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Anxiety and self-perceived health status in Parkinson's disease

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Abstract

Both anxiety and depression are associated with lower self-perceived health status (HS) in persons with Parkinson's disease (PD). Given the high co-morbidity with depression and other non-motor symptoms, it is unclear whether anxiety disorders, in general, versus specific anxiety subtypes have an independent effect on HS in PD. To examine this question, comprehensive assessments of motor and non-motor symptoms from 249 subjects with idiopathic PD followed in three community-based movement disorders neurology practices were analyzed. HS was measured using the 8-item PD Questionnaire (PDQ-8). Psychiatric diagnoses were established by consensus using a panel of six psychiatrists with expertise in geriatric psychiatry and movement disorders. Stepwise multiple regression analyses were used, with the PDQ-8 score as the dependent variable, to identify independent predictors of HS among motor, psychiatric, and other non-motor variables. Among the anxiety disorders, only anxiety associated with motor fluctuations was an independent predictor of HS after accounting for co-morbid depression and other clinical features. In addition, depressive disorders were also an independent predictor of lower HS. Prevention or treatment of state-dependent anxiety may improve HS in persons with PD.

Keywords

Parkinson's disease; Non-motor symptoms; Anxiety; Psychiatric disorders; Quality of Life; Fluctuations

Introduction

Self-perceived health status (HS), measured as a self-rated assessment of the impact of health on one's ability to perform physical, emotional, and social activities, is an important therapeutic outcome in the treatment of patients with Parkinson's disease (PD).[1–4] HS is distinguished from quality of life (QOL) in that HS represents the impact of health on

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to health status.[1] Relative to the general population, patients with PD report a lower level of HS that further declines with increasing disease severity.[5,6] Both motor deficits and non-motor symptoms, particularly depression and anxiety, are important predictors of HS. [7–9]

A better understanding of the relative contributions of depression and anxiety to HS in PD is needed. Attempts to account for the contribution of psychiatric determinants of HS in PD have been confounded by high rates of co-morbidity between anxiety, depression, and other non-motor symptoms.[10–15] Although anxiety is among the most frequently occurring non-motor symptoms in PD and anxiety disorders are present in 40% of patients, most studies of HS or QOL in PD have focused on depression while the contribution of anxiety has been overlooked.[12,13,16]

The few studies examining anxiety symptoms in PD suggest that anxiety adversely affects HS. Anxiety severity is associated with lower HS across all domains of the 39-item Parkinson's Disease Questionnaire (PDQ-39), even after controlling for motor symptoms. [7,11] Furthermore, self-rated anxiety symptoms account for an additional 17% of variance in HS after controlling for depression.[9]

Since anxiety disorders comprise a heterogeneous group of conditions that involve either persistent or episodic anxiety phenomena, e.g., generalized anxiety versus panic disorder, it is important to determine whether anxiety subtypes have a differential impact on HS. This is particularly significant in PD because clinically significant anxiety disturbances often do not conform to Diagnostic and Statistical Manual for Mental Disorders 4th edition Text Revision (DSM-IV-TR) criteria. Frequently, anxiety is associated with the clinical features of PD. [12,16] Common examples are episodic anxiety associated with fluctuations in motor symptoms and antiparkinsonian medications, social phobia related to public exposure of motor symptoms, and disabling anticipatory anxiety resulting from fears that motor symptoms will affect function.[17,18] In an earlier analysis based on a subset of the current sample, lower HS, based on the 8-item Parkinson's Disease Questionnaire (PDQ-8), was associated selectively with diagnoses of panic disorder and DSM-IV-TR Anxiety Disorder Not Otherwise Specified (NOS), a diverse group with clinically significant anxiety.[16] However, the sample size in that study was inadequate to explore contributions of the Anxiety Disorder, NOS subtypes. Now with a larger sample size, the relationship between HS and anxiety disorder subtypes, depressive disorders, PD motor symptoms, and demographic characteristics was examined using multivariate analyses. Given their specific relationship to PD phenomena, it was predicted that the anxiety disorder subgroups would have a differential impact on HS. Clarification of the relative impact of anxiety on HS will help prioritize treatment strategies when such subtypes are present.

