotherapy and

19 (4.6%) with DAs in association with MAO-B inhibitors. The duration of treatment with levodopa did not differ between patients with and without WO ( $3.70 \pm 3.58$  vs.  $3.42 \pm 2.55$ ;  $p = 0.3104$ ), whilst the mean daily levodopa dosage was higher in patients with WO ( $439.4 \pm 217.0$  vs.  $370.6 \pm 179.3$ ;  $p = 0.0002$ ).

Regression logistic analysis found age, gender, UPDRS part II score and duration of anti-Parkinson treatment significantly associated with WO. In details, every increase of one year of age was associated with a 5.0% risk reduction of WO diagnosis (95% CI 0.928–0.973,  $p < 0.0001$ ), while women showed a 80.1% higher risk of experiencing WO than men (95% CI 1.134–2.861,  $p = 0.0126$ ). Moreover, it has been calculated an increased risk of WO,

**Table 2**

Frequency of experienced symptoms and WO symptoms, as reported by subjects, through the WOQ-19, stratified by disease duration: the DEEP study.

Disease duration	<2.5 years (n = 55)	2.5–5.0 years (n = 130)	5.0–10 years (n = 238)	>10 years (n = 194)	Total (n = 617)
Experienced and WO symptoms, n (%)					
Tremor					
Experienced	36 (65.5%)	93 (71.5%)	166 (69.7%)	131 (67.5%)	426 (69.0%)
WO	18 (32.7%)	51 (39.2%)	119 (50.0%)	104 (53.6%)	292 (47.3%)
Difficulty in speech					
Experienced	18 (32.7%)	47 (36.2%)	99 (41.6%)	115 (59.3%)	279 (45.2%)
WO	7 (12.7%)	22 (16.9%)	38 (16.0%)	66 (34.0%)	133 (21.6%)
Weakness					
Experienced	29 (52.7%)	91 (70.0%)	158 (66.4%)	155 (79.9%)	433 (70.2%)
WO	7 (12.7%)	34 (26.2%)	83 (34.9%)	87 (44.8%)	211 (34.2%)
Problems with balance					
Experienced	22 (40.0%)	51 (39.2%)	119 (50.0%)	127 (65.5%)	319 (51.7%)
WO	4 (7.3%)	21 (16.2%)	52 (21.8%)	60 (30.9%)	137 (22.2%)
Slowness of movements					
Experienced	43 (78.2%)	97 (74.6%)	210 (88.2%)	174 (89.7%)	524 (84.9%)
WO	16 (29.1%)	53 (40.8%)	141 (59.2%)	134 (69.1%)	344 (55.8%)
Reduced dexterity					
Experienced	38 (69.1%)	83 (63.8%)	192 (80.7%)	170 (87.6%)	483 (78.3%)
WO	13 (23.6%)	42 (32.3%)	124 (52.1%)	122 (62.9%)	301 (48.8%)
General stiffness					
Experienced	15 (27.3%)	56 (43.1%)	133 (55.9%)	133 (68.6%)	337 (54.6%)
WO	4 (7.3%)	35 (26.9%)	94 (39.5%)	108 (55.7%)	241 (39.1%)
Muscle cramps					
Experienced	27 (49.1%)	66 (50.8%)	127 (53.4%)	111 (57.2%)	331 (53.6%)
WO	4 (7.3%)	18 (13.8%)	39 (16.4%)	46 (23.7%)	107 (17.3%)
Difficulty getting out of chair					
Experienced	18 (32.7%)	42 (32.3%)	112 (47.1%)	123 (63.4%)	295 (47.8%)
WO	2 (3.6%)	15 (11.5%)	59 (24.8%)	82 (42.3%)	158 (25.6%)
Anxiety					
Experienced	26 (47.3%)	65 (50.0%)	122 (51.3%)	113 (58.2%)	326 (52.8%)
WO	8 (14.5%)	15 (11.5%)	46 (19.3%)	45 (23.2%)	114 (18.5%)
Sweating					
Experienced	11 (20.0%)	35 (26.9%)	83 (34.9%)	104 (53.6%)	233 (37.8%)
WO	0 (0.0%)	7 (5.4%)	15 (6.3%)	32 (16.5%)	54 (8.8%)
Mood changes					
Experienced	22 (40.0%)	53 (40.8%)	108 (45.4%)	98 (50.5%)	281 (45.5%)
WO	7 (12.7%)	13 (10.0%)	46 (19.3%)	45 (23.2%)	111 (18.0%)
Numbness					
Experienced	9 (16.4%)	21 (16.2%)	52 (21.8%)	53 (27.3%)	135 (21.9%)
WO	1 (1.8%)	3 (2.3%)	15 (6.3%)	18 (9.3%)	37 (6.0%)
Panic attacks					
Experienced	3 (5.5%)	9 (6.9%)	28 (11.8%)	33 (17.0%)	73 (11.8%)
WO	1 (1.8%)	1 (0.8%)	7 (2.9%)	13 (6.7%)	22 (3.6%)
Cloudy mind					
Experienced	8 (14.5%)	31 (23.8%)	80 (33.6%)	75 (38.7%)	194 (31.4%)
WO	2 (3.6%)	5 (3.8%)	29 (12.2%)	33 (17.0%)	69 (11.2%)
Abdominal discomfort					
Experienced	13 (23.6%)	36 (27.7%)	48 (20.2%)	53 (27.3%)	150 (24.3%)
WO	1 (1.8%)	2 (1.5%)	11 (4.6%)	13 (6.7%)	27 (4.4%)
Feelings of hot/cold					
Experienced	6 (10.9%)	21 (16.2%)	54 (22.7%)	50 (25.8%)	131 (21.2%)
WO	1 (1.8%)	3 (2.3%)	11 (4.6%)	15 (7.7%)	30 (4.9%)
Pain					
Experienced	12 (21.8%)	43 (33.1%)	84 (35.3%)	64 (33.0%)	203 (32.9%)
WO	0 (0.0%)	13 (10.0%)	21 (8.8%)	31 (16.0%)	65 (10.5%)
Aching					
Experienced	8 (14.5%)	37 (28.5%)	81 (34.0%)	74 (38.1%)	200 (32.4%)
WO	2 (3.6%)	14 (10.8%)	30 (12.6%)	44 (22.7%)	90 (14.6%)

