EXPERT OPINION

A non-comparative assessment of tolerability and efficacy of duloxetine in the treatment of depressed patients with Parkinson's disease

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Objective: Depression is a comorbidity affecting quality of life (QoL) in patients with Parkinson's disease (PD) and requires appropriate treatment. This study evaluated the tolerability, safety, and efficacy of duloxetine 60 mg once daily for 12 weeks in PD patients with major depressive disorder (MDD).

Research and design methods: Non-comparative, open-label, multi-center study.

Main outcome measures: Tolerability was evaluated by discontinuation rate (acceptable if ≤ 19%) due to treatment-emergent adverse events (TEAEs) and motor symptoms (UPDRS). Safety measures were TEAEs, the UKU side effect rating scale, vital signs, weight, laboratory tests, and ECG. Efficacy measures included HAMD-17, BDI, CGI-S, PGI-I, and pain VAS. QoL was measured by PDQ-39.

Results: Of the 151 patients enrolled, 8.6% (95% upper CI: 13.3%) discontinued the study due to TEAEs. Worsening in PD-related tremor and rigidity was not observed, activities of daily living significantly improved and UKU subscales progressively decreased. Clinically significant abnormalities in laboratory findings were limited to four cases of hypercholesterolemia and one increase of total bilirubin, CPK, and fasting glucose. Blood pressure, weight, and ECG did not change from baseline. HAMD-17 and PDQ-39 total score and individual domains, BDI, CGI-S, and PGI-I total scores significantly improved.

Conclusions: Duloxetine seems well tolerated and likely effective in the treatment of depression associated with PD, with no detrimental effects in PD signs and symptoms.

Keywords: depression, duloxetine, efficacy, Parkinson's disease, safety, tolerability

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1. Introduction

Depression is a psychiatric disorder frequently associated with Parkinson's disease (PD), occurring in 40 – 50% of PD patients [1,2], with at least 17% suffering from major depressive disorder (MDD) [3]. In 25% of cases it precedes the onset of motor symptoms [4] playing a relevant role in the natural history of the disease, associated with increased disability and reduced quality of life (QoL) [5,6].

Mechanisms underlying depression in PD are not yet fully elucidated but it is believed that the degenerative process may alter neurotransmitter systems

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other than widespread dopamine deficiency (e.g., the noradrenergic and serotonergic brainstem nuclei) [7]. This may account for the depression resistance to dopamine replacement strategies, justifying the need for specific treatments [8]. Recently a 12-week randomized, double-blind, placebo-controlled trial comparing pramipexole with placebo in patients with mild-to-moderate PD was carried out. The results suggest that pramipexole should be considered in the management of patients with PD and clinically significant depressive symptoms [9].

Currently, tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) represent the preferred pharmacotherapy for depression treatment in PD. Although SSRIs present theoretical tolerability advantages, they can induce/increase motor disability and other PD symptoms, as confirmed by a literature search of 127 reports of SSRI-induced movement disorders [10,11]. On the other hand, a recent randomized study showed that there were no significant efficacy differences between paroxetine and venlafaxine in treating patients with PD and various forms of depression [12].

In addition to venlafaxine, duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressant medication with weak effects on dopamine reuptake both *in vitro* and *in vivo*. It displays a threefold greater relative potency at the 5-HT reuptake transporter site than at the NE site [13] and its safety and effectiveness in the treatment of emotional/physical symptoms of depression have been assessed through placebo- and active-controlled clinical studies [13-18]. When given in elderly MDD patients in doses of up to 120 mg/day, it provides rapid and sustained antidepressant efficacy without compromising the safety profile [18].

Thus, duloxetine could reduce depressive symptoms in PD patients due to its action on both the neurotransmission pathways potentially involved in the pathogenesis of depression in PD. Based on this background, this study aimed primarily at obtaining more information on the safety and tolerability rather than on efficacy of duloxetine in MDD PD patients, to help clinicians in making evidence-based decisions when choosing the most appropriate pharmacotherapy.

2. Patient and methods

2.1 Patient population

The study population included patients of both sexes with PD aged between 30 and 75 years and MDD diagnosed on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and confirmed by the Mini International Neuropsychiatric Interview (MINI) Depression Module. Inclusion criteria, severity scales scores to be fulfilled, and exclusion criteria are reported in **Table 1**. Eligible patients also needed to have satisfactory cognitive function as indicated by a score ≥ 24 on the Mini Mental State Examination (MMSE) total score.

All participants signed a written informed consent before any study-related procedure was started. The study protocol was approved by the reference Ethic Committee of each participating site.

