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The impact of depressive symptoms in early Parkinson disease

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Abstract

Background—Depressive disorders may affect up to 50% of patients with Parkinson disease (PD) and are associated with increased disability and reduced quality of life. No previous study has systematically examined the impact of depressive symptoms in early, untreated PD.

Methods—We administered the 15-item Geriatric Depression Scale (GDS-15) as part of two NIH-sponsored phase II clinical trials in PD, enrolling 413 early, untreated PD subjects. We used linear mixed models to examine the relationship of depressive symptoms, measured by the GDS-15, with motor function and activities of daily living (ADLs), as measured by the Unified PD Rating Scale (UPDRS). A time-dependent Cox model was used to examine the effect of demographic and clinical outcome measures as predictors of investigator-determined time to need for symptomatic therapy for PD.

Results—A total of 114 (27.6%) subjects screened positive for depression during the average 14.6 months of follow-up. Forty percent of these subjects were neither treated with antidepressants nor referred for further psychiatric evaluation. Depression, as assessed by the GDS-15, was a significant predictor of more impairment in ADLs ($p < 0.0001$) and increased need for symptomatic therapy of PD (hazard ratio = 1.86; 95% CI 1.29, 2.68).

Conclusions—Clinically important depressive symptoms are common in early Parkinson disease (PD), but are often not treated. Depressive symptoms are an important contributor to disability and the decision to start symptomatic therapy for motor-related impairment in early PD, highlighting the broad importance of identifying and treating depression in this population.

Depression in some form affects up to 50% of patients with Parkinson disease (PD),^{1,2} and is associated with increased disability³⁻⁵ and reduced quality of life.^{6,7} However, several studies have found that clinically significant depression in PD (dPD) is underdiagnosed,^{8,9} in part because symptoms of depression such as fatigue and insomnia may be attributed to PD.⁷ Because of the overlap between symptoms of PD and symptoms of depression, the recognition and impact of dPD may vary throughout the course of PD. Here we report on the frequency of depression in early PD and the relationship between depression and motor function, activities of daily living (ADL), and treatment decisions in a cohort of over 400 newly diagnosed patients with PD.

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METHODS

We pooled data from two phase II clinical trials enrolling early, untreated subjects with PD. To be eligible for these trials potential subjects could not be taking any symptomatic treatment for their PD. Depression of any type was not an exclusion criterion. In the first trial (FS1), 200 subjects with PD within 5 years of the diagnosis of PD were randomized to creatine (n = 67), minocycline (n = 66), or placebo (n = 67), and followed for 18 months.¹⁰ In the second trial (FS-TOO),¹¹ 213 subjects with PD were randomized to coenzyme Q10 (n = 71), GPI-1485 (n = 71), or placebo (n = 71), and were followed for 12 months. Both studies were double blinded and conducted at more than 40 overlapping sites using the same criteria for the diagnosis of PD.

Outcome measures

Recent publications support a cutoff score of ≥ 5 on the 15-item Geriatric Depression Scale Short Form (GDS-15) as appropriate for identifying major and minor depression in PD.^{12, 13} This cutoff produces 87% accuracy (88% sensitivity and 85% specificity) for major or minor depression based on Diagnostic and Statistical Manual of Mental Disorders, fourth edition, criteria using the Structured Clinical Interview (SCID).^{12, 14} The GDS-15 was assessed every 6 months and at the time that investigators determined that the subject needed symptomatic therapy for their PD symptoms. As part of the clinical trials (FS1 and FS-TOO), study investigators further evaluated subjects who scored ≥ 5 on the GDS-15, to assess for clinically significant depression or suicidal ideation and determine the need for either psychiatric consultation or antidepressant therapy. These outcomes (referral, antidepressant therapy) were recorded at the visit in which a patient screened positive for depression. We also used the concomitant medication log to assess whether a patient was ever prescribed antidepressants during the study for the indication of depression or depression/anxiety. We analyzed the GDS-15 as a dichotomous variable, < 5 or ≥ 5 , because of the reported accuracy for detecting major and minor depression in PD.¹² Therefore, while a SCID was not performed, we use the term depression to refer to those who screened positive and have either depressive disturbances or less well-defined depressive symptoms.

