Movement Disorders
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RESEARCH ARTICLE

Characteristics and Treatment of Anxiety Disorders in Parkinson's Disease

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ABSTRACT: **Background:** Anxiety disorders are common in Parkinson's disease (PD) and are undertreated. The current study investigates demographic and PD-specific factors associated with *Diagnostic and Statistical Manual* (DSM-IV) anxiety disorders and subsyndromal anxiety in PD. It also examines the use of pharmacological and nonpharmacological treatments for anxiety in PD. **Methods:** Ninety nondemented PD patients completed a semistructured interview. Logistic regression models were constructed examining associations between several demographic, disease-specific, and treatment factors, as well as both current syndromal, DSM-IV anxiety disorders, and subsyndromal anxiety. **Results:** Associations were found between current DSM-IV anxiety disorder, as well as female gender, younger age, more severe stages of PD, and poor activities of daily living. Subsyndromal anxiety was related to a younger onset age of PD. Relationships were also found between both anxiety groups and more complications of PD therapy, as well as higher depression scores. There were no associations between anxiety and levodopa equivalent daily dosage, motor disability, and cognition. In our sample, 57% of patients with current DSM-IV anxiety disorders or subsyndromal anxiety were not currently treated with pharmacotherapy. Of those who currently received such treatment, 83% still experienced current anxiety disorders. Results suggest that anxiety is poorly recognized and treated in PD. **Conclusions:** Clinical trials investigating the efficacy of pharmacotherapy, tailored psychotherapy, and combination therapy primarily focusing on anxiety are much needed, with the aim of establishing novel targeted treatment protocols for the management of subtypes of anxiety disorders in PD.

Parkinson's disease (PD) is traditionally considered a movement disorder; however, increasing interest has been directed toward nonmotor symptoms, such as anxiety, owing to their significant clinical impact. Anxiety in PD has been found to contribute to greater disability and a 50% poorer quality of life, compared to PD patients without anxiety disorders.[1] Despite its significance, anxiety in PD often remains underdiagnosed or unresolved after treatment.[2]

Prevalence estimates of anxiety disorders in PD range from 13% to 43%, and this variability has been largely attributed to differences in instrumental measures and diagnostic criteria.[3] Commonly reported anxiety disorders in PD include generalized anxiety disorder, panic disorder, and social phobia.[3,4] The *Diagnostic Statistical Manual* (DSM-IV)[5] residual category of "Anxiety disorder not otherwise specified" (Anxiety disorder NOS) is used to describe anxiety symptoms that do not meet DSM-IV diagnostic criteria, but have a significant impact on the patient's daily life. This category of subsyndromal anxiety has been estimated to exist in 2% to 25% of PD patients, and we have speculated that this category includes a PD-specific phenomenon.[3] Together with syndromal (DSM-IV) anxiety disorders, the present study aims to examine characteristics of subsyndromal anxiety in PD.

Research investigating factors associated with anxiety in PD is mixed. Younger patient age, female gender, presence of

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motor fluctuations, and a previous history of anxiety are most consistently associated with an increased risk of anxiety in PD patients.[3,6–10] A recent systematic review[10] reported that autonomic symptoms, PD duration, severity and frequency of symptoms, and staging of disease were also associated with depression and anxiety disorders in PD. The relationship between anxiety and lateralization of motor symptoms, antiparkinsonian medication, or dominant motor symptomatology (postural instability gait dysfunction vs. tremor) remains contested.[3,10] The identification of potential risk factors may facilitate the development of preventative measures to decrease the burden of anxiety in PD. Although a high proportion of PD patients reported to experience subsyndromal anxiety, to date, no studies have examined factors specifically associated with this category of anxiety in PD or have compared associations between subsyndromal and syndromal (DSM-IV) anxiety disorders in PD. This study examines characteristics of anxiety in line with anxiety group membership in PD.

Anxiety is recognized as a common and debilitating comorbidity in PD, yet treatment data are scarce and no solid treatment recommendations currently exist. Management of PD often is focused on physical manifestations, rather than mental health aspects.[4] When psychological issues are addressed, pharmacological treatment is typically directed toward comorbid depression and anxiety is examined secondarily.[2] Despite the limited supporting evidence, benzodiazepines or selective serotonin reuptake inhibitors (SSRIs) are generally favored as the pharmacological treatment of choice for anxiety in PD.[2,11–13] Cognitive behavioral therapy has also been suggested as an effective approach to treat anxiety in PD.[4] The paucity of clinical trials in this area increases the risk of anxiety in PD being undertreated or poorly managed, contributing to worse outcomes for patients. Higher levels of anxiety have also been shown to predict a poorer response to antidepressant treatment, implying that depressed PD patients with severe anxiety may require more-intensive or alternative treatment strategies.[14] It is clear that further research into treatment options for anxiety in PD is needed. The present study aims to investigate pharmacological and nonpharmacological treatment in PD.