Methods

Participants

Subjects with idiopathic PD were recruited from a pool of 747 patients with PD followed in three community-based movement disorder neurology practices using a two-stage screening approach. Each neurologist mailed letters inviting their patients with PD to participate in a study evaluating the psychometric properties of depression rating scales [the Methods of Optimal Detection of Depression in PD (MOOD-PD) study]. Consenting individuals were excluded if Mini-Mental State Exam (MMSE) score was < 24. 269 subjects completed the screening visit. Secondary diagnostic psychiatric interviews were conducted in those who screened positive for a possible depressive disorder, based on the following criteria: (1) endorsed any degree of depression, apathy, anxiety, or irritability, as per self- or informant-report, (2) had current use of a psychiatric medications, or (3) reported a history or a current

diagnosis of a depressive disorder, or (4) every fourth negative screen (i.e., not meeting criteria 1, 2, or 3). Because only 10 of the first 143 subjects failed to qualify for diagnostic interviews based on these criteria, all subsequent study participants meeting the MMSE criterion completed diagnostic interviews. Nine other subjects discontinued participation or were lost to follow-up before the diagnostic interview and one participant did not complete the PDQ-8. The 249 subjects who completed diagnostic interviews and the PDQ-8 are the focus of this analysis. Our previous report included the first 127 of these subjects.[16] The study was approved by the Johns Hopkins Institutional Review Board, and informed consent was obtained from each participant and an informant when available.

Assessments

The screening visit included the MMSE, the Unified Parkinson's Disease Rating Scale (UPDRS), calculation of L-dopa equivalents,[19] Northwestern University Disability Scale (NUDS),[20] and an informant interview (n=223), administered by a trained study coordinator to obtain collateral information on psychiatric symptoms and diagnoses. The UPDRS Motor sub-score (part III) and H&Y were rated by the treating neurologist. Self-reported HS was measured by the PDQ-8, with higher scores indicating lower HS (n=249). [21]

A psychiatric diagnostic examination, conducted by a geriatric psychiatrist, used the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-Patient edition [22] (SCID) plus supplemental questions to establish lifetime psychiatric, medical, family, and social history, current cognitive, and motor status, and disturbances not included in the SCID (such as fluctuation-associated anxiety). A narrative summary of the history and mental state exam was prepared for each subject.

Consensus psychiatric diagnoses

As described previously, a panel of six psychiatrists with expertise in geriatric psychiatry and movement disorders used best-estimate diagnostic procedures[23] to establish consensus DSM-IV-TR current and lifetime psychiatric diagnoses in each subject. For each subject, two panel psychiatrists reviewed all available materials from the screening and diagnostic interviews (interviewing psychiatrist's narrative summary, the SCID diagnoses, clinician-rated scales, informant data, and neurological records) to determine independent diagnoses. All cases were then reviewed and discussed by the full panel to establish final consensus diagnoses when there were discrepancies between the two diagnosing psychiatrists or the diagnosing and interviewing psychiatrists. In order to capture clinically significant psychiatric disturbances that are not adequately characterized by DSM-IV-TR criteria, the panel assigned the DSM diagnosis "Anxiety Disorder Not Otherwise Specified (NOS)". In DSM-IV-TR, Anxiety disorder NOS includes mixed anxiety-depressive disorders, significant social phobic symptoms related to the social impact of having a general medical condition (e.g., PD), situations in which the disturbance is severe enough to warrant a diagnosis of Anxiety Disorder but the individual fails to report enough symptoms for full criteria for any specific Anxiety Disorder, and situations in which the clinician has concluded that an Anxiety Disorder is present but is unable to determine whether it is primary, due to a general medical condition, or substance-induced (e.g. anxiety associated with motor fluctuations related to dopaminergic therapy). Using these DSM guidelines, subjects with Anxiety Disorder, NOS were categorized into five subgroups based on presence of similar clinical symptoms: 1) fluctuation-associated anxiety (apprehension and fear occurring during motor or medication wearing-off periods), 2) anticipatory anxiety (excessive fear before planned events or when preparing for activities in the future, e.g. preparing to travel), 3) generalized worry (pervasive unease and excessive concern or obsession over mundane things that is clinically significant but lacking specific symptoms

so as to fail to meet full DSM criteria for generalized anxiety or obsessive-compulsive disorder), 4) 'panic-like' anxiety (episodic attacks of intense fear and worry that do not meet full criteria for panic disorder), 5) phobic-avoidant anxiety (excessive fear and avoidance of situations or objects because of PD-related phenomenon e.g. fear of heights, falling, or social interaction as a result of PD-related motor complications).

