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Journal

Movement disorders clinical practice, 2(4)

ISSN

2330-1619

Authors

Bega, Danny
Luo, Sheng
Fernandez, Hubert
et al.

Publication Date

2015-12-01

DOI

10.1002/mdc3.12205

Peer reviewed

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Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Impact of Depression on Progression of Impairment and Disability in Early Parkinson's Disease

Danny Bega, MD,[1] Sheng Luo, PhD,[2] Hubert Fernandez, MD,[3] Kelvin Chou, MD,[4] Michael Aminoff, MD,[5] Sotirios Parashos, MD, PhD,[6] Harrison Walker, MD,[7] David S. Russell, MD, PhD,[8] Chadwick W. Christine, MD,[5] Rohit Dhall, MD,[9] Carlos Singer, MD,[10] Ivan Bodis-Wollner, MD,[11] Robert Hamill, MD,[12] Daniel Truong, MD,[13] Zoltan Mari, MD,[14] Sofya Glazmann, CCRP,[11] Meilin Huang,[2] Emily Houston,[12] Tanya Simuni, MD,[1] on behalf of the NET PD LS1 investigators

Abstract: **Background:** Depression is one of the most common nonmotor symptoms associated with Parkinson's disease (PD), yet the impact of depression on progression of disease is unclear.

Objective: The aim of this study was to prospectively characterize the relationship between depressive symptoms and measures of disease progression in a large sample of patients with early, medically treated PD.

Methods: Baseline and longitudinal Beck Depression Inventory (BDI) scores from participants in the NINDS Exploratory Trials in PD Long Term Study 1 were correlated with changes in multiple measures of disease severity over 5 years. Multivariate analysis of predictors of change in BDI was performed.

Results: Of 1,741 participants, 746 completed 5-year assessments and were included. Mean age was 62.00 years (standard deviation [SD]: 9.22) and mean disease duration was 1.69 years (SD, 1.16). Mean BDI score was 6.24 (SD, 5.02) at baseline and 8.57 (SD, 6.60) at 5 years. Baseline BDI score was strongly associated with rate of change in all examined measures of disease severity. In multivariate analysis, BDI 5-year change was associated with change in UPDRS Part I (excluding depression item; $P < 0.01$), 33-item Parkinson's Disease Questionnaire ($P < 0.01$), EuroQOL Five Dimensional Questionnaire ($P = 0.02$), and Total Functional Capacity ($P < 0.01$), but was not associated with motor or cognitive measures. This model explained 68.8% of the variance 5-year change of the BDI score.

Conclusions: Worse baseline BDI scores are associated with a decline in multiple measures of disease severity in PD. Worsening of BDI at 5 years was associated with worsening in UPDRS Part I and quality-of-life measures, but not with motor or cognitive measures.

Depression is one of the most common nonmotor symptoms associated with Parkinson's disease (PD), and a major determinant of health-related quality of life (HRQoL).[1–3] The reported prevalence of depression in PD varies widely, but may be as high as 90%.[4–7] This prevalence is higher than in other diseases with comparable physical disability.[8] Multiple validated measures for depression in PD exist, both for screening purposes and assessing severity of depression. The Beck Depression Inventory (BDI) is one of these validated measures.[9] Other valid measures commonly used in PD studies include the Hamilton Depression Rating Scale (HAM-D), the Hospital Anxiety and Depression Scale (HADS), the Montgomery Asberg Depression Rating Scale (MADRS), and the Geriatric Depression Scale (GDS).[1,9] Using these measures, depressive symptoms are associated with disease outcomes across the spectrum of PD severity when assessed cross-sectionally.[1,2,7,10–15] In particular, depression has been associated with

[1]Northwestern University, Chicago, Illinois, USA; [2]University of Texas Health Science Center, Houston, Texas, USA; [3]Cleveland Clinic, Cleveland, Ohio, USA; [4]University of Michigan, Ann Arbor, Michigan, USA; [5]University of California San Francisco, San Francisco, California, USA; [6]Minneapolis Clinic, Minneapolis, Minnesota, USA; [7]University of Alabama at Birmingham, Birmingham, Alabama, USA; [8]Institute for Neurodegenerative Disorders, New Haven, Connecticut, USA; [9]Muhammad Ali Parkinson Center, Phoenix, Arizona, USA; [10]University of Miami, Miami, Florida, USA; [11]State University of New York, Syracuse, New York, USA; [12]University of Vermont, Burlington, Vermont, USA; [13]Parkinson and Movement Disorders Institute, Fountain Valley, California, USA; [14]Johns Hopkins University, Baltimore, Maryland, USA

