PARKINSONALLIANCE

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Sensory Changes
Cognitive Changes
Depression Anxiety Hallucinations
Gastrointestinal Disturbance Urinary Changes
Sleep Disturbance and Fatigue
Autonomic System
Sexual Dysfunction

Non-Motor Symptoms of Parkinson's Disease: The Patient's Perspective

INTRODUCTION

Parkinson's disease (PD) is now being characterized by both motor disturbance and a wide array of non-motor symptoms (NMS)[1,2]. NMS in PD are a strikingly diverse set of symptoms. Sleep, fatigue, mood, cognition, pain and autonomic disorders (e.g., problems with the regulation of heart rate, blood pressure, body temperature, perspiration, and bowel and bladder functions), for example, have been recognized as important components of the disease, but only more recently has the significant impact of these symptoms on quality of life (QOL) become more appreciated[3-7].

A consistent body of evidence suggests that a variety of NMS can precede the first occurrence of classical motor features in Parkinson's disease (PD). Early symptoms may include changes in smell, Rapid Eye Movement Sleep Behavior Disorder (RBD; including vivid dreams and acting out dreams), constipation, and mood disturbances such as depression and anxiety, and the period when they arise has been referred to as the premotor phase of PD[8-11]. Although the frequency and time of onset of premotor symptoms relative to the occurrence of the first PD motor symptoms are not well-established, in some studies, neurological symptoms (e.g., sensory changes or memory dysfunction), mood disorders, musculoskeletal pain, and cardiovascular or other autonomic complaints have been reported to precede the onset of motor symptoms by up to 10 years[12,13]. NMS also appear to evolve over the course of the disease with upwards of 50% of patients experiencing NMS by 20 years[1,2].

Despite increased awareness of NMS and the high burden of NMS in most patients, NMS remain frequently neglected, undocumented, and undertreated. NMS is a major cause of disability in PD, though these symptoms remain under-recognized by health care providers[5,6]. Given the limited awareness and diverse manifestation of NMS, such symptoms present one of the biggest challenges for management by the clinician. Understanding and managing these symptoms is important not only for quality of life but even for survival, as NMS can be a significant predictor of mortality[2,7]. What remains evident is that there is a significant gap in the understanding of the patients' perspective on their experience with NMS.

OBJECTIVES

- To learn about the patients' perspective about the severity and frequency of NMS of PD.
- To understand the impact of NMS on daily life experiences and quality of life (QOL).
- To provide general comments about and recommendations for treatment related to NMS.

METHODS

- Participants were recruited from prior survey participation that was conducted by The Parkinson Alliance (PA), announcements at PD support groups, announcements in medical clinics, and The PA website.
- There were 1,164 individuals who participated in this survey. Participants included individuals with Deep Brain Stimulation (DBS) and without Deep Brain Stimulation (Non-DBS), with 275 participants with PD who underwent DBS (**DBS group**) and 889 individuals with PD without DBS (**Non-DBS group).** See Table 1 for demographics and clinical features.
- Approximately 85% completed their survey independently, whereas, 15% of participants required assistance.
- Participants represented 50 states, with California (13%), New York (12%), New Jersey (12%), Florida (9%), Texas (9%), Arizona (7%), Pennsylvania (7%), Minnesota (3%), Colorado (2%), and Massachusetts (2%) being the states with the most participants. There were 31 international participants.

Measures: **1.** The Demographic Questionnaire; 2. The Non-Motor Symptom Scale (NMSS); 3. Additional questions assessing the impact of non-motor symptoms on everyday life:

The Demographic Questionnaire:

- The self-report questionnaire inquired about basic demographic information (e.g., sex status, marital status, education) as well as pertinent clinical information.

Non-Motor Symptom Scale (NMSS [14,15]):

The NMSS evaluates 30 non-motor symptoms in PD. Items are included in nine domains (Cardiovascular including falls; Sleep; Fatigue; Mood/Cognition; Perceptual problems/hallucinations; Attention/Memory; Gastrointestinal tract; Urinary; Sexual Function; Miscellaneous—pain; changes in smell and taste; weight changes; excessive sweating). Each item evaluates separately frequency and severity, and scores from 0 (not present) to 12 (maximum frequency and severity) by multiplication of both concepts ('symptom burden'). The total scores for the domains are obtained by the sum of the corresponding item scores.

Impact of Non-Motor Symptoms on Everyday Life (questions developed by The Parkinson Alliance):

- This self-report questionnaire included 4 additional items addressing whether or not NMS interfere with day-to-day activities, the most bothersome symptoms, satisfaction with treatment for NMS, and quality of life (QOL). In this survey, QOL was rated as "excellent," "good," "fair," "poor," and "worst imaginable." "Fair" is defined as having a more "neutral" perspectives on QOL, where such individuals do not see themselves as having a "good" QOL [more often than not], but they do not identify as having a "poor" QOL [more often than not].

Comparisons based on age and disease duration groups:

- Age: There were 15 participants who were under age 50 (the youngest PD group). Age groups were further divided into a **Younger PD group** (ages 50-69 years of age) and an **Older PD group** (ages 70+ years).
- Disease Duration: In previous research pertaining to individuals with PD, the average time from symptom onset to development of motor complications was 6 years. Previous research has divided groups into **Early Stage (<6 years)** and **Advanced Stage PD (6+ years)** to define a valid partition between early and advanced disease states[16,17]. To better illustrate the impact of disease duration on anxiety variables in individuals with PD, the **Advanced Stage PD group** was further divided into **Early Advanced Stage PD (6-10 years)** and **Late Advanced Stage PD (11+ years)**.
- The results will be presented using the entire sample and groups matched on age (Younger PD and Older PD groups) and disease duration.

Factors to consider when interpreting the results:

- This study used a survey-based methodology. Generalizability of the results may be limited. Sample sizes noted in the sections below may vary somewhat within specific groups (e.g., younger, older, early, advanced, etc.), since some individuals may not have responded to a specific question. Research has found that some individuals with PD, particularly as cognition becomes more severely impaired, may have reduced insight/awareness into or appreciation of their difficulties, a factor warranting consideration when interpreting self-report questionnaires. Importantly, the subjective report in this survey serves to highlight the "patient's perspective" about his or her experience with NMS.

