Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease

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ABSTRACT

Objectives: Depression and antidepressant use, especially selective serotonin reuptake inhibitors (SSRIs), are common in Parkinson disease (PD). The objective of this clinical trial was to assess the efficacy of atomoxetine, a selective norepinephrine reuptake inhibitor (SNRI), for the treatment of clinically significant depressive symptoms and common comorbid neuropsychiatric symptoms in PD.

Methods: A total of 55 subjects with PD and an Inventory of Depressive Symptomatology–Clinician (IDS-C) score ≥ 22 were randomized to 8 weeks of atomoxetine or placebo treatment (target dosage = 80 mg/day). Depression response ($>50\%$ decrease in IDS-C score or Clinical Global Impression–Improvement [CGI-I] score of 1 or 2) was assessed using intention-to-treat modeling procedures. Secondary outcomes included global cognition, daytime sleepiness, anxiety, apathy, and motor function.

Results: There were no between-groups differences in a priori–defined response rates. Using a more liberal response criterion of $>40\%$ decrease in IDS score from baseline, there was a trend ($p = 0.08$) favoring atomoxetine. Patients receiving atomoxetine experienced significantly greater improvement in global cognition ($p = 0.003$) and daytime sleepiness ($p = 0.001$), and atomoxetine was well-tolerated.

Conclusions: Atomoxetine treatment was not efficacious for the treatment of clinically significant depressive symptoms in PD, but was associated with improvement in global cognitive performance and daytime sleepiness. Larger studies of SNRIs in PD for disorders of mood, cognition, and wakefulness are appropriate.

Classification of evidence: This interventional study provides Class II evidence that atomoxetine (target dosage = 80 mg/day) is not efficacious in improving clinically significant depression in PD.

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GLOSSARY

ADHD = attention-deficit/hyperactivity disorder; **AS** = Apathy Scale; **CGI-I** = Clinical Global Impression–Improvement; **CI** = confidence interval; **dPD** = depression in Parkinson disease; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **ESS** = Epworth Sleepiness Scale; **GDS-15** = 15-item Geriatric Depression Scale; **ICC** = intraclass correlation coefficient; **IDS-C** = Inventory of Depressive Symptomatology–Clinician; **LC** = locus ceruleus; **MMSE** = Mini-Mental State Examination; **NNT** = number needed to treat; **OR** = odds ratio; **PD** = Parkinson disease; **SNRI** = selective norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor; **STAI** = State Anxiety Inventory; **TCA** = tricyclic antidepressant; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Depression occurs in up to 50% of patients with Parkinson disease (PD), and is associated with functional impairment,^{1,2} reduced quality of life,³ and caregiver distress.⁴ In addition, depression in PD (dPD) is frequently comorbid with anxiety, apathy, disorders of sleep and wakefulness, and cognitive impairment.

Up to 25% of patients with PD are taking an antidepressant at any given time, most commonly a selective serotonin reuptake inhibitor (SSRI).⁵ However, a recent meta-analysis

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found no evidence for SSRI efficacy in dPD, with a diminished effect compared with geriatric depression.⁶

Placebo-controlled studies with tricyclic antidepressants (TCAs) have been promising. In 2 studies, TCA-treated patients experienced significant improvement in depression compared with placebo,^{7,8} with 1 study also showing benefit for anxiety and disturbed sleep.⁷ However, TCAs can be difficult to utilize in PD due to aggravation of orthostatic hypotension, constipation, and cognitive impairment.

Given the significant noradrenergic deficits that occur in PD,⁹ the association between norepinephrine and depression in general, and a primary noradrenergic mechanism of many TCAs,¹⁰ we conducted a randomized, double-blind, placebo-controlled study of atomoxetine for clinically significant depressive symptoms in PD. Atomoxetine, a selective norepinephrine reuptake inhibitor (SNRI) approved for the treatment of attention-deficit/hyperactivity disorder (ADHD), has shown evidence of having antidepressant properties.¹¹ A small open-label study of reboxetine, an SNRI used in Europe, for patients with dPD found significant decreases in depression scores with treatment.¹² We hypothesized that atomoxetine would be efficacious for the treatment of depression and common comorbid nonmotor symptoms in PD.