*Correspondence to: Dr. Danny Bega, Department of Neurology, Northwestern University Feinberg School of Medicine, 710 North Lake Shore Drive, Abbott Hall, 1409, Chicago, IL 60611, USA; E-mail: danny.bega@northwestern.edu
Keywords: Parkinson's disease, depression, beck depression inventory, NET-PD.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 16 March 2015; revised 17 April 2015; accepted 1 May 2015.
Published online 14 July 2015 in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12205

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doi:10.1002/mdc3.12205

longer PD disease duration and higher H & Y score,[1,7,16] worse UPDRS scores,[7,17] greater disability,[17,18] postural-instability gait predominant (PIGD) PD phenotype,[11,12] worse quality of life (QoL),[2] and lower cognition.[18] However, there is little consistency in the literature with regard to depressive symptoms as predictors of progression of any of these aspects of disease.

In the absence of validated biomarkers of disease progression, the importance of determining whether clinical markers, such as depression, can predict PD disease outcomes cannot be overstated. Several large data sets of patients with early PD have been examined systematically to better understand the relationship between depressive symptoms and disease progression. In the DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) study, depression in patients with early untreated PD was analyzed using the HAM-D.[16] In a multivariate analysis, higher HAM-D score was found to be associated with decline in physical health-related QoL.[13] In the NINDS Exploratory Trials in Parkinson's Disease Futility Study 1 (NET-PD FS1) data set, another large cohort of early untreated PD patients, depressive symptomatology, as measured by the BDI, was found to be a significant contributor to the decision to start dopaminergic therapy for motor symptoms.[14] Other studies, however, have not reached similar conclusions.[15,19] In the present study, we aimed to further characterize and clarify the relationship between depressive symptoms as measured by BDI and disease progression in PD by analyzing the NET-PD LS1 (Long-Term Study 1) data set with the aim of determining the impact of depression on progression of specific outcomes of PD disability, impairment, and QoL. Unlike many previous studies, this data set included patients with early PD already on symptomatic therapy, which constitutes a large portion of the clinical population. We anticipated that a higher baseline BDI would be associated with greater deterioration in all assessed measures of cognitive, functional, and motor disability.

Patients and Methods

Sample

We analyzed data from NET-PD LS1, a multicenter, double-blind, placebo-controlled phase III study of creatine in patients with early treated PD. At enrollment, all patients were within 5 years from diagnosis and had been receiving dopaminergic therapy (levodopa or dopamine agonist) for at least 90 days, but no more than 2 years. There was no set BDI cutoff for inclusion or exclusion in the study. Patients were recruited from 45 sites in the United States and Canada. The detailed study design and characteristics of study participants have been published elsewhere.[20] The primary aim of the study was to test the hypothesis that daily administration of creatine (10 g/day) is more effective than placebo in slowing clinical decline in PD between baseline and the 5-year follow-up visit. Enrollment occurred from 2007 to 2010 and the study was terminated for futility in September 2013 after interim analysis demonstrated nonsuperiority of creatine versus placebo. The present analysis was performed on the final locked database as of 5 May 2014.

Specific Aims/Objectives

The primary aim of this post-hoc analysis was to correlate baseline depressive symptoms with the rate of change of the major measures of disease severity included in the data set, with the hypothesis that more-severe depressive symptoms would correlate with faster progression in all measures of motor, cognitive, and functional disability. Depressive symptom severity was measured by the BDI. The BDI consists of 21 items to assess intensity of depression, each scored 0 to 3, and has been shown to have maximal discriminatory ability (highest sum of sensitivity and specificity) in differentiating between nondepressed and depressed patients with PD at a cut-off point of 13 of 14.[21]

A secondary aim was to correlate the change in BDI from baseline to 5 years with the change in each disease severity measure from baseline to 5 years. We predicted that an increase in BDI score from baseline to 5 years would also correlate with progression of each disability variable assessed. In order to assess which variable had the greatest association with BDI, a reverse analysis was conducted so that a multivariate model could assess the relative contribution of each variable to BDI as an outcome measure. As an exploratory aim, we also assessed the natural history of depression in the cohort by evaluating the BDI score longitudinally, both as continuous and binary variables (<14 vs. ≥14), while controlling for use of antidepressants.