2.2 Study design and treatment

This study consisted of four periods:

1) Period I (3 to 10-day screening phase): each subject's enrolment eligibility was assessed. Baseline data (including lab test analysis and ECG) were collected and non-permitted medications discontinued.
2) Period II (1 week): duloxetine 30 mg/day was given to patients.
3) Period III (11 weeks): duloxetine dose was increased up to 60 mg/day (two capsules). Visits took place every 7 days in the first three weeks and every two weeks thereafter.
4) Period IV (optional 2-week taper period): at the end of period III (or after its first week in case of early discontinuation), duloxetine dose could be halved at 7-day intervals.

Duloxetine was administered with meals within an hour of eating, either in the morning or in the evening (switches allowed), based on physician decision and clinical judgment. Dose decreases were not permitted and were considered cause of discontinuation. Patients had to receive stable dosages of antiparkinsonian agents for ≥ 4 weeks before entry, to be kept unchanged throughout the study. Antipsychotic, other antidepressant, anticonvulsant, anticoagulant, narcotic, psychostimulant, tryptophan, triptan, antimanic, herbal preparation, narcotic, and monoamine oxidase inhibitor drugs were non-permitted.

Episodic use of benzodiazepines or certain hypnotics (i.e., 10 days maximum intermittent or consecutive use in total) was allowed within predefined dose limits. Patients were encouraged not to use benzodiazepines or hypnotics the night before a scheduled visit and not to alter their intake of caffeine or nicotine.

2.3 Outcome measures

The primary end point was discontinuation rate due to adverse events (AEs) while the Unified Parkinson's Disease Rating Scale (UPDRS) [19] was the secondary tolerability end point to follow the longitudinal course of PD. Details for all the study outcome measures are reported in **Table 2**. The Visual Analog Scale for pain (VAS) [20] used in this study was, inadvertently, only 93 mm long instead of 100 mm. The sponsor decided to maintain this VAS and used it for all subjects who participated in the study. However, because all the analyses performed using this scale cannot be compared to those of other studies, results will be not presented here.

2.4 Statistical analysis

Tolerability was evaluated by measuring the discontinuation rates due to treatment-emergent adverse events (TEAEs).

Table 1. Inclusion/exclusion criteria.

Inclusion criteria	Details
MDD diagnosis	MDD diagnosed on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and confirmed by the Mini International Neuropsychiatric Interview (MINI) Depression Module
Severity scales scores to be fulfilled	A clinician-rated 17-item Hamilton Depression Rating Scale (HAM-D-17) total score ≥ 15
	Beck Depression Inventory (BDI) total score ≥ 13
	Clinical Global Impression-Severity (CGI-S) score ≥3
PD diagnosis and staging	A clinical diagnosis of idiopathic PD according to the United Kingdom Parkinson's Disease Society Brain Bank Criteria (UK PD SBBC) with a 1 to 3 disease stage on the Modified Hoehn and Yahr Staging Scale [36]
Exclusion criteria	
Existing condition	Any current primary DSM-IV Axis I diagnosis other than MDD or any Axis II disorder which, in the investigator's opinion, would interfere with compliance with the study protocol
	Atypical or secondary parkinsonism due to drugs or diseases
	Motor conditions likely to require a change of the antiparkinsonian treatment during the study
	Patients judged by the investigator to be at serious risk of suicide, and/or with a HAM-D-17 score on item 3 (suicide) ≥ 3
	Clinically significant laboratory abnormalities or serious, unstable medical illness, including any cardiovascular, hepatic, renal, respiratory, hematologic, endocrine disease
	Narrow-angle glaucoma;
	Use of fluoxetine in the past 30 days or monoamine oxidase inhibitors (MAOI) in the past 2 weeks or any other non-permitted medication in the past week
	Electroconvulsive therapy (ECT) within the past year
	Pregnant or breastfeeding females, or females at risk of pregnancy

Main inclusion/exclusion criteria for this study are presented alongside the severity scales scores to be fulfilled. All the criteria must be met by patients to enter the study.

Duloxetine was defined as 'well tolerated' if the upper 95% confidence interval (CI) of discontinuation rates within the 12 weeks of treatment was ≤ 19%. This was estimated based on duloxetine data from placebo-controlled acute-phase trials with MDD patients that showed around 14% of discontinuation due to AEs [14-18,21]. Under these assumptions, when considering a sample size of 131, a one-sided 95.0% CI for a single proportion using the large sample normal approximation extends 0.050 from the observed proportion for an expected proportion of 14% (withdrawn for AEs). Assuming a 12% drop-out rate for reasons other than AE, a total of 150 subjects had to be enrolled.

Safety and tolerability analyses were conducted in the safety population (SP; i.e., patients who received at least one dose of duloxetine), while efficacy analyses were conducted in the intention-to-treat (ITT) population (i.e., patients in the SP with post-baseline data).

