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Brief Report

Tolerability of Paroxetine in Parkinson's Disease: A Prospective Study

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Summary: Depression is a common finding in patients with Parkinson's disease (PD). Traditionally, depression has been treated with tricyclic antidepressants, which are often associated with undesirable side effects that may limit their use in PD. Few studies have been performed with selective serotonin reuptake inhibitors (SSRIs) in these patients. We assessed the tolerability of the SSRI antidepressant paroxetine (10–20 mg once per day) in 65 outpatients with PD and depression for a period of at least 3 months. Treatment was continued for 125.3 ± 89.6 days (mean ± standard deviation) in 52 patients. In these subjects the Hamilton Disease Rating Scale improved from 21.7 ± 6.4 to 13.8 ± 5.8 ($p < 0.001$). Overall, 13 patients stopped paroxetine after 9.6 ± 10.6 days because of adverse reactions. Two patients reported increased "off" time and tremor that reversed after treatment was stopped. No risk factors for intolerance were identified. Paroxetine is a safe and effective drug to treat depression in PD. **Key Words:** Depression—Parkinson's disease—SSRI—Paroxetine—Safety—Tolerability.

The most frequent neuropsychiatric symptom in Parkinson's disease (PD) is depression, which is observed in up to 46% of patients with PD.[1]

Until recently, depression was treated mainly with tricyclic antidepressants (TCAs), which are associated with side effects such as postural hypotension, and memory and cognitive impairment.[1,2] These side effects limit their use, particularly in PD in which cognitive decline and dysautonomic symptoms often coexist.[3,4]

The introduction of selective serotonin uptake inhibitors (SSRIs) has offered a new means with a more positive adverse effect profile to treat depression in PD. However, a recent review of the literature identified 127 reports of SSRI-induced movement disorders, including 25 cases of parkinsonism, which caused discontinuation of SSRI treatment in 14 patients.[5] In addition, several reports have suggested that worsening of motor conditions may occur in patients with PD who were treated with SSRIs.[6,7]

One possible explanation is that these drugs increase central serotonergic activity which may inhibit dopamine release in the striatum. This could be critical in PD in which dopamine levels are already reduced by the disease process.[8]

Paroxetine has been shown to be an effective and safe SSRI both in the general population and in the elderly; it is more effective and better tolerated than TCAs.[9]

To better evaluate the tolerability and safety of SSRI treatment in PD, we have prospectively evaluated a group of depressed patients treated with paroxetine for at least 90 days, closely monitoring them to assess whether changes in their motor performance occurred during this period.

METHODS

Sixty-five consecutive outpatients in various stages of PD were included in the study. They all had depression diagnosed according to *Diagnostic and Statistical*

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Manual of Mental Disorders, 4th edition (DSM-IV) criteria and had a Hamilton Depression Rating Scale (HDRS) score >16. All patients had been on constant maintenance doses of their antiparkinsonian medication for at least 6 weeks before study entry. Patient clinical characteristics are listed in Table 1.

Patients were given a starting dose of 10 mg paroxetine once per day, which was increased to 20 mg once per day after 4 weeks. The duration of treatment was 3 months. Patients who tolerated paroxetine were allowed to continue treatment after the study ended, when additional therapeutic benefit was expected from continuation of the drug.

Antiparkinsonian medications were held constant throughout the study.

At baseline, parkinsonian and depressive symptoms were evaluated by means of the Unified Parkinson's Disease Rating Scale (UPDRS) and HDRS, respectively. The UPDRS scores were assessed 1 to 2 hours after the first morning dose of levodopa and/or a dopamine agonist. A physical examination was performed and general information was collected concerning any concomitant disorders and general well-being. Patients were monitored by regular telephone calls every 2 weeks; questions concerned severity of parkinsonian symptoms, general well-being, and compliance with study treatment. They were instructed to return to the center after 3 months or earlier in the event of undesirable effects. At the post-treatment visit the UPDRS and HDRS evaluations as well as the physical examination were repeated; information was collected on concomitant disorders, general well-being, and compliance with study treatment. Patients who continued treatment after the end of the study were monitored by regular phone calls every 4 weeks.

The primary parameter for the assessment of drug tolerability was the number of patients withdrawn from the study because of adverse reactions.

The mean values of the main clinical features (age, sex, Hoehn & Yahr stage, mean "on" motor UPDRS score, concomitant antiparkinsonian treatment) of patients who had tolerated paroxetine well and had completed the study were compared with those in the group who had withdrawn prematurely because of adverse reactions. These numbers were tabulated and analyzed descriptively. Any differences were to be analyzed further by means of analysis of variance.

RESULTS

Fifty-two (80%) patients completed the planned treatment period of 3 months. All of them took the study medication as prescribed.

The remaining 13 (20%) stopped paroxetine treatment prematurely after a period of 11.8 ± 11.7 days (mean ± standard deviation; range, 1–30 days); six of 13 (9.2% of the total) withdrew after no more than 2 days of treatment. The reason for withdrawal in each case was because of adverse reactions. These are listed in Table 2.

All adverse reactions developed within the first month of treatment and were reversible when treatment was stopped, including the effects on motor conditions, which resolved within 2 days.