Instruments

The measures of disease severity and functional status used as response variables were: UPDRS Part I (mentation, behavior, and mood) without the depression item (to avoid colinearity in the analysis of depression), UPDRS Part II (activities of daily living), UPDRS Part III (motor), UPDRS Part IV (complications of therapy), and UPDRS sum of score of Parts I and III[22]; Modified Rankin Scale (mRS; ordinal variable, as well as dichotomized at <2 vs. ≥2), which is a widely used functional outcome measure where higher values indicate greater disability[23]; Total Functional Capacity (TFC), which consists of five items, with a maximal score (best) of 13, for assessing the abilities of individuals to work, manage money, perform activities of daily living (ADLs), and live at home[24]; Symbol Digit Modalities Test (SDMT; response between 0 and 110), which screens cognitive impairment using a substitution task where higher values indicate better performance[25]; the Scales for Outcomes in Parkinson's-Cognition (SCOPA-COG), which is a validated cognitive assessment scale for which higher scores indicate better cognitive function[26]; EuroQOL Five Dimensional Questionnaire (EQ-5D), which is a brief health status self-assessment in which higher values indicate worse perceived health, and EQ-5D Visual Analog Scale (EQ-5D VAS) in which high values indicate better perceived health[27]; QoL using the 39- and 33-item Parkinson's Disease Questionnaire (PDQ-39) and (PDQ-33; without emotional domain to avoid colinearity in the analysis of depression), where lower scores indicate better perceived health status[28]; L-dopa equivalence dose (LED) base-

doi:10.1002/mdc3.12205

line calculated based on the formula reported by Tomlinson et al.[29]; and PD subtype (postural instability or tremor predominant subtype) calculated based on the formula by Jankovic et al.[16] The primary outcome measure was the correlation between the longitudinal change in each variable and the baseline BDI. Assessments were conducted at baseline and annually thereafter until study completion, with the exception of mRS, TFC, and SCOPA-COG, which were measured only at baseline and 5-year time points. mRS was also unique in that it was measured in relation to PD-specific disability at baseline, but in relation to overall disability at year 5.

Statistical Analysis

In order to assess the association between rate of change for each variable and baseline BDI, we fit (generalized) linear mixed models for each measure of disease severity and baseline BDI score. All analyses were run while adjusting for confounding from the following variables: demographic data, age, sex, employment, race, handedness, disease severity, and disease duration. To address the secondary aims, we fit (generalized) linear models for the change from baseline to 5 years of each measure of disability and the BDI score change from baseline to 5 years, while adjusting for the same confounding variables. These univariate analyses were conducted using BDI as a continuous measure and as a dichotomized measure (<14 and ≥14).

In order to assess which variable had the greatest contribution to the BDI in a multivariate model, we reversed the analysis and used change in BDI as the outcome measure, while using the changes in each measure of disease severity as risk factors. We computed the coefficient of determination (R^2), which is a useful tool for model goodness of fit and describes the data variance explained by the model.

In order to assess the natural history of depressive symptoms in this cohort, we fit (generalized) linear mixed models for BDI score and the use of antidepressants (with antidepressant treated as a covariate) while adjusting for confounding from the same variables, as stated above. We also evaluated longitudinal PDQ emotions (PDQe) subscore as another self-reported measure of depressive symptoms while controlling for the use of antidepressants (use vs. no use, low vs. high dose, and subgroups including selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants [TCAs], and other). Low- versus high-dose distinction was based on the average doses used in clinical practice for each antidepressant as assessed by one of the investigators. Again, BDI analysis was conducted as a continuous variable and as a dichotomized variable (<14 and ≥14). We fit linear mixed models for PDQe subscore and the use of antidepressants while adjusting for confounders. We also calculated the biserial correlation of dichotomized BDI (<14 and ≥14) and PDQe at baseline and 5 years.

Results

The main study enrolled 1,741 subjects. The 746 subjects that completed 5-year assessments were included in the analysis.

