PARKINSONALLIANCE

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Dyskinesia, Off-States and Parkinson's Disease: The Patient's Perspective

INTRODUCTION

Definition of Key Terms:

Dyskinesia: uncontrollable involuntary movements that are different from tremors.

- *L-Dopa-induced dyskinesia:* **Levodopa-induced dyskinesia** is a form of **dyskinesia** associated with **levodopa** (**L-Dopa**), used to treat Parkinson's disease.
- *Motor fluctuations:* a decline in the usual benefit from a dose of levodopa. Instead of the smooth, uninterrupted control of symptoms of Parkinson's disease (PD) that levodopa offers early in the disease, symptoms return before the next dose is scheduled, or are only partially controlled by a given dose[1].
    - *Wearing off*: the return of PD symptoms before the next scheduled dose of levodopa. It is the most common form of motor fluctuation.
    - *Morning off*: the predictable occurrence of PD symptoms in the morning, before the first dose of levodopa takes effect.
    - *On-State:* improved control/management of symptoms of Parkinson's disease (stiffness, slowness, tremor, etc.) due to the beneficial effect of PD medication.
    - *Partial on:* when there is an incomplete benefit from a dose of levodopa.
    - *Delayed on*: when symptoms persist for a longer time after taking a dose of levodopa.
    - *Off-State:* anti-parkinsonism medication effects begin wearing off, and symptoms of PD become more pronounced (i.e., increased stiffness, slowness, tremor, etc.).

Long-term pharmacological treatment of Parkinson's disease (PD) can result in motor fluctuations and dyskinesias[2], which can have an adverse impact on social interactions and quality of life. Fluctuations in the motor response to Parkinson's medications are frequently associated with L-dopa-induced dyskinesias[2]. It is now well-recognized that the combination of a significant deficit of dopamine producing brain structures and L-dopa dose (>600 mg/day) are the two main factors conditioning the onset and sensitivity underlying motor fluctuations[2]. Dyskinesias can occur even at lower doses of L-Dopa.

L-Dopa-induced-dyskinesias have a prevalence ranging from 30% to 80% of individuals with PD under chronic treatment with levodopa[3-5]. Onset of dyskinesias can vary; dyskinesias have been found as early as a few weeks after initiating levodopa therapy in young PD patients, and at 10 years about 90% of individuals with PD have motor fluctuations and dyskinesias[6]. Dyskinesias usually occur within three to six years after the initiation of treatment[7-10]. Younger age, younger age of onset, disease duration, disease severity, duration of treatment, and total dose of levodopa were found to be predictors of L-dopa-induced dyskinesias[11,12].

Dyskinesias may be mild, and not interfere with daily living, or they may be more debilitating than the cardinal symptoms of PD (i.e., tremor; rigidity, gait and balance, slowness of movement), markedly impairing quality of life[13]. Dyskinesias can sometimes be managed with L-dopa reduction, or with medications to directly control the movements (such as Amantadine), or with Deep Brain Stimulation (DBS) surgery[14]. Research has found that dyskinesias and motor fluctuations are related to depression and anxiety, with dyskinesias and emotional distress from dyskinesias impacting quality of life[15-18].

Despite increased awareness of the impact of dyskinesias on individuals with PD, the relationship between dyskinesias, depression, anxiety, and quality of life from the patient's perspective warrants further investigation across disease duration and age cohorts.

OBJECTIVES

- To learn about the patients' perspective of dyskinesias' impact on day-to-day function.
- To understand the relationship between dyskinesias, emotional well-being, and quality of life (QOL).
- To provide general comments about and recommendations for treatment related to dyskinesias.

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 935 individuals who participated in this survey. Participants included individuals with Deep Brain Stimulation (DBS; 236 (25%) participants) and without Deep Brain Stimulation (Non-DBS; 686 (75%) participants). See Table 1 for demographics and clinical features.
- Approximately 82% completed their survey independently, whereas, 18% of participants required assistance from another individual (i.e., family, care provider).
- Participants represented 50 states, with California (14%), New York (12%), New Jersey (11%), Florida (10%), Texas (10%), Arizona (7%), Pennsylvania (6%), Minnesota (3%), Colorado (3%), Tennessee (2%), and Massachusetts (2%) having the most participants. There were 32 (3%) international participants.

Questionnaires/Measures: 1. The Demographic Questionnaire; 2. Unified Dyskinesia Rating Scale (UDysRS); 3.Patient Reported Outcome Measure – Anxiety Short Form; 4. Patient Reported Outcome Measure – Depression Short Form.

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 pertaining to dyskinesias and quality of life.

