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Prevalence of Anxiety Disorders and Anxiety Subtypes in Patients With Parkinson's Disease

Gregory M. Pontone, MD[1], **James R. Williams, MHS**[2], **Karen Anderson, MD**[4], **Gary Chase, PhD**[8], **Susanne Goldstein, MD**[6], **Stephen Grill, MD, PhD**[6], **Elaina S. Hirsch, BS**[1], **Susan Lehmann, MD**[1], **John T. Little, MD**[1,5], **Russell L. Margolis, MD**[1], **Peter V. Rabins, MD**[1], **Howard Weiss, MD**[3,7], and **Laura Marsh, MD**[1,3]

[1]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD

[2]Department of Mental Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD

[3]Department of Neurology and Neurological Sciences, Johns Hopkins University School of Medicine, Baltimore, MD

[4]Departments of Psychiatry and Neurology, University of Maryland Medical Center, Baltimore, MD

[5]Departments of Psychiatry and Neurology, Georgetown University School of Medicine, Washington, DC

Abstract

Anxiety disorders are common in Parkinson's Disease (PD), but are not well-characterized. This study determined the prevalence and clinical correlates of all DSM-IV-TR anxiety disorder diagnoses in a sample of 127 subjects with idiopathic PD who underwent comprehensive assessments administered by a psychiatrist and neurologist. A panel of six psychiatrists with expertise in geriatric psychiatry and/or movement disorders established by consensus all psychiatric diagnoses. Current and lifetime prevalence of at least one anxiety disorder diagnosis was 43% (n=55) and 49% (n=63), respectively. Anxiety Disorder Not Otherwise Specified, a DSM diagnosis used for anxiety disturbances not meeting criteria for defined subtypes, was the most common diagnosis (30% lifetime prevalence, n=38). Compared to non-anxious subjects, panic disorder (n=13) was associated with earlier age of PD onset [50.3(12.2) vs. 61.0(13.7) years, p<.01], higher rates of motor fluctuations [77% (10/13) vs. 39% (25/64), p=.01] and morning dystonia [38% (5/13) vs. 13% (8/62), p<.03]. This high prevalence of anxiety disorders, including disturbances often not meeting conventional diagnostic criteria, suggests that anxiety in PD is likely under-diagnosed and under-treated and

Correspondence to: Laura Marsh, M.D., Johns Hopkins University School of Medicine, 600 N. Wolfe Street- Phipps 300, Baltimore, MD 21287, lmarsh@jhmi.edu/ o:410-502-6945; f: 410-614-3676.
[6]Parkinson's and Movement Disorders Center of Maryland, Elkridge, Maryland
[7]Department of Neurology, Sinai Hospital, Baltimore, Maryland
[8]Department of Health Evaluation Science, Pennsylvania State University, Hershey, Pennsylvania (Posthumous)

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refined characterization of anxiety disorders in PD is needed. In addition, certain anxiety subtypes may be clinically useful markers associated with disease impact in PD.

Keywords

Parkinson's disease; Non-motor symptoms; Anxiety; Psychiatric disorders

Introduction

Clinically significant anxiety disturbances occur in up to 40% of Parkinson's disease (PD) patients, a prevalence markedly higher than in healthy or comparably disabled elderly controls.(1;2) Furthermore, the presence of an anxiety disorder in persons with PD correlates with greater disability (3;4) and worse health-related quality of life.(5)

As a diagnostic group, anxiety disorders are heterogeneous, including both sustained conditions such as generalized anxiety disorder (GAD) and episodic disturbances such as phobias and panic disorder. In PD samples, panic disorder, GAD and phobias are reported to be the most prevalent anxiety disorder subtypes.(1;2;6-8) Anxiety disturbances that are unique to PD, such as episodic anxiety associated with fluctuations in motor symptoms and antiparkinsonian medications, are also reported. (3;4;7) For example, in a university based movement disorders clinic (n=42), 29% of PD subjects had *Diagnostic and Statistical Manual of Mental Disorders (DSM)-III* anxiety diagnoses, but an additional 40% had anxiety symptoms that did not meet criteria for a DSM diagnosis.(7) In one of the largest studies (n=90) of psychiatric comorbidity in PD, panic disorder was reported as the most prevalent anxiety disorder, but results were skewed as patients with motor fluctuations were excluded and only three anxiety subtypes were assessed.(1)

The frequent co-occurrence of anxiety and PD raises the possibility of shared etiological processes.(2;3;7;8) For instance, family members of probands with PD have an increased risk of anxiety (and depression),(9) and development of an anxiety disorder is associated with the later development of PD.(10) These studies did not subdivide anxiety into specific disorders; thus it is unclear whether the association is due to one or more anxiety subtypes or some latent factor.