TABLE 1 Demographic and disease severity characteristics of cohort

Variable	Baseline (N = 1,741) Mean (SD, min, max)	Two-Sided *P* Value[a]	Baseline for Subjects With 5-Year Data (N = 746) Mean (SD, min, max)	Five-Year (N = 746) Mean (SD, min, max)
Age	61.79 (9.64, 24, 87)	0.68	62 (9.22, 33, 85)	67 (9.22, 38, 90)
Disease duration	1.54 (1.08, 0, 5.5)	<0.01	1.69 (1.16, 0.1, 5.3)	6.69 (1.16, 5.1, 10.3)
UPDRS Part I	1.32 (1.37, 0, 10)	0.01	1.14 (1.19, 0, 6)	2.25 (2.02, 0, 11)
UPDRS Part II	7.16 (3.95, 0, 28)	0.06	6.8 (3.64, 0, 21)	11.04 (6.08, 0, 45)
UPDRS Part III	17.76 (8.37, 0, 54)	0.14	17.05 (7.58, 2, 42)	22.56 (11.66, 1, 82)
UPDRS Part I (ND)	1.03 (1.1, 0, 7)	<0.01	0.89 (0.99, 0, 5)	1.81 (1.68, 0, 10)
UPDRS Part IV	1.33 (1.57, 0, 13)	0.09	1.21 (1.51, 0, 13)	2.95 (2.38, 0, 15)
BDI_total	6.87 (5.54, 0, 44)	0.02	6.24 (5.02, 0, 30)	8.57 (6.60, 0, 42)
TFC_total	12.04 (1.42, 3, 13)	0.07	12.17 (1.27, 5, 13)	10.34 (2.71, 0, 13)
SCOPA-COG	30.27 (5.35, 4, 43)	0.75	30.33 (5.39, 4, 43)	28.58 (7.07, 3, 42)
SDMT_total	44.45 (11.72, 0, 81)	0.49	44.14 (11.19, 6, 81)	42.36 (14.77, 0, 81)
EQ-5dhlth	81.33 (13.85, 2, 100)	0.39	82.38 (12.19, 5, 100)	75.86 (16.03, 0, 100)
EQ-5d_total	0.81 (0.18, −0.09, 1)	<0.01	0.84 (0.16, −0.02, 1)	0.73 (0.22, −0.43, 1)
PDQ-39_mobility	11.52 (16.2, 0, 97.5)	<0.01	9.01 (13.55, 0, 90)	22.66 (23.44, 0, 100)
PDQ-39_ADL	15 (15.57, 0, 100)	0.02	13.16 (13.81, 0, 100)	24.48 (20.83, 0, 100)
PDQ-39_emotional	14.07(14.93, 0, 91.67)	<0.01	12.14 (13.47, 0, 87.5)	17.92 (18.25, 0, 95.83)
PDQ-39_stigma	12.94 (16.39, 0, 100)	0.09	11.39 (14.8, 0, 100)	13.41 (17.47, 0, 100)
PDQ-39_social	5.29 (11.60, 0, 83.33)	0.09	4.42 (10.34, 0, 75)	8.18 (14.67, 0, 100)
PDQ-39_cognition	15.03 (15.11, 0, 81.25)	0.02	13.31 (13.78, 0, 75)	22.98 (18.58, 0, 93.75)
PDQ-39_communic	11.29 (14.57, 0, 91.67)	0.02	9.95 (13.74, 0, 91.67)	19.22 (19.90, 0, 100)
PDQ-39_discomfort	20.84 (19.06, 0, 100)	0.07	18.96 (17.37, 0, 83.33)	27.76 (21.94, 0, 100)
PDQ-33[b]	13.12 (10.61, 0, 78.57)	<0.01	11.46 (9.34, 0, 65.3)	19.77 (14.37, 0, 81.61)
mRS[c]	1.22 (0.48, 0, 3)	0.30	1.20 (0.45, 0, 3)	1.75 (0.87, 0, 5)
% Antidepressant	22.86	0.63	21.98	30.56
No. of BDI ≥14 (%)	206 (11.83%)	0.05	68 (9.12%)	132 (17.69%)

[a]*P* value represents the *P* value for the full cohort of subjects (N = 1,741) and the subset that had 5-year data (N = 746; Wilcoxon's sum-rank test) cohort.
[b]PDQ-33 is the score of all PDQ-39 summation except emotional part and then divided by 7.
[c]mRS scores were measured in relation to PD disability at baseline versus overall disability at year 5.

doi:10.1002/mdc3.12205

Table 1 shows the demographic characteristics for all subjects at baseline (N = 1741) and at 5 years (N = 746). There were significant differences in baseline characteristics between the entire cohort and the 5-year outcome subset. Specifically, the 5-year cohort had longer disease duration ($P < 0.01$), lower UPDRS Part I baseline score ($P = 0.01$), better mobility ($P < 0.01$) and emotional ($P < 0.01$) subscores of PDQ-39, and better PDQ-33 score ($P < 0.01$). Mean age of the cohort was 62 years (standard deviation [SD]: 9.22), and mean disease duration was 1.69 years (SD, 1.16). Mean baseline BDI score was 6.24 (SD, 5.02) and increased to 8.57 (SD, 6.60) by 5 years. At baseline, 11.8% (n = 206) of subjects had a BDI ≥14, and at 5 years 17.6% (n = 132) had a BDI ≥14.

In the univariate analysis, baseline BDI score was strongly associated with rate of change of all measures of disease severity and disability examined regardless of whether BDI was assessed as a continuous variable or dichotomized. Coefficients of association and *P* values between baseline BDI and all measures of disease severity are provided in Table 2. Of note, coefficients of association were of greater magnitude when we ran the analysis with the BDI as a dichotomized variable. The change of BDI from baseline to 5 year was also associated with the changes from baseline to 5 years of all major measures of disability except TFC score ($P = 0.51$), SDM score ($P = 0.64$), and PD subtype ($P = 0.1$; Table 3).