Unified Dyskinesia Rating Scale (UDysRS[19]):

The UDysRS reports patients' perception of the impact of their dyskinesia. There are 10 questions covering the domains of: Speech; Chewing and Swallowing; Eating; Dressing; Hygiene; Handwriting; Doing Hobbies and Other Activities; Walking and Balance; Engaging in Public and Social Settings; Emotional Settings. Scores range from 0 to 4 (0=normal; no problems to 4=Severe problems). A total score is also calculated, with higher scores reflecting greater dyskinesia interference in day-to-day functions.

Patient Reported Outcome Measurement Information System (PROMIS) – Anxiety Short Form[20]:

The PROMIS Anxiety scale consists of 7 items inquiring about symptoms of anxiety over a 7-day time frame. Scale items include: feeling fearful, anxious, worried, nervous, uneasy, and tense, and having difficulty focusing on anything other than anxiety. The response options are on a 5-point rating scale that ranges from 1 ("never") to 5 ("always") and provide a Total Score.

Patient Reported Outcome Measurement Information System (PROMIS) – Depression Short Form[20]:

The PROMIS Depression scale consists of 8 items inquiring about symptoms of depression over a 7-day time frame. Scale items include: feeling worthless, helpless, sad, like a failure, depressed, unhappy, and hopeless, and having nothing to look forward to. The response options are on a 5-point rating scale that ranges from 1 ("never") to 5 ("always") and provide a Total Score.

Comparisons based on age and disease duration groups:

- Age: For the purpose of the survey report, age groups were divided into a **Younger PD group** (≤ 69 years of age) and an **Older PD group** (≥ 70 years).
- Disease Duration: Research has pointed out that dyskinesias can occur within 3 to 6 years after the initiation of L-dopa treatment[7-10]. Other research pertaining to individuals with PD, the average time from symptom onset to development of motor complications was 6 years[21,22]. Thus, 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[21,22]. 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 cognitive difficulties become more apparent, 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 dyskinesias.

RESULTS

- The summary of the demographic information and clinical characteristics of the participants in this study can be found in Table 1.
  - There were 935 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 **(51 years)** than the **Non-DBS group (63 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 60 (range: 35-76 years), with the average duration since DBS being 7 years (range: 0-27 years).

Table 1. Demographics and Clinical Features of the Sample

	DBS (*n* =236)	Non-DBS (*n* =686)
Average Age in Years (range)	68 (47-91)	72 (41-98)
Duration of PD in Years (range)*	16 (2-42)	8 (0-42)
Average Age of PD Diagnosis (range)*	51 (29-74)	63 (30-94)
Average Age at Time of DBS in Years (range)	60 (35-76)	n/a
Average Duration since DBS in Years (range)	7 (0-26)	n/a
Target: STN	45%	n/a
GPi	9%	n/a
Not Sure	46%	n/a
Male	57%	55%
Female	43%	45%
Married	80%	75%
Lives Alone	13%	16%
Race		
Caucasian	95%	94%
Latino/Hispanic	2%	2%
African American	1%	<1%
Asian	1%	2%
American Indian	0%	<1%
Native Hawaiian or Pacific Islander	0%	<1%
Other	<1%	<1%
Education		
<12 years	3%	4%
High School	8%	9%
Some College or Associate's Degree	28%	24%
College	28%	26%
Graduate/Advanced Degree	33%	37%

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

DYSKINESIAS AND THE IMPACT ON DAY-TO-DAY EXPERIENCES (See Table 2)

- A significant portion of participants in this survey reported that dyskinesias adversely impact day-to-day functions, including Speech; Chewing and Swallowing; Eating; Dressing; Hygiene; Handwriting; Doing Hobbies and Other Activities; Walking and Balance; Engaging in Public and Social Settings; Emotional Settings.
  - Using the Unified Dyskinesia Rating Scale (UDysRS[19]), the impact of dyskinesias on day-to-day functions was reported in the highest frequency for the following functions: walking and balance, handwriting, social engagement in public settings, and activities involving increased excitement and emotional settings (See Table 2).
- Dyskinesias are reported within the **Early** and **Advanced** stage PD, with greater reports of the impact of dyskinesis on day-to-day functions as disease progression increased.
- Disease duration was a better predictor than age for the experience of dyskinesia interference on day-to-day function, though the **Younger** PD group (less than 70 years of age) reported day-to-day dyskinesia symptom interference in greater frequency than the **Older** PD group (70 years and older).

- While the **Younger** and **Older** PD groups report a similar pattern of increasing dyskinesia as the disease progresses, generally, the **Younger** PD group reported dyskinesia interference in higher frequency across disease duration groups (see Table 2).
- The most significant increase in dyskinesia interference on day-to-day functions for both **Younger** and **Older** PD groups occurs after 6 years, a period of time known for increased motor complication for PD due to disease progression and increased medication use.