Mean ± standard deviation (SD) is reported for continuous variables, while percentages are reported for categorical variables.

Paired-sample T-test, both as individual test or as part of a mixed-model repeated measures (MMRM) analysis, was used to assess any statistically significant difference between the pre- and post-treatment of the tolerability and efficacy continuous outcome measures. In the T-test analysis, the last observation carried forward (LOCF) method was used in the management of missing post-baseline data and confirmed by MMRM analysis when appropriate. This was based on a mixed model analysis of covariance (ANCOVA) with estimation of model parameters obtained with maximum likelihood. No correction for multiplicity has been carried out. An observed case (OC) analysis was also performed in the assessment of changes from baseline of total UPDRS score and Section II and III scores.

Adverse events were coded using the MedDRA dictionary version 12.0. Events were considered as TEAEs if they started/worsened in the SP after the date of consent. Vital signs were also analyzed by the percentage of subjects who had extreme values at any time after baseline or at the end point: extreme values for standing and supine heart rate were set at > 100 beats per minute (bpm) and increase of 10 bpm from baseline; extreme values for supine systolic/diastolic blood pressure were set at ≥ 140/90 mmHg and an increase from baseline of at least 10 mmHg (or limited to an increase of 10 mmHg from baseline only for diastolic blood pressure). Sustained hypertension was defined as at least three consecutive visits with extreme blood pressure (either only diastolic or only systolic, or both diastolic and systolic). Orthostatic hypotension was also evaluated as a difference between standing and supine of at least 20 mmHg for either diastolic or systolic blood pressure. Changes from baseline to end point (last available data within the treatment period) in each of the laboratory tests were collected in descriptive tables. A treatment-emergent abnormal laboratory value was defined as a change from normal baseline to abnormal value at the relevant post-baseline visits.

Table 2. Outcome measures for this study.

Outcome measure		Notes
Tolerability		
	Discontinuation rate due to adverse events (TEAEs)	Primary tolerability objective
	Unified Parkinson's Disease Rating Scale (UPDRS) Section I	Secondary tolerability objective
	Unified Parkinson's Disease Rating Scale (UPDRS) Section II	Secondary tolerability objective
	Pittsburgh Sleep Quality Index (PSQI)	Secondary tolerability objective
Safety		
	TEAEs	
	Vital signs	Supine and standing systolic and diastolic blood pressure and pulse
	Body weight	
	Laboratory tests	Hematology, blood chemistry with thyroid hormones and urinalysis
	ECG	
	Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale	Completed by both patients and clinicians
Efficacy		
	Hamilton Depression Rating Scale 17 items (HAMD-17) [37]	Mean change from baseline to end point; response rate, defined as 50% reduction from baseline to end point; remission rate, defined as total score of ≤ 7 at end point;
	Clinical Global Impression-Severity (CGI-S) [38]	
	Patient's Global Impressions of Improvement (PGI-I) [38]	Scores range: from 1 (very much improved) to 4 (no change) and 7 (very much worse)
	Beck Depression Inventory (BDI) [39]	
	Visual Analog Scale for pain [20]	Reported in the Case Report Form was only 93 mm long instead of 100 mm
Quality of life	Parkinson's Disease Questionnaire – 39 Item version (PDQ-39) [40]	

Outcome measures are presented by category. Notes identify the primary and secondary objectives of the study.

3. Results

Between March 2007 and June 2009, 167 patients were screened, 151 (mean age: 63.6 years, 43.7% male) were enrolled (SP: n = 151 patients), and 119 (78.8%) completed this study. **Figure 1** shows the patients' disposition flow diagram.

Two patients did not have post-baseline data and were excluded from the efficacy ITT analysis (n = 149). Sixty-three (41.7%) and 40 (26.5%) patients were in stage 2 and 2.5 PD based on the Modified Hoehn and Yahr Staging Scale, respectively. In the SP (n = 151) the mean ± SD Hoehn and Yahr was 1.99 ± 055. The mean MMSE total score at baseline was 28.3 ± 1.8 (range 24 – 30). Two patients (1.3%) did not meet the MINI criteria for MDD diagnosis. The mean baseline CGI-S score was 4.0 ± 0.7 and the mean baseline HAMD-17 total score was 19.2 ± 3.5. A satisfactory compliance to treatment, defined in the range between 80 and 100% of the planned dose, was reported in 133 patients (89.3%). The mean duration of treatment was 10.9 ± 54.0 weeks (range 0 – 16). The mean daily dose in compliant patients was 55.3 ± 5.9 mg (range 30 – 59). In the ITT population, 88 patients always took the study drug in the morning, 49 patients always took the study drug in the evening, and 12 changed time of dosing during the study.