RESULTS

- The summary of the demographic information and clinical characteristics of the participants in this study can be found in Table 1.
    - There were 1,164 individuals who participated in this survey.
    - The average age of the participant was 71 years, with an average disease duration of 10 years.
    - Just over half of the participants were male and the majority of the participants were Caucasian with over half of the participants having a college degree or graduate degree.
    - The **Non-DBS group** was older than the **DBS group (average: 72 versus 68 years, respectively).** By

contrast, the **DBS group** had a significantly younger average age at PD diagnosis **(52 years)** than the **Non-DBS group (64 years)** and a longer duration of PD (**DBS: 16 years; Non-DBS: 8 years).** Sex (male greater than female), marital status (the majority being married), race (the majority being White/Caucasian), and education (the majority having higher education) were comparable between groups.

- The average age at the time of DBS surgery was 61 (range: 32-81 years), with the average duration since DBS being 7 years (range: 0-26 years).

Table 1. Demographics and Clinical Features of the Sample

	DBS (*n* =275)	Non-DBS (*n* =889)
Average Age in Years (range)	68 (42-90)	72 (39-98)
Duration of PD in Years (range)*	16 (2-47)	8 (0-47)
Average Age of PD Diagnosis (range)*	52 (22-75)	64 (20-93)
Average Age at Time of DBS in Years (range)	61 (32-81)	n/a
Average Duration since DBS in Years (range)	7 (0-26)	n/a
Target: STN	41%	n/a
GPi	9%	n/a
Not Sure	50%	n/a
Male	57%	56%
Female	43%	44%
Married	79%	76%
Lives Alone	13%	17%
Race		
Caucasian	93%	95%
Latino/Hispanic	2%	2%
African American	2%	<1%
Asian	2%	1%
American Indian	0%	0%
Native Hawaiian or Pacific Islander	0%	0%
Other	<1%	<1%
Education		
<12 years	4%	3%
High School	11%	10%
Some College or Associate's Degree	26%	23%
College	28%	26%
Graduate/Advanced Degree	31%	38%

* Clinically significant difference between groups
n/a = not applicable

NON-MOTOR SYMPTOM SEVERITY AND FREQUENCY

- On average it appears that both age and disease duration impact the severity and frequency of many NMS. Moreover, there are a greater number of individuals reporting higher symptoms of severity and frequency as disease duration and age increase.
- Disease duration is a better predictor for NMS than age.
- An individual with PD may have low frequency of symptoms, yet still experience significant distress from the symptom.

Table 2. Non-Motor Symptoms experienced by participants

- This table presents the percentage of individuals endorsement of individual symptoms both in terms of SEVERITY and FREQUENCY, across age and disease duration groups.

There is variability between age and disease duration groups, but it is evident that the longer the disease duration and the greater one's age, the increased likelihood one may experience numerous NMS.

Table 2. Non-Motor Symptoms Experienced by Participants

	Early PD Group (< 6 years duration)		Advanced PD Group 6-10 years duration		Advanced PD Group 11+ years duration	
	Younger (50-69) (n =141-153)[1]	Older (70+) (n =170-201) [1]	Younger (50-69) (n =122-131)[1]	Older (70+) (n =178-209) [1]	Younger (50-69) (n =161-174)[1]	Older (70+) (n =218-244) [1]
Light-headeness dizziness weakness Severity						
None	29%	35%	26%	33%	31%	27%
Mild (little distress)	51%	44%	48%	40%	43%	42%
Moderate (some distress) to Severe (major distress)	20%	21%	26%	27%	26%	31%
Light-headedness dizziness weakness Frequency						
Rarely (<1 per week)	29%	25%	26%	20%	32%	31%
Often (1 per week)	15%	17%	17%	19%	17%	13%
Frequent to daily (few times per wk to daily)	29%	30%	36%	34%	30%	35%
Falls due to fainting Severity						
None	90%	89%	83%	86%	77%	71%
Mild (little distress)	7%	7%	10%	11%	14%	18%
Moderate (some distress) to Severe (major distress)	3%	4%	7%	3%	9%	11%
Falls due to fainting Frequency						
Rarely (<1 per week)	14%	22%	29%	20%	29%	28%
Often (1 per week)	1%	1%	4%	3%	4%	5%
Frequent to daily (few times per wk to daily)	2%	4%	2%	2%	7%	9%
Fall aslseep daytime Severity						
None	40%	42%	40%	39%	33%	26%
Mild (little distress)	45%	40%	42%	44%	40%	37%
Moderate (some distress) to Severe (major distress)	15%	18%	18%	17%	27%	37%
Fall asleep daytime Frequency						
Rarely (<1 per week)	25%	18%	21%	18%	23%	20%
Often (1 per week)	16%	13%	15%	22%	18%	17%

Frequent to daily (few times per wk to daily)	26%	35%	32%	28%	33%	44%
Fatigue Severity						
None	13%	8%	13%	8%	7%	9%
Mild (little distress)	44%	48%	35%	43%	32%	29%
Moderate (some distress) to Severe (major distress)	43%	37%	52%	38%	61%	62%
Fatigue Frequency						
Rarely (<1 per week)	16%	19%	9%	13%	12%	10%
Often (1 per week)	21%	22%	19%	25%	19%	18%
Frequent to daily (few times per wk to daily)	51%	53%	61%	55%	64%	66%
Difficulty falling and staying asleep Severity						
None	16%	35%	15%	28%	18%	23%
Mild (little distress)	37%	35%	31%	36%	31%	28%
Moderate (some distress) to Severe (major distress)	47%	30%	54%	36%	51%	49%
Difficulty falling and staying asleep Frequency						
Rarely (<1 per week)	7%	20%	12%	18%	18%	12%
Often (1 per week)	25%	17%	18%	24%	15%	19%
Frequent to daily (few times per wk to daily)	55%	27%	58%	38%	56%	52%
Restlessness in Legs Severity						
None	39%	44%	35%	38%	28%	33%
Mild (little distress)	33%	35%	36%	36%	40%	33%
Moderate (some distress) to Severe (major distress)	28%	21%	29%	26%	32%	34%
Restlessness in Legs Frequency						
Rarely (<1 per week)	19%	23%	16%	20%	27%	19%
Often (1 per week)	17%	16%	15%	17%	15%	18%
Frequent to daily (few times per wk to daily)	34%	28%	39%	35%	36%	36%
Loss of interest in surroundings Severity						
None	60%	57%	46%	49%	38%	44%
Mild (little distress)	23%	31%	36%	32%	34%	33%
Moderate (some distress) to Severe (major distress)	17%	12%	18%	19%	28%	21%
Loss of interest in surroundings Frequency						
Rarely (<1 per week)	18%	20%	23%	23%	26%	26%
Often (1 per week)	13%	19%	18%	20%	18%	18%
Frequent to daily (few times per wk to daily)	17%	16%	21%	21%	27%	24%
Loss of interest in activities Severity						
None	33%	27%	28%	22%	18%	24%