METHODS **Participants.** The study population consisted of 55 patients with idiopathic PD recruited from The Parkinson's Disease and Movement Disorders Center at Pennsylvania Hospital (n = 41) and the Parkinson's Disease Research, Education and Clinical Center at the Philadelphia Veterans Affairs Medical Center (n = 14). The diagnosis of possible or probable PD¹³ was confirmed by the patient's movement disorder neurologist.

The primary measure of depression symptom severity was the Inventory for Depressive Symptomatology–Clinician Rated (IDS-C),¹⁴ a 30-item (scores 0–84, increasing scores indicating greater depression severity) comprehensive instrument that is increasingly used as a primary outcome measure in major depression treatment studies in the general population.¹⁵ In this study, patients were at least moderately depressed, as determined by a baseline IDS-C score ≥ 22 .

Subjects were excluded for the following reasons: Mini-Mental State Examination (MMSE)¹⁶ score < 15 ; consumption of > 14 alcoholic beverages a week; a history of bipolar disorder, schizophrenia, or schizoaffective disorder; deep brain stimulation within the previous 6 months; current use of monoamine oxidase inhibitors; and current or planned pregnancy or nursing. Patients currently on an antidepressant were permitted to participate and continue the antidepressant if they had received an

adequate antidepressant trial (minimum 6-week duration at a therapeutic dose).

Standard protocol approvals, registration, and patient consents. The Institutional Review Board at each participating institution approved the study, and written informed consent was obtained from subjects prior to study participation. This clinical trial was posted on clinicaltrials.gov (NCT00304161).

Design. This was an 8-week, randomized, double-blind, placebo-controlled study. The Investigational Drug Service at the University of Pennsylvania maintained the blind. The Investigational Drug Service was responsible for purchasing the study drug, preparing drug kits, and creating and implementing the randomization table. Numbered drug kits were provided by Investigational Drug Service and administered to study participants by trained research personnel. Everyone directly involved with the study participants as well as the participants themselves were blinded to study group assignment. Recruitment spanned a period of 4 years from July 2004 to August 2008, at which time the blind was broken and data analysis began.

All subjects were randomized to atomoxetine 40 mg/day or placebo. At the end of 2 weeks, the dosage of atomoxetine or placebo was increased to 80 mg/day for the duration of the study, although patients were allowed to continue study participation at 40 mg/day if a decrease in study medication was clinically indicated.

Eligibility was determined at screening. Patients provided informed consent and were assessed with the MMSE and the 15-item Geriatric Depression Scale (GDS-15).¹⁷ Patients with possible clinically significant depression, determined by GDS-15 score ≥ 5 , were scheduled for a baseline visit after at least a 1-week delay. At baseline, eligible and willing patients with an IDS-C score ≥ 22 were entered into the clinical trial.

Assessments. Study participants were assessed in person at baseline, week 2, week 4, and week 8 (study completion). Five trained research staff over the course of the study evaluated subjects with an extensive psychiatric battery including the IDS-C (intraclass correlation coefficient [ICC] ≥ 0.945 with Principal Investigator's (D.W.) assessment or training tape at 4 time points over the course of the study), a semi-structured interview to determine a *DSM-IV-TR*¹⁸ diagnosis of major depressive episode, the State Anxiety Inventory (STAI)¹⁹ to assess anxiety, the Apathy Scale (AS)²⁰ as a measure of apathy, and the Epworth Sleepiness Scale (ESS)²¹ as a measure of daytime sleepiness. The primary and secondary outcome measures presented here were chosen on the basis of measuring severity of psychiatric symptoms or cognitive deficits that might respond to atomoxetine treatment.

The IDS-C was administered at all study visits, and the rest of the psychiatric measures and the MMSE were administered at baseline and study completion. D.W. administered the Clinical Global Impression–Improvement (CGI-I) scale at all postbaseline visits, the Unified Parkinson's Disease Rating Scale (UPDRS) at baseline, week 4, and study completion, and queried about possible side effects at all study visits using the Treatment Emergent Symptom Scale.²² Blood pressure (sitting and standing) and pulse were measured at each study visit.

