RESEARCH ARTICLE

Preexisting Bipolar Disorder Influences the Subsequent Phenotype of Parkinson's Disease

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ABSTRACT: Background: Patients with bipolar spectrum disorders (BSDs) exhibit an increased risk of Parkinson's disease (PD).
Objective: The aim is to investigate whether a previous diagnosis of BSDs influences the phenotype of PD.
Methods: Of 2660 PD patients followed for at least 6 years (6–27), 250 (BSD-PD) had BSDs, 6–20 years before PD diagnosis; 48%–43% had a PD or BSD family history, and 34 carried glucocerebrosidase (*GBA*) and Parkin (*PRKN*) mutations. The cohort was split into a subset of 213 BSD-PD patients, compared with 426 matched PD patients without BSDs, and a subset of 34 BSD-PD and 79 PD patients carrying *GBA* or *PRKN* mutations. Carriers of mutations absent in BSD-PD patients and of synuclein triplication were excluded. Structured clinical interviews and mood disorder questionnaires assessed BSDs. Linear mixed models

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evaluated the assessment scales over time. Thirteen BSD-PD patients underwent subthalamic nucleus deep brain stimulation (STN-DBS) and were compared with 27 matched STN-DBS-treated PD patients.

Results: Compared to PD patients, BSD-PD showed (1) higher frequency of family history of PD (odds ratio [OR] 3.31; 2.32–4.71) and BSDs (OR 6.20; 4.11–9.35) 5); (2) higher incidence of impulse control disorders (hazard ratio [HR] 5.95, 3.89–9.09); (3) higher frequency of functional disorders occurring before PD therapy (HR, 5.67, 3.95–8.15); (4) earlier occurrence of delusions or mild dementia (HR, 7.70, 5.55–10.69; HR, 1.43, 1.16–1.75); and (5) earlier mortality (1.48; 1.11–1.97). Genetic BSD-PD subjects exhibited clinical features indistinguishable from nongenetic BSD-PD subjects. STN-DBS-treated BSD-PD patients showed no improvements in quality of life compared to the control group.

Conclusions: BSDs as a prodrome to PD unfavorably shape their course and are associated with detrimental neuropsychiatric features and treatment outcomes.

Key Words: bipolar spectrum disorders; Parkinson's disease; glucocerebrosidase mutation; parkin mutation; subthalamic nucleus deep brain stimulation

Bipolar spectrum disorders (BSDs), which include bipolar I disorder, bipolar II disorder, and cyclothymic disorder, are rarely discussed in Parkinson's disease (PD), PD with dementia, and dementia with Lewy bodies.[1-3] Recent reviews of neuropsychiatric disorders in PD list only impulse control disorders (ICDs), psychosis with delusions and hallucinations, somatic symptoms and functional disorders (SFDs).[4-7] Earlier literature, instead, explicitly cited mania or hypomania among the possible complications of PD, addressing caveats.[8,9] Several case reports have indicated the prior occurrence or co-occurrence of BSDs in PD patients.[10-28] The 2006 international guidelines on subthalamic nucleus deep brain stimulation (STN-DBS)[29] in PD, included hypomania as a preoperative concern, and more recent guidelines repeat the concern.[30] The disappearance of mania/hypomania from the list of psychiatric complications of PD is likely due to the conceptual reframing of nonmotor aspects of PD and identification of ICDs as a specific psychiatric aspect of PD[7] appearing in patients exposed to dopamine agonist (DA) treatments. ICDs include risky behaviors like gambling, hypersexuality, shopping sprees, bulimia, aggressive driving, or hoarding and were first identified as a clinical entity related to dopaminergic treatment exposure by Andew Lees,[31] who named the disorder hedonistic homeostatic behavior.

ICDs of PD became a unique clinical entity and gained a wide space on social media, driven by individual and class-action lawsuits related to DAs.[32,33] However, the behaviors listed among ICDs are quite similar to those listed by the DSM-5[34] as distinctive aspects of BSDs.

Moreover, a recent large population study and a meta-analysis study [35,36] confirmed earlier epidemiological findings[37-39] and indicated that BSDs are associated with a 3.4 (2–5.6, confidence interval [CI] 95%) increased risk for PD—a result highlighted by editorials.[40,41] These studies suggested that the prevalence of BSDs in PD is higher than in control populations. Following the epidemiological reports, new studies addressed BSDs in PD, generically naming the described disorders as hypomania.[42-45] Guided by earlier literature,[8-27] and also because, in several legal instances, two senior authors of the present paper were asked to provide an earnest analysis for compensation claims, which were at the time prevalent on social and public media,[46-49] we started testing all PD patients in our cohort using psychiatric scales and interviews to assess BSDs. When the last epidemiological studies were published,[35,36] we thought we could present our data for discussion. A long-term follow-up allowed the exploration of genetic predispositions and treatment outcomes in patients who had been diagnosed with BSDs before the onset of PD motor symptoms.

We tested the following hypotheses: (1) a prior diagnosis of BSDs (ie, BSDs assessed before the onset of motor PD symptoms) affects motor symptom progression; (2) BSDs affect nonmotor and psychiatric symptoms of PD; (3) BSDs are related to identifiable genetic predispositions; and (4) PD treatment outcomes are affected in those with a previous diagnosis of BSDs.