In the multivariate analysis (Table 4), using change in BDI from baseline to 5 years as the outcome measure, BDI score change was associated with 5-year UPDRS Part I score change (with depression item removed [ND]; $P < 0.01$), but not UPDRS ADL change ($P = 0.28$) or UPDRS motor score change ($P = 0.19$). It was also associated with PDQ-33 change ($P < 0.01$) and EQ-5D VAS change ($P = 0.02$). It was not associated with 5-year change of cognitive measures ($P = 0.17$ for SCOPA-COG). This was a fairly representative model, with these four significant variables (TFC, UPDRS Part I [ND], PDQ-33, and EQ-5D VAS) and other adjusted covariates explaining approximately 68.8% of the variation of the BDI score 5-year change based on the R^2_{LR} calculation.

At baseline, 22% of patients were using antidepressants, compared to 30.5% at 5 years (Table 1). Higher baseline BDI score was associated with higher baseline antidepressant use ($P = 0.045$) and "higher dose" antidepressants ($P < 0.01$) in the cohort at large, but when we analyzed only those patients who completed the 5-year analysis, there was no significant relationship at baseline or at 5-year follow-up (Table 5). Higher PDQe score was also associated with higher baseline antidepressant use ($P < 0.01$, data not shown). The correlation between 5-year PDQe score and 5-year dichotomized BDI score was 0.77.

Discussion

Our analysis demonstrates that worse baseline depressive symptoms, as measured by BDI score, were associated with greater decline in multiple measures of motor and cognitive function, QoL, and disability in a large cohort of PD patients with relatively early disease. This observation is particularly significant when considering the overall low BDI score (mean, 6.87; n = 1,741) and low prevalence of depressive symptomatology as defined by BDI score of ≥14 (11.8%) in this cohort. Though BDI is not intended for the formal diagnosis of mood disorders, it is considered a reliable, valid measure of depression in PD and has been used for estimating the prevalence of depression in this population.[30,31] Though conclusions about causality cannot be made from this study, depressive symptoms, even in the absence of depression in early disease, may be an important clinical predictor of future multimodal disease progression. Our results add evidence that fills a gap previously noted by Post et al., who stated that "limited evidence" exists for depression as a prognostic factor for progression of disability in PD.[19] However, some studies (mostly small, prospective studies) did conclude that depres-

TABLE 2 Univariate analysis of the associations of baseline BDI with changes in each of the major measures of disability in PD (N = 1,741)

	BDI Continuous			BDI Dichotomized (<14 vs. ≥14)		
Variable	Coefficient	95% CI	*P* Value	Coefficient	95% CI	*P* Value
UPDRS_total	0.67	[0.62, 0.72]	<0.01	8.54	[7.62, 9.47]	<0.01
UPDRS Part I	0.12	[0.12, 0.13]	<0.01	1.52	[1.42, 1.62]	<0.01
UPDRS Part I (ND)	0.08	[0.08, 0.09]	<0.01	1.02	[0.92, 1.11]	<0.01
UPDRS Part II	0.28	[0.26, 0.30]	<0.01	3.24	[2.95, 3.54]	<0.01
UPDRS Part III	0.27	[0.23, 0.30]	<0.01	3.57	[3.01, 4.14]	<0.01
UPDRS Part IV	0.08	[0.08, 0.09]	<0.01	0.94	[0.81, 1.07]	<0.01
TFC	−0.09	[−0.11, −0.08]	<0.01	−1.27	[−1.49, −1.04]	<0.01
SCOPA-COG	−0.08	[−0.12, −0.04]	<0.01	−1.47	[−2.14, −0.80]	<0.01
SDMT	−0.24	[−0.28, −0.19]	<0.01	−2.51	[−3.30, −1.72]	<0.01
PDQ-33	1.17	[1.12, 1.21]	<0.01	14.29	[13.47, 15.77]	<0.01
PDQ-39	1.23	[1.19, 1.27]	<0.01	15.16	[14.35, 15.97]	<0.01
EQ-5D	−0.01	[−0.02, −0.01]	<0.01	−0.17	[−0.18, −0.16]	<0.01
EQ-5D VAS	−1.00	[−1.06, −0.94]	<0.01	−11.74	[−12.76, −10.73]	<0.01
LED	4.28	[3.32, 5.25]	<0.01	48.28	[31.86, 64.70]	<0.01
PIGD vs. TD	−0.01	[−0.02, −0.01]	<0.01	−0.15	[−0.25, −0.06]	<0.01

