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Case report

Vortioxetine for the treatment of depressive episodes associated with Parkinson's disease: a case series of six patients

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SUMMARY

Objectives
We present six case reports of patients with Parkinson's disease (PD) at various stages, who experienced major depressive episodes that were successfully treated with vortioxetine.

Methods
The patients whose cases are reported in this manuscript were treated in the setting of daily clinical practice.

Results
Of the six cases presented (2 females and 4 males, aged between 56 and 80 years) three had long-standing PD. The remaining three cases were diagnosed with PD at presentation. Most patients had a history of depressive episodes preceding the onset of the motor symptoms typical of PD, or experienced depressive symptoms concomitantly with the onset of the movement disorder. Most patients had therefore been previously exposed to conventional antidepressant medications. Vortioxetine proved consistently effective on depression and related aspects and was generally well tolerated. Symptoms of depression commonly shown by patients with PD, including apathy, cognitive function and sleep disturbances, responded particularly well to vortioxetine.

Conclusions
These observations suggest that vortioxetine has a potential for the management of depressive episodes occurring in the complex and heterogeneous population of patients with PD. Vortioxetine also appears to be well tolerated when taken concomitantly with antiparkinsonian medications. This potential is worth investigating in adequately designed, prospective studies.

Key words: cognitive function, major depressive, multimodal antidepressant, Parkinson, vortioxetine

Introduction

Depression is one of the most frequently reported neuropsychiatric disturbances in patients with Parkinson's disease (PD) [1], with a prevalence ranging from 20 to 35% [2]. The 1-year incidence of minor depression is 18% [3], and annual rates of newly diagnosed major depression disorder, following the diagnosis of PD, range from 1.9 to 10% [1]. Besides causing distress and affecting quality of life, depressive episodes can negatively impact other disease aspects including motor and cognitive impairments, functional disability, and psychiatric comorbidities [1].

The mechanism behind depression in PD remains poorly understood. Psychological factors and disability are relevant determinants, but neu-

rological factors related to neurodegenerative disease are also involved [1]. Supporting this view is the fact that the neurodegenerative process associated with PD affects not only the dopaminergic system, but also results in the loss of noradrenergic and serotonergic neurons [1]. According to the prevailing hypothesis, changes in all these neuronal systems play a key role in the pathophysiology of depression in PD [2].

Treatment of depression in PD is indicated when depressive symptoms are persistent and contribute to distress or dysfunction [1]. Evidence suggests that multiple antidepressant classes are potentially efficacious in the treatment of depression in PD [4, 5]. For example, according to a recent network meta-analysis including 45 publications (8,890 patients), selective serotonin reuptake inhibitors (SSRIs) were highly effective for the treatment of depression in PD patients and improved activities of daily living and motor function, albeit with a relevant profile of adverse events [6]. Serotonin noradrenalin reuptake inhibitors (SNRIs) emerged as the safest medications with high efficacy for depression, while their effectiveness on activities of daily living and motor function was limited [6].

Vortioxetine is a newer-generation antidepressant that combines two separate modes of action: inhibition of the serotonin (5-HT) transporter and a strong affinity for several 5-HT receptors, potentially leading to enhanced antidepressant activity [7-9]. More specifically, vortioxetine acts as an antagonist at 5-HT_3, 5HT1D and 5-HT_7 receptors, as a partial agonist at 5-HT_{1B} receptors, and as a full agonist at 5-HT_{1A} receptors [7]. The net effect of this pharmacological profile is the enhancement of serotonin, noradrenalin, dopamine, acetylcholine, and histamine levels in specific areas of the brain [10]. A new classification system for psychotropic drugs proposed by a Task Force of the European College for Neuropsychopharmacology classifies vortioxetine as an antidepressant with a multimodal mechanism of action that combines modulation of 5-HT receptor activity with inhibition of the serotonin transporter [7]. Vortioxetine was approved by the US Food and Drugs Administration and by the European Medicines Agency in 2013 for the treatment of major depressive episodes in adults [11,12]. The recommended dose ranges from 5 to 20 mg/day; in patients aged < 65 years and ≥ 65 years the recommended starting dose is 10 mg/day and 5 mg/day, respectively [11].