respectively equal to 7.9% for each point increase in UPDRS part II score (95% CI 1.017–1.144,  $p = 0.0117$ ), and equal to 13.0% for each additional year of anti-Parkinson treatment duration (95% CI 1.031–1.245,  $p = 0.0094$ ). The estimated risk for WO diagnosis resulted unmodified even for ever tobacco smokers and alcohol consumers.

### 3.3. WO and QoL

Subjects with WO reported worse QoL, as assessed by PDQ-8, than subjects without WO ( $32.7 \pm 19.2$  vs.  $21.4 \pm 15.7$ ,  $p < 0.0001$ ). The number of motor symptoms ( $0.34008$ ;  $p < 0.0001$ ) as well as non-motor symptoms ( $0.33595$ ;  $p < 0.0001$ ) correlated with PDQ-8 score. By linear regression analysis, the presence of WO symptoms, as identified by WOQ-19, corresponded to an increase of 1.15 points of the PDQ-8 score ( $p < 0.0001$ ). Moreover, disease severity assessed by H&Y scale ( $p = 0.0003$ ) and the need for caregiver assistance ( $p < 0.0001$ ) also showed a negative impact on patient's QoL.

## 4. Discussion

Our results indicate WO is a potentially “early” phenomenon, as already 41.8% of the PD patients with <2.5 years disease duration reported symptoms according to the WOQ-19 and 21.8% according to neurologist assessment. The prevalence of WO was higher in subjects with longer disease duration, and patients with >10 years of disease duration were diagnosed in 80.4% and 76.8% of the cases, respectively by WOQ-19 and by neurologist assessments. As expected, the vast majority of patients with WO were on levodopa (94%). Interestingly, the levodopa treatment duration did not significantly differ between patients with and without WO and logistic regression analysis revealed that the time since initiation of levodopa did not predict occurrence of WO. Similarly in a recent observational study [12], even if frequency of WO symptoms increased with the total duration of levodopa treatment, the changes were minimal and 86.7% of patients treated for <1 year with levodopa were rated as having WO based on WOQ-9 questionnaire vs. 89.5% for <5 years, and 92.7% for >5 years of levodopa treatment.