Each measure of disability was the response variable, whereas the BDI variable was the risk factor. All measures of disability, except TFC and SCOPA-COG, had annual measurements. TFC and SCOPA-COG were measured at baseline and year 5. PIGD versus TD is the ratio of tremor/PIGD.
[a]Coefficient for each variable refers to the change in the variable score that is associated with each unit increase in the BDI score. For example, the LED increases by 4 units with every unit increase in BDI score.
CI, confidence interval.

doi:10.1002/mdc3.12205

TABLE 3 Univariate analysis of the associations of change in BDI (from baseline to 5 years) with change in each of major measure of disability (from baseline to 5 years; N = 746)

Variable	Coefficient	95% CI	*P* Value
UPDRS_total	1.03	[0.87, 1.20]	<0.01
UPDRS Part I	0.17	[0.15, 0.19]	<0.01
UPDRS Part I (ND)	0. 12	[0.10, 0.13]	<0.01
UPDRS Part II	0.37	[0.31, 0.43]	<0.01
UPDRS Part III	0.50	[0.38, 0.62]	<0.01
UPDRS Part IV	0.09	[0.07, 0.12]	<0.01
TFC	−0.02	[−0.06, 0.03]	0.51
SCOPA-COG	0.15	[0.04, 0.27]	<0.01
SDMT	0.05	[−0.15, 0.24]	0.64
PDQ-33	1.42	[1.31, 1.54]	<0.01
PDQ-39	1.48	[1.37, 1.59]	<0.01
EQ-5D	−0.01	[−0.01, −0.005]	<0.01
EQ-5D VAS	−0.38	[−0.65, −0.11]	<0.01
LED	3.17	[0.77, 5.57]	0.01
PIGD vs. TD[a]	−0.02	[−0.03, −0.003]	0.10

[a]PIGD versus TD is the ratio of tremor/PIGD.
CI, confidence interval.

TABLE 4 Multivariate analysis of the association of BDI change (from baseline to 5 years) with change in major measurement of disability (from baseline to 5 years) in PD (N = 746)

Variable	Coeff.[a]	95% CI	*P*-value
UPDRS Part I (ND)	0.87	[0.59, 1.14]	<0.01
UPDRS Part II	−0.06	[−0.16, 0.05]	0.28
UPDRS Part III	0.03	[−0.01, 0.07]	0.19
UPDRS Part IV	0.09	[−0.09, 0.27]	0.30
TFC	0.26	[0.07, 0.45]	<0.01
SDM	0.02	[−0.02, 0.06]	0.28
SCOPA-COG	0.05	[−0.02, 0.13]	0.17
PDQ-33	0.26	[0.22, 0.30]	<0.01
EQ-5D	−1.96	[−4.29, 0.37]	0.10
EQ-5D VAS	−0.03	[−0.06, −0.01]	0.02
Age	−0.03	[−0.08, 0.02]	0.27
Gender (male vs. female)	−0.38	[−1.22, 0.45]	0.36
Race (white as reference group)			0.32
American Indian	−2.97	[−12.48, 6.54]	0.54
Asian	−0.003	[−2.26, 2.26]	1
Black	−1.04	[−3.62, 1.53]	0.43
Duration	0.18	[−0.15, 0.50]	0.28
Treatment (treatment vs. placebo)	0.16	[−0.59, 0.90]	0.68

Each measure of disability was the independent variable, while the BDI was the dependent variable (reverse analysis).
[a]Coefficient means the BDI total score change for a given variables score increase.
BDI, Beck Depression Inventory; PD, Parkinson's disease; CI, confidence interval; TFC, total functional capacity; SCOPA-COG, Scales for Outcomes in Parkinson's-Cognition; PDQ, Parkinson's Disease Questionnaire; EQ-5D VAS, EuroQOL Five Dimensional Questionnaire Visual Analog Scale.

sion is associated with progression in individual domains, such as cognitive decline,[32] ADL decline,[33] progression of H & Y,[33] and HRQoL.[13] Though depression was described as a predictor of UPDRS decline in one study,[34] it was not found to be a predictor of need for initiation of dopaminergic therapy in another.[15] Our study is particularly valuable given the large size of the cohort, the long duration of follow-up, and the assessment of multiple variables simultaneously.

Of significance, in our multivariate model, the BDI was associated with a measure of daily function (the TFC), and measures of QoL (the PDQ-33 and EQ-5D VAS), but not with specific motor or cognitive measures. There was also a significant association with UPDRS Part I (ND), which is a crude assessment of nonmotor impairment. Indeed, these four significant variables, two of which are measures of QoL, along with the other adjusted covariates, explained 68% of the variability in BDI score. A similar relationship between depression and QoL has been shown previously in the Global Parkinson's Disease Survey in which BDI score was shown to explain 58.2% of variability in the outcome of HRQoL.[2] It is instructive that, in our study, the association is noted even in a cohort of patients with relatively low BDI scores who do not meet the customary BDI cutoff for clinically significant depressive symptomatology. This highlights the importance of assessment for depressive symptoms in the PD population at large. Unfortunately, the design of this study would not allow for assessment of whether treatment of patients with low BDI scores would lead to improved QoL scores.

