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ORIGINAL RESEARCH

SEND-PD in Parkinsonian Syndromes: Results of a Monocentric Cross-Sectional Study

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Introduction: Neuropsychiatric symptoms in particular impair health-related quality of life (QoL) of patients with Parkinson's disease and atypical Parkinsonian syndromes. For this reason, various scales have been developed for detection of neuropsychiatric symptoms, such as the Scale for evaluation of neuropsychiatric disorders in Parkinson's disease (SEND-PD).

Objective: First, the objective of this study was to explore the interrelation between the SEND-PD and clinical parameters in patients with Parkinson's disease and thus confirm its validity. In addition, the applicability in a well-defined cohort of patients with atypical Parkinsonian syndromes was investigated for the very first time.

Methods: A clinically well-defined cohort of 122 patients with Parkinson's disease (PD), 55 patients with Progressive Supranuclear Palsy (PSP) and 33 patients with Multiple System Atrophy (MSA) were analyzed. First, the SEND-PD was correlated with established disease-specific scores in patients with PD. Next, the results of the SEND-PD were compared between the different Parkinsonian syndromes.

Results: The SEND-PD showed a strong significant correlation with several scores, especially the UPDRS I (Rho = 0.655) and GDS-15 (Rho = 0.645). Depressive burden was significantly higher in MSA patients in comparison to the PD patient cohort (PD, 3.8 ± 3.3; MSA, 5.45 ± 3.87), while PSP patients showed significantly less psychotic (PD 1.6 ± 2.1; PSP 0.6 ± 0.9) and impulse control disorders (PD 0.3 ± 1.0; PSP 0.02 ± 0.1).

Conclusion: The SEND-PD is a useful, brief and highly applicable screening tool for neuropsychiatric symptoms in PD, but not in atypical Parkinsonism, as their unique neuropsychiatric symptom composition is not fully captured.

Keywords: neuropsychiatric symptoms, SEND-PD, Parkinsonian syndromes

Introduction

Parkinson's disease (PD), the second most common neurodegenerative disease, has an increasing incidence and prevalence between 1990 and 2019, up to a current prevalence of around 106/100,000.[1,2] In particular, the number of patients with PD in the older population over the age of 65 grew considerably.[2] PD is associated with increasing rates of disability, reduced quality of life, caregiver burden and huge economic costs.[1,3,4] Beside typical motor symptoms, there is a large entity of non-motor symptoms (NMS) causing considerable disability.[5] Common NMS are pain, hyposmia, rapid eye movement sleep disorders, autonomic dysfunction (such as constipation, drooling of saliva, orthostatic hypotension), cognitive and neuropsychiatric symptoms (NPS).[6,7] The latter include in particular anxiety, depression, cognitive decline, psychosis and apathy.[8]

Atypical forms of Parkinsonism, such as Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP), are considerably rarer than PD, with a prevalence of between 3–5/100,000.[9] The growing incidence of these diseases

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could be due to the greatly revised and improved diagnostic criteria.[9–11] Atypical Parkinsonian syndromes show a faster disease progression than PD with an average disease duration of seven to ten years.[9,12,13] Similar to PD, symptoms of MSA and PSP are not limited to motor features. In PSP patients, bradyphrenia, apathy, personality changes and fronto-executive dysfunction are common NPS. In contrast, anxiety and depression seem to be the major neuropsychiatric symptoms in MSA.[14] Therefore, it is an essential need to address and treat NPS early at all stages of these diseases as part of a holistic patient management in all cases of Parkinsonism.

Clinical tools are commonly applied to assess the typical neuropsychiatric symptoms of Parkinsonian syndromes, as objective imaging and laboratory biomarkers have not yet been established.[8] For patients with PD, assessments are often utilized that were actually developed for other conditions, such as the 15-item Geriatric Depression Scale (GDS-15) for depression or the Montreal Cognitive Assessment (MoCA) for cognitive function.[15,16] On the other hand, there are clinical tools specifically tailored to PD patients to evaluate certain NPS, such as the Parkinson's Anxiety Scale (PAS) for anxiety.[17] The majority of instruments tend to be too extensive for regular use in everyday clinical practice and are usually symptom-oriented, meaning that the broad spectrum of NPS would only be captured by the combination of several tools. The short Scale for the Evaluation of Neuropsychiatric Disorders in Parkinson's Disease (SEND-PD) published in 2012 aimed to address this issue.[18] The SEND-PD is an interview-based 12-item scale developed designed to screen and estimate the severity of neuropsychiatric symptoms in Parkinson's patients.[18] The SEND-PD consists of the three subdomains psychotic symptoms, mood/apathy and impulse control disorders and was validated in a large cohort of PD patients.[19] So far, there are no investigations using the SEND-PD in patients with PSP and MSA.