Patients and Methods

Cohort Selection

A clinical cohort of PD patients referred to our Movement Disorders Tertiary Center was enrolled between January 1992 and September 2013. The study was approved by the Local Ethics Committee (protocol no. 2098, June 11, 2020, and July 26, 2018, amendment of August 2, 2018), according to the Declaration of Helsinki. Informed consent was obtained from all participants.

A total of 8012 PD patients were enrolled after completing at least two follow-up visits at 3 and 6 years, ± 6 months, after the first assessment (Fig. 1).

A total of 5270 subjects were excluded due to irregular follow-up or to medical comorbidities and treatments impacting on features and progression of parkinsonian motor symptoms, cognition, and psychiatric symptoms. The remaining 2272 were followed every 6 months for at least 6 years. A 12-year follow-up evaluation was completed in 84% of patients. At the first clinical assessment, subjects diagnosed with PD were evaluated for history or presence of psychiatric

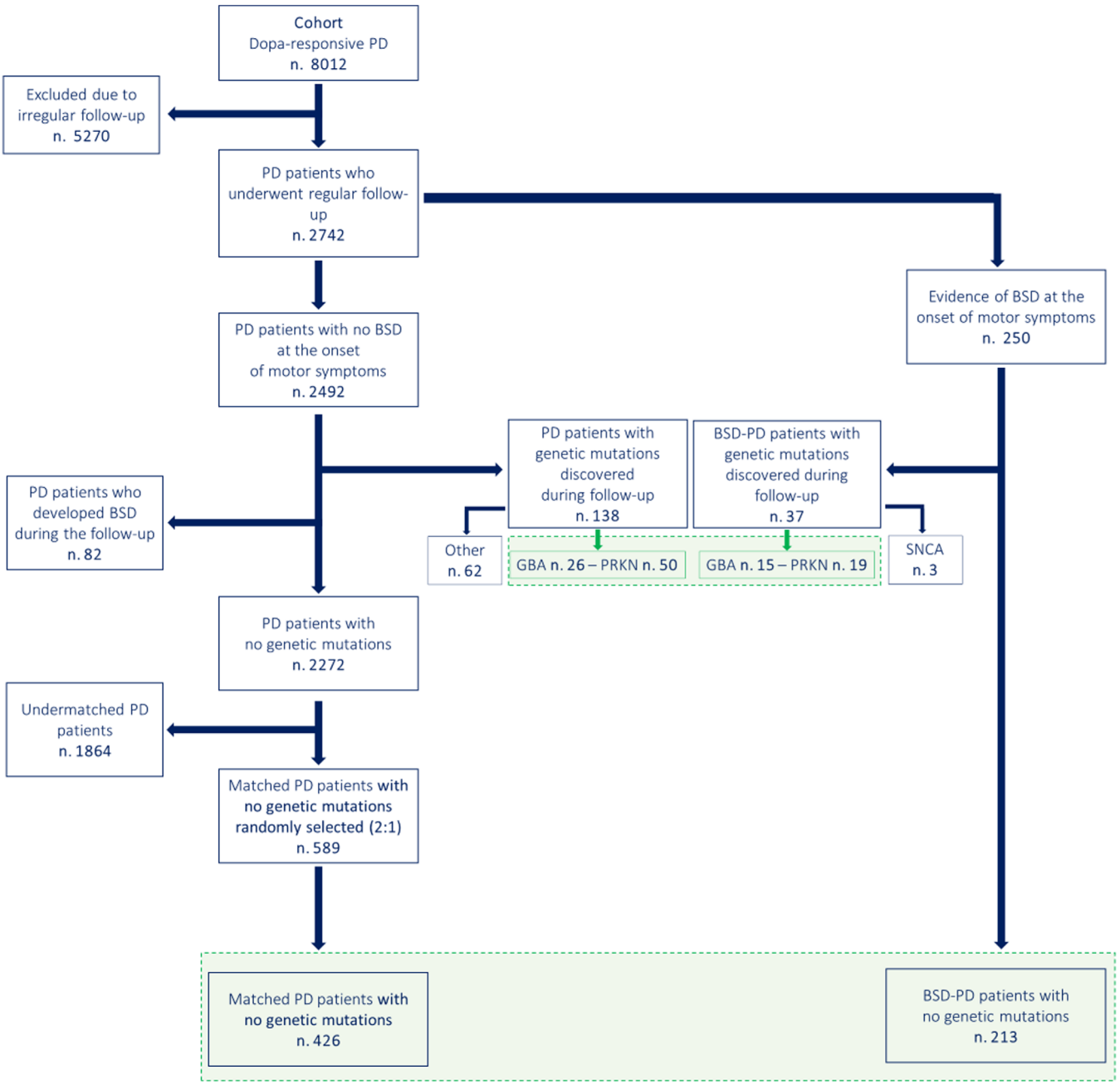

FIG. 1. Flowchart and design of the study. The flowchart depicts the cohort's enrollment and the subsequent distinction of the main groups for cross-sectional (light blue) and longitudinal (green) analyses. The picture also identifies the genetic subsets of Parkinson's disease (PD)-related genetic mutations. BSD-PD, bipolar spectrum disorder-Parkinson's disease; *GBA*, β-glucocerebrosidase-related PD; *PRKN*, *Parkin 2*-related PD; SNCA, *α-synuclein* triplication. [Color figure can be viewed at wileyonlinelibrary.com]