3.1 Tolerability and safety

Treatment-emergent adverse events were reported in 41 patients (27.2%), and considered to be treatment-related in 31 (20.5%). Thirteen patients (8.6%) discontinued the study due to TEAEs. The 95% CI upper limit computed by means of the normal approximation was 12.4%, while the exact limit based on binomial distribution was 13.3%. Both limits are ≤ 19% chosen to consider the drug tolerability acceptable. The most common TEAEs that caused early study discontinuation were diarrhea and tremor (in two patients each), nausea, vomiting, sepsis (preceded by acute kidney failure secondary to urinary retention), somnolence, syncope, visual hallucinations, decreased libido, psychotic disorder, and hypertension (in one patient each).

Treatment-emergent adverse events by system organ class (SOC) and preferred term in order of decreasing frequency for those events that occurred in ≥ 1% of treated subjects are reported in **Table 3**. No cases of bleeding or hyponatremia were observed.

Three (2%) patients reported serious AEs. Urinary retention, acute renal failure, and sepsis (one patient), and atrial

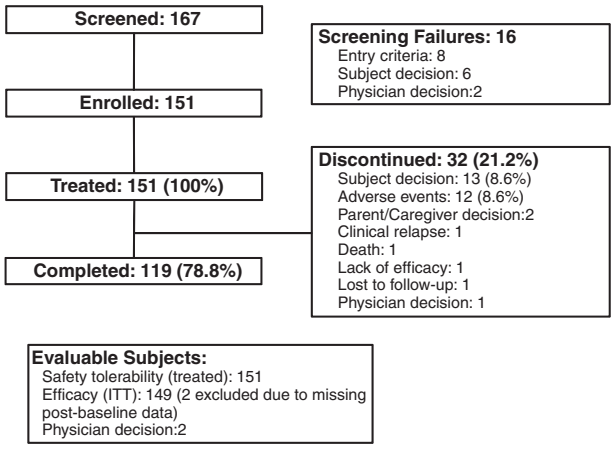


Figure 1. Patient disposition and analysis population.

Table 3. TEAEs (treatment-emergent adverse events) reported in at least 1% of treated subjects by system organ class (SOC) and preferred term (safety population).

System organ class and Preferred term	n (%)
Ear and labyrinth disorders	
Vertigo	2 (1.3)
Gastrointestinal disorders	
Aptyalism	3 (2.0)
Constipation	5 (3.3)
Diarrhea	2 (1.3)
Nausea	6 (4.0)
General disorders and administration site conditions	
Asthenia	3 (2.0)
Metabolism and nutrition disorders	
Hypercholesterolemia	3 (2.0)
Nervous system disorders	
Headache	3 (2.0)
Somnolence	3 (2.0)
Tremor	2 (1.3)
Psychiatric disorders	
Agitation	2 (1.3)
Anxiety	2 (1.3)
Psychotic disorder	2 (1.3)
Renal and urinary disorders	
Urinary retention	2 (1.3)
Skin and subcutaneous tissue disorders	
Hyperhidrosis	2 (1.3)

fibrillation (one patient) were considered treatment-related, while cerebral hemorrhage (one patient) was considered possibly related to duloxetine. Sepsis and cerebral hemorrhage were fatal.

Treatment-emergent adverse events were reported in 16/88 (18.2%) and 19/49 (38.8%) patients who always took the study drug, respectively, in the morning and in the evening.

Among the clinically significant abnormalities of safety laboratory parameters reported as TEAEs, one out of four cases of hypercholesterolemia, the increase of creatine phosphokinase (CPK), and hyperglycaemia were considered not treatment-related while no abnormalities for urinalysis parameters were observed.

Vital signs did not show significant changes, except for heart rate (HR) (**Table** 4). Heart rate extreme values were reported in two patients. Nobody had clinically significant changes in ECG.

One case of hypertension and another of orthostatic hypotension were reported as TEAEs. Seven patients (4.6%) had sustained hypertension, and 8 (5.3%) had orthostatic hypotension according to definition (see Experimental Procedures). Body weight remained substantially unchanged throughout the study.

The UPDRS did not show significant changes, except for an improvement in the MMRM analysis of total UPDRS score and of Section II total score at Week 12 (**Table** 4). The LOCF analysis of changes from baseline to end point of the single items is shown in **Table** 4. Mixed-model repeated measures analysis confirmed all the observed effects, with an additional significant decrease of tremor at rest in left hand and of posture (**Table** 4). The results in groups of tremor and rigidity-related items (tremor at rest as sum of items 16 – 20; postural tremor as sum of items 21 – 22; and rigidity as sum of items 1 – 5) did not show any trend over time and no statistical significance was found. Also, the Section III subscales body bradykinesia and hypokinesia total score did not show any relevant change throughout the study. This was also observed for tremor at rest, postural tremor, and rigidity. The results of Section II total score and Section III total score of UPDRS measured at baseline, Weeks 1, 2, and 12 are shown in **Figure 2**. The OC analysis largely confirmed the findings of LOCF and MMRM analyses showing no detrimental effect on motor symptoms (total UPDRS score: mean change: -1.2, $p = 0.002$; Section II total score: mean change: -0.6, $p = 0.004$; Section III total score: mean change: -0.6, $p = 0.06$).

