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ORIGINAL RESEARCH

Quantifying the Tolerability of Dopamine Agonist Antiparkinsonian Medication Side Effects: A Best-Worst Scaling Survey

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Purpose: To identify dopamine agonist (DA) medication side effects that people with Parkinson's (PwP) disease view as most and least tolerable and how this impacts their decisions to initiate and remain on treatment.

Patients and Methods: An online survey was conducted with PwP and care partner proxies for patients with more advanced Parkinson's disease (PD) who were recruited from Michael J. Fox Foundation patient networks and online PD community. The survey contained a best-worst scaling (BWS) component to assess patient tolerability of 10 DA medication side effects identified through literature and qualitative research. Descriptive and statistical analyses were conducted to address the study objectives.

Results: According to the 102 survey respondents, the three least tolerable side effects were sudden/overwhelming sleepiness, hallucinations, and compulsive behaviors. Lightheadedness, headache, and nausea were the three most tolerable side effects. Results were similar between those who were diagnosed ≤5 years and >5 years prior. The least tolerable side effects were associated with an unwillingness to start or continue taking DA medications.

Conclusion: Findings demonstrate that patients' tolerance of potential adverse effects can potentially impact treatment initiation and continuation. Thus, healthcare providers for PwP should discuss medication side effect profiles with their patients prior to treatment initiation and as medication therapy is reviewed and evaluated to promote treatment adherence and positive health outcomes.

Keywords: dopamine agonist, Parkinson's disease, side effects, tolerability, best-worst scaling

Introduction

Approximately 930,000 individuals in North America were living with Parkinson's disease (PD) in 2020, and a 29% increase to 1.2 million people is anticipated by 2030.[1] Globally, PD prevalence increased from 2.5 million people in 1990 to 6.1 million in 2016,[2] doubling then to 11.77 million in 2021.[3] A recent projection estimated that by 2050, 25.2 million people worldwide will be living with PD.[4]

Levodopa-based therapies and dopamine agonists (DAs) are common treatment approaches in PD.[5,6] Both have demonstrated efficacy in relieving PD motor symptoms and are associated with problematic adverse effects.[7] Approximately 30% of people with Parkinson's (PwP) develop involuntary dyskinesia after 3 years of levodopa therapy, increasing to 80% over time with prolonged levodopa therapy.[8] Within 2 years of initiating levodopa, 50% of PwP experience OFF periods, where motor and non-motor symptoms return before their next scheduled medication dose. OFF times occur more often and affect more PwP as levodopa treatment continues (70% experience OFF times after 9 years; 100% after 20 years).[9,10]

DAs, used as PD monotherapy or co-administered with levodopa, have a lower dyskinesia risk compared to levodopa. They are also used as adjuvant therapy for patients experiencing extended OFF times.[5] However, DAs are associated with

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various adverse events, including postural hypotension, peripheral edema, nausea, vomiting, hallucinations, and excessive daytime sleepiness.[5,7,11–15] Development of impulse control disorders (ICDs) (eg, hypersexuality, compulsive buying, compulsive gambling) is also a serious concern with DA therapy. A cross-sectional study of more than 3000 PwP in Canada and the US reported a 2- to 3.5-fold increased odds of ICDs in those taking DAs.[16]

Providers, patients, care partners, and other stakeholders recognize the need for more tolerable PD treatments. Currently, trials are being conducted with new DA agonist formulations that may have milder side effect profiles than currently available DA medications.[17,18] As PD treatments evolve, it is important to gain a comprehensive understanding of PwP's tolerance of, and willingness to trade off, side effects associated with this medication class. Using a best-worst scaling (BWS) survey, we aimed to identify the specific side effects that PwP view as most and least tolerable and how these effects impact their medication-taking decisions.