Analyses. The study was powered to detect a 30% differential in response rates between atomoxetine and placebo treatment, leading to a projected study population of 80 randomized subjects. Over the 4-year period of funding that supported the study, 55 subjects were recruited.

The criteria for the 2 primary measures of treatment response were a >50% decrease in IDS-C score from baseline and a final CGI-I score of 1 or 2. Remission was defined as a final IDS-C score ≤13. Secondary analyses involved examining treatment group differences in global cognition, daytime sleepiness, anxiety, apathy, and motor function.

Descriptive univariate analyses included calculating means and standard deviations for continuous outcomes and percentages for categorical outcomes. Tests of significance across treatment groups included *t* tests for equality of means for continuous measures and χ^2 tests for categorical measures. Longitudinal, intent-to-treat mixed-effects modeling procedures were used to test and estimate treatment group differences in both continuous and binary outcome measures over time, regardless of dropout or missing data, thus making use of all available data and not limiting the analyses to complete cases. The models adjusted for clustering at the patient level and included main effect and interaction terms (i.e., time by treatment group) at each follow-up visit. To control for potential between-group baseline differences, the baseline score for each measure was included as a covariate in the appropriate model. Contrasts for continuous outcomes were modeled using SAS PROC MIXED, and for binary outcomes using SAS PROC GENMOD (SAS version 9.0, SAS Institute, Cary, NC). *p* < 0.05 was considered significant.

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RESULTS Clinical and demographic characteristics.

Study completion rates for the atomoxetine and placebo patients were 79% and 78%. Table 1 presents sociodemographic characteristics and baseline values for PD variables and primary and secondary outcome measures of interest (e.g., depression, apathy, daytime sleepiness, anxiety symptoms, and cognitive performance) for the full sample and stratified by treatment group. The majority of the sample was white (96.4%) and male (66.0%). Participants were on average 64.3 (SD = 10.5) years old, with an average PD duration of 6.9 (SD = 6.2) years. Approximately two-thirds (62%) of participants met criteria for major depression. Over half (53.1%; 15 in atomoxetine and 14 in placebo groups) were currently taking an antidepressant in the recommended therapeutic range for a minimum of 6 weeks. Comparisons across treatment arms indicate that there were no significant differences between patients receiving placebo and atomoxetine on any background or baseline variables, with the exception of a slightly higher mean MMSE score in the placebo group.

Of study completers, 97.7% (42/43) of subjects were taking 80 mg/day of atomoxetine or placebo equivalent at the final visit. For this group, mean (SD) medication adherence was 96.4% (8.6%) for the final 4 weeks of the study. Participant flow through the trial is shown in figure 1.

Depression outcomes. Results from the longitudinal, mixed-effects models showed reductions in depressive symptoms (i.e., continuous IDS score) at each follow-up visit relative to baseline, but no treatment group differences for these outcomes (mean between-group difference for change in IDS score at week 8 adjusted for baseline score = 1.67 points [SE = 2.30], *p* = 0.47).

When modeling IDS response (i.e., ≥50% decrease in IDS score since baseline) as a binary outcome, results indicated that atomoxetine and placebo groups did not differ in response rates at 8 weeks (22.7% vs 9.5% for atomoxetine and placebo; odds ratio [OR] = 2.79; 95% confidence interval [CI] = 0.48–16.33; *p* = 0.25), which translates to a number needed to treat (NNT) of 7.6 (figure 2). However, using a more liberal response criterion of >40% decrease in IDS score since baseline to allow for nonresponse in IDS physical items that might have been present secondary to PD rather than depression, there was a trend for atomoxetine-treated patients to have a superior response (31.8% vs 9.5%; OR = 4.43; 95% CI = 0.80–24.54; *p* = 0.08).