The initial aim of this study was to verify the usefulness of the SEND-PD as a brief and clinically feasible screening instrument for common NPS by analyzing the correlation of the SEND-PD with established disease-specific scores. Furthermore, the study intended to evaluate for the first time the potential of the SEND-PD to identify typical NPS in patients with atypical Parkinsonian syndromes.

Methods

Participants

Patient data were obtained in the Department of Neurology of Hannover Medical School. Approval for prospective collection of patient data was obtained from the local ethics committee (Ethics committee: Hannover Medical School, Carl-Neuberg-Straße 1, 30625 hannover, Lower Saxony, Germany, ethikkommission@mh-hannover.de, +49-511-532-3443. Ethics vote number: 8666_BO_K_2019). The study was executed in conformity with the Helsinki Declaration.

Patients were recruited from January 2020 to October 2022. A total of 122 PD, 55 PSP and 33 MSA patients were included. All patients gave their written informed consent. The recruitment, clinical examination, diagnosis and a detailed data review were performed by a movement disorder specialist. The clinical diagnosis of PD, PSP and MSA was based on the established diagnostic criteria.[10,20,21]

Measures

The motor examination part of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson Disease Rating Scale (MDS-UPDRS III) was conducted on all patients, irrespective of whether they were suffering from PD or an atypical Parkinsonian syndromes.[22] Beyond that, patients with PD completed the MDS-UPDRS-I and -II, which evaluates motor and non-motor experiences of daily living, and patients with atypical Parkinsonian syndromes completed additional disease-specific scores, namely PSP Rating Scale (PSPRS) and Unified Multiple System Atrophy Rating Scale (UMSARS).[22–24]

Montreal Cognitive Assessment (MoCA) test was performed with all participating patients. The MoCA test is one of the most widely used tools to screen for cognitive impairment, ranging from 0 to 30 points, with a score of 25 or below considered as clinically significant cognitive decline.[25]

All participants were asked to fill in the Geriatric Depression Scale (GDS-15). The GDS-15 is a clinical questionnaire specifically designed to screen for signs of depression in the elderly population.[26]

To assess health-related quality of life the Parkinson's disease Questionnaire (PDQ-8) was applied in all patients. The PDQ-8 is a self-administered questionnaire, designed to evaluate the overall well-being and functioning of PD patients and to assess the impact of the disease on everyday life. A score between 0% and 100% is awarded, whereby higher scores demonstrate a higher disease burden.[27]

The Scale for Evaluation of Neuropsychiatric Disorders in Parkinson's disease (SEND-PD), developed and published by Pablo Martinez-Martin et al in 2012, was specifically designed to test for NPS in patients with PD.[18] SEND-PD screens for 3 major NPS complexes namely psychotic symptoms, including aggressiveness, delusions, misperceptions and hallucinations, impulsive control disorders and mood disorders, comprising apathy, social and verbal withdrawal, anxiety and fear as well as depressive symptoms. Each Domain contains 3 to 5 questions regarding the specific symptom group. The patients and their caregivers (if available) are asked to rate the symptom from 0 to 4, whereby the severity of the symptom ranges from not present, scored 0, to being a severe burden for the patient and requiring therapeutic interventions, which is scored as a 4.[18] The present study used the German translation form validated in 2016.[28]

To evaluate the potential impact of dopaminergic medication on the severity of NPS, the individual levodopa equivalent dose (LED) was calculated based on the latest work by Jost et al.[29]

Analyses

For statistical analysis, IBM SPSS (Armonk, NY, USA) and GraphPad PRISM 9 (San Diego, CA, USA) were used. For metric data, mean and standard deviation (SD) were displayed. Shapiro–Wilk-test was performed to test for normal distribution. Since none of the evaluated variables were normally distributed, Mann–Whitney U, Kruskal–Wallis and Dunn's test post-hoc were used for the analyses. Categorical data were analyzed by performing chi-squared test. Spearman rank correlation coefficient was used to measure linear correlation between SEND-PD's total score and subscores of other established scores (MoCA, UPDRS I, II, III, PDQ-8, GDS-15), LED and demographic patient properties. The effect size was determined on the basis of Cohen et al.[30] To correct for multiple testing, the level of significance was set to $\alpha = 0.05/n$ (with n being the number of analyzed predictors). Post hoc power analysis was performed using G*Power software (latest ver. 3.1.9.7; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). The calculated power for our sample size (n = 210) was 0.9065665 ($\alpha = 0.05$, F = 0.25).

