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ORIGINAL RESEARCH

Exploring Preferences and Priorities in Advanced Parkinson's Disease: A Discrete Choice Experiment

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ABSTRACT

***Introduction*:** Treatments for advanced Parkinson's disease (aPD) are differentiated by efficacy, safety, and modality-related characteristics. As the disease progresses and motor fluctuations worsen, many patients require more frequent dosing or consideration of device-aided therapies, including subcutaneous infusions, intestinal gel delivery systems, or deep brain stimulation. Assessing treatment preferences is valuable to ensure people with aPD (PwP) and care partners (CPs) are satisfied with a treatment's impact on both motor function and quality of life, potentially increasing adherence and effectiveness.

***Methods*:** A total of 304 participants (223 PwP, 81 CPs) from the USA, UK, and Germany were included in the study. A discrete choice experiment (DCE) was used to elicit preferences over treatment characteristics. In the DCE, respondents were presented with a series of choice tasks, each consisting of two hypothetical treatments described by varying levels of seven attributes: daily hours of ON time without troublesome dyskinesia (ONwoTD), frequency of early morning OFF time (EMO), risk of mild-to-moderate

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skin reactions, risk of severe side effects requiring hospitalization, route of administration (ROA), frequency of pill regimen, and frequency of device maintenance. Analyses with a random parameter logit model were used to estimate attribute conditional relative importance (CRI) and explore how people would trade off across attributes.

***Results*:** The average PwP age was 65.7 years (SD 8.6), time since diagnosis was 10.0 years (SD 4.4), and self-reported OFF time was 4.0 h/day (SD 2.4). Within the survey design, ROA emerged as the most important attribute (CRI 35.3), followed by hours of ONwoTD (CRI 26.4). All other attributes were of similar importance. Nonsurgical treatments were strongly preferred, with oral pills being the most preferred, followed by infusion device without surgery (subcutaneous infusion).

***Conclusions*:** PwP prioritized efficacy (ONwoTD) and ROA when considering treatment options. Understanding these preferences may enhance informed and meaningful decision-making between healthcare providers and PwP.

Keywords: Advanced Parkinson's disease; Attribute relative importance; Benefit–risk tradeoffs; Discrete choice experiment; Neurology; Patient preference; Patient-centered care

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Key Summary Points

Why carry out this study?

Advanced Parkinson's disease (aPD) presents complex treatment challenges due to increasing symptom severity, shortening of efficacy of oral levodopa medications, and consideration of device-aided therapies, which vary in invasiveness, efficacy, safety, and convenience.

There is a lack of data on the preferences of people with advanced Parkinson's (PwP), especially regarding newer subcutaneous therapies and the role of care partners (CPs) in decision-making.

Using a discrete choice experiment, the study aimed to quantify preferences of PwP for aPD treatments, focusing on trade-offs between specific treatment characteristics.

What was learned from the study?

Route of administration and ON time without troublesome dyskinesia were the most important attributes. Nonsurgical treatments—especially oral pills and subcutaneous infusions—were strongly preferred over invasive surgical options, if possible.

PwP and CPs (serving as proxies for PwP) are willing to accept significant risks of specific adverse events (i.e., mild-to-moderate skin reactions and severe side effects requiring hospitalization) for improved efficacy and less invasive treatments, indicating that these risks are secondary to symptom control.

These findings emphasize the supportive role of CPs in treatment management and indicate that their perspectives should be considered alongside those of PwP in shared decision-making.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder that primarily affects

movement but also involves cognitive, gastrointestinal, behavioral, and other non-motor symptoms [1]. The standard first-line treatment for motor symptoms is oral levodopa/carbidopa, which is highly effective in managing symptoms during the early stages of the disease [2]. However, as PD advances, its therapeutic duration shortens, frequently necessitating increased dosing frequency—often five or more times per day [3].