The efficacy and safety of vortioxetine have been investigated in a comprehensive program of large randomized, double-blind, placebo-controlled, and active-referenced trials [13], including one study conducted in elderly patients (≥ 65 years) [14] and one study investigating vortioxetine for maintenance therapy [15]. These studies have mostly demonstrated statistically significant improvements in overall symptoms of depression in adults with major depressive disorder based on the Montgomery-Åsberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale scores.

A series of trials have specifically investigated the effects of vortioxetine on cognitive symptoms of depression [14,16,17]. An improvement in cognitive function in patients with major depressive disorder was observed in patients aged ≥ 65 years [14]. In this study, patients treated with vortioxetine performed better than the placebo group in cognitive tests (Digit Symbol Substitution Test [DSST]; Rey Auditory Verbal Learning Test scores) measuring processing speed, verbal learning, and memory [14]. These findings were confirmed in successive studies in adult patients [16-18], and in a meta-analysis that compared the cognitive effects of various classes of antidepressants [19].

Overall, clinical trials with vortioxetine (5-20 mg/day) have revealed a favorable safety and tolerability profile. According to an analysis of data pooled from 11 randomized placebo-controlled acute treatment studies (3,018 patients treated with vortioxetine; six studies included venlafaxine as active reference) and five open-label long-term extension studies (2,457 patients treated for up to 52 weeks with vortioxetine), the most common treatment-emergent adverse events associated with vortioxetine were nausea (20.9-31.2%) and vomiting (2.9-6.5%), the incidence of which reached a plateau at 15 mg/day [20]. For vortioxetine, the incidence of treatment-emergent adverse events associated with insomnia and sexual dysfunction was 2.0-5.1% and 1.6-1.8 *versus* 4.0 and 1.0% for placebo, respectively. Vortioxetine had no effect compared with placebo on clinical laboratory parameters, body weight, heart rate or blood pressure. It did not show any clinically relevant effect on electrocardiogram parameters, including the QTcF interval. Long-term treatment with vortioxetine was not associated with new or unexpected adverse events.

As vortioxetine is approved for the treatment of major depressive episodes in adults it was of interest to investigate its potential as a valid treatment option for the management of depression in patients with PD. In this report, we present six cases of patients with PD at various stages, who experienced major depressive episodes that were successfully treated with vortioxetine. All patients described in this case series gave informed consent.

Case reports

Case 1

A 56-year-old man presented to our out-patient clinic because of persistent low mood, anxiety, and insomnia, which he had experienced over the past few months. He had been absent from work for 1 month, had low ap-

petite, and had lost interest in all his usual activities. He was very concerned about his condition, but was unable to react. According to the patient's wife, substantial sleep disturbances, with agitation and screaming, had started well before the onset of low mood. The patient had been prescribed paroxetine for the depressive episode by his physician, which had however been discontinued after 10 days because of nausea, vomiting, and strong agitation. In addition, the patient reported to be feeling physically unwell, with slowness of movements, a slight tremor of the left hand, and a sense of agitation and instability when standing. Another matter of concern to the patient was the fact that his brother had been diagnosed with PD.

The physical exam revealed the typical motor symptoms of PD, including tremor at rest, rigidity and limited mobility of the left upper extremity, as well as a mask-like face expression. A question about his sense of smell revealed that the patient had hyposmia. He had no cognitive impairment related to dementia, as assessed using the Mini-Mental State Examination (MMSE). The diagnosis of PD was confirmed by brain magnetic resonance imaging (MRI), ^{18}F-DOPA positron emission tomography, and laboratory tests. PD was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS). Main depressive symptoms shown by the patient were low mood, anxiety, apathy, and sleep disturbances. These symptoms were severe.

The patient initiated dopaminergic therapy with low-dose levodopa (up to 300 mg/day) combined with rasagiline (1 mg/day). Combined therapy was selected to achieve a rapid and substantial improvement of motor symptoms. The patient was also encouraged to start physical activity. Motor symptoms improved rapidly and substantially. Antidepressant treatment with vortioxetine was initiated after 1 month from presentation. Vortioxetine (10 mg tablets) was selected because of its favorable safety profile in terms of body weight, sexual function, and cognitive function. The initial dose was 5 mg/day (for 7 days), successively increased by 5 mg per week to reach a final dose of 20 mg/day. Alprazolam (0.5 mg tablets) was prescribed to treat anxiety (1/2 of the recommended dose in the morning and 1/2 in the afternoon; full dose in the evening to improve sleep). After 1 month of treatment with the prescribed therapy, the patient had a marked improvement both in motor function and mood. After 3 months, PD assessment showed a substantial improvement across all items of the UPDRS questionnaire, with the best results being achieved for non-motor symptoms, and for apathy in particular. The patient resumed his normal life and discontinued alprazolam during the day. At the last visit (6 months after presentation), the patient continued to be well, with no changes needed in his treatment.