- There is a strong relationship between dyskinesias and frequency of taking PD medications
  - 33% of the participants take medications 1 to 3 times per day, while 64% take PD medications 4 or more times per day (see Figure 1).
  - The greater the frequency of taking PD medication, the greater the report of dyskinesias (See Figure 2).
  - Participants who took PD medications 1 to 3 times per day reported less dyskinesias than participants who reported taking PD medications 4 or more times per day (See Figure 2).
  - **Younger** PD group who took PD medications 4 or more times per day reported greater dyskinesia interference on day-to-day functions than the **Older** PD group across disease duration cohorts. (See Figure 2).

Figure 1. Frequency of taking PD medications per day (whole sample: N=935)

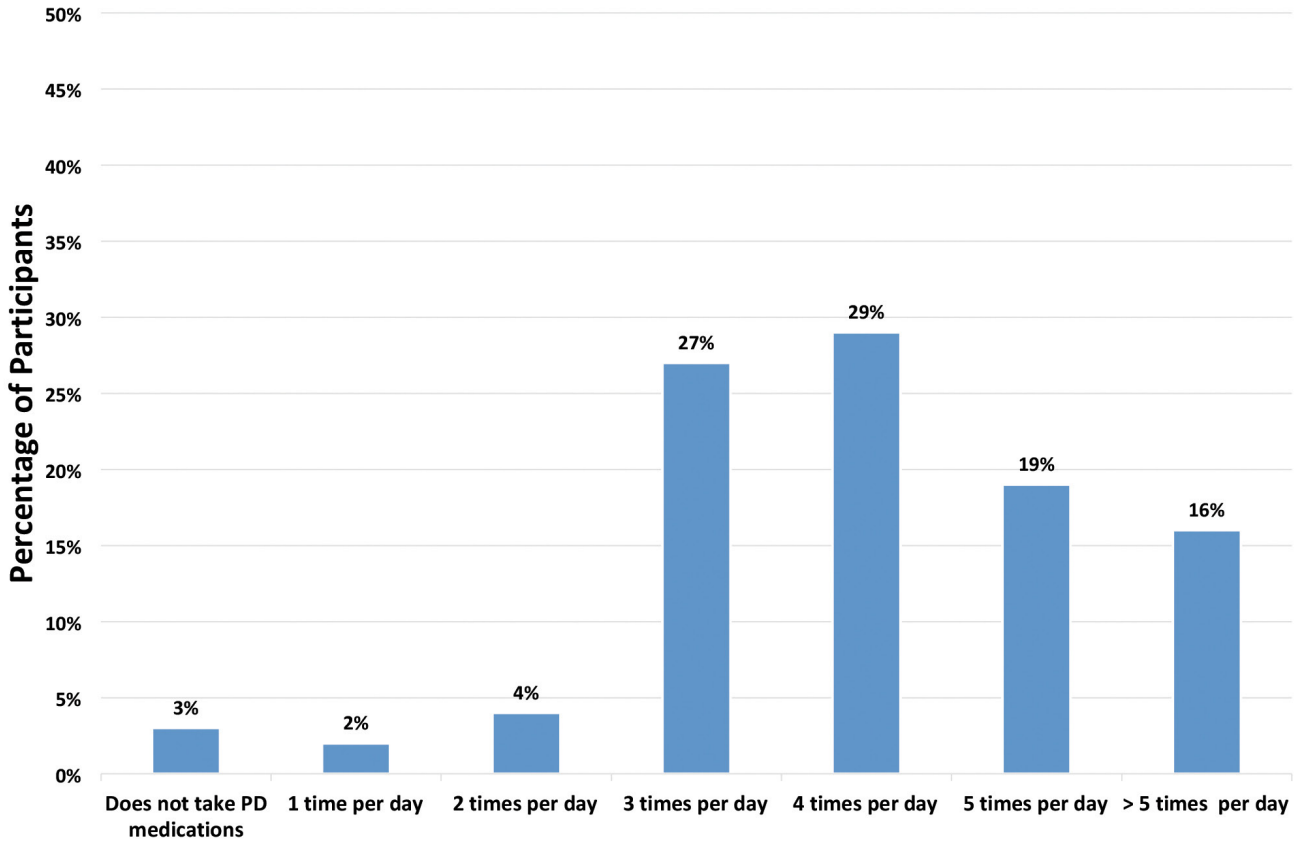