Materials and Methods

Survey

This study used an online survey with a BWS component to measure patient priorities regarding DA medication side effects. The BWS method is commonly employed in healthcare research[19] and has been used to assess patient treatment preferences across multiple therapeutic categories and disease states,[20–24] including PD.[25–27] It is an efficient method of elicitation and is often considered to be less cognitively demanding than other methods as only a small number of options are available for consideration in each choice set (further described below).[28]

Through a review of the literature[5,7,11–15] and our previous qualitative analyses,[29] we identified 10 medication effects associated with DAs to include in the BWS questionnaire: compulsive behaviors, dyskinesia, edema, hallucinations, headache, lightheadedness, morning akinesia, nausea, sudden/overwhelming sleepiness, and vomiting. These were the most frequently mentioned and discussed PD medication adverse effects in semi-structured interviews and focus groups we previously conducted with PwP and care partners.[29] Participants were provided additional descriptions for some of the adverse effects: compulsive behaviors – "compulsive gambling, sex addiction, compulsive shopping, compulsive eating"; dyskinesia – "uncontrollable twitches, jerks, twisting, and writhing movements"; edema – "swelling caused by fluid in legs, ankles, feet"; morning akinesia – "extreme difficulty with moving your muscles when you first wake up"; and sudden/overwhelming sleepiness – "falling asleep while driving or speaking with friends".

Additionally, respondents were asked to identify the single side effect from the above list they considered to be least tolerable. This direct elicitation response was compared to BWS results. We also asked respondents how likely they would be to start a medication that could potentially cause the effect or discontinue a medication if they experienced that least tolerable side effect. We collected demographic and clinical information, as well as information on their previous or current DA utilization.

A nearly identical survey was available for care partners of PwP with more advanced PD. We asked interested care partners to answer as a proxy for the PwP in order to provide the patient perspective. This study was reviewed and approved by The University of Texas Institutional Review Board (#00005780) and complies with the Declaration of Helsinki. Individuals interested in participating in the survey were informed about the study, according to IRB guidelines, before accessing the survey. Completion and submission of the anonymous survey served as consent.

BWS Tasks

For a total of 15 BWS tasks, respondents were asked to select the "most tolerable" and "least tolerable" side effects. Each task included a subset of four effects for respondents to consider. The subset of effects included in each question set were determined based on a balanced incomplete block design (BIBD) methodology, a type of experimental design that generates a balanced comparison of side effects when not all combinations are possible.[30] Each effect appeared an equal number of times and each effect was shown in the same sets with other effects an equal number of times. The order of questions and the order of the items within each question were randomized to avoid having participants respond to potential patterns in question order. An example BWS question is provided in Figure 1.

Considering only these 4 side effects below, in your opinion, which one would be MOST TOLERABLE, and which one would be LEAST TOLERABLE to you?		
Most Tolerable (most willing to deal with)		**Least Tolerable** (least willing to deal with)
○	**COMPULSIVE BEHAVIORS** (compulsive gambling, shopping, eating, sex addiction)	○
○	**NAUSEA**	○
○	**EDEMA** (swelling caused by fluid in legs, ankles, feet)	○
○	**HALLUCINATIONS**	○

Figure 1 Best-worst question example.

Setting and Respondents

Survey respondents were recruited between October and December 2024 from the Michael J. Fox Foundation Buddy Network and Lived Patient Experience Network. An online survey was offered to PwP who are currently taking or had previously taken DAs and to care partners willing to serve as a proxy for a person with more advanced PD.

Eligibility for PwP included: (1) a self-reported diagnosis of PD; (2) diagnosed with PD at least 6 months before taking the survey; (3) had taken or were currently taking a DA prescribed for PD; (4) ≥18 years of age; and (5) proficient in English. Care partners were eligible if they were the primary unpaid care partner of a person with advanced PD who also met the other required criteria. We asked care partners about the current PD stage of the PwP they were representing using modified Hoehn & Yahr (H&Y) score descriptions.[31] If they chose "severe disability, but still able to walk or stand unassisted" or "wheelchair-bound or bedridden unless aided", we considered the PwP to have advanced disease and the care partner was eligible to participate.