Explicit characterization of anxiety subtypes in PD and their clinical correlates may provide insights that guide future investigations of the pathophysiology and treatment of anxiety disturbances in PD. Diagnostic clarity is critical for the validation of anxiety symptom rating scales in PD samples, a priority established recently by a Movement Disorder Society Task Force.(11) We therefore examined the prevalence of anxiety disorder subtypes in a community physician-based sample of subjects with idiopathic PD, determined how well these disorders are described by DSM-IV-TR nosology, and investigated the associations of specific types of anxiety with demographic and clinical factors.

Methods

Subjects were adult men and women with idiopathic PD (12) recruited from the practices of three community-based movement disorder specialists. Consenting individuals with PD were screened and excluded if their Mini-Mental State Exam (MMSE) score was < 24. Initially, diagnostic psychiatric interviews were conducted only in subjects identified by self-report or informant as endorsing any degree of depression, apathy, anxiety, or irritability, taking psychiatric medications, or reporting a history or a current diagnosis of a depressive disorder as well as in 25% of those not meeting these criteria. As only 10 of the first 143 subjects

screened negative based on these criteria, diagnostic interviews were conducted in all subsequent study participants meeting MMSE criterion. Of the 157 individuals who completed screening, 127 completed diagnostic interviews and are the focus of this analysis, 13 were excluded for dementia, 10 screened negative for mood symptoms or were not the 4th negative screen and did not undergo diagnostic interviews, and 7 withdrew from the study after screening due to lack of interest (3) or medical conditions (4) that prevented follow-up visits.

The diagnostic examination was conducted by a psychiatrist using the Schedule for Clinical Interview and Diagnosis (SCID) for DSM, 4th edition, Text Revision (DSM-IV-TR) (13) plus supplemental questions regarding lifetime psychiatric, medical, family, and social history, current cognitive, mental, and motor status, and disturbances not included in the SCID (such as non-motor mood fluctuations). For 123 of the 127 subjects, an informant (e.g., spouse, other family member, or caregiver) was interviewed separately by a research coordinator. Using a modification of best-estimate diagnostic procedures,(14) a panel of six psychiatrists with expertise in geriatric psychiatry and/or movement disorders established by consensus all final psychiatric diagnoses, according to the DSM-IV-TR.(15) For each subject, this included joint review of information from the diagnostic interviews and informant data. The DSM-IV-TR diagnosis of Anxiety Disorder, Not Otherwise Specified (NOS) was used to classify clinically significant anxiety that did not meet DSM criteria for specific anxiety disorder diagnoses. PD symptoms were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) motor and complications of therapy sub-scores (16) and Hoehn and Yahr Stage (HY).(17) Health related quality of life (HrQOL) in PD was quantified using the 8-item Parkinson's Disease Questionnaire (PDQ-8), with lower scores indicating better HrQOL.(18)

Group differences in demographic variables (age, gender) and clinical characteristics (MMSE, rates of co-morbid depression, age at PD onset, symptom duration, HY stage, UPDRS motor sub-score, total L-DOPA equivalents,(19) and UPDRS motor complications items) were compared between subjects without a lifetime anxiety disorder and 1) subjects with any lifetime anxiety disorder or 2) with a specific anxiety disorder (panic disorder, agoraphobia without panic, social phobia, specific phobia, and anxiety disorder NOS), using χ^2 for categorical data and t-tests for continuous variables. The small group sizes of the OCD, GAD, and posttraumatic stress disorder (PTSD) diagnoses precluded statistical comparisons in this sample. Uncorrected p-values of 0.05 or less were considered statistically significant. The study was approved by the Johns Hopkins IRB, with all participants and their informants providing written informed consent.