The other clinical outcome measures collected included parts I to III of the Unified PD Rating Scale (UPDRS) and the Hoehn and Yahr (H&Y) Staging Scale for PD severity and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) for cognition.¹⁵ The primary outcome of the clinical trials was change in total UPDRS scores from baseline until investigators determined that the subject needed symptomatic therapy due to disability from PD symptoms.

Statistical models

Linear regression (mixed effect) was used to model repeated visits of ADLs, as measured by part II of the UPDRS, and motor function, as assessed by part III of the UPDRS. The independent variables included in each model were study treatment group, age at baseline, gender, length of follow-up, determination of need for symptomatic therapy for PD, and repeated visits of clinical measures including the GDS-15 ≥ 5 , RBANS change from baseline, and part III of the UPDRS change from baseline (only used for ADL model). These two mixed effect linear regression models included a random effect for subject, which takes into account the repeated measures among subjects.

To evaluate the role of depression on the need for symptomatic therapy, we used a time-dependent Cox regression to model the time to the need for symptomatic therapy (dependent variable). The covariates included in the model were study treatment group, age at baseline, gender, repeated visits of GDS-15 ≥ 5 , total UPDRS change from baseline, RBANS change

from baseline, and H&Y change from baseline. The latter four were time-varying covariates. The time-dependent Cox regression is an extension of ordinary Cox proportional hazard regression, adapted for covariates that vary over time for the same individuals. The assumption of proportional hazards over time is relaxed.

RESULTS

Baseline frequency and incidence of depression

Baseline demographics and depression status are shown in table 1. Of the 413 participants, 101 (24.5%) reported a history of depression. Fifty-seven (13.8%) participants had a GDS-15 score ≥ 5 at baseline. Compared to non-depressed subjects, subjects who screened positive for depression had more severe PD measured by UPDRS scores ($p < 0.01$), but were at comparable H&Y stages. At baseline, 46 participants (11%) were receiving antidepressants for the treatment of depression. During the average 14.6 months of follow-up, there were 57 (16%) incident cases of depression (GDS-15 ≥ 5) among subjects who were not depressed at baseline. Overall, 114 of the 413 (27.6%) subjects experienced depression during the study. The median GDS score among subjects who screened as depressed was 6, reflecting a mild level of depressive symptoms.

Of the 114 patients who screened positive for depression, 28 (25%) were already receiving treatment for their depression, but had persistent depressive symptoms. Forty subjects (35%) were started on antidepressant therapy or referred for psychiatric evaluation at the time of the screening or later in the study. However, 46 participants (40%) were never treated with antidepressants nor referred for psychiatric evaluation. More severely depressed subjects were more likely to be treated. Among the 57 incident cases of depression, 8 of 52 participants (15%) with GDS between 5 and 9 (mild) compared with 4 of 5 participants (80%) with GDS > 9 (moderate to severe) were either started on pharmacologic therapy for their depression or referred for a psychiatric evaluation at that visit.

Impact of depression on function and initiation of symptomatic therapy

We assessed the impact of depression scores on measures of motor function and the investigator-determined need for symptomatic therapy for PD. A total of 402 (97%) subjects had data available for the UPDRS motor and ADL assessments. The mixed effects linear model for the UPDRS part III, motor, revealed that after adjusting for covariates, a GDS-15 score of ≥ 5 over time is not significantly associated with worse motor scores (table 2). However, the mixed effects linear model for the UPDRS part II, ADL, shows that after adjusting for covariates, a GDS-15 score of ≥ 5 over time is significantly associated with more impaired ADLs (table 3), corresponding to an average (SE) UPDRS ADL score increase of 1.28 points (± 0.33) ($p < 0.0001$).