symptoms. A total of 250 PD subjects with a previous history of BSDs were included in the BSD-PD group. The subjects who exhibited BSD symptoms only at follow-up visits were excluded, to avoid potential confounders due to dopaminergic treatments. Genotyping was performed in all subjects with a family history of parkinsonism or of dementia or psychiatric disorders (475 patients) and led to the identification of 175 carriers of PD-related genetic mutations (online supplemental Appendix e-1): the only mutations identified in BSD-PD patients were *PRKN* (19 patients), *GBA* (15 patients), and a triplication of the *α-synuclein* gene in 3 patients. *PRKN* and *GBA* mutations were also identified in 76 PD patients without BSDs. Therefore, carriers of *PRKN* and *GBA* mutations were investigated separately (genetic patients). All carriers of other genetic mutations were excluded (Fig. 1); the 3 BSD-PD patient carriers of *α-synuclein* triplication were excluded as they have been

described in previous studies (Fig. 1; online supplemental Appendix e-1).

A total of 213 BSD-PD patients with no PD genetic mutations were matched for gender, age, age at PD onset, and L-dopa equivalent daily dose (LEDD) with 589 PD patients. As per study design (2:1), of the 589 PD pool, 426 subjects were randomly and blindly selected to constitute the control PD group to be compared with BSD-PD subjects.

Study Design

The study consisted of cross-sectional and longitudinal evaluations of three distinct groups, all derived from the original cohort of PD patients:

1. The core study compared 213 BSD-PD patients to 426 matched PD patients without BSD, investigated motor, nonmotor, and psychiatric variables.
2. A substudy of 34 BSD-PD patients who over the years were found to be carriers of *GBA* or *PRKN* mutations was compared to 76 PD carriers of the same mutations, addressing the same variables.
3. An interventional substudy of 13 BSD-PD patients who underwent STN-DBS was compared to 27 PD patients without BSDs who underwent the same procedure during the same period.

PD and BSD Diagnoses

PD was diagnosed following the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria and L-dopa responsiveness.[50] Dopamine transporter (DaT) 123I–ioflupane single-photon emission computed tomography (DAT-SCAN SPECT) was performed in all BSD-PD patients and 87% of PD patients 1 to 3 years after the clinical manifestation of parkinsonism and the withdrawal of drugs to avoid possible interferences (online supplemental Appendix e-2).[51,52] BSD-PD patients were admitted to the study only if DAT-SCAN SPECT confirmed PD diagnosis. Iatrogenic, vascular, functional, and atypical parkinsonisms were ruled out and excluded from the original cohort.

The BSD diagnosis was determined at the first evaluation, according to current diagnostic criteria (DSM-IV,[53] IV-TR,[54] and DSM-5[34]). We either confirmed a previous diagnosis performed by psychiatrists (144 of 250 patients) or verified the history of manic/hypomanic symptoms and exposure to treatments with psychiatric interviews, interviews of relatives and general practitioners, and scores of mood disorder scales (106 of 250). All BSD-PD patients presented with symptoms 6 to 24 years before motor PD symptoms had appeared. A second confirmation for all BSD diagnoses was obtained by independent psychiatrists, who, also, ruled out the presence of schizoaffective, narcissistic, and borderline personality disorders (online supplement Appendix e-3). BSD-related symptoms, including depression with/without psychotic traits, were documented by both categorical and qualitative rating scales. Current or historical exposure to antidepressants and/or neuroleptics was recorded in all patients.

Baseline Assessments of BSD-Related Symptoms

In all patients, Structured Clinical Interview for DSM-IV (SCID),[55] Young Mania Rating Scale (YMRS),[56] and (from the year 2000) Mood Disorder Questionnaire (MDQ)[57] were administered. All the results were interpreted by independent psychiatrists. In particular, YMRS scores above 20, and MDQ scores indicative of mania, were considered an indication of BSD.

Semistructured interviews conducted by expert psychiatrists further assessed the presence of BSD features. According to DSM-5,[34] of 213 BSD-PD patients, 111 were diagnosed as bipolar I, 90 as bipolar II, and 12 as cyclothymic. Of 34 genetic PD patients, 12 were bipolar I and 22 bipolar II.

Longitudinal Assessments

The longitudinal evaluations of BSD symptoms included the estimation of depression severity by Becks Depression Inventory (BDI).[58,59] Structured interviews evaluated the presence and severity of ICD and SFD symptoms. Symptom Checklist-90 (SCL-90) items,[60,61] rated SFDs and also ICDs before 2012 and was, after, converted into ICD scales.[62] These scales list hypersexuality, gambling, shopping, hoarding, and similar behaviors as ICD items.[62] The presence of simple and complex hallucinations or delusions was assessed using the Neuropsychiatric Inventory (NPI)–related items (b)[63] and semistructured interviews.[64]

The Mini-Mental State Examination (MMSE)[65] and the Dementia Rating Scale-2 (DRS-2)[66] were used to evaluate cognitive deficits. Mild dementia was diagnosed in subjects with MMSE scores ranging from 23 to 18. MMSE scores lower than 18 supported a dementia diagnosis.