This is a marked greater prevalence than previously estimated in the literature. Older studies had showed that about 10% of patients per year develop motor fluctuations after initiation of treatment

with levodopa [13], and within 4–6 years of treatment up to 40% of patients develop WO [14], while almost all subjects would fluctuate after 10 years [1,15]. More recent studies are consisted with ours and have documented that fluctuations of parkinsonian features may occur from the very early stages and WO symptoms can be observed in patients a few months after the initiation of levodopa treatment [16,17]. Up to 50% of patients experience motor fluctuations already by 2 years of treatment [18–20]. Our results confirm the finding of WO in a large percentage of patients with disease duration of <2.5 years but clarify that manifestations are predominantly motor symptoms (Table 2).

Despite many studies have been conducted in PD patients with fluctuations, these differed in the definition of WO, heterogeneity of study populations, different treatment regimens in accordance with different standard of care that has changed over time. Most of the data are extrapolated from interventional studies that may be biased and probably are not representative of the overall population of patients with PD; in these studies the identification of WO was usually not among the primary objectives and howsoever different assessment methodologies have been applied. Moreover, the epidemiological data available to date have largely focused on motor fluctuations while non motor symptoms, difficult to assess but no less bothersome, have been often overlooked [3,21–24]. The strengths of our results are the large population-based study, focused to collect data about WO phenomenon and its related manifestations in a large sample of clinically well-characterized patients with PD, in standardized manner, using both clinical assessment and the WOQ-19, which today represents one of the most sensitive methods for WO screening. Assuming WO as transverse phenomenon in the clinical course of PD, we chose an observational design, including subjects under different treatments at all stages of the disease, aiming to photograph the WO phenomenon in a context of the current clinical practice. In addition, our study has allowed to assess the impact of WO symptoms on patient's QoL.

Concerning clinical assessment, the rates of WO diagnosis performed by our neurologists were generally higher compared to other studies [12]. This could be due to heterogeneity of study populations, or more likely because all our examining physicians were movement disorders specialists, who had been specifically trained with the task of completing a well-structured interview focused to identify WO. Greater awareness and experience in collecting data from patient medical history and asking the “right”

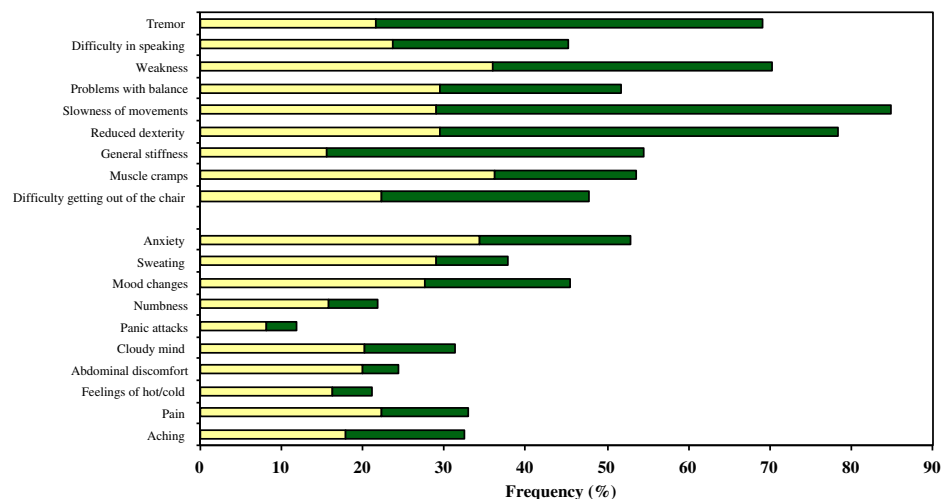


Fig. 2. Frequency of symptoms reported by patients through the WOQ-19: relative rates of subjects who experienced each symptom either as a WO manifestation (green) or not (yellow).



questions can help make a more timely diagnosis of WO. In addition, patients filled-out the WOQ-19 just before being evaluated by neurologists, and the order of these two diagnostic steps was not randomized. A bias is plausible, as the patient after the completion of the WOQ-19 could be more willing to report symptoms to the neurologist, in this increasing the percentage of diagnosis of WO by the neurologist.