Pittsburgh Sleep Quality Index (PSQI) showed a significant improvement over time confirmed by both LOCF and MMRM analysis (**Table** 4; $p < 0.001$ for both analyses).

Figure 3 shows the baseline, 6- and 12-month treatment results of UKU psychological, neurological, autonomic, and other systems subscales. The mean score of the psychological, neurological, and autonomic subscales progressively decreased from baseline to end point. The mean changes from baseline to Week 12 in the analysis of raw data were -3.8 ± 4.2 for the psychological subscale, -1.2 ± 1.9 for the neurological subscale, and -0.7 ± 1.2 for the autonomic subscale. The extent of the decrease in the LOCF analysis did not differ from that resulting from taking into account raw data only. No significant changes from baseline in the other systems subscale were observed. The analysis of the patient's and clinician's scoring of the interference of side effects with the patient's daily performance did not show statistically significant changes from

Table 4. Safety results: mean change from baseline.

Item	Mean change from baseline	
Vital signs		
Blood pressure (mmHg)		
Systolic		
Supine	-0.30 ± 8.71	p = 0.682
Standing	0.17 ± 8.03	p = 0.797
Diastolic		
Supine	-0.45 ± 6.29	p = 0.391
Standing	0.12 ± 6.16	p = 0.816
Heart rate		
Supine	1.16 ± 4.93	p = 0.005
Standing	1.61 ± 5.49	p < 0.001
UPDRS		
MMRM analysis (at Week 12)		
UPDRS total score (at Week 12)	-1.1	p = 0.006
Section II	-0.5	p = 0.007
LOCF/MMRM Week 12 significance for single item		
Salivation (Section II, item 6)	-0.1	p = 0.009/0.002
Turning in bed and adjusting bedclothes (Section II, item 12)	-0.1	p = 0.033/0.018
Facial expression (Section III, item 19)	-0.1	p = 0.007/0.003
MMRM Week 12 significance for single item		
Tremor at rest in left hand (Section III, item 20)	-0.1	p = 0.003
Posture (Section III, item 28)	-0.1	p = 0.015
PSQI		
LOCF Analysis		
Visit 6	-2.8 ± 3.1	p < 0.001
Visit 8	-3.3 ± 3.5	p < 0.001
Visit 10	-3.2 ± 3.5	p < 0.001
MMRM Analysis		
Visit 6	-2.8 ± 0.2	p < 0.001
Visit 8	-3.3 ± 0.2	p < 0.001
Visit 10	3.3 ± 0.2	p < 0.001

Safety results for vital signs, UPDRS, and PSQI scales are presented. Data are reported as mean ± SD along with p value.

baseline: the mean change from baseline to Week 12, when analyzing either raw data or applying the LOCF method, was 0.1 in both patient's and clinician's rating.

3.2 Efficacy

The LOCF results of HAMD-17 at each visit are shown in **Figure 4**. A significant decrease in HAMD-17 total score and in any individual domain ($p < 0.001$ in both the LOCF and the MMRM analyses from baseline to all time-points) was observed (**Table 5**). The significant effects on HAM-D-17 total score were maintained irrespective of the time of dosing. Response and remission rates at end point were 60.4 and 45.6% in the LOCF analysis and 84.8 and 59.7% in the MMRM analysis.

The mean CGI-S score progressively decreased from baseline to Week 12 ($p < 0.001$ in both the LOCF and the MMRM analyses, **Table 5**). The improvement from baseline of PGI-I categories (data not shown) correlated significantly with the improvements of CGI-S (Spearman r correlation coefficient: 0.50, $p < 0.001$).

The mean BDI total score was 21.6 ± 6.1 at baseline and 9.7 ± 6.1 at Week 12: the change from baseline was significant (**Table 5**), irrespective of the time of dosing.