When patients experience motor fluctuations with oral levodopa/carbidopa, alternative therapies that bypass the oral route can be considered, such as device-aided therapies (DATs). These involve a device implanted in the body or worn externally, and include deep brain stimulation (DBS), intestinal gel formulations of levodopa/carbidopa or levodopa/entacapone/carbidopa, and subcutaneous infusions of foslevodopa/foscarbidopa or apomorphine formulations [4]. DATs have different levels of efficacy, safety, and tolerability, along with route of administration (ROA). Whereas DBS involves hardware implanted into the brain, and intestinal pumps require surgical tube placement, subcutaneous infusions avoid invasive procedures and have also shown efficacy in reducing motor fluctuations and dyskinesia [5, 6]. In addition to DATs, some patients require adjunctive oral treatment.

Given the complexity of PD and the expanding array of therapeutic options, selecting the most appropriate treatment for advanced PD (aPD) is a decision requiring nuanced consideration of patient preferences, clinical factors, and potential trade-offs [7]. As clinical management shifts toward personalized care, understanding how people with aPD (PwP) weigh the trade-offs between efficacy, safety, convenience, and invasiveness becomes essential. For physicians, this highlights the practical need to actively integrate patient preferences into treatment recommendations to ensure therapies are both effective and acceptable in daily life. While some patients may prioritize the convenience of oral formulations, others may benefit more from continuous infusion therapies or surgical interventions. Quantitative preference elicitation methods offer a structured approach to capture these values, enabling clinicians and policymakers to align treatment strategies with patient priorities. Despite a number of published PD patient preference and discrete choice experiment (DCE) studies [8–20], significant knowledge gaps remain. No studies to date have included perspectives on subcutaneous therapies or considered input from care partners (CPs), who often play a crucial role in managing aPD [21].

The objective of this study was to elicit PwP preferences for various characteristics of treatments for aPD, exploring their conditional relative importance (CRI) and the benefit–risk trade-offs PwP are willing to make.

METHODS

This online survey-based study collected primary data from PwP or CPs of PwP (acting as proxy for PwP report) residing in the USA, UK, or Germany. First, a scoping review of the published literature was conducted to inform the initial list of treatment attributes that were considered relevant for the study. Building on this, 16 in-depth qualitative interviews with PwP and CPs were conducted to select the key treatment attributes that would be included in the DCE survey instrument. Once developed and pretested with 12 PwP, the survey was then administered online to PwP or CPs of PwP to elicit preferences for the attributes included. Centralized ethics approval was obtained from SALUS IRB, USA, on 20 September 2023 (Reference number 21091). All procedures in this study followed the guidelines outlined in the Declaration of Helsinki (1964) and its later amendments, along with good clinical practice of the International Council for Harmonisation [22]. All subjects provided informed consent to participate in the study.

Study Population

The study population consisted of adults aged ≥ 30 years residing in the USA, UK, or Germany able to speak, read, and provide informed consent in the local language who self-reported being diagnosed with PD at least 5 years prior, who experienced ≥ 2 h per day of OFF time (proxy criteria for aPD [23]), and who were taking oral PD medications. Those having an

atypical or secondary parkinsonism diagnosis, taking medication for Alzheimer disease, having severe cognitive impairment, or having significant visual impairment were excluded.

To avoid excluding underserved PwP [24] who struggle with online surveys due to symptom severity, the study also included CPs to serve as proxy respondents for PwP. For inclusion, CPs had to be aged ≥ 18 years and not be a professional or paid CP; additionally, they had to provide ≥ 12 h of care/week for a person meeting PwP criteria for inclusion in the study; reside in the USA, UK, or Germany; and be able to speak, read, and provide informed consent in the local language.

As the study aimed to mimic the decision situation where oral treatment no longer provides adequate symptom control and the patient needs to consider DATs for the first time, we limited the number of participants with previous or current DAT experience to 20%. Their inclusion helps avoid bias from excluding individuals who may prioritize DATs, ensuring that their therapeutic preferences are also represented. All participants received an honorarium for their participation, and those who participated in the qualitative phase were eligible for the quantitative phase.

