Clinical Implications of the National Institute of Neurological Disorders and Stroke Criteria for Diagnosing Psychosis in Parkinson's Disease

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The effect of psychotic symptoms in Parkinson's disease (PD) is variable among patients, and different methods to assess psychosis may yield conflicting results. A sample of 102 patients with a diagnosis of idiopathic PD underwent neurological, psychiatric, and neuropsychological assessment. Participants were divided into three groups: those who met *DSM* criteria for psychotic disorder, those who had psychotic symptoms but did not meet *DSM* criteria, and those without any psychotic symptoms. The first group had significantly worse sleep and worse cognitive and psychopathological symptoms compared with the other two groups. Results suggested that patients meeting *DSM* criteria for psychotic disorder comprise a separate clinical category.

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Parkinson's disease (PD) psychosis is a condition associated with many negative outcomes. Patients with PD and psychotic symptoms were found to be at higher risk for cognitive decline,[1] increased caregiver distress,[2] and nursing home placement[3,4] compared with those without psychotic symptoms. The prevalence of psychosis among patients with PD is estimated between 16% and 75%.[5–8] The large discrepancy in prevalence estimates can mostly be accounted for by the use of different definitions of psychosis across the literature. PD psychosis is defined in various studies as the presence of any perceptual disturbance such as illusions, hallucinations, or false sense of presence[7]; presence of hallucinations and/or delusions with or without insight[9,10]; presence of hallucinations and/or delusions but only with significant impairment of insight and functionality[1,11]; or any symptom that requires treatment with an antipsychotic medication.[12] The lack of a unified set of criteria for PD psychosis may be an obstacle for understanding the condition, because the pool of participants in different studies may consist of samples of distinct populations, thus weakening the validity of results obtained.

Aiming to overcome this limitation, a work group from the National Institutes of Health National Institute of Neurological Disorders and Stroke (NINDS) proposed a set of criteria for PD psychosis.[13] The NINDS diagnostic criteria for PD-associated psychosis include the presence of at least one of the following symptoms: illusions, false sense of presence, hallucinations, and delusions. The symptoms are necessarily associated with a formal diagnosis of PD as defined by the U.K. Brain Banks Network criteria, and symptoms of PD must precede the psychotic syndrome (Table 1). The consensus that any sort of perception disturbance including mild hallucinations or a false sense of perception would be sufficient for the diagnosis of PD-associated psychosis is based on evidence that suggests these phenomena are major risk factors for poor prognosis, which includes progression to severe impairment in insight and functionality.[14] It is further proposed that mild symptoms such as visual hallucinations and a false sense of presence are part of a spectrum of PD psychosis, which may progress to more severe thought disorders, impaired insight, and poor function.[7]

However, including such a broad set of symptoms, from mild perception alteration to severe thought disorder, in the diagnostic criteria may make it too inclusive and limit clinical use, despite epidemiological and prognostic value. For instance, it is unclear whether patients with mild hallucinations will benefit from the same treatment as those with severely impaired insight. Broadly inclusive criteria are also likely to select heterogeneous samples of patients, which poses an obstacle to the validity of further studies on the matter. The purpose of this study was to investigate the prevalence of psychosis associated with PD in our population using both the NINDS and *DSM-IV-TR* criteria (Table 1). *DSM* is the standard reference manual for diagnosis, clinical practice,

and research in the mental health field. We also aimed to evaluate clinical factors linked with the diagnosis of PD-associated psychosis.

METHODS

Participants were recruited from the Movement Disorders Clinic of the Hospital Santa Marcelina of São Paulo, Brazil, which receives community referrals from several catchment areas. From 2012 to 2014, consecutively referred patients receiving treatment for idiopathic PD were selected for further evaluation.

