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Pharmacologic treatment of anxiety disorders in Parkinson's disease

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Abstract

Objective—Neither best practices nor an evidence-base for the pharmacologic treatment of anxiety in Parkinson's disease has been established. This study investigated pharmacologic treatment of anxiety disorders in idiopathic Parkinson's disease and the associated clinical features.

Design—Cross-sectional.

Setting—Three community-based movement disorder neurology practices

Participants—250 subjects with Parkinson's disease.

Measurements—Anxiety disorder diagnoses were established by consensus using a panel of six psychiatrists with expertise in geriatric psychiatry and movement disorders. Current medications were provided by the treating neurologists at the time of interview.

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Results—Amongst subjects with anxiety disorders only, 53% were untreated with medications. However, when anxious subjects with comorbid depressive disorders were included, 70.8% were on medications effective for treatment of anxiety. Subjects with anxiety and comorbid depressive disorders were more likely to be treated for their psychiatric disturbances than subjects with anxiety disorders alone (Odds Ratio 8.33) as were subjects with comorbid motor fluctuations (Odds Ratio, 3.65). There were no differences in the types of anti-anxiety medications used in regard to the presence of depression or motor fluctuations.

Conclusions—These findings suggest that over half of non-depressed Parkinson's disease patients with clinically significant anxiety are untreated with medication. A better understanding of the role of clinical features associated with anxiety in PD, such as depression and motor fluctuations, may improve the recognition and treatment of anxiety disorders in this population.

Keywords

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

Introduction

Clinically significant anxiety occurs in up to 40% of individuals with Parkinson's disease (PD) and adversely affects physical disability and health-related quality of life.(1–9) Despite this, no randomized controlled trials (RCTs) have directly investigated the pharmacologic treatment of anxiety in PD. The reasons for the lack of studies on treatment for anxiety in PD are likely multi-factorial. In any case, they are a barrier to evidence-based interventions for a highly prevalent psychiatric problem in this population.

In the absence of evidence-based pharmacologic treatments for PD-related anxiety disorders, important considerations are raised by the prescribing patterns for treatment of anxiety disorders in the general population. In the general population, anxiety disorders affect 3.2% to 14.2% of older adults.(10) A recent article by Bryant et al., reviews the current literature and points out that anxiety disorders in older adults are more common than depressive disorders in community samples, but are often underreported because of increased heterogeneity in clinical presentation which may not be captured using current diagnostic criteria.(11) Both pharmacologic and non-pharmacologic interventions are known to be effective. However, older adults are more often seen in primary care settings where pharmacologic treatments are prescribed 48% of the time.(12) Benzodiazepines are the most commonly prescribed medication; antidepressants are used less frequently. For example, in one longitudinal study of aging, 7% of elderly subjects with anxiety disorders were treated with antidepressants and 43% were prescribed benzodiazepines.(13) A meta-analysis of 32 studies of treatments focused on anxiety disorders in older non-PD adults (mean age 60 years or older), found relatively few controlled pharmacotherapy trials (only 13 of the 32). In addition, the meta-analysis showed that pharmacotherapy interventions were more effective than behavioral interventions and resulted in substantial improvement of anxiety symptoms and only moderate improvement of depressive symptoms.(14) For PD patients, it is not known if there is also a preference for use of benzodiazepines, which would be concerning given the adverse effects of such agents on patients with PD, a typically older group with known cognitive dysfunction, complex medication regimens, and an increased risk for falls.

Several additional and inherent challenges have perhaps hindered studies on the treatment of anxiety in PD. First, similar to the non-PD geriatric population, anxiety disorders are heterogeneous with multiple subtypes, including some that are PD-specific and comorbid

with depressive disorders in up to 65% of subjects with PD.(1–4,15) Thus, inclusion criteria for a trial that targets anxiety disorders are not straightforward as compared to, for example, a treatment trial focusing on major depression. Second, depression and anxiety are often treated with the same agents and it may be unclear which condition is the primary target of treatment. Third, anxiety and depression impact treatment outcomes when they occur together rather than alone. For instance, in a treatment trial investigating citalopram for PD-depression, improvement in depression was associated with a reduction in anxiety.(16) Finally, diagnostic schemes for anxiety disorders in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision (DSM-IV-TR) do not indicate whether the condition is in remission or partial remission; this nosology for major depression in DSM-IV-TR facilitates tracking of clinical response.

