RESEARCH ARTICLE

Tricyclic Antidepressants Delay the Need for Dopaminergic Therapy in Early Parkinson's Disease

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ABSTRACT: This study examined whether antidepressants delay the need for dopaminergic therapy or change the degree of motor impairment and disability in a population of early Parkinson's disease (PD) patients. Preclinical studies have indicated that antidepressants modulate signaling pathways involved in cell survival and plasticity, suggesting they may serve to both treat PD-associated depression and slow disease progression. A patient-level meta-analysis included 2064 patients from the treatment and placebo arms of the following trials: FS1, FS-TOO, ELLDOPA, QE2, TEMPO, and PRECEPT. Depression severity was determined at baseline, and antidepressant use was reported in a medication log each visit. Kaplan–Meier curves and time-dependent Cox proportional hazards models determined associations between depression severity and antidepressant use with the primary outcome, time to initiation of dopaminergic therapy. ANCOVAs determined associations with the secondary outcome, degree of motor impairment and disability, reported as annualized change in UPDRS scores from baseline to final visit. When controlling for baseline depression, the initiation of dopaminergic therapy was delayed for subjects taking tricyclic antidepressants compared with those not taking antidepressants. No significant differences were found in UPDRS scores for subjects taking antidepressants compared with those not taking antidepressants. Tricyclic antidepressants are associated with a delay in reaching the end point of need to start dopaminergic therapy. The lack of change in overall UPDRS scores suggests the delay was not attributable to symptomatic effects. © 2012 *Movement* Disorder Society

Key Words: Parkinson's disease; depression; antidepressants; disease modifying; retrospective study

Additional Supporting Information may be found in the online version of this article.

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Depression is a common comorbid disorder in Parkinson's disease (PD), affecting 40%–50% of patients.[1,2] Given its impact on disability and quality of life, recognition and treatment of depressive symptoms are important in disease management.[3] Molecular mechanisms associated with the actions of antidepressant drugs suggest they have the potential to produce disease-modifying effects in PD.[4–8] To date, clinical trials that have investigated antidepressant therapy in PD have focused primarily on safety and treatment of depression, and therefore lack the appropriate methodology and time course to determine whether antidepressants affect disease progression or disability. Therefore, the primary objective of this study was to assess whether antidepressant treatment modified the timing of need for dopamine

pharmacotherapy in a population of early PD patients. Utilizing an integrated database compiled from 6 completed clinical trials from the Parkinson's Study Group (PSG) and the *N*europrotection *E*xploratory *T*rials in *P*arkinson's *D*isease Project (NET-PD), we examined whether antidepressant treatment alters the temporal course of disease progression, inferred from time to dopaminergic therapy, in early PD patients.

Materials and Methods

Study Population

A retrospective cohort study was conducted utilizing data from the following PSG and NET-PD clinical trials: ELLDOPA,[9] QE2,[10] TEMPO,[11] PRECEPT,[12] FS1,[13] and FS-TOO.[14] These trials included recently diagnosed PD patients not requiring dopaminergic therapy and assessed the efficacy of an adjunctive study drug or placebo over various durations of 6 months to 2 years. There were no enrollment exclusions for antidepressant use except for MAOIs, and subjects were required to maintain a stable regimen for 60 days prior to enrollment. One exception was the TEMPO study; it excluded antidepressant use except for amitriptyline, paroxetine, sertraline, fluvoxamine, and trazodone. Details of the study populations are provided in Supplemental Table 1.

End Point

The primary end point for the analyses in this study was time to initiation of dopaminergic therapy, defined as the number of days from baseline until the study investigator determined that the subject had reached a sufficient level of disability to warrant symptomatic therapy. This end point is a reliable measure of disease progression in early PD and has been utilized in a number of clinical trials to assess novel interventions.[15] In addition, the percentage of subjects who had not reached the end point at 1 year was reported in the unadjusted Kaplan–Meier curves. This time point was chosen because it is the halfway point for the average duration of the longest study (approximately 2 years); therefore, any significant changes at this time may represent an important and perhaps clinically meaningful finding. As the treatment medication for the ELLDOPA study was levodopa, subjects from this study were excluded from the analyses of the primary outcome. The secondary outcome, degree of disability and impairment, was reported as annualized change in total (parts I–III), mental (part I), activities of daily living (ADL) (part II), motor (part III), and tremor (tremor items in parts II and III) UPDRS scores from baseline to final visit defined as (UPDRS score at last assessment − UPDRS score at baseline)/number of days between the 2 assessments × 365.25.

