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Defining Atypical Anxiety in Parkinson's Disease

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ABSTRACT: Background: Anxiety is a major complication in Parkinson's disease (PD). Many PD patients experience clinically significant anxiety not meeting Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) anxiety disorder criteria. This atypical anxiety (anxiety disorder not otherwise specified [NOS]) is often under-recognized and its diagnosis is underdeveloped.

Objectives: This study aimed to identify the demographic, psychiatric, and clinical characteristics of anxiety disorder NOS in PD.

Methods: A cross-sectional design studied a convenience sample of 184 PD patients without dementia recruited from neurology outpatient clinics. A semi-structured interview using DSM-IV criteria categorized PD patients into current anxiety disorder NOS (n = 28), DSM-IV anxiety disorders (n = 42) or no anxiety (n = 86) groups. Logistic regression modeling identified characteristics associated with the anxiety disorder NOS group compared to DSM-IV anxiety and no anxiety groups.

Results: The anxiety disorder NOS group was associated with motor complications of PD therapy, episodic, persistent and social anxiety symptoms, depression, non-motor experiences of daily living, poor quality of life, and female sex compared to the no anxiety group. Compared to DSM-IV anxiety, those with anxiety disorder NOS demonstrated greater global cognitive impairment, more severe motor complications of PD therapy, a greater severity and functional impact of dyskinesias, and greater complexity of motor fluctuations. Persistent, episodic, and social anxiety symptoms did not significantly differ between anxiety disorder NOS and DSM-IV anxiety groups.

Conclusions: These findings suggest that PD-specific symptoms characterize anxiety in a subgroup of PD patients who do not fulfill DSM-IV criteria for anxiety disorders.

Anxiety is one of the most poorly understood and undertreated non-motor symptoms in Parkinson's disease (PD).[1] The prevalence of Diagnostic and Statistical Manual of Mental Disorders (DSM) anxiety disorders in PD is estimated to be 31%[2]; 3 times more prevalent than the general elderly population.[3] However, a high proportion (13.3%) of PD patients experience clinically significant anxiety that does not meet DSM criteria for a diagnosable disorder.[2] Patients in this atypical category are diagnosed with unspecified anxiety disorder according to the DSM Fifth Edition (DSM-5), or anxiety disorder not otherwise specified (NOS) according to earlier editions. We used DSM Fourth Edition (DSM-IV) criteria and "anxiety disorder NOS" terminology as our study commenced in 2011 before the availability of the DSM-5. Our conclusions are not affected by changes in diagnostic criteria. Despite its prevalence, nearly 70% of PD patients with anxiety disorder NOS are untreated.[1] Accordingly, anxiety is considered 1 of the top 3 unmet needs in over 40% of PD patients[4] and avenues to reducing anxiety are high research priorities.[5]

The undertreatment of anxiety disorder NOS in PD can be explained by the complex symptomatology of anxiety in PD. Both the motor symptoms of PD and motor complications

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resulting from the dopaminergic medication (eg, levodopa) used to manage motor symptoms, appear to be related to anxiety.[6] Indeed, 75% of PD patients experience mood and/or anxiety symptoms during fluctuations between medicated "on" and "off" states, whereby anxiety increases as dopaminergic medication wears-off.[6–9] Furthermore, dyskinesias incurred by chronic dopaminergic medication use[10] have also been associated with anxiety.[11,12] This complex interplay between anxiety and motor fluctuations in PD can result in cyclical symptoms of anxiety, which are not consistently captured by anxiety disorder NOS criteria and impacts the use of anxiety rating scales.[13–15] Consequently, anxiety in PD patients is often under-recognized and poorly treated.[4]

There appears to be consensus in the literature that anxiety disorder NOS is capturing PD-specific anxiety, such as episodic anxiety associated with wearing-off dopaminergic medications.[4,14–16] In the few studies investigating the characteristics of anxiety disorder NOS in PD, motor complications of therapy seem to play an important role in the anxiety experienced by these patients. Specifically, a subgroup of PD patients with anxiety disorder NOS reported anxiety during wearing-"off" periods.[15] Moreover, patients with anxiety disorder NOS in our previous study reported social withdrawal because of medication "off" periods and worry related to both motor symptoms and wearing-off.[16] We have also demonstrated an association between anxiety disorder NOS and a higher overall motor complications of therapy score on the Movement Disorder Society Unified Parkinson's Disease Rating Scale Motor Complications subscale (MDS-UPDRS-IV).[1,17]

However, uncertainty about the nature of the PD-related anxiety captured by anxiety disorder NOS still remains. Improved characterization of these symptoms may facilitate increased recognition and more effective diagnosis and treatment of these patients. Given the reported associations between motor fluctuations, wearing-off, and anxiety in PD, we sought to build on our previous research (n = 90)[1] by incorporating a comprehensive investigation of PD motor symptoms and motor complications of therapy.[1,6–9,15] Although we previously demonstrated a greater overall motor complications of therapy severity score in PD patients with anxiety disorder NOS, we used a larger sample in the present study to investigate specific motor complications measured by MDS-UPDRS-IV items: time spent with, functional impact, and severity of dyskinesias; the functional impact, complexity, and severity of motor fluctuations; time spent in the "off" state and "off"-state dystonia. To the authors' knowledge, this is the first study to characterize anxiety disorder NOS in PD according to the motor symptoms arising as complications of PD therapy. For improved identification of anxiety disorder NOS in PD, the aims of this study were as follows: to investigate the phenomenology of anxiety disorder NOS based on its symptomatic characteristics; and to identify similarities and convergences in the profile of PD patients with anxiety disorder NOS compared to those with DSM-IV diagnosable anxiety disorders.