At present, it is not known which pharmacologic agents are used most often to treat anxiety disorders in PD, what characteristics are significant amongst patients receiving these treatments, or how comorbid depression influences the likelihood of receiving treatment or moderates other variables. In the absence of evidence-based pharmacologic treatments, knowledge of current prescribing patterns offers a starting point on which to base risk-benefit and efficacy studies in future RCTs. In order to investigate these issues and inform the design of clinical trials for treatment of anxiety disorders in PD, this study examined patterns in pharmacologic treatment and the clinical features associated with the treatment of anxiety disorders in PD.

Methods

Participants

Subjects were 250 men and women with idiopathic PD(17) recruited from three community-based movement disorder neurology practices using a two-stage approach described previously as part of the Methods of Optimal Detection of Depression in PD (MOOD-PD) study.(3,6) Patients with idiopathic PD at each practice were mailed letters inviting their participation in the research study. Individuals were excluded if Mini-Mental State Exam (MMSE)(18) score was < 24. The study was approved by the Johns Hopkins Institutional Review Board and informed consent was obtained from each participant and informant.

Assessments

The screening visit (Visit 1) included the MMSE, the Parkinson's Disease Questionnaire (PDQ-8),(19) the Unified Parkinson's Disease Rating Scale (UPDRS),(20) calculation of levodopa equivalents,(21) and the Northwestern University Disability Scale (NUDS).(22) Subjects were scheduled for Visit 2, a diagnostic psychiatric interview, if they were identified by self-report or informant as endorsing any degree of depression, apathy, anxiety, or irritability or reported a history of depressive disorder. In addition, every fourth subject screening negative for these criteria underwent a diagnostic interview. As only 10 of the first 143 subjects seen at Visit 1 screened negative based on these criteria, diagnostic interviews were conducted in all subsequent study participants meeting the MMSE criterion. Informant interviews (n=223), administered by a trained study coordinator at Visit 2, provided collateral information on psychiatric symptoms and diagnoses. The UPDRS Motor sub-score (part III) and Hoehn and Yahr Stage (H&Y) (23) were rated by the treating movement disorder specialist neurologist. UPDRS part III scores and established criteria for determining akinetic-rigid, tremor-dominant, and mixed subtypes (24), were used to classify each subject.

Psychiatric diagnostic examinations, conducted by geriatric psychiatrists, used the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-

Patient edition (25) (SCID) plus supplemental questions to establish lifetime psychiatric, medical, family, and social history, current cognitive, and motor status, and disturbances not included in the SCID (such as fluctuation-associated anxiety and other non-motor fluctuations). A narrative summary of the history and mental state exam was prepared for each subject. As described previously, psychiatric diagnoses were established using best-estimate diagnostic procedures by a panel of six psychiatrists with expertise in geriatric psychiatry and movement disorders.(6)

Designation of current and past anxiety disorder diagnoses was determined by the expert panel. Current disorders were defined as those that, at the time of evaluation, were symptomatic or believed to be in remission as a consequence of ongoing treatment. A past history of an anxiety disorder diagnosis was defined as an anxiety syndrome that was evident in the past, but for which the individual had no current symptoms at the time of evaluation and was not being prescribed medications or other treatments traditionally used to treat that anxiety disorder. Lifetime anxiety is the combined number of current and past cases.

Anxiety treatment status for each patient was determined by the expert panel using the comprehensive diagnostic evaluation, informant interview, and retrospective chart review. In order to track clinical treatment or non-treatment, the panel, after consensus, recorded the treatment status for each diagnosed psychiatric disturbance according to the following rubric: 1) Symptomatic, not receiving needed treatment, 2) Symptomatic, receiving treatment, 3) Symptomatic, not receiving unneeded treatment (e.g., very mild disturbances that meet diagnostic criteria but do not warrant intervention, such as a specific phobia, for which medication treatment is rarely indicated or only on an as-needed basis), 4) Asymptomatic, receiving treatment, or 5) Not applicable. When indications for use of a particular psychiatric drug was not explicit in the notes or apparent based on historical course, treatment was inferred based on "standard clinical practice" for drugs commonly used to treat anxiety disorders. Sleep aids and hypnotics (e.g. zolpidem, eszopiclone, zaleplon) were not regarded as anxiety treatments.