Exposure

Subjects taking antidepressants during the study were classified in 2 ways: those reporting in the medication log taking any antidepressant and those taking a particular class of antidepressant (SSRI, SNRI, tricyclic, amitriptyline hydrochloride specifically, atypical, >1 antidepressant). Days of exposure were determined based on reported start and stop dates of medication use. IN addition, subjects were classified by depression severity. Depression severity was classified as none, mild, or moderate/severe based on cutoffs from 3 depression scales used in the included studies. Mild depression was defined by a loss of interest in normal activities, unusual irritability, and reduced motivation in work, home, or social activities. Moderate/severe depression was defined by considerable distress or agitation, significant difficulties with work or domestic activities, loss of self-esteem, or feelings of uselessness and guilt. Depression severity was determined within each study as follows: the Geriatric Depression Scale (GDS)[16] was administered to subjects in the FS1 and FS-Too trials, the Hamilton Depression Rating Scale (HDRS)[17] was administered to subjects in the ELLDOPA and QE2 trials, and the Beck Depression Inventory (BDI)[18] was administered to subjects in the TEMPO and PRECEPT trials.

Statistical Models

Kaplan–Meier curves were generated to assess the median time to therapy and the percentage of subjects who had not reached the end point at 1 year for baseline depression severity, overall antidepressant use, and specific antidepressant classes. To evaluate the independent role of antidepressants on the need for therapy, we used time-dependent Cox regression models. These models are an extension of the ordinary Cox proportional hazard regression, adapted for covariates that vary over time for the same individuals. Antidepressant use was included in the models as a cumulative proportion of study time the subject was taking medication each day of the study. Hazard ratios (HRs) and 95% confidence intervals (CIs) were generated for delay in dopaminergic therapy associated with depression severity and antidepressant use. Analyses were performed using ANCOVAs with annualized rate of change in total and subcomponent UPDRS scores as dependent variables and baseline exposure to antidepressants, depression severity, and potential confounders as predictor variables. Confounding variables that were accounted for in all adjusted analyses were: age, sex, race, treatment group, study, site, baseline UPDRS score, and prestudy antidepressant use. All analyses were performed using SAS 9.2.

TABLE 1. Patient characteristics at baseline for each study

	Elldopa	FS1	FSToo	Precept	QE2	Tempo	Combined
Total per study (n)	361	200	213	806	80	404	2064
Age, mean (SD)	64.56 (10.91)	62.33 (10.38)	61.03 (10.36)	59.69 (10.26)	61.30 (11.26)	60.84 (10.8)	61.22 (10.67)
Male (%)	67.59	63.00	65.26	64.39	65.00	63.61	64.78
Race, white (%)	90.58	92.50	89.67	95.66	96.25	94.80	93.70
Prestudy AD use (%)	16.34	19.00	17.84	17.99	20.00	9.65	16.23
Total UPDRS, mean (SD)	25.89 (11.02)	23.68 (9.46)	22.34 (8.85)	24.62 (10.53)	23.35 (9.69)	25.03 (10.84)	24.54 (10.42)
Not depressed (%)	85.60	82.50	89.67	81.14	93.75	79.70	83.14
Mildly depressed (%)	13.85	10.5	7.98	12.66	6.25	12.87	11.97
Moderately/severely depressed (%)	0.55	7.00	2.35	6.20	0.00	7.43	4.89

Results

Baseline Characteristics and Depression Severity

A total of 2064 patients compiled from both treatment and placebo groups were included in the analyses. Of these, 451 were taking some form of antidepressant anytime during the study. Patient baseline characteristics were similar among the studies (Table 1). Approximately 15% of untreated subjects presented with mild or moderate/severe depression when they entered the study. Most subjects treated with an antidepressant at baseline fell into the "not depressed" or "mild depression" categories, with a small percentage being classified with "moderate/severe" depression. However, moderate/severe depression was more common among subjects taking an SSRI (16.87%) than a tricyclic (7.41%), SNRI (3.45%), or atypical antidepressant (5.71%) at baseline.