Clinical charts reported acute psychiatric conditions, such as delirium, related or unrelated to treatment manipulations, and catatonia.

Motor symptoms were assessed using the modified Hoehn and Yahr (H&Y)[67] scale and the Unified Parkinson's Disease Rating Scale (UPDRS).[68] REM sleep behavior disorders (RBD), hyposmia, and constipation were rated as categorical variables;[69-71] pain was included in SCL-90 ratings.[70]

Data from 3-, 6-, and 12-year follow-up visits were analyzed.

Pharmacological Management

No exclusion criteria were applied to drugs used to manage motor symptoms. None of the investigated patients used anticholinergic therapy; 78 BSD patients were treated with lithium 3 to 8 years after the onset of PD motor symptoms; none of the patients had been treated with lithium before the onset of motor

symptoms. Valproate, tricyclics, and typical or atypical neuroleptics were not used or withdrawn. Clozapine (6.25–300 mg/d) and quetiapine (25–300 mg/d) were the only antipsychotic drugs prescribed. Depression was treated with venlafaxine (75 patients), duloxetine (62 patients), escitalopram (56 patients), paroxetine (82 patients), or mirtazapine (48 patients).

LEDD was adjusted according to patients' needs. DAs were administered to 1214 PD (of 2492) and 131 PD-BSD patients, with regimens ranging from 25 to 100 LEDD. After 2004, DAs were progressively withdrawn according to guidelines.[72] Dopamine agonist withdrawal syndrome[73] (DAWS) was diagnosed if severe dysphoria and dysautonomia occurred after withdrawal, thereby prompting the reintroduction of treatment and tapering with add-on antidepressants.

STN-DBS

STN-DBS treatment was performed in 13 BSD-PD and 27 PD patients between 2003 and 2008. At that time, international[29,74] and national criteria and guidelines[30,75] did not consider BSDs as exclusion criteria for the procedure, leaving the decision to clinical judgment. Clinical outcomes were evaluated using the UPDRS,[68] Clinical Global Impression,[76] and Parkinson's Disease Quality of life, eight-item scale.[77]

Statistics

Data are reported as mean ± standard deviation (SD) and absolute number and percentage for continuous and categorical and dichotomous variables, respectively. The differences between groups were evaluated by χ^2 test for categorical and dichotomous variables (presence/absence of symptoms). Logistic regression models were used to produce odds ratio (OR), with a 95% CI to assess BSD association with other variables. Linear mixed models (LMM)[78] were used to investigate changes (evaluated by test scores) in mood, cognitive, psychotic, and motor symptoms, considering time (baseline, 3-, 6-, and 12-year follow-up) and groups (BSD-PD and PD). LMM provides multiplicative models highlighting interactive effects among predictors and additive models for each predictor's individual effects on a given outcome and avoids family-wise error types.

To evaluate the BSD risk according to time-dependent PD neuropsychiatric and cognitive symptoms (delusion, depression, ICDs, SFDs, mild dementia, and dementia), Cox proportional hazards models were applied.[79] To avoid truncation, age at onset of PD motor symptoms was used as the time scale.[79] Hazard ratio (HR) and 95% CI were calculated from Cox-model estimates.

Analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). All statistical tests were two sided, and statistical significance was defined at P-value <0.05.

Results

Cross-Sectional Analysis

Demographic variables and baseline clinical features of the 213 BSD-PD and 426 matched PD patients are presented in Tables 1 and 2. Family history of PD and/or BSD patients was threefold (OR 3.31; 95% CI, 2.32–4.71) and sixfold (OR 6.20; 4.11–9.35) more frequent in BSD-PD.

PD phenotypes at onset (tremor dominant or akinetic); age of onset for wearing off; and dyskinesia, RBD, hyposmia, and constipation were similar in both groups. The response to pharmacological therapy was not different between the two groups. Despite a similar exposure to DAs (60% of subjects in both groups), the risk of DAWS was higher in the BSD-PD group (OR 5.57; CI, 3.12–9.95). Higher exposure to antidepressants and neuroleptics was observed in the BSD-PD group (OR 2.02; CI, 1.74–2.35; and 2.45; 1.83–3.28, respectively).

BSD-PD patients exhibited significantly increased prevalence of neuropsychiatric symptoms, including ICDs, SFDs, delusions, and depression. There was also a higher prevalence of catatonia in BSD-PD patients ($P < 0.001$) (Table 2). Conversely, there was no difference in the frequency of delirium, hallucinations, and delusions associated with LEDD.

Mild dementia appeared at a younger age in BSD-PD patients. The overall prevalence of dementia was similar in the two groups.

The mortality rate occurring before age 75 years was higher in BSD-PD patients (OR 1.48; CI, 1.11–1.97).

Longitudinal Study

As shown by Tables 1 and 2 and online supplemental Table e-1 and Figure e-1, BSD-PD patients exhibited an increased risk for neuropsychiatric symptoms. In BSD-PD patients, ICDs were observed before the onset of PD and PD therapy (HR: 5.95; 95% CI, 3.89–9.09). Increased incidence of ICDs was observed after DA initiation in BSD-PD compared to PD (HR: 4.16; 95% CI: 3.09–5.60).