TABLE 5 Associations between 5-year BDI and 5-year antidepressant use (N = 746)

Variable	Coefficient	95% CI	*P* Value
Antidepressant 5-year use vs. no	1.82	[−1.58, 5.22]	0.29
Antidepressant high dose vs. low dose	1.09	[0.80, 2.99]	0.26
Subgroup			
SSRI vs. others	1.80	[−1.34, 4.95]	0.26
SNRI vs. others	2.48	[−0.72, 5.67]	0.13
TCAs vs. others	0.49	[−2.58, 3.55]	0.75
Significant demographic statistics			
Enroll year	7.31	[0.62, −14.01]	0.03

Please refer to text for explanation of analysis.
[a]Race were merged as: American Indian/Alaskan Native into Asian, and Native Hawaiian or Other Pacific into Black or African American.
[b]Coefficient means the 5-year BDI_total score change for an additional variable's score increase at 5 years.
CI, confidence interval.

The lack of association between longitudinal changes in BDI and the measures of motor disability was unexpected. Whereas Holroyd et al. came to a similar conclusion, finding that depression was associated with UPDRS ADL score, but not with motor score,[18] several previous studies have reported strong associations between UPDRS scores and depression.[7,17] Our data suggest that it may be the nonmotor items on the UPDRS that drive this association. Analysis of previously completed NET-PD Phase II studies indicated depression as one of the major variables contributing to the initiation of dopaminergic therapy in a PD untreated cohort.[14] This is consistent with our finding that each unit of BDI score increase was associated with a 48-unit incremental increase in LED. This highlights the point that the decision to increase dopaminergic therapy may not be driven solely by motor dysfunction and points to a possible role for nonmotor impairment in PD treatment decision making.

The lack of association between severity of depressive symptoms and measures of cognition (SCOPA-COG and SDMT) was unexpected. In the univariate model, SCOPA-COG, but not SDMT, was significantly associated with depression score; this may reflect an association between subjective cognitive

doi:10.1002/mdc3.12205

complaints and depression, which may not translate to more-objective findings. However, neither measure was significant in the multivariate analysis, despite the fact that a relationship between depression and cognitive function has been demonstrated in previous studies.[32,35] In a study following 70 PD patients for 4 years, Starkstein et al. concluded that there was more-rapid evolution of cognitive impairment among patients with greater baseline depression.[32] In a cross-sectional study of 82 PD patients, Fernandez et al. found that BDI score inversely correlated with Mini–Mental State Examination score.[35] The lack of association in our study may be explained by the use of different cognitive assessments, the low prevalence of depression in our cohort, or the effective treatment with antidepressants in many of the subjects.

The natural history of depression in PD has not been well defined. Although one study found that depression rates actually decline over the first 2 years after diagnosis of PD,[36] our study of early treated patients suggests that depressive symptoms do worsen over time and with greater disability. One study in particular[6] showed that mild depressive symptoms may herald more-severe depressive symptoms later on, and whether this is a cause or result of other modes of dysfunction in PD is unclear. The causal relationship between PD progression and depression, if there is one, remains unclear. Therefore, the results of the study must be interpreted with caution. Although our study was not designed to analyze whether treating depression had any impact on any disease progression variables, the result that treatment of depression did not even significantly impact the progression of BDI itself makes it unlikely that it would impact other variables.

The limitation of this study is the lack of a clinical assessment interview for depression; however, BDI is a well-accepted validated screening tool for depression. The study also lacks detailed information on other strategies for depression management, such as psychotherapy or counseling. Another limitation is the arbitrary separation of antidepressant use into "high" and "low" doses, and the fact that the indication for use of antidepressants (i.e., depression vs. anxiety) could not be assessed with this data set. This study should not be considered an assessment of prevalence of depression in early treated PD, given that the study enrolled a selected cohort of participants who might not be reflective of the PD population, although there was no BDI cutoff for enrollment. Likewise, the generalizability of the data may be limited by the fact that the 5-year cohort was biased toward having lower baseline depression scores and potentially milder disease. In assessing the "natural history" of depression in this cohort, we focused on change in BDI from study initiation to the 5-year endpoint; annual interim assessments of depression would have made this a more complete analysis, but were not available in the data set. The strength of the study is the large size of the cohort that was followed for 5 years with a wide scope of validated assessments that allowed us to run association analyses.