Case 2

A 61-year-old female teacher was referred by her physician to our clinic with a diagnosis of suspected PD. The patient had reported problems with her handwriting, which had become smaller and irregular. She had also noticed slowness and awkwardness in her fine movements, especially with regard to the right extremities. The patient was affected by hyposmia and constipation and had suffered from depression for 4 years. She was in treatment for depression with sertraline (50 mg/day). Over the past year, depressive symptoms had reappeared, despite antidepressant therapy, along with sleep disturbances and anxiety. The medical history of the patient included an intervention of hysterectomy at the age of 48, an intervention of breast lump resection, and thyroid nodules with normal thyroid function. The patient had hypertension and was also in treatment with ACE-inhibitors because of a nephritis event that had occurred when she was 45 years old. The patient's father, who had been affected by PD, had died at the age of 92.

The neurologic assessment revealed mild hypomimia and clumsiness in fine motor skills involving the right upper extremity; gait and arm swings were normal. Brain MRI and thyroid examination did not reveal any abnormality. Six months after presentation, the patient again underwent a physical examination that revealed a worsening of the motor symptoms affecting the right upper extremities. Based on these findings, PD was diagnosed. Neuropsychological assessment did not reveal any abnormality, while assessment of depression using the Beck Depression Inventory (BDI)-II provided a score of 21. Due to the family history of PD, genetic testing for Gaucher's disease was proposed. The patient underwent testing and was found to be a heterozygous carrier of a pathologic mutation in the glucocerebrosidase (GBA) gene (A>G substitution at position 1216 in exon 9 resulting in the substitution Asn409Ser in the enzyme). Given the limited extent of motor symptoms, antiparkinsonian treatment was not initiated. It was decided to discontinue treatment with sertraline due to the lack of efficacy of this SSRI antidepressant. After a few weeks, the patient started treatment with low-dose vortioxetine. Titration to the final dose of 10 mg/day was gradual due to nausea, which resolved rapidly. After a few weeks of treatment with vortioxetine, anxiety, mood, and sleep quality improved. Acceptance of the disease was also improved. As motor symptoms had begun to interfere with the patient's professional activity, it was decided to start a therapy with an inhibitor of monoamine oxidase B (rasagiline 1 mg/day). The therapy was well tolerated and moderately effective on motor symptoms. The patient continued treatment with vortioxetine (10 mg/day) and rasagiline (1 mg/day) with a relatively good control of depressive and motor symptoms.

Case 3

A 60-year-old man was referred to our center for motor symptoms (rigidity and akinesia) affecting his right body side. The patient had been affected by these symptoms for 3 years. Furthermore, 4 years before presentation the patient had also suddenly experienced depressive episodes with symptoms including apathy, lack of initiative, loss of appetite with substantial loss of weight, crying for no reason, and general loss of interest. The onset of depression had been accompanied by the onset of back pain and forward falling while walking. The patient had been diagnosed with asthenia by his physician and had been prescribed S-adenosyl methionine 400 mg/day for 15 days, folic acid 5 mg/day, and Griffonia-based food integrators, without any improvement. He had then been referred to a psychiatrist who diagnosed major depressive disorder and prescribed a treatment with escitalopram (10 mg/day). At the control visit after 30 days, the patient had reported no improvement. He had therefore consulted another psychiatrist who had confirmed the diagnosis of major depressive disorder and prescribed paroxetine (20 mg/day). This treatment had been associated with a modest improvement, mainly of asthenia. Family history was negative for severe neuropsychiatric diseases. The patient's father had died at 70 years of lung cancer.

