VORTIOXETINE IMPROVES DEPRESSIVE SYMPTOMS AND COGNITION IN PARKINSON'S DISEASE PATIENTS WITH MAJOR DEPRESSION: AN OPEN-LABEL PROSPECTIVE STUDY

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Introduction

Depression has been strongly associated with Parkinson's disease (PD), with previous studies estimating the prevalence rate to be between 2.7 to 90%[1]. A systematic review found the weighted prevalence of major depressive disorder to be 17% in PD patients, that of minor depression to be 22%, and that of dysthymia to be 13%[2]. Clinically significant depressive symptoms were present in 35% of patients. Depression is a key determinant of a reduced quality of life (QoL) in PD[3]. Depression has also been associated with sleep disturbances, fatigue, cognitive dysfunction, and decreased functional ability with impairment of activities of daily living (ADL)[4]. Despite the magnitude and impact of depression in PD, there is a shortage of properly conducted large, randomized, clinical trials of antidepressants in PD.

The primary objective of the present prospective open-label single-arm study (VOPARK, an open label study of the effectiveness and safety of VOrtioxetine in PARKinson's disease patients with depression) was to analyze the effectiveness of vortioxetine on depressive symptoms in PD patients with major depression (dPD). Secondary objectives were to analyze the effectiveness of vortioxetine on apathy, cognitive function, fatigue, QoL, and functional capacity for ADL in dPD patients, as well as its safety and tolerability[5].

Methods

A total of 30 consecutive dPD patients were included in the study corresponding to eight neurology sites from Galicia (Spain). The study visits included 3 visits: baseline, 4 weeks and 12 weeks. Vortioxetine was administered as a once-daily 10 mg pill, with the possibility of increasing the dose at the neurologist's indication. However, in patients aged ≥65 years old, according to the product data sheet or other considerations made by the neurologist, the first dose should be 5 mg.

Inclusion criteria:

- ✓ Diagnosis of Parkinson's disease according to the United Kingdom Parkinson's Disease Society Brain Bank criteria
- ✓ Diagnosis of major depression according to Diagnostic and Statistical Manual of Mental Health Disorders, 5th Edition (DSM-5) criteria
- ✓ 17-item Hamilton Depression Rating Scale (HAM-D_{17}) score ≥16
- ✓ Undergoing stable dopaminergic treatment and no expectations of dose or drug changes in the next 3 months
- ✓ No dementia criteria
- ✓ Older than 40 years old

Exclusion criteria:

- × Contraindication to being treated with vortioxetine according to the product data to receive at baseline evaluation or to
- × have received up to 15 days before the baseline evaluation a selective serotonin reuptake inhibitor (SSRI) and/or serotonin–norepinephrine reuptake inhibitor (SNRI)
- × Being pregnant and/or breastfeeding
- × Other disabling concomitant neurological diseases (e.g. stroke, severe head trauma, neurodegenerative disease, etc.)
- × Other severe and disabling concomitant non-neurological diseases (oncological, autoimmune, etc.)

Results

Patient demographics:

- The mean time from symptom onset in PD was 4.16 ± 3.11 years. All patients were receiving an antiparkinsonian treatment with a majority on levodopa treatment. Data on patient demographics are illustrated in **(Table 1)**.

Table 1: Data on sociodemographic aspects, comorbidities, antiparkinsonian drugs and other therapies at baseline (N = 30)

Age	66.23 ± 10.27 (48–83)	Family cases of depression (%)	33.3
Gender (males) (%)	73.3	Family cases of PD (%)	26.7
Race (%)			
Caucasian	100	Time from symptoms onset	4.16 ± 3.11 (0.33–11)
Other	0		
		Motor fluctuations (%)	60
Civil status (%):		Dyskinesia (%)	23.3
Married	53.3		
Widowed	23.3	Treatment for PD (%):	
Single	10	Levodopa	96.7
Divorced	10	MAO-B inhibitor	76.7
Other	3.4	COMT inhibitor	23.3
		Dopamine agonist	60
Living style (%)		Amantadine	6.7
With the partner	56.7		
Alone	20	L-dopa daily dose (mg)	505.71 ± 392.56 (0–1910)
With a son/daughter	20	LEDD (mg)	765.25 ± 477.63 (100–2150)
Other	3.3		
		Other treatments (%):	
Habitat (%):		Amitriptiline	6.6
Rural (<5000)	10	Trazodone	10
Semiurban (5000–20,000)	26.7	Mirtazapine	3.3
Urban (>20,000)	63.3	Benzodiazepine	43.3
		Antipsychotic	3.3
Comorbidities (%):		Analgesic	20
Arterial hypertension	40		
Diabetes mellitus	6.7	Number of anti-PD drugs	2.86 ± 1.3 (1–6)
Dyslipemia	36.7	Number of non-PD drugs	2.82 ± 2.8 (0–9)
Hiperuricemia	3.3	Total number of drugs	5.68 ± 2.96 (1–13)
Cardiomyopathy	3.3	Number of pills for PD	4.87 ± 2.26 (1–9.5)
Cardiac arrhythmia	3.3	Number of pills for other cause	2.62 ± 2.49 (0–8.5)
Smoking	6.7	Total number of pills	7.5 ± 2.68 (3–13.75)
Alcohol consumption	0		

The results represent % or mean ± SD (range). COMT, catechol-O-methyltransferase; LEDD, levodopa equivalent daily dose; MAO-B, Monoamine oxidase-B; PD, Parkinson's disease.