Impact of Depression Severity and Antidepressants on Initiation of Dopaminergic Therapy

The unadjusted median time to therapy for subjects taking any antidepressant was significantly shorter than that for those not taking antidepressants at baseline (363 vs 449 days; $P = .002$; Fig. 1A). However, when antidepressant use was stratified by specific class of antidepressant at baseline, the median time to therapy was delayed, and the percentage of subjects not meeting the end point at 1 year was greater for subjects taking amitriptyline ($P = .02$) and atypical antidepressants (including bupropion, mirtazapine, trazodone, and wellbutrin; $P = .01$) compared with those not taking antidepressants (Fig. 1C).

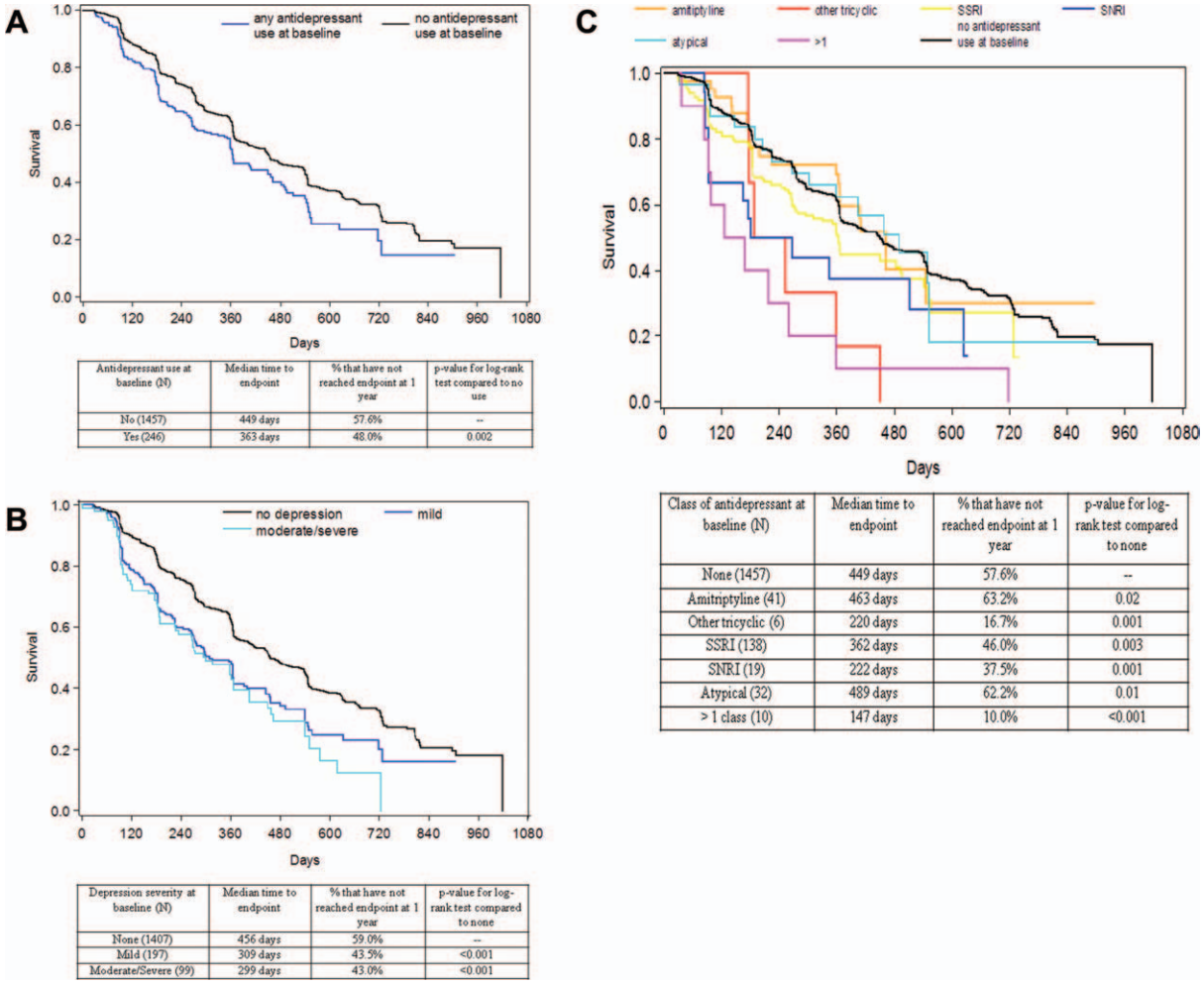
When controlling for depression (and other confounders; see Materials and Methods section for a detailed list), subjects taking tricyclics, amitriptyline in particular, had a lower probability of initiating dopaminergic therapy (HR, 0.3; $P = .004$; HR, 0.3; $P = .01$; Table 2. When controlling for antidepressant use (any or each individual class), mild depression was associated with a higher probability of starting dopaminergic therapy (HR, 1.4; $P < .004$ for all models; Table 3). However, moderate/severe depression was not significantly associated with the same outcome. We explored the potential interaction between baseline depression severity and time-dependent tricyclic use by running a model with separate time-dependent indicator variables for tricyclic use among the 3 categories of depression. This model did not fit the data significantly better than the model with only a single variable for tricyclic use (chi-square [2 *df*] = 2.4; $P = .30$).

