Published in final edited form as:

J Neuropsychiatry Clin Neurosci. 2006 ; 18(3): 377–383.

Escitalopram for Major Depression in Parkinson's Disease: An Open-Label, Flexible-Dosage Study

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Abstract

Depression and antidepressant use are common in Parkinson's disease, but the benefit of selective serotonin reuptake inhibitor (SSRI) treatment in this population has not been established. The authors treated 14 Parkinson's disease patients with major depression with escitalopram in an open-label study. Although treatment was well tolerated and correlated with a significant decrease in Inventory of Depressive Symptomatology score, response and remission rates were only 21% and 14%, respectively. However, half of the subjects met Clinical Global Impression-Improvement criteria for response. In Parkinson's disease, either SSRIs may have limited antidepressant effects, or the use of existing depression diagnostic and rating instruments may be problematic.

Parkinson's disease, the second most common neurodegenerative disease, is often accompanied by neuropsychiatric complications, including depression. Prevalence estimates for depression in Parkinson's disease typically range between 20% and 40%,¹ depending on the population studied, the types of depression included, and the criteria used for symptom attribution (i.e., inclusive versus etiologic criteria).

Approximately 20% to 25% of Parkinson's disease patients are on an antidepressant at any given time, most commonly a selective serotonin reuptake inhibitor (SSRI).² The efficacy of SSRIs for the treatment of depression in Parkinson's disease has not been demonstrated, as both placebo-controlled studies published to date yielded negative findings.^{3,4} A number of open-label studies with various SSRIs for the treatment of depression in Parkinson's disease found treatment to be beneficial,^{5–10} but results often were reported either for completers only or without outcome data.^{5,6,8,9}

In addition to questions about efficacy, concerns exist about the impact of SSRI treatment on motor symptoms. In non-Parkinson's disease patients, SSRI-induced akathisia, dystonia, parkinsonism, and tardive dyskinesia-like states have been reported.¹¹ In Parkinson's disease, anecdotal experience² and retrospective reviews¹² suggest that SSRIs can worsen motor symptoms in some patients. The results of open-label treatment studies suggest that SSRI treatment does not worsen parkinsonism overall, but these studies analyzed data only for those who completed the study.^{5,6,8}

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Supported by a grant from the Forest Laboratories, Inc., Jersey City, NJ.

Several other nonmotor disorders commonly co-occur with depression in Parkinson's disease, including anxiety,¹³ executive impairment,¹⁴ psychosis,¹⁵ apathy,¹⁶ and affective lability,¹⁷ but it is not clear whether they are affected by antidepressant treatment or moderate treatment response. Regarding anxiety, there is preliminary evidence that SSRI treatment improves anxiety symptoms in the context of depression in Parkinson's disease.¹⁰ Regarding cognitive function, SSRI treatment does not appear to worsen global cognition (i.e., Mini-Mental State Examination score),¹⁰ but its impact on executive and memory abilities, specifically, has not been studied.

Escitalopram, the *S*-enantiomer of citalopram, is approved for the treatment of major depression. At daily dosages of 10 to 20 mg, it is equivalent in efficacy to citalopram, has a low incidence of side effects, and has minimal drug-to-drug interaction.¹⁸ These latter properties make escitalopram an attractive drug for use in Parkinson's disease patients, who typically take multiple medications and experience numerous somatic symptoms. We report results of an open-label, flexible-dosage study of escitalopram treatment for major depression in Parkinson's disease.

METHOD

Subjects

Subjects were patients with Parkinson's disease who were being seen for routine psychiatric care or were screened for depression as part of an ongoing research study at the Parkinson's Disease Centers at the Philadelphia Veterans Affairs Medical Center (PVAMC) or the University of Pennsylvania. Patients with a diagnosis of possible or probable idiopathic Parkinson's disease,¹⁹ confirmed by a movement disorders specialist (M.B.S. or J.D.), a Mini-Mental State Examination (MMSE)²⁰ score of >24, a DSM-IV diagnosis of a major depressive episode when interviewed with the Structured Clinical Interview for DSM-IV (SCID),²¹ and a 24-item Hamilton Depression Rating Scale (HAM-D)²² score of ≥ 16 met primary study inclusion criteria. Exclusion criteria included a recent history of substance abuse or any other DSM-IV Axis I diagnosis besides major depression. Patients taking stable doses of benzodiazepines were allowed to participate. For patients taking an antidepressant at screening, a 2-week washout period was necessary before baseline (4 weeks for fluoxetine). An inclusive scoring method was used for all diagnostic and rating instruments. The study was approved by the PVAMC and the University of Pennsylvania Institutional Review Boards, and all subjects gave written informed consent.