At presentation, the patient scored 2 on the 5-point Hoehn and Yahr scale for PD staging. The patient also underwent brain MRI that did not reveal any abnormalities. Brain scintigraphy with dopamine transporter (DaT) scan, on the contrary, showed a marked deficiency in receptor tracer uptake at the right striatum, which confirmed the diagnosis of idiopathic PD. The patient started a therapy with transdermal rotigotine (6 mg/day) and levodopa/carbidopa (100 mg/25 mg, three times a day). Paroxetine was replaced by the SNRI venlafaxine (75 mg/day). This treatment was associated with an improvement of depression, but the patient continued to show low acceptance of his condition. He then had an accident at work that caused a relapse of asthenia and depression. Venlafaxine was replaced by vortioxetine (10 mg/day initially, followed by 15 mg/day). In 20 days the patient resumed all his activities and his acceptance of PD improved. The choice of vortioxetine was determined by the multimodal mechanism of action of this molecule and by its favorable profile of adverse events with, possibly, a lack of negative effects on movement. At 9 months from presentation at our clinic, the patient continued to be in treatment with vortioxetine with a beneficial effect on his mood, while motor and cognitive functions were not affected. Depression, assessed using the BDI score, had improved from 22/39 at presentation to 11/39 at the last visit.

Case 4

An 80-year-old male patient, who had been in treatment for 4 years for PD, presented with symptoms of depression. These included marked social withdrawal, anxiety, lack of interests in activities that he used to like (stamp collection and traveling with his wife), and a negative view of the future. The patient was also irritable and verbally aggressive, two traits that he had never shown before. He was not entirely aware of these behavioral changes, which were pointed out by his wife. Depression assessment using the BDI provided a score of 18. PD stage was 2 according to the Hoehn and Yahr scale, while the UPDRS-III score was 28.

The first manifestations of PD, 4 years before when the patient was 76 years old, had been characterized by the typical motor symptoms, including bradykinesia, hypokinesia, rigidity, and asymmetrical rest tremor. These symptoms had been accompanied by severe asthenia and orthostatic hypotension. PD diagnosis had been confirmed by brain MRI and I^{123}-FP-CIT (DaTscan). The medical history of the patient included hypertension, elevated blood cholesterol, valve replacement surgery, and prostatectomy 10 years before due to prostate cancer. For PD the patient had been in treatment with rotigotine (2 mg/day) and selegiline (5 mg/day) with good control of motor symptoms and fatigue. After 2 years, due to the worsening of motor symptoms, antiparkinsonian therapy had been intensified with the addition of low-dose levodopa (100 mg, three times a day), with beneficial effects on motor symptoms. With the intensified therapy the patients was able to resume his normal life and was completely independent in all basic and instrumental activities of everyday life.

For the treatment of depression and irritability, it was decided to use vortioxetine (5 mg/day) after discontinuation of selegiline. At the control visit after 3 months, the patient showed a slight behavioral improvement; according to the patient's wife, irritability and verbal aggressions had decreased. Also reduced was the anxiety towards new activities. The patient confirmed to be feeling better. With regard to motor symptoms, the patient reported a slight but marked improvement especially in the gait that appeared to be more fluid than before, with no differences for fine motor skills alterations. The UPDRS-III score was 19 and was markedly improved compared with the score at presentation. The patient did not report any falls or any other relevant event. Sleep had also improved with a lower frequency of REM sleep behavior disorder. Depressive symptoms improved substantially and only few, minor symptoms were persistent (BDI score, 8). Because of the good response and the good tolerability, the dose of vortioxetine was increased to 10 mg/day, while antiparkinsonian therapy remained unchanged. At the following visit at 6 months from vor-

tioxetine introduction, the patient was stable in terms of motor symptoms (UPDRS-III score, 15). The patient still presented mild left hypokinesia and bradykinesia, with mildly awkward alternate movements, though slightly improved compared with the previous visit. Depressive symptoms were absent according to the Patients' wife (BDI score, 5 at the assessment). Apathy, which had been reported by the patient as well as by his wife, was also substantially improved. Treatment with vortioxetine 10 mg/day was well tolerated with no adverse events, despite the advanced age of the patient and his comorbidities.

Case 5

A 73-year-old female patient, who had been diagnosed with PD 10 years before, presented to our clinic to undergo a planned neurological examination. The patient had a history of mild hypertension and depression. Depression had been successfully treated with venlafaxine (15 mg/day). At presentation the patient was in treatment with levodopa/carbidopa/entacapone (125 mg, 1 tablet 4 times a day) plus pramipexole (2.1 mg/day, extended-release). Other concomitant treatments included the ACE-inhibitor ramipril (2.5 mg/day). Extrapyramidal symptoms were well controlled. Off-time was about 1.5 hours/day. During the day, no dyskinesias were reported. The UPDRS-III was 16, and the PD stage according to the Hoehn and Yahr scale was 2.5. The patient's mood appeared good. The diagnosis of PD was confirmed and the patient continued with her current therapy. The next neurological examination was planned within 5 months.