Results

As shown in Table 1, nearly 50% of patients in the sample had a lifetime anxiety disorder; 20% had two or more anxiety diagnoses. Anxiety disorder NOS was the most common anxiety diagnosis. Among the 38 subjects with anxiety disorder NOS, 15 had excessive and recurrent situational anxiety related to motor deficits (e.g., fear of falling or fear and aversion of crowded places because of freezing of gait), 13 had clinically significant anxiety corresponding to ‘wearing off’ of antiparkinsonian medications, 12 had panic attack-like episodes not meeting DSM criteria for panic attack or disorder, 5 had persistent excessive anxiety and worry that did not meet DSM-IV-TR criteria for a diagnosis of GAD and 6 had more than one of these forms of anxiety.

Table 2 compares demographic and parkinsonian features between subjects with (n=63) and without (n=64) a lifetime DSM-IV-TR anxiety diagnosis. Subjects with a lifetime anxiety disorder were more likely to have a family psychiatric history, to have a lifetime history of a depressive disorder, to be taking an antidepressant, and to report a lower quality of life (Table 2). Co-occurrence of a current anxiety diagnosis and a current depressive disorder diagnosis

was 65%. Rates of dopamine agonist use were lower in subjects with a lifetime anxiety disorder, but l-dopa equivalency dose was comparable among patients with and without anxiety. There were no group differences in gender distribution (χ^2=0.19, p=0.66) or in any of the other demographic or parkinsonian features.

In comparisons of the specific anxiety diagnoses to the non-anxious group (n=64), panic disorder had differences in eight clinical features. (Table 3) Current age was younger in social phobia (n=11) [age=60.1(10.9) vs. 68.8(11.3) years, (p=.02)] compared to non-anxious subjects. Quality of life was poorer in subjects with anxiety NOS than in subjects with no anxiety diagnoses [7.6(4.8) vs. 5.3(4.5), p=.01]. There was a higher prevalence of depressive disorder in the anxiety NOS(p=.03) and specific phobia(p=.04) subgroups relative to the non-anxious group. The agoraphobia and social phobia groups did not have a higher prevalence of comorbid depressive disorders. There were no other group differences between the non-anxious group and any of the other anxiety diagnoses.

Discussion

In this community physician-based sample, lifetime prevalence was 49%and current prevalence was 43% for anxiety disorders in individuals with PD. This high prevalence of anxiety disturbances in PD underscores its prominence as a significant psychiatric co-morbidity in PD. Previous estimates have ranged from 28%-40%,(1;2;6;7;10;20;21) lower than observed in our study but still elevated over the rate in the general population or in medically ill groups with comparable physical disability.(2;7;22;23) The high prevalence rate in our study, despite ascertainment in a community sample in which lower rates of psychiatric comorbidity might be expected,(22) is likely the result of the comprehensive assessment strategies used in this study, including informant input, and the inclusion of all anxiety diagnoses, including Anxiety Disorder, NOS. We tentatively conclude that the nearly 50% rate of anxiety reported provides the best available estimate of the true rate of anxiety associated with community-based PD populations. The high rate of anxiety sufficiently severe to merit diagnosis as a disorder underscores the prominence of anxiety as a significant co-morbid feature of PD.

The most common diagnosis in our sample was Anxiety Disorder NOS, with a lifetime prevalence of 30%. In DSM-IV-TR, the Anxiety Disorder, NOS category is used for “disorders with prominent anxiety or phobic avoidance that do not meet criteria for any specific Anxiety Disorder.” Previous smaller studies describing anxiety in PD that did not fit into specific DSM categories found similar rates to our study (21-40%).(6;7) but the atypical nature of the anxiety in these subjects was not delineated. We found that over half of the subjects with the Anxiety Disorder NOS had anxiety related to motor fluctuations in the form of ‘wearing-off’ panic attacks or situational anxiety with phobic avoidance related to fear of experiencing off-periods or freezing.

The reason for the correlation between motor fluctuation and atypical forms of anxiety is not clear. In PD patients with motor fluctuations, anxiety could be a conditioned phenomenon in which “off periods” become associated with a fear of the inability to move. Alternatively, excessive anxiety or an underlying pathology associated with both anxiety and PD causes subjects to have a higher frequency of motor fluctuations. Regardless of the mechanism, the DSM-IV-TR diagnostic criteria do not consistently capture episodic anxiety associated with motor fluctuations because the episodes do not fit into preexisting diagnostic categories. Fluctuation-associated anxiety has previously been shown to correlate with level of disability, emphasizing the importance of recognition of this form of anxiety.(3;4) This is of particular importance as fluctuation associated anxiety, and other PD-specific forms of anxiety, may be related to dopamine,(24) and may not respond to the anxiety treatments used in the general population.