Patients were evaluated by a neurologist who specialized in movement disorders to confirm a diagnosis of idiopathic PD as defined by the U.K. Parkinson's Disease Society Brain Bank clinical diagnostic criteria.[15] A structured clinical interview was conducted to record demographic data, medical history, and medication history. Participants were evaluated using the second, third, and fourth subscales of the Unified Parkinson's Disease Rating Scale (UPDRS). The first subscale of the UPDRS was not used because many items involve psychiatric symptoms that may present as confounding factors in our analysis.[16] PD progression was measured with the Hoehn and Yahr scale.[17] Activities of daily living were measured with the Schwab and England daily activity scale.[18] Addenbrooke's Cognitive Examination–Revised (ACE-R) was utilized for global cognitive assessment.[19] Quality of life was assessed using the Parkinson's Disease Questionnaire.[20] Sleep was assessed using the Scales for Outcomes in Parkinson's Disease,[21] and diurnal somnolence was measured with the Epworth Sleepiness Scale.[22] The National Institute of Mental Health (NIMH) criteria for psychosis in PD were also used during the evaluation.[13] Determination of the clinical subtype of PD followed guidance published by Jankovic et al.[23] According to this model and from the UPDRS items held in the "off" condition, we calculated tremor scores (sum of items 16, 20, and 21 divided by 9) and postural instability gait disorder (PIGD) score (sum of items 13, 14, 15, 29, and 30 divided by 5) for each patient. The division of tremor score by PIGD score provides a value to be interpreted as follows: ≤1 corresponds to the postural instability and gait disorder subtype, >1 and ≤1.5 correspond to the undetermined subtype, and values >1.5 correspond to the tremor dominant subtype. The equivalent L-dopa daily dose was calculated according to the protocol by Tomlinson et al.[24]

Participants and a family member were separately evaluated by a psychiatrist who applied the Structured Clinical Interview for the DSM-IV-TR and the Brief Psychiatric Rating Scale (BPRS). Patients were classified as "psychotic" if they met DSM-IV-TR criteria for a psychotic disorder due to a medical condition–Parkinson's Disease (293.8).[25] As specified by the manual, individuals were only included in this category if their psychotic symptoms appeared after PD onset and if these symptoms involved impaired reality testing and/or represented significant distress.[25] Individuals who had psychotic symptoms according to NINDS criteria, but did not meet DSM-IV-TR criteria for a psychotic disorder due to a medical condition, were classified as "subsyndromal." Patients with a history of any psychotic disorder before PD onset were excluded.

The diagnosis of dementia was made during neurologic assessment and was aided by formal neuropsychological testing by a trained neuropsychologist, following the PD assessments recommendation for research settings by the Movement Disorder Society Task Force on dementia in PD.[26] Neuropsychological testing included visual and verbal memory, constructive ability, and attention/executive function. Visual and verbal memory was assessed with the Visual Reproduction and Logical Memory subtests of the Wechsler Memory Scale–Revised and the Rey Auditory-Verbal Learning Test. Constructive ability was tested with the Block Design subtest–WAIS and the Rey

TABLE 1. Criteria Used for PD-Associated Psychosis According to *DSM-5* and the NINDS, NIMH Work Group[a]

Criteria for PD-Associated Psychosis
NINDS, NIMH Work Group: Proposed Diagnostic Criteria for PD-Associated Psychosis
A. Characteristic symptoms
Presence of at least one of the following symptoms:
Illusions
False sense of presence
Hallucinations
Delusions
B. Primary diagnosis
U.K. Brain Bank criteria for PD
C. Chronology of the onset of symptoms of psychosis
The symptoms in criterion A occur after the onset of PD
D. Duration
The symptom(s) in criterion A are recurrent or continuous for 1 month
E. Exclusion of other causes
The symptoms in criterion A are not better accounted for by another cause of parkinsonism, such as dementia with Lewy bodies, psychiatric disorders such as schizophrenia, schizoaffective disorder, delusional disorder, mood disorder with psychotic features, or a general medical condition including delirium
DSM-5: Psychotic Disorder Due to Another Medical Condition[b]
A. Prominent hallucinations or delusions
B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of another medical condition
C. The disturbance is not better explained by another mental disorder
D. The disturbance does not occur exclusively during the course of a delirium
E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

[a] NIMH, National Institute of Mental Health; NINDS, National Institute of Neurological Disorders and Stroke; PD, Parkinson's disease.

[b] Reprinted from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC, APA, 2013. Copyright © 2013, American Psychiatric Association. Used with permission.