Statistical Methods

Welch's t-tests, χ^2 tests, Fisher's exact test, and logistic regressions were used to compare demographic and clinical differences between participants with and without an anxiety disorder. Graphical diagnostics were used to identify large departures from normality. Participants with specific phobia only, a disorder not traditionally treated with medications, were excluded when comparing treated anxiety vs. untreated anxiety. Analyses were conducted using STATA statistical software (Version 9.0) (StataCorp, 2005). Statistical significance was set *a priori* at an unadjusted $\alpha=0.05$.

Results

Table 1 compares subjects with a lifetime history of at least one anxiety disorder (n=120) to subjects with no history of current or past anxiety. Amongst those with a lifetime history of an anxiety disorder, 89 had current anxiety disorders that are typically treated with medication in standard clinical practice. (Table 2) Amongst subjects with anxiety disorders only (n=38), 53% were untreated with medications. (Table 3) However, when anxious subjects with and without comorbid depressive disorders were included, 70.8% were on medications effective for treatment of anxiety. As a group, the 63 treated subjects were more likely to have a comorbid depressive disorder and to experience motor fluctuations than the 26 untreated subjects. There were no significant differences in treatment rates by motor subtype (tremor-dominant, akinetic-rigid, or mixed), in subjects with current anxiety disorders, with or without a comorbid depressive disorder.

Anxiety subjects with a current comorbid depressive disorder had an 8.33 times greater odds [Odds ratio 8.33, 95% CI: 2.88–24.1, $\chi^2(1)=17.59$, $p<0.001$] of pharmacological treatment than subjects with anxiety disorders alone. Comparing treated anxious subjects with comorbid depression ($n=45$) to treated non-depressed anxious subjects ($n=18$), depressed subjects had [mean(SD)]: fewer years of education [15.1(2.5) vs. 16.8(2.9) years, t -test, $t(61) = 2.29$, $p=0.03$], worse self-perceived health status on the PDQ-8 [9.5(4.9) vs. 5.3(4.6), $t(61) = 3.15$, $p=0.003$], and a greater likelihood of early morning dystonia [31.8% ($n=14$) vs. 5.9% ($n=1$), $\chi^2(1, n=15) = 4.45$, $p=0.04$]. The proportion of treated subjects with anxiety alone (47.4%, 18/38) compared to depression alone (67.3%, 33/49) was similar ($\chi^2(1, n=87) = 3.52$, $p=0.06$).

Anxious subjects with motor fluctuations, with or without comorbid depression, had a 3.65 times greater odds [Odds ratio 3.65, 95%CI: 1.25–10.9, $\chi^2(1)=7.16$, $p<0.01$] of pharmacological treatment than subjects without motor fluctuations. As compared to treated anxious subjects without motor fluctuations ($n=24$), anxious subjects with motor fluctuations ($n=39$): were younger [mean(SD); 68.1(11.1) vs. 62.1(8.7), $t(61) = 2.39$, $p=0.02$], with worse self-perceived health status on the PDQ-8 [9.4(5.1) vs. 6.7(4.9), $t(61) = 2.13$, $p=0.04$], greater likelihood of a family psychiatric history [%(n), 76.9%(30) vs. 47.8%(11, $n=23$), $\chi^2(1, n=62)=5.47$, $p=0.02$], younger age at PD symptoms onset [51.7(9.9) vs. 61.6(12.7) years, $t(61) = 3.46$, $p=0.001$], longer PD symptom duration [10.9(6.4) vs. 6.9(3.9) years, $t(61) = 2.80$, $p=0.007$], higher rate of early morning dystonia [33.3%(13) vs. 9.1%(2, $n=22$), $\chi^2(1, n=61)=4.46$, $p<0.0001$], and a higher l-dopa equivalent daily dose [833.2(519.8) vs. 365.4(234.8) mg, $t(61) = 4.15$, $p=0.0001$]. There were no differences in dopamine agonist use between the groups. When 45 subjects with anxiety plus comorbid depressive disorders were excluded, prevalence of motor fluctuations was 20% higher in the pharmacologically treated anxiety disorder only group ($n=18$), as compared to those with untreated anxiety disorders ($n=20$). However, this difference between treated and untreated subjects with anxiety based on the presence of motor fluctuations was no longer statistically significant. (Table 3)

Table 4 lists the number of subjects on treatment, by drug class, which could impact anxiety. SSRIs were the most frequently prescribed medication in those with anxiety disorders, including those without comorbid depression (the 'anxiety only' group). (Table 4) In anxiety subjects with and without current depressive disorders, 96% ($n=25$) of those on more than one anxiety medication were taking a benzodiazepine. There were no differences in psychiatric medications prescribed, by class or combination, when a depressive disorder was comorbid with anxiety or when comparing anxious subjects with and without motor fluctuations. Hypnotics were prescribed to one subject with anxiety only and to four subjects with anxiety and depression.