Specific phobia (19%), panic disorder (10%), and social phobia (9%) were the next most prevalent anxiety disorders in our sample, consistent with some previous studies.(1;2;6-8) One study found much higher rates (50%) of social phobia in PD patients.(25) As compared to prevalence estimates in the general population elderly (>60 years),(22;23;26) panic disorder, agoraphobia, specific phobia, and social phobia are more prevalent in our sample whereas PTSD is less prevalent; rates of OCD are similar across samples. These differential prevalence rates support our hypothesis that select anxiety disorders are associated with the etiology or neurodegenerative process of PD. Previous epidemiological studies show that anxiety, without specification of subtype, increases the risk of developing PD;(10;21) our results suggest that specific forms of anxiety may be most correlated with future PD. For example, 8 of 11 with social phobia had symptoms many years before the onset of PD (Table 3). By contrast, median age onset of specific phobia was 40 years in our sample, which is relatively later than the childhood onset of specific phobia in the general population. This later appearance of specific phobias may be related to emerging autonomic dysfunction, which is present in PD and regarded as integral to the pathophysiology of specific phobias.(27)

Panic disorder, of the anxiety subtypes frequent enough for statistical analysis in our study, was uniquely associated with an earlier age of PD onset and fluctuations in motor function. Earlier age of PD onset has been associated with a greater degree of genetic influence and subjects with young-onset genetic causes of PD are typically more prone to motor complications of treatment.(28) One possible implication of our findings is that panic disorder may be a marker for a discrete phenotype in PD. Consistent with this interpretation, panic disorder, including cases with panic onset before clinical motor symptoms, have been reported in PD associated with mutations in *parkin* and *LRRK2*.(29-31) From the standpoint of pathophysiology, the association of panic disorder with locus coeruleus and noradrenergic dysfunction in both PD and the general population (27;32-34) is consistent with Braak's theory (35) that the earliest pathological processes in PD involve non-dopaminergic systems in the lower brainstem. Specifically, damage to the locus coeruleus could account for a variety of non-motor manifestations of PD, including sleep disturbances, autonomic symptoms, and anxiety.(36;37) In addition, locus coeruleus dysfunction and anxiety-attacks have been associated with dyskinesia, on-off motor fluctuations, and other complications of antiparkinsonian treatment.(4;24;36;37) Whether PD subjects with panic disorder represent a subgroup with disproportionate involvement of the locus coeruleus and noradrenergic system is unclear.

The high lifetime and current co-occurrence of anxiety and depressive disorders in PD that we detected is consistent with previous findings.(1;7;20) Interestingly, we did not find a higher prevalence of anxiety in women, in contrast with the general population in which women have a higher prevalence of anxiety disorders than men.(1;7;38) While needing replication, this result supports the hypothesis that anxiety disorders are uniquely associated with PD, and may differ from anxiety disorders in the general population. As in previous investigations of PD, we found evidence that quality of life is worse for patients with anxiety disorders.(5;39) What our evidence indicates, however, is that this association is specific to particular subtypes of anxiety (Anxiety Disorder NOS and panic disorder), additional support for utility of distinguishing among different subtypes of anxiety disorder in PD.

Several limitations of this study are worth noting. First, individuals with psychiatric symptoms may have been more likely to participate in our study, thus yielding higher prevalence rates. In addition, exclusion of the 10 subjects who screened negative for mood symptoms and did not progress to a diagnostic interview could lead to overestimation of prevalence ranging from 0.11% to 3.62%, depending upon the number of screen-negative cases that would have been diagnosed with an anxiety disorder. Recall bias could also influence the information subjects or informants provided during the clinical interviews, affecting lifetime prevalence. We

attempted to limit this bias by reaching consensus diagnoses using a combination of a semi-structured interview, medical records, and an outside informant. Also, because of the exploratory nature of this study, we have reported associations without correcting for multiple comparisons; thus, replication of our findings in other samples is necessary. Finally, sample size limited comparisons of all identified anxiety subgroups or resulted in insufficient power in analyses. As this was a cross-sectional study, we were also unable to draw conclusions regarding the significance of higher rates of dopamine agonist use in the non-anxious group.