TABLE 2. Clinical and Demographical Features of 102 Patients With Idiopathic PD, Divided Into Psychotic Symptom Subgroups[a]

Characteristic	Psychotic (N=16, 15.7%)	Subsyndromal (N=34, 33.3%)	Nonpsychotic (N=52, 51%)	p Value
Men[b]	15 (93.8)	16 (47.1)	37 (71.2)	0.003[f]
Age, years[c]	69.0 (13.5)	64.5 (9.9)	61.9 (9.9)	0.062
Years of education[c]	5.2 (4.3)	5.5 (3.9)	6.7 (3.6)	0.232
Age of PD onset, years[c]	58.6 (12.5)	56.9 (10.3)	54.4 (10.3)	0.316
H&Y scale score 4–5[b]	7 (43.8)	2 (6.1)	4 (8.3)	<0.001[e]
PIGD[b]	10 (62.5)	22 (64.7)	20 (38.5)	0.036[g]
Equivalent L-dopa, mg[c]	647.5 (250.2)	669.8 (329.3)	597.9 (224.3)	0.465
Diagnosis of dementia[b]	10 (62.5)	10 (29.4)	14 (26.9)	0.026[e]
PDQ-39 score[d]	132.4 (199.1)	82.5 (130.0)	61.0 (109.7)	0.002[e]
S&E score[c]	54.3 (17.8)	74.4 (17.0)	76.9 (17.5)	<0.001[e]

[a] Data are presented as means (standard deviations) unless indicated otherwise. H&Y, Hoehn and Yahr scale; PD, Parkinson's disease; PDQ-39, Parkinson's Disease Questionnaire; PIGD, postural instability gait disorder; S&E, Schwab and England daily activity scale.
[b] Chi-square test. Data are given as N (%).
[c] Analysis of variance.
[d] Kruskal-Wallis test.
[e] Group 1>group 2=group 3.
[f] Group 1>group 3>group 2.
[g] Group 1=group 2>group 3.

Complex Figure Test. Attention and executive function were evaluated with the Trail Making Test Parts A and B and the Stroop Test.

This study was approved by the local research ethics committee.

Each patient subgroup (psychotic, subsyndromal, and nonpsychotic) was treated as a dependent variable. A series of univariate analyses were performed to compare independent and dependent variables, by means of the chi-square, one-way analysis of variance, and the Kruskal-Wallis test, depending on the statistical distribution of the variables. A multivariate analysis of variance (MANOVA) was performed to investigate the difference in dependent variables among the clinical subgroups in a multivariate fashion. The model had the following dependent variables: duration of PD in years, sleep scales regression component, and UPDRS, BPRS, and ACE-R scores. Sleep scales were reduced to a one-dimensional variable using principal component regression for the MANOVA. Post hoc analyses were conducted using the Scheffé test, and level of significance for multiple analyses was adjusted using the Bonferroni correction.

RESULTS

The clinical and demographic features for the 102 participants included in the final analysis are shown in Table 2. Two of the evaluated patients were not included in the final analysis because of previous diagnoses of psychotic syndrome (one of bipolar disorder, one of schizophrenia). Sixteen patients (15.7%) met *DSM-IV-TR* criteria for psychotic disorder due to a medical condition, and 34 patients (33.3%) manifested subsyndromal symptoms. All participants were receiving antiparkinsonian drug treatment; the equivalent L-dopa dosages are described in Table 2. None of the patients were using anticholinergic drugs at the time of the evaluation.

The mean age of the total sample was 63.9 years (SD=10.7), with a mean age of disease onset of 55.9 years (SD=10.7) and a mean duration of PD of 7.9 years (SD=4.8). Mean equivalent dose of L-dopa was 629.4 mg (SD=266.9). There was no significant difference among the subgroups concerning these variables. Sixty-eight participants (66.7%) were men, 13 (12.7%) had Hoehn and Yahr stage 4 or 5 disease, and 34 (33.3%) met criteria for dementia. All of these conditions were more prevalent in individuals with psychosis. Fifty-one participants (49%) met criteria for PIGD, which was more prevalent among individuals with psychosis according to *DSM* criteria and among those with subsyndromal symptoms compared with individuals without psychosis (chi-square=6.67, df=2, p=0.036).

Results from the multivariate analysis are shown in Table 3. There was no difference among subgroups regarding duration of the disease. Patients from the psychotic subgroup had more severe PD symptoms, more psychopathological symptoms, more sleep disturbances, and worse performance in cognitive screening than those in the subsyndromal and nonpsychotic groups.