Results

Patient Characteristics

Demographic and basic clinical data are displayed in Table 1. One hundred and twenty-two patients with PD, 55 patients with PSP and 33 patients with MSA were included. Patients with MSA were significantly younger than patients with PD or PSP (MSA, 62.3 ± 9.1 years; PD, 68.3 ± 11.0 years; PSP, 69.6 ± 8.2; Kruskal–Wallis test, p = 0.001). The observed sex distribution did not differ significantly between cohorts. The mean disease duration was significantly higher in PD compared to PSP and MSA (PD, 5.7 ± 5.8 years; PSP, 0.5 ± 1.0 years; MSA, 1.1 ± 1.8 years; Kruskal–Wallis test, p < 0.001). Moreover, PD patients showed a significantly higher LED than PSP and MSA patients (PD, 571.5 ± 657.2 mg; PSP, 238.8 ± 278.5 mg; MSA, 319.6 ± 398.3 mg; Kruskal–Wallis test, p < 0.001).

Global and Neuropsychiatric Symptom Burden

Table 2 illustrates the data on common disease-specific symptom scores and NPS-oriented scales to provide a comprehensive overview of disease severity and the burden of NPS. Further, the cohort of patients with PD was subdivided into three groups with different disease severity, namely mild (Hoehn and Yahr 1–2), moderate (Hoehn and Yahr 3) and severe (Hoehn and Yahr 4–5).[31]

Patients with moderate and severe PD performed significantly worse on the MoCA (mild, 25.0 ± 3.7; moderate, 21.2 ± 4.3; severe, 21.1 ± 4.9; Kruskal–Wallis test, p < 0.001), showed significantly more motor symptoms as measured by the UPDRS III (mild, 24.1 ± 10.5; moderate, 35.5 ± 13.8; severe, 44.7 ± 18.9; Kruskal–Wallis test, p < 0.001) and significantly reduced quality of life as recorded by the PDQ-8 (mild, 18.8 ± 17.1; moderate, 21.1 ± 14.; severe, 33.2 ± 14.6; Kruskal–Wallis test, p < 0.001)

Table 1 Patient Characteristics

	PD (n=122)	PSP (n=55)	MSA (n=33)
Sex, female, n (%)	54 (44.3)	26 (47.3)	17 (51.5)
Age in years (mean ± SD)	68.3 ± 11.0	69.6 ± 8.2	62.3 ± 9.1**
Disease duration in years (mean ± SD)	5.7 ± 5.8***	0.5 ± 1.0	1.1 ± 1.8
Levodopa equivalent dose (LED) in mg (mean ± SD)	571.5 ± 657.2	238.8 ± 278.5***	319.6 ± 398.3**
Clinical phenotype, n (%)			
Akinetic-rigid	58 (47.5)		
Tremor-dominant	18 (14.8)		
Equivalent	45 (36.9)		
PSP Richardson S.		49 (89.1)	
Other PSP variants		5 (9.1)	
MSA-P			19 (57.6)
MSA-C			14 (42.4)
H & Y			
1	14	2	0
1,5	1	1	0
2	35	3	1
2,5	4	4	3
3	44	21	14
4	21	21	11
5	3	2	2

Notes: **p < 0.01, ***p < 0.001, Kruskal–Wallis test. The date of diagnosis was unknown in 3 PD and one MSA patients. For one PSP and one PD patient, clinical subtype was not documented. For another PSP patient Hoehn and Yahr scale was not documented, as well as for 2 MSA patients.
Abbreviations: H & Y, Hoehn and Yahr; MSA, Multiple system atrophy; MSA-C, cerebellar variant of multiple system atrophy; MSA-P, parkinsonian variant of multiple system atrophy; PD, Parkinson's disease; PSP, Progressive supranuclear palsy; SD, standard deviation.