In conclusion, this investigation supports and extends previous findings demonstrating the high prevalence of anxiety in PD and the prominence of anxiety diagnoses in PD that do not fall into discrete DSM diagnostic categories. This study provides preliminary data suggesting that certain anxiety diagnoses are uniquely associated with PD and may be clinically useful as a marker associated with disease impact. Specifically, our study presents evidence suggesting that panic disorder and its association with younger age of PD onset and fluctuations in motor function represents an important anxiety subtype in this population. Anxiety disorders that do not meet DSM criteria have been overlooked in the literature and may be unrecognized in clinical practice despite their impact on quality of life and likely impact on disability.

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Table 1
Current and Lifetime Prevalence of DSM-IV-TR Anxiety Disorders in PD

DSM-IV-TR Anxiety Disorder	Current Prevalence % (n)	Lifetime Prevalence % (n)	Anxiety Median Age of Onset (years)
Any anxiety disorder	43 (55)	49 (63)	44
Two or more Anxiety disorders	13 (17)	20 (25)	---
Panic disorder	7.1 (9)	10 (13)	42
Agoraphobia without panic	1.6 (2)	4 (5)	59
Social phobia	7.9 (10)	8.7 (11)	23
Specific phobia	13 (17)	19 (24)	40
Obsessive-Compulsive disorder	0.8 (1)	1.6 (2)	42
Generalized anxiety disorder	3.2 (4)	3.2 (4)	59
Posttraumatic stress disorder	0.0 (0)	1.6 (2)	43
Anxiety disorder NOS	25 (32)	30 (38)	60

Table 2
Demographic and PD Features: PD patients with and without a Lifetime Anxiety Disorder

Demographic Features	Total sample (n=127)	Non-Anxious (n=64)	Anxiety Disorder (n=63)	p-value
Current Age (years)	67.0 (11.0)	68.8 (11.3)	65.1 (10.6)	.057
Gender (male/female)	83/44	43/21	40/23	.662
MMSE	28.1 (1.8)	28 (2.0)	28.2 (1.6)	0.726
Lifetime History Depressive Disorder, % (n)	65% (82)	55% (35)	75% (47)	**0.019**
Antidepressant Therapy, % (n)	47% (60)	38% (24)	57% (36)	**0.027**
Family Psychiatric History, % (n)	42% (53)	31% (20)	54% (33)	**0.010**
Quality of Life (PDQ-8)	6.2 (4.7)	5.3 (4.5)	7.1 (4.7)	**0.025**
PD Features				
Age Symptom onset (years)	59.0 (13.1)	61.0 (13.7)	57.0 (12.1)	0.088
Symptom Duration (years)	7.9 (5.5)	7.8 (5.9)	8.0 (5.1)	0.812
Hoehn and Yahr Stage	I-18, I ½-2 II-64, II ½-23 III-14, IV-5, V-1	I-6, I ½-1 II-31, II ½-14 III-9, IV-2, V-1	I-12, I ½-1 II-33, II ½-9 III-5, IV-3, V-0	0.447
UPDRS Motor Subscore	18.0 (10.2)	18.5 (10.9)	17.4 (9.4)	0.558
Total L-DOPA Equivalents	646 (412)	639 (356)	656 (463)	0.813
Agonist Use, %(n)	31% (39)	39% (25)	22% (14)	**0.039**
Presence of Motor Fluctuations	45.7% (58)	39.0% (25)	52.4% (33)	0.132

Mean (SD); UPDRS, Unified Parkinson's Disease Rating Scale

Table 3
Clinical Correlates of Panic disorder in PD

Clinical Features	Non-Anxious (n=64)	Panic Disorder (n=13)
Age (years)	68.8 (11.3)	59.6 (11.9)**
Lifetime History Depressive Disorder %(n)	55% (35)	85% (11)*
Age PD motor symptom onset (years)	61.0 (13.7)	50.3 (12.2)**
Presence of Motor fluctuations %(n)	39.0% (25)	77% (10)**
Unpredictable off periods %(n)	23% (14/62)	62% (8)**
Early morning dystonia %(n)	13% (8/62)	38% (5)*
Family Psychiatric History %(n)	31% (20)	69% (9)**
Health-related Quality of Life (PDQ-8)	5.3 (4.5)	9.3 (4.9)**

Mean(SD),

* $p \leq 0.05$,

** $p \leq 0.01$