Method

Design and Participants

A total of 184 PD patients meeting United Kingdom Parkinson's Disease Society Brain Bank criteria for idiopathic PD[18] were recruited from outpatient neurology clinics in Brisbane, Australia. Data was collected from March 2011 to July 2019, and overlaps with our previous study (n = 90).[1] Novel components of this extension of our previous study include a larger sample size (n = 184) and extensive examination of motor complications and anxiety symptoms. To understand the anxiety symptoms in PD patients with anxiety disorder NOS, the Parkinson's Anxiety Scale (PAS),[19] made available after the initiation of our previous investigations,[1,9] was administered. Moreover, the Liebowitz Social Anxiety Scale (LSAS)[20] was administered, given reports of social anxiety concerns in this group and the high proportion of PD patients who experience social anxiety. Participants with another neurological disease, diagnosis of dementia based on neurologist report, or scoring <25 in the Standardized Mini Mental State Examination (SMMSE)[21] were excluded.

Data Collection Procedure

Participants completed a self-report questionnaire and attended a 90–120-minute interview assessing their global cognition, psychological, and parkinsonian symptoms. Participants were interviewed in their medicated "on" state and within 2 weeks of completing self-report measures.

Measures

Participants' age, sex, years of education, self-reported anxiety and apathy symptoms, and antiparkinson medication dosages were collected using the questionnaire. Tomlinson and colleagues' guidelines were used to calculate levodopa equivalent daily dose (LEDD).[22] The MDS-UPDRS and the Hoehn and Yahr (H&Y) Scale measured PD severity and progression.[17,23] The SMMSE[21] and Parkinson's Disease Cognitive Rating Scale (PD-CRS)[24] assessed global cognitive impairment, whereby lower scores indicate greater global cognitive impairment. Anxiety severity was assessed using the Hamilton Anxiety Scale (HAM-A),[25] PAS,[19] and LSAS.[20] The following measures assessed depression, apathy and quality of life, respectively: Hamilton Depression Rating Scale (HAM-D),[26] Starkstein Apathy Scale (SAS)[27] and Parkinson's Disease Questionnaire (PDQ-8).[28]

Anxiety disorders were diagnosed using DSM-IV criteria for current anxiety disorders via the Mini International Neuropsychiatric Interview Plus (MINI-Plus) in consultation with a psychiatrist (G.J.B.) and a research specialist in PD neuropsychiatry (N.N.D.)[29,30] Information about PD-specific symptomology (motor and non-motor PD symptoms and complications of therapy) was acquired via unscripted follow-up questions during the MINI-Plus assessment when patients referenced PD-specific symptoms related to their anxiety. Diagnosable disorders are listed in Table 1. According to DSM-IV criteria, an anxiety disorder must cause clinically significant distress or impairment in

TABLE 1 *Frequency of DSM-IV diagnosable anxiety disorders (n = 42)*

DSM-IV anxiety disorder	Frequency with DSM-IV anxiety disorder
Generalized anxiety disorder	22 (52%)
Panic disorder	7 (12%)
Agoraphobia	21 (50%)
Social phobia	18 (43%)
Specific phobia	5 (12%)
Obsessive-compulsive disorder	5 (12%)

Abbreviations: DSM-IV, Diagnostic and Statistical Manual Edition IV.
Thirty-one patients (74%) had concurrent DSM-IV anxiety diagnoses.

important areas of functioning. For example, generalized anxiety disorder (GAD) involves at least 6 months of prominent tension, worry and apprehension about everyday occurrences, and at least 3 of 6 other symptoms (eg, irritability).[29] Patients identified as having clinically significant anxiety symptoms impacting their daily functioning, but not meeting the DSM-IV criteria for diagnosable disorders (eg, persistent worries about PD symptoms), were diagnosed with anxiety disorder NOS. We have previously described this categorization.[31]

Data Analysis

Univariate and multivariate multinomial logistic regression models were constructed. Logistic regression assumes that continuous predictors are linearly related to log odds.[32] MDS-UPDRS Total and MDS-UPDRS-I yielded significant predictor by log odds interactions, thereby violating this assumption.[33] Therefore, these variables were dummy-coded.[34] As there were no cut-off guidelines for the MDS-UPDRS Total and subscale scores at time of publication, categorization by quartiles was attempted. However, sparsity of higher scores incurred wide confidence intervals (CI). Therefore, MDS-UPDRS Total and MDS-UPDRS-I scores were categorized using median splits. Bonferroni corrections were not applied as analyses were exploratory.[35]

Results

A total of 171 participants were eligible for analysis. Less than 5% of total values were missing. Little's missing completely at random (MCAR) test indicated the data were MCAR, χ^2 (121, 171) = 141.44, $P = 0.099$. Therefore, missing values were imputed using expectation maximization. Scores were considered univariate outliers at 3.29 standard deviation (SD) from the mean, which indicates a score is more extreme than the mean of the sample with $P < 0.001$.[36] All outliers were removed and the final sample comprised 156 participants; 62 (40%) were female, 94 (60%) were male and 14 participants (9%) were drug-naïve, whereas all others used levodopa. Participants' ages ranged from 43–86 years ($M = 67.90$ years, SD = 8.29). Twenty-eight (18%) participants met criteria for anxiety disorder NOS, 42 (27%) were diagnosed with a current DSM-IV anxiety disorder and 86 (55%) had no anxiety disorder.