Figure 2. PD medication frequency and dyskinesias

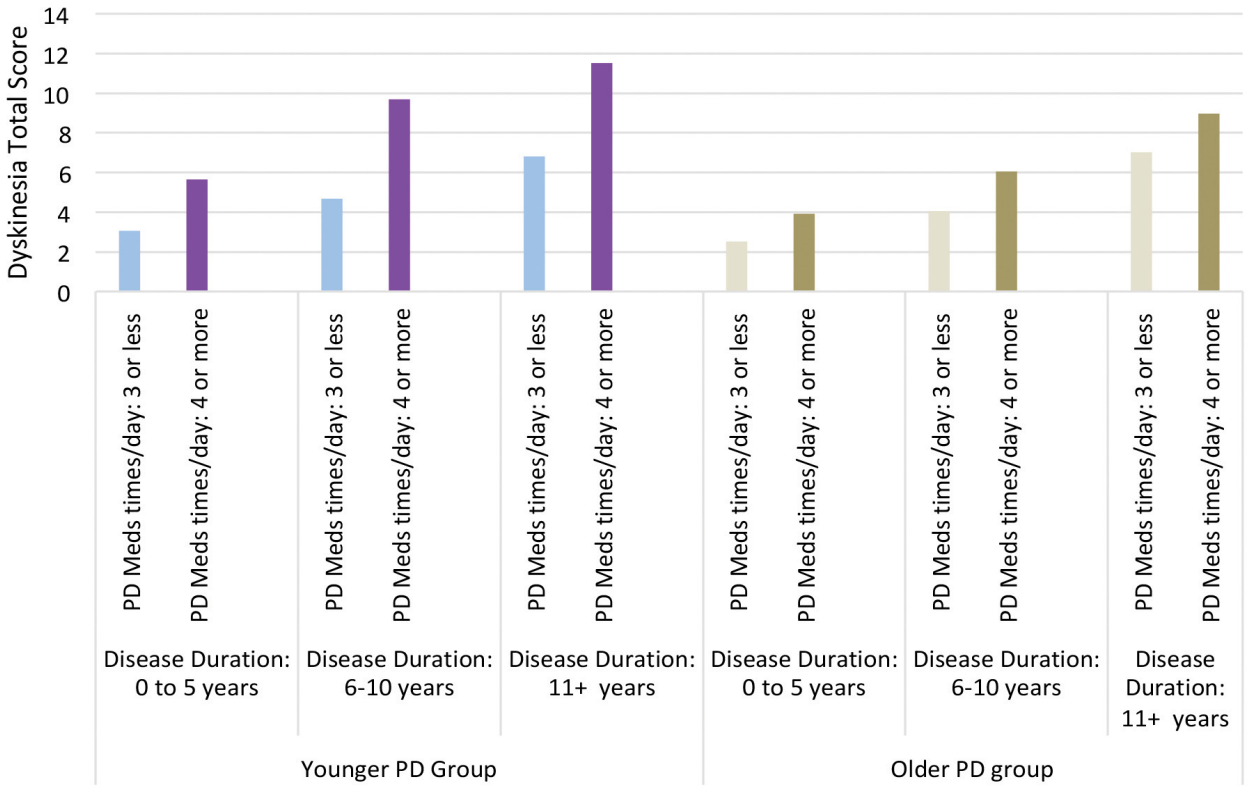


Table 2. Non-Motor Symptoms Experienced by Participants

	AGE GROUP: YOUNGER (< 69 years)			AGE GROUP: OLDER (>70 years)		
	Early PD Group	Advanced PD Group		Early PD Group	Advanced PD Group	
	< 6 yrs duration (n=101)	6-10 yrs PD (n=110)	11+ yrs PD (n=153)	< 6 yrs duration (n=147)	6-10 yrs PD (n=176)	11+ yrs PD (n=223)
Percentage of the day spent with on-dyskinesia						
None/Normal	58%	39%	36%	71%	49%	42%
LESS THAN 50% of on-time during the day	37%	54%	54%	25%	47%	48%
GREATER THAN 50% of on-time during the day)	5%	7%	10%	4%	4%	10%
Speech (dyskinesias impacted speech)						
No problems/Normal	79%	56%	48%	87%	67%	57%
Slight/Mild (no interference to few problems)	20%	38%	42%	11%	30%	33%
Moderate to Severe (problems interfere with daily function)	1%	6%	10%	2%	3%	10%

