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Frequency and correlates of co-morbid psychosis and depression in Parkinson's disease

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Abstract

Though both psychosis and depression are common in Parkinson's disease (PD), it is not clear if an association between the two disorders exists. One hundred and thirty PD patients were divided into four groups based on a comprehensive psychiatric assessment: (1) no depression or psychosis (47.7%); (2) psychosis only (16.2%); (3) depression only (26.2%); and (4) psychosis and depression (10.0%). Co-morbid psychosis and depression did not occur more frequently than expected by chance ($P = .77$). Psychosis was associated with dopamine agonist use ($P = .02$), depression with mild-cognitive impairment ($P = .03$), and their co-occurrence with higher daily levodopa dosages ($P<.01$). These results suggest that psychosis and depression in PD are distinct neurobehavioral disorders.

Keywords

Parkinson's disease; Depression; Psychosis; Co-morbidity

1. Introduction

Numerous psychiatric complications are common in Parkinson's disease (PD). The most prevalent and well-studied disorders in specialty care settings are depression (20-40%), psychosis (15-30%), and dementia (20-30%) [1-3].

By chance alone, psychosis and depression should co-occur in PD. If the two disorders have similar risk factors or neurobiological underpinnings, the co-occurrence of psychosis and depression would be greater than expected by chance alone, and previous research suggests that there may be an association between the two disorders [4-7]. If so, this may be due to common risk factors, including increasing age [6,8], greater cognitive impairment [4,9], and greater PD severity [6,9]. Other purported risk factors for individual disorders include exposure to most dopaminergic therapies (psychosis) [10], and female sex, predominantly right-sided motor symptoms, and treatment with higher levodopa doses (depression) [9,11,12].

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Though psychosis and depression have been reported to commonly co-occur in PD, the relationship between the two disorders has not been studied in detail. Specifically, we sought to: (1) determine the frequency of depression, psychosis, and co-morbid psychosis and depression in a sample of PD patients; (2) determine if an association exists between the two disorders; and (3) probe for clinical correlates of co-morbid psychosis and depression.

2. Methods

2.1. Subjects

The study population consisted of a convenience sample of 130 outpatients with a diagnosis of possible or probable idiopathic PD [13], confirmed by a movement disorders specialist. Subjects were established patients at the Parkinson's Disease Centers at the University of Pennsylvania (N = 25) or the Philadelphia Veterans Affairs Medical Center (VAMC) (N = 105), and were evaluated as part of a study of the frequency and correlates of depression in PD. The typical subject was an older white male (Table 1), reflecting the fact that the majority of subjects were male patients at the Philadelphia VAMC.

2.2. Procedures

The Institutional Review Boards at the University of Pennsylvania and the Philadelphia VAMC approved the study, and written informed consent was obtained prior to study participation. A trained research assistant administered the psychiatric and neuropsychological instruments and conducted a chart review. If the subject demonstrated memory impairment on clinical interview, collateral information about the presence of psychotic symptoms was sought from an informed other(s). Neurological assessments were completed by movement disorders' neurologists, nurses with expertise in PD, or a geriatric psychiatrist (DW) with training in the administration of neurological assessments.

2.3. Measures

2.3.1. Demographic and clinical characteristics—As part of the screening process patients provided the following information: age, sex, race, years of education, current medications, duration of PD, and initial side predominance of PD.

2.3.2. Psychiatric—Depression was assessed with the 15-item Geriatric Depression Scale (GDS-15) [14], which is a self-rated depression screening questionnaire (range = 0-15, higher scores indicating greater severity of depression). A GDS-SF cutoff of ≥5, which has demonstrated good sensitivity and specificity for a DSM-IV-TR [15] diagnosis of depression in PD [16], was used to indicate the presence of clinically significant depression.

Psychosis was assessed with the Parkinson's Psychosis Rating Scale (PPRS) [17], a 6-item clinician-administered questionnaire (range 6-24, higher scores indicating greater severity of psychosis). As three of the items on the PPRS are not specific to psychosis (i.e., sleep disturbances, confusion, and sexual preoccupation), only the three items that queried for visual disturbances (either hallucinations or illusions) and paranoid ideation were used for analyses (range 3-12, higher scores indicating greater severity of psychosis). For the purposes of this study, a subject was considered to be experiencing psychosis if any of these three items was endorsed.

Global cognition was assessed with the Mini-Mental State Examination [18]. Daytime sleepiness was assessed with the Epworth Sleepiness Scale (ESS) [19] (range = 0-24, higher scores indicating greater somnolence).

2.3.3. Neurological—Severity of PD was assessed with the Unified Parkinson's Disease Rating Scale UPDRS [20] motor section (UPDRS items #18-31, range = 0-108, higher scores indicating greater motor impairment). Prior to study initiation, all UPDRS motor section raters viewed the UPDRS Teaching Tape [21] and received a certification documenting acceptable interrater reliability (i.e., rating scores that fit within the 95% confidence interval range established by 3 experts on all 4 test videotapes of PD subjects) [22].