Among the 28 participants with anxiety disorder NOS, qualitative evaluations during the MINI-Plus assessment revealed that 5 (18%) had clinically significant anticipatory anxiety (eg, related to motor-"off" periods), 8 (29%) had excessive and recurrent anxiety related to motor symptoms (eg, embarrassment), 14 (50%) had persistent excessive anxiety not meeting criteria for a diagnosis of GAD, 7 (25%) experienced panic not meeting criteria for panic disorder, 1 (4%) had agoraphobia-like symptoms, and 8 (29%) had more than 1 of these forms of anxiety (Table 1).

A consecutive subsample of 82 participants completed self-report measures of anxiety symptoms and apathy (PAS, LSAS, and SAS), included in an updated version of the patient questionnaire. The subsample comprised of 38 (46%) females and 44 (54%) males, ranging from 48 to 83 years (Mean [M] = 68.27 years, Standard deviation [SD] = 8.18). Nine (11%) participants were drug-naïve, all others used levodopa. Eight (10%) participants had anxiety disorder NOS, 27 (33%) had a DSM-IV anxiety disorder, and 47 (57%) had no anxiety disorder. Patient characteristics are summarized in Table 2.

Results of Univariate Logistic Regression Models (Adjusted for Age and Sex)

Univariate multinomial logistic regression models were constructed to identify the demographic, clinical, and psychiatric characteristics of anxiety disorder NOS compared to no anxiety and DSM-IV anxiety disorder groups (Table 3). Comparisons of the DSM-IV anxiety disorders to the no anxiety groups are reported in tables throughout the results for completion. In comparison to patients with no anxiety, the anxiety disorder NOS group demonstrated higher scores for HAM-A (OR, 95% CI = 1.27, 1.13–1.42; $P < 0.001$), HAM-D (OR, 95% CI = 1.28, 1.14–1.44; $P < 0.001$), PAS (OR, 95% CI = 1.18, 1.02–1.36; $P = 0.024$), PAS-persistent anxiety (OR, 95% CI = 1.28, 1.03–1.60; $P = 0.030$), PAS-episodic anxiety (OR, 95% CI = 1.52, 1.02–2.26; $P = 0.040$), LSAS total (OR, 95% CI = 1.04, 1.01–1.08; $P = 0.024$), LSAS-fear subscale (OR, 95% CI = 1.07, 1.00–1.15; $P = 0.044$), MDS-UPDRS-I (non-motor experiences of daily living) (OR, 95% CI = 4.24, 1.70–10.57; $P = 0.002$), and MDS-UPDRS-IV (motor complications of therapy) scores (OR, 95% CI = 1.38, 1.15–1.64; $P < 0.001$). Female sex (OR, 95% CI = 2.44, 1.02–5.85; $P = 0.046$) and a poorer quality of life (OR, 95% CI = 1.31, 1.06–1.61; $P = 0.013$) were also associated with the anxiety disorder NOS group compared to the no anxiety group.

Compared to those with DSM-IV anxiety disorders, the anxiety disorder NOS group showed lower HAM-A (OR, 95%

TABLE 2 *Descriptive statistics for demographic, clinical, and psychiatric characteristics of anxiety disorder NOS, DSM-IV diagnosable anxiety disorders, and no anxiety groups*

