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The Course of Depressive Symptoms in Early Parkinson's Disease

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Abstract

Background—Little is known about the course of depressive symptoms in Parkinson's disease (PD).

Methods—We studied the course of clinically significant depressive symptoms using data from two clinical trials that followed 413 early, untreated PD subjects for 12–18 months. We measured depressive symptoms with the 15-item Geriatric Depression Scale (GDS-15); a score of ≥ 5 indicates clinically significant depressive symptoms. We used a time-dependent Cox model to examine the association between demographic variables, PD severity, and medication use on the time to resolution of depressive symptoms.

Results—114 of 413 (27.6%) subjects screened positive for depression during the study, with a median GDS-15 score of 6, indicating mild symptoms. Within 6 months, 47% of subjects experienced remission of clinically significant depressive symptoms. Subjects with mild depressive symptoms were more likely to develop moderate to severe depressive symptoms ($GDS \geq 10$) than those without prior symptoms (relative risk = 6.16). Increasing severity of depressive symptoms, older age, and longer PD duration predicted a lower likelihood of symptom resolution (hazard ratios 0.83 to 0.92).

Conclusions—Mild depressive symptoms have a variable course, with remission and development of more sustained and severe symptoms occurring over time. More severe depressive symptoms may herald a protracted course.

Keywords

Parkinson's disease; depression; clinical course; prognosis

Introduction

Depressive symptoms affect up to 50% of patients with Parkinson's disease (PD).^{1,2} The severity of depressive symptoms may be assessed by several instruments. The Geriatric Depression Scale (GDS) and the 15-item GDS (GDS-15) are particularly useful as screening

tools to detect clinically significant depressive symptoms in PD.³ Depressive symptoms in PD (dPD) are associated with reduced quality of life⁴ and increased disability.⁵ Despite the importance of dPD, it is often not accurately diagnosed and treatment is often suboptimal. Moreover, little is known about the clinical course. We monitored depressive symptoms with the GDS-15 in a cohort of 413 early, untreated PD patients enrolled in two clinical trials. Here we report on the course of dPD and predictors of duration and severity.

Methods

We pooled data from two phase II clinical trials enrolling early, untreated PD subjects (NET-PD FS1 and FS-TOO).^{6, 7} To be eligible for these trials potential subjects could not be taking any symptomatic treatment for their PD, and they were followed for 12–18 months. A depression diagnosis of any type was not an exclusion criterion. Descriptions of these cohorts and the clinical trial procedures have been published.^{5–7}

Statistical Models

We used a time-dependent Cox regression to model the time to remission of depressive symptoms (defined as a return to GDS-15 score <5) among baseline cases of depression and then combined baseline and incident cases. A cutoff score of ≥ 5 on the GDS-15 was used to signify clinically significant depressive symptoms, as this cut-off point has been shown to have good discriminant validity for differentiating depressed (either major or minor depressive episodes) from non-depressed PD patients.^{3, 8, 9} The covariates included in the model for baseline cases of depression were: age, gender, duration of PD diagnosis, study (FS1 or FS-TOO), treatment group, baseline total Unified Parkinson's Disease Rating Scale (UPDRS) score,¹⁰ baseline GDS-15 score, baseline Hoehn and Yahr¹⁰ (HY) stage, baseline score on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, a measure of cognitive impairment),¹¹ symptomatic PD therapy use (time dependent), and initiation of antidepressant medications (time dependent). Not all variables were captured at interim visits when incident cases were detected. The covariates for the model of combined baseline and incident cases were age, gender, duration of PD diagnosis, study (FS1 or FS-TOO), treatment group, UPDRS total and GDS-15 scores at the time that the subject screened positive for depression, symptomatic PD therapy use (time dependent), and initiation of antidepressants (time dependent). The combined analysis with baseline and incident cases did not include HY or RBANS because they were not collected at all interim visits. The time-dependent Cox regression is an extension of ordinary Cox proportional hazard regression, allowing for covariates that vary over time for the same individuals.

Results

Baseline Characteristics and Medication Use

The baseline demographics for this cohort, including non depressed subjects, were previously published.⁵ Overall, 114 of the 413 (27.6%) subjects screened positive for depression sometime during the study; there were 57 subjects (13.8%) with a baseline GDS-15 score ≥ 5 and 57 incident cases (13.8%) of clinically-significant depressive symptoms among subjects who were not depressed at baseline. Fifty-three (46%) of the 114 were treated with antidepressants. Thirty of these 53 were on antidepressants at entry to the study or were started prior to screening positive for depression in the study and 23 started antidepressants after screening positive at baseline or during the study. Selective serotonin reuptake inhibitors (SSRIs) were the most commonly used antidepressants, and one subject took a tricyclic antidepressant (TCA) (Table 1). During the course of the studies, 52 of the depressed subjects were determined to have sufficient disability to warrant initiation of antiparkinson medications and 40 started on levodopa or a dopamine agonist.