Patients and Methods

Participants

A convenience sample of PD patients was recruited from neurology outpatient clinics in Brisbane and the Queensland Parkinson's Project database.[15] Patients with signs of dementia, as identified by neurologists or cognitive rating scales (<24 on the Standardized Mini–Mental State Examination[16] or <64 on the Parkinson's Disease-Cognitive Rating Scale[17]), and those who had previously undergone neurosurgery were excluded. Written informed consent was obtained from all participants before commencing the study and ethical approval was given by human ethics committees of the University of Queensland (Brisbane, Queensland, Australia) and the Royal Brisbane & Women's Hospital (Herston, Queensland, Australia).

Data Collection

Anxiety

Anxiety disorders and coexisting depression were diagnosed according to DSM-IV criteria using the Mini–International Neuropsychiatric Interview (MINI-plus).[18] Subsyndromal anxiety was carefully identified by a panel of experts consisting of a movement disorders neurologist, two psychiatrists specialized in PD, a registered clinical psychologist specialized in older persons' mental health, and a research fellow specialized in neuropsychiatry in PD. The MINI-plus interview and the PD-anxiety motor questionnaire were used to assist with this categorization. PD patients identified as having significant anxiety symptoms, but not meeting the DSM-IV criteria (Anxiety disorder NOS), and those who had PD-related anxiety and reported causing significant distress as a result of their anxiety were included in the subsyndromal anxiety category. PD-related anxiety included anxiety symptoms relating to motor symptoms and iatrogenic complications (e.g., motor fluctuations and impulse control disorders). A detailed description of this categorisation has been a focus of another article using this data set (Dissanayaka NNW, O'Sullivan JD, Pachana NA, et al, unpublished data, 2014) [Correction added on 2 June 2015, after first online publication: ref. 19 changed to unpublished data]. The Hamilton Anxiety (HAM-A) and Depression (HAM-D) rating scales were used to measure symptoms and severity of anxiety.[19]

Other Rating Scales

The International Parkinson and Movement Disorder Society UPDRS (MDS-UPDRS) was used to measure the severity of PD.[20] The H & Y staging and the Schwab and England Activities of Daily Living scales (S&E) were also applied. Patient quality of life was measured using the Parkinson's Disease Questionnaire (PDQ-8).[21]

Treatment and Demographics

A self-report questionnaire was administered to obtain demographic information, current medication, and history of treatment for anxiety and depression. This questionnaire is similar to the one used in our previous studies.[1,15]

Life Events

The life events of each participant were obtained qualitatively during the interview. A total number of life events was calculated from a list of potential life events adapted from the original Social Readjustment Rating Scale.[22] The list included major personal illness, surgery or injury, major decline in health of spouse or partner, major decline in health of other close family member or close friend, breakup or major conflict in a close personal relationship, death of someone close to (e.g., spouse or partner), retirement/redundancy, emigration/having to move, natural disaster (fire, flood, drought, earthquake, and so on.) or

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house fire, major loss or damage to personal property, being robbed, being forced to take part in unwanted sexual activity, legal troubles or involvement in a court case, drug/gambling addiction, and other major impacting events.

Statistical Analysis

The SPSS (21.0; SPSS, Inc., Chicago, IL) package was used for statistical analysis. Participants were categorised into three groups: (1) Current DSM-IV anxiety disorder; (2) current subsyndromal anxiety; and (3) no current anxiety disorder. Binary logistic regression models adjusted for age and gender were constructed to examine factors associated with (1) current DSM-IV anxiety versus no current anxiety, (2) current subsyndromal anxiety versus no current anxiety, and (3) current DSM-IV anxiety disorder versus current subsyndromal anxiety. Similarly, associations between treatment and anxiety, and quality of life and anxiety, were examined using binary logistic regression analysis adjusted for age and gender. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A P value of <0.05 was considered significant. No corrections were made for multiple comparisons given the exploratory nature of the study.