Table 2 Disease-Specific Scores and Neuropsychiatric Symptoms

	PD (n=122)				PSP (n=55)	MSA (n=33)
	Total	Mild (n=50)	Moderate (n=48)	Severe (n=24)		
MoCA (mean ± SD)	22.8 ± 4.5	25.0 ± 3.7	21.2 ± 4.3†††	21.1 ± 4.9†††	22.8 ± 4.4	24.1 ± 4.2
UPDRS I (mean ± SD)	12.6 ± 6.7	11.7 ± 6.6	12.4 ± 5.9	14.8 ± 8.2		
UPDRS III (mean ± SD)	32.8 ± 15.9	24.1 ± 10.5	35.5 ± 13.8†††	44.7 ± 18.9†††	35.7 ± 15.3	42.8 ± 17.3***
PSPRS (mean ± SD)					32.5 ± 12.8	
UMSARS I and II (mean ± SD)						45.5 ± 13.7
GDS-15 (mean ± SD)	4.3 ± 3.3	3.8 ± 3.1	4.8 ± 3.4	4.7 ± 3.4	4.9 ± 3.6	6.8 ± 3.3***
PDQ-8 (mean ± SD)	23.3 ± 16.2	18.8 ± 17.1	21.1 ± 14.1	33.2 ± 14.6†††	25.3 ± 15.6	37.6 ± 20.3***
SEND-PD total (mean ± SD)	5.7 ± 4.9	6.0 ± 5.1	4.8 ± 4.2	6.8 ± 5.5	4.8 ± 4.2	6.4 ± 4.1
SEND-PD psychosis (mean ± SD)	1.6 ± 2.1	1.6 ± 2.1	1.3 ± 1.9	2.1 ± 2.3	0.6 ± 0.9**	0.7 ± 0.9
SEND-PD mood/apathy (mean ± SD)	3.8 ± 3.3	3.9 ± 3.5	3.3 ± 3.1	4.3 ± 3.4	4.3 ± 3.8	5.5 ± 3.9*
SEND-PD ICD (mean ± SD)	0.3 ± 1.0	0.4 ± 1.2	0.1 ± 0.4	0.3 ± 1.1	0.02 ± 0.1*	0.2 ± 0.5

Notes: †relates to the comparison within the PD cohort, * relates to the comparison between the diseases, *p < 0.05, **p < 0.01, †††and ***p < 0.001, Kruskal–Wallis test. The severity of PD was categorized according to the work of Martínez-Martín et al into mild (Hoehn and Yahr 1–2), moderate (Hoehn and Yahr 3) and severe (Hoehn and Yahr 4–5).[31]
Abbreviations: GDS-15, Geriatric depression scale; H & Y, Hoehn and Yahr; MoCA, Montreal Cognitive Assessment test; MSA, Multiple system atrophy; PD, Parkinson's disease; PDQ8, Parkinson's disease questionnaire; PSP, Progressive supranuclear palsy; PSPRS, PSP Rating Scale; SD, standard deviation; SEND-PD, Scale for Evaluation of Neuropsychiatric Disorders in Parkinson's disease; Unified Multiple System Atrophy Rating Scale, UMSARS; UPDRS, Unified Parkinson Disease Rating Scale.

than patients with mild PD. Those instruments primarily focused on the assessment of neuropsychiatric symptoms (UPDRS I, SEND-PD, GDS-15) did not show any significant differences between patients with different disease severities.

In addition, the comparisons between the different Parkinsonian syndromes revealed differences in the symptom burden, particularly in the cohort of MSA patients. Accordingly, the quantity of motor symptoms was significantly higher in MSA patients than in PD patients (UPDRS III, PD, 32.8 ± 15.9; PSP, 35.7 ± 15.3; MSA, 42.8 ± 17.3; Kruskal–Wallis test, $p < 0.001$). Further, the extent of depressive symptoms was significantly greater than in PD and PSP patients (GDS-15, PD, 4.3 ± 3.3; PSP, 4.9 ± 3.6; MSA, 6.8 ± 3.3; Kruskal–Wallis test, $p < 0.001$). Consequently, MSA patients showed a significant impairment in quality of life compared to the other cohorts (PDQ-8, PD, 23.3 ± 16.2; PSP, 25.3 ± 15.6; MSA, 37.6 ± 20.3; Kruskal–Wallis test, $p < 0.001$).