For WO diagnosis through the WOQ-19 we arbitrarily adopted a cut-off of at least two symptoms reported as fluctuating along with medication intake. This cut-off has been identified in the validation study as the best compromise in sensitivity and specificity [8]. In the present study WOQ-19 data were not analysed for different cut-offs, and most likely higher values would be in better agreement with the neurologist's decision. Nevertheless, also our data showed a marked discrepancy in perception between patients and neurologists, which has already been extensively discussed in previous studies [6,12,25,26], and we agree that WO is potentially verifiable at every stage of disease, and it is often underestimated by the routine clinical assessment [4,12,15,16]. In our population, almost three out of four WO manifestations were motor symptoms (Table 2, Fig. 2), with slowness of movements (55.8%) and reduced dexterity (48.8%) being the most common motor features, anxiety (18.5%) and mood changes (18.0%) the most common non motor features. Non-motor symptoms were generally less frequently experienced, in proportion less frequently reported as fluctuating with treatment. The number of WO symptoms, both motor and non motor, increased in accordance with disease duration (Fig. 1, Table 2), and correlated significantly with QoL. Each additional symptom indicated by patients through the WOQ-19 was associated with proportional worsening of the PDQ8 score. We found this result interesting also because highlight that the WOQ-19 could be potentially exploited not only in qualitative (diagnosis of WO), but also in quantitative terms (number of symptoms). Future studies could investigate the correlation between WOQ-19 and other clinical features, in addition to QoL, and eventually validated as measures of follow-up outcome.

In our cohort, patients with WO were significantly younger and the percentage of women was higher than in patients without WO. Every additional year of age was associated with a 5.0% risk reduction of WO, whilst female gender was associated with an 80.1% higher risk of WO. These findings are comparable to those observed in a similar study, in which patients with WO were

significantly younger and with a higher ratio of women, than those without WO [5]. Conversely, in a British community-based study, younger patients developed dyskinesias sooner than older patients, but there was no correlation with motor fluctuations, moreover men and women did not differ in the occurrence of motor fluctuations or dyskinesias [1]. Thus, in a recent prospective study, female gender was found associated with a shorter time to levodopa-induced dyskinesias and younger age at diagnosis was reported as associated with higher likelihood and shorter latency to develop dyskinesias [27].

Our study has some limitations. This is a cross-sectional study and potential risk factors for WO development and prognostic effect of different treatment choices were not assessed. The cohort size of patients with short disease duration is small, perhaps because the broad inclusion criteria have favoured the recruitment of patients at more advanced stages. Therefore for statistical reasons we were forced us to gather data of patients into groups with a relatively wide range of disease duration. Some important clinical variables, such as treatment duration and dose were omitted from the regression model analysis because only partially available. Finally, through the WOQ-19 patients can only report the presence/absence of fluctuating symptom, but not the degree of severity. Therefore, the information provided by the questionnaire is nevertheless partial and still needs to be integrated with the clinical assessment.

## 5. Conclusions

To our knowledge this is the largest epidemiological study targeting the WO phenomenon as primary objective. Our results indicated WO as potentially observable across all disease stages and that affect patient's QoL. Since WO can be effectively treated by changes in medication dose and kind its recognition is critical given its negative implications on quality of life [28–30].

## Acknowledgements

This study was supported by an educational grant issued by Novartis Pharma S.p.A., Italy. The authors are grateful to Medidata S.r.L. for data collection and analysis and to Shalom Haggiag for helping writing the manuscript.