The time-dependent Cox model for time to need for symptomatic therapy (table 4) includes all 413 (100%) participants. GDS-15 score ≥ 5 , UPDRS change, RBANS change, and H&Y score change (modeled as time dependent covariates) were all significant predictors of the time to need for symptomatic therapy. The magnitude of the relationship varied with the strongest predictors of the need for symptomatic therapy being H&Y, hazard ratio (95% CI) of 11.89 (8.10, 17.44), followed by the GDS-SF hazard ratio of 1.83 (1.27, 2.63) and the total UPDRS 1.14 (1.12, 1.16).

DISCUSSION

This study assessed the impact of depression in early, untreated PD. We used data from two clinical trials, controlling for treatment assignments and other covariates. There are three main

findings. First, depression is common in this cohort, whether by self-report or by a quantitative measure of depressive symptoms using the GDS-15. A total of 114 (27.6%) subjects had clinically significant, generally mild depressive symptoms during the study. Second, 40% of those who screened positive by the GDS-15 did not receive antidepressants or psychiatric referral. Third, depressive symptoms are associated with clinically important impairments in ADLs and increase the likelihood of starting on medications for PD. The effect of depression on ADL scores is comparable to the effect seen with an increase of six points on the motor section of the UPDRS (table 3). Additionally, the presence of depression, even when controlling for impaired motor function, contributes to the clinician's assessment of the need to initiate symptomatic therapy for PD.

Reported prevalence and incidence rates for depression in PD are highly variable.¹⁶ This is in part due to different assessment techniques and populations. In this study, we used a validated screening instrument, the GDS-15, rather than a diagnostic interview. In a study using the Beck Depression Inventory (BDI) with a cutoff of ≥ 10 , 44% of a clinic population screened positive for clinically important depressive symptoms.⁹ In a similar, clinic convenience sample, 34% of patients met DSM-IV criteria for major or minor depression.⁸ Both of these studies were conducted in established PD cases with an average H&Y score of approximately 2.5 and PD duration of over 7 years. The slightly lower point prevalence rates for depression in our study compared to other studies may be due to the particular PD population, which had a mean duration since diagnosis of PD of only 7.9 (10.0) months, or the screening instrument. Importantly, while this is a large cohort, this is not a population-based sample. Prevalence and incidence estimates in a clinical trial cohort may not be generalizable.

Previous clinic-based studies showed high rates of under-recognition and undertreatment of symptoms of depression in PD.^{8,9} In the study by Weintraub et al.,⁸ almost two thirds of subjects meeting criteria for depression were not treated. Similarly, studies by Richard and Kurlan¹⁷ and Shulman et al.⁹ found that clinicians did not recognize or treat depression in 50% or more of dPD patients. Our findings are consistent with depression screening efforts in the primary care literature which suggest that up to 60% of patients may be correctly identified as depressed and treated.¹⁸ However, as seen in this study, many treated patients remain depressed and may require more intensive psychiatric treatment.

Subjects with moderate to severe depression (GDS-15 > 9) were more likely to receive treatment or referral than those with mild depression (GDS-15 between 5 and 9). This suggests that most cases of dPD fall below the threshold of clinical intervention. In addition to overlap with PD symptoms, dPD may go untreated because it is mild and not thought to require antidepressant or other interventions. Additionally, less evidence is available to support treatment of minor depression in the elderly, as compared to major depression.¹⁹ As suggested by this study, dPD is largely comprised of minor depression.^{1,20} In a community-based study using the Montgomery and Asberg Depression Rating Scale, Tandberg et al. found that 5.1% of patients with PD were moderately to severely depressed, whereas 45.5% of the cohort had mild depressive symptoms.² That being said, mild depressive disturbances are associated with reduced functional ability,^{4,21} increased caregiver burden,²² and reduced quality of life.⁶ Evidence suggests that the detection and treatment of mild depressive symptoms in PD may improve these outcomes.^{7,16,23-25}