Mild (little distress)	36%	43%	36%	46%	38%	37%
Moderate (some distress) to Severe (major distress)	31%	30%	36%	32%	44%	39%
Loss of interest in activities Frequency						
Rarely (<1 per week)	23%	25%	23%	25%	24%	22%
Often (1 per week)	19%	23%	17%	29%	24%	23%
Frequent to daily (few times per wk to daily)	32%	31%	35%	31%	37%	37%
Nervousness for no reason Severity						
None	42%	50%	35%	48%	39%	41%
Mild (little distress)	33%	33%	39%	36%	32%	37%
Moderate (some distress) to Severe (major distress)	20%	17%	26%	16%	29%	22%
Nervousness for no reason Frequency						
Rarely (<1 per week)	22%	24%	25%	26%	24%	25%
Often (1 per week)	16%	17%	23%	21%	19%	22%
Frequent to daily (few times per wk to daily)	24%	15%	22%	18%	29%	22%
Sad and depressed Severity						
None	33%	35%	29%	33%	22%	23%
Mild (little distress)	43%	45%	39%	46%	46%	44%
Moderate (some distress) to Severe (major distress)	24%	20%	32%	21%	32%	33%
Sad and depressed Frequency						
Rarely (<1 per week)	25%	25%	27%	31%	31%	31%
Often (1 per week)	23%	27%	19%	18%	26%	23%
Frequent to daily (few times per wk to daily)	25%	20%	29%	25%	27%	29%
Flat Moods Severity						
None	35%	35%	28%	30%	22%	26%
Mild (little distress)	44%	45%	41%	49%	41%	46%
Moderate (some distress) to Severe (major distress)	21%	20%	51%	21%	37%	28%
Flat Moods Frequency						
Rarely (<1 per week)	19%	27%	16%	29%	19%	24%
Often (1 per week)	29%	21%	22%	27%	20%	26%
Frequent to daily (few times per wk to daily)	25%	24%	36%	20%	43%	31%
Difficulty experiencing pleasure Severity						
None	37%	40%	32%	30%	23%	27%
Mild (little distress)	43%	35%	35%	49%	37%	40%
Moderate (some distress) to Severe (major distress)	20%	25%	33%	21%	40%	33%

Difficulty experiencing pleasure Frequency						
Rarely (<1 per week)	21%	20%	19%	26%	26%	26%
Often (1 per week)	22%	24%	21%	25%	24%	26%
Frequent to daily (few times per wk to daily)	25%	22%	33%	23%	35%	29%
Hallucinations Severity						
None	80%	81%	72%	72%	66%	57%
Mild (little distress)	16%	12%	19%	22%	23%	28%
Moderate (some distress) to Severe (major distress)	4%	7%	9%	6%	11%	15%
Hallucinations Frequency						
Rarely (<1 per week)	20%	17%	22%	22%	28%	25%
Often (1 per week)	5%	7%	5%	8%	9%	13%
Frequent to daily (few times per wk to daily)	5%	7%	12%	11%	11%	19%
Delusions Severity						
None	96%	94%	92%	94%	88%	85%
Mild (little distress)	2%	5%	5%	3%	8%	8%
Moderate (some distress) to Severe (major distress)	2%	1%	3%	3%	4%	7%
Delusions Frequency						
Rarely (<1 per week)	10%	16%	16%	14%	21%	23%
Often (1 per week)	1%	2%	1%	3%	4%	6%
Frequent to daily (few times per wk to daily)	2%	2%	2%	2%	4%	8%
Diplopia Severity						
None	76%	73%	70%	65%	57%	56%
Mild (little distress)	16%	15%	15%	16%	19%	23%
Moderate (some distress) to Severe (major distress)	8%	12%	15%	19%	24%	21%
Diplopia Frequency						
Rarely (<1 per week)	11%	18%	15%	13%	14%	19%
Often (1 per week)	8%	5%	7%	8%	13%	11%
Frequent to daily (few times per wk to daily)	12%	14%	19%	25%	26%	25%
Concentration difficulty Severity						
None	28%	29%	19%	28%	22%	22%
Mild (little distress)	53%	45%	50%	46%	42%	50%
Moderate (some distress) to Severe (major distress)	19%	26%	31%	26%	36%	28%
Concentration difficulty Frequency						
Rarely (<1 per week)	23%	24%	19%	22%	23%	26%
Often (1 per week)	25%	20%	29%	29%	23%	28%