On the a priori defined response criteria for the CGI-I (i.e., score of 1 or 2), there were no between-

Table 1 Baseline study sample characteristics by randomized group assignment^a

Variable	Full sample (n = 55)	Atomoxetine (n = 28)	Placebo (n = 27)
Sociodemographics			
Age, y	64.3 (10.5)	63.8 (9.5)	64.9 (11.5)
Male	36 (66.0)	20 (71.4)	16 (59.3)
Caucasian	53 (96.4)	27 (96.4)	26 (96.3)
PD indices			
PD duration, y	6.9 (6.2)	7.9 (6.6)	5.7 (5.6)
UPDRS part III score	22.6 (11.4)	23.5 (12.7)	21.6 (10.0)
Current antidepressant use	94 (53.1)	13 (46.4)	13 (48.1)
Outcome measures			
Inventory of Depressive Symptoms	35.7 (6.9)	35.1 (7.3)	36.4 (6.7)
Geriatric Depression Scale	8.8 (2.8)	9.4 (2.9)	8.2 (2.5)
State Anxiety Inventory	56.2 (10.4)	55.9 (10.5)	56.5 (10.4)
Mini-Mental State Examination	28.1 (2.4)	27.4 (2.9)	28.9 (1.3)
Apathy Scale	17.4 (6.3)	18.1 (7.9)	16.7 (4.8)
Epworth Sleepiness Scale	11.6 (4.8)	11.4 (4.6)	11.8 (5.2)

Abbreviations: PD = Parkinson disease; UPDRS = Unified Parkinson's Disease Rating Scale.

^a Cell values represent mean (SD) for continuous variables and n (%) for categorical variables. *p* Values based on χ^2 and *t* tests for treatment group differences in categorical and continuous variables. Ranges were as follows: age (39–80 years); PD duration (0–31 years); UPDRS part III (3–60); Inventory of Depressive Symptoms (22–51); Geriatric Depression Scale (2–14); State Anxiety Inventory (33–76); Mini-Mental State Examination (18–30); Apathy Scale (4–39); Epworth Sleepiness Scale (4–22).

Figure 1 Participant flow through the trial

group differences in response rates at week 8 (45.5% and 33.3% for atomoxetine and placebo; OR = 1.67; 95% CI = 0.48–5.74; $p = 0.42$), a NNT of 7.6 (figure 3). Using a more liberal CGI-I response criterion (i.e., score of 1, 2, or 3), there still was no difference in response rates between the groups (63.6% and 42.9%; OR = 2.33; 95% CI = 0.69–7.95; $p = 0.18$).

There were no between-group differences in remission rates (3/28 [10.7%] for atomoxetine vs 0/27 [0%] for placebo, Fisher exact $p = 0.12$), a NNT of 9.3. Using a more liberal remission definition of IDS-C score ≤ 19 (i.e., at most mild depressive symptoms), patients randomized to atomoxetine

were more likely to experience remission (8/28 [28.6%] vs 2/27 [7.4%], Fisher exact $p = 0.04$). Concurrent antidepressant treatment did not have an impact on any of the depression outcome measures (data not shown).

Other outcomes. Examination of cognitive status (MMSE score) and daytime sleepiness (ESS score) did find significant treatment group differences in change in outcome over time (table 2). Specifically, patients randomized to atomoxetine experienced an improvement in global cognition relative to patients on placebo over the course of 8 weeks (mean group difference = 1.31 [SE = 0.41], $p = 0.003$). In addition,

Figure 2 Depression response at week 8 based on change in Inventory of Depressive Symptomatology (IDS) score by treatment group

tion, patients receiving atomoxetine experienced greater reductions in daytime sleepiness from baseline to week 8 relative to placebo (mean group difference = -2.90 [SE = 0.83], $p = 0.001$). Finally, there was a suggestion for a greater reduction in anxiety with atomoxetine treatment (mean group difference = -4.69 [SE = 2.62], $p = 0.08$).

Adverse events. Constipation (25.9%) and insomnia (14.8%) were the 2 most common adverse events in atomoxetine-treated patients. There was a trend for constipation to be more common in atomoxetine-treated than in placebo-treated patients ($p = 0.05$), while nausea/vomiting was less common in

atomoxetine-treated patients ($p = 0.02$). Regarding cardiovascular adverse events, only one study participant (randomized to placebo) experienced a >20 mm increase in either systolic or diastolic blood pressure compared with baseline, and no patients experienced a $>20\%$ increase in pulse compared with baseline. Four serious adverse events requiring hospitalization occurred during the study, 2 in atomoxetine-treated patients (suicide ideation several weeks after study termination in 1 patient, and exacerbation of congestive heart failure in another) and 2 in placebo-treated patients (chest pain and possible anxiety attacks in 1 patient, and urosepsis in another); none of the serious adverse events were thought to be related to study treatment. There were no between-group differences in UPDRS motor scores throughout the course of the study ($p = 0.87$).