An increased frequency of SFDs, before and after PD diagnosis, was observed in the BSD-PD group (HR: 5.67; 95% CI: 3.95–8.15; and HR: 1.55; 95% CI:1.18–2.03, respectively). BSD-PD subjects also exhibited increased frequency and younger age of onset for delusions (HR: 7.70; 95% CI: 5.55–10.69), depression (HR: 3.43; 95% CI: 2.76–4.24), and mild dementia (HR: 1.43; 95% CI 1.16–1.75).

Longitudinal Changes in the LMM Analysis

According to LMM predictive assessments of longitudinal variations, a multiplicative effect was observed for MMSE, DRS-2, BDI, and SCL-90 scores, showing

TABLE 1 *Demographic and clinical features of patients without genetic mutations*

	BSD-PD (n = 213)	PD (n = 426)	*P*-value*	Odds ratio; CI**
Demographics				
Sex, n males (%)	139 (65.3)	270 (63.4)	0.64	1.01; 0.99–1.03
Age at onset PD, mean age ± SD	59.86 ± 9.35	58.90 ± 9.58	0.23	1.09; 0.77–1.53
Age at onset BSD, mean age ± SD	47.26 ± 8.02	–		
Family history of PD, n (%)	103 (48.36)	94 (22.07)	<0.001	3.31; 2.32–4.71
Family history of BSD, n (%)	90 (42.25)	45 (10.56)	<0.001	6.20; 4.11–9.35
Tremor onset, n (%)	143 (67.14)	275 (64.55)	0.52	1.12; 0.79–1.59
Bradykinesia onset, n (%)	169 (79.34)	346 (81.22)	0.57	0.89; 0.59–1.34
Death before 75 years, n (%)	30 (14.08)	26 (6.10)	<0.001	1.48; 1.11–1.97
Follow-up (6–26 years), mean age ± SD	72.37 ± 8.09	72.16 ± 7.59	0.76	1.00; 0.98–1.03
Follow-up (0–12 years), mean age ± SD	70.18 ± 8.99	69.11 ± 8.91	0.15	1.01; 0.99–1.03
Matching at baseline				
UPDRS total score[a]	26.49 ± 7.24	27.44 ± 7.33	0.53	
Hoehn and Yahr	1.9 ± 0.5	2.1 ± 0.4	0.06	
MMSE score	27.61 ± 1.15	27.65 ± 1.35	0.66	
LEDD	551.56 ± 156.41	553.52 ± 152.79	0.88	
Drug exposure				
Dopamine agonists, n (%)	131 (61.50)	256 (60.09)	0.73	1.06; 0.76–1.49
Dopamine agonist withdrawal syndrome, n (%)	42 (19.7)	18 (4.2)	<0.001	5.57; 3.12–9.95
Antidepressants, n (%)	152 (71.36)	108 (25.35)	<0.001	2.02; 1.74–2.35
Neuroleptics, n (%)	76 (35.68)	33 (7.75)	<0.001	2.45; 1.83–3.28

*P-values from the statistical comparisons for demographics, drug exposure, and motor symptoms.
**Odds ratio and 95% CI for demographics and drug exposure.
[a]UPDRS subscores are presented in online supplemental Table e-3.
Abbreviations: BSD-PD, bipolar spectrum disorder-Parkinson's disease; CI, confidence interval; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; LEDD, L-dopa equivalent daily doses.

an increased risk for earlier worsening of cognition, depression, and psychiatric symptoms in BSD-PD patients over time (online supplemental Table e-2 and Figures e-2, e-3). Conversely, for the NPI-total score, only an additive effect was observed for BSD-PD subjects. As for motor symptom changes, despite the presence of a multiplicative effect for H&Y scores and additive effects for UPDRS scores, a substantial overlap between the two groups was observed (online supplemental Figure e-4). For LEDD variations, only time effect was found, indicating no differences between the groups.

Bipolar Disorder I and II Comparisons

LMM also compared the 111 patients with bipolar disorder I and 90 patients with bipolar disorder II, assessing MMSE, UPDRS, H&Y, BDI, and NPI scores: time effect was invariably <0.001, assessing the effect of progression, but group and time per group comparisons resulted in values ranging from <0.1984 to <0.479.

YMRS changes through time did not predict progression of motor or psychiatric scores, <0.1349.

Age onset of BSDs was not predictive of PD symptom progression.

Genetic Substudy

PRKN patients in both groups were younger than *GBA* carriers, as shown in Table 3. Online supplemental Figure e-2 shows the age of onset of ICDs, SFDs, and delusions in comparison with the onset of motor symptoms.

ICDs appeared before the manifestation of motor symptoms in 9 GBA BSD-PD patients and SFDs in 10. The occurrence of delusions, hallucinations, and SFDs was higher in GBA BSD-PD than GBA PD patients. DA treatment induced ICDs in 19 patients (6 GBA BSD-PD, 13 GBA PD). Catatonia was observed in 2 BSD-PD carriers of GBA mutations (Table 3).