Frequent to daily (few times per wk to daily)	28%	30%	35%	26%	37%	30%
Forget short time Severity						
None	36%	25%	23%	27%	23%	21%
Mild (little distress)	38%	46%	45%	43%	47%	41%
Moderate (some distress) to Severe (major distress)	26%	29%	32%	30%	30%	38%
Forget short time Frequency						
Rarely (<1 per week)	21%	23%	28%	24%	28%	20%
Often (1 per week)	18%	23%	18%	22%	25%	24%
Frequent to daily (few times per wk to daily)	29%	33%	35%	33%	30%	39%
Forget to do things Severity						
None	48%	39%	38%	38%	36%	35%
Mild (little distress)	38%	44%	41%	41%	42%	40%
Moderate (some distress) to Severe (major distress)	14%	17%	18%	21%	22%	25%
Forget to do things Frequency						
Rarely (<1 per week)	25%	26%	31%	23%	28%	19%
Often (1 per week)	14%	18%	16%	26%	23%	25%
Frequent to daily (few times per wk to daily)	18%	20%	19%	19%	21%	26%
Sialorrhea Severity						
None	58%	49%	57%	41%	37%	32%
Mild (little distress)	31%	32%	33%	37%	41%	33%
Moderate (some distress) to Severe (major distress)	11%	19%	10%	22%	22%	35%
Sialorrhea Frequency						
Rarely (<1 per week)	18%	19%	22%	19%	21%	15%
Often (1 per week)	14%	13%	13%	14%	19%	14%
Frequent to daily (few times per wk to daily)	17%	28%	19%	31%	29%	46%
Swallowing difficulty Severity						
None	53%	45%	43%	40%	28%	43%
Mild (little distress)	34%	38%	41%	43%	48%	36%
Moderate (some distress) to Severe (major distress)	13%	17%	16%	17%	24%	21%
Swallowing difficulty Frequency						
Rarely (<1 per week)	26%	19%	29%	21%	26%	26%
Often (1 per week)	8%	14%	17%	19%	20%	14%
Frequent to daily (few times per wk to daily)	21%	28%	20%	26%	14%	30%
Constipation Severity						
None	25%	23%	15%	20%	17%	14%

Mild (little distress)	33%	33%	27%	39%	30%	34%
Moderate (some distress) to Severe (major distress)	42%	44%	58%	41%	53%	52
Constipation Frequency						
Rarely (<1 per week)	17%	19%	19%	16%	19%	17%
Often (1 per week)	23%	26%	25%	30%	23%	29%
Frequent to daily (few times per wk to daily)	37%	38%	45%	38%	46%	43%
Urinary Urgency Severity						
None	19%	19%	21%	18%	13%	13%
Mild (little distress)	33%	44%	34%	32%	37%	30%
Moderate (some distress) to Severe (major distress)	48%	37%	45%	50%	50%	57%
Urinary Urgency Frequency						
Rarely (<1 per week)	11%	19%	20%	11%	15%	10%
Often (1 per week)	17%	21%	17%	21%	17%	20%
Frequent to daily (few times per wk to daily)	56%	43%	47%	52%	58%	59%
Void within 2 hours Severity						
None	20%	26%	19%	18%	19%	21%
Mild (little distress)	42%	50%	43%	45%	42%	37%
Moderate (some distress) to Severe (major distress)	38%	24%	38%	37%	39%	42%
Void within 2 hours Frequency						
Rarely (<1 per week)	13%	17%	12%	13%	15%	14%
Often (1 per week)	18%	24%	21%	22%	20%	24%
Frequent to daily (few times per wk to daily)	53%	38%	49%	49%	50%	47%
Nocturia Severity						
None	15%	10%	15%	9%	12%	10%
Mild (little distress)	42%	49%	39%	41%	37%	30%
Moderate (some distress) to Severe (major distress)	43%	41%	46%	50%	51%	60%
Nocturia Frequency						
Rarely (<1 per week)	7%	7%	9%	8%	6%	6%
Often (1 per week)	11%	12%	10%	9%	12%	11%
Frequent to daily (few times per wk to daily)	70%	74%	72%	75%	71%	73%
SEX interest LOW Severity						
None	45%	44%	45%	40%	35%	43%
Mild (little distress)	21%	20%	20%	30%	24%	16%
Moderate (some distress) to Severe (major distress)	34%	36%	35%	20%	41%	41%

SEX interest LOW Frequency						
Rarely (<1 per week)	12%	12%	14%	14%	19%	12%
Often (1 per week)	10%	14%	10%	13%	16%	12%
Frequent to daily (few times per wk to daily)	32%	30%	33%	31%	35%	36%
SEX interest HIGH Severity						
None	70%	74%	69%	72%	69%	64%
Mild (little distress)	17%	14%	19%	15%	13%	22%
Moderate (some distress) to Severe (major distress)	13%	12%	12%	13%	18%	14%
SEX interest HIGH Frequency						
Rarely (<1 per week)	10%	11%	15%	17%	16%	16%
Often (1 per week)	12%	10%	8%	8%	11%	16%
Frequent to daily (few times per wk to daily)	16%	14%	19%	13%	13%	14%
Sexual dysfunction Severity						
None	42%	44%	44%	46%	35%	40%
Mild (little distress)	18%	19%	26%	13%	23%	13%
Moderate (some distress) to Severe (major distress)	40%	37%	30%	41%	42%	47%
Sexual dysfunction Frequency						
Rarely (<1 per week)	17%	11%	23%	13%	17%	16%
Often (1 per week)	12%	14%	10%	10%	15%	12%
Frequent to daily (few times per wk to daily)	29%	27%	24%	30%	31%	30%
Pain Severity						
None	46%	55%	48%	49%	38%	46%
Mild (little distress)	29%	27%	22%	24%	31%	22%
Moderate (some distress) to Severe (major distress)	25%	18%	30%	27%	31%	32%
Pain Frequency						
Rarely (<1 per week)	9%	16%	16%	14%	15%	16%
Often (1 per week)	19%	16%	9%	13%	21%	15%
Frequent to daily (few times per wk to daily)	34%	22%	36%	32%	37%	32%
Changes in taste or smell Severity						
None	41%	26%	24%	29%	23%	30%
Mild (little distress)	19%	30%	24%	27%	27%	55%
Moderate (some distress) to Severe (major distress)	40%	44%	52%	44%	50%	15%
Changes in taste or smell Frequency						
Rarely (<1 per week)	10%	12%	11%	9%	14%	14%
Often (1 per week)	10%	13%	11%	16%	15%	10%

Frequent to daily (few times per wk to daily)	44%	53%	57%	52%	57%	52%
Weight Change Severity						
None	77%	83%	76%	77%	70%	80%
Mild (little distress)	13%	10%	10%	13%	16%	10%
Moderate (some distress) to Severe (major distress)	10%	7%	14%	10%	14%	10%
Weight Change Frequency						
Rarely (<1 per week)	10%	13%	13%	18%	21%	22%
Often (1 per week)	5%	6%	9%	6%	6%	8%
Frequent to daily (few times per wk to daily)	7%	6%	10%	6%	13%	5%
Excessive sweating Severity						
None	52%	70%	49%	63%	47%	58%
Mild (little distress)	23%	19%	25%	22%	23%	22%
Moderate (some distress) to Severe (major distress)	25%	11%	26%	15%	30%	20%
Excessive sweating Frequency						
Rarely (<1 per week)	12%	16%	17%	13%	18%	22%
Often (1 per week)	12%	11%	14%	16%	14%	10%
Frequent to daily (few times per wk to daily)	30%	16%	27%	17%	33%	32%

[1] The range represents the different number of respondents across domains.