Variable (unit; scale range)	Total sample mean (SD)	Anxiety NOS mean (SD)	DSM anxiety mean (SD)	No anxiety mean (SD)
Demographic and clinical characteristics measured in total sample (n = 156)				
Sex (M/F)	94/62	14/14	19/23	61/25
Age (yr)	67.90 (8.29)	67.46 (9.60)	66.48 (8.13)	68.74 (7.90)
SMMSE (0–30)	28.62 (1.59)	28.61 (1.52)	29.24 (1.17)	28.33 (1.71)
PD-CRS (0–134)	95.46 (15.60)	94.71 (17.97)	97.64 (13.47)	94.64 (15.82)
HAM-D (0–60)	6.81 (5.72)	7.96 (5.07)	12.31 (5.74)	3.74 (3.17)
HAM-A (0–52)	6.40 (5.76)	7.86 (4.86)	11.71 (2.32)	3.33 (3.60)
PDQ-8 (0–8)	2.66 (2.20)	3.07 (1.20)	3.67 (2.32)	2.03 (2.01)
MDS-UPDRS Total (0–199)	40.33 (16.66)	38.93 (11.34)	46.11 (19.90)	37.97 (15.86)
MDS-UPDRS-I (0–16)	9.77 (5.92)	10.86 (3.57)	14.15 (6.82)	7.27 (4.61)
MDS-UPDRS-II (0–52)	9.43 (5.57)	8.96 (5.09)	10.51 (5.79)	9.06 (5.61)
MDS-UPDRS-III (0–108)	21.13 (10.59)	19.11 (8.85)	21.45 (11.47)	21.63 (10.71)
MDS-UPDRS-IV (0–23)	1.68 (2.49)	3.25 (3.04)	1.87 (2.71)	1.08 (1.90)
H&Y staging	1.83 (0.69)	1.96 (0.64)	1.77 (0.70)	1.87 (0.70)
Years education (yr)	12.29 (4.30)	11.69 (5.40)	12.83 (3.17)	12.22 (4.39)
PD duration (yr)	4.96 (4.73)	6.49 (4.04)	3.61 (2.68)	5.11 (5.52)
LEDD (mg)	529.86 (372.09)	673.35 (371.74)	450.73 (322.06)	521.78 (385.49)
Psychiatric characteristics measured in subsample (n = 82)				
Sex (M/F)	44/38	2/6	13/14	29/18
Age (years)	68.27 (8.18)	65.50 (8.77)	67.96 (8.07)	68.91 (8.21)
PAS (0–48)	9.79 (7.06)	11.50 (7.58)	15.11 (5.67)	6.45 (5.68)
Persistent anxiety (0–20)	5.98 (4.18)	7.25 (3.73)	8.85 (3.32)	4.11 (3.69)
Episodic anxiety (0–16)	1.93 (2.23)	2.38 (2.33)	3.44 (2.46)	0.98 (1.48)
Avoidance behavior (0–12)	1.89 (2.08)	1.88 (2.42)	2.81 (2.47)	1.36 (1.58)
LSAS (0–144)	35.32 (27.59)	42.32 (25.64)	56.06 (23.83)	22.22 (21.97)
Fear or anxiety (0–72)	18.26 (13.96)	21.38 (11.00)	28.52 (12.64)	11.83 (11.34)
Avoidance behavior (0–72)	15.70 (13.60)	16.37 (12.25)	24.77 (12.75)	10.31 (11.53)
SAS (0–42)	13.27 (5.98)	14.75 (5.80)	16.42 (5.86)	11.21 (5.29)

SMMSE, Standardized Mini Mental State Examination; PD-CRS, Parkinson's Disease Cognitive Rating Scale; HAM-D, Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale; PDQ-8, Parkinson's Disease Questionnaire; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; LEDD, levodopa equivalent daily dose; H&Y, Hoehn and Yahr; PAS, Parkinson's Anxiety Scale; LSAS, Liebowitz Social Anxiety Scale; SAS, Starkstein Apathy Scale.

CI = 0.87, 0.78–0.97; $P = 0.009$) and HAM-D scores (OR, 95% CI = 0.86, 0.77–0.95; $P = 0.003$). Avoidance behavior was significantly associated with DSM-IV anxiety compared to the no anxiety group (PAS OR, 95% CI = 1.54, 1.14–2.08; $P = 0.005$; LSAS OR, 95% CI = 1.10, 1.05–1.16; $P < 0.001$). Finally, when compared to the DSM-IV anxiety group, the anxiety disorder NOS group demonstrated greater MDS-UPDRS-IV scores (OR, 95% CI = 1.19, 1.01–1.42; $P = 0.044$).

Results of a Multivariate Model Investigating Motor Complications of Therapy in Anxiety Disorder NOS

A multivariate multinomial logistic regression model investigated the independent contributions of the severity of motor

TABLE 3 *Univariate multinomial logistic regression models comparing demographic, psychiatric, clinical, and global cognitive characteristics for anxiety disorder NOS, DSM-IV diagnosable anxiety disorders, and no anxiety groups*