Attribute Identification

The identification of attributes for inclusion in the qualitative phase of the DCE was informed by a scoping literature review [8–10, 12–16, 25–33]. The initial list of attributes was discussed during semi-structured 1-h qualitative interviews [34] with 16 PwP and CPs conducted online in two waves of eight interviews. In addition to exploring priorities in treatments and impact of the condition, the qualitative interviews were used to evaluate and refine the candidate attributes for inclusion in the quantitative phase of the DCE [35]. Participants rated each attribute based on its relevance and clarity, and noted whether differences between levels were meaningful. Attribute selection emphasized tradability (the ability to make trade-offs) and nonredundancy, ensuring attributes aligned with the research question, regulatory needs, and health technology assessments. Attributes were excluded if they overlapped, were too dominant, or posed methodological challenges [36].

Audio recordings were transcribed and analyzed using a targeted content analysis approach to capture participant perceptions. First, a member of the research team reviewed each transcript and noted all relevant quotes from participants regarding each attribute discussed. Next, content analysis of the quotes was organized by each of the attributes presented to the participants to identify stakeholders' perceptions on the relevance and importance of each attribute. The analysis led to attribute refinement, followed by the second wave of interviews to validate the revised list.

Survey Instruments

Using insights gained from the qualitative interview, the study team finalized the set of attributes for the DCE. The same list of attributes was used in two versions of the surveys—one for PwP and one for CPs—which were created to collect equivalent data on treatment preferences across both groups. The survey instrument was then refined with 12 pretest interviews conducted in July 2023. Pretest participants confirmed that the attributes were relevant, their description appropriate, the tasks comprehensible, and the trade-offs feasible. In particular, the study team tested the feasibility of the choice task with seven attributes and worked on simplifying levels to avoid confusion and burden to respondents. The survey was revised to improve attribute descriptions, enhance clarity, reduce cognitive burden, and minimize attribute correlation. The final list of attributes and levels, along with their descriptions, can be found in Table 1. Among the seven attributes included, two focused on efficacy (i.e., daily hours of ON time without troublesome dyskinesia [ONwoTD] and frequency of early morning OFF time [EMO]; two focused on safety (i.e., risk of mild-to-moderate skin reactions and risk of severe side effects requiring hospitalization); and three focused on convenience (i.e., ROA, frequency of pill regimen, and frequency of device maintenance). Notably, the two safety attributes were selected to include a

Table 1 Final list of attributes, descriptions, and associated levels

Attribute labels	Levels
ON time without troublesome dyskinesia Parkinson's causes many different symptoms like shaking, stiffness, slowness of movement, balance issues, or muscle cramps. When we talk about "ON time" we mean the period when these Parkinson's symptoms are mostly controlled by your medication	3 h 6 h 10 h 13 h
Early morning OFF time Opposite to good ON time, OFF time refers to when you experience symptoms such as shaking, stiffness, slowness of movement, balance issues, or muscle cramps, which can affect your daily activities, potentially leading to falls In the survey, early-morning OFF time means that you have OFF time symptoms upon waking up	Occasionally: once a week Sometimes: 3 times a week Very often: 7 times a week
Risk of mild to moderate skin reaction When using most treatments for Parkinson's, it is possible for the person to experience symptoms such as nausea, vomiting, diarrhea, or constipation However, certain Parkinson's treatments are also associated with different risks of mild-to-moderate skin reaction. They may experience redness, pain, itchiness, or soreness that are manageable and typically do not require medical attention	5 out of 100 patients 30 out of 100 patients 60 out of 100 patients 90 out of 100 patients
Risk of severe side effects requiring hospitalization Different treatments are also associated with different risks of experiencing severe side effects that may lead you to being admitted to hospital For example, you may experience severe infections around the implanted medical device requiring antibiotics administered into the veins, have bleeding in the brain or stroke after the surgery, have stomach bleeding, hallucinations or even psychosis (which means you may lose temporary touch with reality), or fainting that can lead to a fall and fracture	1 out of 100 patients 10 out of 100 patients 20 out of 100 patients