There are other potential explanations for the gap between the GDS-15 screening and the subsequent lack of treatment of depression. First, the GDS-15 may not be a valid instrument for identifying clinically significant depressive disturbances in newly diagnosed patients with PD, or different cutoff scores may be applicable to this population. Because this study did not use DSM criteria or a standardized interview such as the SCID, we cannot ensure the diagnostic accuracy of psychiatric disturbances of the screening instrument or the movement disorders

specialist. However, the GDS-15 has been validated in both the elderly²⁶ and in a range of patients with PD^{12,13} with good accuracy for major and minor depression. Second, investigator clinical behavior may be different in a clinical trial setting compared to clinical practice. However, an explicit effort was made in these clinical trials to screen for depression and allow for the provision of appropriate care; antidepressants were not restricted medications and most subjects with moderate to severe depression were treated. These findings raise the concern of limited recognition and treatment of clinically significant depressive symptoms in PD, even in the setting of a screening effort with a validated, self-report instrument, at movement disorders centers.

The relationship between motor impairment and depression is complicated. Subjects who screened positive for depression had more impairment at baseline on both ADL and motor sections of the UPDRS. This finding is not surprising and is consistent with other studies^{3-5, 27} and the idea that dPD is a reflection of more extensive PD pathology, such as more cell loss in the ventral tegmental area.^{20,28,29} Over time, depression scores were independently associated with increased impairment in ADLs, but were not significantly associated with increased motor impairment. Previous studies have found that depression was associated with greater motor progression^{5,30} and impairments in fine motor skills.³¹ However, regression analyses were not used in these studies to isolate the effects of depression on motor progression from other confounding variables.^{5,30} Over time, it appears that depression does not actually influence the progression of motor signs, but increases the disability associated with a given level of motor manifestations of PD.

Depression scores were significantly associated with the clinicians' determination of the need for symptomatic therapy for PD. Even when controlling for UPDRS scores, depressed subjects were 83% more likely to be judged as needing symptomatic therapy (for PD) compared to non-depressed subjects. The decision to start PD medications in patients with depression may reflect a clinical judgment to treat depressive symptoms and motor function with PD medications. However, the decision to initiate symptomatic therapy for PD typically focuses on impairments in gait, occupation, and ADLs, and involves patient reported disability and findings on examination. Thus, one explanation for our results is that depressed subjects may have reported more disability for a given level of motor impairment than non-depressed subjects, leading to treatment of motor symptoms rather than treatment of depression.

The main limitation of this study is the absence of a standardized method for establishing depressive diagnoses. We used the GDS-15, a validated screening tool, to assess for clinically important depressive symptomatology and the use of antidepressants or referral for further psychiatric health evaluation as a marker for the treatment of depression. The discrepancy between the screening instrument and clinical care cannot be explained without a diagnostic interview or more formal psychiatric assessment.

Results from this large cohort of subjects with early PD suggest that depression, particularly mild depression, is common early in the disease and is associated with increased disability. Treatment of dPD is limited, but depressive symptoms result in more frequent treatment for motor-related impairment. Future studies in PD may further evaluate the impact of different models of service that have been used in the primary¹⁸ care setting to enhance recognition and management of depression in PD.

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Table 1
Baseline characteristics by Geriatric Depression Scale (GDS) score

	GDS < 5, n = 356	GDS ≥ 5, n = 57
Age, y, mean (SD)	61.8 (10.3)	60.8 (11.1)
Months from diagnosis, mean (SD)	8.2 (10.1)	5.9 (9.0)
Male, n (%)	228 (64)	37 (65)
Non-Hispanic white, n (%) [*]	329 (92)	47 (82)
More than 12 y of education, n (%)	263 (74)	39 (68)
History of depression (active or resolved), n (%) [*]	67 (19)	34 (60)
Already treated with antidepressant medications at baseline, n (%) [†]	33 (9)	11 (19)
UPDRS total, mean (SD) [*]	22.0 (8.7)	29.1 (9.5)
UPDRS mental, mean (SD) [*]	0.8 (1.0)	2.9 (1.8)
UPDRS ADL, mean (SD) [*]	5.7 (3.1)	8.1 (3.7)
UPDRS motor, mean (SD) [*]	15.5 (6.7)	18.1 (6.8)
Hoehn & Yahr, mean (SD)	1.5 (0.5)	1.5 (0.5)
RBANS, mean (SD) [†]	99.7 (15.4)	94.6 (14.7)

UPDRS = Unified Parkinson's Disease Rating Scale (higher scores indicate more impairment); ADL = activities of daily living; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status (lower scores indicate more impairment).