The planned visit had to be anticipated because of the occurrence of a depressive episode characterized by social withdrawal, anhedonia, negative thoughts, as well as subjective worsening of motor symptoms. The patient's husband confirmed that the patient appeared inattentive, apathetic and less focused. Motor symptoms had only slightly worsened from the previous visit (UPDRS-III, 19; Hoehn and Yahr scale score, 2.5; off-time, 2 hours/day; MMSE 29/30). The neuropsychological exam revealed moderate depression, with normal cognitive function and mildly impaired executive function. It was therefore decided to intensify dopaminergic therapy (levodopa/carbidopa/entacapone (125 mg, 1 tablet 5 times/day) plus pramipexole (same dose as before) and to add antidepressant medication (venlafaxine, up to 150 mg/day). The patient also underwent brain MRI that showed small areas of nonspecific gliosis of the periventricular white matter. At the control after 60 days, no improvement in depression was reported, while motor symptoms had decreased (UPDRS-III score, 11). Body weight had increased by 3 kg, due to greater food intake not directly related to antidepressant therapy. The patient did not perceive any improvement of motor symptoms and had negative feelings about her life expectancy. Neuropsychological findings were similar to those of the previous visit and confirmed the patient's difficulties in concentrating and problem solving. It was therefore decided to discontinue venlafaxine and to introduce vortioxetine (up to 10 mg/day). At the planned visit 3 months after vortioxetine introduction, both the patient and her husband described a substantial improvement with increased attention and ability in daily activities. The patient appeared more focused and motivated. Motor symptoms were stable, with no relevant off-periods. No changes in current antiparkinsonian treatment were therefore made. At the next visit after 3 months, mood improvement and motivation persisted. Neuropsychological assessment revealed a significant improvement in executive function, divided attention and working memory. The patient had lost weight (2.5 kg). Stable motor symptoms, mood control and normal cognitive function were also reported in the following visits.

Case 6

A 73-year-old male patient, diagnosed with PD at the age of 64 years and referred to our center, had developed sleeping disturbances, characterized by difficulties in falling asleep and short sleep duration, loss of appetite, and loss of interest in his daily activities. The patient had a university degree and had occupied until recently an executive position. At presentation, he was taking the antidepressant escitalopram (10 mg/day) added to antiparkinsonian therapy. The addition of antidepressant medication had been suggested by a friend psychiatrist to treat the depressive episode. However, escitalopram had proven ineffective and depression had worsened over the past year.

The patient had hypertension for which he had been prescribed calcium antagonists and angiotensin II receptor antagonists. With regard to his medical history, at 45 he had experienced an episode of major depression that had been successfully treated. At 66, he had undergone prostatectomy. The UPDRS score at PD diagnosis was 8. The patient had started antiparkinsonian therapy with rasagiline followed, after about 2 years, by the addition of levodopa/carbidopa (100 mg, twice daily). This treatment had proven overall effective and had been maintained over the past 9 years, with only minor adjustments. A dopamine agonist (pramipexole) could not be added because it was associated with increased agitation.

At presentation, the patient was in treatment with levodopa/carbidopa (250/25 3/4 tablets, 4 times a day plus 1/2), melevodopa (100 mg, twice daily), rasagiline (1 mg/day), and alprazolam (5 drops 3 times a day). The UPDRS-III score was 23. The patient had a negative view of life, thought his death was imminent,