Results

Ninety PD patients participated in the study. There were 56 males and 34 females and their mean age was 67.0 years (standard deviation [SD] = 9.1). Mean onset age was 58.5 years (SD = 10.2) and the mean age of PD diagnosis was 60.9 years (SD = 10.0). Of the 90 patients, 25.6% (N = 23) were diagnosed with current DSM-IV anxiety disorders, 26.7% (N = 24) were categorized in the subsyndromal anxiety group, and 47.8% (N = 43) reported no current anxiety. A detailed description of patient characteristics and frequencies of anxiety subtypes can be found elsewhere in our article using the same data set (Dissanayaka NNW, O'Sullivan JD, Pachana NA, et al, unpublished data, 2014).

Factors Associated With Anxiety in PD

Gender, Age, and Onset Age

Univariate logistic regression models suggested that female gender (OR, 95% CI = 10.70, 3.27–35.04; $P < 0.001$) and younger age (OR, 95% CI = 0.89, 0.83–0.96; $P = 0.004$) were significantly associated with current DSM-IV anxiety disorder, compared to those without current anxiety. There were no significant gender or age differences between the subsyndromal anxiety and no-anxiety groups (Table 1). A younger age of onset was significantly associated with the subsyndromal anxiety group (but not the DSM-IV anxiety group), compared to the no-anxiety group (OR, 95% CI = 0.94, 0.88–1.00; $P = 0.04$).

Severity and Treatment of PD

Compared to the no-anxiety group, the DSM-IV anxiety disorder group had a higher total MDS-UPDRS score (OR, 95% CI = 1.08, 1.03–1.14; $P = 0.002$), MDS-UPDRS I-non-motor symptoms score (OR, 95% CI = 1.49, 1.20–1.85; $P < 0.001$), MDS-UPDRS-II-ADL (activities of daily living) score (OR, 95% CI = 1.21, 1.05–1.39; $P = 0.008$), and MDS-UPDRS-IV-therapy complications score (OR, 95% CI = 1.32, 1.05–1.65;

TABLE 1 Results of the binary logistic regression analysis examining the factors associated with anxiety in PD

Variable	DSM vs. No Anxiety OR (95% CI)	*P* Value	NOS vs. No Anxiety OR (95% CI)	*P* Value	DSM vs. NOS OR (95% CI)	*P* Value
Current age	0.89 (0.83–0.96)	0.004	0.94 (0.89–1.00)	0.06	0.98 (0.92–1.04)	0.44
Gender (M/F)	10.70 (3.27–35.04)	<0.001	1.89 (0.62–5.80)	0.27	5.67 (1.61–19.97)	0.007
PD onset age[a]	0.94 (0.87–1.02)	0.12	0.94 (0.88–1.00)	0.04	1.03 (0.96–1.10)	0.40
Age PD diagnosis[a]	0.95 (0.89–1.02)	0.15	0.95 (0.90–1.00)	0.06	1.01 (0.95–1.07)	0.74
Duration of PD[a]	0.92 (0.78–1.08)	0.31	1.03 (0.92–1.14)	0.65	0.89 (0.74–1.06)	0.18
MDS-UPDRS total[b]	1.08 (1.03–1.14)	0.002	1.02 (0.97–1.06)	0.48	1.08 (1.02–1.14)	0.007
I	1.49 (1.20–1.85)	<0.001	1.20 (1.06–1.37)	0.005	1.29 (1.09–1.52)	0.003
II	1.21 (1.05–1.39)	0.008	1.01 (0.91–1.13)	0.83	1.15 (1.01–1.31)	0.04
III	1.03 (0.96–1.11)	0.35	0.97 (0.91–1.04)	0.41	1.06 (0.98–1.15)	0.14
IV	1.32 (1.05–1.65)	0.02	1.31 (1.07–1.61)	0.01	1.00 (0.84–1.19)	0.99
H & Y staging[b]	3.76 (1.15–12.26)	0.03	1.53 (0.49–4.78)	0.46	2.67 (0.77–9.29)	0.12
S&E ADL scale[b]	0.91 (0.85–0.98)	0.01	0.96 (0.90–1.02)	0.19	0.97 (0.92–1.03)	0.32
LEDD[b]	1.00 (1.00–1.00)	0.64	1.00 (1.00–1.00)	0.57	1.00 (1.00–1.00)	0.47
MMSE[b]	1.66 (0.92–3.01)	0.09	1.01 (0.76–1.35)	0.93	1.68 (0.95–2.99)	0.08
PDCRS[b]	0.99 (0.94–1.04)	0.73	0.98 (0.95–1.03)	0.45	1.02 (0.97–1.08)	0.42
HAMD-17[b]	1.71 (1.20–2.43)	0.003	1.29 (1.10–1.51)	0.001	1.31 (1.10–1.55)	0.003
HAM-A[b]	2.63 (1.11–6.23)	0.03	1.50 (1.21–1.86)	<0.001	1.61 (1.16–2.22)	0.004
Number of stressful life events[b]	2.21 (1.17–4.21)	0.02	1.24 (0.72–2.13)	0.44	1.33 (0.78–2.29)	0.29
Lifetime history of depressive disorder[b]	8.75 (2.07–37.01)	0.003	0.52 (0.14–1.92)	0.33	20.54 (3.60–117.42)	0.001