Study Design

The study was a 12-week open-label trial of escitalopram. Subjects started escitalopram at 10 mg/day, and the dosage was increased to 20 mg/day after 4 weeks if treatment was well-tolerated and the subject had not been rated as "very much improved" or "much improved" on the Clinical Global Impression-Improvement (CGI-I).²³ The dosage could be decreased to 5 mg/day at any point, if clinically indicated. Study visits were at end of Weeks 2, 4, 6, 8, and 12.

Assessments

At baseline and all study visits, a trained research assistant administered the Hamilton Depression Rating Scale (HAM-D), Inventory of Depressive Symptomatology (IDS),²⁴ and Hamilton Anxiety Rating Scale (HAM-A).²⁵ The Apathy Scale¹⁶ and the Center for Neurologic Study-Lability Scale (Lability Scale)²⁶ were administered at baseline and at study completion. The principal investigator (Dr. Weintraub) administered the Unified Parkinson's Disease Rating Scale (UPDRS),²⁷ including the Hoehn and Yahr stage,²⁸ four times during

the course of the study and the CGI-I at all post-baseline visits without knowledge of any other study ratings.

We also assessed patients with a series of neuropsychological instruments at baseline and study completion, including the MMSE, Hopkins Verbal Learning Test–Revised (HVLT-R),²⁹ Tower of London-Drexel (TOL^{DX}),³⁰ and Trail Making Test A and B (TMT-A and TMT-B).³¹ The HVLT-R assesses verbal learning and memory; TOL^{DX} assesses planning, problem-solving and working memory; TMT-A assesses psychomotor speed; and TMT-B assesses mental tracking and cognitive flexibility.

Data Analysis

A priori, the primary outcome measures were designated as the change in the IDS score and the final CGI-I score, and the change in HAM-D score was a secondary outcome measure for depression. The IDS is a 30-item instrument (scores ranged from 0 to 84, higher scores indicating greater severity of depression) that covers a broader range of depressive symptoms than the HAM-D³² and therefore may possibly be a more sensitive instrument for measuring depression severity.

Intent-to-treat analyses with last observation carried forward were performed, and all subjects who took at least one dose of study medication were included (N=14). Response for the primary outcome measures was set as a $\geq 50\%$ decrease in IDS score or a score of 1 or 2 on the CGI-I, while remission was set as an IDS score < 14 , as recommended.²⁴ For the HAM-D, response was set as a $\geq 50\%$ decrease in score, and remission was set as a score ≤ 8 . For the IDS, HAM-D, and HAM-A, repeated measures of analysis of variance (rANOVA) were performed and 95% confidence intervals (CIs) were calculated for the change in score; for all other measures, we performed the Wilcoxon signed-ranks test. For correlations, we used Spearman's rank correlation (r_s). As this was a pilot study to probe for moderators of treatment response, we did not make a correction for multiple comparisons; a p value of < 0.05 was considered significant.

RESULTS

Subject Characteristics

Fourteen subjects (13 men, one woman) entered the clinical trial, and 12 completed it. Mean values included: age = 72.1 (SD=8.0) years, duration of Parkinson's disease=5.4 (SD=4.3) years, Hoehn and Yahr stage =2.8 (SD=0.5), and years of education =14.0 (SD=2.6).

Based on baseline IDS and HAM-D values, subjects on average had major depression of moderate severity (Table 1). They also experienced elevated levels of anxiety, apathy, and affective lability. Cognitively, subjects scored in the average range on the MMSE and the HVLT-R ($z=-0.53$ and -0.80 on the HVLT-R immediate and delayed free recall tests, respectively), but had low average or impaired scores on tests of executive function ($z=-1.33$ on TMT-B; $z=1.69$ on TOL^{DX}-TMS; $z=2.14$ on TOL^{DX}-EXTS).

Affect Measures

There were significant decreases in both IDS ($F = 4.29_{5,9}$, $p = 0.03$) and HAM-D ($F = 7.77_{5,9}$, $p < 0.01$) scores over the course of the study (Table 1 and Figure 1). The mean decrease in IDS score was 7.8 units (95% CI=3.0, 12.6), equivalent to a 25.9% decrease. Similarly for the HAM-D score, the mean decrease was 7.5 units (95% CI=3.1, 11.9), equivalent to a 37.7% decrease over the course of the study.

Examining rates of response and remission, 21.4% of subjects met criteria for response and 14.2% for remission using the IDS, and 35.7% met criteria for both response and remission using the HAM-D (i.e., all HAM-D responders were also remitters). On the CGI-I, 50.0% of subjects met criteria for response, with no subjects reporting worsening in their condition.

All significant improvement in depression occurred by either Week 4 (using the HAM-D) or Week 6 (using the IDS) (Figure 1). All but one of the seven subjects who were rated as responders on the CGI-I had achieved this score by Week 6.