Duration and Severity of Depressive Symptoms and Duration

The median GDS-15 score among the 114 depressed subjects was 6 at their initial positive screening, consistent with mild depressive symptoms (i.e., GDS-15 score = 5–9). Depressive symptoms remained mild over 6–18 months of follow-up with median GDS-15 scores of 7–8. Remission of clinically significant depressive symptoms, defined as GDS-15 score <5, occurred within 6 months for 47% of the subjects (Figure 1). However, subjects who had mild depressive symptoms during the study were subsequently more likely to develop moderate to severe depressive symptoms (i.e., GDS score ≥ 10), than those without prior depressive symptoms. Seven of 64 subjects with prior mild depressive symptoms developed a GDS score ≥ 10 compared to 6 of 338 without clinically-significant depressive symptoms during the study (relative risk = 6.16 [95% CI 2.14, 17.73]).

Predictors of Clinical Course

The Cox-Hazard model for time to remission of depressive symptoms was performed first for the baseline depression cases only (Table 2) and then for baseline and incident cases combined. Among the 57 subjects with depression at baseline, higher GDS-15 score, older age, and longer PD duration were associated with a reduced likelihood of remission, with hazard ratios (HR) between 0.83 and 0.92. Additionally, use of antidepressants was strongly associated with a reduced likelihood of remission, with a HR 0.13. Higher HY score and worse RBANS score were associated with a higher chance of remission. Neither total UPDRS score nor initiation of antiparkinson medication was significantly associated with remission. In the model including both baseline and incident cases of depression, only initiation of antidepressants remained a statistically significant predictor and was associated with a reduced likelihood of remission (data not shown).

Discussion

This study assessed the course of clinically significant depressive symptoms in early PD subjects followed for 12–18 months. We used data from two clinical trials that were designed to evaluate progression of PD, controlling for treatment assignment and other covariates. Most subjects who screened positive on the GDS-15 had mild depressive symptoms that remained mild. Thirteen (11.4%) of the 114 subjects who screened positive for depression had moderate to severe symptoms. Nearly half of the subjects had remission of clinically significant depressive symptoms within 6 months as measured by the GDS-15. However, mild depressive symptoms were associated with a more than 6-fold increased risk of developing moderate to severe depressive symptoms compared with absence of depressive symptoms. Additionally, higher GDS-15 scores were associated with a lower likelihood of remission. Just a one point increase on the GDS-15 reduced the chances of remission by 17%.

There is little information about the course of depression in PD. One clinic-based study followed 187 PD subjects for a median of 14 months. Similar to our study in early PD, 27% of the cohort screened positive for depression using the Beck Depression Inventory.¹² Only 15.9% of those who were depressed at baseline remained depressed at the final visit. Subjects who remain depressed had higher baseline BDI scores. Another study examining a range of PD subjects showed that after 1 year, 63% of subjects with minor depression were likely to be in remission, but only 11% of subjects who initially had major depression were in remission.¹³ Consistent with prior studies, we found that the majority of cases of depression in early PD were in remission by 6–9 months, but that greater depression severity was associated with a lower chance of remission.

We found a more than 6-fold increase in risk of more severe depressive symptoms among those who had minor symptoms. Similarly, findings in a community setting and general medical

patients suggest that minor or subthreshold depression may predict subsequent major depression.¹⁴ Chronic illness has also been associated with an increased risk for conversion from subthreshold depression to major depression.¹⁵ While many of the community-based studies have had follow-up periods of one year, some have followed subjects for more than 10 years. Studies with longer follow-up will help to clarify the evolution of depressive symptoms during the course of PD and help inform treatment decisions. Our findings clearly indicate, however, that careful monitoring of depressive symptoms in PD is warranted.

We modeled remission of depressive symptoms in two ways to maximize the value of our data. The model including only baseline cases allowed us to include important covariates that were not measured at all visits, such as cognition (RBANS) and HY stage. The model using both baseline and incident cases provided a larger sample size but shorter follow-up period among incident compared with baseline cases. For baseline cases, in addition to more severe depression, older age and longer PD duration were associated with protracted depression. Prior studies support these findings and suggest that advanced age and longer disease duration may be risk factors for incident depression in PD.^{12, 13, 16–19} Higher HY stage was associated with a greater chance of remission, but total UPDRS score was not associated with the course of depressive symptoms. There is not a clear relationship between motor impairment and depressive symptoms in any stage of PD.²⁰ All subjects started the study with HY stage of I–II. The emergence of postural instability and development of HY stage III can be highly variable in early PD when postural instability is measured by the pull test.²¹ Thus, this finding should be interpreted with caution. Similarly, the association with RBANS was modest and the RBANS showed little change (mean change $-1.48, \pm 10.8$) during this study, suggesting either that cognition did not decline appreciably during the course of the study or that the RBANS may have been insensitive to progression of cognitive impairment in this cohort. The combined analysis using incident cases did not replicate these findings (data not shown). This may be due to the different variables in the model or differences between incident cases and baseline cases. Because of the small and inconsistent effects, these findings require replication.