2.4. Statistical analysis

All statistical procedures were performed with SPSS 13.0 for Windows [23]. Comparisons between psychotic and non-psychotic subjects and between depressed and non-depressed subjects were made using a two-sample *t*-test (for continuous variables) and the χ^2-test (for categorical variables). Comparisons between the four groups (those with neither psychosis nor depression, with psychosis only, with depression only, and with psychosis plus depression) were made using multinomial logistic regression. $P<.05$ was considered to be significant for all analyses. As these analyses represented a preliminary probe for defining the characteristics of PD patients with co-morbid psychosis and depression, a correction for multiple comparisons was not made.

3. Results

3.1. Subject characteristics

Regarding the frequency of psychosis and depression irrespective of co-morbidity, 26.2% of subjects were currently experiencing psychotic symptoms, and 36.2% had clinically significant depression (Table 1). The most common psychotic symptom was visual disturbances, followed by paranoia. Regarding co-morbidity, 10% of subjects had co-occurring psychosis and depression, a frequency not greater than that expected by chance alone ($\chi^2 = .09_{[1]}$, $P = .769$). Of all patients with psychosis, 38.2% (13/34) had co-morbid depression; conversely, 27.6% (13/47) of depressed patients also experienced psychotic symptoms. Based on a review of the clinical records, no patient with both psychosis and depression met DSM-IV-TR criteria for mood-congruent psychotic features.

3.2. Correlates of psychosis and depression

Psychosis was associated with treatment with a dopamine agonist and a higher levodopa dose, but no other clinical or demographic characteristics, though there was a trend for longer duration of PD to be associated with psychosis (Table 2). Depression was associated with a higher daily levodopa dose and lower MMSE scores, and there was a trend for younger patients to experience depression.

3.3. Correlates of co-morbid psychosis and depression

Separately classifying subjects with co-morbid psychosis and depression in the regression models, between-group differences were seen for dopamine agonist exposure, daily levodopa dose, and global cognitive abilities (Table 3). Specifically, patients with depression and psychosis were significantly more likely to be taking a dopamine agonist than patients with depression alone. Additionally, patients with both psychosis and depression were taking a higher levodopa dose than each of the other three groups. Finally, the co-morbid group had greater global cognitive impairment than both the unimpaired group and the patients with psychosis only.

4. Discussion

We found that both psychosis (26.2%) and depression (36.2%) are common in PD patients receiving specialty care. In addition, co-morbid psychosis and depression are present in approximately 10% of patients, a frequency not greater than that expected by chance alone. Of the demographic and clinical characteristics studied, an association was found for treatment with a dopamine agonist (psychosis), lower MMSE score (depression), and higher daily levodopa dose (both psychosis and depression). Treating patients with co-morbid psychosis and depression as a distinct entity, this group's clinical profile included treatment with a dopamine agonist, a higher daily levodopa dose, and greater cognitive impairment.

Several limitations bear mentioning. First, the sample was predominantly elderly white males receiving specialty care, so our findings cannot be applied to PD patients in general. Second, the small sample size at one of the sites did not allow us to examine inter-site differences. Third, when dividing the study population into four groups, the sample sizes for some of the groups were small, limiting our ability to detect between-group differences for some clinical and demographic characteristics. Finally, the study population was relatively unimpaired from a cognitive standpoint, which may have affected the clinical correlates of disorders studied. For instance, by including patients with greater cognitive impairment we may have demonstrated an association between psychosis and lower MMSE scores.

The association between dopamine replacement therapies and psychosis in PD is controversial. It was once thought that treatment with higher dosages or particular classes (e.g., dopamine agonists) of dopamine replacement therapies was the primary etiology of psychosis in PD [24]. While numerous case series, epidemiological studies, and treatment studies have found psychosis to be related to levodopa [25] and dopamine agonist [26,27] use, several other recent epidemiological studies have not found an association between antiparkinsonian medication and the occurrence of psychosis [6,28,29]. Regardless the exact association between antiparkinsonian medications and psychosis, it is now thought that the etiology of psychosis in PD is multi-factorial, including other risk factors such as increasing age [6], longer duration and greater severity of PD [5,6], executive [30] and other forms of cognitive impairment [5-7], visual impairment [5], and increasing severity of depression [5-7].

In our sample, dopamine agonist exposure was associated with psychosis, regardless the presence of co-morbid depression. In the multinomial logistic regression model, patients with depression only were significantly less likely to be taking a dopamine agonist, consistent with preliminary research that this medication class may have antidepressant properties in PD [31]. Though causality cannot be established in a cross-sectional study, these two findings suggest that for PD patients with co-occurring psychosis and depression, dopamine agonist treatment is the most common cause of the psychotic symptoms, while the depressive symptoms likely are secondary to other factors.

