PRDOA 5 (2021) 100119

Contents lists available at ScienceDirect

Clinical Parkinsonism & Related Disorders

journal homepage: www.sciencedirect.com/journal/clinical-parkinsonism-and-related-disorders

High frequency of psychosis in late-stage Parkinsoń s disease

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ARTICLE INFO

Keywords:
Parkinson's disease
Late-stage
Psychosis
Psychiatric comorbidities

ABSTRACT

Background: Psychosis is a frequent non-motor symptom in Parkinson's disease (PD). Estimates of the frequency of Parkinsoń s disease psychosis (PDP) vary widely. Knowledge about the frequency and phenomenology of psychosis in late-stage (LS) PD patients is limited.
This study aimed to determine the frequency of psychosis in LSPD patients through clinical diagnostic interview (CDI) (gold standard), according to NINDS/NIMH diagnostic criteria for PDP. The secondary objectives were to characterize the phenomenology, to test selected instruments and assess their adequacy in comparison to CDI, and to assess the psychiatric comorbidities.
Methods: A cross-sectional study including LSPD patients (patients with $\geq$ 7 years from symptoms onset and Hoehn and Yahr scale score $>$ 3 or a Schwab and England scale score $<$ 50% in the ON condition) was conducted. Patients were subjected to psychiatric, neurological, and neuropsychological evaluations. Each patient was interviewed by a psychiatrist who performed a CDI.
Results: 92 LSPD patients were included. 55.4% experienced psychotic symptoms according to NINDS/NIMH diagnostic criteria for PDP. Hallucinations were present in 94.1% and delusions in 29.4% of the psychotic patients. Visual hallucinations were the most common (88.23%) psychotic symptom. 72.5% of LSPD patients with psychotic symptoms had at least one comorbid psychiatric diagnosis. Lower frequency of psychosis was found when the assessment was performed only through selected instruments rather than CDI.
Conclusions: A high frequency (55.4%) of psychotic symptoms and comorbid psychiatric (72.5%) diagnosis were found in LSPD patients. The use of CDI, in addition to structured scales may increase the sensitivity of detecting psychotic symptoms.

1. Introduction

Psychosis is a frequent non-motor symptom (NMS) in Parkinson's disease (PD) [1]. Its presence increases with disease progression and is associated with poor prognosis such as greater motor disability, affective dysfunction, nursing home placement, dementia, and mortality [2–4].

The clinical features of psychotic symptoms in PD have a different pattern than that seen in other psychotic disorders such as schizophrenia or mood disorders with psychotic features. Therefore, the criteria applied to other psychiatric illnesses (e.g., the Diagnostic and Statistical Manual of Mental Disorders [DSM]) may be limited when describing the diversity of psychotic phenomena in PD. In addition, although psychosis

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https://doi.org/10.1016/j.prdoa.2021.100119
Received 27 September 2021; Received in revised form 10 November 2021; Accepted 17 November 2021
Available online 24 November 2021

in PD has common mechanisms with other psychotic disorders, the neurobiology responsible for psychosis in PD is different [5]. Psychotic symptoms in PD include hallucinations, mostly visual, and delusions, which, simplistically, define psychosis. But there are also atypical symptoms, mentioned as minor psychotic phenomena, which include sense of presence, passage hallucinations and illusions [6]. Standardized diagnostic criteria for PD psychosis (PDP) were suggested for the first time in 2007 by a National Institute of Neurological Disorders and Stroke (NINDS)/National Institute of Mental Health (NIMH) working group [6]. To better define and standardize the unique features of PDP, these proposed diagnostic criteria include passage/presence hallucinations and illusions which are not usually present in other psychotic disorders, besides hallucinations and delusion [6].

Estimates of the prevalence of PDP vary widely [5]. Reasons for this variability include the use of different criteria to define psychosis, the choices made to assess different psychotic phenomena, and the different samples of PD patients included in the studies. In general, the characteristic minor phenomena of PDP have been excluded from most studies [6]. For all these reasons, it is difficult to estimate the true prevalence of PDP. It is well established that PDP is more frequent with advancing disease [5] and a high frequency of psychosis and neuropsychiatric symptoms have recently been reported in a multicenter cohort of late-stage (LS) parkinsonism using the Neuropsychiatric Inventory (NPI) [7]. LSPD patients still represent "an orphan" population, whose clinical criteria have been recently proposed [8–9] but still poorly described due to the difficult for those patients to be included into clinical studies. At the same time the high rate of disability of those patients requires a significant medical and non-medical management. The presence of psychosis and co-morbid psychiatric disorders in LSPD has never been reported using the NINDS/NIMH diagnostic criteria in addition to a clinical psychiatric interview.