TABLE 1. *Demography, severity of Parkinson's disease, and concomitant treatment at baseline*

Characteristics	All patients (n = 65)	Completed patients (n = 52)	Withdrawn patients (n = 13)
Age (yrs, mean ± SD)	65.1 ± 8.5	66.6 ± 7.8	59.2 ± 9.3
Sex (% M/F)	38.5/61.5	40.4/59.6	30.8/69.2
Disease duration (yrs, mean ± SD)	6.3 ± 3.8	6.9 ± 3.9	4.0 ± 2.8
Hoehn & Yahr stage (mean ± SD)	2.5 ± 0.8	2.6 ± 0.7	2.0 ± 0.9
Motor UPDRS score in "on" conditions (mean ± SD)	25.4 ± 10.8	26.7 ± 10.4	20.1 ± 11.3
HDRS score (mean ± SD)	20.6 ± 3.1	21.7 ± 6.4	19.2 ± 2.8
Levodopa (% patients)	89.2	96.2	61.5
Dosage of levodopa (mg/day, mean ± SD)	553.2 ± 261.4	549.1 ± 257.7	534.4 ± 302.0
Dopamine agonists	58.4	57.7	61.5
Bromocriptine	1.5	2.0	0
Pergolide	30.8	28.8	38.5
Ropinirole (% patients)	26.1	26.9	23.0
Other antiparkinsonian agents (% patients)	32.3	30.8	38.5

SD, standard deviation.

Characteristics of the patients with Parkinson's disease treated with 10 to 20 mg paroxetine for moderate depression: comparison among the whole cohort and two subgroups (completed patients, who tolerated SSRI treatment, and patients withdrawn because of adverse reactions). Levodopa was combined with either benserazide or carbidopa, whereas the dopamine agonists included 3 to 17.5 mg ropinirole per day, 0.75 to 2.25 mg pergolide per day, and 15 mg bromocriptine per day. Other antiparkinsonian agents included amantadine, metixene, selegiline, tolcapone, and trihexyphenidyl.

TABLE 2. *Adverse reactions to paroxetine*

Description	No. of patients
Anxiety	4 (6.2%)
Nausea*	4 (6.2%)
Increased "off" time duration and exacerbation of parkinsonian tremor	2 (3.1%)
Agitation	1 (1.5%)
Confusion	1 (1.5%)
Headache	1 (1.5%)

* Associated with diarrhea in one case.
Adverse reactions that caused discontinuation of treatment with paroxetine.

The characteristics of the patients who withdrew prematurely because of adverse reactions were compared with those of the patients who completed the study. Patients who withdrew because of adverse reactions tended to be younger and to have less severe PD of shorter duration that was treated less frequently with levodopa. However, these differences were not statistically significant (Table 1).

In the patients who completed the study, paroxetine induced a significant improvement in the HDRS score, which diminished to 13.8 ± 5.8 ($p < 0.001$). The reduction mainly regarded anxiety and sleep-related symptoms.

At the end of the study, treatment was discontinued in 25 patients because the desired therapeutic benefit had been achieved and maintenance treatment was deemed not necessary. Treatment was continued in 27 patients (41.5%). The total duration of treatment in the patients who tolerated paroxetine was 155.8 ± 88.4 days (mean ± standard deviation; range, 90–365 days).

DISCUSSION

Our results suggest that paroxetine is a safe therapeutic option for the treatment of depression in patients with PD. No severe adverse reactions occurred and all the undesirable effects observed resolved completely within 48 hours after discontinuation of the drug. Moreover, none of the undesirable effects recorded were unexpected, including the two cases (3%) of worsening of PD symptoms.

These results apply to the therapeutic regimen given in this study, which consisted of a starting dose of 10 mg to test tolerability, increased to the lowest effective dose in depression (20 mg) after 4 weeks of treatment. We cannot make any statements related to the tolerability of further increases in daily dosage up to the highest recommended daily dose of 50 mg once per day.

To our knowledge, this is the largest prospective study on the tolerability of SSRI treatment for depression in PD. It is also one of the few studies in the literature with the assessment of the tolerability of an SSRI antidepressant as the primary objective.

Few studies have been performed with antidepressants in patients with PD. An extensive literature search for a recent meta-analysis identified only 12 controlled studies overall and none with SSRIs.[10]

There appears to be only one fully published study concerning the tolerability of an SSRI in PD as the primary objective, namely, a retrospective chart review of 23 outpatients all treated with fluoxetine.[11] Three cases (13%) of worsening of parkinsonian symptoms were found, more than in our study (two cases, 3%). The difference may be the result of different assessment methods, the use of a different SSRI, or, more likely, to chance, because their sample size was small.

There does not appear to be any information in the literature on additional risk factors for SSRI-induced movement disorders. Increased serotonergic activity may inhibit dopamine release from dopaminergic neurons[8]; consequently, patients with neuronal diseases that reduce dopaminergic activity, such as PD, appear to be at greater risk. A few reports have suggested that female gender and age ≥60 years might be predisposing factors, besides PD.[12] Our findings do not support these reports, because we found only a modest trend with age, but in the opposite direction.

Levodopa was given less frequently to patients who withdrew from the study. This suggests that the adverse reactions to treatment were not the result of an interaction between paroxetine and this antiparkinsonian agent. No interaction was observed across a wide range of other antiparkinsonian agents, including dopamine agonists, which were received by similar proportions of completed and withdrawn patients.

Another hypothesis put forth in the literature on the basis of the case reports is that SSRI-induced parkinsonism seems to occur within the first month of treatment.[12] Indeed, the two cases observed in our study occurred within this time period. This is an important finding because it suggests that patients with PD should be monitored more closely during the first month of SSRI antidepressant treatment to detect possible exacerbations of PD.

In theory, it would seem reasonable to extrapolate all our data on paroxetine to the SSRI class, because the adverse event profile of paroxetine is broadly similar to that of other SSRIs.[9] However, in view of the paucity of data on other SSRIs in PD, and the practice of evidence-based medicine, this extrapolation appears to be premature.

In conclusion, paroxetine is a safe therapeutic option for the management of depression in PD at daily doses of 10 to 20 mg once per day. Although sporadic and transient motor worsening may develop in some patients, it does not seem possible to predict which patients may be more susceptible. Placebo-controlled studies are required to confirm this finding.

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