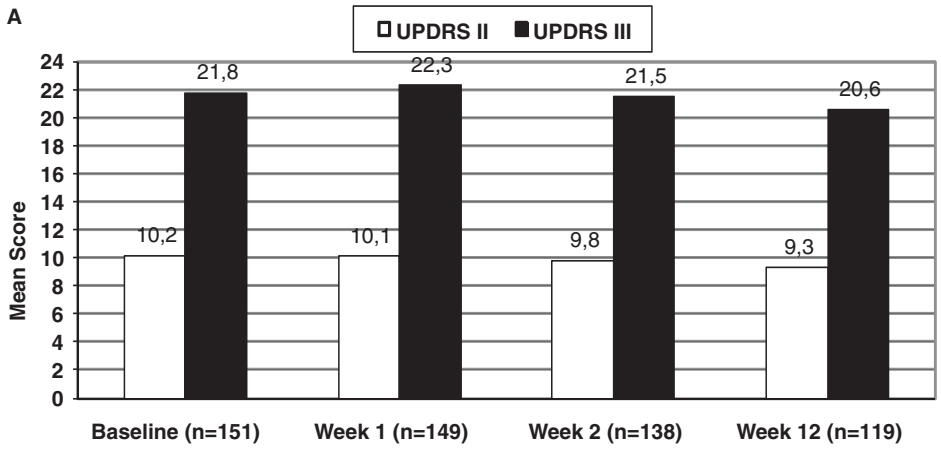
3.3 Quality of life

A significant improvement from baseline to end point was observed in the average total score of PDQ-39 and in each single domain considered apart from mobility, where only a slight numerical improvement was observed. The mean change in total score at LOCF analysis was -7.7 ± 9.9 ($p < 0.001$). The most significant improvements ($p < 0.001$) in the single domains were observed for emotional well-being (-21.1 ± 20.3), stigma (-12.3 ± 21.6), cognitive impairment (-7.4 ± 16.7), and bodily discomfort (-6.8 ± 21.1).

4. Discussion

Diagnosis of depression in PD is challenging because of the clinical overlap of symptoms of these two conditions [22],

A



B

UPDRS section II		
LOCF analysis		
	Mean ± SE	P value
Week 1	0.0 ± 0.1	0.963
Week 2	-0.1 ± 0.1	0.755
Week 12	-0.4 ± 0.2	0.057
MMRM analysis		
	Mean ± SE	P value
Week 1	0.0 ± 0.1	0.912
Week 2	-0.1 ± 0.2	0.662
Week 12	-0.5 ± 0.2	**0.007**

UPDRS section III		
LOCF analysis		
	Mean ± SE	P value
Week 1	0.5 ± 0.4	0.234
Week 2	-0.6 ± 0.4	0.169
Week 12	-0.1 ± 0.4	0.869
MMRM analysis		
	Mean ± SE	P value
Week 1	0.5 ± 0.4	0.214
Week 2	-0.4 ± 0.4	0.229
Week 12	-0.6 ± 0.3	0.096

Figure 2. A. UPDRS, Section II and III total scores at baseline, Weeks 1, 2, and 12 in raw data (safety population). B. UPDRS visit-wise absolute change versus baseline (LOCF and MMRM).

LOCF: Last observation carried forward; MMRM: Mixed-model repeated measures; n = 149; UPDRS: Unified Parkinson's Disease Rating Scale.

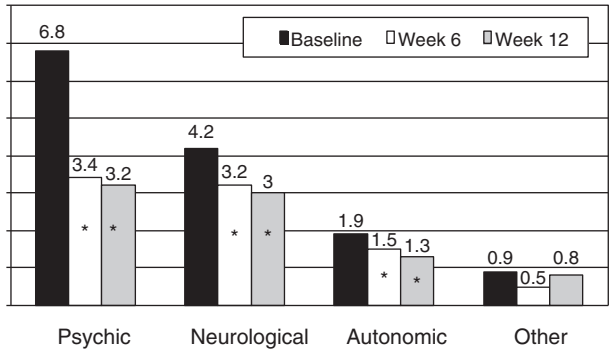


Figure 3. UKU subscales at baseline, Weeks 6 and 12 (means with standard deviations in bars) (safety population).

and despite the advances in pharmacotherapy there is still little evidence on the best antidepressant for the treatment of MDD PD patients.

Considering its proven consolidated efficacy and safety profile in the treatment of MDD and the satisfactory spectrum of tolerability in elderly patients [18], this study aimed at assessing tolerability of duloxetine in depressed PD patients.

The primary tolerability objective was evaluated based on the '*a priori*' criterion that duloxetine was well tolerated if the discontinuation rate within Week 12 was ≤ 19%. This was based on i) an overall reported rate of discontinuation around 14% in acute-phase clinical trials in patients with MDD without any comorbidity [14-18,21]; ii) when considering MDD patients who have a medical comorbidity, an additional 5% discontinuation rate due to TEAEs was considered acceptable. A higher rate of treatment discontinuation would put the patient at risk of non-adherence to other PD treatments, and hence of poor PD symptoms control; and iii) discontinuation rates in patients treated with SSRIs and other antidepressants reported in literature is around 20% [23-25].