In this study, we aimed to determine the frequency of psychosis in LSPD patients through clinical diagnostic interview (CDI), according to the NINDS/NIMH diagnostic criteria for PDP. The secondary objectives were to characterize the phenomenology of psychosis in LSPD, to test the selected validated instruments for PDP evaluation and to assess their adequacy in comparison to CDI, and to evaluate the comorbid psychiatric disturbances in LSPD psychotic patients.

2. Methods

In a cross-sectional study, a clinical observation was performed to evaluate the presence of psychiatric disturbances (psychotic disorders, mood disorders, anxiety disorders, impulsive-compulsive disorders, other) and characterize the neuropsychiatric symptoms occurring in a hospital-based sample of LSPD patients.

2.1. Recruitment

Patients were consecutively recruited at the Santa Maria University Hospital Movement Disorders outpatient clinic. Patients provided full written informed consent before any study procedures were performed. When patients lacked the capacity to provide full written informed consent, a personal or legal nominee was asked to provide the informed consent according to the Mental Capacity Act (2005). The study was approved by the local ethics committee.

The inclusion criteria were 1) PD according to the UK Brain Bank criteria [10]; 2) LSPD (patients with $\geq$ 7 years from symptoms onset and Hoehn and Yahr scale (H&Y) [11] score $>$ 3 or a Schwab and England scale (S&E) [12] score $<$ 50% in the ON condition) [8]. Patients were excluded if they presented dementia before PD onset or dementia within 1 year following PD diagnosis, or if they had delirium at the moment of clinical evaluation. *Delirium was* diagnosed according to the DSM-5 criteria [13].

2.2. Assessment procedures and data collection

Patients underwent to psychiatric, neurological, and neuropsychological evaluations, performed by a psychiatrist, a movement disorders expert, and a neuropsychologist, respectively.

2.2.1. Psychiatric assessment

Each patient was interviewed by a trained psychiatrist who performed a CDI. The CDI was considered the gold standard method for PDP diagnosis, in agreement with the NINDS/NIMH diagnostic criteria [6]. Details of medical and PD history, drug therapy, and demographic variables were obtained by direct interview with the patient and a reliable informant (family caregivers or formal caregivers from nursing homes) as well as through review of the patient's clinical neurologic records. Around 95% of all evaluations took place in a single session and were conducted either in patient́s homes or in nursing homes.

Current and past psychiatric diagnoses were established according to the DSM-5 classification [13]. (1) A clinical and disorder-centered interview was used, as recommended by the American Psychiatric Association and the World Health Organization. (2) Given the expected communication challenges of LSPD patients, including verbal language impairment, their medical records were reviewed, and interviews with the caregivers were also conducted, in a complementary fashion. (3) The Brief Psychiatric Rating Scale (BPRS) was applied [14]. The BPRS consists of 18 items ranging from 1 (not present) to 7 (extremely severe). (4) Psychotic symptoms were considered present if the patient described hallucinations, delusions, or "minor" phenomena, namely illusions (misperceptions of real stimuli) or sense of presence/passage. "Minor phenomena", which are not part of the description of other psychotic disorders, were incorporated in our study to be inclusive. Psychotic symptoms had to be recurrent or continuous for at least 1 month and appear in clear consciousness. Patients with delirium as the sole cause of psychotic symptoms were not categorized as having psychosis.

Patients were classified as being "Psychosis-positive" according to the NINDS/ NIMH diagnostic criteria for PDP. The NINDS/ NIMH diagnostic criteria for PDP include: (1) the presence of at least one of the following characteristic symptoms – illusions, false sense of presence, hallucinations, delusions; (2) a diagnosis of PD made according to UK Brain Bank criteria and made prior to the onset of psychotic symptoms; (3) the psychotic symptoms have to be recurrent or continuous for at least one month; and (4) exclusion of other causes such as dementia with Lewy bodies, schizophrenia, schizoaffective disorder, delusional disorder, mood disorder with psychotic features and delirium [6].