DISCUSSION

Our results suggested that patients with PD who met formal *DSM* criteria for a psychotic disorder due to a medical condition presented a different clinical profile than those who only had mild psychotic phenomena, suggested by the NINDS/NIMH Work Group as sufficient for psychosis. Patients with psychosis had a higher prevalence of dementia, more severe PD symptoms, and more psychopathological and sleep disturbance symptoms. Moreover, patients with mild psychotic phenomena (i.e., those in the subsyndromal group) did not differ from those without any psychotic symptoms with regard to these variables.

The association between psychotic symptoms and the aforementioned clinical features has been described in previous studies. Fénelon et al.[6] found that the presence of hallucinations was independently associated with daytime somnolence. An association between other sleep disturbances and psychosis, using different definitions of the latter, was also previously demonstrated.[9,27] Some authors proposed a causative relationship between daytime REM sleep rhythm and hallucinatory phenomena in patients with PD[28,29] and suggested a direct link between PD sleep disorder and psychotic symptoms. Cognitive deficits were also associated with psychosis in PD,[6] and diagnosis of dementia predicted the development of psychosis.[9] Neuropsychological studies also suggested the existence of different subgroups within patients with PD and psychotic symptoms. In these studies, patients with delusions and severe

TABLE 3. Multivariate Analysis of Variance of 102 Patients With Idiopathic PD, Divided Into Psychotic Symptom Subgroups[a]

Variable	Psychotic (N=16, 15.7%)	Subsyndromal (N=34,33.3%)	Nonpsychotic (N=52,51%)	Mean Squares	df	p Value	Post Hoc Test for Multiple Comparisons
Duration of PD (years)	10.1 (3.7)	7.3 (3.9)	7.1 (5.6)	44.11	2	0.181	—
UPDRS score	85.5 (22.8)	61.3 (20.2)	62.7 (23.8)	2668. 31	2	0.009	Group 1>Group 2; p=0.012 Group 1>Group 3; p=0.016 Group 2=Group 3; p=1.000
BPRS score	23.5 (9.2)	10.9 (5.5)	9.7 (4.7)	819.78	2	<0.001	Group 1>Group 2; p<0.001 Group 1>Group 3; p<0.001 Group 2=Group 3; p=1.000
Sleep component	0.72 (0.8)	−0.15 (0.8)	−0.25 (1.0)	4.08	2	0.013	Group 1>Group 2; p=0.036 Group 1>Group 3; p=0.013 Group 2=Group 3; p=1.000
ACE-R score	46.0 (15.1)	66.2 (15.3)	71.7 (18.9)	2533.60	2	<0.001	Group 1>Group 2; p=0.005 Group 1>Group 3; p<0.001 Group 2=Group 3; p=0.721

[a] Data are presented as means (standard deviations). ACE-R, Addenbrooke's Cognitive Examination–Revised; BPRS, Brief Psychiatric Rating Scale; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale (subscales 2–4).

thought disorder had more severe cognitive deficits in all areas compared with individuals with hallucinations only.[30,31]

Although previous studies have found an association between PD duration and psychotic symptoms,[1,6,8] we did not find the same result. A selection bias might have contributed to negative results. Our sample was recruited from a tertiary health care center, which was likely to have more patients with severe disease burden, including patients with rapidly progressing disorder. The relative small sample size was also a limitation, because the separation of participants into three different groups diluted the total sample, especially for the subgroup with psychotic syndromes, and weakened the statistical power of the analyses. Another limitation of our study was its cross-sectional design; it did not describe the disease course as some previous studies have. Furthermore, although *DSM-IV-TR* was revised to a fifth edition (*DSM-5*) in 2013, the definition of psychotic disorder due to a medical condition remained unchanged. Both manuals required prominent hallucinations or delusions, and the diagnosis of a psychotic disorder could not be based solely on mild hallucinations and perception alterations with preserved insight.[32]

Although a cross-sectional analysis suggested that patients in the subsyndromal and psychotic groups differed significantly, longitudinal studies showed disease progression.[1,9,14] Patients with longer disease duration, along with sleep disturbances and cognitive impairments, were found to be at risk for the development of minor visual hallucinations.[6] Subsequently, patients with only mild hallucinations and perception alterations were found to be at risk for the development of severe thought alterations,[14] which in turn progressed to severe functional impairment and dementia.[1] This progression suggested that the evolution of psychotic symptoms, from mild perception disturbances to frank psychosis and dementia, comprised a spectrum of PD-associated psychosis, which runs parallel to the course of PD.[7] Indeed, age and disease progression over time were associated with progressive motor and cognitive symptoms, and both correlated with neuropathological findings and neuronal loss.[33]