This study shows that the discontinuations due to TEAEs were < 19%, thus indicating that the underlying PD and the concomitant treatments did not increase the risk of treatment discontinuation as compared to the use of duloxetine in the acute treatment of adult MMD patients without PD comorbidity. The AEs spectrum was aligned with the known duloxetine tolerability profile. Furthermore, it should be considered that some of the AEs (e.g., central nervous system or psychiatric disorders) may be a symptomatic component of PD or may be

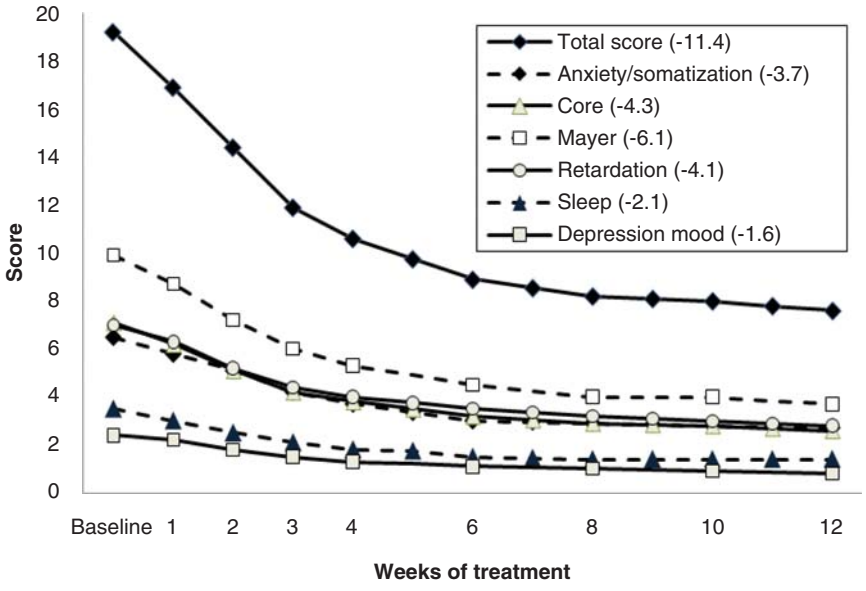


Figure 4. HAM-D-17 (total score and domains) results at each visit. Values are means, with absolute mean changes from baseline to Week 12 reported in legend (values in brackets) (ITT population).
HAM-D-17: Hamilton Depression Rating Scale; ITT: Intent-to-treat.

Table 5. Efficacy results: Results for HAM-D-17 total-score, CGI-S, and BDI are presented.

Item	Mean change from baseline	
HAM-D-17 total score		
LOCF analysis [mean change ± SD]		
To all visits	-7.45 ± 4.90	95% CI = -8.25 to -6.66
To end point	-10.1 ± 6.5	$p < 0.001$
MMRM analysis [mean change ± SE]		
To end point	-11.4 ± 0.5	$p < 0.001$
CGI-S		
LOCF analysis [mean change ± SD]		
To Week 12	-1.5 ± 1.3	$p < 0.001$
MMRM analysis [mean change ± SE]		
To Week 12	-1.7 ± 0.1	$p < 0.001$
BDI		
LOCF analysis [mean change ± SD]		
To Week 12	-11.98 ± 7.82	-13.39 to -10.58

Data are reported as mean ± SD along with p value or 95% CI as indicated for each outcome.

caused by concomitant medications, thus rendering the causal relationship with duloxetine difficult to assess.

Regarding the two patients that died after presenting serious AEs, one experienced acute kidney failure secondary to urinary retention which led to hospitalization and more than 2 months later, to sepsis and death. These events were considered as treatment-related. However, other contextual clinical elements must be taken into account. Firstly, the patient's medical history included benign prostatic hyperplasia and hypertrophy. These conditions may have also contributed to urinary retention. Secondly, the patient died of sepsis more than 2 months after the urinary retention probably due to the prolonged immobilization syndrome and sacral and calcaneal decubitus ulcers.

The other patient experienced a cerebral hemorrhage during the month following the conclusion of the study while still on duloxetine. This patient had a medical history of a right carotid artery occlusion treated with endoarterectomy 3 years prior to the study, and was concomitantly treated with ticlopidine (antiplatelet agent). These conditions and concomitant treatments may have posed an increased hemorrhagic risk. However, since it was impossible to rule out the causality relationship, the hemorrhagic event was considered possibly related to duloxetine. These two cases reaffirm the importance of considering the comorbidities when choosing an antidepressant in elderly PD patients.