Statistical Analyses

Descriptive statistics were used to summarize the collected survey variables for the overall group of respondents. Using a 5-year cutoff between earlier and later stage disease,[32,33] results for those who were initially diagnosed with PD ≤ 5 years prior were compared to those diagnosed for >5 years.

Conditional logit regression (CLR) with effects coding was used for the BWS analysis. The CLR model is based on a sequential best-worst assumption, anticipating respondents to select the most tolerable effect first, followed by the least tolerable effect in each task. Resulting regression coefficients were then transformed to ratio-scaled preference weights, ranging from 0 to 100, which provide a more intuitive interpretation of the regression coefficients.[34] Stata Version 18 MP was used for all analyses.

Results

Full survey responses were received from 102 individuals. The majority of respondents were PwP (N=95, 93.1%) and seven (6.9%) were care partners. Table 1 displays the characteristics of the survey respondents. Overall, 54.9% were female and the mean age was 62.3 (sd=7.8) years. Three-fourths (74.5%) were White, 11.8% Black, and 7.8% Hispanic. The majority attended college and 41.2% had a graduate degree. 72.5% reported other health conditions, with 26.5% indicating anxiety and 17.6% indicating depression. Respondents reported a mean of 6.7 (sd=5.1) years since PD diagnosis. Most (63.7%) were currently taking a DA. For those who were no longer taking a DA (36.3%), the most common reason for discontinuation was negative side effects of the medication.

A larger proportion of those diagnosed with PD for >5 years were female compared to those diagnosed ≤5 years earlier. Compared to the ≤5 years group, those diagnosed for >5 years were older, a smaller proportion were White, and a larger proportion were managing other health conditions. These differences were not statistically significant.

Table 1 Survey Respondent Characteristics

Characteristic	Overall N=102	Diagnosed ≤5 Years N=51	Diagnosed >5 Years N=51	P value
Gender, N (%)				0.233
Female	56 (54.9)	25 (49.0)	31 (60.8)	
Male	46 (45.1)	26 (51.0)	20 (39.2)	
Age at index, mean (sd)	62.3 (7.8)	61.1 (7.7)	63.6 (7.7)	0.110
Age groups, N (%)				0.236
<50 years	3 (2.9)	3 (5.9)	–	
50–59 years	28 (27.5)	16 (31.4)	12 (23.5)	
60–69 years	52 (51.0)	25 (49.0)	27 (52.9)	
70–79 years	18 (17.6)	7 (13.7)	11 (21.5)	
≥80 years	1 (1.0)	–	1 (2.0)	
Race/Ethnicity, N (%)				0.249
White	76 (74.5)	39 (76.5)	37 (72.6)	
Black	12 (11.8)	3 (5.9)	9 (17.7)	
Hispanic	8 (7.8)	6 (11.8)	2 (3.9)	
Other/Prefer not to answer	6 (5.9)	3 (5.9)	3 (5.9)	
Highest level of education, N (%)				0.542
High school degree	5 (4.9)	2 (3.9)	3 (5.9)	
Some college	13 (12.8)	8 (15.7)	5 (9.8)	
Associate's degree	8 (7.8)	6 (11.8)	2 (3.9)	
Bachelor's degree	29 (28.4)	12 (23.5)	17 (33.3)	
Some graduate school	5 (4.9)	3 (5.9)	2 (3.9)	
Graduate degree	42 (41.2)	20 (39.2)	22 (43.1)	
Managing other conditions, N (%)	74 (72.5)	34 (66.7)	40 (78.4)	0.183
Anxiety	27 (26.5)	11 (21.6)	17 (33.3)	
High blood pressure	26 (25.5)	10 (19.6)	16 (31.4)	
High cholesterol	21 (20.6)	8 (15.7)	13 (25.5)	
Depression	18 (17.6)	8 (15.7)	10 (19.6)	
Pain	13 (12.8)	6 (11.8)	7 (13.7)	
Diabetes	10 (9.8)	4 (7.8)	6 (11.8)	
Heart disease	4 (3.9)	2 (3.9)	2 (3.9)	
Lung disease	4 (3.9)	2 (3.9)	2 (3.9)	
Kidney disease	1 (1.0)	–	1 (2.0)	
Currently taking DA, N (%)	65 (63.7)	33 (64.7)	32 (62.7)	0.837
Apomorphine	5 (4.9)	1 (2.0)	3 (5.9)	
Pramipexole	29 (28.4)	16 (48.5)	13 (25.5)	
Ropinirole	22 (21.6)	14 (27.5)	9 (17.6)	
Rotigotine	9 (8.8)	2 (3.9)	7 (13.7)	
Previously taken DA, N (%)	37 (36.3)	18 (35.3)	19 (37.3)	0.088
Primary reason for discontinuation, N (%)				
Side effects	19 (18.6)	10 (19.6)	9 (17.6)	
Not working well	13 (12.7)	6 (11.8)	7 (13.7)	
Cost	2 (2.0)	–	2 (3.9)	
Other/not sure	3 (2.9)	2 (3.9)	1 (2.0)	