Correlation of SEND-PD with Established Disease-Specific Scores in PD

SEND-PD's total score and subscores for psychotic symptoms, mood and impulse control disorders were checked for correlation with other commonly used scores to evaluate clinical symptoms in Parkinsonism. Moreover, age and disease duration were included into analysis. Results are displayed in Table 3.

The total SEND-PD score showed a positive correlation with the PDQ-8, GDS-15, UPDRS I and II, as well as with the total UPDRS score. In particular, the correlation of the SEND-PD with the GDS-15 and the UPDRS I was strong according to Cohen's classification.[30] There was a weak, but significant negative correlation of the SEND-PD with the MoCA test (Rho = −0.237, $p = 0.005$). A similar pattern was observed for SEND-PD's subscale for mood disorders and subscale for psychotic symptoms. The impulse control subscale only showed a weak significant positive correlation with the UPDRS I (Rho = 0.296, $p = 0.01$) and a significant negative correlation with age (Rho = −0.286, $p \leq 0.01$).

Neither the total score nor the subscores of SEND-PD showed a significant correlation with the total LED or with the LED of individual drug classes, eg, dopamine agonists.

Comparison of SEND-PD in PD, PSP and MSA

The following results are illustrated in Figure 1. SEND-PD's total score (PD, 5.7 ± 4.9; PSP, 4.8 ± 4.2; MSA, 6.4 ± 4.1; Kruskal–Wallis test, $p = 0.216$) and the mood/apathy domain (PD, 3.8 ± 3.3; PSP, 4.3 ± 3.8; MSA, 5.5 ± 3.9; Kruskal–Wallis test, $p = 0.054$) did not differ between the PD, PSP and MSA patient population. However, in a pairwise post-hoc comparison, MSA patients exhibited significantly more depressive symptoms ($p = 0.047$). The subscores for psychotic symptoms and impulse control disorders differed significantly between PD and PSP patients, showing a higher neuropsychiatric burden in these particular domains to the disadvantage of PD patients (psychotic domain: PD, 1.6 ± 2.1; PSP, 0.6 ± 0.9; Kruskal–Wallis test, $p = 0.007$; impulse control disorder domain: PD, 0.3 ± 1.0; PSP 0.02 ± 0.1; Kruskal–Wallis test, $p = 0.049$).

Table 3 SEND-PD Correlation with Other Scores and Patient Age, n = 122 PD Patients

	Age	Disease duration	MoCA, total	PDQ8	GDS-15	UPDRS I	UPDRS II	UPDRS III	UPDRS IV	UPDRS, total	LED, total
SEND-PD psychotic symptoms	−0.047	0.089	−0.187	0.249*	0.423**	0.455**	0.308**	0.089	0.204*	0.306**	0.127
SEND-PD mood disorders	−0, 145	0.033	−0.257**	0.591**	0.654**	0.617**	0.377**	0.101	0.073	0.371**	0.031
SEND-PD Impulse control disorders	−0.286**	−0011	−0.010	0.179	0.149	0.296**	0.043	−0.183*	0.029	0.036	0.060
SEND-PD total score	−0.136	0.058	−0.237*	0.540**	0.645**	0.655**	0.391**	0.074	0.136	0.371**	0.084

Notes: Rho: < 0.3 no or weak correlation, 0.3–0.5 moderate correlation, > 0.5 strong correlation; *p ≤ 0.05, **p ≤ 0.01; Spearman correlation.
Abbreviations: GDS-15, Geriatric depression scale; LED, levodopa equivalent dose; MoCA, Montreal Cognitive Assessment test; PDQ8, Parkinson's disease questionnaire; SEND-PD, Scale for Evaluation of Neuropsychiatric Disorders in Parkinson's disease; UPDRS, Unified Parkinson Disease Rating Scale.