Impact of Depression Severity and Antidepressant Use on Degree of Disability

A total of 2029 subjects (98%) had data available for UPDRS assessments. Baseline antidepressant use (any or by class) did not significantly affect the rate of change in any of the UPDRS outcomes when compared with subjects not taking antidepressants (Table 4). Although, not surprisingly, when stratified by depression severity, untreated subjects with moderate/severe depression had a significant worsening on the mental component of the UPDRS compared with untreated, nondepressed subjects (least-square mean, 2.2 vs 0.8; $P = .04$).

Discussion

Our findings suggest that early PD patients treated with tricyclics, amitriptyline in particular, experience a significant delay in the initiation of dopaminergic therapy. Amelioration of depression in this PD population is likely less responsive to SSRIs than to tricyclics, as evidenced by baseline depression scores and previous findings in cohorts of early PD patients.[19,20] The lack of change in UPDRS scores suggests that the lower rate of reaching the end point is not associated with less worsening in motor function. This could be a result of better control of symptoms not captured by the UPDRS, such as depressive symptoms, although the probability of initiating dopaminergic therapy was adjusted for depression. It could also be a result of relatively better treatment of tremor compared with other motor symptoms, assuming that tremor is a target symptom in the decision to start dopaminergic treatment. Finally, although impossible to confirm in



Antidepressant use at baseline (N)	Median time to endpoint	% that have not reached endpoint at 1 year	p-value for log-rank test compared to no use
No (1457)	449 days	57.6%	--
Yes (246)	363 days	48.0%	0.002

Depression severity at baseline (N)	Median time to endpoint	% that have not reached endpoint at 1 year	p-value for log-rank test compared to none
None (1407)	456 days	59.0%	--
Mild (197)	309 days	43.5%	<0.001
Moderate/Severe (99)	299 days	43.0%	<0.001

Class of antidepressant at baseline (N)	Median time to endpoint	% that have not reached endpoint at 1 year	p-value for log-rank test compared to none
None (1457)	449 days	57.6%	--
Amitriptyline (41)	463 days	63.2%	0.02
Other tricyclic (6)	220 days	16.7%	0.001
SSRI (138)	362 days	46.0%	0.003
SNRI (19)	222 days	37.5%	0.001
Atypical (32)	489 days	62.2%	0.01
> 1 class (10)	147 days	10.0%	<0.001