Other Non-Motor Measures

There was a suggestion of a decrease in HAM-A score with treatment ($F=3.45, 9, p=0.05$), with a mean decrease in score of 2.7 units (95% CI=0.7, 6.1), equivalent to a 22.2% decrease, but there were no changes in the Apathy Scale or Lability Scale with treatment (Table 1). Regarding cognition, there were no changes in global cognition (i.e., MMSE score), memory, or executive function over the course of the study.

Motor Measures and Tolerability

There were no significant changes in motor symptoms or psychomotor speed with escitalopram treatment, though there was nearly a five-point drop in the total UPDRS motor score and a suggestion of improvement on the tremor and rigidity subscales (Table 1). In addition, the mean daily L-dopa dosage remained the same (459 versus 512 mg/day, $z=-1.1, p=0.27$). Regarding adverse events, two subjects terminated within several days of starting antidepressant treatment due to worsening of baseline nausea and confusion, respectively. All subjects who completed the study were able to tolerate either 10 or 20 mg of escitalopram daily.

Moderators of Treatment Response

We examined the association between baseline clinical characteristics and improvement in depression for 12 variables (Apathy Scale,¹ Lability Scale,¹ HAM-A,¹ HVLT-R scores,³ TOL^{DX} scores,² and UPDRS sub-scores⁴). Higher Apathy Scale ($r_s=-0.66, p=0.01$) and lower HVLT-R delayed free recall ($r_s=0.68, p<0.01$) scores at baseline were associated with less improvement on the IDS. Regarding motor symptoms, greater baseline postural instability was associated with less improvement in HAM-D ($r_s=-0.56, p=0.04$) and IDS ($r_s=-0.58, p=0.03$) scores.

DISCUSSION

We found that open-label escitalopram treatment was well tolerated in the treatment of major depression in Parkinson's disease, but most patients experienced only a partial response. Probing for moderators of treatment response, we found that certain nonmotor (greater apathy and poorer verbal memory) and motor (less postural stability) symptoms were associated with worse outcomes.

There are several limitations to this study. First, it was open-label with a small number of subjects, so any statements about the effects of treatment must be considered speculative. Second, the population was nearly all male and received specialty care. Third, the mean age was relatively high compared with other treatment studies for depression in Parkinson's disease. Fourth, when probing for moderators of treatment response, a correction for multiple comparisons was not made. Thus, the results of this study cannot be generalized to the Parkinson's disease population at large and are best used to generate hypotheses to test in future large-scale controlled studies.

A study-specific factor that may have contributed to the limited antidepressant response was the relatively high mean age of our sample compared with previous studies in Parkinson's disease. There is research suggesting that very old (i.e., ≥ 75 years of age) depressed patients may have a more limited response to SSRI treatment.³³

Though age may have played a role in our findings, our results suggest a limited response to SSRI treatment of depression in Parkinson's disease. Although most open-label antidepressant studies for depression in Parkinson's disease have reported significant improvements in depression rating scale scores with SSRI treatment,^{5–10} mean decreases in such scores have only been between 27% and 38%.^{7,9,10} This is in contrast to results reported for large open-label studies in non-Parkinson's disease elderly patients. For instance, in the largest open-label SSRI study to date for geriatric depression, the mean decrease in depression rating scale score was 61%.³⁴ In large-scale comparison studies for geriatric depression, both response rates and mean decreases in depression rating scale scores for patients treated with an SSRI are typically $>50\%$.^{35–38} If there is a limited response to SSRI treatment in Parkinson's disease, possible explanations include disease-related pan-monoaminergic deficiencies and disruptions in key cortico-striatal pathways,^{39–42} both of which may impair the ability of the Parkinson's diseased brain to respond appropriately to traditional anti-depressants.

Other possible explanations for the limited response to antidepressant treatment relate to complexities in the diagnosis and rating of depression in Parkinson's disease. For instance, symptom overlap between depressive symptoms and core Parkinson's disease symptoms is well known,¹ and diagnostic inaccuracies may have led to the inclusion of non-depressed patients in the study. In addition, numerous items on the IDS and HAM-D query about symptoms which occur commonly in Parkinson's disease without depression (e.g., fatigue, insomnia, problems with concentration, decreased activity level, and psychomotor slowing), so suboptimal instrument specificity and sensitivity may have limited our ability to detect a treatment response. In support of this explanation, we did find that more patients were considered CGI-I responders than IDS and HAM-D responders, possibly because the CGI-I scale instructs the rater to make a global determination of improvement after weighing all relevant factors.