Table 2 Best-Worst Scaling Tolerability Rankings of Side Effects

Side Effect	Tolerability Rank	CLR Coefficient	95% CI	Transformed Coefficient[a]	Transformed 95% CI
Lightheadedness	1	1.922	1.760 to 2.085	23.670	23.031 to 24.280
Headache	2	1.665	1.509 to 1.820	21.721	21.228 to 22.132
Nausea	3	0.947	0.802 to 1.091	15.737	15.702 to 15.750
Edema	4	0.228	0.102 to 0.355	10.053	9.924 to 10.189
Morning akinesia	5	0.171	0.040 to 0.303	9.654	9.483 to 9.831
Vomiting	6	−0.600	−0.718 to −0.482	5.266	5.147 to 5.399
Dyskinesia	7	−0.909	−1.046 to −0.772	4.032	3.860 to 4.220
Compulsive behaviors	8	−1.011	−1.164 to −0.859	3.683	3.471 to 3.912
Hallucinations	9	−1.156	−1.298 to −1.014	3.234	3.072 to 3.412
Sudden/overwhelming sleepiness	10	−1.257	−1.350 to −1.165	2.949	2.929 to 2.978

Notes: [a]CLR coefficients were transformed to ratio-scaled preference weights. For rank: 1 = most tolerable; 10 = least tolerable.
Abbreviations: CLR, conditional logistic regression; CI, confidence interval.

Best-Worst Scaling Conditional Logistic Regression Results

CLR analyses resulted in a ranking of side effects, with 1 being the least tolerable and 10 the most tolerable (Table 2). Overall, the least tolerable side effect was s*udden/overwhelming sleepiness*, followed by *hallucinations* and *compulsive behaviors*. The most tolerable side effect was *lightheadedness*, followed by *headache* and *nausea*. Figure 2 displays the ratio-scaled preference weights for each side effect overall and for those diagnosed ≤5 or >5 years prior. Shorter bars represent less tolerable effects.