Table 1 continued

Attribute labels	Levels
Route of administration When we discuss "How you receive your treatment", we would like you to think about the way the medication is administered to you Most people receive treatment by taking oral pills throughout the day. To keep the treatment working, you may need to take the pills 4 to 8 times per day It is also possible to receive the treatment using a device. The device gives you the treatment without interruption. You might or might not need to take pills together with the device To get the device you might need surgery or not	Only oral pills: The medication is taken as a pill, by mouth. You may need to take pills 4 to 8 times per day, at very specific times of the day for the treatment to work well. You can stop the medication if and when you choose to (but will lose its effects) Device for infusion under the skin; No surgery required: The medication is delivered as a continuous infusion under the skin (subcutaneous) via a small needle and tube, using an external portable pump carried in a pouch (or carrying accessory) for 16 or 24 h a day Device for infusion in the intestine; Stomach surgery required: a small hole (called a "stoma") is created in the stomach to place a medication delivery port. This will be done at the hospital, and it will not require you to stay overnight. The medication is delivered as a continuous infusion through a tube placed into your small intestine via the delivery port, using an external portable pump carried in a pouch (or carrying accessory) for 16 h a day Device for electrostimulation of the brain; Brain surgery required: Electrodes (i.e., thin metal wires) are placed into your brain during surgery and a neurostimulator (like a pacemaker) is implanted under your skin in the upper chest or abdomen. This will be done at the hospital, and it will require you to stay overnight
Frequency of pill regimen People with Parkinson's often need to take pills multiple times during the day, either as their main treatment or together with their main treatment to manage Parkinson's symptoms or side effects With a device you might be able to reduce or eliminate pills. However, with some options, even if you decide to use a device, you may need to take additional pills	No need to take pills (0 times a day) Pills taken 4 times in a day Pills taken 8 times in a day

Table 1 continued

Attribute labels	Levels
Device maintenance All treatments require some action from a person with Parkinson's or their caregivers. This may be remembering to take pills, putting medication into the device, or charging the device Some treatments require more action than others. In particular, if you use a device, you might need to do something to make sure it works properly. This could be changing the site of infusion, disconnecting the tube from the pump or flushing the tube to prevent clogging, or charging the device. We will refer to this as device maintenance In this survey, we would like you to think about the number of times in a week you or your caregiver need to perform device maintenance	None Once every 3 days Once per day

high probability/low impact adverse event and a low probability/high impact adverse event. Constraints were also added to the experimental design to avoid illogical attribute combinations (see Supplementary Materials).

Given the number of possible combinations of two-alternative choice tasks generated by seven attributes with three to four levels each, a full factorial design was unfeasible. Therefore, a fractional factorial efficient design following ISPOR guidelines was developed using Ngene (ChoiceMetrics, version 1.3) [37, 38]. The final design consisted of 48 choice tasks spread over 6 blocks, resulting in 8 choice tasks per participant (48/6 = 8). Participants were randomly assigned to one block, with task order randomized within blocks. A sample choice task is shown in Fig. 1. Each DCE task included a three-alternative choice task which included an opt-out option followed by a two-alternative (i.e., forced-choice) task if the opt-out was initially selected.

Sleep problems are highly prevalent in aPD and directly affect health-related quality of life [39]. However, the inclusion of sleep problems in the DCE was not feasible. Therefore, to evaluate the impact of sleep problems on treatment choice, participants were also asked to completed two direct elicitation tasks after completing the DCE: one without the sleep problems attribute and another with it [40]. Each task presented three options: treatment A (hypothetical subcutaneous infusion device), treatment B (hypothetical oral therapy), or "Neither," with a follow-up comparison if "Neither" was selected (Fig. S1 in the Supplementary Materials). In the choice task which included the sleep problems attribute, the oral therapy profile reflected typical sleep problems due to overnight medication wear-off [3], while the subcutaneous option represented 24-h continuous delivery, shown in published trials to improve sleep as reported in PDSS-2 scores [5, 6].