2.2.2. Neurologic and functional assessment

Neurological assessment was performed using the Movement Disorders Society – Unified Parkinson Disease Rating Scale (MDS-UPDRS) (Parts I-IV) [15].

Neuropsychiatric functions were also assessed by the same neurologist and included behavioral symptoms using the NPI [16].

2.2.3. Neuropsychological assessment

Dementia (D) was diagnosed according to the MDS PDD Level II criteria [17] based on neuropsychological and functional autonomy assessment and mild cognitive impairment (MCI) was diagnosed using the MDS MCI Level II criteria [18] (comprehensive assessment).

2.3. Statistical analysis

Comparative analyses, i.e., PDP vs. not PDP patients, were carried out in relation to demographic and clinical variables. Comparisons between both groups were conducted using the Chi-Square test, or Fisher's Exact test, and the Mann-Whitney *U* test, as appropriate. The McNemáŕs test was used to determine if there were differences on dichotomous dependent variables.

An univariate analysis including age onset, current age, gender,

years of education, disease duration, cognition, and motor and non-motor features, neuropsychiatric symptoms, psychiatric comorbidities (all factored detailed in Table S1, Supplementary material) was run to evaluate independent factors associated to the presence of psychosis. Second, all the significant factors were included in a logistic regression analysis to determine predictors of psychosis.

All the analyses were performed with SPSS 26.0 (SPSS, Chicago, IL) using two-tailed p-values with a level of significance considered to be 0.05. Table 1

3. Results

3.1. Patient demographics and clinical characteristics

Ninety-two (92) LSPD patients (57.6% female) were enrolled in the study, with a mean age of 75.8 years (SD ± 6.9; range: 56–90), 15.9 years (SD ± 6.7; range: 7–39) of disease duration.

Table 1
Demographic and clinical characteristics of LSPD patients.

	LSPD (N = 92) Mean (SD)	LSPD-Psychosis-Positive (N = 51) Mean (SD)	LSPD-Psychosis Negative (N = 41) Mean (SD)	p
Sex (M/F)	39/53 (42.4%/ 57.6%)	24/27 (47.1%/ 52.9%)	15/26 (36.6%/ 63.4%)	0.312
Age (yrs)	75.8 (6.9)	76.4 (6.4)	75.2 (7.5)	0.747
Disease duration (yrs)	15.9 (7.2)	15.9 (6.7)	16.0 (7.9)	0.592
Age at onset (yrs)	59.0 (10.6)	59.3 (8.9)	58.6 (12.5)	0.762
Levodopa (% yes)	98.7	100	97.1	0.436
LEDD*	856.90 (418.31)	789.30 (351.79)	949.60 (485.44)	0.187
Antipsychotic† (quetiapine/ clozapine)(%yes)	47.8	60.8	31.7	**0.006**
Clozapine mg/day		32.35 (28.66)	17.5 (8.15)	
Quetiapine mg/day		89.29 (49.70)	69.64 (24.37)	
Antidemential (% yes)	44.6	54.9	31.7	**0.028**
Hoehn & Yahr stage (Med ON)	4.1 (1.2)	4.2 (1.0)	3.9 (1.4)	0.162
Schwab & England (Med ON)	33.7 (13.5)	30.8 (12.1)	37.6 (14.4)	**0.048**
MDS-UPDRS 1.2 Hallucinations and Psychosis	1.3 (1.4)	2.0 (1.4)	0.4 (0.9)	**<0.001**
MDS-UPDRS Part I	23.3 (6.7)	25.6 (5.8)	20.3 (6.7)	**0.001**
MDS-UPDRS Part II	35.7 (9.3)	37.1 (8.8)	33.8 (9.7)	0.103
MDS-UPDRS Part III	60.4 (17.5)	63.0 (17.1)	57.0 (17.8)	0.105
MDS-UPDRS Total Part I + II + III	117.5 (28.2)	123.2 (25.6)	110.3 (30.0)	0.052
NPI total	20.0 (16.6)	24.2 (18.5)	15.3 (12.2)	**0.014**
NPI delusions	1.2 (2.4)	1.9 (2.9)	0.4 (1.2)	**0.001**
NPI hallucinations	1.9 (2.9)	2.8 (3.3)	0.6 (1.6)	**<0.001**
BPRS total score	35.9 (9.3)	39.7 (8.9)	31.3 (7.7)	**<0.001**
MMSE score	21.9 (5.8)	20.2 (5.5)	23.8 (5.7)	**0.003**