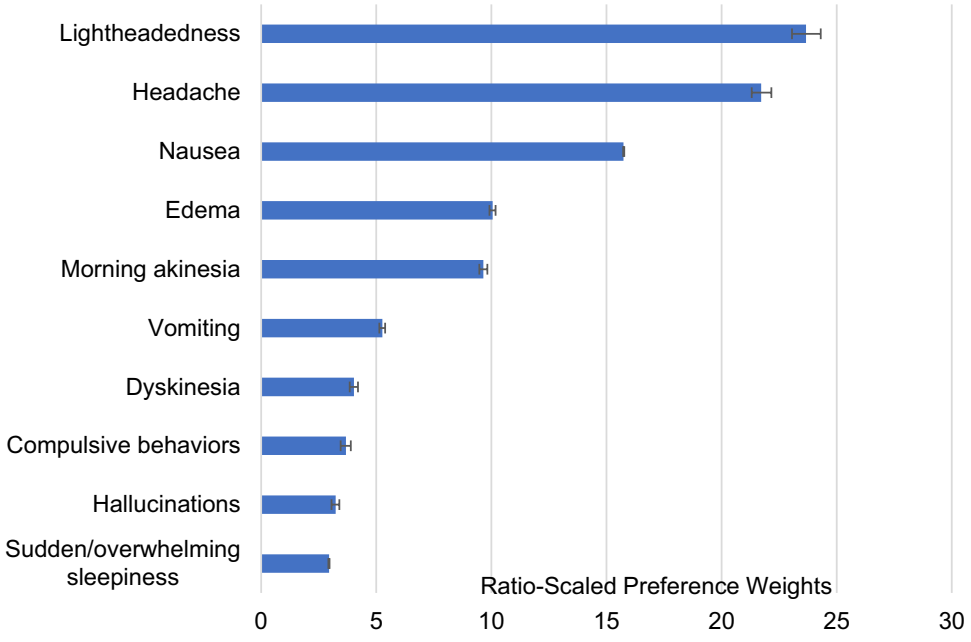

Figure 2 Side effect tolerability scores.
Notes: Longer bars = more tolerable; shorter bars = less tolerable.

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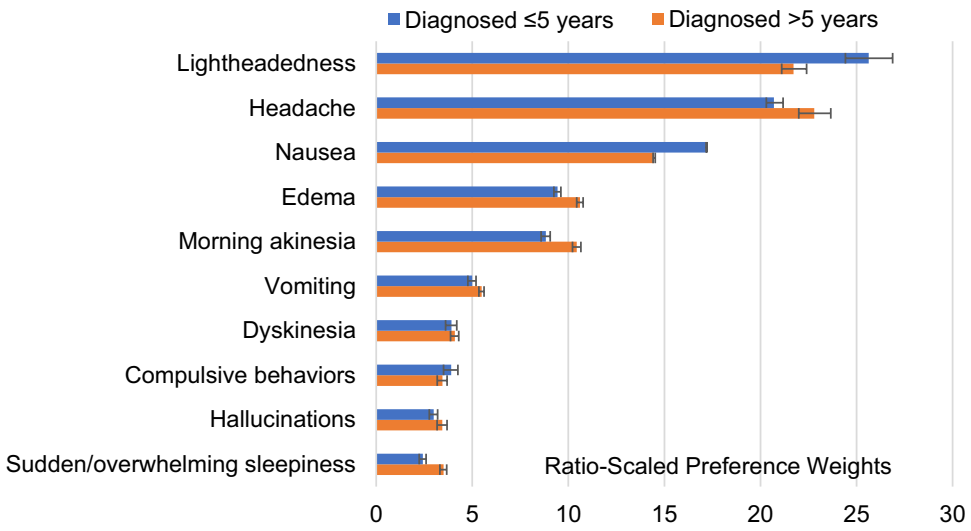

Figure 3 Side effect tolerability scores of respondents diagnosed with Parkinson's disease ≤5 and >5 years prior.
Notes: Longer bars = more tolerable; shorter bars = less tolerable.

The order of tolerability rankings were the same for those with an initial PD diagnosis ≤5 years prior (n=51) as that for all respondents (n=102), with the least tolerable side effect of *sudden/overwhelming sleepiness*, followed by *hallucinations* and *compulsive behaviors* (Figure 3). For those diagnosed >5 years prior, *hallucinations* was the least tolerable side effect, followed closely by *compulsive behaviors* (3.448 vs 3.444). These were followed by *sudden/overwhelming sleepiness* for the >5 year group.