Chewing and Swallowing (dyskinesia caused problems with chewing or swallowing food or pills)						
No Problems/Normal	84%	66%	56%	88%	75%	67%
Slight/Mild (no interference to few problems)	15%	32%	39%	11%	24%	30%
Moderate to Severe (problems interfere with daily function)	1%	2%	5%	<1%	1%	2%
Eating (dyskinesias caused problems with handling food or using utensils)						
No problems/Normal	76%	58%	55%	84%	70%	61%
Slight/Mild (no interference to few problems)	23%	40%	38%	15%	29%	35%
Moderate to Severe (problems interfere with daily function)	1%	2%	7%	1%	1%	4%
Dressing (dyskinesias caused problems with dressing)						
No Problems/Normal	77%	55%	52%	84%	67%	57%
Slight/Mild (no interference to few problems)	22%	43%	43%	14%	30%	35%
Moderate to Severe (problems interfere with daily function)	1%	2%	5%	2%	3%	8%
Hygiene (dyskinesias caused problems with bathing, brushing hair, brushing teeth, etc.)						
No problems/Normal	82%	64%	56%	88%	72%	67%
Slight/Mild (no interference to few problems)	17%	33%	33%	11%	24%	29%
Moderate to Severe (problems interfere with daily function)	1%	3%	11%	1%	4%	4%
Handwriting (dyskinesias caused problems with writing)						
No Problems/Normal	71%	52%	42%	77%	63%	53%
Slight/Mild (no interference to few problems)	22%	29%	31%	17%	27%	20%
Moderate to Severe (problems interfere with daily function)	7%	19%	27%	6%	10%	27%
Doing Hobbies or other activities (dyskinesias interfered with doing your hobbies or other things that you like to do)						
No problems/Normal	71%	51%	42%	81%	66%	60%
Slight/Mild (no interference to few problems)	25%	37%	38%	15%	30%	24%
Moderate to Severe (problems interfere with daily function)	4%	12%	20%	4%	4%	16%
Walking and Balance (dyskinesias caused problems with balance and walking)						
No Problems/Normal	73%	44%	38%	75%	65%	48%
Slight/Mild (no interference to few problems)	20%	44%	38%	19%	27%	31%
Moderate to Severe (problems interfere with daily function)	7%	12%	24%	6%	8%	21%

Public and Social Settings (dyskinesias caused problems when in public/social settings)						
No problems/Normal	70%	46%	41%	82%	61%	54%
Slight/Mild (no interference to few problems)	26%	41%	43%	17%	33%	37%
Moderate to Severe (problems interfere with daily function)	4%	13%	16%	1%	6%	9%
Exciting or Emotional Setting (dyskinesias caused problems cause problems during emotional conversations, exciting movies, or other highly stimulating situations)						
No Problems/Normal	74%	44%	36%	80%	63%	57%
Slight/Mild (no interference to few problems)	21%	47%	50%	18%	32%	31%
Moderate to Severe (problems interfere with daily function)	5%	9%	14%	2%	5%	12%

Dyskinesias, Emotional Well-being and Quality of Life (Whole Sample: N= 935):

- A high prevalence of depression and anxiety was evident for the participants in this study.
- There was a significant relationship between emotional well-being and dyskinesias, with participants indicating that anxiety had greater impact on dyskinesias and dyskinesias have a greater impact on anxiety when compared to depression and dyskinesia.
- 47% of the participants are experiencing **anxiety**, with 28% of the participants experiencing moderate to severe anxiety **(see Figure 4).**
    - Participants reported that dyskinesias made symptoms of anxiety worse:
        - 19% a little bit
        - 18% somewhat
        - 9% quite a bit
        - 2% extremely
        - 52% indicated that dyskinesias did not impact anxiety symptoms
    - Participants reported that anxiety symptoms made dyskinesia symptoms seem worse:
        - 17% a little bit
        - 16% somewhat
        - 12% quite a bit
        - 3% extremely
        - 52% indicated that anxiety symptoms did not impact dyskinesias
- 37% of the participants are experiencing **depression**, with 18% of the participants experiencing moderate to severe depression **(see Figure 3).**
        - Participants reported that dyskinesias made depressive symptoms worse:
        - 18% a little bit
        - 14% somewhat
        - 6% quite a bit
        - 1% extremely
        - 61% indicated that dyskinesias did not impact symptoms of depression

- Participants reported that depressive symptoms made dyskinesia symptoms seem worse:
  - 16% a little bit
  - 11% somewhat
  - 6% quite a bit
  - 1% extremely
  - 66% indicated that depression symptoms did not impact dyskinesias