Variable	Anxiety NOS vs. no anxiety OR (95% CI)	*P*	Anxiety NOS vs. DSM Anxiety OR (95% CI)	*P*	DSM anxiety vs. no anxiety OR (95% CI)	*P*
Demographic, clinical and global cognitive characteristics measured in total sample (n = 156)						
Sex[a]	2.44 (1.02–5.85)	0.046*	0.83 (0.32–2.15)	0.696	2.95 (1.37–6.35)	0.006**
Age	0.98 (0.93–1.03)	0.467	1.01 (0.96–1.07)	0.634	0.97 (0.93–1.01)	0.967
SMMSE[b]	1.02 (0.76–1.37)	0.879	0.69 (0.47–1.02)	0.065	1.48 (1.06–2.07)	0.020*
PD-CRS[b]	0.98 (0.95–1.02)	0.289	0.99 (0.95–1.03)	0.590	0.99 (0.96–1.02)	0.604
HAM-D[b]	1.28 (1.14–1.44)	<0.001***	0.86 (0.77–0.95)	0.003**	1.50 (1.32–1.70)	<0.001***
HAM-A[b]	1.27 (1.13–1.42)	<0.001***	0.87 (0.78–0.97)	0.009**	1.46 (1.30–1.65)	<0.001***
PDQ-8[b]	1.31 (1.06–1.61)	0.013*	0.89 (0.72–1.10)	0.291	1.47 (1.21–1.78)	<0.001***
MDS-UPDRS Total[b,c]	1.75 (0.71–4.32)	0.221	0.65 (0.24–1.76)	0.369	2.70 (1.19–6.14)	0.017*
MDS-UPDRS-I[b,c]	4.24 (1.70–10.57)	0.002**	0.61 (0.22–1.68)	0.340	6.95 (2.95–16.29)	<0.001***
MDS-UPDRS-II[b]	0.41 (0.17–1.03)	0.059	0.95 (0.87–1.03)	0.222	1.07 (1.00–1.15)	0.061
MDS-UPDRS-III[b]	0.99 (0.95–1.04)	0.719	0.97 (0.92–1.02)	0.217	1.02 (0.99–1.07)	0.235
MDS-UPDRS-IV[b]	1.38 (1.15–1.64)	<0.001***	1.19 (1.01–1.42)	0.044*	1.15 (0.97–1.37)	0.108
Years education[b]	0.96 (0.87–1.06)	0.404	0.94 (0.84–1.05)	0.290	1.02 (0.93–1.12)	0.683
LEDD[b]	1.00 (1.00–1.00)	0.054	1.00 (1.00–1.00)	0.018*	1.00 (1.00–1.00)	0.383
Psychiatric characteristics measured in subsample (n = 82)						
PAS[b]	1.18 (1.02–1.36)	0.024*	0.92 (0.81–1.05)	0.224	1.28 (1.14–1.43)	<0.001***
Persistent anxiety[b]	1.28 (1.03–1.60)	0.030*	0.91 (0.73–1.13)	0.382	1.41 (1.20–1.66)	<0.001***
Episodic anxiety[b]	1.52 (1.02–2.26)	0.040*	0.83 (0.58–1.19)	0.311	1.83 (1.36–2.46)	<0.001***
Avoidance behavior[b]	1.22 (0.77–1.92)	0.386	0.79 (0.51–1.23)	0.298	1.54 (1.14–2.08)	0.005**
LSAS[b]	1.04 (1.01–1.08)	0.024*	0.98 (0.95–1.01)	0.329	1.06 (1.03–1.09)	<0.001***
Fear or anxiety[b]	1.07 (1.00–1.15)	0.044*	0.96 (0.90–1.02)	0.212	1.12 (1.06–1.18)	<0.001***
Avoidance behavior[b]	1.06 (0.98–1.13)	0.139	0.96 (0.89–1.02)	0.199	1.10 (1.05–1.16)	<0.001***
SAS[b]	0.18 (0.29–1.06)	0.058	0.95 (0.83–1.09)	0.477	1.21 (1.09–1.35)	<0.001***

Univariate multinomial logistic regressions were conducted to compare current DSM-IV Anxiety, Anxiety NOS and no anxiety disorder groups. Odds ratios (OR) and 95% confidence intervals (CI) are presented.
[a]Male was the reference category.
[b]Adjusted for age and sex.
[c]Scores dummy-coded using median splits.
*$P < 0.05$. **$P < 0.01$. ***$P < 0.001$.
SMMSE, Standardized Mini Mental State Examination; PD-CRS, Parkinson's Disease Cognitive Rating Scale; HAM-D, Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale; PDQ-8, Parkinson's Disease Questionnaire; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; LEDD, levodopa equivalent daily dose; PAS, Parkinson's Anxiety Scale; LSAS, Liebowitz Social Anxiety Scale; SAS, Starkstein Apathy Scale.

complications of therapy (MDS-UPDRS-IV) to anxiety disorder NOS, controlling for variables that demonstrated significance during univariate analyses. The direct approach was used as no a priori hypotheses were developed about the relative importance of variables.[34] To control for collinearity and clinically meaningful relationships between variables,[37] the model excluded global disease severity (MDS-UPDRS Total), non-motor experiences of daily living (MDS-UPDRS-I), HAM-A, PDQ-8, and LEDD. The model comprised 5 variables, meaning a sample of at least 50 was appropriate[38]; sex, age, SMMSE, HAM-D, and MDS-UPDRS-IV (Table 4). Greater MDS-UPDRS-IV severity scores were significantly associated with the anxiety disorder NOS group compared to both the no anxiety group (OR, 95% CI = 1.33, 1.08–1.62; $P = 0.007$) and the DSM-IV anxiety group (OR, 95% CI = 1.41, 1.14–1.74; $P = 0.001$).

TABLE 4 *Multivariate multinomial logistic regression model examining independent contributions of severity of complications of therapy (MDS-UPDRS-IV) to anxiety disorder NOS, adjusted for sex, age, global cognition, and depression severity (n = 156)*

Variable	Anxiety NOS vs. no anxiety OR (95% CI)	*P*	Anxiety NOS vs. DSM anxiety OR (95% CI)	*P*	DSM anxiety vs. no anxiety OR (95% CI)	*P*
Sex[a]	2.15 (0.76–6.29)	0.163	0.94 (0.28–3.11)	0.920	2.28 (0.77–6.79)	0.137
Age	1.01 (0.95–1.08)	0.737	0.97 (0.90–1.04)	0.334	1.05 (0.98–1.20)	0.192
SMMSE	0.90 (0.64–1.26)	0.534	0.49 (0.30–0.80)	0.005**	1.83 (1.13–2.97)	0.013*
HAM-D	1.22 (1.08–1.38)	0.001**	0.79 (0.70–0.90)	<0.001***	1.54 (1.34–1.78)	<0.001***
MDS-UPDRS-IV	1.33 (1.08–1.62)	0.007**	1.41 (1.14–1.74)	0.001**	0.94 (0.74–1.20)	0.609

A multinomial logistic regression model was constructed to compare anxiety disorder NOS, DSM-IV anxiety disorders, and no anxiety groups. $\chi^2(10, n = 156) = 101.99$, $P < 0.001$; $R^2 = 0.48$ (Cox-Snell); 0.56 (Nagelkerke).