Non-Motor Symptom Domains

- In Table 3, the average for each symptom domain across age and disease duration groups can be seen.
  - Higher scores reflect greater symptom severity and frequency than lower scores.
  - On average, it appears that individuals with longer disease duration and increased age appear to report higher scores within each domain compared to those earlier in the disease process and those who were younger.

The longer the disease duration and the greater one's age, the increased likelihood one may experience NMS.

Table 3. Non-Motor Symptoms Domains

	Early PD Group (< 6 years duration)		Advanced PD Group 6-10 years duration		Advanced PD Group 11+ years duration	
	Younger (50-69) (n =144-153)[1]	**Older (70+) (n =182-208) [1]**	**Younger (50-69) (n =123-130)[1]**	**Older (70+) (n =182-208) [1]**	**Younger (50-69) (n =167-173)[1]**	**Older (70+) (n =215-238) [1]**
Subdomains	Mean	Mean	Mean	Mean	Mean	Mean
Cardiovascular	1.44	1.40	1.94	1.64	1.91	1.95
Sleep & Fatigue	8.51	7.14	9.81	7.82	10.09	10.38
Mood & Cognition	8.14	7.19	9.27	7.31	11.46	9.35
Perceptual Problems	0.91	1.17	1.63	1.75	2.49	2.56
Attention & Memory	3.44	4.31	4.77	4.49	5.01	5.52

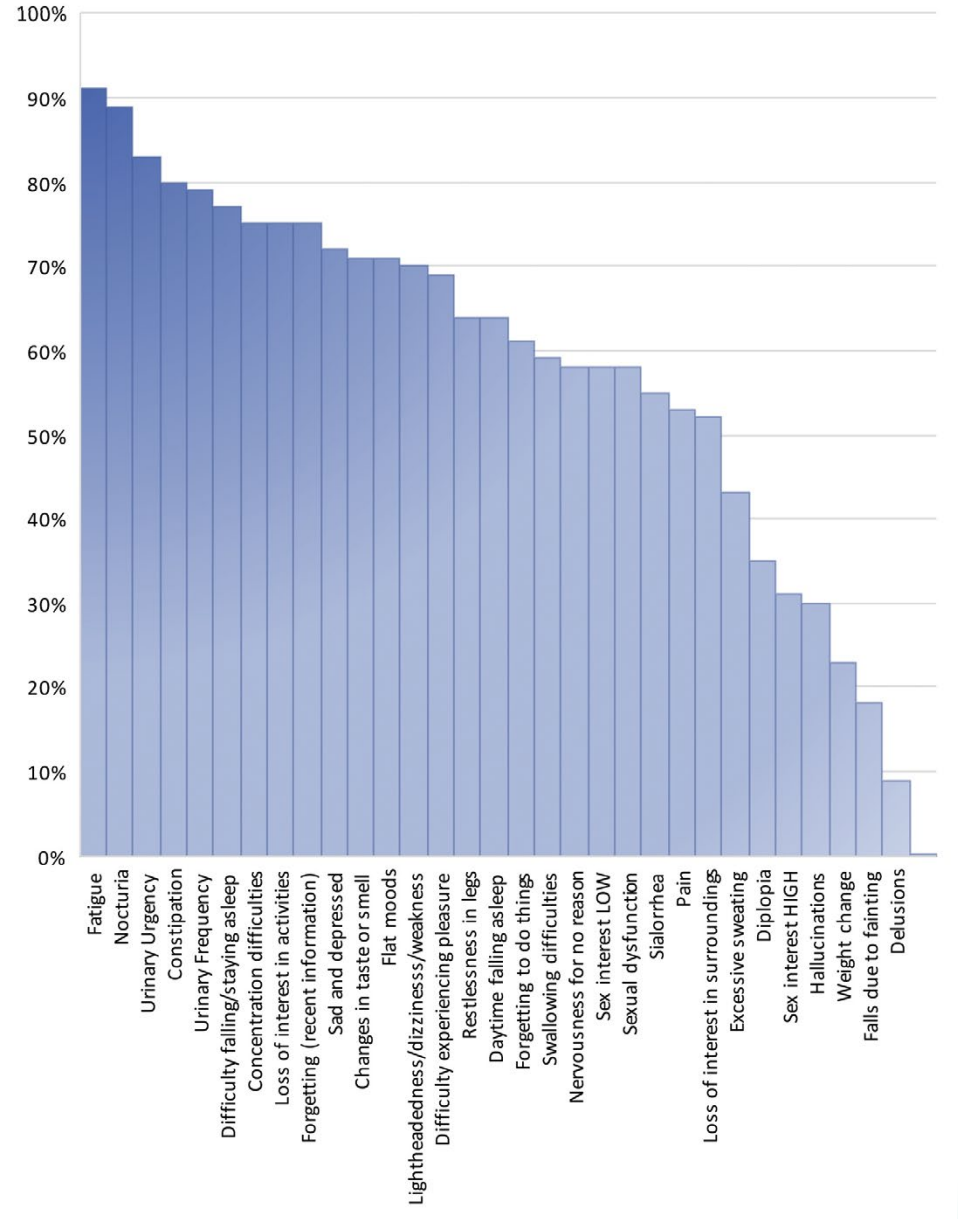
Gastrointestinal Tract	4.04	4.95	4.81	5.15	6.10	6.72
Urinary	9.09	7.40	8.22	9.04	9.33	10.35
Sexual Function LOW	4.72	4.91	4.18	4.81	5.51	5.79
Sexual Function HIGH	3.09	3.51	2.77	3.44	3.77	4.01
Miscellaneous: (pain; smell/taste/; weight changes; excessive sweating)	6.70	5.74	8.11	6.83	8.55	6.87

[1] The range represents the different number of respondents across domains.