Figure 3. Depression Severity

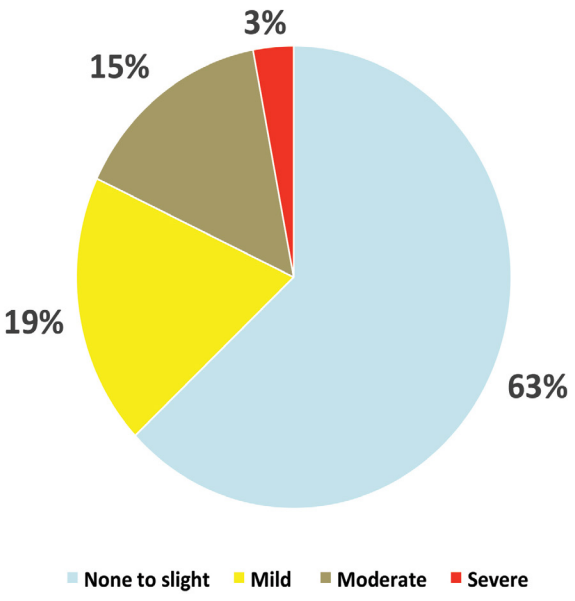
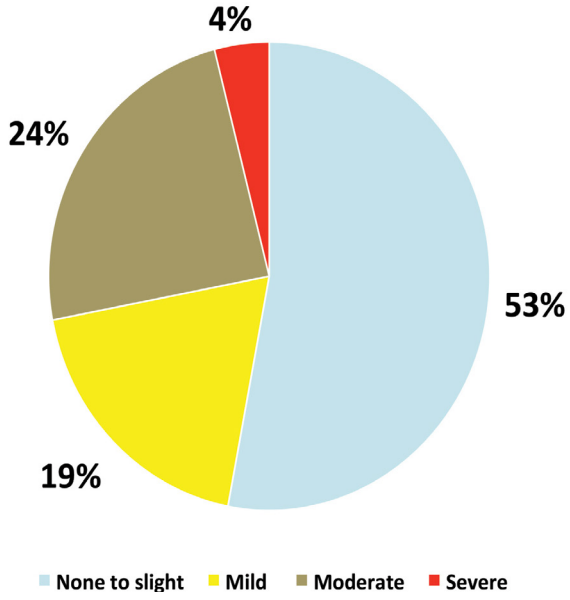


Figure 4. Anxiety Severity



OFF-STATES:

Off-states are also highly prevalent for the participants. When asked about how much of the day was an Off-state experienced, the participants indicated:

- No Off-states (Normal): 23%
- <25% of the day: 45%
- 26 to 50% of the day: 21%
- 51 through 75% of the day: 8%
- More than 75% of the day: 2%
- Not applicable (do not take medications): 1%

Participants reported that Off-states adversely impact the level of independence at home:

- 32% Not at all
- 27% a little bit
- 21% somewhat
- 10% quite a bit
- 4% extremely
- 6% Not applicable

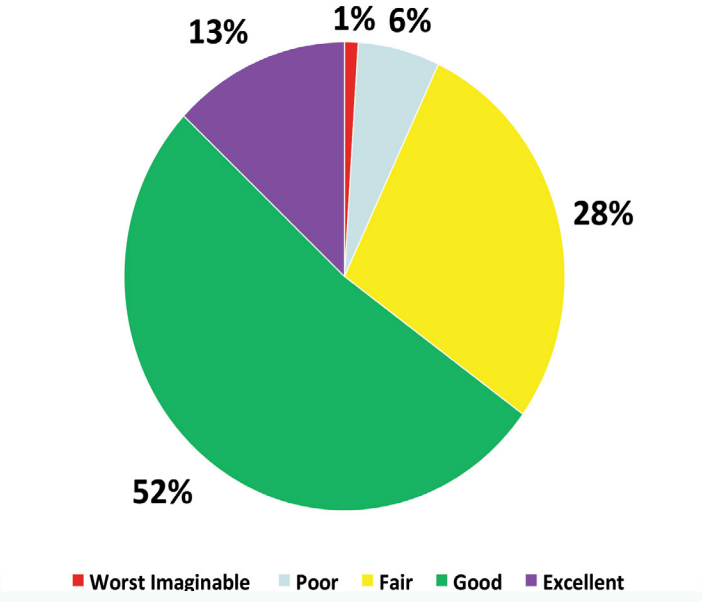
Participants reported that Off-states adversely impact engagement in social activities:

- 26% Not at all
- 27% a little bit
- 23% somewhat
- 13% quite a bit
- 5% extremely
- 6% Not applicable

QUALITY OF LIFE (QOL):

- 65% of the participants reported "good" to "excellent" QOL, while 34% reported "poor" to "fair" QOL, and 1% reporting worst imaginable QOL **(See Figure 5).**
- Dyskinesias had a significant impact on QOL, with 29% of the participants indicating that QOL was somewhat to extremely impacted by dyskinesias.
    - 44% Not at all
    - 27% a little bit
    - 18% somewhat
    - 10% quite a bit
    - 1% extremely
- Off-states, likewise, had a significant impact on QOL, with 43% of the participants reporting that QOL was somewhat to extremely impacted by OFF-states:
    - 26% Not at all
    - 31% a little bit
    - 24% somewhat
    - 15% quite a bit
    - 4% extremely