[a]Male was the reference category.

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$.

SMMSE, Standardized Mini Mental State Examination; HAM-D, Hamilton Depression Rating Scale; PDQ-8, Parkinson's Disease Questionnaire; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; LEDD, levodopa equivalent daily dose.

Results of Univariate Models Investigating the Symptoms of Motor Complications of Therapy in Anxiety Disorder NOS

To follow-up the higher MDS-UPDRS-IV scores observed in the anxiety disorder NOS group compared to the DSM-IV anxiety and no anxiety groups, univariate logistic regression models were constructed using MDS-UPDRS-IV items. Excluding 2 outliers, the sample comprised 154 participants; 28 with anxiety disorder NOS, 42 participants with DSM-IV anxiety, and 84 without anxiety (Table 5).

The anxiety disorder NOS group, compared to the no anxiety group, demonstrated greater motor complications of therapy across all items except functional impacts of dyskinesias and motor fluctuations, and painful "off"-state dystonia (Table 6). Compared to the DSM-IV anxiety group, the anxiety disorder NOS group demonstrated greater functional impacts of dyskinesias (OR, 95% CI = 2.52, 1.00–6.35; $P = 0.049$), overall dyskinesia severity (OR, 95% CI = 1.43, 1.02–2.00; $P = 0.040$) and complexity of motor fluctuations (OR, 95% CI = 2.36, 1.07–5.19; $P = 0.033$). A follow-up multivariate regression model demonstrated the association between complexity of motor fluctuations and anxiety disorder NOS (compared to the DSM-IV anxiety group) was independent of the functional impact of dyskinesias (Table 7; OR, 95% CI = 2.58, 1.01–6.58; $P = 0.047$). Therefore, the relationship between anxiety disorder NOS and the functional impact of dyskinesias demonstrated dependency on the

TABLE 5 *Descriptive statistics for severity of motor complications of therapy (MDS-UPDRS-IV) items (n = 154)*

Variable (unit; scale range)	Total sample mean (SD)	Anxiety NOS mean (SD)	DSM anxiety mean (SD)	No anxiety mean (SD)
Age (yr)	68.86 (8.32)	67.46 (9.60)	67.14 (8.56)	68.90 (7.76)
Sex (M/F)	94/60	14/14	20/22	60/24
Time spent with dyskinesias (0–4)	0.41 (0.88)	0.93 (1.09)	0.43 (1.02)	0.23 (0.65)
Functional impact of dyskinesias (0–4)	0.14 (0.41)	0.46 (0.64)	0.19 (0.51)	0.00 (0.00)
Total dyskinesia severity score (0–8)	0.55 (1.19)	1.39 (1.64)	0.62 (1.41)	0.23 (0.65)
Time spent in the "off" state (0–4)	0.37 (0.59)	0.64 (0.73)	0.43 (0.67)	0.25 (0.46)
Functional impact of motor fluctuations (0–4)	0.31 (0.73)	0.46 (0.92)	0.31 (0.64)	0.26 (0.70)
Complexity of motor fluctuations (0–4)	0.33 (0.66)	0.64 (0.83)	0.24 (0.43)	0.27 (0.67)
Total motor fluctuations severity score (0–12)	1.01 (1.70)	1.75 (2.12)	0.98 (1.54)	0.79 (1.56)
Painful "off"-state dystonia (0–4)	0.13 (0.47)	0.11 (0.32)	0.26 (0.54)	0.07 (0.46)

The total dyskinesia severity score is the sum of severity scores for time spent with dyskinesias and the functional impact of dyskinesias. The total motor fluctuations severity score is the sum of severity scores for time spent in the "off" state, functional impact of motor fluctuations, and complexity of motor fluctuations.

TABLE 6 *Association between motor complications of therapy (MDS-UPDRS-IV items) and anxiety disorder NOS (n = 154)*

Variable	Anxiety NOS vs. no anxiety OR (95% CI)	P	Anxiety NOS vs. DSM anxiety OR (95% CI)	P	DSM anxiety vs. no anxiety OR (95% CI)	P
Time spent with dyskinesias	2.13 (1.30–3.48)	0.003**	1.55 (0.97–2.47)	0.065	1.37 (0.82–2.30)	0.227
Functional impact of dyskinesias	–	–	2.52 (1.00–6.35)	0.049*	–	–
Total dyskinesia severity score	2.14 (1.41–3.25)	<0.001***	1.43 (1.02–2.00)	0.040*	1.50 (0.98–2.29)	0.062
Time spent in the "off" state	2.92 (1.42–6.02)	0.004**	1.61 (0.78–3.30)	0.196	1.82 (0.92–3.62)	0.087
Functional impact of motor fluctuations	1.29 (0.74–2.24)	0.368	1.31 (0.71–2.40)	0.392	0.99 (0.57–1.72)	0.962
Complexity of motor fluctuations	1.99 (1.12–3.56)	0.020*	2.36 (1.07–5.19)	0.033*	0.85 (0.40–1.78)	0.658
Total motor fluctuations severity score	1.32 (1.05–1.68)	0.019*	1.25 (0.96–1.62)	0.092	1.06 (0.83–1.35)	0.638
Painful "off"-state dystonia	1.14 (0.34–3.89)	0.833	0.56 (0.18–1.73)	0.310	2.06 (0.86–4.89)	0.104

Univariate multinomial logistic regression models were constructed to compare current anxiety disorder NOS, current DSM-IV anxiety disorders, and no anxiety groups. All variables were adjusted for age and sex. Odds ratios (OR) and 95% confidence intervals (CI) are presented. Dashes indicate the results are not applicable as the mean severity reported in the no anxiety group did not exceed zero.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

complexity of motor complications (OR, 95% CI = 1.95, 0.74–5.12, $P = 0.176$).