Discussion

Non-depressed subjects with clinically significant anxiety disorders were untreated with pharmacologic agents in more than one-half of community ascertained PD subjects. A comorbid depressive disorder was associated with an 8-fold increase in the odds of pharmacologic treatment, suggesting that anxiety in the absence of depression is more likely to remain untreated. In anxious subjects with and without comorbid depressive disorders, individuals with motor fluctuations had a 3.65 greater odds of being prescribed medications to treat anxiety than those without motor fluctuations. Contrary to prescribing patterns in non-PD geriatric populations, where benzodiazepines are the most commonly prescribed medication for anxiety, SSRIs were the most common treatment for anxiety in PD, even in the non-depressed 'anxiety only' group. The under-treatment of anxiety is not specific to PD and is common in aging populations.(10,12–13) Several factors are likely contributors to

this situation; the most salient involve failure to detect anxiety and limited effectiveness of medications, such as benzodiazepines, in elderly populations because of their greater vulnerability to side effects such as cognitive impairment and falls.(10–13)

This report presents novel data demonstrating that comorbid depression in anxious PD subjects increases the likelihood of being prescribed pharmacological treatment. The reported comorbidity between anxiety and depression of 71.4% in our sample is consistent with the upper limit of the range 19%–92% reported in other studies.(1–4,15) Although our study did not include a measure of anxiety severity, comorbid anxiety and depression may represent a condition of greater severity than either disorder alone; greater overall distress in such individuals may increase the likelihood of clinical attention. Alternatively, in the absence of depression, anxiety may remain untreated because of a failure to identify anxiety disorders, which are often undiagnosed in PD and the elderly in general.(3,10,11) Furthermore, time constraints in non-mental health clinical settings may limit opportunities to screen for both anxiety and depression. When psychiatric screening does occur, however, depression-oriented scales, in which anxiety symptoms serve as markers of depression severity, are more likely to be used.(26,27)

In our sample, motor fluctuations were associated with a 3.65 greater odds of being prescribed psychiatric medications to treat anxiety disorders compared to subjects without motor fluctuations. Subjects suffering from motor fluctuations and anxiety may be more likely to come under clinical scrutiny in a neurology clinic compared to subjects with anxiety in the context of optimally treated motor symptoms. Consistent with this view, Richard et al found that subjects with motor fluctuations were more likely than non-fluctuators to report histories of anxiety and depression, and to use psychotropic medications.(28) In addition, several studies suggest that fluctuations in plasma levodopa and the clinical phenomenon of "wearing-off" can also cause both motor and non-motor (mood and anxiety) fluctuations.(9,29,30) However, a recent study by Leentjens et al. suggests that the relationship between anxiety and motor fluctuations is more complex and not simply a product of wearing-off.(31) Further study is needed to determine whether motor fluctuations and anxiety treatment status are associated and whether optimizing anti-Parkinson's treatment to reduce fluctuations improves anxiety in PD.

The most commonly prescribed medications in our study were SSRIs, followed by benzodiazepines, and other antidepressant classes. There were no differences in types of medications prescribed for treatment when a depressive disorder was comorbid with anxiety compared to those with anxiety alone. This suggests that anxiety and depression may be most often treated with the same medications in PD patients. Alternatively, since studies in the elderly non-PD samples showed higher rates of benzodiazepine use, it may be that the prescribers in this study were aware of the increased risk of falls, cognitive impairment, and dependency associated with benzodiazepines in the elderly, especially elderly with PD, and selected drugs with a more favorable side effect profile.(32) There were also no differences in psychiatric medications prescribed in anxious subjects with motor fluctuations as compared to those without motor fluctuations; however, fluctuators used more than twice the daily dose of levodopa equivalents.