Non-Motor Symptoms across the whole sample

- Figure 1 provides the percentage of individuals reporting that they experience the respective symptom [any severity – mild (little distress) to severe (major distress)] for the whole sample.
- 24 out of 31 symptom categories were experienced by more than 50% of the participants. (Note: Table 2 illuminates the number of participants reporting moderate to severe symptoms, which is a considerable number of participants).
- The symptoms that tended to be endorsed the most included fatigue, urinary problems (i.e., nocturia (getting up at night to go to the bathroom), urinary frequency and urgency), constipation and sleep difficulties, and the symptoms that were the least reported included delusions, falls due to fainting, weight change and hallucinations.

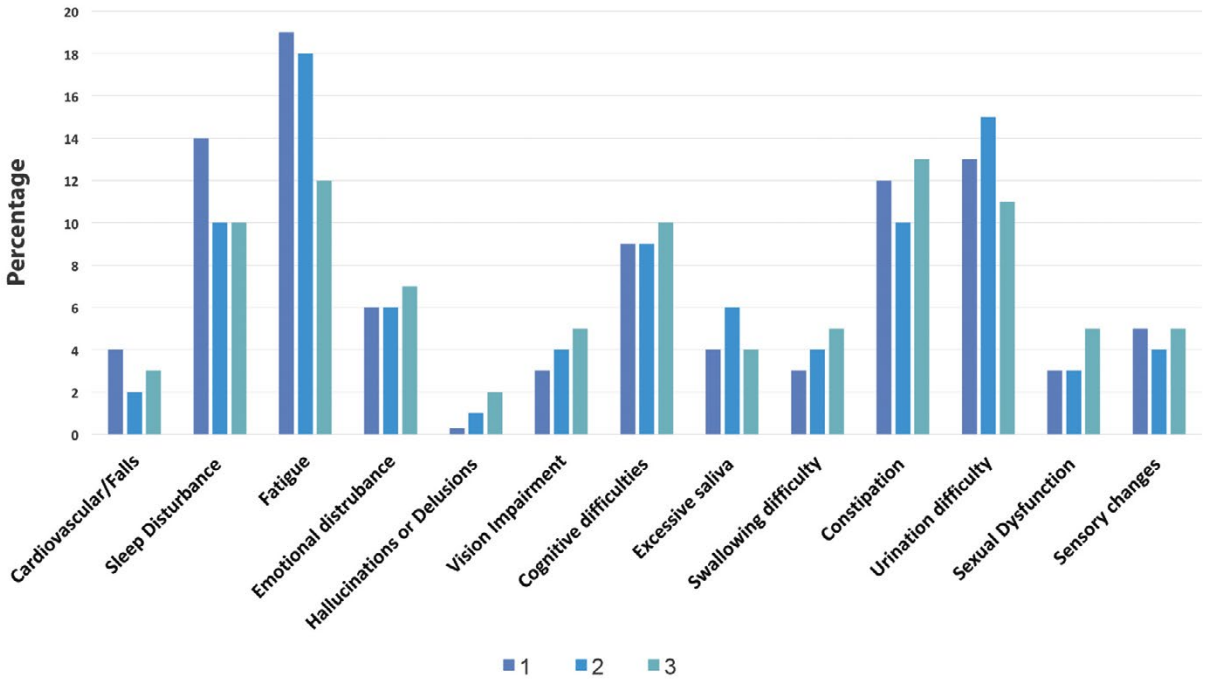
Figure 1. Non-Motor Symptom occurrence across the whole sample (N = 1164)



Most bothersome Non-Motor Symptoms

- Figure 2 illustrates the percentage of individuals who ranked a symptom as either their first, second or third most bothersome symptom.
- On average, fatigue, sleep disturbance, urination difficulties, constipation, and cognitive difficulties were the most commonly ranked "most bothersome symptoms."

Figure 2. Percent reporting the most bothersome symptoms for the whole sample (N = 1164)

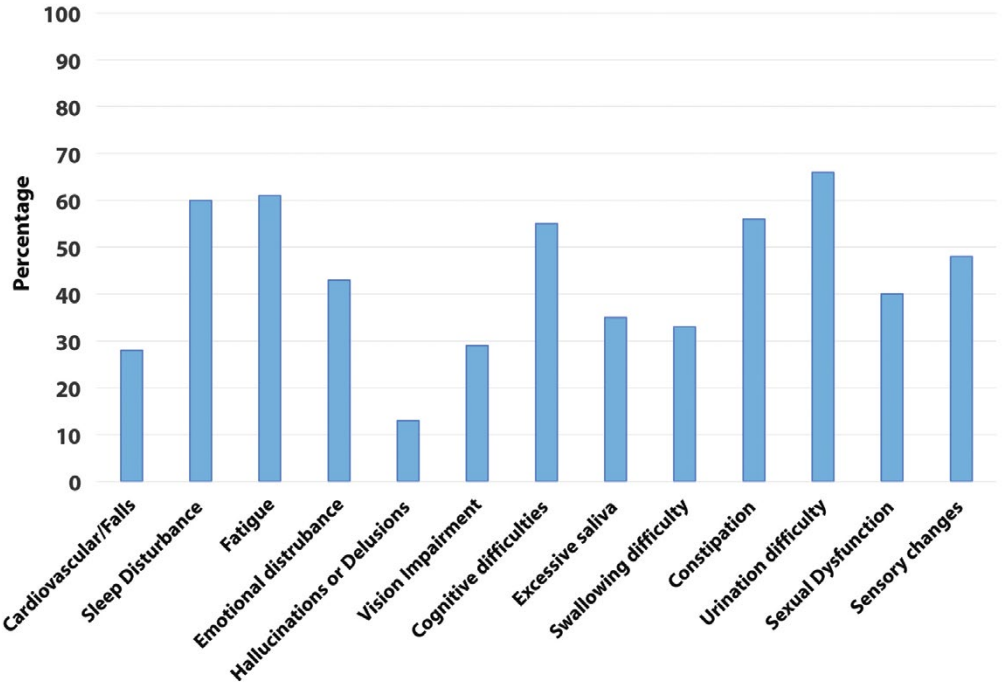


Rank Order: "1" being the most bothersome; "2" second most bothersome; "3" third most bothersome

An impact of NMS on day-to-day living:

- Participants indicated that NMS have a significant adverse impact on day-to-day living.
- Urination difficulty, fatigue, sleep, constipation, and cognitive difficulties were the symptoms most commonly reported to impact day-to-day living (See Figure 3).