DISCUSSION Our primary finding was that atomoxetine did not demonstrate efficacy for the treatment of clinically significant dPD based on traditionally defined response criteria. Using a more liberal criterion for treatment response to allow for symptom overlap between depression and PD symptoms, there was a suggestion for improvement in depression with atomoxetine, which was paralleled by a trend in favor of decreased severity of anxiety in atomoxetine-treated patients. In addition, significant improvements in global cognition and daytime sleepiness were found with atomoxetine treatment.

Regarding study limitations, the sample size was relatively small, possibly precluding detection of a significant treatment effect on the 2 primary measures of treatment response. Second, the diagnostic criteria for depression which are typically used in clinical trials were not used as an inclusion criterion. However, as existing diagnostic criteria for major depression may not apply well to patients with neurodegenerative diseases,^{23,24} we chose to define our population by severity of depressive symptoms rather than by presence of a specific depression diagnosis. Third, antidepressant use at baseline was common in our population, suggesting a high percentage of patients who may have been refractory to antidepressant treatment. However, there was no difference in depression outcome measures on the basis of baseline antidepressant treatment status. Fourth, the IDS has not been previously validated as a depression rating scale in PD, but it is increasingly used in large depression treatment studies in the general population.¹⁵ Finally, the clinical significance of the improvements in daytime sleepiness and global cognition seen with atomoxetine treatment was not assessed, but the between-group end-of-study difference in ESS score crossed the recommended

Figure 3 Depression response at week 8 based on Clinical Global Impression-Improvement (CGI-I) score by treatment group

Table 2 Differences in secondary outcome measures by treatment group

	Study visit			
	Baseline	Week 2	Week 4	Week 8
Mini-Mental State Examination^a				
Atomoxetine	28.12 (0.19)	—	—	28.92 (0.22)
Placebo	28.31 (0.19)	—	—	27.80 (0.22)
Effect (mean group difference in change since baseline, <i>p</i> value)	—	—	—	1.31 (0.41) <i>p</i> = 0.003
Epworth Sleepiness Scale^a				
Atomoxetine	11.69 (0.38)	—	—	9.78 (0.43)
Placebo	11.73 (0.39)	—	—	12.72 (0.45)
Effect (mean group difference in change since baseline, <i>p</i> value)	—	—	—	−2.90 (0.83) <i>p</i> = 0.001
State Anxiety^a				
Atomoxetine	56.08 (1.37)	47.17 (1.44)	47.93 (1.44)	48.00 (1.56)
Placebo	56.23 (1.45)	50.13 (1.48)	52.45 (1.57)	52.84 (1.60)
Effect (mean group difference in change since baseline, <i>p</i> value)	—	−2.81 (2.48) <i>p</i> = 0.26	−4.37 (2.54) <i>p</i> = 0.09	−4.69 (2.62) <i>p</i> = 0.08
Apathy Scale^a				
Atomoxetine	17.77 (0.55)	—	—	15.86 (0.63)
Placebo	17.42 (0.59)	—	—	17.32 (0.66)
Effect (mean group difference in change since baseline, <i>p</i> value)	—	—	—	−1.80 (1.22) <i>p</i> = 0.14
UPDRS part III score^a				
Atomoxetine	22.16 (0.87)	—	21.09 (0.94)	21.36 (0.98)
Placebo	22.01 (0.90)	—	21.03 (0.98)	20.94 (1.02)
Effect (mean group difference in change since baseline, <i>p</i> value)	—	—	−0.08 (1.65) <i>p</i> = 0.96	0.28 (1.70) <i>p</i> = 0.87

Abbreviation: UPDRS = Unified Parkinson's Disease Rating Scale.