Statistical Methods

T-tests and χ^2 tests were used to compare the demographic and clinical differences between participants with and without an anxiety disorder, in addition to differences between distinct anxiety diagnoses and clinically significant anxiety symptom clusters. Multivariate linear regressions were used to test the hypothesis that specific anxiety disorders would have a selective relationship with HS. First, a saturated multivariate model was fit with the PDQ-8 as the dependent variable and the demographic variables, clinical variables, and anxiety categories listed in Table 1 as the independent variables. Then, likelihood-ratio testing was used to test reduced models sequentially and to determine the best fitting and most parsimonious model. Discrete psychiatric diagnoses and clinically significant anxiety symptom clusters were modeled as binary variables (including all DSM anxiety disorders and anxiety subtypes 1–5 as above, depression, psychotic disorders, and co-morbid anxiety and depressive disorders). UPDRS Part-III factor scores (tremor, rigidity, bradykinesia, and axial impairment) were used to improve the specificity of relationship between HS and motor symptoms.[24] Duration of dyskinesia, as rated by UPDRS Part IV, was treated as a binary variable (dyskinesias present/absent) to account for its skewed distribution. Interaction terms were used to assess the effect of co-morbid depression and anxiety diagnoses. Analyses were conducted using STATA statistical software (Version 9.0) (StataCorp, 2005). Statistical significance was set *a priori* at an unadjusted $\alpha=0.05$.

Results

An anxiety disorder was present in 104 subjects (42%, 95% CI: 32.0–51.2) (Table 1). Non-DSM specific anxiety syndromes were present in 55 subjects (22%, 95% CI:10.8–33.2). Thirty subjects (12%, 95% CI:8.24–16.7) had multiple anxiety diagnoses. Co-morbidity with depression was high; 57 subjects with an anxiety disorder also had a current depressive disorder (55%, 95% CI:44.7–64.6).

Table 1 used univariate analyses to compare subjects with anxiety to non-anxious subjects. Univariate analyses comparing complications of therapy from the UPDRS-IV between subjects with no anxiety and at least one active anxiety disorder and no anxiety and fluctuation-associated anxiety are presented in Table 2.

Of the 21 subjects with fluctuation-associated anxiety, 12 had more than one anxiety diagnosis including two with panic disorder, three with generalized anxiety disorder, two with social phobia, and five with a specific phobia. In addition to worse HS, Tables 1 and 2 show that fluctuation-associated anxiety is distinguished by greater prevalence in females, younger age onset of PD, longer disease duration, higher daily l-dopa equivalent dose, and more prevalent complications of therapy.

Multivariate linear regression tested the association between HS and anxiety disorders while controlling for demographic, psychiatric, medication, and PD-related clinical variables. When modeled as a single class of disorders, having at least one current anxiety disorder was not associated with HS after adjustment. However, when anxiety disorders were modeled as individual diagnostic categories only fluctuation-associated anxiety was independently associated with HS in the final multivariate model which accounted for 48% of the variance (Table 3). Other independent predictors of lower HS in the final model were

major depression, younger age, greater bradykinesia and UPDRS duration of dyskinesias, and ADL disability. Interaction terms for co-morbid psychiatric diagnoses were not statistically significant.

Discussion

The present study assessed the impact of anxiety disorder subtypes on HS in PD. We report a novel and selective association between fluctuation-associated anxiety, a non-DSM 'PD-specific' anxiety subtype, and HS. Other anxiety subtypes were not independently associated with HS after multivariate adjustment. Diagnosis of depression, younger age, ADL disability, bradykinesia and dyskinesia were also associated with poorer HS.