and expressed the wish to sleep for extended periods during the day. The levodopa/carbidopa dosage was increased to 250/25 mg, 1 tablet 4 times/day; he was also prescribed pramipexole (0.26 extended-release, 1 tablet/day. At the next visit no improvement was reported and the patient's wife requested a new neurological visit. Based on the findings of this visit [UPDRS, 20; MMSE, 24; Columbia University Scale for the evaluation of suicide risk, 9 (no immediate risk of suicide)] the patient was prescribed vortioxetine (10 mg in drop-formulation; 10 drops/day) added to delorazepan (15-20 drops/day) with progressive down-titration and discontinuation of escitalopram. At the next visit after about 20 days, the patient did not report any improvement and said to be feeling slow and foggy; his wife added that the patient was napping for extended periods in the morning and seemed very apathetic. By contrast, nausea and appetite had improved. Blood tests and head CT examination did not reveal any abnormalities. The vortioxetine dose was increased (15 drops/day), while the delorazepan treatment was maintained unchanged. After about 1 month, the patient showed a marked improvement in mood and sleep duration in the night; also improved were daytime somnolence, motor performance (UPDRS, 17), and cognitive function (MMSE, 29). The patient was no longer thinking about death and had resumed his daily activities. At the last visit, after about 1 month, motor UPDRS score was 19, and MMSE score was 29. No dyskinesias were reported.

Discussion

Patients affected by PD frequently experience depressive episodes as comorbidity, which can negatively influence the course of motor disease and the occurrence of other neuropsychiatric disturbances. Currently, there are no guidelines for the treatment of PD-associated depression, and no optimal therapy has been identified to date. Treatment for depression should therefore be chosen based on the patient's medical status, severity of depression, patient's preference, and neurologist's expertise in using antidepressants [3]. To our knowledge, this is the first time the use of vortioxetine has been described for the treatment of major depressive episodes in patients with PD. Overall, the present case series highlights the relevance of this non-motor comorbidity in the management of patients with PD. PD-related depression needs to be promptly recognized and assessed by appropriate tools. The effective treatment of depressive episodes may have a positive impact on motor and non-motor manifestations of the disease, including cognitive changes (cases 5 and 6), sleep disturbances (cases 2 and 5), and apathy (cases 1 and 4). Of the six cases presented (2 females, 4 males, age ranging from 56 to 80 years) three had long-standing PD (cases 4, 5, and 6). In the remaining three cases, PD was diagnosed conclusively at presentation. With the exception of case 4, all patients had a history of depressive disorder with the onset of motor symptoms, or experienced depressive episodes concomitantly with the onset of PD motor symptoms. All patients with a history of depression had already been treated with antidepressant medications (mostly SSRIs and SNRIs). In the six cases described, the choice of vortioxetine was motivated primarily by its relatively favorable safety and tolerability profile compared with that of other antidepressant medications [20]. The favorable safety and tolerability profile of vortioxetine was confirmed in our case series with no reports of unexpected or unacceptable adverse events. This was true also for an 80-year-old patient (case 4) who had never been previously exposed to antidepressant medication.

Although the case series described here was heterogeneous, especially in terms of medical history and PD characteristics, among neuropsychiatric disease manifestations there was a remarkable prevalence of apathy. Apathy responded well to treatment with vortioxetine. Thanks to a rapid and substantial response, patients were able to resume their daily activities, with a positive impact on other depression- and PD-related outcomes. Apathy, defined as a substantial loss of motivation not caused by emotional distress, cognitive impairment, or diminished level of consciousness, is common in neurocognitive disorders [2]. In PD, apathy can manifest early and its prevalence ranges between 16.5 and 40% [2]. Risk factors are severe motor symptoms and cognitive decline [2]. A recent prospective randomized trial compared, for the first time, the efficacy of SSRIs (paroxetine, escitalopram) and an SNRI (duloxetine) in improving depressive symptoms and apathy, as well as gait instability, in patients with PD (n = 55) [5]. The study found that both depressive and motor symptoms were significantly improved from baseline to 10 weeks by the two antidepressant classes, with no statistically significant differences between treatment groups. A tendency for reduced apathy was observed at 10 weeks with both SSRIs and the SNRI, but the changes from baseline to 10 weeks did not reach statistical significance. Therefore, the effectiveness of the SSRI and SNRI classes on PD-related apathy is currently unclear.

Case 2 describes the effective treatment of depression with vortioxetine in a patient affected by PD with a GBA mutation. Gaucher's disease is a lysosomal storage disorder caused by a mutation in the gene encoding for the enzyme GBA. Heterozygous carriers do not present the disease, but have a 20- to 30-fold increased risk of developing PD compared with wild-type individuals [21]. At the same time, at least 7% of people affected by PD have mutations in the *GBA* gene [22], with a pattern of protein accumulation similar to that of idiopathic PD and

parkinsonism caused by storage of alpha-synuclein [23]. Patients with PD and mutations of the *GBA* gene are not clinically distinct from patients with idiopathic disease (identical neuroimaging findings, including functional studies related to the dopaminergic system) [24]. In case 2, the antidepressant therapy was changed before discovering that the patient carried a *GBA* mutation. The ineffective SSRI was replaced by the newer-generation antidepressant, vortioxetine.