Direct Elicitation Results

Overall, when respondents were asked to choose the single least tolerable side effect from the list of 10 negative medication effects, *compulsive behaviors* was the most frequently chosen option (n=24, 23.5%) (Table 3). This was followed by *hallucinations* and *sudden/overwhelming sleepiness* which were both selected as least tolerable by 21.6% of respondents. 15.7% selected dyskinesia as least tolerable, and <10% selected one of the remaining effects. The top three

Table 3 Direct Elicitation Choice of Least Tolerable Side Effects

Side Effect	Overall (N=102) N (%)	Diagnosed ≤5 Years (N=51) N (%)	Diagnosed ≤5 Years (N=51) N (%)
Compulsive behaviors	24 (23.5)	9 (17.6)	15 (29.4)
Hallucinations	22 (21.6)	12 (23.5)	10 (19.6)
Sudden/overwhelming sleepiness	22 (21.6)	14 (27.5)	8 (15.7)
Dyskinesia	16 (15.7)	8 (15.7)	8 (15.7)
Vomiting	8 (7.8)	3 (5.9)	5 (9.8)
Headache	4 (3.9)	2 (3.9)	2 (3.9)
Edema	2 (2.0)	–	2 (3.9)
Morning akinesia	2 (2.0)	1 (2.0)	1 (2.0)
Lightheadedness	1 (1.0)	1 (2.0)	–
Nausea	1 (1.0)	1 (2.0)	–

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least tolerable side effects identified by direct elicitation (*compulsive behaviors, hallucinations, sudden/overwhelming sleepiness)* were the same as those identified by BWS, but in reverse order.

The order of least tolerable side effects was the same between BWS analysis and direct elicitation for those initially diagnosed ≤5 years earlier. 27.5% of this group selected *sudden/overwhelming sleepiness* as least tolerable, while 23.5% and 17.7% chose *hallucinations* and *compulsive behaviors*, respectively. For those diagnosed >5 years, 29.4% selected *compulsive behaviors* and 19.6% selected *hallucinations* as least tolerable, with *sudden/overwhelming sleepiness* and *dyskinesia* each being selected by 15.7%. In the BWS analysis for this group, *hallucinations* were identified as less tolerable than *compulsive behaviors*.

Side Effect Impact on PD Medication Initiation and Discontinuation

Participants were asked to report their willingness to start a medication that has the potential of the side effect they reported as least tolerable via direct elicitation. The majority of respondents (77.5%) indicating *compulsive behaviors* as the least tolerable side effect reported that they were unlikely to initiate a medication that had the potential for this side effect (Figure 4). Nearly 82% and 95.5% of those with the least tolerable side effects of *hallucinations* and *sudden/overwhelming sleepiness*, respectively, were unlikely to initiate a PD medication that could produce these effects. 100% of the respondents who chose *compulsive behaviors* and *sudden/overwhelming sleepiness* as the least tolerable side effects indicated they were likely to stop a PD medication if they were to experience those effects (Figure 5). This was also the case for 95.4% of those who chose *hallucinations* as least tolerable. Proportions were similar between those initially diagnosed with PD ≤5 and >5 years earlier.

Discussion

This survey study aimed to explore side effect tolerability of PD medications, specifically DAs, using BWS methodology. The top three least tolerable medication side effects among the 10 side effects presented to survey respondents (n=102) were *sudden/overwhelming sleepiness, hallucinations*, and *compulsive behaviors*. The top three most tolerable effects were *lightheadedness, headache*, and *nausea.*

We found that the least tolerable side effects identified via BWS and direct elicitation methods were similar. For those initially diagnosed with PD ≤5 years prior, the identified least tolerable effects (ie, (1) *sudden/overwhelming sleepiness*, (2) *hallucinations*, (3) *compulsive behaviors*) were directly aligned. The same top three least tolerable effects were