Based on our results, factors contributing to development of co-morbid depression in the context of psychosis may include treatment with higher levodopa doses and the presence of mild cognitive impairment. We found that although these two variables were associated with depression in univariate analyses, in the multivariate logistic regression model they were only associated with the occurrence of co-morbid psychosis and depression. If true, this suggests that previous research reporting an association between depression and both greater cognitive impairment [9] and higher levodopa doses [11] may have been confounded by the co-occurrence of psychotic symptoms. It also under-scores the importance of accounting for psychiatric and cognitive co-morbidity when determining the correlates of psychiatric disorders in PD.

In summary, we found that although both psychosis and depression are common in PD patients receiving specialty care, their co-occurrence is not greater than that expected by chance. We also found preliminary evidence for the existence of a distinct clinical profile for co-morbid psychosis and depression, characterized by treatment with both a dopamine agonist and a higher levodopa dose in a patient with mild cognitive impairment.

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Table 1

Demographic and clinical characteristics (N = 130)

Variable	Mean (SD) or percentage
Demographics	
Age	71.4 (8.8)
Sex (% male)	87.5%
Race (% white)	93.8%
Education (# years)	15.4 (8.1)
Psychosis	
Any psychotic symptom (% yes)	26.2%
Hallucinations (% yes)	23.8%
Paranoia (% yes)	6.2%
Depression	
GDS positive (% yes)	36.2%
Motor	
PD duration (# years)	7.0 (5.4)
Sidedness (% right-sided PD)	41.9%
Levodopa/carbidopa dosage (mg/day)	442.1 (349.8)
Dopamine agonist (% yes)	51.2%
UPDRS motor score	22.7 (11.2)
Cognition	
MMSE score	27.9 (2.1)
Other	
ESS score	10.1 (5.1)

Table 2

Demographic and clinical correlates of psychosis and depression

Variable (Mean [SD] or %)	Psychosis			Depression		
	Non-psychotic *N* = 96 (73.8%)	Psychotic *N* = 34 (26.2%)	*P*-value (χ^2 or *t*-test)	Non-depressed *N* = 83 (63.8%)	Depressed *N* = 47 (36.2%)	*P*-value(χ^2 or *t*-test)
Age (# years)	71.9 (8.6)	69.9 (9.2)	.25	72.6 (7.6)	69.5 (10.2)	.08
Education (# years)	14.6 (3.3)	14.2 (3.4)	.52	14.7 (3.5)	14.1 (3.1)	.35
Duration of PD (# years)	6.5 (4.9)	8.5 (6.2)	.05	7.1 (5.6)	6.9 (5.0)	.81
Sidedness (% right-sided PD)	42.7	41.2	.99	42.2	42.6	.79
Levodopa/carbidopa dosage (mg/day)	392.3 (312.4)	578.5 (406.4)	<.01	375.8 (311.9)	555.0 (380.5)	<.01
Dopamine agonist use (% yes)	44.1	72.7	<.01	54.4	46.8	.41
UPDRS score	22.1 (11.2)	24.8 (11.0)	.26	22.4 (12.0)	23.3 (9.6)	.70
MMSE score	28.1 (1.8)	27.6 (2.7)	.24	28.3 (1.6)	27.3 (2.6)	.03
ESS score	10.0 (5.3)	10.5 (4.5)	.67	9.8 (5.2)	10.7 (4.7)	.35

Table 3

Characteristics of subjects with co-morbid psychosis and depression[a]

Variable (mean [SD] or %)	No psychosis or depression (NP or ND) *N* = 62 (47.7%)	Psychosis only (P) *N* = 21(16.2%)	Depression only (D) *N* = 34 (26.2%)	Psychosis and depression (P and D) *N* = 13 (10.0%)	χ^2 (*P*-value)
Age (# years)	73.0 (6.8)	71.3 (9.8)	70.1 (10.9)	67.8 (8.2)	4.93 (.18)
Education (# years)	14.9 (3.6)	14.0 (3.0)	14.0 (2.7)	14.4 (4.1)	2.22 (.53)
Duration of PD (# years)	6.7 (5.0)	8.1 (7.1)	5.9 (4.8)	9.2 (4.8)	4.39 (.22)
Sidedness (% right-sided PD)	45.2	33.3	38.2	53.8	3.24 (.78)
Levodopa/carbidopa dosage (mg/day)	343.1 (290.7)	467.9 (356.4)	477.7 (334.1)	757.3 (432.0)	15.34 (<.01)
Dopamine agonist use (% yes)	49.2	70.0	35.0	76.9	10.14 (.02)
UPDRS score	22.2 (12.3)	23.2 (11.1)	21.8 (8.8)	27.3 (10.8)	2.15 (.54)
MMSE score	28.3 (1.5)	28.4 (1.8)	27.7 (2.1)	26.4 (3.4)	8.81 (.03)
ESS score	9.5 (5.3)	10.8 (4.9)	11.0 (5.1)	9.9 (3.7)	2.32 (.51)

[a] Multinomial logistic regression (X^2 and *P*-value presented for overall model).