Discussion

This study identified characteristics associated with anxiety disorder NOS in persons with PD compared to those without anxiety and those with DSM-IV anxiety disorders. A greater overall severity of motor complications of PD therapy was observed in the anxiety disorder NOS group compared to the DSM-IV anxiety group. Moreover, the anxiety disorder NOS group experienced more time spent with dyskinesias and in the "off" state, a greater complexity of motor fluctuations, and a higher severity of dyskinesias and motor fluctuations compared to patients without anxiety. Interestingly, patients with anxiety disorder NOS also demonstrated a greater functional impact and severity of dyskinesias, and more complex motor fluctuations than patients with DSM-IV anxiety disorders. Specifically, PD patients with anxiety disorder NOS, compared to the DSM-IV anxiety group, demonstrated a 0.43-fold increase in the odds of experiencing more severe dyskinesias, a 2.52-fold increase in the odds of experiencing greater functional impacts of dyskinesias, and a 2.36-fold increase in the odds of experiencing more complex motor fluctuations. This suggests that motor complications of therapy are more frequently related to anxiety disorder NOS than diagnosable DSM-IV anxiety disorders, particularly as no associations were evident in the DSM-IV anxiety group compared to the no anxiety group.

TABLE 7 *Association between complexity of motor fluctuations, functional impact of dyskinesias, and anxiety disorder NOS*

Variable	OR (95% CI)	P
Functional impact of dyskinesias	1.95 (0.74–5.12)	0.176
Complexity of motor fluctuations	2.58 (1.01–6.58)	0.047*

Multivariate logistic regression comparing current anxiety disorder NOS and current DSM-IV anxiety disorder groups are presented, adjusted for age and sex. Odds ratios (OR) and 95% confidence intervals (CI) are presented.
*$P < 0.05$.

Motor complications of PD therapy have previously been suggested to be associated with anxiety in PD.[11,39] Anxiety experienced during "off" periods has been shown to improve with dopaminergic medication.[40] Similarly, PD patients may self-administer extra medication to address anxiety in anticipation of an "off" period.[41] It is therefore possible that the anxiety disorder NOS group self-administered additional medication to manage anxiety about their motor fluctuations, which were more complex compared to the DSM-IV anxiety and no anxiety groups. As increased doses of dopaminergic medication can incur dyskinesias, the overuse of medication might explain the associations observed between motor fluctuations and dyskinesias in the anxiety disorder NOS group. Although some patients with anxiety disorder NOS have previously demonstrated panic attacks and situational anxiety related to wearing-off and motor fluctuations,[14,42] to the authors' knowledge, this study is the first to characterize motor complications of PD therapy (ie, dyskinesias, time in the "off" state, motor fluctuations and dystonia) in anxiety disorder NOS.

The present findings also demonstrated that persistent, episodic (panic) and social anxiety symptoms were associated with anxiety disorder NOS compared to patients without anxiety, as evidenced by PAS and LSAS results. However, avoidance behavior (measured by the PAS and LSAS) was not associated with anxiety disorder NOS compared to the no anxiety group. There were no significant differences in the severity of persistent and episodic anxiety experienced by persons with anxiety disorder NOS compared to DSM-IV anxiety disorders, indicating these

anxiety symptoms are applicable for all patients experiencing anxiety. However, avoidance behavior was associated with the DSM-IV anxiety disorders group, suggesting anxiety disorder NOS might advance to social phobia if unmanaged symptoms progressed to avoidance behavior. These findings are consistent with literature demonstrating panic attacks not meeting DSM-IV criteria for panic disorder[14,19] and social anxiety are common in PD,[43] whereby some patients with anxiety disorder NOS experience aversions to social situations related to motor symptoms.[14] To the authors' knowledge, these are the first findings to characterize social anxiety symptoms in anxiety disorder NOS.

Moreover, greater global cognitive impairment measured by the SMMSE (but not the PD-CRS) was associated with anxiety disorder NOS compared to the DSM-IV anxiety group. This is interesting, given global cognitive impairment did not differ between the anxiety disorder NOS and no anxiety groups. Furthermore, a lack of association between anxiety disorder NOS compared to DSM-IV disorders, and the more comprehensive global cognitive measure, PD-CRS, may be because of other cognitive impairments found in the PD-CRS but not covered in the SMMSE. The association between cognitive impairment and anxiety in PD remains debated.[39,44–47]

Overall, the remaining results were consistent with previous findings. Patients with anxiety disorder NOS demonstrated a greater severity of anxiety and depression than those with no anxiety, yet lower severities compared to those with DSM-IV anxiety disorders, as expected.[48] Non-motor experiences of daily living (MDS-UPDRS-I) were associated with the anxiety disorder NOS group compared to the no anxiety group, yet did not differ compared to the DSM-IV anxiety group. Apathy was not associated with anxiety disorder NOS, yet was associated with DSM-IV anxiety compared to the no anxiety group. This association is regarded as unclear.[49–51] Female sex and a poorer quality of life were associated with the anxiety disorder NOS and DSM-IV anxiety groups compared to the no anxiety group, as anticipated.[11,52–57] Although younger age and anxiety have previously been associated in PD,[14,43,54,58] age was not associated with the anxiety disorder NOS group.