Anxiety presenting as a feature of non-motor fluctuations is recognized as a specific clinical problem, but its management remains ambiguous. Up to 66% of patients with PD and motor fluctuations experience anxiety.[18,25] While temporal correlates of anxiety, motor fluctuations, and dosing of dopaminergic medications have been examined,[26] fluctuation-associated anxiety as a discrete psychiatric disturbance that warrants specific treatment has been overlooked. One reason may be that non-motor fluctuations are regarded as a primary function of dopaminergic therapy, and therefore fall under the purview of neurological management. Another reason, however, may be that the current DSM nosological system fails to capture PD-specific psychiatric disturbances. This is clinically significant because long-term levodopa treatment almost inevitably leads to motor and non-motor fluctuations. In our sample, for example, anxiety disorders were associated with a longer duration of PD, and the group with fluctuation-associated anxiety had the longest duration of PD. Although subjects with fluctuation-associated anxiety were on significantly higher doses of l-dopa, total daily l-dopa equivalent dose[19] did not contribute to group differences in the final regression model. Failure to find this group effect was unexpected given the central role of l-dopa on fluctuations. While anxiety and mood fluctuations are related to measured l-dopa plasma levels, these effects may depend more on the rate of increase in l-dopa than the total dose; the experience of anxiety fluctuations may follow a different temporal pattern unrelated to l-dopa plasma levels.[27]

The basis for a selective relationship between fluctuation-associated anxiety and HS, as measured by the PDQ-8, is unclear. While the combined group of anxiety disorders in our series was associated with worse HS relative to subjects without anxiety diagnoses, the small number of patients in individual anxiety subgroups may have prevented detection of HS differences. Compared to non-anxious PD subjects, we found that the group with fluctuation-associated anxiety had a higher proportion of women, a younger age onset and longer duration of PD, a higher daily l-dopa dose, and greater dopaminergic complications of therapy. The PDQ-8 asks subjects to rate how often in the last month they have experienced certain problems "due to having Parkinson's disease." While the small sample size precludes conduction of an item analysis of the PDQ-8, the close association between motor symptoms and problems listed on the PDQ-8, e.g., muscle spasms, difficulties communicating, or social embarrassment, may contribute to higher scores in patients with motor fluctuations. For episodic anxiety disorders, in which anxiety symptoms are not directly linked to PD symptoms, correspondence to a PD-specific HS scale may be less likely. The presence of the fluctuation-associated anxiety subtype and its impact on HS in PD may also reflect a contribution of motor fluctuation severity that is not captured by the current version of UPDRS Part-IV.

Similar to other studies, we found that a depressive diagnosis, bradykinesia, dyskinesia, and disability correlated with poorer HS in PD.[1–4,7] At the time of the interview, 47% of the total sample had a depressive diagnosis, which was independently correlated with worse HS.

Although co-morbid anxiety and depression were common in our sample (55%), the interaction between these disorders was not associated with lower HS in the multivariate model. Other psychiatric disorders including psychosis were also unassociated with HS in the model. The association between younger age and poorer HS is consistent with previous studies.[28] Younger patients tend to report worse HS, even after accounting for disease severity, suggesting that the impact of PD on HS is moderated in part by independent psychosocial factors.[28]

The selective relationship between fluctuation associated-anxiety and HS raises an important consideration for clinical trials. In clinical trials that assess HS as an outcome, particularly those evaluating motor therapies for patients with advanced PD, anxiety and depressive disorders are likely to contribute independently to the HS measure, in addition to the effects of the primary motor intervention, e.g., deep brain stimulation. In clinical settings, recognizing effects of anxiety fluctuations on emotional, social, and physical functioning may encourage multidisciplinary approaches to management of these disabling phenomena, as opposed to a limited focus on medication manipulations to reduce motor fluctuations. Cognitive-behavioral therapy, for example, effectively reduces anxiety and depressive symptoms, and may be an important adjunctive treatment to consider when patients present with motor and non-motor fluctuations.[29] However, it is also important to recognize that other anxiety subtypes, including other subgroups of the Anxiety Disorder NOS classification, are not less important because of an absence of a discrete relationship with HS. By definition, diagnosis of a psychiatric disorder requires the presence of clinically significant distress or disability as a result of symptoms.