^{*} $p \leq 0.01$.

[†] $p \leq 0.05$.

Table 2
Multivariable linear regression analysis of UPDRS motor scores

Predictor	Regression coefficient $\pm$ SE
Age at baseline, y	-0.22 ± 0.03 ($p < 0.0001$)
Male gender	1.90 ± 0.66 ($p < 0.005$)
Length of follow-up until symptomatic therapy, mo	0.13 ± 0.01 ($p < 0.0001$)
Investigator determined need for PD therapy	6.01 ± 0.65 ($p < 0.0001$)
RBANS change from baseline (higher score is better)	-0.04 ± 0.03 ($p = 0.18$)
GDS-15 ≥ 5 at baseline	0.97 ± 1.07 ($p = 0.37$)
GDS-15 ≥ 5 over time	1.36 ± 0.74 ($p = 0.06$)

Model of Unified Parkinson's Disease Rating Scale (UPDRS) motor score repeated measures (up until time initiated symptomatic therapy). Regression coefficients are adjusted for all covariates displayed in the table (treatment arm effects not shown). The length of follow-up (mo) is the total follow-up for each subject before initiating symptomatic therapy. $R^2 = 82\%$.

RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; GDS = 15-item Geriatric Depression Scale Short Form.

Table 3
Multivariable linear regression analysis of UPDRS ADL scores

Predictor	Regression coefficient $\pm$ SE
Age at baseline, y	-0.05 ± 0.02 ($p < 0.001$)
Male gender	0.26 ± 0.33 ($p = 0.44$)
Length of follow-up until symptomatic therapy, mo	0.04 ± 0.01 ($p < 0.0001$)
Investigator determined need for PD therapy	2.31 ± 0.33 ($p < 0.0001$)
RBANS change from baseline (higher score is better)	-0.02 ± 0.01 ($p = 0.14$)
GDS-15 ≥ 5 at baseline	1.26 ± 0.53 ($p < 0.05$)
GDS-15 ≥ 5 over time	1.28 ± 0.33 ($p < 0.0001$)
UPDRS motor change from baseline over time	0.21 ± 0.02 ($p < 0.0001$)

Model of Unified Parkinson's Disease Rating Scale (UPDRS) activities of daily living (ADL) score repeated measures (up until time initiated symptomatic therapy). Regression coefficients are adjusted for all covariates displayed in the table (treatment arm effects not shown). The length of follow-up (mo) is the total follow-up for each subject before initiating symptomatic therapy. $R^2 = 86\%$.

RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; GDS-15 = 15-item Geriatric Depression Scale.

Table 4

Time-dependent Cox regression model of time to investigator determined need for symptomatic therapy for Parkinson disease

Predictor	(Adjusted) hazard ratio	95% CI
Age, y	0.99 ($p = 0.13$)	(0.98, 1.00)
Male gender	1.16 ($p = 0.34$)	(0.85, 1.59)
GDS-15 ≥ 5 (0 = No, 1 = Yes)	1.83 ($p = 0.0012$)	(1.27, 2.63)
Total UPDRS change from baseline (higher score is worse)	1.14 ($p < 0.0001$)	(1.12, 1.16)
RBANS change from baseline (higher score is better)	1.05 ($p = 0.0006$)	(1.02, 1.07)
Hoehn & Yahr change from baseline	11.89 ($p < 0.0001$)	(8.10, 17.44)

Model adjusts for all covariates in the table. Fifteen-item Geriatric Depression Scale (GDS-15), total Unified Parkinson's Disease Rating Scale (UPDRS) change, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) change, and Hoehn & Yahr change are time dependent covariates.