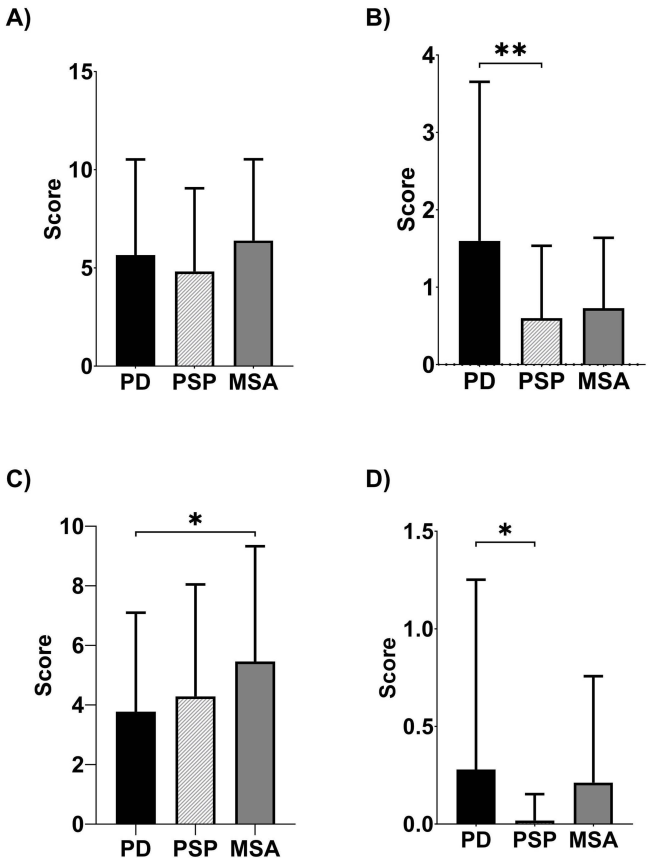

Figure 1 Comparison of SEND-PD results in PD, PSP and MSA.
Notes: The mean values ± standard deviation of the total SEND-PD-score (**A**), as well as the domains for psychosis (**B**), for mood/apathy (**C**) and for ICD (**D**), are shown. *p < 0.05, **p < 0.01, Kruskal–Wallis-test.
Abbreviations: ICD, Impulse Control Disorder; MSA, Multiple System Atrophy; PD, Parkinson's Disease; PSP, Progressive Supranuclear Palsy.

Discussion

This study aimed to analyze NPS in PD and atypical Parkinsonian syndromes by using the SEND-PD. In this study, a strong positive correlation between SEND-PD's total score with UPDRS I, PDQ-8 and GDS-15 was found. Furthermore, the total neuropsychiatric burden was similar between PD and atypical Parkinsonian syndromes assessed by the SEND-PD, while there were significant differences in the subcategories.

Association of SEND-PD with UPDRS-I, GDS-15 and PDQ-8 in PD Patients

Apart from motor symptoms, patients with PD suffer from a variety of symptoms including autonomic dysfunction, sleep disturbances, pain, cognitive impairment and other NPS.[32] These very NPS are common in all stages of PD and reduce QoL.[5,33,34] Therefore, they should be assessed regularly in the course of disease. SEND-PD was designed for a fast and comprehensive evaluation of neuropsychiatric symptoms in PD.[18] SEND-PD's original version showed a strong correlation of individual SEND-PD items with the respective items of UPDRS I.[19] The strong positive relation of the total SEND-PD score with the UPDRS-I score was confirmed by this study. Most likely, this is a result of the close relation between the two scales in terms of structure and content.[19] The mean scores in the respective subgroups of patients with different severity of PD in our cohort also reflect the strong relation of SEND-PD and UPDRS I, given that both scores rise, albeit not significantly, in relation to the severity of the disease. For these reasons, the SEND-PD appeared to be a valid and well-applicable instrument, even in PD cohorts with different compositions and disease severity.[32,35]

The correlation with PDQ-8 was strongest for the mood disorder/apathy subscale of the SEND-PD. PDQ-8 and the longer version PDQ-39 are commonly used tools to measure PD patient's QoL. Several studies showed a particularly strong correlation of poor QoL with depression/apathy and anxiety, which is in line with the demonstrated results.[36–38]

To our knowledge, the relation between GDS-15 and SEND-PD has not been examined before. The observed strong correlation could be due to the fact that the largest proportion of the total SEND-PD score in the cohort studied comes from the mood/apathy domain. Depression and apathy are among the most common NPS in the course of the disease, resulting in a higher non-motor symptom burden, impairments of activities in daily living and reduced QoL.[5,33,39] A meta-analysis with a total of 21 selected studies identified several tools for measuring depression in PD patients, including the GDS-15 with the highest sensitivity in this very case.[16] The considerable correlation between the total SEND-PD, the mood/apathy domain and the GDS-15 observed may imply that the SEND-PD is suitable for an appropriate identification of depression. The only recommended scale for detecting apathy in PD is the Apathy Scale (AS).[40,41] As this survey was not carried out in the cohort examined, no well-founded comparisons can be made with regard to the use in PD patients. A further investigation of this issue would be beneficial in the future, as the GDS-15 and its subscore GDS-3a, respectively, do not validly detect the symptom apathy.[42]