Our data suggest that the PDQ-8 is a useful outcome measure for HS in studies that include patients with non-motor anxiety fluctuations. Although the term HS has been used synonymously with “quality of life”, HS can be distinguished by its focus on the perceived impact of PD on functioning rather than an assessment of the subject's internal experiences and level of life satisfaction despite the burdens of the disease.[1,3] Whether the selective association with HS would be limited to fluctuation-associated anxiety using other HS or quality of life scales has not been examined. A number of PD-specific and generic HS and quality of life measures are available, and the choice of instruments should be based on the goals of the study.[30] The measurement of anxiety and depressive symptoms within the PDQ-8 and other HS instruments introduces a confound in any analysis that investigates the relationship between affective disturbances and HS.[4] In the case of the PDQ-8, two of eight items overlap directly with DSM-IV-TR criteria for Major Depression: “Felt depressed” and “Had problems with your concentration.”[31] It is therefore not surprising that the PDQ-8 and the diagnosis of DSM-IVTR depression are highly correlated because the same clinical symptoms are assessed. The high rate of co-morbidity between anxiety, depression, and other PD-related symptoms may account for the bivariate associations between panic disorder and social phobia with lower HS in Table 1.

Another limitation to this study is the absence of validated criteria for defining non-DSM ‘PD-specific’ anxiety disorders. This may make replication of our findings difficult. To account for this and improve diagnostic accuracy, we used previously reported descriptions of fluctuation-associated anxiety and ‘panic-like’ anxiety to improve generalizability[17,18] and best-estimate diagnostic procedures that included an expert panel to determine all clinically significant psychiatric disturbances. In addition, previous work on the prevalence of neuropsychiatric symptoms using cluster analysis with the Neuropsychiatric Inventory in non-demented PD patients identified a subgroup of patients with medium-high scores on anxiety and medium-low scores on depression with low scores on most other symptoms.[32] This “anxiety” cluster identified by Kulisevsky et al appears to share many of the same

characteristics found in the anxiety subgroups identified in this study, supporting the assertion that this may be a valid clinical entity.

In summary, fluctuation-associated anxiety in PD is a significant predictor of lower HS, as measured by the PDQ-8. The heterogeneity of anxiety disorders and their high co-morbidity with depressive diagnoses must be accounted for when interpreting HS data from subjects with PD. The selective association of fluctuation-associated anxiety with HS suggests that it is a distinct clinical subtype of anxiety disorders that is specific to PD and warrants future research on its etiology, treatment, and contribution to HS outcomes when motor aspects of PD are the main focus of therapeutic interventions.

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References

Additional references #1, #27, and #32 were added at the request of the reviewers.

- [1]. Den Ouden BL, Van Heck GL, De Vries J. Quality of Life and Related Concepts in Parkinson's Disease: A Systematic Review. *Mov Disord.* 2007; 22:1528–37. [PubMed: 17523198]
- [2]. Karlsen KH, Tandberg E, Arslan D, Larsen JP. Health related quality of life in Parkinson's disease: A prospective longitudinal study. *J Neurol Neurosurg Psychiatry.* 2000; 69:584–89. [PubMed: 11032608]
- [3]. Schiehser DM, Han SD, Lessig S, Song D, Zizak V, Filoteo JV. Predictors of health status in nondepressed individuals with Parkinson's disease. *Arch Clin Neuropsychology.* 2009; 24:99–09.
- [4]. Schrag A. Quality of life and depression in Parkinson's disease. *J Neurol Sci.* 2006; 248:151–57. [PubMed: 16797028]
- [5]. Gomez-Esteban JC, Zarranz JJ, Lezcano E, Tijero B, Luna A, Velasco F, et al. Influence of motor symptoms upon the quality of life of patients with Parkinson's disease. *Eur Neurol.* 2007; 57:161–65. [PubMed: 17213723]
- [6]. Schrag A, Jahanshahi M, Quinn N. How does Parkinson's disease affect quality of life? A comparison with quality of life in the general population. *Mov Disord.* 2000; 15:1112–18. [PubMed: 11104193]
- [7]. Carod-Artal FJ, Ziolkowski S, Mourao Mesquita H, Martinez-Martin P. Anxiety and depression: Main determinants of health-related quality of life in Brazilian patients with Parkinson's disease. *Parkinsonism Relat Disord.* 2008; 14:102–8. [PubMed: 17719828]
- [8]. Quelhas R, Costa M. Anxiety, depression, and quality of life in Parkinson's disease. *J Neuropsychiatry Clin Neurosci.* 2009; 21:413–19. [PubMed: 19996250]
- [9]. Rahman S, Griffin HJ, Quinn NP, Jahanshahi M. Quality of life in Parkinson's disease: The relative importance of the symptoms. *Mov Disord.* 2008; 23:1428–34. [PubMed: 18543333]
- [10]. Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, et al. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disord.* 2009; 24:1641–9. [PubMed: 19514014]
- [11]. McKinlay A, Grace RC, Dalrymple-Alford JC, Anderson T, Fink J, Roger D. A profile of neuropsychiatric problems and their relationship to quality of life for Parkinson's disease patients without dementia. *Parkinsonism Relat Disord.* 2008; 14:37–42. [PubMed: 17627863]
- [12]. Menza MA, Robertson-Hoffman DE, Bonapace AS. Parkinson's disease and anxiety: Comorbidity with depression. *Biol Psychiatry.* 1993; 34:465–70. [PubMed: 8268331]