When treated anxious subjects were divided into two subgroups based on presence or absence of a comorbid depressive disorder, subjects with comorbid depression and anxiety reported worse health status on the PDQ-8, a lower level of education, and higher rates of early morning dystonia. These findings are consistent with previous studies showing that depression and lower education adversely affect ability to cope with burdens of the disease and are associated with a lower quality of life and self-perceived health.(33,34) In our sample, we also found that treated anxious subjects with motor fluctuations, as compared to

treated anxious subjects without fluctuations, were younger and had an earlier age of PD onset, longer duration of PD, greater likelihood of early morning dystonia, and higher daily doses of l-dopa. They also reported lower self-perceived health and were more likely to have a family psychiatric history. Many of these features are consistent with a PD subgroup experiencing atypical anxiety specifically associated with motor fluctuations (n=21) identified in an earlier study from this sample.⁽⁶⁾ This subgroup with motor fluctuations may need optimization of dopaminergic drugs for the motor symptoms of PD in place of or in addition to standard anxiety treatments.

This study has several limitations. First, we were only able to infer pharmacologic treatment of anxiety in cases when anxiety was comorbid with depression and the target of treatment was not specifically indicated by the treating neurologist or other clinician. Many of the drugs reported are used for additional indications, e.g. as hypnotics or pain management. Therefore, it is possible they were prescribed for symptoms other than anxiety and depression. As this study was cross-sectional, it is possible that subjects untreated for anxiety at the time of the study were started on treatment, but withdrawn because of poor tolerance. In addition, there was no way to know if individuals were on a therapeutic dose of a psychiatric medication or if the duration of treatment was sufficient. Non-pharmacological treatment was not consistently reported or captured as part of this study; therefore, the overall treatment rate may be higher. The study used DSM-IV-TR criteria for anxiety disorders rather than anxiety scales and therefore, the severity and degree of treated remission is not recorded as it is for depression (e.g., major depression, recurrent, moderate, partial remission). We did identify individuals with more than one anxiety disorder, which may be considered a proxy for severity, and found no difference in treatment compared to patients with only one anxiety disorder. Finally, limited sample size precluded analyses by specific anxiety diagnosis.

In summary, our findings suggest that anxiety disorders are untreated in up to one-half of affected PD subjects. Comorbid depression is associated with a greater likelihood of being treated and depression and anxiety disorders are most often treated with the same agents, SSRIs. Finally, treatment for anxiety was associated with a greater frequency of motor fluctuations, suggesting that motor complications may be an important factor when evaluating and treating anxiety in PD.

Efficacy and effectiveness studies on pharmacological treatment of PD-related anxiety are needed to address a clinically significant problem. To guide development of efficacy trials to treat anxiety in PD, future studies are needed that address several issues: 1) explain the basis for non-treatment of anxiety in up to one-half of subjects, (e.g., non-detection, medication intolerance, or lack of familiarity with anxiety treatments) and 2) investigate the impact of comorbid depression and motor complications on treatment response. Identification of distinct PD-related features, like motor fluctuations, in association with anxiety may re-define certain anxiety disorders so that they are more closely aligned with the pathological processes of PD.

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Table 1

Demographic and clinical characteristics: PD subjects with and without a lifetime anxiety disorder