A weak but significant negative relation of age for the impulse control disorders domain was observed. This and the fact that less than a fourth of all patients reporting impulse control disorders were female, was in accordance with known risk factors for impulse control disorders in PD.[43,44] Besides to age and gender, the specific dopaminergic drug therapy constitutes a major risk factor for the occurrence of impulse control disorders, in particular the use of dopamine agonists. For this reason, it was particularly surprising that there was no correlation with either the total LED or the LED of dopamine agonists in the studied cohort. Currently, there is only one validated screening instrument for impulse control disorders, namely the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP).[45,46] Essentially, the three sections of this self-administered questionnaire (impulse control disorders, compulsive behavior, compulsive medication use) correspond to those of the SEND-PD impulse control disorders domain, with the difference that each section is composed of additional questions. As the QUIP identifies the broad spectrum of impulse control disorders and related behaviors with high sensitivity and specificity, a comparison of these two screening instruments would be extremely interesting. A simultaneous comparison with Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS), which is based on QUIP, could test whether this very domain of the Send-PD is not only suitable for screening for impulse control disorders but also for assessing the severity of this symptom complex.[47]

In summary, the SEND-PD emerged as a practical tool for the detection of certain neuropsychiatric symptoms in clinical practice, particularly due to its brevity. Nevertheless, precisely due to this strength, the SEND-PD does not encompass all NPS. Therefore, to comprehensively evaluate all NPS, including symptoms such as anxiety, additional assessments are necessary.[17]

Use of SEND-PD in Atypical Parkinsonian Disorders

As with the PD patients, a clinically well-defined PSP and MSA patient cohort in terms of sex, age and subtype distribution was analyzed.[12,13] While both patient cohorts showed an even distribution of SEND-PD total score compared to each other and to the PD patient cohort, there were differences between the groups in terms of SEND-PD subdomains.

The leading NPS of patients with MSA is undoubtedly depression.[48] Within the analyzed MSA patient cohort, even a higher depressive burden in comparison to the PD patients was detected using SEND-PD. Depressive symptoms in MSA patients were extensively studied.[49,50] Pilo et al found that depressive symptoms are common in MSA patients as recorded by the Beck Depression Inventory (BDI) and are comparable in frequency and severity to those of patients with Parkinson's disease.[51] Consistent with the results presented here, Schrag et al demonstrated higher levels of depressive symptoms in patients with MSA compared to PD when measured with the BDI.[52] However, the patients compared in that study had an identical disease duration. By contrast, patients with MSA in our cohort were significantly younger and had been ill for less time, which makes the presented severity of the depressive symptoms more surprising. A difference between MSA subtypes regarding depression was not observed in several studies.[14,53] Although MSA patients exhibit some degree of cognitive impairment, especially deficits in frontal executive dysfunction, severe impairment of cognitive function is rare in MSA, whereas it is a common in PSP and later stages of PD.[13,14,50] Combined with the disabling features of the disease and the shortened life expectancy, this can lead to greater awareness of anxiety, feelings of isolation and other clinical features of depression, but also to the ability to recognize and name these symptoms.[48,54] The

high burden of motor symptoms observed in our cohort, compared to patients with PD and PSP, in combination with the largely preserved cognitive function, supported this assumption.

In the present study, the overall rate of psychosis was low in the MSA patient groups (MSA 0.7 ± 0.9). Interestingly, the incidence of psychosis was similar in PD and MSA patients. Fabbrini et al reported that up to 5% of MSA patients experience visual hallucinations.[14] The authors emphasized that these symptoms are not typical for MSA and should require careful re-evaluation of the diagnosis.[14,48] In view of the relatively limited and typical composition of NPS in MSA patients, the SEND-PD did not appear to be suitable as a screening instrument, as it covers domains that are uncommon for this patient group. As previously mentioned, depressive symptoms and anxiety are in the foreground in this patient, as well as frontal executive dysfunction.[48,55] The SEND-PD only captures a small part of the complexity of depressive disorders so that comprehensive scores such as the Beck Depression Inventory (BDI) or the GDS apparently address them more completely.