- [13]. Nuti A, Ceravolo R, Piccinni A, Dell'Agnello G, Bellini G, Gambaccini G, et al. Psychiatric comorbidity in a population of Parkinson's disease patients. *Eur J Neurol*. 2004; 11:315–20. [PubMed: 15142224]
- [14]. Shulman LM, Taback RL, Bean J, Weiner WJ. Comorbidity of the nonmotor symptoms of Parkinson's disease. *Mov Disord*. 2001; 16:507–10. [PubMed: 11391746]
- [15]. Henderson R, Kurlan R, Kersun JM, Como P. Preliminary examination of the comorbidity of anxiety and depression in Parkinson's disease. *J Neuropsychiatry Clin Neurosci*. 1992; 4:257–64. [PubMed: 1498578]
- [16]. Pontone GM, Williams JR, Anderson KE, Chase G, Goldstein SA, Grill S, et al. Prevalence of anxiety disorders and anxiety subtypes in patients with Parkinson's disease. *Mov Disord*. 2009; 24:1333–8. [PubMed: 19425086]
- [17]. Racette BA, Hartlein JM, Hershey T, Mink JW, Perlmutter JS, Black KJ. Clinical features and comorbidity of mood fluctuations in Parkinson's disease. *J Neuropsychiatry Clin Neurosci*. 2002; 14:438–42. [PubMed: 12426412]
- [18]. Witjas T, Kaphan E, Azulay JP, Blin O, Ceccaldi M, Pouget J, et al. Nonmotor fluctuations in Parkinson's disease: Frequent and disabling. *Neurology*. 2002; 59:408–13. [PubMed: 12177375]
- [19]. Romito LM, Scerrati M, Contarino MF, Bentivoglio AR, Tonali P, Albanese A. Long-term follow up of subthalamic nucleus stimulation in Parkinson's disease. *Neurology*. 2002; 58:1546–50. [PubMed: 12034798]
- [20]. Canter GJ, De La Torre R, Mier M. A method for evaluating disability in patients with Parkinson's disease. *J Nerv Ment Dis*. 1961; 133:143–47. [PubMed: 13876261]
- [21]. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The PDQ-8: Development and validation of a short-form Parkinson's disease questionnaire. *Psychology & Health*. 1997; 6:805–14.
- [22]. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, J. Structured clinical interview for DSM-IV-TR axis I disorders, research version, non-patient edition (SCID-I/NP). Biometrics Research, New York State Psychiatric Institute; New York: November. 2002
- [23]. Leckman JF, Sholomskas D, Thompson WD, Belanger A, Weissman MM. Best estimate of lifetime psychiatric diagnosis: A methodological study. *Arch Gen Psychiatry*. 1982; 39:879–83. [PubMed: 7103676]
- [24]. Levy G, Tang MX, Cote LJ, Louis ED, Alfaró B, Mejia H, et al. Motor impairment in PD: relationship to incident dementia and age. *Neurology*. Aug 22; 2000 55(4):539–44. [PubMed: 10953188]
- [25]. Gunal DI, Nurichalichi K, Tuncer N, Bekiroglu N, Aktan S. The clinical profile of nonmotor fluctuations in Parkinson's disease patients. *Can J Neurol Sci*. 2002; 29:61–4. [PubMed: 11858538]
- [26]. Maricle RA, Nutt JG, Carter JH. Mood and anxiety fluctuation in Parkinson's disease associated with levodopa infusion: Preliminary findings. *Mov Disord*. 1995; 10:329–32. [PubMed: 7651451]
- [27]. Kulisevsky J, Pascual-Sedano B, Barbanj M, Gironell A, Pagonabarraga J, Garcia-Sanchez C. Acute effect of immediate and controlled-release levodopa on mood in Parkinson's disease: A double-blind study. *Mov Disord*. 2007; 22:62–7. [PubMed: 17115388]
- [28]. Schrag A, Hovris A, Morley D, Quinn N, Jahanshahi M. Young-versus older-onset Parkinson's disease: Impact of disease and psychosocial consequences. *Mov Disord*. 2003; 18:1250–6. [PubMed: 14639664]
- [29]. Veazey C, Cook KF, Stanley M, Lai EC, Kunik ME. Telephone-administered cognitive behavioral therapy: A case study of anxiety and depression in Parkinson's disease. *J Clin Psychol Med Settings*. 2009; 16:243–53. [PubMed: 19404724]
- [30]. Marinus J, Ramaker C, van Hilten JJ, Stiggelbout AM. Health related quality of life in Parkinson's disease: A systematic review of disease specific instruments. *J Neurol Neurosurg Psychiatry*. 2002; 72:241–48. [PubMed: 11796776]
- [31]. Peto V, Jenkinson C, Fitzpatrick R. PDQ-39: A review of the development, validation and application of a Parkinson's disease quality of life questionnaire and its associated measures. *J Neurol*. 1998; 245(Suppl 1):S10–4. [PubMed: 9617716]