Limitations

Given the use of a convenience sample, sampling bias may have occurred, and prevalence rates cannot be concluded. The present study is unable to assume causality in the associations identified with anxiety in PD. Moreover, this study limited data collection to patients without dementia, meaning findings cannot be generalized to PD dementia. Although we adhered to sample size recommendations,[38] the findings are limited by a relatively small sample of patients with anxiety disorder NOS. Whether participants were receiving anxiety treatments was not considered, meaning any confounding effects of anxiety treatment were not accounted for when analyzing data because of the relatively small sample size. For example, benzodiazepines, prescribed for anxiety, can improve cramping and sleep symptoms of PD.[59,60]

Finally, because the study commenced in 2011 before the publication of the DSM-5 criteria, we used the DSM-IV criteria to diagnose anxiety disorders. Compared to the DSM-IV, the DSM-5 criteria has removed the requirement for individuals to recognize their anxiety is excessive or unreasonable for agoraphobia, specific phobia, and social anxiety disorder (previously social phobia) as evidence suggested that older persons frequently misattributed phobic fears to aging.[61] Additionally, obsessive–compulsive disorder (OCD) is not classified as an anxiety disorder in the DSM-5.[62] However, all 5 patients with OCD in this study had at least 1 other DSM-IV anxiety disorder: (1) GAD and OCD; (2) social phobia, GAD, and OCD; (3) specific phobia, social phobia, GAD, and OCD; (4) agoraphobia, social phobia, GAD, and OCD; and (5) agoraphobia, specific phobia, GAD, and OCD. Therefore, changes to diagnostic criteria do not affect our conclusions.

Practical Implications and Directions for Future Research

The findings suggest that anxiety disorder NOS in PD captures a distinct and undefined subgroup of PD patients experiencing anxiety characterized by motor complications of therapy, global cognitive impairment and episodic, persistent, and social anxiety symptoms. The identification of these characteristics could serve to facilitate the recognition and treatment of clinically significant anxiety in PD patients. A practical suggestion could be made that clinicians formally check on anxiety when motor complications and/or other psychiatric conditions and/or cognitive decline is present or uncovered. As the etiology of anxiety in PD is a complex interplay of neurobiological and psychological factors that develop over time,[16] it is unclear whether the presentation of anxiety disorder NOS in PD can be explained by a psychological reaction to motor complications or neurobiological underpinnings. Further research investigating the etiology of anxiety in this group is warranted.

Future studies should incorporate both "on" and "off" states, investigate the relationship between side of PD onset, anxiety, and cognitive impairment, and include persons with PD dementia. Longitudinal and neuroimaging studies are recommended. Given that anxiety is a reported risk factor for cognitive decline and dementia in older adults,[63–66] treating anxiety might delay cognitive impairment in PD.[67] These findings facilitate the development of treatments addressing anxiety, thereby potentially preventing cognitive deficits.

Finally, future research should focus on the development of guidelines to optimally identify and diagnose PD-specific anxiety and may warrant the inclusion of PD-specific subtypes within subsequent DSM editions (eg, anxiety disorder secondary to PD, wearing-off anxiety subtype). Research should then consider tailored interventions to treat PD-specific anxiety.

Conclusions

Using multinomial logistic regression modeling, we presented novel evidence that anxiety disorder NOS in PD captures an undefined subgroup of PD patients experiencing anxiety

characterized by PD-specific symptoms. Building on our earlier study, the present findings demonstrated that anxiety disorder NOS is associated with a greater severity and time spent with dyskinesias; more time spent in the "off" state; a greater complexity, functional impact and severity of motor fluctuations; and episodic, persistent and social anxiety symptoms compared to those without anxiety. Moreover, those with anxiety disorder NOS demonstrated greater global cognitive impairment, a greater functional impact and severity of dyskinesias, and a greater complexity of motor fluctuations compared to those with diagnosable DSM-IV anxiety disorders. Future research should investigate the association between anxiety and dyskinesias, "on/off" fluctuations and cognitive impairment to facilitate the development of guidelines for the identification and treatment of atypical anxiety disorders in PD.

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Author Roles

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

E.J.F.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B
G.J.B.: 1A, 1B, 1C, 3B
J.D.O.: 1B, 3B
J.Y.: 1A, 1B, 1C, 3B
R.M.: 1A, 3B
N.N.D.: 1A, 1B, 1C, 2A, 2C, 3B

Disclosures

Ethical Compliance Statement: Written informed consent was obtained from all participants before commencing the study. The Human Research Ethics Committees of the University of Queensland, Princess Alexandra Hospital and Royal Brisbane and Women's Hospital provided ethical approval for this study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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