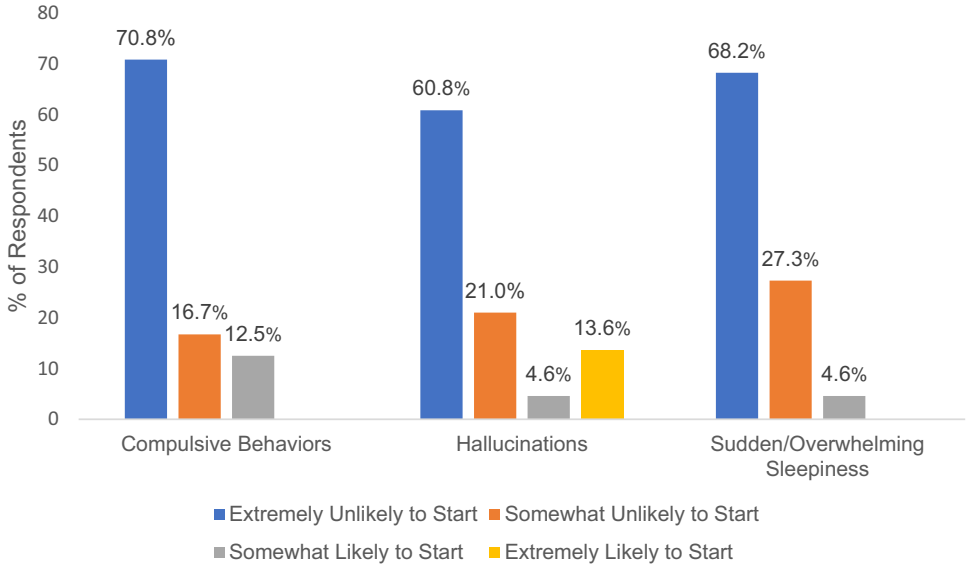

Figure 4 Likelihood of starting a medication for Parkinson's with the potential of the least tolerable side effect.

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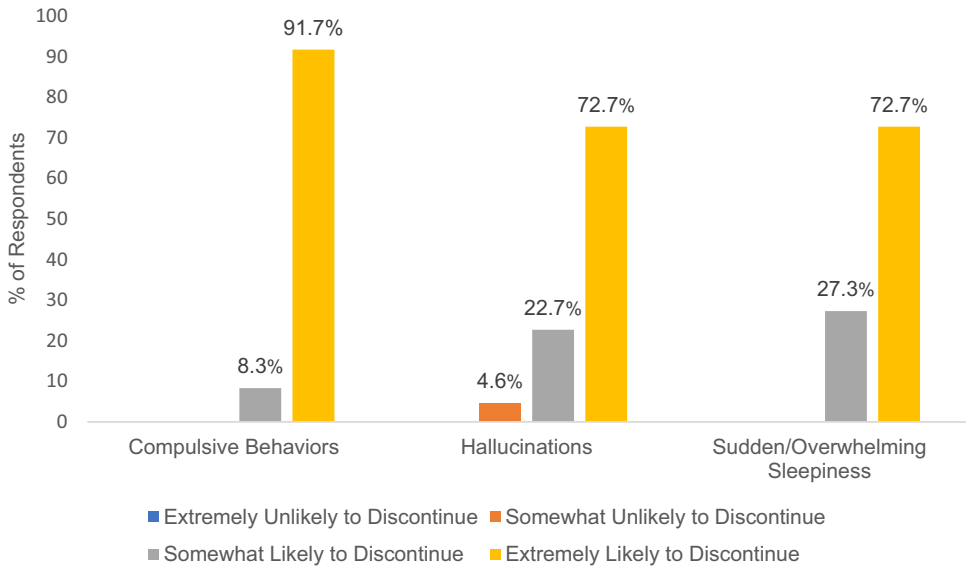

Figure 5 Likelihood of discontinuing a medication for Parkinson's if the least tolerable side effect was experienced.

identified using BWS and direct elicitation in those initially diagnosed >5 years prior, though *hallucinations* were the least tolerable effect determined via BWS, while direct elicitation resulted in *compulsive behaviors* as least tolerable.