This is a comparison between current DSM-IV anxiety, current Anxiety disorder NOS, and no current anxiety groups. ORs and 95% CIs and *P* values are shown.
[a]Adjusted for gender only.
[b]Adjusted for age and gender.
MMSE, Mini–Mental State Examination.
PDCRS, Parkinson's disease Cognitive Rating Scale.

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$P = 0.02$). Higher MDS-UPDRS-I (OR, 95% CI = 1.20, 1.06–1.37; $P = 0.005$) and MDS-UPDRS-IV scores (OR, 95% CI = 1.31, 1.07–1.61; $P = 0.01$) were also observed in the subsyndromal anxiety group, compared to the no-anxiety group. The MDS-UPDRS-III-motor scores was not associated with both anxiety disorders groups (Table 1). Compared to the subsyndromal anxiety group, the DSM-IV anxiety disorder group had higher MDS-UPDRS total (OR, 95% CI = 1.08, 1.02–1.14; $P = 0.007$), MDS-UPDRS-I (OR, 95% CI = 1.29, 1.09–1.52; $P = 0.003$), and MDS-UPDRS-II (OR, 95% CI = 1.15, 1.01–1.31; $P = 0.04$) scores.

Higher H & Y scores (OR, 95% CI = 4.45, 1.29–15.44; $P = 0.02$) and lower S&E scores (OR, 95% CI = 0.91, 0.85–0.98; $P = 0.01$) were observed in the DSM-IV anxiety disorder group, compared to the no-anxiety group. There was no association between levodopa equivalent daily dose (LEDD), and anxiety disorders groups compared to the no anxiety group.

Depression, Anxiety, and Cognitive Rating Scale Scores

Compared to the no-anxiety group, both DSM-IV anxiety disorders and subsyndromal anxiety groups had significantly higher HAM-A (DSM-IV anxiety: OR, 95% CI = 2.63, 1.11–6.23; $P = 0.03$; subsyndromal anxiety: OR, 95% CI = 1.50, 1.21–1.86; $P < 0.001$), and HAM-D (DSM-IV anxiety: OR, 95% CI = 1.71, 1.20–2.43; $P = 0.003$; subsyndromal anxiety: OR, 95% CI = 1.29, 1.10–1.51; $P = 0.001$) scores. Significantly higher scores for both scales were observed in the DSM-IV anxiety disorder group, compared to the subsyndromal anxiety group (HAM-A: OR, 95% CI = 1.61, 1.16–2.22; $P = 0.004$; HAM-D: OR, 95% CI = 1.31, 1.10–1.55; $P = 0.003$). There was no significant association between anxiety and cognitive scores (Table 1).

History of Depression and Stressful Life Events

The DSM-IV anxiety disorder group had a higher lifetime history of depression, compared to the no-anxiety (OR, 95% CI = 8.75, 2.07–37.01, $P = 0.003$) and the subsyndromal anxiety groups (OR, 95% CI = 20.54, 3.60–117.42; $P = 0.001$). The DSM-IV anxiety disorder group reported more stressful life events than those who did not have anxiety (OR, 95% CI = 2.21, 1.17–4.21; $P = 0.02$).