Figure 3. Percentage of participants reporting an impact of NMS on day-to-day living (N=1164)

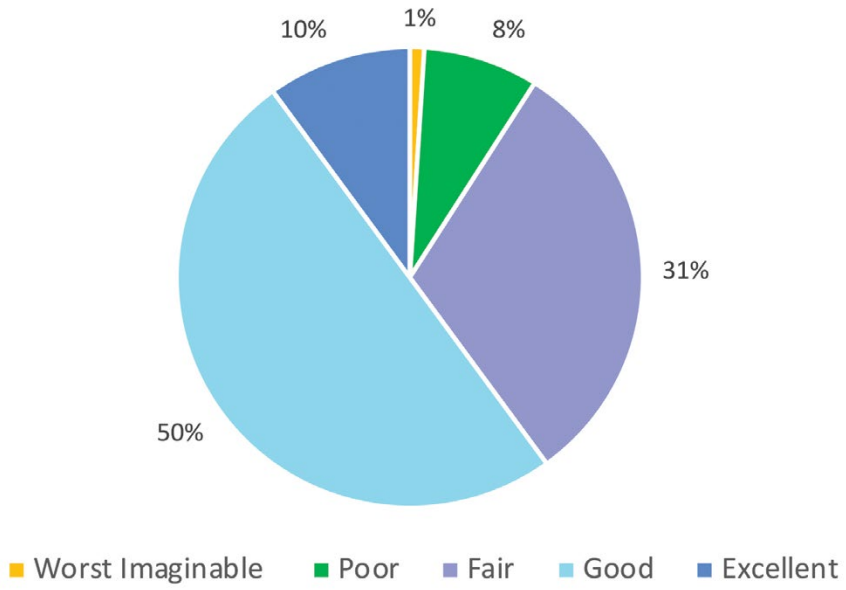


TREATMENT OF NON-MOTOR SYMPTOMS (N = 1,137)

- The extent to which participants reported satisfaction with how NMS are being treated:
  - Satisfied: 25%
  - Somewhat satisfied: 33%
  - Not satisfied: 25%
  - Not sure: 10%
  - Not applicable: 7%

QUALITY OF LIFE (QOL):

- 60% of the participants reported "good" to "excellent" QOL, while 39% reported "poor" to "fair" QOL, and 1% reporting worst imaginable QOL.
- NMS did have a significant relationship to ratings of QOL.
- The NMS having the strongest relationship with perceived qual ity of life was cognitive difficulties followed by sleep disturbance.



PARTICIPANT COMMENTS

- "Non-motor symptoms of PD can be its most disturbing feature either because they become more noticeable as the disease progresses or because they are important factors in judging one's quality of life."
- "Thank you for having a survey for non-motor symptoms. Most people don't understand my struggles because I don't have the shakes yet. There are a lot of underlying issues that people don't see."
- "This survey has arrived at a very opportune time. I have so much difficulty with non-motor symptoms and no one to talk to about them. I feel now like I have somebody that understands how these symptoms impact my life. Because there are no 'meds' to help with these concerns, I have to just adapt and adjust my life style to accommodate the effects they present in my daily routine."
- "This was excellent and important survey. …, non-motor symptoms are something ignored... I think it should be part of an annual evaluation of people with PD since many of the items may not be covered in a chat with the PD Specialist."
- "Very interesting. I feel less alone..."

Examples of specific non-motor symptoms reported to be impacting quality of life:

- "My inability to remember words I have used all my life really bothers me. Any inability to smell my wife's perfume is a real loss to me. I have noticed lately being not able to form sentences, almost a stutter."
- " Pain is [my] most bothersome symptom…. Urinary control problems along with constipation. Loss of taste and sore tongue also make eating difficult."
- "The only real bothersome problem is excessive sweating."
- "Urinary incontinence is a major problem for me."
- "Slow thinking, that's what bothers me the most."
- "Cardiovascular has impacted me the most."

SUMMARY AND DISCUSSION

Parkinson's disease (PD) is now being characterized by both motor disturbance and a wide array of non-motor symptoms (NMS)[1,2]. NMS in PD are a strikingly diverse set of symptoms. Recently, sleep, fatigue, mood, cognition, pain and autonomic disorders (e.g., problems with the regulation of heart rate, blood pressure, body temperature, perspiration, and bowel and bladder functions) have been recognized as important components of the disease, with a consistent impact on patients' health state and quality of life[3-7]. NMS can occur throughout the disease course. Such symptoms can begin long before motor symptoms manifest, and NMS have also been found to occur in upwards of 50% of patients by 20 years of having PD[1,2]. Despite increased awareness of NMS and the high burden of NMS in most patients, NMS remain frequently neglected, undocumented, and undertreated, and there remains a significant gap in the understanding of the patients' perspective on their experience with NMS.

TAKE HOME POINTS FROM THIS SURVEY:

Objective 1: To learn about the patients' perspective about the severity and frequency of NMS of PD.

- 24 out of 31 symptom categories were experienced (at any severity ranging between mild to severe) by more than 50% of the participants.
- Generally, both age and disease duration (independent of one another) may impact the severity and frequency of the NMS.
    - There are a greater number of individuals reporting higher symptom severity and frequency as disease duration and age increase.
    - Disease duration is a better predictor for NMS than age. The longer one has PD, the more likely he or she is to experience NMS.
- The symptoms that tended to be reported the most included fatigue, urinary problems (i.e., getting up at night to go to the bathroom, urinary frequency and urgency), constipation and sleep difficulties, and the symptoms that were the least reported included delusions, falls due to fainting, weight change and hallucinations.