PSP patients showed the lowest mean values for psychotic symptoms (PSP 0.6 ± 0.9 vs PD 1.6 ± 2.1 vs MSA 0.7 ± 0.9) and impulse control disorders domain (PSP 0.02 ± 0.1 vs PD 0.3 ± 1.0 vs MSA, 0.2 ± 0.5). In line with the results shown here and similar to MSA, psychotic symptoms were reported to be less frequent than in PD and their presence should raise suspicion for the possibility of a misdiagnosis.[14] Furthermore, the significantly longer disease duration of patients with PD may have influenced the overall higher scores in the psychosis domain. It is well-known that the disease progression in PD is correlated with the development of psychosis.[56] This also reflects the moderate increase in psychosis subscore of the SEND-PD in relation to the disease severity.

As of our knowledge, there has only been one study that comparatively investigated ICDs in PSP. Since the NPS of PSP are mainly based on a hypodopaminergic metabolism and patients by definition exhibit a poor response to dopaminergic drug therapy, psychosis and ICDs do not appear to play a relevant role in PSP as a manifestation of hyperdopaminergic stimulation.[10,12,14,57,58]

Patients with PSP present with complex and prominent NPS that may precede common motor symptoms.[59] Considering the main NPS of PSP, namely apathy, bradyphrenia, frontal desensitization and changes in behavior and personality, the vast majority of these symptoms are not represented in SEND-PD.[14] The only symptom generally addressed by the SEND-PD is that of depressive symptoms and apathy. Accordingly, other scores, such as the Frontal Behavioral Inventory (FBI) and the Neuropsychiatric Inventory (NPI), seem to be more appropriate for identifying neuropsychiatric symptoms of PSP.[60–62] In a number of studies, the NPI in particular was capable of identifying a large proportion of the typical NPS of PSP in patients, namely apathy, anxiety, disinhibition and irritability.[63,64] Especially the symptom apathy was regularly detectable with high sensitivity and emerged as the leading symptom in PSP with a prevalence up to 62%.[64] Due to its similar configuration, the FBI also showed strengths in the detection of common NPS in PSP, not in addition to NPI but rather as an alternative.[60,65] Since the FBI is comparatively more focused on symptoms of frontal lobe dysfunction, it lags behind in the detection of depression. However, in contrast to the MSA, the complexity and specificity of the NPS of PSP requires a specially developed and validated screening instrument.

Limitations

This study reports data from a monocentric cross-sectional study, which limits the number of participants. Since a non-significant part of the PD patient population (5–10%) is younger than 50 years of age and these patients may present with different neuropsychiatric symptoms, eg, more frequent impulse control disorders, this could be a bias of this study.[32,43,44] One possible explanation is that in this cohort the vast majority were inpatients. Another limitation could concern the comparability of findings between groups with different Parkinsonian syndromes. In this regard, the presentation of NPS could be affected by the different age structure, namely the younger patients in the MSA cohort. However, the age structure with the earlier disease onset is typical of the disease and therefore difficult to eradicate.[9]

Conclusion

SEND-PD is a suitable and clinically adequate screening tool for the majority of NPS in Parkinson's disease, as confirmed by its strong correlation with established instruments such as the GDS-15 and UPDRS I. Since these conditions can severely reduce patients' QoL and are potentially treatable, it is essential to diagnose them early and reliably.

As NPS differ in atypical Parkinsonian syndromes like MSA and PSP, the SEND-PD does not seem to be an optimal screening instrument for these very diseases. With regard to MSA, alternative established instruments appear to be better suited for identifying typical NPS; due to the complexity of NPS in PSP, a screening instrument designed for this purpose is urgently needed. Lastly, there is still a need for further investigation of specific NPS (eg, ICD in PSP) in atypical Parkinsonian syndromes.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing the First Draft, B. Review and Critique.

L.VS: 1A, 1B, 2B, 3A
S.G.: 1A, 1B, 1C, 2A, 2B, 2C, 3A
J. D.-L.: 1C, 3B
S.M.R.: 1C, 3B
J.H.: 1C, 3B
L.K.: 1C, 3B
S.U.: 1C, 3B
I.J.: 1C, 3B
M.H.: 1C, 3B
S.S.S.: 1C, 3B
G.U.H.: 1B, 1C, 3B
F.W.: 1C, 3B
M.K.: 1A, 1B, 1C, 2C, 3B

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author Dr. Stephan Greten upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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All authors declare that there is no conflict of interest.

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