Figure 5. Quality of Life



PARTICIPANT COMMENTS: Examples

- "As a person with early onset PD, I feel dyskinesia is by far the most difficult aspect of having Parkinson's. The inability to predict and control my movements creates an umbrella of anxiety that hovers over life's daily activities. Dyskinesia…causes great embarrassment and people who are not familiar with the movements associated with dyskinesia and social situation feel awkward."
- "Dyskinesia and off states are huge in PD. If I could get rid of those life would be pretty good."
- "Anxiety creates Dyskinesia and Dyskinesia creates anxiety."
- "Anxiety or tension…increase Dyskinesia"
- "Dyskinesia is a despicable part of the drugs and the disease…"
- "Dyskinesia is very annoying and uncomfortable. I feel I have to explain why I am jumping all over the place to strangers. When I am home I twist until my shoes and socks come off my foot. When I lie down to rest I sometimes move so much I need to get up…"
- "Dyskinesia makes it harder to concentrate on what needs to get done -- writing, using computer, choosing words -- it is an extra distraction especially when there are time constraints and more than one or two projects that need to be done."
- "My dyskinesia -- both on and off - seems to be affected by my quality of rest and by my diet."
- "My neurologist and I have reduced the amount of Carbidopa/Levodopa I'm taking by 1 pill per day, and I believe this has helped my dyskinesia somewhat. She added Amantadine (twice daily) at the same time."
- "I hate having dyskinesia. I keep my medication on lower range of dosage to keep from having them. I would rather loose movement then deal with the whole experience of having dyskinesia."
- "The "off-states" issue is a MAJOR problem for me...!!There is almost no consistency of meds that I can count on.... I live in fear of freezing/off.....!"
- "I had very bad Dyskinesia pre-DBS. Since DBS I have had no Dyskinesia for 3 years."
- "The DBS has improved my overall health 100%."

SUMMARY AND DISCUSSION

Long-term pharmacological treatment of Parkinson's disease (PD) can result in motor fluctuations and dyskinesias, which can have an adverse impact on social-interactions and quality of life. Fluctuations in the motor response to Parkinson's medications are frequently associated with L-dopa-induced dyskinesias. Dyskinesias and motor fluctuations are related to depression and anxiety, with dyskinesias and emotional distress adversely impacting quality of life[15-18].

TAKE HOME POINTS FROM THIS SURVEY:

Objective 1. To learn about the patients' perspective about dyskinesias impact on day-to-day function.

- A high prevalence of dyskinesias was reported. Dyskinesias adversely impacted day-to-day functions, including Speech; Chewing and Swallowing; Eating; Dressing; Hygiene; Handwriting; Doing Hobbies and Other Activities; Walking and Balance; Engaging in Public and Social Settings; Emotional Settings.

- There is a strong relationship between dyskinesia and frequency of taking medications
  - 36% of the participants took PD medications ≤3 times per day and 64% took PD medications ≥ 4 times per day
  - The greater the frequency of taking PD medication in one day, the greater the frequency of dyskinesia-induced functional difficulties were reported.
- Most significant increase in dyskinesia interference on day-to-day functions for both **Younger** (less than 70 years of age) and **Older** (70 years and older) PD groups occurs after several years following PD diagnosis.
  - Around 6 years following diagnosis is a period of time known for increased motor complication for PD, due to disease progression and increased medication use.
- The **Younger** PD group reported day-to-day dyskinesia interference in greater frequency than the **Older** PD group, consistent with prior reports[23].
- Off-states were also highly prevalent for the participants in this study: 45% had Off-states <25% of the day, 29% had Off-states 26-75% of the day, and 2% had Off-states more than 75% of the day.
  - Approximately 65% of the participants reported that Off-states adversely impact "independence" and "engagement in social activities."

Objective 2. To understand the relationship between dyskinesias, emotional well-being, and quality of life (QOL).

- There was a significant association between emotional well-being and dyskinesias, with participants indicating that anxiety had greater impact on dyskinesias and dyskinesias had a greater impact on anxiety when compared to the relationship between dyskinesia and depression.
- 47% of the participants are experiencing **anxiety**, with 28% experiencing moderate to severe anxiety.
  - The majority of the participants indicating that anxiety makes dyskinesia symptoms worse, and dyskinesia symptoms can heighten feelings of anxiety.
- 37% of the participants are experiencing **depression**, with 18% experiencing moderate to severe depression.
  - The majority of the participants indicating that depression can adversely impact symptoms of dyskinesia, and dyskinesia symptoms can heighten feelings of depression.
- 65% of the participants reported "good" to "excellent" QOL, while 34% reported "poor" to "fair" QOL, and 1% reporting worst imaginable QOL.
  - Dyskinesias had a significant impact on QOL, with 29% of the participants indicating that QOL was somewhat to extremely adversely impacted by dyskinesias.