TABLE 2 *Comparison of motor, nonmotor, neuropsychiatric and, cognitive symptoms*

	BSD-PD (n = 213)	PD (n = 426)	*P*-value*
Motor symptoms			
Wearing off, mean age ± SD	66.70 ± 8.93	68.23 ± 9.01	0.04
Dyskinesia, mean age ± SD	63.87 ± 9.09	64.87 ± 9.96	0.22
Nonmotor symptoms[a]			
Presence of RBD, hyposmia, constipation, n (%)	67 (31.46)	154 (36.15)	0.24
Neuropsychiatric symptoms[b]			
Exposure to DAs, n (%)	131 (61.50)	256 (60.09)	0.73
Presence of ICD before DAs, n (%)	82 (38.50)	29 (6.81)	<0.001
Onset of ICD before DAs, mean age ± SD (82 vs. 29)	50.69 ± 8.09	54.24 ± 10.09	0.06
Presence of ICD with DAs, n (%)	119 (55.87)	71 (16.67)	<0.001
Onset of ICD after DAs, mean age ± SD (119 vs. 71)	56.97 ± 9.92	56.99 ± 10.31	0.99
Dopamine agonist withdrawal syndrome, n (%)	42 (19.7)	18 (4.2)	<0.001
SFD before PD diagnosis, n (%)	98 (46.01)	42 (9.86)	<0.001
SFD after PD diagnosis, n (%)	35 (16.43)	69 (16.20)	<0.001
Onset of SFD, mean age ± SD	55.74 ± 6.76	62.17 ± 4.03	<0.001
Presence of hallucinations, n (%)	145 (68.08)	296 (69.48)	0.71
Onset of hallucinations, mean age ± SD	65.39 ± 8.81	64.67 ± 9.17	0.44
Presence of delusions, n (%)	124 (58.22)	51 (11.97)	<0.001
Onset of delusions, mean age ± SD	49.35 ± 8.13	68.75 ± 7.96	<0.001
Delusions or hallucinations due to drug, n (%)	39 (18.31)	85 (19.95)	0.62
Presence of depression, n (%)	170 (79.81)	176 (41.31)	<0.001
Onset of depression, mean age ± SD	52.11 ± 8.05	59.07 ± 9.73	<0.001
Presence of delirium, n (%)	21 (9.86)	33 (7.75)	0.37
Delirium in mild dementia, n (%)	21 (9.86)	27 (6.34)	0.11
Catatonia, n (%)	14 (6.57)	6 (1.14)	<0.001
Cognitive impairment[a]			
Presence of mild dementia, n (%)	142 (66.67)	255 (59.86)	0.09
Onset of mild dementia, mean age ± SD	65.63 ± 5.90	67.63 ± 6.38	0.002
Presence of dementia, n (%)	73 (34.27)	118 (27.70)	0.09
Onset of dementia, mean age ± SD	70.78 ± 6.09	72.25 ± 4.90	0.07

Hazard ratios and 95% confidence intervals are reported in online supplemental Table e-1. Longitudinal comparison of motor, nonmotor, and neuropsychiatric symptoms between groups is shown in online supplemental Figure e-1, e-2, and e-3.

*P values from the statistical comparisons for motor, nonmotor, and neuropsychiatric symptoms, including cognitive impairment.

[a]Interviews of the patient and the caregiver evaluated the presence of nonmotor symptoms. The prevalence of each nonmotor symptom is presented in online supplemental Table e-3.

[b]Survival analyses were performed on neuropsychiatric symptoms and cognitive impairment.

Abbreviations: BSD-PD, bipolar spectrum disorder-Parkinson's disease; RBD, REM sleep behavior disorder; DA, dopamine agonist; ICD, impulse control disorder; SFD, somatic symptoms and functional disorders.

For *PRKN* mutation carriers, ICDs, SFDs, and delusions were higher in BSD-PD than PD carriers of the same mutation. In one *PRKN* carrier with BSD-PD and dementia, akinetic-negativism type catatonia was observed.

HRs for psychiatric symptoms were similar in carriers of *PRKN* and *GBA* mutations and in the groups of patients without known genetic mutations (online supplemental Table e-1 and Figure e-4).

TABLE 3 *Clinical characteristics of genetic BSD-PD and PD groups*

	GBA BSD-PD (n = 15)	GBA PD (n = 26)	PRKN BSD-PD (n = 19)	PRKN PD (n = 50)
Age at onset PD	58.87 ± 9.66	63.80 ± 8.04	39.37 ± 5.92	45.34 ± 6.10
Family history PD (%)	5 (33.33)	26 (100.00)	11 (57.89)	50 (100.00)
Family history BSD (%)	6 (40.00)	9 (34.62)	9 (47.37)	23 (46.00)
Age at onset BSD	44.80 ± 5.41	–	31.37 ± 3.02	–
Dystonia at onset (%)	–	–	12 (63.16)	17 (34.00)
Tremor at onset (%)	8 (53.33)	16 (61.54)	10 (52.63)	23 (46.00)
Akinesia at onset %	6 (40.00)	11 (42.31)	7 (36.84)	21 (42.00)
DA exposure (%)	6 (40.00)	15 (57.69)	12 (63.16)	26 (52.00)
ICD with DA (%)	6 (40.00)	13 (50.00)	12 (63.16)	19 (38.00)
ICD before treatment (%)	9 (60.00)	5 (19.23)	13 (68.42)	17 (34.00)
SFD (%)	10 (66.67)	7 (26.92)	13 (68.42)	7 (14.00)
Delusions (%)	12 (80.00)	9 (34.62)	3 (15.79)	6 (12.00)
Hallucinations (%)	15 (100.00)	22 (84.62)	12 (63.16)	12 (24.00)
Catatonia (%)	2 (13.33)	–	1 (5.26)	–
DAWS (%)	4 (26.67)	6 (23.08)	3 (15.79)	8 (16)
Wearing off (age at onset)	63.93 ± 8.82	67.28 ± 7.92	41.28 ± 5.66	51.31 ± 6.03
Dyskinesia (age at onset)	64.71 ± 8.62	69.09 ± 7.83	42.22 ± 6.81	53.04 ± 6.21
Dementia (%)	5 (33.33)	12 (46.15)	6 (31.58)	21 (42.00)
Follow-up duration (y)	7.80 ± 1.70	6.15 ± 1.71	7.95 ± 1.96	8.56 ± 2.82
YMRS	30.27 ± 6.13	6.25 ± 3.86	29.42 ± 6.97	9.83 ± 3.16