^a Estimated cell values, mean (SE), adjusted for baseline score on measure.

cutoff score for excessive daytime sleepiness,²⁵ and the 1-point difference in MMSE scores may underestimate end-of-study differences in cognitive abilities, given the insensitivity of the MMSE to detect mild cognitive impairments in patients with PD.²⁶

Depression and antidepressant use, particularly SSRIs, are common in PD.⁵ However, evidence for the efficacy of SSRIs for dPD is lacking.⁶ To date, stronger evidence, albeit from a limited number of small studies,^{7,8,27} exists for the efficacy of TCAs, which affect both the noradrenergic and serotonergic systems to varying degrees. While atomoxetine, which is selective for the noradrenergic system, has not undergone extensive study as an antidepressant, it has been shown to be beneficial for depressed patients in the general population who are nonresponsive to SSRIs.¹¹ Studies with another SNRI, the European compound reboxetine, have demonstrated promising results for depression resistant to SSRI treatment, and a small open-label reboxetine study in patients with dPD found significant improvement in depression scores with treatment.¹²

The findings suggest that medications increasing noradrenergic tone may be beneficial for other common nonmotor symptoms in PD. There is prominent loss of norepinephrine neurons in the locus ceruleus (LC) in PD,^{9,28} and atomoxetine inhibition of norepinephrine reuptake likely enhances the postsynaptic effects of LC activation in each target area.²⁹ The LC is recognized as a major wakefulness-promoting nucleus,²⁹ so atomoxetine may have alerting effects in PD based on possible enhancement of LC activity. In addition, although atomoxetine is not classified as a stimulant, it appears to possess some stimulant-like effects,³⁰ which may have contributed to decreased daytime sleepiness in our subjects. Excessive daytime sleepiness occurs in up to half of patients with PD, and atomoxetine may offer an alternative to modafinil and stimulants, for which there is mixed evidence for efficacy in PD.^{31,32}

The LC is thought to play an important role in the regulation of cognitive performance, including attentional modulation,³³ and LC neuronal loss is associated with dementia in PD.³⁴ Given its primary

attention-enhancing effects,³⁵ it is not surprising that atomoxetine would be associated with improvements in global cognitive performance in our sample, and additional research is needed to replicate these findings and determine if atomoxetine treatment is associated with improvements in specific cognitive domains. In a preliminary open-label study, atomoxetine was shown to enhance executive functioning in patients with PD without dementia.³⁶ Atomoxetine increases both norepinephrine and dopamine levels in the prefrontal cortex, as dopamine uptake in this region occurs via norepinephrine transporters.³⁷ Therefore, if atomoxetine has cognitive enhancing effects in PD, a disease with cognitive deficits linked to impairments in cortico-striatal dopaminergic pathways,³⁸ it may be due to enhanced noradrenergic or dopaminergic tone in frontal brain regions. It is possible that stimulants, also approved for ADHD, may have similar cognitive-enhancing effects in PD.

Compared with commonly used TCAs, which target not only the noradrenergic system but to varying degrees other neurotransmitter systems (e.g., serotonergic, cholinergic, and histaminergic), atomoxetine is a selective norepinephrine reuptake inhibitor. Thus, potentially troubling side effects that can occur with TCA use due to their anticholinergic or antihistaminergic effects would not be expected to occur commonly with atomoxetine use. In support of this, we found that atomoxetine was well-tolerated in this study. Larger studies of SNRIs in PD for disorders of mood, cognition, and wakefulness are appropriate given these preliminary findings, good tolerability, and limited options currently available for the treatment of these disorders.

AUTHOR CONTRIBUTIONS

D.W. participated in the conception and design of the study and drafted the manuscript. S.M. and T.R.T.H., both affiliated with the University of Pennsylvania, recommended statistical analysis and analyzed study data. A.D.S., J.E.D., H.I.H., A.C., S.S.H., and M.B.S. assisted with study design and subject recruitment. E.M. and S.N. recruited patients and administered study-related assessments. All authors participated in the writing of the manuscript. D.W. had access to all data in the study and held final responsibility for the decision to submit the paper.

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DISCLOSURE

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