- [32]. Kulisevsky J, Pagonabarraga J, Pascual-Sedano B, Garcia-Sanchez C, Gironell A. Prevalence and correlates of neuropsychiatric symptoms in Parkinson's disease without dementia. *Mov Disord*. 2008; 23:1889–96. [PubMed: 18709682]

Table 1
Demographic and clinical features by current anxiety disorder status compared to individuals with no anxiety diagnosis

Anxiety Diagnosis	n	Age	Sex	MMSE	Age PD onset	PD duration	Hoehn&Yahr	Daily LDOPA dose	UPDRS part III	UPDRS part IV	NUDS	PDQ-8
Total Sample	249	66.3(10.3)	M166/F83	28.3(1.6)	58.0(12.8)	8.3(6.4)	2.2(0.7)	610.5(436.8)	18.1(11.0) n=241	3.6(3.2) n=236	41.7(6.0)	6.2(4.7)
No anxiety diagnosis	145	67.9(10.1)	M99/F46	28.4(1.6)	60.5(12.3)	7.4(5.7)	2.2(0.7)	578.1(353.1)	17.1(10.2) n=141	2.8(2.7) n=139	42.2(5.8)	5.3(4.5)
At least one anxiety diagnosis	104	64.0(10.1)**	M67/F37	28.2(1.6)	54.4(12.6)***	9.6(7.0)**	2.2(0.7)	655.7(530.6)	19.5(12.0) n=100	4.7(3.5) n=97***	41.0(6.1)	7.4(4.8)***
Anxiety Disorder Subtypes												
Agoraphobia	4	73.1(4.4)	M3/F1	27.3(1.0)	65.0(7.3)	8.1(4.9)	2.5(1.1)	495.0(98.8)	18.3(12.0)	3.8(3.6)	39.8(7.8)	8.8(7.2)
Generalized anxiety disorder	9	64.5(6.8)	M4/F5	27.6(1.1)	54.8(10.5)	9.8(4.5)	2.2(0.6)	562.2(422.7)	23.1(10.4) n=8	6.1(4.0)***	41.4(3.8)	7.2(4.2)
Obsessive/Compulsive disorder	2	55.9(5.6)	M2	29.0(1.4)	45.0(11.3)	10.9(5.7)	2.8(0.4)	757.5(1050.1)	33.0(1.4)	3.5(3.5)	45.5(0.7)	9.0(1.4)
Panic disorder	13	60.5(9.6)*	M12/F1*	28.2(1.8)	50.2(11.7)**	10.3(7.6)	2.3(0.8)	808.1(626.1)	25.9(12.5)**	5.2(3.0)**	39.6(7.7)	8.9(4.6)**
Social phobia	17	63.6(10.7)	M14/F3	28.5(2.0)	55.1(12.2)	8.4(6.0)	1.9(0.4)	523.8(427.4)	16.2(8.5)	6.0(3.1) n=13***	41.1(5.7)	8.7(5.0)**
Specific phobia	39	62.4(10.1)**	M27/F12	28.4(1.6)	53.4(13.0)**	9.0(7.2)	2.1(0.6)	688.2(561.1)	20.6(13.9) n=37	4.6(3.3) n=37***	41.5(5.8)	6.7(4.7)
Anxiety Disorder Not Otherwise Specified - Subgroups												
a) anticipatory	7	60.9(11.0)	M4/F3	28.6(1.1)	55.6(11.4)	5.4(2.7)	1.8(0.8)	281.4(290.5)*	15.3(7.2)	2.8(4.3) n=6	45.4(2.1)	6.3(4.4)
b) fluctuating non-associated	21	64.1(8.3)	M7/F14**	27.8(1.5)	51.7(10.9)**	12.4(8.1)***	2.5(1.0)	982.1(494.1)***	22.0(15.4)	6.7(3.3)***	39.6(7.1)	9.8(4.2)***
c) generalized worry	11	68.1(11.4)	M8/F3	27.3(1.8)*	58.9(13.4)	9.2(5.5)	2.4(0.6)	522.7(417.9)	15.3(8.5) n=10	3.4(3.7) n=10	40.4(5.8)	5.6(5.5)
d) panic-free	7	69.6(8.1)	M4/F3	28.9(1.5)	61.9(10.0)	7.8(3.6)	1.9(0.6)	627.9(579.7)	20.4(6.8) n=5	2.9(3.0)	40.6(8.1)	6.9(5.1)
e) phobic avoidant	9	63.7(13.8)	M7/F2	28.0(1.4)	56.8(14.6)	6.9(5.3)	2.2(0.4)	407.8(256.3)	17.5(9.5) n=8	2.6(1.7)	41.4(4.5)	6.9(5.8)
Mean (SD)												