LSPD- Late-Stage Parkinson's Disease; LSPD- Psychosis Positive – LSPD patients with psychotic symptoms; Psychosis Negative– LSPD patients without psychotic symptoms; N - number of patients; LEDD- Levodopa equivalent daily-dose calculated according to recognized standard conversions; NPI- Neuropsychiatric Inventory; BPRS- Brief Psychiatric Rating Scale; MMSE- Mini-Mental State Exam.

†In the psychotic group (n = 51), 17 (33.3%) patients were taking clozapine with a mean dose of 32.35 mg/day (SD 28.66; 12.50–125) and 14 (27.5%) patients were taking quetiapine with a mean dose of 89.29 mg/day (SD 49.70; 25–150). In the non-psychotic group (n = 41), six (14.6%) patients were taking clozapine with a mean dose of 17.5 mg/day (SD 8.15; 6.25–25) and seven (17.1%) patients were taking quetiapine with a mean dose of 69.64 mg/day (SD 24.37;23–100).

3.2. Frequency of psychosis and diagnostic subgroups

According to the NINDS/NIMH diagnostic criteria for PDP, fifty-one (55.4%) of the 92 LSPD patients had current psychotic symptoms. Of the 51 patients with current psychosis, 21 (41.18%) had also experienced psychosis in the past, 29 (56.86%) had never had psychotic symptoms, and for one patient there was insufficient information about past symptoms. Of the 92 patients, 20 (21.7%) had experienced psychotic symptoms in the past but did not experience psychosis currently which means patients did not fulfill criteria for PDP in the moment they were evaluated by CDI but it was possible to identify retrospectively periods, of at least one month, in the past, when the patients fulfilled criteria for PDP.

There were no statistically significant differences between psychotic vs. non-psychotic group concerning sex, current age, disease duration, age at disease onset, H&Y stage, MDS-UPDRS Parts I + II + III, and levodopa intake or levodopa equivalent daily dose (LEDD) [19] (Table 1).

The psychotic group had a higher BPRS total score ($p < 0.001$), BPRS positive (11 suspiciousness + 12 hallucinations + 15 unusual thought content items) subscore ($p < 0.001$) compared to the non-psychotic group as well as MDS-UPDRS Part I question 1.2 subscore, MDS-UPDRS Part I total, NPI total score, NPI hallucination and delusion subscores ($p < 0.05$). The MMSE score of the psychotic group was significantly worse and the S&E (Med ON) slightly lower, if compared with the non-psychotic group (p 0.003 and p 0.048, respectively).

60.8% of the psychotic group were taking an antipsychotic drug compared to 31.7% of the non-psychotic-group (p 0.006) and at a higher dose (See Table 1 for treatment details).

Hallucinations were present in 94.1% (48) and delusions in 29.4% (15) of the patients with psychosis, that is, 52.2% (hallucinations) and 16.3% (delusions) of the total sample of 92 LSPD patients. Minor psychotic phenomena were present in 27.5% of patients with psychotic symptoms (Table 2).

Visual hallucinations were the most common (88.2%) psychotic symptom and auditory hallucinations (31.4%) were the second most common. Persecutory followed by jealousy were the most common delusions.

3.3. Frequency of psychosis according to MDS-UPDRS 1.2, NPI delusions and NPI hallucinations compared to CDI

86 (93.5%) and 87 (94.6 %) out of the 92 enrolled patients have been evaluated also by means of the MDS-UPDRS Part I and of the NPI, respectively.

Using the MDS-UPDRS 1.2 $\geq$ 1 score, NPI delusions $\geq$ 1 score and NPI hallucinations $\geq$ 1 score criteria for diagnosing psychosis, the frequency of psychosis was 52.3%, 33.3%, and 43.7% respectively.