FIG. 1. Kaplan–Meier curves showing median time to end point based on antidepressant treatment and depression severity. **A:** Survival curves for subjects taking any antidepressant (blue) compared with those who did not take antidepressants (black). **B:** Survival curves for subjects taking different classes of antidepressants: tricyclics (red), amitriptyline (orange), atypical (turquoise), SSRI (yellow), SNRI (blue), >1 antidepressant (pink) or no antidepressant (black) during the study. **C:** Survival curves for subjects based on depression severity at baseline: no depression (black), mild depression (blue), or moderate/severe depression (turquoise). Curves include raw data (days to end point) and are not adjusted for confounders.

this study, the delay in the need of dopaminergic treatment may represent a disease-modifying effect of tricyclics, in line with preclinical studies.

Although antidepressants are safe and effective in treating depression in PD,[19–22] we have a limited understanding of their potential effects on neurodegeneration. However, results from several preclinical studies show various classes of antidepressants modulate the signaling pathways involved in cell survival and plasticity.[6–8,23–25] More recently, both paroxetine[23] and fluoxetine[26] were shown to prevent the loss of dopaminergic neurons by inhibiting inflammation and oxidative stress in the 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP) mouse model of PD. Furthermore, our laboratory found chronic amitriptyline treatment was neuroprotective for the dopamine system in the 6-hydroxydopamine rat model of parkinsonism.[27] Finally, a recent open-label clinical trial demonstrated that treatment with select SSRIs restored brain-derived neurotrophic factor serum levels and attenuated motor deficits in PD patients already receiving dopamine therapy.[22] Combined, these findings suggest that antidepressant treatment can evoke

TABLE 2. Survival analysis for time to initiation of dopaminergic therapy depending on antidepressant use

All subjects	HR	95% CI	*P* value
Time-dependent antidepressant use (any)	0.9	(0.6, 1.3)	.63
Time-dependent tricyclic use	0.3	(0.1, 0.7)	.004[a]
Time-dependent amitriptyline use	0.3	(0.1, 0.7)	.01[a]
Time-dependent SSRI use	0.9	(0.6, 1.4)	.64
Time-dependent SNRI use	0.9	(0.2, 3.1)	.82
Time-dependent atypical use	2.3	(0.9, 5.4)	.06

Time-dependent use indicates cumulative proportion of study time subjects were taking medications. Models adjusted for baseline UPDRS score, baseline age, sex, race, treatment group, study, site, baseline depression status (none, mild, moderate/severe), and prestudy antidepressant use (yes or no; or prestudy tricyclic, amitriptyline, SSRI, SNRI, atypical use depending on main medication). Survival analyses exclude ELLDOPA because some patients were taking levodopa.
[a]Significant $P < .05$.

TABLE 3. Survival analysis for time to initiation of dopaminergic therapy depending on depression severity

Group	HR	95% CI	*P* value
Baseline depression status (controlling for antidepressant use)			
None (referent)	1.0	—	—
Mild	1.4	(1.1, 1.7)	.003[a]
Moderate/severe	1.0	(0.7, 1.3)	.92
Baseline depression status (controlling for tricyclic antidepressant use)			
None (referent)	1.0	—	—
Mild	1.4	(1.1, 1.7)	.002[a]
Moderate/severe	1.0	(0.7, 1.3)	.93
Baseline depression status (controlling for amitriptyline use)			
None (referent)	1.0	—	—
Mild	1.4	(1.1, 1.7)	.002[a]
Moderate/severe	1.0	(0.7, 1.3)	.98
Baseline depression status (controlling for amitriptyline use)			
None (referent)	1.0	—	—
Mild	1.4	(1.1, 1.7)	.004[a]
Moderate/severe	1.0	(0.7, 1.3)	.86
Baseline depression status (controlling for amitriptyline use)			
None (referent)	1.0	—	—
Mild	1.4	(1.1, 1.7)	.002[a]
Moderate/severe	1.0	(0.8, 1.3)	.98
Baseline depression status (controlling for amitriptyline use)			
None (referent)	1.0	—	—
Mild	1.4	(1.1, 1.7)	.002[a]
Moderate/severe	1.0	(0.7, 1.3)	.93