Demographic Features	Total Sample (n = 250)	Non-anxious (n = 130)	Anxiety Disorder (n = 120)	Test for Significance
Age (yr) mean (SD)	65.8 (10.3)	68.0 (10.1)	63.4 (10.0)	t[248] = 3.63, p=0.0003*
Gender (male/female)	167/83	92/38	75/45	χ^2 (1), p=0.17
Years of education mean (SD)	16.2 (3.0)	16.4 (3.0)	15.9 (3.0)	t[248]=1.31, p=0.20
MMSE mean (SD)	28.3 (1.6)	28.3 (1.6)	28.3 (1.6)	t[248]=0.11, p=0.92
Quality of life (PDQ-8) mean (SD)	6.2 (4.7) n = 249	5.1 (4.4) n = 129	7.4 (4.8)	t[248]=3.98, p=0.0001*
Family history of PD [% (n)]	24.4 (61)	19.2 (25)	30.5 (36) n = 118	χ^2 (1), p=0.04*
Family psychiatric history [% (n)]	42.1 (104)	28.5 (37)	57.3 (67)	χ^2 (1), p<0.0001*
PD features	Total Sample (n = 250)	Non-anxious (n = 130)	Anxiety Disorder (n = 120)	Test for Significance
Age symptom onset (yr) mean (SD)	58.0 (12.8)	61.3 (12.4)	54.5 (12.3)	t[248]=4.33, p=0.0001*
Symptom duration (yr) mean (SD)	8.3 (6.4)	7.3 (5.8)	9.4 (6.8)	t[248]=2.72, p=0.008*
Hoehn & Yahr Stage	I-34, I ½-7	I-19, I ½-2	I-15, I ½-5	χ^2 (6), p=0.73
	II-111, II ½-52	II-54, II ½-30	II-57, II ½-22	
	III-34, IV-9, V-3	III-19, IV-4, V-2	III-15, IV-5, V-1	
UPDRS motor sub-score mean (SD)	18.1 (11.0) n = 242	17.2 (10.2) n = 126	19.1 (11.8) n = 116	t[240]=1.31, p=0.20
Presence of motor fluctuations [% (n)]	43.2 (108)	30.8 (40)	56.7 (68)	χ^2 (1), p<0.0001*
Presence of early morning dystonia [% (n)]	15.2 (36)	12.1 (15)	18.6 (21)	χ^2 (1), p=0.17
Presence of unpredictable off periods [% (n)]	25.7 (61)	16.1 (20)	36.3 (41)	χ^2 (1), p<0.0001*
Total L-dopa equivalents mean (SD)	611.3 (436.1)	565.9 (337.4)	660.5 (519.5)	t[248]=1.72, p=0.09
Agonist use [% (n)]	31.2 (78)	36.9 (48)	25.0 (30)	χ^2 (1), p=0.05*
Psychiatric Features and Comorbidities	Total Sample (n = 250)	Non-anxious (n = 130)	Anxiety Disorder (n = 120)	Test for Significance
Hamilton Rating Scale for Depression-17 total score mean (SD)	7.3 (5.2)	6.1 (4.4)	8.6 (5.8)	t[248]=3.83, p=0.0002*
Antidepressant therapy [% (n)]	43.2 (108)	30.9 (40)	58.3 (70)	χ^2 (1), p<0.0001*
Lifetime history depressive disorder [% (n)]	53.6 (134)	44.6 (58)	63.3 (76)	χ^2 (1), p=0.003*

UPDRS, Unified Parkinson's Disease Rating Scale

Test for significance - χ^2 (#) = chi-squared (degrees of freedom), t[#] = paired t-test [degrees of freedom], p-value

Table 2

Treated vs. Untreated Current Anxiety Disorders With and Without Current Depressive Disorders

Demographic Features	Treated Anxiety, +/- depressive disorders (n = 63)	Untreated Anxiety, +/- depressive disorders (n = 26)	Test for Significance
Age (yr) mean (SD)	64.4 (10.0)	63.4 (9.6)	t[87]=0.42, p=0.68
Gender (male/female)	40/23	18/8	χ^2 (1), p=0.61
Years of education mean (SD)	15.6 (2.7)	15.9 (4.0)	t[87]=0.41, p=0.69
MMSE mean (SD)	28.0 (1.8)	28.3 (1.4)	t[87]=0.64, p=0.53
Quality of life (PDQ-8) mean (SD)	8.3 (5.2)	6.3 (4.0)	t[87]=1.79, p=0.08
Family history of PD [% (n)]	27.4 (17) (n=62)	20.0 (5) (n=25)	χ^2 (1), p=0.47
Family psychiatric history [% (n)]	66.1 (41)	45.8 (11)	χ^2 (1), p=0.09
PD Features			
Age symptom onset (yr) mean (SD)	55.5 (11.9)	54.7 (11.4)	t[87]=0.30, p=0.77
Symptom duration mean (SD)	9.4 (5.9)	9.2 (7.9)	t[87]=0.16, p=0.87
Hoehn & Yahr Stage	I-5, I ½-1 II-30, II ½-15 III-7, IV-4, V-1	I-6, I ½-1 II-13, II ½-4 III-1, IV-1 V-0	χ^2 (6), p=0.41
UPDRS motor sub-score mean (SD)	20.8 (12.8) (n=60)	16.2 (8.5) (n=25)	t[83]=1.64, p=0.11
Presence of motor fluctuations [% (n)]	61.9 (39)	30.8 (8)	χ^2 (1), p=0.007*
Presence of early morning dystonia [% (n)]	24.6 (15) n = 61	9.1 (2) n = 22	χ^2 (1), p=0.13
Presence of unpredictable off periods [% (n)]	45.9 (28) n = 61	22.7 (5) n = 22	χ^2 (1), p=0.06
Total L-dopa equivalents mean (SD)	655.0 (488.4)	554.6 (495.2)	t[87]=0.88, p=0.39
Agonist use [% (n)]	17.5 (11)	30.8 (8)	χ^2 (1), p=0.17
Psychiatric Features and Comorbidities			
Hamilton Rating Scale for Depression-17 total score mean (SD)	9.5 (6.0)	7.0 (5.5)	t[87]=1.81, p=0.08
Presence of comorbid depressive disorder [% (n)]	71.4 (45)	23.1 (6)	χ^2 (1), p<0.001*
Presence of multiple anxiety disorders [% (n)]	33.3 (21)	34.6 (9)	χ^2 (1), p=0.91