## Appendix 1. The Deep study group

Fabrizio	Stocchi	Dipartimento di Neurologia IRCCS San Raffaele Pisana di Roma	Roma
Laura	Vacca	Dipartimento di Neurologia IRCCS San Raffaele Pisana di Roma	Roma
Peter P.	Pramstaller	Neurologia Ospedale di Bolzano	Bolzano
Maurizio	Facheris	Neurologia Ospedale di Bolzano	Bolzano
Mario	Guidotti	Neurologia Ospedale Valduce	Como
Elisabetta	Corengia	Neurologia Ospedale Valduce	Como
Giulio	Riboldazzi	Neurologia Ospedale di Circolo e Fondazione Macchi	Varese
Serena	Leva	Neurologia Ospedale di Circolo e Fondazione Macchi	Varese
Alberto	Priori	Neurologia Fondazione Ospedale Maggiore Policlinico	Milano
Filippo	Cogiamanian	Neurologia Fondazione Ospedale Maggiore Policlinico	Milano
Gianni	Pezzoli	Centro Parkinson Istituti Clinici di Perfezionamento	Milano
Canesi	Margherita	Centro Parkinson Istituti Clinici di Perfezionamento	Milano
Alberto	Albanese	Neurologia I Fondazione IRCCS Istituto Nazionale Neurologico C. Besta; Università Cattolica del Sacro Cuore	Milano
Paola	Soliveri	Neurologia I Fondazione IRCCS Istituto Nazionale Neurologico C. Besta	Milano
Daniele	Picco	Neurologia Riabilitativa Fondazione Salvatore Maugeri IRCCS Veruno	Veruno
Fabrizio	Pisano	Neurologia Riabilitativa Fondazione Salvatore Maugeri IRCCS Veruno	Veruno
Leonardo	Scarzella	Neurologia Ospedale Evangelico Valdese	Torino
Alessia	Tavella	Neurologia Ospedale Evangelico Valdese	Torino
Leonardo	Lopiano	Neurologia 4 A.S.O. Molinette	Torino

(continued on next page)

(continued)

Maurizio	Zibetti	Neurologia 4 A.S.O. Molinette	Torino
Michele	Tinazzi	U.O. Neurologia Ospedale Civile Maggiore – Borgo Trento	Verona
Sarah	Ottaviani	U.O. Neurologia Ospedale Civile Maggiore – Borgo Trento	Verona
Franco	Zalvania	Clinica Neurologica Nuovo Ospedale Sant'Agostino-Estense	Modena
Sara	Contardi	Clinica Neurologica Nuovo Ospedale Sant'Agostino-Estense	Modena
Rocco	Quatralè	UO Neurologia Arcispedale Sant'Anna	Ferrara
Mariachiara	Sensi	UO Neurologia Arcispedale Sant'Anna	Ferrara
Roberto	Ceravolo	U.O. Neurologia Ospedale Santa Chiara	Pisa
Carlo	Rossi	U.O. Neurologia Ospedale Santa Chiara	Pisa
Massimo	Cincotta	Neurologia Azienda Sanitaria Firenze – Piero Palagi	Firenze
Paola	Vanni	Neurologia Azienda Sanitaria Firenze – Piero Palagi	Firenze
Ubaldo	Bonucelli	U.O. Neurologia Ospedale Versilia	Camaiore
Paolo	Del Dotto	U.O. Neurologia Ospedale Versilia	Camaiore
Maria Gabriella	Ceravolo	Clinica Neuroriabilitazione Az. Ospedali Riuniti	Ancona
Marianna	Capecchi	Clinica Neuroriabilitazione Az. Ospedali Riuniti	Ancona
Roberta	Marchese	Centro Parkinson – Dipartimento Neuroscienze Università degli Studi di Genova	Genova
Tiziano	Tamburini	Centro Parkinson – Dipartimento Neuroscienze Università degli Studi di Genova	Genova
Astrid	Thomas	CeSI-Centro Studi Invecchiamento Fondazione Università Gabriele D'Annunzio	Chieti
Iole	Borrelli	CeSI-Centro Studi Invecchiamento Fondazione Università Gabriele D'Annunzio	Chieti
Roberto	Marconi	Neurologia Ospedale della Misericordia	Grosseto
Lucia	Grasso	Neurologia Ospedale della Misericordia	Grosseto
Paolo	Stanzione	Clinica Neurologica Policlinico Tor Vergata	Roma
Valerio	Pisani	Clinica Neurologica Policlinico Tor Vergata	Roma
Anna Rita	Bentivoglio	Neurologia Università Cattolica S. Cuore Policlinico Gemelli	Roma
Giovanna	Loria	Neurologia Università Cattolica S. Cuore Policlinico Gemelli	Roma
Maria Francesca	De Pandis	U.O. Riabilitazione Parkinson Ospedale San Raffaele Cassino	Cassino
Giovanna	Federici	U.O. Riabilitazione Parkinson Ospedale San Raffaele Cassino	Cassino
Valentino	Manzo	Neurologia, Padiglione F,Amb UVA AORN A. Cardarelli	Napoli
Alfonso	Mauro	Struttura Dipartimentale Neuropsicologia AORN San Giovanni di Dio e Ruggi di Aragona	Salerno
Paolo	Barone	Centro Parkinson Dipartimento Scienze Neurologiche Università Federico II Napoli	Napoli
Marina	Picillo	Centro Parkinson Dipartimento Scienze Neurologiche Università Federico II Napoli	Napoli
Stefano	Ruggieri	Neurologia Istituto Mediterraneo Neuromed	Pozzilli
Nicola	Modugno	Neurologia Istituto Mediterraneo Neuromed	Pozzilli
Paolo	Lamberti	Neurologia "Amaducci" Az. Osp. Univ. Policlinico Consorziale	Bari
Claudia	Dell'Aquila	Neurologia "Amaducci" Az. Osp. Univ. Policlinico Consorziale	Bari
Giulio	Cicarelli	Neurologia A.O.R.N. San Giuseppe Moscati	Avellino
Aldo	Quattrone	Clinica Neurologica Università Magna Grecia	Catanzaro
Giuseppe	Nicoletti	Clinica Neurologica Università Magna Grecia	Catanzaro
Antonino	Cannas	Neurologia Policlinico Universitario di Monserrato	Monserrato
Paolo	Solla	Neurologia Policlinico Universitario di Monserrato	Monserrato
Mario	Zàppia	Clinica Neurologica I Policlinico Universitario	Catania
Alessandra	Nicoletti	Clinica Neurologica I Policlinico Universitario	Catania
Letterio	Morgante	Clinica Neurologica Policlinico G. Martino	Messina
Francesca	Morgante	Clinica Neurologica Policlinico G. Martino	Messina
Marco	D'Amelio	Neurologia Az. Osp. Univ. Policlinico "P. Giaccone"	Palermo
Valeria	Terruso	Neurologia Az. Osp. Univ. Policlinico "P. Giaccone"	Palermo
Roberto	Eleopra	SOC Neurologia Az. Osp. Univ. S.Maria della Misericordia	Udine
Marco	Mucchiut	SOC Neurologia Az. Osp. Univ. S.Maria della Misericordia	Udine
Manuela	Pilleri	U.O. Malattia di Parkinson IRCCS Ospedale San Camillo	Venezia
Roberta	Biundo	U.O. Malattia di Parkinson IRCCS Ospedale San Camillo	Venezia
Stefania	Nasseti	U.O.C. Neurologia Ospedale Bellaria	Bologna
Roberto	Michelucci	U.O.C. Neurologia Ospedale Bellaria	Bologna