Time-dependent use indicates cumulative proportion of study time subjects were taking medications. Models adjusted for baseline UPDRS score, baseline age, sex, race, treatment group, study, site, baseline depression status (none, mild, moderate/severe), and prestudy antidepressant use (yes or no; or prestudy tricyclic, amitriptyline, SSRI, SNRI, atypical use depending on main medicaiton). Survival analyses exclude ELLDOPA because some patients were taking levodopa.
[a]Significant *P* value compared with no baseline depression.

changes in the brain that may reduce the rate of DA cell degeneration in PD.

Prior clinical studies had not specifically addressed the neuroprotective potential of antidepressants. The data provided here suggest antidepressants may have neuroprotective properties and encourage prospective clinical studies. However, these results should be interpreted with caution, as depression and disability are closely intertwined, and it is difficult to separate the effects of antidepressant therapy from symptomatic relief of depression, which can contribute greatly to the quality of life.[28] For example, Ravina and colleagues[29] showed depressed PD patients were more likely to complain of symptoms, which resulted in a faster time to dopaminergic therapy than were nondepressed PD patients. Although we included both depression and antidepressant use as confounds in this study, there is a possibility that a putative disease-modifying effect elicited by chronic tricyclic use is the result of antidepressant efficacy and may not be reflective of a neuroprotective effect, especially considering the recent data by Mendez et al[20] demonstrating tricyclics provide superior relief of depressive symptoms than do SSRIs or placebo. It is regrettable that our data could not be adjusted for differences in antidepressant efficacy among the various antidepressants, but several of the source studies did not include post-intervention depression scales; therefore, the results may indeed represent greater antidepressant efficacy of tricyclics than a direct neuroprotective effect. The lack of changes in disability as measured by UPDRS among antidepressants and/or between depressed and nondepressed treated subjects supports this argument but may also suggest that a longer follow-up to determine differences in disability would have been necessary to examine whether the disability difference between groups could widen over time in favor of nondepressed or tricyclic-treated subjects.

Properly designed, well-controlled antidepressant studies are rare in PD patients; however, numerous open-label trials have been conducted to assess whether antidepressants are safe and effective in PD. These studies provided evidence that antidepressants from various classes are safe and effective at alleviating depressive symptoms in depressed PD patients.[19,21,30] However, the end point/outcome measures of the aforementioned studies were not appropriate to determine whether antidepressants are capable of modifying the progression of PD. The short duration and lack of controls in these studies necessitate more research to ascertain whether antidepressants could provide disease-modifying effects in PD. To this end, we examined whether antidepressant treatment influenced the progression of symptoms over a more extensive time course (6–24 months). We found no differences in annualized UPDRS scores for subjects taking antidepressants compared with those who were not. In fact, both treated and nontreated subjects exhibited an expected rate of decline (between 8 and 11 points) for early PD patients,[31] suggesting antidepressants do not have a symptomatic effect on motor disability. In addition, independent classes of antidepressants did not significantly affect UPDRS scores. However, subjects taking amitriptyline experienced the smallest degree of worsening (7.4 points/year) compared with those taking other classes of antidepressants (except atypical antidepressants) and those not taking antidepressants (Table 4). This lack of significant differences between groups may be a result of the limitations of our study. First, the population comprised patients early in the disease course (<5 years); therefore, the extent of symptoms experienced at this stage of disease may not be large enough to detect significant differences between groups. Second, we compiled data from multiple studies with varying durations, which may have diluted the magnitude of disability for studies with a longer time course. Third, we categorized subjects by the class of antidepressant taken, which may have made the sample size too small to detect significant differences between the groups.