The use of antidepressants was associated with a lower likelihood of remission of depressive symptoms. In this cohort, more severely depressed PD patients were more likely to be treated with antidepressants.⁵ Thus, this finding likely represents confounding by severity, such that those with a worse prognosis were more likely to be treated with antidepressants.²² Among the 114 subjects who screened positive for depression, 53 were treated with antidepressants; 33 received an SSRI, 1 received a TCA, and the remainder received other antidepressants alone or in combination with an SSRI. Two recently completed randomized, double-blinded, placebo-controlled clinical trials suggest that both SSRIs and TCAs may be effective for treating depression in PD.^{23, 24} Thus, there is no reason to believe that treatment with antidepressants would actually reduce the likelihood of remission of depressive symptoms.

The main limitation of this study is the absence of psychiatric diagnostic interviews for establishing depressive or other affective diagnoses.²⁵ However, the GDS-15 is validated as a depression screening tool in the geriatric population and scores of ≥ 5 are predictive of clinically significant depressive disturbances in PD.³ The GDS-15 was not designed to measure response to therapy and may have over- or under-estimated rates of remission.

Additionally, we adjusted for important covariates, but did not eliminate the potential for bias inherent in an observational study, and we found evidence of confounding by symptom severity.

Mild depressive symptoms in PD are common, and single episodes of clinically significant symptoms appear to be limited to 6–9 months in duration for most subjects. However, greater

symptom severity reduced the likelihood of remission and, for some subjects, these mild symptoms may portend development of more severe depressive symptoms.

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Figure 1.
Kaplan Meier plot of time to remission

Table 1

Characteristics and medication use among subjects screening positive for depression

	Baseline Cases (n=57)	Incident Cases (n=57)
	Mean (sd)	Mean (sd)
Age(years)	60.8 (11.1)	61.4 (10.9)
Months from Diagnosis	5.9 (9.1)	6.0 (6.6)
Male, No (%)	37 (65%)	33 (58%)
Non-Hispanic Whites, No (%)	47 (82%)	50 (88%)
History of Depression (active or resolved), No (%)	34 (60%)	24 (42%)
Prior Use of Antidepressants **	11 (19%)	19 (33%)
Antidepressant started during study (after case): *	17 (30%)	6 (11%)
SSRI	21 (37%)	12 (21%)
Tricyclic	0 (0%)	1 (2%)
Other	2 (4%)	6 (11%)
More than One	5 (9%)	6 (11%)
Started Parkinson's therapy: *	34 (60%)	18 (32%)
Levodopa	12 (21%)	7 (12%)
Dopamine Agonist	13 (23%)	8 (14%)
Other	9 (16%)	3 (5%)
GDS score (when screened positive)	7.44 (2.61)	6.60 (1.97)
Baseline UPDRS Total *	29.1 (9.5)	24.2 (9.9)
Baseline UPDRS Mental *	2.9 (1.8)	1.5 (1.3)
Baseline UPDRS ADL *	8.1 (3.7)	6.5 (3.4)
Baseline UPDRS motor	18.1 (6.8)	16.1 (7.5)
Baseline Hoehn and Yahr	1.5 (0.5)	1.6 (0.5)
Baseline RBANS	94.6 (14.7)	95.6 (16.4)

UPDRS= Unified Parkinson's Disease Rating Scale. Higher scores indicate more impairment.

RBANS= Repeatable Battery for the Assessment of Neuropsychological Status. Lower scores indicate more impairment.

*
p≤0.05**
Prior use of antidepressants refers to before baseline (for baseline cases) or before incident case.

Table 2

Cox Regression model of time to depression remission (return to GDS < 5)

Variable	Hazard Ratio	95% Hazard Ratio Confidence Limits		p-value
Age, yr	0.91	0.86	0.96	0.001
Gender (reference is Female)	1.11	0.55	2.26	0.77
Duration of PD Diagnosis, mo	0.92	0.86	0.98	0.01
Baseline GDS	0.83	0.70	0.98	0.03
Baseline UPDRS Total	1.02	0.97	1.06	0.52
Baseline Hoehn & Yahr	2.47	1.07	5.73	0.03
Baseline RBANS Total Score (reverse coded)	1.03	1.01	1.06	0.01
Symptomatic Therapy Use*	1.3	0.51	3.22	0.60
Started Antidepressants	0.13	0.37	0.04	0.0002

Model adjusts for study, treatment group, and all variables shown in table. RBANS was reverse coded so that higher score is worse. For all other scales a higher score is worse.

* Time varying covariates. Overall model $R^2=0.4$