## References

- [1] Schrag A, Quinn N. Dyskinesias and motor fluctuations in Parkinson's disease. A community-based study. *Brain* 2000;123:2297–305.
- [2] Sethi KD. The impact of levodopa on quality of life in patients with Parkinson disease. *Neurologist* 2010;16:76–83.
- [3] Stacy M, Bowron A, Guttman M, Hauser R, Hughes K, Larsen JP, et al. Identification of motor and nonmotor wearing-off in Parkinson's disease: comparison of a patient questionnaire versus a clinician assessment. *Mov Disord* 2005;20:726–33.
- [4] Stacy M. The wearing-off phenomenon and the use of questionnaires to facilitate its recognition in Parkinson's disease. *J Neural Transm* 2010;117:837–46.
- [5] Silburn PA, Mellick GD, Vieira BI, Danta G, Boyle RS, Herawati L. Utility of a patient survey in identifying fluctuations in early stage Parkinson's disease. *J Clin Neurosci* 2008;15:1235–9.
- [6] Martinez-Martin P, Tolosa E, Hernandez B, Badia X. ValidQUICK Study Group. Validation of the "QUICK" questionnaire—a tool for diagnosis of "wearing-off" in patients with Parkinson's disease. *Mov Disord* 2008;23:830–6.
- [7] Antonini A, Martinez-Martin P, Chaudhuri RK, Merello M, Hauser R, Katzenschlager R, et al. Wearing-off scales in Parkinson's disease: critique and recommendations. *Mov Disord* 2011;26:2169–75.
- [8] Abbruzzese G, Antonini A, Barone P, Stocchi F, Tamburini T, Bernardi L, et al. Linguistic, psychometric validation and diagnostic ability assessment of an Italian version of a 19-item wearing-off questionnaire for wearing-off detection in Parkinson's disease. *Neurol Sci* 2012;33:1319–27.
- [9] Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. *Arch Neurol* 1999;56:33–9.
- [10] Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hayman N. The PDQ-8: development and validation of a short-form Parkinson's Disease Questionnaire. *Psychol Health* 1997;12:805–14.
- [11] Bareš M, Rektorová I, Jech R, Farníková K, Roth J, Růžicka E, et al. Does WOQ-9 help to recognize symptoms of non-motor wearing-off in Parkinson's disease? *J Neural Transm* 2012;119:373–80.
- [12] Marsden CD, Parkes JD. Success and problems of long-term levodopa therapy in Parkinson's disease. *Lancet* 1977;1:345–9.
- [13] Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord* 2001;16:448–58.
- [14] Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa. *Ann Neurol* 1996;39:37–45.
- [15] Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, Lang A, et al. Levodopa and the progression of Parkinson's disease. *N Engl J Med* 2004;351:2498–508.
- [16] the Parkinson Study Group. Does levodopa slow or hasten the rate of progression of Parkinson's disease? *J Neurol* 2005;252:IV37–42.