TABLE 4. Influence of antidepressant use on UPDRS scores (annualized rate of change)

		Total UPDRS		Mental UPDRS		ADL UPDRS		Motor UPDRS		Tremor UPDRS	
	n	LSM (SE)	*P* value	LSM (SE)	*P* value	LSM (SE)	*P* value	LSM (SE)	*P* value	LSM (SE)	*P* value
Baseline antidepressant use (any)											
Yes	292	9.4 (3.5)	.80	1.5 (0.8)	.66	3.4 (1.3)	.93	4.7 (2.7)	.64	1.3 (0.7)	.90
No	1737	10.4 (1.4)	—	1.1 (0.3)	—	3.2 (0.5)	—	6.1 (1.1)	—	1.2 (0.3)	—
Baseline antidepressant use (by class)											
Tricyclic	52	8.0 (4.6)	.66	1.2 (1.1)	.90	2.3 (1.7)	.62	4.3 (3.6)	.66	0.4 (0.9)	.48
SSRI	162	11.3 (3.7)	.78	1.5 (0.9)	.69	4.4 (1.4)	.43	5.7 (2.9)	.94	1.7 (0.8)	.52
SNRI	28	8.5 (5.4)	.76	2.5 (1.2)	.28	2.2 (2.0)	.62	3.8 (4.2)	.62	0.1 (1.1)	.34
Atypical	34	1.6 (5.0)	.10	0.6 (1.2)	.69	1.8 (1.9)	.46	−0.7 (3.9)	.10	1.2 (1.0)	.95
>1 antidepressant class	16	15.2 (6.6)	.46	2.7 (1.5)	.31	2.5 (2.5)	.80	9.9 (5.1)	.46	2.0 (1.4)	.54
None	1737	10.2 (1.4)	—	1.1 (0.3)	—	3.2 (0.5)	—	5.9 (1.1)	—	1.1 (0.3)	—
Baseline antidepressant use (by amitriptyline and other tricyclics)											
Amitriptyline	42	7.6 (4.9)	.61	1.3 (1.1)	.86	2.2 (1.8)	.59	3.9 (3.8)	.60	0.7 (1.0)	.64
Other tricyclic	10	9.8 (8.0)	.97	0.9 (1.9)	.93	2.9 (3.0)	.93	6.0 (6.2)	.99	−0.4 (1.6)	.35
Baseline antidepressant use (yes/no)/depression severity (none, mild, moderate/severe)											
Yes and none	193	9.7 (3.6)	0.83	1.2 (0.8)	0.65	3.2 (1.3)	0.97	5.2 (2.8)	0.64	1.2 (0.7)	0.86
Yes and mild	63	10.3 (4.3)	0.95	2.2 (1.0)	0.18	4.7 (1.6)	0.38	4.1 (3.4)	0.48	1.7 (0.9)	0.77
Yes and mod/severe	36	7.8 (4.9)	0.59	0.7 (1.1)	0.97	2.0 (1.8)	0.54	5.1 (3.8)	0.7	1.2 (1.0)	0.9
No and none	1493	10.6 (1.1)	—	0.8 (0.3)	—	3.2 (0.4)	—	6.6 (0.9)	—	1.4 (0.2)	—
No and mild	179	10.6 (1.9)	0.99	0.7 (0.5)	0.98	3.5 (0.7)	0.65	6.4 (1.5)	0.87	0.8 (0.4)	0.13
No and moderate/severe	65	10.3 (3.0)	0.91	2.2 (0.7)	.04[a]	3.2 (1.1)	0.96	4.8 (2.3)	0.43	1.1 (0.6)	0.71

Models adjusted for baseline UPDRS score, baseline age, sex, race, treatment group, study, site, baseline depression status (none, mild, moderate/severe), and prestudy antidepressant use (yes or no; or prestudy tricyclic, amitriptyline, SSRI, SNRI, atypical use depending on main medication).
[a]Significant *P* value (<.05) compared with no antidepressant use and not depressed. LSM, least squares mean; ADL, activities of daily living.