No cases of Post Traumatic Stress Disorder were identified. Unified Parkinson's Disease Rating Scale (UPDRS) Northwestern University Disability Scale(NUDS) 8-Item Parkinson's Disease Questionnaire(PDQ-8)

* p<.05,

** p<.01,

*** p<.001

Table 2

Motor complications of therapy from Unified Parkinson's Disease Rating Scale (UPDRS) part IV comparing subjects with no anxiety diagnosis to subjects with at least one anxiety diagnosis and fluctuation associated anxiety.

UPDRS part IV complications of therapy		No anxiety diagnosis, n=139	At least one anxiety diagnosis, n=97	Fluctuation-associated anxiety, n=21
Dyskinesias	duration	0.4 (0.6)	0.8 (1.0) ***	1.1 (1.1) ***
	disability	0.2 (0.5)	0.4 (0.8) **	0.6 (0.9) **
	pain	0.1 (0.4)	0.3 (0.7) **	0.4 (0.7) **
Early Morning Dystonia		12.2%	19.6%	38.1% **
Fluctuations	predictable offs	25.2%	44.3% **	76.2% ***
	unpredictable offs	16.5%	39.2% ***	66.7% ***
	sudden offs	9.4%	26.8% ***	47.6% ***
	proportion of the day off	0.4 (0.6)	0.8 (0.7) ***	1.1 (0.6) ***
Other Complications	anorexia, nausea, vomiting	15.1%	16.5%	9.5%
	sleep disturbances	60.4%	66.0%	66.7%
	symptomatic orthostasis	32.4%	34.0%	42.9%

Mean (SD)

Fluctuation associated anxiety and at least one anxiety diagnosis were not compared because the groups overlap.

*
p<.05,

**
p<.01,

p<.001

Table 3

Multivariate regression for demographic and clinical predictors of self-perceived health status using the PDQ-8

QOL predictors	β coefficient	SE	95% CI	P
Age	-.119	.024	-.166 -.072	<0.0001
Northwestern University Disability Scale	-.302	.043	-.386 -.217	<0.0001
Depressive disorders	3.09	.480	2.14 4.03	<0.0001
Fluctuation-associated anxiety	1.85	.822	.230 3.47	0.025
UPDRS Bradykinesia Subscore	.127	.063	.002 .251	0.046
UPDRS Dyskinesias Duration	.800	.380	.052 1.55	0.036

Unified Parkinson's Disease Rating Scale (UPDRS)