Unlike studies on other antidepressants, the results here show that duloxetine seem to induce neither motor AEs, nor to be associated with the development of movement disorders. Notably, duloxetine treatment was not associated with any detrimental effect on PD signs and symptoms (see results of overall total score, Section II and III subscores, and single items of UPDRS). Duloxetine had a neutral effect on PD-related tremor and rigidity, and produced significant improvements in posture salivation, turning in bed and adjusting bedclothes, and facial expression. Furthermore, in the evaluation of complaints and

of their interference with the daily activities by means of the UKU subscale scores, there was no evidence of worsening of side effects from baseline to end point, and the mean scores of the psychological, neurological, and autonomic subscale showed clinically significant decreases (i.e., improvements) during the course of the study.

Laboratory parameter abnormalities were limited to four cases of hypercholesterolemia, one case of elevation of total bilirubin, one increase in CPK and one hyperglycaemia. Of these, three cases of hypercholesterolemia and the increase in total bilirubin were drug-related; however, concomitant medications might have contributed to develop these adverse reactions. No clinically significant laboratory alterations of hepatic or renal function were reported. Other safety parameters (blood pressure, weight, and ECG), even if largely exploratory, did not significantly change, with the exception of HR, thus confirming duloxetine's good safety profile. Heart rate increase could become clinically significant particularly in those PD patients with a comorbid cardiovascular autonomic dysfunction [26]. In such patients, duloxetine should be used with caution and HR increase carefully monitored.

With regard to sustained hypertension and orthostatic hypotension, the a posteriori analyses identified the first mainly in those patients with borderline hypertension at Visits 1 or 2, that is, before starting duloxetine treatment, while the second was identified after careful review of data in the case report forms. None of the identified sustained hypertension cases (n = 7) was considered clinically significant nor reported as an AE. Only one case of orthostatic hypotension (among the eight found a posteriori) was reported as AE, although it was not treatment-related.

Notably, orthostatic hypotension and supine hypertension are frequent symptoms in PD and are known to be part of cardiovascular autonomic dysfunction. Orthostatic hypotension is also a possible side effect of dopamine agonist therapy [26] as well as COMTIs and L-dopa. Therefore, the post-baseline analysis of both these AEs was largely explorative.

Standardized diagnostic DSM-IV criteria (i.e., the MINI interview) and appropriate rating scales for the assessment of the outcome of depression in PD (i.e., the HAM-D-17 and the BDI) allowed a reliable patient selection [27]. Particularly, the high response and remission rates observed on HAM-D-17 seems to suggest the possible efficacy of duloxetine in treating MDD even in complex patients such as PD patients. The changes observed in depressive symptoms were also paralleled by significant improvements in general health status, possibly suggesting that clinicians confirm what is felt by patients.

Sleep quality is often disrupted in patients with PD. Its assessment through the PSQI questionnaire showed a statistically significant improvement, which due to its high amplitude seems to be clinically relevant. Neuropsychiatric symptoms, especially depression, and night-time sleep disorders are among the variables that have the greatest effect on QoL in PD patients [28,29]. Therefore, these results, which need to be confirmed in a randomized trial using also more specific PD sleep questionnaires such as SCOPA-sleep or PD Sleep Scale [30,31], might be of great clinical relevance.

Symptom improvements were observed irrespective of the time of dosing (morning or evening). In this study, allowing physicians to decide the timing of duloxetine administration-mimicked as closely as possible the usual clinical practice, where this decision is based on the different clinical features of the individual MDD PD patient. Furthermore, the decision to start with 30 mg/day of duloxetine for the first week of treatment is justified by previous studies suggesting that initial dosing of 30 mg once daily is better tolerated than the double dose [32-35].

This study provides some evidence in support of the good tolerability of duloxetine administered for 12 weeks in PD patients, but it should be regarded as a preliminary pilot study, particularly when evaluating efficacy results. The open-label design was chosen because it is considered the most appropriate and similar to the usual clinical practice, but the lack of an active comparator or even placebo arm strongly limits the conclusions about efficacy. Furthermore, sleep quality has been assessed with PSQI scale only and it might be worth to see whether the same findings will be obtained also adopting a PD sleep questionnaire.

Randomized controlled clinical trials are needed to compare the acute and long-term tolerability and efficacy of duloxetine with that of other antidepressant drugs commonly used in the treatment of MDD PD patients. Important information is also lacking on long-term response and remission with antidepressant treatment, as well as on the potential interference of these long-term effects with Parkinsonian symptoms.

5. Conclusions

In conclusion, this study showed that a 12-week treatment with duloxetine 60 mg/day was well tolerated in MDD PD patients with no detrimental effects on PD signs and symptoms.

However, these results should be treated with caution because of possible concomitant physical comorbidities other than PD. This fact should drive physicians to prescribe the safest and most appropriate therapy for depression in PD, keeping in mind the possible risk linked to the use of a drug in presence of pre-existing conditions.

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