Once comparing MDS-UPDRS item 1.2 vs. CDI, the presence/absence of psychosis was concordant in 69 (80.2 %) of the 86 patients. 10 patients (11.6%) who were classified as experiencing psychosis by clinical evaluation were not psychotic according to the MDS-UPDRS 1.2 item, but this finding did not reach statistical significance ($p = 0.6276$). The Kappa coefficient was 0.604 indicating a moderate strength of agreement.

Table 2
Frequency of psychotic symptoms in LSPD- Psychosis-Positive (N = 51).

		Frequency (%)	N
Hallucinations	Any	94.1	48
	Visual	88.2	45
	Audit	31.4	16
Delusions	Any	29.4	15
	Persecutory	19.6	10
	Jealousy	9.8	5
Minor psychotic phenomena	Any	27.5	14

Once comparing the NPI vs. CDI, the presence/absence of psychosis was concordant in 55 (63.2 %) of the 87 patients: 23 (26.4%) agreed on the presence of psychosis and 32 (36.8 %) agreed on its absence. Twenty-six patients (29.9 %) were classified as psychotic by CDI but not psychotic according to NPI delusions. The two instruments differ ($p = 0.001$) and have a fair strength of agreement (Kappa coefficient 0.294).

The presence of psychosis was concordant in 66 (75.9%) of 87 patients between the NPI hallucinations item and CDI. However, 16 patients classified as psychotic by CDI were not psychotic according to the NPI hallucinations item. Once again, the two instruments differ ($p = 0.027$) and have a moderate strength of agreement (Kappa coefficient 0.525).

3.4. Correlations between psychosis and cognitive performance Table 3

In 71 of the 92 LSPD patients underwent a neuropsychological battery.

Forty-three patients (60.6%) were classified as demented, 23 patients (32.4%) as having MCI and five (7.0%) were cognitively intact. There was a significant statistical association (p 0.000872) between the presence of psychosis and dementia with 65.1% of demented patients experiencing psychotic symptoms.

3.5. Frequency of psychiatric comorbidities associated with psychosis

In the psychotic group, 37 patients (72.5%) had at least one comorbid psychiatric diagnosis. Thirteen patients (25.5%) had two or more comorbid psychiatric diagnoses.

Mood Disorders (mostly depressive disorders) were the most common comorbid psychiatric diagnosis (32 of 51 patients with psychosis) followed by impulsive-compulsive disorders (14 of 51 patients with psychosis) and anxiety disorders (5 out of 51 patients).

The frequency of psychiatric comorbidities was not statistically different between the psychotic and non-psychotic groups although the psychotic group had a higher frequency of two or more comorbidities compared to the non-psychotic-group ($p < 0.001$).

3.6. Psychosis predictors

At the univariate analysis, diagnosis of MCI, dementia, use of anti-dementia treatment, NPI total score, MMSE score, S&E on, MDRS-UPDRS Part I, MDS-UPDRS Total Part I + II + III and the number of psychiatric comorbidities correlated with PDP (Table S1, Supplementary material). At the multi regression analysis, only a higher number of psychiatric comorbidities (OR 5.759, $p < 0.001$), and higher NPI total score (OR 1.040, p 0.021) kept significance as risk factors for psychosis (Table 4).

4. Discussion

In agreement with the CDI, we found 55.4% of LSPD patients experience current psychotic symptoms. To the best of our knowledge, this is the first study to evaluate the overall frequency of psychosis in LSPD patients using a CDI, considered the gold standard method for diagnosis [20].

The clinical features of psychotic symptoms were in line with most published studies showing a different pattern than that seen in other psychotic disorders such as schizophrenia or mood disorders with psychotic features [13]. Therefore, criteria applied to other psychiatric illnesses have limited utility for describing the diversity of psychotic phenomena in PD. Using DSM 5 criteria, psychotic symptoms in PD would be classified in most cases as Psychotic Disorder Due to Another Medical Condition or less frequently as Medication-Induced Psychotic Disorder in the Schizophrenia Spectrum and Other Psychotic Disorders chapter [13].