Despite epidemiological data that suggested a progression from mild perception disturbances to severe impairment, the implications of diagnosing all ends of this spectrum as "PD psychosis" should be reconsidered. Individuals with only subsyndromal symptoms do not seem to be otherwise different from patients without psychotic symptoms, with respect to clinical variables. Consequently, it is not clear whether all patients within the "PD psychosis spectrum" will benefit from the same treatment. It is worth pointing out that clinical trials that suggested clozapine as an effective treatment of PD psychosis used a criteria similar to those of *DSM*.[11] It has been proposed that even patients within the early stages of PD psychosis should be treated with antipsychotic agents in a preventive fashion.[10] The implications of this recommendation should be carefully considered, weighing the risks and burdens involved in the prescription of an antipsychotic drug to a patient with mild symptoms. It is possible that different treatments may be suited for different stages of the disease, which can only be accomplished by narrowing the criteria to specific subgroups. For instance, in the early stages of PD, mild psychotic symptoms might be amenable to antiparkinsonian drug reduction (particularly amantadine and anticholinergics[12]) or coping strategies that educate the patient on the nature of the phenomena.[34,35] Furthermore, considering the association of cognitive deficits and severe forms of thought disorder, treatment of dementia may be effective for comorbid psychotic symptoms in this group of patients. Indeed, some studies showed that use of acetylcholinesterase inhibitors is inversely related to psychotic symptoms.[12] Trials investigating further interventions are being developed for psychosis in PD.[36,37]

In addition to the development of novel treatments, future studies should investigate interventions for different stages of PD psychosis. Studies that use broadly inclusive

criteria risk creating heterogeneous samples of patients with different clinical presentations and possibly neuropathological disturbances under the same diagnosis, thereby decreasing the validity of the studies and increasing the likelihood of negative results. An approach that considers subgroups of patients with PD manifesting different core symptoms and/or stages of the disease may lead to the development of specific and more effective treatment for individual patients. Furthermore, distinct clinical presentations of PD may have different underlying neurobiological substrates. One example is recognition of the PIGD subtype. A large cohort found PIGD along with hallucinations to be a major predictor of dementia.[38] It is possible that this phenotype represents a more severe form of the disorder with higher indices of progression to cognitive impairment and, consequently, to dementia and psychosis. This categorization is grounded in neuropathological findings: Selikhova et al.[39] ascertained that patients with non–tremor-dominant PD had significantly a higher mean pathological grading of cortical Lewy bodies and more cortical amyloid-beta plaque load and cerebral amyloid angiopathy than other PD groups. The analysis of patients with pathologically defined neocortical Lewy body disease confirmed the link between akinetic-rigid onset, cognitive decline, and Lewy body deposition in the neocortex.[39] It is interesting to note that in our sample, PIGD was found to be more prevalent among patients in both the psychotic and subsyndromal groups, suggesting a possible link of this subtype of PD and perception abnormalities. The involvement of biomarkers, such as neuroimaging and neurophysiology, may prove useful in the study of biological signatures of the disease and may be an asset for understanding both PD subgroups and the psychosis spectrum.

CONCLUSIONS

Despite evidence suggesting that mild psychotic symptoms present a risk factor for worse prognosis, including cognitive impairment and frank psychosis, a diagnosis of PD psychosis based solely on the presence of such subsyndromal symptoms should be reconsidered. Concerning motor and nonmotor symptoms, patients with PD and mild psychotic symptoms manifest little clinical difference compared with patients without psychotic symptoms. By contrast, those meeting formal *DSM* criteria exhibit more severe impairment, with cognitive deficits and psychopathological symptoms. It is possible that this subgroup is responsible for yielding worse outcomes among individuals with psychotic symptoms in previous studies. Therefore, patients with different manifestations of PD and psychotic symptoms are likely to require and respond to different approaches in both clinical and research settings.

Despite this difference among individuals with distinct severity of perception disturbances, results from previous studies suggest that the range of psychotic symptoms—from mild perception alteration to severe delusions—in PD might represent a continuum of PD-associated psychosis. Future studies focusing on the PD psychosis spectrum, possibly bringing together clinical subtypes and neurobiological variables, may result in further understanding of PD psychosis and its treatment.

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