Improvements in depressive symptoms:

- **Depressive symptoms were reduced by 53%** as measured via the **HAM-D_{17} total score** (ie. from 21.5 ± 4.75 at baseline to 10.44 ± 7.54 at Week 12) **(Figure1)**

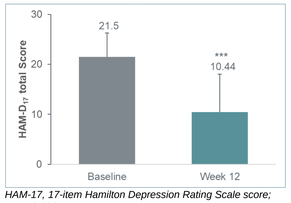
Improvements in cognitive symptoms:

- The Parkinson's Disease-Cognitive Rating Scale (PD-CRS) is a cognitive screening battery that includes subtests to assess cortical and subcortical functions. This battery is composed by a total of 9 task explicitly designed for a brief and separate scoring of: (1) Frontal Subcortical tasks (sustained attention, working memory, alternating and action verbal fluency, clock drawing, immediate and delayed free recall verbal memory); (2) Posterior Cortical tasks (confrontation naming and clock copying)[6]
- **Cognitive symptoms were reduced by 8%** as measured via the **PD-CRS** (ie. from 80.66 ± 19.14 at baseline to 86.81 ± 20.45 at Week 12) **(Figure 2)**

Improvements in quality of life:

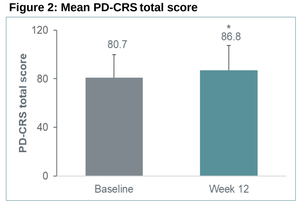
- The 39-item Parkinson's disease Questionnaire (PDQ-39) has eight domains ranging from 0 to 100; being the higher the score, the worse the health- related quality of life[7]
- The **health-related quality of life improved by 24%** as measured via the **PDQ-39** (ie. from 49.56 ± 9.39 at baseline to 38.25 ± 22.6) **(Figure 3)**
- The 8-item indexed shortened version of the World Health Organization Quality of Life Instrument-Abbreviated Version (EUROHIS-QOL8) has eight domains, the higher the score the better the global quality of life[8]
- The **global quality of life improved by 12%** as measured via the **EUROHIS-QOL8** (ie. from 25.1 ± 4.99 at baseline to 28.19 ± 4.38) **(Figure 4)**

Figure 1: Mean HAM-D_{17} total score



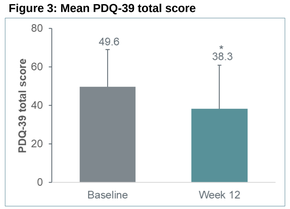
*HAM-17, 17-item Hamilton Depression Rating Scale score; *** p<0.0001*

Figure 2: Mean PD-CRS total score



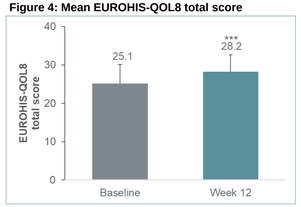
*PD-CRS, Parkinson's Disease Cognitive Rating Scale; *p<0.01*

Figure 3: Mean PDQ-39 total score



*PDQ-39, 39-item Parkinson's disease Questionnaire; *p<0.01*

Figure 4: Mean EUROHIS-QOL8 total score



*EUROHIS-QOL8, 8-item indexed shortened version of the World Health Organization Quality of Life Instrument-Abbreviated Version; ***p<0.0001*

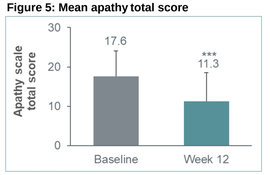
Improvements in apathy and fatigue:

- A **35% reduction in apathy (Figure 5)** and **28% reduction in fatigue (Figure 6)** was observed during the 12-week study period

Improvements in clinical global impression:

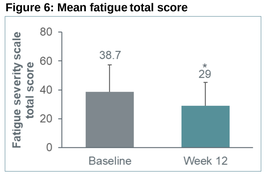
- At Week 12, 23 patients out of 27 **(85%) felt better regarding the patient clinical global impression (PGI-C)**; eight very much improved; nine much improved; six minimally improved; two no changes; and two minimally worse. **Similar improvements** were also recorded with the **clinician clinical global impression (CGI-C) (Figure7)**

Figure 5: Mean apathy total score



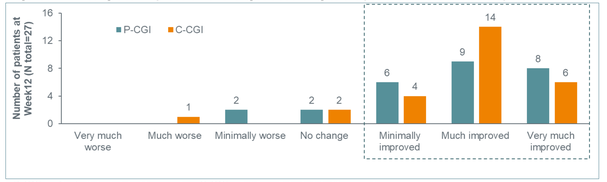
****p<0.0001*

Figure 6: Mean fatigue total score



**p<0.01*

Figure 7: Clinical global impression of changes according to the patient's and clinician's opinion



P-CGI, patient clinical global impression; C-CGI, clinician clinical global impression

Conclusions

By Week 12 post-treatment with 5-20mg/day vortioxetine:

- ✓ 53% significant reduction in depressive symptoms (HAM-D_{17}) were observed
- ✓ Significant improvement in cognitive symptoms (PD-CRS) were observed
- ✓ Significant improvements in health-related (PDQ-39) and global quality of life (EUROHIS-QOL8) were observed
- ✓ 35% significant reduction in apathy and 28% significant reduction in fatigue were observed
- ✓ 85% of patients felt their condition improved according to both P-CGI and C-CGI

In conclusion, this study observed that PD patients improved in terms of their depressive symptoms, cognition, quality of life, apathy, and fatigue, 3 months after starting treatment with vortioxetine. Based on these findings vortioxetine could be a good option for treating depression in patients with PD in clinical practice.

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Disclosures

Informed consent was obtained from all subjects involved in the study. The protocol and the statistical analysis plan are available on request. Deidentified participant data are not available for legal and ethical reasons. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Comité de Ética de la Investigación Clínica de Galicia from Spain (2020/129; 31/MAR/2020). The present study is a study promoted by an independent researcher (promoter: Diego Santos García). Lundbeck Spain has financed its expenses.

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