Regarding the time course of response, there was no significant improvement in depression rating scales or CGI-I ratings after 4 to 6 weeks of treatment. This suggests that Parkinson's disease patients who have not responded to 6 weeks of SSRI treatment at an adequate dosage are not likely to respond to an extended trial.

The small change in HAM-A scores over time contrasted with previous SSRI studies reporting significant improvement in comorbid anxiety in depression in Parkinson's disease.^{9,10} Similar to the possible limitations in using existing depression rating scales in Parkinson's disease, the HAM-A may not be the ideal anxiety measure in Parkinson's disease, as it is heavily weighted toward autonomic symptoms.

Escitalopram treatment did not adversely affect cognitive abilities, suggesting that SSRI treatment in Parkinson's disease is well tolerated from this standpoint. This stands in contrast to concerns about using therapeutic dosages of tricyclic antidepressants (TCAs) in this population.⁴³

Our results were consistent with those of most previous open-label studies showing that SSRI treatment is well-tolerated overall and does not worsen motor function specifically.^{5–8,10} On the contrary, there was even a suggestion of improvement in tremor and rigidity symptoms. The study completion rate was 86% (12 of 14), and 83% (5 of 6) of patients treated with the highest recommended dosage tolerated it, suggesting that it is possible to use maximal SSRI dosages in this population.

Probing for possible moderators of treatment response, greater apathy and poorer free recall at baseline corresponded with a more limited antidepressant treatment response. It is possible that some patients classified as depressed, partly based on meeting DSM-IV criteria for anhedonia, actually were experiencing a loss of interest in the context of apathy, which typically does not respond to SSRI treatment.⁴⁴ Postural instability was the only Parkinson's disease-related feature associated with antidepressant response. Perhaps patients with different subtypes of Parkinson's disease, including those with prominent postural instability early in the illness, may be less likely to respond to antidepressant treatment than patients who have classical Parkinson's disease symptoms only (i.e., tremor, rigidity, and bradykinesia).

In conclusion, SSRI treatment in Parkinson's disease appears to be well tolerated from all standpoints. Treatment lessens the severity of depression, though usually not enough to meet traditional criteria for response or remission. This suboptimal response may be due to either disease-related factors or to limitations in existing diagnostic and rating instruments when applied to depression in Parkinson's disease. Though large-scale, placebo-controlled studies are needed to determine the efficacy of SSRIs in depression in Parkinson's disease, it would be prudent both to explore alternate treatments for depression and to develop disease-specific depression assessment tools in this population.

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FIGURE 1a.
Change in Inventory of Depressive Symptomatology (IDS) Score

TABLE 1

Impact of Treatment on Affect, Cognition, and Motor Function*

	Baseline	Study Completion	p value
<i>Affect</i>			
Inventory of Depressive Symptomatology	Mean (SD)	Mean (SD)	0.03
Hamilton Depression Rating Scale	27.2 (5.5)	19.4 (6.0)	<0.01
Hamilton Anxiety Rating Scale	20.6 (3.5)	13.1 (6.3)	0.05
Liberty Scale	13.8 (4.3)	11.1 (5.1)	0.84
Apathy Scale	13.8 (3.6)	14.1 (4.3)	0.87
<i>Cognition</i>			
MMSE	19.1 (6.1)	19.1 (7.3)	0.57
HVLT-R	28.1 (1.4)	28.3 (1.6)	0.94
Immediate free recall (# correct)	21.1 (6.2)	21.3 (7.8)	0.71
Delayed free recall (# correct)	6.6 (3.6)	6.5 (3.7)	0.94
Recognition recall (# correct)	9.1 (3.0)	9.6 (2.2)	0.44
Trail Making Test-B			0.10
Completion time (sec)	193.5 (105.4)	201.9 (109.6)	0.50
Errors	2.2 (2.8)	1.1 (0.6)	0.16
<i>TOL^{DX}</i>			
Total move score (TOL ^{DX} -TMS)	57.1 (29.8)	56.6 (35.0)	
Execution time (TOL ^{DX} -EXTS) (sec)	473.1 (222.9)	465.6 (262.4)	
<i>Motor</i>			
UPDRS			
Total motor score	31.0 (8.9)	27.2 (12.2)	0.16
Tremor subscore	2.5 (2.4)	1.9 (1.9)	0.08
Rigidity subscore	6.9 (4.1)	5.2 (3.8)	0.09
Bradykinesia subscore	14.4 (6.5)	13.5 (7.5)	0.54
Postural instability subscore	4.2 (2.1)	4.1 (2.4)	0.27
Trail Making Test A (sec)	70.3 (44.8)	68.6 (46.5)	0.81

* Repeated measures analysis of variance (IDS, HAM-D, and HAM-A) or Wilcoxon signed rank test (all other measures)