Several studies [21–23] have already shown that visual hallucinations are the most common psychotic symptom in PDP. In our study, most patients with psychotic symptoms did not present insight, although they did recognize past psychotic symptoms. This suggests that patients may retain insight initially but lose it as the disease progresses. Most patients with hallucinations retained insight initially [21–22]. The absence of insight impacts the difficulty of diagnosing psychosis in LSPD. Psychotic symptoms were not reported spontaneously. Sometimes patients even denied their presence when questioned directly. It was only possible to ascertain the presence of some psychotic symptoms through a CDI and complementary information from caregivers. The frequency of delusions found in our study was significantly lower (29,4%) compared to Chou KL et al study [24] that found a frequency of delusions as high as 76%, with the delusion that another person was stealing from the subject occurring most frequently (33%) followed by delusions of infidelity (29%) and the delusion that the subject was not in their own home (29%) [24]. However, patients included in Chou KL et al study had a lower HY stage ($3.0 + -0.7$ in Chou study vs $4.1 + -1.2$ in our study) and different criteria to diagnose psychosis (two-week duration) was applied [24].

We found that LSPD patients with psychosis have a high frequency of comorbid psychiatric disorders. Specifically, 72.5% of LSPD patients with psychotic symptoms had at least one comorbid psychiatric diagnosis. Depressive disorders were the most common comorbid psychiatric diagnosis. According to Tandberg E [25], psychosis is a significant risk factor for the presence of major depressive disorder, with both depression and psychosis having an impact on functional impairment and caregiver burden. In our study, in most cases, patients did not have mood-congruent psychotic features. This may mean psychotic phenomena were independent of the affective disorder, as described by Marsh [26].

Contrary to what was observed in Marsh [26], we found a high rate of psychosis comorbid with impulsive-compulsive disorders, which may be related to the on-going dopaminergic treatment.

As previously reported by some authors [22,27–29], cognitive impairment may be a risk factor for the development of psychosis. Our study confirms this finding, with a significant statistical association between the presence of psychosis and dementia and 65.1% of demented patients experiencing psychotic symptoms.

As expected, the frequencies of psychosis and psychiatric comorbidities in LSPD that we report here are higher than those observed in early and mid-stage samples [26]. Clinical sampling and sociodemographic characteristics as well as the different methodologies used most likely explain the different frequency rates. In fact, in our study, a CDI by a trained psychiatrist was made in addition to the use of rating scales (MDS-UPDRS, NPI, and BPRS). Although there were statistically significant differences between psychotic and non-psychotic groups concerning the MDS-UPDRS Part I question 1.2 hallucinations and psychosis subscore and the NPI hallucination and delusion subscores, we wanted to compare the performance of these instruments vs. the CDI for diagnosing psychosis. The frequency we found was similar to the ones reported in few previous studies that reported on hallucinations/psychosis among LSPD patients. Indeed 41% (vs. 43.7% in our sample) of hallucinations have been reported in a large cohort of 623

Table 3
Correlations between psychosis and cognitive performance.

		Groups*			
		Dementia	Mild Cognitive Impairment	Cognitively Intact	Total
Psychosis	Yes n (%)	28 (65.1%)	6 (26.1%)	0	34
	No n (%)	15 (34.9%)	17 (73.9%)	5 (100%)	37
Total		43	23	5	71

*p value = 0.000872

Table 4
Demographic and disease-related variables considered as potential predictors of psychosis in PD: Multivariate analysis

Independent Variable	β	S.E.	Wald	df	p-Value	OR	95% C.I. para OR	
							Inferior	Superior
N_comorbidities: 2–3 vs 0–1	1.751	0.493	12.603	1	**<0.001**	**5.759**	**2.191**	**15.141**
NPI total	0.039	0.017	5.335	1	**0.021**	**1.040**	**1.006**	**1.075**

LSPD patients in agreement with the NPI [7] or 56% (52.3% in our sample) of psychosis in a smallest cohort of 50 patients, in agreement with the MDS-UPDRS item 1.2 [7]. At the same time, comparison among those tests and the CDI have been not performed previously, particularly among LSPD patients. Our findings may call into question the adequacy of these instruments in screening psychosis and highlight the importance of evaluating psychosis through other instruments and CDI. In particular, we found a higher BPRS total score as well as a BPRS positive comparing PDP vs non-PDP, meaning this may be a useful evaluation tool for psychosis. This may suggest that the CDI may be more sensitive to the detection of psychotic symptoms especially in patients with cognitive impairment and lack of insight. Clinicians may underdiagnose psychotic symptoms as they may be not reported spontaneously or even denied during direct questioning.