- [18] Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a randomized controlled trial. *Parkinson Study Group. J Am Med Assoc* 2000;284:1931–8.
- [19] Sato K, Hatano T, Yamashiro K, Kagohashi M, Nishioka K, Izawa N, et al. Prognosis of Parkinson's disease: time to stage III, IV, V, and to motor fluctuations. *Mov Disord* 2006;21:1384–95.
- [20] Stocchi F. Prevention and treatment of motor fluctuations. *Parkinsonism Relat Disord* 2003;9:S73–81.
- [21] Adler CH. Relevance of motor complications in Parkinson's disease. *Neurology* 2002;58:S51–6.
- [22] Witjas T, Kaphan E, Azulay JP, Blin O, Ceccaldi M, Pouget J, et al. Nonmotor fluctuations in Parkinson's disease: frequent and disabling. *Neurology* 2002;59:408–13.
- [23] Politis M, Wu K, Molloy S, G Bain P, Chaudhuri KR, Piccini P. Parkinson's disease symptoms: the patient's perspective. *Mov Disord* 2010;25:1646–51.
- [24] Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB. Effect of psychiatric and other nonmotor symptoms on disability in Parkinson's disease. *J Am Geriatr Soc* 2004;52:784–8.
- [25] Stacy MA, Murphy JM, Greeley DR, Stewart RM, Murck H, Meng X, et al. The sensitivity and specificity of the 9-item wearing-off Questionnaire. *Parkinsonism Relat Disord* 2008;14:205–12.
- [26] Melo LM, Chien HF, Barbosa ER. Identification of wearing-off manifestations (reduction of levodopa effect) in Parkinson's disease using specific questionnaire and comparison of the results with routine ambulatory evaluations. *Arq Neuropsiquiatr* 2010;68:506–10.
- [27] Hassin-Baer S, Molchadski I, Cohen OS, Nitzan Z, Efrati L, Tunkel O, et al. Gender effect on time to levodopa-induced dyskinesias. *J Neurol* 2011;258:2048–53.
- [28] Nissinen H, Kuoppamäki M, Leinonen M, Schapira AH. Early versus delayed initiation of entacapone in levodopa-treated patients with Parkinson's disease: a long-term, retrospective analysis. *Eur J Neurol* 2009;16:1305–11.
- [29] Fung VS, Herawati L, Wan Y. Movement disorder Society of Australia clinical research and trials group; QUEST-AP Study Group. Quality of life in early Parkinson's disease treated with levodopa/carbidopa/entacapone. *Mov Disord* 2009;24:25–31.
- [30] Antonini A, Chaudhuri KR, Martinez-Martin P, Odin P. Oral and infusion levodopa-based strategies for managing motor complications in patients with Parkinson's disease. *CNS Drugs* 2010;24:119–29.