Hazard ratios and 95% confidence intervals are reported in online supplemental Table e-1.
The comparison of neuropsychiatric symptoms between PD and BSD-PD group is presented in online supplemental Figure e-4.
Abbreviations: BSD, bipolar spectrum disorder; PD, Parkinson's disease; GBA, β-glucocerebrosidase-related PD; PRKN, *Parkin 2*–related PD; DA, dopamine agonist; ICD, impulse control disorder; SFD, somatic symptoms and functional disorders; DAWS, dopamine agonist withdrawal syndrome; YMRS, Young Mania Rating Scale.

TABLE 4 *Clinical outcomes of patients treated with STN-DBS*

	BSD-PD (n = 13)		PD (n = 27)	
Gender n males (%)	5 (38.46)		13 (48.15)	
Age at onset of PD, mean ± SD	43.67 ± 7.66		44.30 ± 7.99	
Disease duration, mean ± SD	17.50 ± 5.66		16.81 ± 5.23	
Age at STN-DBS, mean ± SD	60.33 ± 7.05		61.22 ± 5.20	
CGI-I patient, mean ± SD	4.42 ± 0.67		1.52 ± 0.58	
CGI-I rater, mean ± SD	1.33 ± 0.49		1.26 ± 0.45	
	Before	**After**	**Before**	**After**
UPDRS total, mean ± SD	53.08 ± 11.41	17.58 ± 4.72	52.26 ± 10.56	18.93 ± 4.60
UPDRS 32–33, mean ± SD	6.67 ± 1.37	1.33 ± 0.78	6.70 ± 1.14	1.37 ± 0.74
UPDRS 36–39, mean ± SD	6.17 ± 0.72	1.00 ± 0.85	6.04 ± 0.81	0.93 ± 0.78
LEDD, mean ± SD	834.17 ± 90.60	354.17 ± 96.43	820.74 ± 98.52	377.04 ± 62.13
PDQ-8, mean ± SD	28.83 ± 2.04	24.00 ± 3.20[a]	28.67 ± 1.83	13.41 ± 2.08
CGI-S, mean ± SD	5.83 ± 0.58	2.25 ± 0.45	5.81 ± 0.83	2.30 ± 0.47

[a]Notice that the only item not showing significant improvement after STN-DBS is PDQ-8 in the 13 BSD-PD patients. $P < 0.0001$ in all other comparisons.
Abbreviations: BSD-PD, bipolar spectrum disorder-Parkinson's disease; STN-DBS, subthalamic nucleus deep brain stimulation; CGI, Clinical Global Impression; CGI-S, Clinical Global Impression-severity of disease; CGI-I, Clinical Global Impression-improvement; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale: items 32–33, dyskinesias; items 36–39, off-status; LEDD, L-dopa equivalent daily dose; PDQ-8, Parkinson's Disease Questionnaire-8.

Outcomes after STN-DBS

STN-DBS reduced dyskinesia in all 13 BSD-PD patients, decreased motor fluctuations in 7, and led to LEDD reduction in all but one. Conversely, all BSD-PD patients reported no improvements in their quality of life and persistence of subjectively severe motor fluctuations. One patient exhibited agitation, delirium, and aggressiveness on waking up from surgery. Five patients showed signs of long-lasting (1–14 months) manic states associated with delusions. The comparison with 27 PD patients revealed differences only in subjective reports of quality of life, which was significantly improved only in the 27 patients without BSDs. Table 4 provides the comparisons.

Qualitative Clinical Elements

As neuropsychiatric disorders can benefit from qualitative descriptions, we summarized four case presentations and narrative case histories, fictionalized and anonymized by expert psychiatrists in the supplementary materials (online supplemental appendices e-4 and e-5).

Inadequate compliance with clinical prescriptions was evidenced by frequent refusal to accept treatment changes, despite side effects: 32 BSD-PD patients, 4 BSD-PD carriers of *PRKN* mutation, and 3 BSD-PD carriers of *GBA* mutations restarted DA treatment, after withdrawal, despite the occurrence of severe ICDs, pedal edema, antecollis with myopathy, and kidney failure. Two of the 13 BSD-PD patients who underwent STN-DBS had concealed the history of their BSDs to gain access to surgical procedures.