One third (31.7%) of the non-psychotic patients was taking an antipsychotic drug. This is not surprisingly, as some of non- PDP patients may have experienced psychotic symptoms in the past and remained under antipsychotic therapy and others were taking those drugs to improve sleep and impulsivity although had never experienced psychotic symptoms. The persistence of psychotic symptoms despite reasonable doses of antipsychotics was also an interesting finding. In the LSPD Psychosis Positive, the mean dose of clozapine was 32.35 mg/day or 89.29 mg/day of quetiapine and had a LEDD of 789.30 (vs. 949.60 in the non-psychotic group). We may hypothesize that even with the reduce of the dopaminergic tone patients maintained psychotic symptoms requiring the use of antipsychotic drugs and this severely disabled PD population did not tolerate higher doses of antipsychotics so the risks associated with the antipsychotic increase may overweigh the benefits on reducing the psychotic symptoms frequency and severity. We may also assume that psychosis development is associated with brain neurodegeneration and PD progression itself (namely a more severe disease, longer disease duration and development of cognitive impairment) being more refractory to antipsychotic medication.

The main limitations of our study are related to methodological aspect. First, this was a cross-sectional study with a hospital-based sample and the frequency of neuropsychiatric symptoms may not apply to other populations. Second, the patient selection may also have introduced bias, as PD patients residing in nursing homes are recognizably more likely to suffer from psychosis. Third, some of the data were collected through caregiver interviews, which may have led to symptom underreporting.

5. Conclusions

Our study shows a high frequency (55.4%) of current psychotic symptoms in LSPD patients and that 72.5% of LSPD patients with psychotic symptoms had at least one comorbid psychiatric diagnosis. The use of CDI in addition to structured scales may increase the sensitivity of detection of psychotic symptoms especially in patients with cognitive impairment and lack of insight.

6. Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

7. Relevant conflict of interest/financial disclosures

Inês Chendo: no conflict of interest to report. No additional disclosures to report.

Margherita Fabbri: no conflict of interest to report. No additional disclosures to report.

Catarina Godinho: no conflict of interest to report. No additional disclosures to report.

Rita Simões: no conflict of interest to report. She received consultancy fees from BIAL – PORTELA & C.a, S.A., Zambon, and AbbVie. No additional disclosures to report.

Catarina Severiano e Sousa: no conflict of interest to report. No additional disclosures to report.

Miguel Coelho: no conflict of interest to report.. He received consultancy fees from Zambon. No additional disclosures to report.

Valerie Voon: no conflict of interest to report. She is funded by the Medical Research Council Senior Clinical Fellowship (MR/P008747/1). No additional disclosures to report.

Joaquim J. Ferreira: no conflict of interest to report. Received grants from GlaxoSmithKline, Grunenthal, Fundação MSD (Portugal), TEVA, MSD, Allergan, Novartis, Medtronic. He received consultancy fees from GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, BIAL, Merck-Serono, Merz, Ipsen, Biogen, Acadia, Allergan, Abbvie, Sunovion - Pharmaceuticals, Zambon, Affiris. He also participated in advisory boards for Bial and expert testimony to Novartis. No additional disclosures to report.

8. Ethical compliance statement

This study was approved by the Ethics Committee of Hospital de Santa Maria, Lisboa, Portugal.

Declaration of patient consent was obtained through an informed written form containing all the information about the study and which was signed in duplicate by the patient or, when it was impossible for the patient to sign (difficulty in understanding, a physical disability that made the writing impossible, or other reasons that did not allow the guarantee of informed consent), by the caregiver, leaving one copy for the patient/caregiver and the other for the investigator.

9. Data availability statement

All data are readily available to research groups upon request.

CRediT authorship contribution statement

Inês Chendo: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Margherita Fabbri:** Investigation, Writing - review & editing. **Catarina Godinho:** Investigation, Writing - review & editing. **Rita Moiron Simões:** Investigation, Writing - review & editing. **Catarina Severiano Sousa:** Investigation, Writing - review & editing. **Miguel Coelho:** Resources, Project administration, Writing - review & editing. **Valerie Voon:** Conceptualization, Methodology, Writing - review & editing. **Joaquim J. Ferreira:** Conceptualization, Methodology, Resources, Project administration, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2021.100119.

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