These three side effects found to be least tolerable among our survey respondents often have a significantly negative impact on quality of life. Undetected and untreated ICDs can have ruinous effects on PwP and their families. ICD prevalence significantly increases with DA exposure, and susceptible patients may develop more than one.[16,35] Screening for ICD risk (eg, younger onset age, male gender) should be conducted before therapy selection. PwP are more likely to experience visual rather than auditory hallucinations.[36,37] Hallucinations, even those that are relatively "minor", can be difficult to manage and are distressing to both PwP and their care partners. However, they are often underreported by patients.[38] Sudden and overwhelming sleepiness resulting in falling asleep without warning is a troublesome effect for many with PD, especially for those whose daily activities (eg, working, driving) require alertness.[39] It was not surprising that our survey respondents who were diagnosed with PD ≤5 years earlier would choose this side effect as the least tolerable. Sleep-related fears, including overwhelming daytime sleepiness, are commonly expressed by PwP.[40]

Healthcare providers should make every effort to educate PwP and their care partners on potential adverse effects of PD medications. In addition, understanding patients' tolerance perspectives regarding side effects will inform prescribing in order to maximize medication adherence and persistence. Medication adverse effects should be a topic of every follow-up visit and providers should ask detailed, proactive questions to elicit information on patients' positive and negative experiences with their medications. Electronic health record systems with pre-templated notes or prompts may facilitate this screening at every visit to draw out information that patients and care partners may not spontaneously report. Medication-taking behavior is highly influenced by patients' beliefs regarding a drug's benefits vs its adverse effects.[41,42] Shared decision-making, which brings together a prescriber's knowledge and a patient's preferences and goals, empowers patients and facilitates improved healthcare outcomes and quality of life.[43,44]

Limitations

This study had several limitations which should be considered when interpreting results. Self-selection and reporting biases could be present as participation was voluntary and the collected information was self-reported. Recall bias could also be present as participants who took DAs in the past were asked to remember their experiences. The study sample was limited to an online community affiliated with a PD foundation – a group more likely to be more engaged in managing their disease (ie, higher patient activation) than the general population of PwP. Further work is needed to survey a broader PD population with more heterogeneity in characteristics such as race/ethnicity, education, technology

access/ability, and access to PD healthcare. We did not collect a full medication history (PD and non-PD therapies) and personal experience with PD medication side effects, which may have added context to the findings.

Conclusion

All medications, including DAs, for the management of PD have potential side effects, and this study found that PwP view sudden/overwhelming sleepiness, hallucinations, and compulsive behaviors as least tolerable. The results highlight the potential negative impact these side effects have on PD treatment initiation and discontinuation. Patients should be encouraged to consider and communicate their medication preferences. Providers should continually screen for adverse effects at each visit, seek to understand their patients' preferences and concerns, and take this information into account when prescribing and adjusting PD medication regimens, in order to promote treatment adherence and positive health outcomes.

Disclosure

Kristin Richards and Michael Johnsrud are employees of The University of Texas at Austin and conducted the research through a grant from Cerevel Therapeutics, which was acquired by AbbVie Inc. while the study was being conducted. Anton Avanceña, also an employee of The University of Texas at Austin, received no funding for this work. Sneha Mantri, a neurologist and movement disorder specialist, and Holly Collier, a person living with Parkinson's disease, were contracted by Cerevel Therapeutics (later, AbbVie) for this work. Sneha Mantri also reports personal fees from AbbVie, during the conduct of the study, and non-financial support from Biogen and Takeda, outside the submitted work. Deb Yarbrough and Alicia Subasinghe are currently employed by AbbVie. Steve Arcona and Rahul Sasané are former employees of AbbVie. The authors report no other conflicts of interest in this work.

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