Discussion

Our study confirms epidemiological studies[35-41] and case reports[10-27] indicating that BSDs are associated with PD and suggests that BSDs may be a prodrome to PD, which is associated with a greater prevalence of psychiatric, somatoform, and cognitive complications; inadequate improvements after STN-DBS; and higher mortality. High genetic susceptibility for BSD-PD is suggested by the high prevalence of a family history of PD and BSD. Although we found only *PRKN* and *GBA* (and synuclein triplication) mutations in our BSD-PD patients, it should be mentioned that previous studies on *leucine-rich repeat kinase 2* (PARK8) and *α-synuclein* (PARK4) mutation carriers also showed BSDs in these patients.[80-82]

We could not provide a reliable estimate of the prevalence of BSD before PD because of referral selection bias related to tertiary center selection and, possibly, to our attention to favor long-term compliance in BSD-PD patients. As previous epidemiological studies reported PD occurrence in BSD populations,[35-39] in a reversed epidemiological design, further epidemiological studies are needed to confirm/challenge prevalence estimates in the present study (250/8012; 3%). Comparison of patients with bipolar I and bipolar II disorders did not show differences in progressions of motor symptoms or psychiatric symptoms or dementia. This was unexpected, as current literature suggests that bipolar I patients are subject to worse clinical outcomes than patients with bipolar II or cyclothymia.[62,83-90] Our interpretation is that the mixed effect of PD symptoms, cognitive decline, and treatments masked and blunted differences. Our sample size of GBA and PRKN carriers is too small to allow a comparison between bipolar disorder I and II patients or between patients with early (adolescent/young adult) and later onset of BSD. Further research in this area is needed.

BSD-PD and PD patients were similar in severity and progression of motor symptoms, and the presence of known nonmotor symptoms like RBD, hyposmia, and constipation did not separate BSD-PD from PD. Also, hallucinations were not statistically different between the two groups (online supplemental Figure e-1). This finding is likely explained by the specific occurrence of visual hallucinations in PD.[2]

The incidence and prevalence of all other neuropsychiatric symptoms, including SFDs, ICDs, and delusions, were significantly increased in the BSD-PD group.

These results call for a discussion regarding psychiatric categorizations.

Various criteria have been suggested to distinguish neuropsychiatric symptoms of PD[2,62,83] from those appearing in DSM-5. The DSM-5 stresses SFD comorbidity with BSDs or with narcissistic and/or borderline personality disorders.[34] Our findings, showing higher SFD prevalence when BSD features are present, are in line with this formulation.

The different disorders listed among PD ICD [3,7,62,83] do not appear in DSM-5 categorizations of compulsions but for hoarding. Indeed, the similarity of ICDs in PD with the symptom list of bipolar disorders is striking. DSM-5[34] describes increased goal-directed activities (sex, social activities) and excessive involvement in high-risk activities (buying sprees, risky economic decisions), closely matching the behavioral disturbances classified as ICDs in PD. The anecdotal evidence gathered by reviewing social media narratives produced by PD patients with severe ICDs supports this notion by describing clear examples of manic states.[47-49]

Also, the finding that some of the BSD-PD patients were self-administering DAs despite medical warnings suggests that DAs may act as an inducer of manic–hypomanic states. Consequently, DAWS could be reframed as the equivalent of depressive episodes triggered by antidepressant withdrawal in bipolar patients. In agreement with our suggestion of a BSD-PD subphenotype, several studies described ICDs appearing before any exposure to

dopaminergic drugs in PD[91,92] and *GBA* and *PRKN* mutation carriers.[93,94] The online supplemental appendix e-6 addresses issues of categorization.

Our findings on delusions and catatonia also support the need to identify BSDs in a subtype of PD patients.

Finally, our data on outcomes of DBS-treated BSD patients indicate an unfavorable outlook. This is consistent with a previous report[95] and highlights the concerns about hypomania/mania noted as potential pre- and postoperative problems in the STN-DBS guidelines.[29] We provide further support to this statement.

Conclusions

PD associated with BSDs can be a phenotypic subtype of PD. Our study indicates that psychiatric examinations are helpful and needed in PD patients, as shown by an earlier report that tested patients undergoing STN-DBS with extensive psychiatric interviews and scales[95,96] and found a high incidence of hypomania. Ours, and these studies, therefore, support the suggestion that, in PD, disorders other than the ones conventionally listed by reviews on neuropsychiatric aspects[1-3] are found if structured interviews and appropriate scales are used. Further studies should investigate the effects of hypomania emerging after the onset of PD motor symptoms or after exposure to treatments and understand whether this subphenotype represents the end of a continuum encompassing all neuropsychiatric aspects of PD or a separate entity related to complex predispositions.

Recent imaging findings in PD psychosis and BSDs highlight a shared dysfunction of the frontal control systems and disconnection with the default mode network[5,84-86] enhancing internal narrative[97] with the appearance of psychotic elements, like hallucinations, delusions, disinhibition, SFDs,[98-101] with cyclic suppression of reality checking. A recent hypothesis suggests that, due to the phylogenetic evolution of the frontal lobes, a process not aligned with the development of subcortical systems equipped with a matching array of modulatory neurotransmitters,[102] the frontal control system can be the weak point that becomes the preferential target for neurodegeneration, producing converging behavioral phenotypes.

Our hypothesis complies with an approach to bipolar disorders based on multiple prototypes, including primary and secondary forms.[103]

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Data availability statement

Dataset available upon request.

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Supporting Data

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