Treatment of Anxiety in PD

Overall, 41 of 90 (34.4%) PD patients reported that they have been treated for anxiety or depressive disorders (Table 2A). Of those with a current diagnosis of a DSM-IV anxiety disorder, 30.4% (7 of 23) had never received any treatment (i.e., pharmacotherapy or psychotherapy or combination therapy), and 52.2% (12 of 23) were currently receiving pharmacological

TABLE 2 Treatment of anxiety in PD

Variable	Total (N = 90)	DSM-Anxiety (N = 23)	Anxiety NOS (N = 24)	No Anxiety (N = 43)
(A) Pharmacological and psychotherapy treatment				
Ever treated for anxiety or depressive disorder, % (n)	34.4 (41)	69.6 (16)	37.5 (9)	14.0 (6)
Pharmacological only	12.2 (11)	8.7 (2)	16.7 (4)	11.6 (5)
Psychotherapy only	4.4 (4)	13.0 (3)	4.2 (1)	0 (0)
Pharmacological and psychotherapy	17.8 (16)	47.8 (11)	16.7 (4)	2.3 (1)
Current pharmacological treatment for anxiety or depressive disorder, % (n)	26.7 (24)	52.2 (12)	33.3 (8)	9.3 (4)
Benzodiazepine	2.2 (2)	0 (0)	8.3 (2)	0 (0)
SSRI	5.6 (5)	8.7 (2)	4.2 (1)	4.7 (2)
SNRI	3.3 (3)	4.3 (1)	8.3 (2)	0 (0)
TCA	6.7 (6)	13.0 (3)	4.2 (1)	4.7 (2)
Miscellaneous	1.1 (1)	0 (0)	4.2 (1)	0 (0)
Combination	7.8 (7)	6.7 (6)	4.2 (1)	0 (0)

Class	Drugs
(B) Current pharmacological treatment in detail	
Benzodiazopines	Diazepam Clonazepam (Paxam) Oxazepam (Alepam)
SSRIs	Sertraline (Zoloft, Setrona) Fluoxetine (Lovan) Paroxetine (Aropax) Escitalopram (Lexapro)
SNRIs	Venlafaxine (Efexor) Duloxetine (Cymbalta)
TCAs	Amitriptyline (Endep) Notriptyline (Allegron) Dosulepin (Dothep)
Miscellaneous	Agomelatine (Valdoxan) Mirtazepine (Avanza) Lithium

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TABLE 3 Results of the binary logistic regression analysis focussed on treatment and quality of life

Variable[a]	DSM vs. No Anxiety OR (95% CI)	*P* Value	NOS vs. No Anxiety OR (95% CI)	*P* Value	DSM vs. NOS OR (95% CI)	*P* Value
Ever treated for anxiety or depression	8.90 (2.21–35.88)	0.002	2.27 (0.70–9.38)	0.15	3.69 (0.98–13.90)	0.05
Current pharmacological treatment for anxiety or depressive disorder	9.32 (1.95–44.57)	0.005	4.37 (1.08–17.78)	0.04	2.07 (0.57–7.53)	0.27
Quality of life (PDQ-8 scores)	1.94 (1.39–2.71)	<0.001	1.65 (1.16–2.34)	0.006	1.36 (1.00–1.84)	0.05

This is a comparison between current DSM-IV anxiety, current Anxiety disorder NOS, and no current anxiety groups. ORs and 95% CIs and *P* values are shown.
[a]Adjusted for age and gender.

treatment. Current pharmacological treatment primarily consisted of benzodiazepines, SSRIs, selective noradrenaline reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs; Table 2B).

Overall, 9 of 24 (37.5%) patients in the current subsyndromal anxiety group reported a history of treatment for anxiety or depressive disorder. In this group, 33.3% were taking antidepressants or anxiolytics at the time of the present study. The DSM-IV anxiety disorder group was more likely to be treated for anxiety or depressive disorders, compared to the no-anxiety group (OR, 95% CI = 8.90, 2.21–35.88; $P = 0.002$), but not the subsyndromal anxiety group (OR, 95% CI = 3.69, 0.98–13.90; $P = 0.05$; Table 3).

Quality of Life

A significantly poorer quality of life was evident in the DSM-IV anxiety disorder (OR, 95% CI = 1.94, 1.39–2.71; $P < 0.001$) and subsyndromal anxiety groups (OR, 95% CI = 1.65, 1.16–2.34; $P = 0.006$), compared to the no-anxiety group. There was no significant difference in quality of life between the DSM-IV anxiety disorder and subsyndromal anxiety groups (OR, 95% CI = 1.36, 1.00–1.84; $P = 0.05$).