GENERAL COMMENTS AND RECOMMENDATIONS:

1. When considering management of intervention for dyskinesias, it is recommended that you speak with your neurologist/movement disorders specialist. Recommendations to follow are for general points of education that have been sighted in the literature and may be worthwhile to discuss with your doctor.
2. Several therapeutic strategies are used to manage dyskinesias, including adjusting existing PD medications, conducting trials of supplemental medications, and having DBS surgery[24-29].
   a. Initial interventions often involve lowering the dose of existing carbidopa/levodopa therapy and discontinuing or adjusting the dose of a levodopa potentiator (a medication that enhances levodopa), such as entacapone.

All dose-adjustment options and drug discontinuations require careful changes in medications and close monitoring to avoid the re-emergence of motor symptoms and to minimize medication-induced dyskinesia[24,29,30].

b. Tambasco and colleagues (2012) provide the following summary for therapeutic management of dyskinesias:

   i. Substitution of immediate release for controlled-release Levodopa. The immediate-release preparation is easier to adjust, as onset of its effects is sooner, and duration of action (and dyskinesias) is shorter than with controlled-release preparations.

   ii. Discontinuation of other treatment that may create or worsen dyskinesias.

   iii. Create lower dose increments for the number of administrations of levodopa.

   iv. Addition of an antidyskinetic agent (medication to treat parkinsonism) such as amantadine, an NMDA receptor antagonist. There is also an extended release capsule with the brand name Gocoviri.

   v. Dyskinesias that may manifest at the beginning and the end of a dosing cycle should be managed by utilizing more frequent doses of levodopa.

3. Deep Brain Stimulation therapy can be an effective intervention, addressing motor symptoms of PD and reducing dyskinesias. Patients with PD who may benefit from surgery include those who have substantial dyskinesias unresponsive to medication adjustments, are levodopa responsive, do not have dementia, and do not have neuropsychiatric impairment [31,32].

4. Intraduodenal Levodopa provides direct delivery of levodopa. The method involves insertion of a permanent access tube in the abdominal wall. Several clinical studies have been conducted using this approach, demonstrating significant reductions in "off " time and dyskinesia after 6 months. It may be an option for patients with marked fluctuations and dyskinesia in whom deep-brain stimulation (DBS) is contraindicated or not possible due to advanced age, or it may provide an alternative to DBS [30].

5. Being aware of **body weight** and diet are important when considering the appropriate levodopa dose[11,33]. Patients with dyskinesia often receive significantly higher levodopa dose in relation to their body weight (i.e., a higher levodopa dose per kilogram body weight); levodopa dose per kilogram body weight is a more significant factor for dyskinesia than just focusing on the levodopa dose alone (doses taking into body weight is better than increasing "standard doses with a cookbook approach" without considering body weight [11,34].

   a. Adjustment of levodopa dose according to body weight during the course of the disease seems to be a significant modifiable risk factor for dyskinesia[11].

   b. Speaking with your movement disorder specialist or **a nutritionist** who specializes in PD may be helpful in gaining awareness of the impact of body weight and diet on dyskinesias and Off-states [33].

6. Regarding Depression and Anxiety:

   a. Have a conversation about anxiety and depression (psychological and biological contributions; physical and psychological symptoms of anxiety and depression) and related treatments with a specialist in movement disorders (e.g., a neurologist, psychiatrist, neuropsychologist, psychologist who are familiar with PD).

   b. Medications for psychological/psychiatric difficulties may be beneficial (i.e., for depression and anxiety).

      i. Cognitive-behavioral psychotherapy (CBT) for individuals with PD (and treatment for family members too, if appropriate) can be an effective treatment for addressing emotional difficulties that

are secondary to, if not directly related to (biological changes) Parkinson's disease [35]. Psychotherapy can assist in validating one's personal experiences, feeling supported, and developing coping strategies to reduce and manage symptoms of depression and anxiety. Such intervention can aid in coping and adjustment to help improve with function, relationships with others, and quality of life.

ii. Medications that facilitate psychological well-being, in conjunction with psychotherapy, may be helpful for participants who experience depression and anxiety. However, caution is indicated when it comes to selecting certain medications, as some medications (e.g., benzodiazepines, anticholinergic medications and dopamine agonists) can cause or worsen cognitive and psychological symptoms. It is recommended that use of psychotropic medications be monitored by a specialist in PD.

***Please visit The Parkinson Alliance website pertaining to patient-centered research to review previously written reports about specific topics related to PD. More comprehensive understanding and treatment guidelines are referenced in each report.**

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