Test for significance - χ^2 (#) = chi-squared (degrees of freedom), t[#] = paired t-test [degrees of freedom], p-value (excludes subjects with specific phobia only, n=15)

Table 3

Treated vs. Untreated Current Anxiety Disorders Without Current Depressive Disorder

Demographic Features	Treated Anxiety (n = 18)	Untreated Anxiety (n = 20)	Test for Significance
Age (yr) mean (SD)	67.1 (9.9)	63.0 (10.5)	t[36]=1.23, p=0.23
Gender (male/female)	13/5	15/5	χ^2 (1), p=0.85
Years of education mean (SD)	16.8 (2.9)	15.7 (4.4)	t[36]=0.93, p=0.36
MMSE mean (SD)	28.3 (1.6)	28.3 (1.4)	t[36]=0.17, p=0.87
Quality of life (PDQ-8) mean (SD)	5.3 (4.6)	5.7 (4.1)	t[36]=0.30, p=0.77
Family history of PD [% (n)]	28.6 (4)	10.5 (2) (n=19)	χ^2 (1), p=0.34
Family psychiatric history [% (n)]	61.1 (11)	42.1 (8) (n=19)	χ^2 (1), p=0.25
PD Features			
Age symptom onset (yr) mean (SD)	57.3 (12.5)	54.0 (11.7)	t[36]=0.85, p=0.41
Symptom duration mean (SD)	10.1 (7.4)	9.5 (8.4)	t[36]=0.25, p=0.81
Hoehn & Yahr Stage	I-2, I ½-1	I-4, I ½-1	χ^2 (5), p=0.39
	II-7, II ½-7	II-11, II ½-2	
UPDRS motor sub-score mean (SD)	III-1, IV-0, V-0	III-1, IV-1 V-0	t[35]=0.62, p=0.54
	17.6 (10.4)	15.7 (7.7) (n=19)	
Presence of motor fluctuations [% (n)]	50.0 (9)	30.0 (6)	χ^2 (1), p=0.21
Presence of early morning dystonia [% (n)]	5.9 (1) (n=17)	11.8 (2) (n=17)	χ^2 (1), p=0.55
Presence of unpredictable off periods [% (n)]	29.4 (5) (n=17)	23.5 (4) (n=17)	χ^2 (1), p=0.70
Total L-dopa equivalents mean (SD)	478.9 (398.2)	575.0 (546.6)	t[36]=0.61, p=0.55
Agonist use [% (n)]	16.7 (3)	35.0 (7)	χ^2 (1), p=0.20
Psychiatric Features and Comorbidities			
Hamilton Rating Scale for Depression-17 total score mean (SD)	6.1 (3.4)	4.7 (2.2)	t[36]=1.55, p=0.13
Presence of multiple anxiety disorders [% (n)]	27.8 (5)	35.0 (7)	χ^2 (1), p=0.64

Test for significance - χ^2 (#) = chi-squared (degrees of freedom), t[#] = paired t-test [degrees of freedom], p-value (excludes subjects with specific phobia only, n=9)

Table 4

Medication Profile for Subjects with Treated Anxiety With and Without Comorbid Depression

	Anxiety Disorder Diagnosis (with and without current depressive disorder), (n=63)	Anxiety Disorder Diagnosis (without current depressive disorder), (n=18)
Medication Type	% (n)	% (n)
SSRI only	30.1 (19)	38.9 (7)
Other Antidepressant only	12.7 (8)	11.1 (2)
Benzodiazepines only	12.7 (8)	22.2 (4)
Propanolol only	3.2 (2)	0 (0)
More than one medication	41.3 (26)	27.8 (5)

Propanolol when indicated for anxiety (social phobia e.g. speaking)

SSRI = selective serotonin reuptake inhibitor

Other Antidepressants included=Venlafaxine, Duloxetine, Mirtazapine, Bupropion, and Nefazodone, * no subjects were prescribed tricyclic antidepressants

(excludes subjects with specific phobia only)