The patient in case 5 was treated in a center for movement disorders because of the prevalence of motor symptoms over other PD-related comorbidities. Over time, the patient also developed mood and cognitive disturbances. The patient had a history of major depression that had been successfully treated with venlafaxine. Her current treatment with venlafaxine, however, failed to alleviate the depressive symptoms. At the current stage of PD, depressive symptoms were associated with executive dysfunction and were distinct from those experienced several years before. This may explain why venlafaxine, which has no demonstrated effect specifically on executive function, was no longer effective. By contrast, multimodal vortioxetine was presumably able to improve mood symptoms via its action on cognitive and executive functions. The effects of vortioxetine on cognitive performance are well documented. The early findings by Katona and coworkers in patients aged ≥ 65 years, who underwent a series of cognitive tests addressing processing speed, verbal learning, and memory [14], were confirmed in a large adult population [17]. In this study, the effect of vortioxetine on cognitive performance was shown to be a direct effect of vortioxetine on cognition and not the consequence of the antidepressant response [17]. A more recent study in patients with acute recurrent major depressive disorder, who self-reported cognitive dysfunction, compared the effect of vortioxetine with placebo on cognitive functioning, including specific measures of attention, executive functioning, and psychomotor speed [16]. The study was active-referenced (duloxetine). Vortioxetine produced significant improvements compared with placebo on cognitive function as measured by the DSST (primary endpoint), a sensitive and widely used test that targets multiple domains of cognition. Vortioxetine was also statistically superior to placebo on other cognitive outcomes tested (perceived deficits questionnaire [PDQ], physician-assessed clinical global impression [CGI-I], University of San Diego performance-based skills assessment [UPSA]) and on depression (MADRS). Path analysis indicated that the cognitive benefit was a direct treatment effect rather than due to alleviation of depressive symptoms. Duloxetine was not significantly different from placebo in terms of DSST or UPSA scores, but was superior to placebo on the PDQ, CGI-I and MADRS assessments. A recent network meta-analysis assessing the relative effect of antidepressants on cognitive dysfunction in major depressive disorder focused on 12 randomized controlled studies using the DSST [19]. The analysis found that vortioxetine was the only antidepressant that improved cognitive dysfunction as assessed with the DSST versus placebo. In addition, vortioxetine was statistically more efficacious than escitalopram, nortriptyline, SSRI and tricyclic antidepressants on the DSST.

Case 6 documents the importance of sleep disturbance and its proper management. Insomnia (which is frequent in PD patients) [25] has also been associated with depression. Sleep disturbance can manifest as difficulty in falling asleep or maintaining sleep. In this case, vortioxetine improved night sleep and reduced daytime sleepiness, in addition to exerting the expected antidepressant effects.

It must be highlighted, however, that there are a number of limitations associated with case series. As results are reported retrospectively, there may be gaps in the availability of data records. The observations described may also be subject to selection bias, which, along with the lack of a control arm, prevent the generalization of treatment outcomes to larger patient populations. Nonetheless, the present case series contains useful information, not only in a research perspective, but also in clinical practice. Indeed, the preliminary data reported here provide support for future undertaking of adequately designed, prospective, double-blind, randomized controlled trials to better assess the role of vortioxetine in PD-associated major depressive disorder.

Conclusions

The observations presented in our case series suggest that vortioxetine may be a valid option for the management of depression in the complex and heterogeneous population of patients with PD. Consistent with evidence from clinical trials, treatment was easy to implement, safe, and well tolerated in these patients, who were all receiving polytherapy for PD and other comorbidities. Further support for the favorable safety and tolerability profile of vortioxetine is the fact that three of the patients were aged > 70 years while one patient was naïve to antidepressant medications. The role of vortioxetine in PD-associated major depressive disorder needs to be further investigated in adequately designed, prospective studies.

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Compliance with Ethics Guidelines

The patients whose cases are reported in this manuscript have been treated in the setting of daily clinical practice, and not as part of a clinical study of any kind. They represent a retrospective analysis and, according to Italian law, no approval from an Ethics Committee or institutional review board is required.

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