Objective 2: To understand the impact of NMS on daily life experiences and QOL.

- Fatigue, sleep disturbance, urination difficulties, constipation, and cognitive difficulties were the most commonly ranked "most bothersome symptoms."
- Participants indicated that NMS have a significant impact on day-to-day living.
    - Urination difficulty, fatigue, sleep, constipation, and cognitive difficulties were the symptoms most frequently reported to impact day-to-day living.
- 60% of the participants rated QOL as "good" to "excellent," while 31% rated QOL as "fair", 8% rated QOL as "poor", and 1% rated QOL as "worst imaginable."
- NMS did have a significant relationship to QOL.

- The NMS having the strongest relationship with perceived QOL was cognitive difficulties followed by sleep disturbance.
- A large percentage of patients were not satisfied with the management and treatment of NMS.

GENERAL COMMENTS AND RECOMMENDATIONS:

1. Management of NMS remains an unmet need for individuals with PD. Although awareness about NMS has grown, there remains a gap in education about and treatment of NMS. The overwhelming evidence that NMS burden drives quality of life of the patient has remained a relatively new frontier for exploration, at least in depth and scope as it relates to assessment and treatment of the spectrum of symptoms.
    - For the person with PD, informing a healthcare provider about the NMS that he/she is experiencing may be helpful in drawing attention to such symptoms. For example, one could create a checklist of the relevant NMS prior to the appointment, and then take the checklist to the healthcare provider to help structure a discussion about the respective symptoms.
    - For the healthcare provider, it will be important to ask the patient directly about NMS so both the patient and the provider can recognize the symptoms and address treatment needs. For example, use of the NMSS or other checklist at each visit could illuminate current troublesome symptoms and track symptoms over time.
2. To best manage NMS, in collaboration with a Movement Disorder's Specialist, **an integrated treatment team will likely lead to better outcomes, particularly working with subspecialists** who can best help with specific NMS.
3. Regarding sleep disturbance and fatigue, having a formal assessment with a sleep specialist may guide appropriate intervention. Use of medications and/or behavioral techniques may be helpful in addressing sleep disturbance.
4. Medications for psychological/psychiatric disturbance may be beneficial (i.e., for depression; anxiety; hallucinations; delusions; and apathy).
5. Cognitive-behavioral psychotherapy for individuals with PD (and treatment for family too, if appropriate) can be an effective treatment for addressing emotional difficulties that are secondary to, if not directly related to (biological changes), NMS adversely impacting day-to-day function, relationships with others, and quality of life. Psychotherapy can assist in validating one's personal experiences, feeling supported, and developing coping strategies.
6. Cognitive rehabilitation may assist in treating cognitive difficulties. Cognitive rehabilitation should emphasize empirically-based intervention, and is commonly conducted by Neuropsychologists, Speech Language Pathologists, and Occupational Therapists.
7. Regarding pain management, integrating pharmacological and behavioral (psychotherapy; exercise; relaxation techniques; etc.) may be helpful in alleviating some of the pain.
8. Other non-medication-based intervention that may be helpful in managing some NMS includes:
    - Exercise
    - Relaxation techniques
    - Yoga
    - Massage Therapy
    - Acupuncture
    - Aromatherapy
    - Music therapy

9. Keeping your doctor/treatment team informed about the experience of autonomic symptoms, including difficulties with urinary functions, gastrointestinal issues, cardiovascular problems, swallowing, sexual disturbance, thermoregulation (managing temperature sensitivity), and light sensitivity, is important in helping to facilitate appropriate intervention.
10. Cardiovascular changes and orthostatic hypotension are common in PD and are significant risk factors for falls, morbidity and mortality. Early identification of risk factors, careful diagnosis, and treatment of vascular disease may help reduce adverse health outcomes related to the severity of autonomic-related disorders.
11. If you are experiencing orthostatic hypotension, some recommendations regarding the management of orthostatic hypotension include (consult with your doctor first, however):
    - Address the use of medications or medication changes. Consultation with your doctor may help address some possible causes for blood pressure changes.
    - Sit up or stand up slowly.
    - Avoid crossing your legs while sitting.
    - Drink plenty of fluids (if swallowing difficulties are present, consult your doctor about fluid intake).
    - Drink little or no alcohol.
12. Swallowing dysfunction is a significant health hazard for individuals with PD[19].
    - Should swallowing difficulties be experienced, consult with your doctor and discuss the possible need for assessment and treatment by a Speech Language Pathologist (specialists in swallowing disorders).
13. The visual system is very sensitive and highly complex with significant implications for functional difficulties in day-to-day activities when disturbances occur. Assessment of visual dysfunction and recommendations for treatment (including medical and rehabilitation intervention) is recommended for individuals with PD.
    - Meeting with a vision specialist (i.e., Neuro-optometrist; Neuro-ophthalmologist) to assess causality of vision difficulties and provide recommendation for treatment may be of help to individuals with vision impairment or loss.
    - Some visual disturbance may benefit from rehabilitation therapy to assist with both restoration of and compensatory strategies for visual difficulties.
14. Treatment for urinary, gastrointestinal, and sexual functioning changes/difficulties can be challenging. Changes in medications or additional medications can assist in treating symptoms within these domains, and nutrition and behavioral intervention may also be of help. Consulting with your doctor can help address some of these issues. Always ask if a new medication has the potential for a negative effect on memory and other intellectual or mental functions. For example, anticholinergic medications used to treat urinary symptoms, e.g., oxybutynin (Detrol), can contribute to memory problems, hallucinations, and confusion. In such cases, the relative risks and benefits of the treatment need to be considered carefully.
    - As it relates to autonomic dysfunction, better patient information, education and understanding about autonomic dysfunction are recommended to better manage these NMS commonly experienced for individuals with PD.

*Please visit The Parkinson Alliance website pertaining to patient-centered research to review previously written reports about specific topics that include many of the NMS. More comprehensive understanding and treatment guidelines are referenced.

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