Fourth, the putative disease-modifying effects of amitriptyline or tricyclics in general may not be adequately captured through the UPDRS motor scale.[32] Incidentally, tremor may have specifically influenced whether subjects received treatment with tricyclics, as its anticholinergic properties may theoretically attenuate tremor, although any such change was insufficient to drive differences in the UPDRS motor score. Because the UPDRS motor score is fairly insensitive to change in early PD,[33] a scale that more directly examines a patient's quality of life may be a more sensitive measure of disease-modifying changes than the UPDRS motor score. It has been suggested by Harrison et al[34] and others[32,35] that the ADL component of the UPDRS may serve as a better marker of disease progression than the other subscales, as it is most responsive to changes over time. Although not significant, we found the mean annualized change in ADL subscore for subjects taking tricyclics was less (2.3) compared with SSRIs (4.4) or subjects not taking antidepressants (3.2); see Table 4. Finally, we did not control for a specific clinical phenotype such as akinetic-rigid versus tremor dominant,[31,36] which could potentially influence the relationship between depression and initiation of dopaminergic therapy. Collectively, these limitations could be overcome in a prospective, well-controlled clinical trial. The data suggest that early tricyclic therapy affords patients more functional time in the early phases of PD (without dopaminergic treatment) and potentially a longer period of adequate disease management and good quality of life with standard dopaminergic therapy, although this remains to be determined by future studies.

Depression is one of the most debilitating and persistent nonmotor symptoms experienced by PD patients. In fact, it may have a greater negative impact on quality of life than motor disability.[37] The reported prevalence and incidence rates for depression in PD are inconsistent because of overlapping symptoms, various assessment techniques, and different populations of patients.[2] However, several clinical studies report that depression is often underrecognized and undertreated in patients with PD.[28,29] Similarly, we report that 348 subjects (17% of the total study population) were classified as having mild to severe depression at baseline. Of these, 248 subjects (71%) were not receiving treatment for depressive symptoms. In addition, mild, untreated depression was associated with an increased probability of beginning dopaminergic therapy. Furthermore, untreated subjects with moderate/severe depression exhibited a significant worsening on the mental component of the UPDRS. Because enrollment criteria included an established antidepressant regimen (>60 days), that many patients taking antidepressants were classified as depressed at baseline suggests their symptoms were not being adequately managed. However, results from a recent randomized trial showed that the tricyclic antidepressant nortriptyline was more efficacious in treating depression in PD patients than placebo, whereas the SSRI paroxetine was not, which suggests that,

compared with the general population, different mechanisms may be involved in PD-associated depression.[20] Likewise, our results indicate SSRIs may not be the optimal choice for treating depression in PD. For example, of the subjects taking an SSRI at baseline, more than 16% reported having moderate/severe depression compared with only 7% of those taking tricyclics. Therefore, depression in PD may result from different neurochemical abnormalities than major depression in the general population. Taken together, these findings highlight the impact of untreated depression in PD and suggest that depressive symptoms are not properly managed in early PD patients.

In summary, these findings support previous evidence that untreated depression contributes to disability in PD. Despite finding no change in UPDRS scores, the association of treated or untreated mild depression with a higher probability of beginning dopaminergic therapy suggests a role for depression in increasing overall disability and possibly accelerating disease progression. Similarly, the association of delayed initiation of dopaminergic therapy with tricyclic antidepressant treatment suggests that this class of drugs specifically may be the most effective in treating PD-related depression, altering the judgment of need for dopaminergic therapy and possibly slowing the course of disease progression. These results also illustrate the importance of treating both the motor and nonmotor symptoms associated with PD, as both types of symptoms contribute greatly to disability. In addition, nonmotor symptoms can exacerbate motor symptoms and decrease the quality of life for patients. Therefore, a therapy that can address both the nonmotor and motor symptoms of PD while slowing disease progression would provide the greatest benefit for PD patients. Prospective clinical trials and long-term follow-up of patients in extension or naturalistic studies are needed to determine the putative disease-modifying effects versus differential efficacy of antidepressant therapy on depressed patients who are optimally treated, depressed patients suboptimally treated or untreated, and nondepressed patients. ■

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