Discussion

The present study focused on characteristics and treatment of anxiety disorders in PD. The study included syndromal DSM-IV anxiety disorders, as well as the residual subsyndromal category of anxiety in PD. A high prevalence of subsyndromal is described in PD literature, but often remains underdiagnosed and thus undertreated in clinical practice. Investigating characteristics of subsyndromal anxiety is a novel aspect of this study. In our sample, 25% of PD patients experienced current DSM-IV anxiety disorders, whereas a further 27% experienced current subsyndromal anxiety. An observed total prevalence of over 50% current anxiety disorders in PD highlighted the importance of focusing on both DSM-IV as well subsyndromal anxiety when treating PD patients.[3]

Factors Associated With DSM-IV and Subsyndromal Anxiety in PD

Gender and age were significantly associated with DSM-IV anxiety, such that women and younger PD patients were more likely to develop anxiety disorders; however, they were not associated with subsyndromal anxiety. The association between anxiety and female gender,[6,8,23–26] and anxiety and younger age,[1,8,9,27] is consistent with previous studies. Both genders and all ages were at risk of developing subsyndromal anxiety.

Although PD onset age and duration were not associated with the DSM-IV anxiety group, the subsyndromal anxiety group showed an increased likelihood of having a younger onset age. Previous studies have also reported an increased risk of anxiety in young-onset PD patients.[1,28,29] The relationship between anxiety and disease duration has suggested mixed results. Whereas some studies have demonstrated a positive correlation between anxiety and duration of PD,[30–35] others have shown no association.[1,8,9,32,36,37]

Consistent with previous studies,[1,8,9,32,36,37] we did not find an association between anxiety and LEDD. We demonstrated that H & Y staging was significantly higher in patients with DSM-IV anxiety, compared to those without anxiety. Interestingly, MDS-UPDRS-III-motor disability scores were not associated with DSM-IV anxiety or subsyndromal anxiety. A positive association between anxiety and severity of PD has previously been reported in some,[1,27,31,34,35,38] but not in all, studies.[8,23,30,32,37] Considering that patients in the present study were interviewed during an ON state of PD medication, our results overall suggest that motor disability at optimal dopaminergic treatment has no association with anxiety. The results also indicate that the management of nonmotor disability in PD remains a challenge in clinical practice and may not be resolved by dopaminergic therapy. Poor management of these nonmotor symptoms can potentially increase anxiety symptoms in PD.

Complications of PD therapy have been repeatedly suggested as being associated with anxiety in PD.[1,6,7,24,29,35,37,39] We demonstrated that the MDS-UPDRS-IV-therapy complications scores were positively associated with both DSM-IV anxiety and subsyndromal anxiety groups. Moreover, patients with DSM-IV anxiety reported significantly higher impairment in activities of daily living (ADLs; higher MDS-UPDRS-II scores), compared to the subsyndromal anxiety and no-anxiety groups. MDS-UPDRS-II scores did not differ between the subsyndromal anxiety and no-anxiety groups. These results suggest that more-severe anxiety is associated with greater impairment in ADLs, contributing to a reduced quality of life in PD, which is consistent with our previous study.[1] The PD-specific quality-of-life measure, PDQ-8, also confirmed a significantly lower quality of life in patients with DSM-IV anxiety disorders and subsyndromal anxiety, compared to those without anxiety.

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Not surprisingly, higher anxiety and depression rating scale scores were found in PD patients with anxiety disorders, compared to those without anxiety. Based on rating scale scores, DSM-IV anxiety disorders suggested more-severe anxiety than the subsyndromal anxiety group. Patients with DSM-IV anxiety disorders reported a significantly high comorbidity of a lifetime history of depression, whereas those with subsyndromal reported no such association. Thirty-nine percent of patients with a current DSM-IV anxiety disorder also had a diagnosis of current depressive disorder. Conversely, the results suggest that subsyndromal anxiety does not necessarily present with comorbid depression, and that this subsyndromal anxiety may be a unique characteristic of PD. Patients with DSM-IV anxiety disorders also reported a greater number of life stressors than patients who did not have anxiety, consistent with previous studies.[40,41] Our sample size was limited to examine relationships between anxiety and each life stressor. Despite speculation that there is a positive relationship between anxiety and cognitive impairment,[33,42–44] the present results for this sample of nondemented PD patients suggested that there is no relationship between anxiety and cognitive scores, consistent with the recent study by Burn et al.[29] Our lack of association between anxiety and cognitive impairment may be owing to the exclusion of patients with global cognitive impairment.