Conclusions

Worse baseline BDI scores, even in the absence of frank depression, are associated with greater decline in multiple measures of disease severity in PD. The strongest association is with QoL, rather than motor and cognitive measures. Screening for depression may be useful prognostically. Speculation about a causal relation between depression and other aspects of disease progression may lead to future studies. Likewise, our conclusions lead to the question of whether early treatment of depression can impact long-term disease outcomes.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

D.B.: 1A, 1B, 1C, 2A, 2B, 2C, 3A
S.L.: 1A, 1B, 1C, 2A, 2B, 2C, 3B
H.F.: 1C, 2C, 3B
K.C.: 1C, 2C, 3B
M.A.: 1C, 2C, 3B
S.P.: 1C, 2C, 3B
H.W.: 1C, 2C, 3B
D.R.: 1C, 2C, 3B
C.C.: 1C, 2C, 3B
R.D.: 1C, 2C, 3B
C.S.: 1C, 2C, 3B
I.B.-W.: 1C, 2C, 3B
R.H.: 1C, 2C, 3B
D.T.: 1C, 2C, 3B
Z.M.: 1B, 1C, 2C, 3B
S.G.: 1C, 2C, 3B
M.H.: 1C, 2C, 3B
E.H.: 1C, 2C, 3B
T.S.: 1A, 1B, 1C, 2A, 2B, 2C, 3B

Disclosures

Funding Sources and Conflicts of Interest: The main NINDS Exploratory Trials in Parkinson's Disease study on which this analysis is based was funded by the National Institutes of Health/National Institute of Neurological Disorders and Stroke. The authors report no conflicts of interest.

Financial Disclosures for previous 12 months: D.B. has received royalties from the *British Medical Journal*. H.F. has received research support from AbbVie, Acadia, Biotie Therapeutics, EMD-Serono, Merck, the Michael J Fox Foundation (MJFF), the International Parkinson and Movement Disorder Society (MDS), the National Institutes of Health/National Institute of Neurological Disorders and Stroke (NIH/NINDS), Novartis, Parkinson Study Group, Synosia, and Teva. He has received honoraria from Prime Education, Inc, Ohio State University, MDS, Carling Communications, Auspex Pharmaceuticals, Britannia, GE Healthcare, Merz Pharmaceuticals, and Pfizer Pharmaceuticals. He has received royalty payments from Demos Publishing. K.C. has received financial support for his research from the NIH. He has received grant support from the NIH, the MJFF, and the Huntington Study Group. He has

doi:10.1002/mdc3.12205

served as a consultant for Medtronic, Inc., and Accordant. He has received royalties from UpToDate and Demos Health. M.A. has received financial support from the NINDS to fund research. He has received royalties from Elsevier, McGaw-Hill, and Oxford University Press for published works. S.P. has received research grant support from the NIH. He is a shareholder and employee of the Minneapolis Clinic of Neurology, Ltd., a for-profit entity. He has participated in clinical and drug trials sponsored by the NIH, the National Parkinson Foundation (NPF), the MJFF, Schering-Plough, Biotie, Synosia, Phytopharm, Schwartz, Impax, Merck, Adamas, Pharma 2B, Chelsea, and Teva. Harrison Walker, MD has received research grant support from the NINDS. D.R. has served as a consultant on the speaker bureau for Teva Neuroscience and GE Healthcare. C.C. has received financial support from the NIH, the MJFF, and Kinemed Inc to fund research. R.D. has received research grant support from the NIH. He has served as a consultant for Impax Pharmaceuticals. He has been a speaker for Teva Pharmaceuticals and UCB Pharma. I.B.-W. has received financial support for research from the MJFF. R.H. has received research grant support from the NINDS. He has also received financial support from the MJFF. D.T. has received research grant support from AbbVie, Acadia Pharmacia, Adamas Pharmaceuticals, Auspex Pharmaceutical, GE Healthcare, Ipsen Pharmaceuticals, Kyowa Hakko Kirin Pharma, Merz Pharmaceuticals, and the NINDS. He also received royalties from Cambridge University Press, Demos Publishing company, and Wiley company. He has received honoraria from Ipsen Pharmaceutical. Z.M. has received financial support for research from the NIH, the MJFF, the NPF, AbbVie, and AVID. He has received consulting honoraria from Navidea. T.S. has served as a consultant and received honoraria from Novartis, Ibsen, General Electric, UCB Pharma, TEVA, IMPAX, Merz, Boehringer Ingelheim, the NPF, and GlaxoSmithKline. She has also received research support from the NIH, the MJFF, TEVA, IMPAX, the NPF, and the Northwestern Memorial Foundation.

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doi:10.1002/mdc3.12205