Treatment of Anxiety in PD

The present study also explored treatment of anxiety in PD. Alarmingly, we note that 57% of PD patients with current DSM-IV or subsyndromal anxiety were untreated, and this is similar to the findings in a previous study that reported 53% untreated anxiety in PD.[45] In our sample, nearly half of the patients with a current DSM-IV anxiety diagnosis were not treated with pharmacological therapy, whereas nearly 70% of patients with subsyndromal anxiety were untreated. Despite anxiety being a major symptom with a detrimental effect on quality of life, the results reveal that it is vastly underdiagnosed and undertreated in PD. Interestingly, of the patients who received pharmacotherapy, 83% still experienced a current anxiety disorder, suggesting that anxiety in PD is difficult to treat and that pharmacological treatment currently used for the management of anxiety disturbances may not prove effective for anxiety in PD. Within pharmacotherapy, we noted that benzodiazepines, SSRIs, SNRIs, and TCAs are commonly used to treat anxiety in the present study sample. Dosages and duration of treatment of these pharmacological treatments were not collected in our study sample and was a limitation. To date, there is only one randomized, controlled study focused on pharmacotherapy for anxiety in PD using a long-acting benzodiazepine, bromazepam.[13] This study and other case reports have suggested that benzodiazepines are a useful treatment for anxiety in PD, although long-term use can produce unfavorable side effects in older adults, including deficits in alertness, cognition, and gait, as well as an increase in falls. All other PD studies with SSRIs and SNRIs have focused on anxiety secondary to depression and have reported favorable outcomes; however, there is no robust empirical evidence to provide recommendations on choice of pharmacotherapy for anxiety in PD.[2,46]

The present study also showed that psychotherapy methods have only been used by 40% of patients with current anxiety. Though there are no studies directly focused on the efficacy of psychotherapy for anxiety in PD, a few recent studies examining cognitive behavioral therapy for depression have shown potential benefits for comorbid anxiety in PD.[47,48] Given that a vast number of anxiety symptoms relate to symptomatology of PD, such psychotherapy approaches should be tailored to these PD-specific anxiety symptoms.[4] A combination of pharmacotherapy and psychotherapy may be more effective when treating severely anxious patients. When anxiety coexists with depression, more-intensive treatment is recommended.[14]

Conclusion and Future Directions

Positive associations were observed between the current DSM-IV anxiety disorder group and female gender, younger age, higher H & Y staging, poor MDS-UPDRS-II-ADL scores, and higher number of life stressors. A younger age of PD onset was associated with the current subsyndromal anxiety group. Both DSM-IV anxiety disorder and subsyndromal anxiety groups demonstrated associations with higher complications of PD therapy, higher depression, and lower quality of life. Anxiety was not associated with dopaminergic dose, motor disability, and cognitive scores. We limited our data collection to patients at the ON state, and future studies can be conducted at both ON and OFF states to further understand the impact of motor fluctuations on anxiety fluctuations in PD, as well as factors associated with anxiety during the OFF state in PD. Moreover, our results are limited to nondemented patients who have not had functional neurosurgery, such as DBS, and therefore investigating the association between anxiety and dementia in PD, as well as those who had neurosurgery, will be another focus for future studies.

The present study clearly demonstrates that anxiety is poorly identified in PD, and thus a majority of anxious patients remain undertreated. Nevertheless, pharmacological treatment seemed effective in only 17% of the anxious PD patients and 83% did not indicate effective response to pharmacological approaches. Randomized, controlled trials investigating the efficacy and effectiveness of pharmacological treatment with a primary focus on anxiety are required to be conducted in PD in the future. Together with pharmacotherapy, the development of novel psychotherapy approaches, which are tailored to address PD-specific anxiety symptomatology, will potentially be a more effective strategy for treating anxiety in PD.[4]

Author Roles

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

N.N.W.D.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B

E.W.: 1C, 2A, 2B, 2C, 3B

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J.D.S.: 1A, 1B, 1C, 2C, 3B
R.M.: 1A, 1B, 1C, 2C, 3B
P.A.S.: 1A, 1B, 1C
D.A.C.: 1A, 1B, 1C, 3B
G.D.M.: 1A, 1C, 3B
G.J.B.: 1A, 1B, 1C, 2C, 3B

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