Ahead of the final analysis, internal validity checks specific to preference studies were conducted on the DCE [41]. These included identifying the following quality assessment indicators:

- Speeders: Participants were replaced if the total survey completion time was less than 360 s or if the DCE portion was completed in under 30 s.
- Straight-liners: Participants were replaced if they consistently chose the same option (e.g., always choosing treatment A. across all DCE tasks.
- Logical consistency: Participants reporting a combined total of ONwoTD and OFF time exceeding 24 h per day were deemed ineligible.

Fig. 1 Example of discrete choice experiment question (used in the UK). *UK* United Kingdom

Statistical Analysis

The choice data were analyzed following ISPOR guidelines [42]. A random parameter logit (RPL) [43] was selected for the final analysis of the DCE data. Given that the forced choice task was only included to obtain data on trade-offs if respondents selected the opt-out, we checked how many participants always selected the opt-out and we did a sensitivity analysis on the data with the opt-out compared to the forced choice. As few participants always selected the opt-out option and statistical tests showed no significant differences in response distributions between non-forced (i.e., with the opt-out) and forced-choice tasks, the analyses presented in this manuscript were based on non-forced choice data (i.e., including the opt-out), consisting of choices among treatment A, treatment B, and "Neither." Data from PwP and CPs were pooled after tests showed no significant differences in preferences or scale. The final model specification is detailed in the Supplementary Materials, along with full statistical methods.

Preference weights were estimated for attribute levels and used to calculate the CRI of each attribute relative to the attributes and levels included in the study, defined as the utility difference between its most and least preferred levels, rescaled to sum to 100. The delta method was used to calculate standard errors and 95% confidence intervals for these differences.

To explore trade-offs, we computed the maximum acceptable risk (MAR) and minimum acceptable benefit (MAB). The MARs were computed for the two risks included in the study (i.e., the additional risk of mild-to-moderate skin reactions or severe side effects), while the MABs were computed for increases in ONwoTD. Both measures were computed from the lowest included in the survey (i.e., 5%, 1%, and 3 h, respectively). The MARs were calculated as the negative ratio of utility gain (caused by getting a better outcome or ROA) to disutility per unit of added risk. The MABs were calculated as the negative ratio of utility loss (caused by getting a worse outcome or ROA) to the utility per unit of added hours of ONwoTD. It is important to note that MAR and MAB represent marginal rates of substitution and should be interpreted

considering everything else constant. They are theoretical trade-off measures derived from the experimental design, and do not account for simultaneous variations in multiple attributes or real-world clinical complexity.

Preference weights were also used to estimate the probability of choosing between two fixed multi-attribute treatment profiles out of five scenarios. The scenarios were defined to simulate treatment decisions and assess how different combinations of ROA, ONwoTD, and risks included in the study would impact choices.

A subgroup analysis using an RPL model assessed the impact of region, country, age, pill burden, OFF time, and type of participant on preferences. Subgroups were prespecified and discussed with experts to avoid multiplicity and bias in selection. An exploratory analysis excluded participants with current or past DAT experience to compare results with the total sample (Table S1 in the Supplementary Materials).

RESULTS

Respondent Characteristics

The study included 304 participants (223 PwP, 81 CPs), nearly half recruited in the USA (48.68%), with 36.18% of respondents from Germany and the remainder from the UK (15.13%). The mean reported age of PwP was 65.73 (SD 8.65). On average, study participants had been diagnosed 10.02 years prior (SD 4.22) and self-reported an average of 4.03 h (SD 2.40) of OFF time/day and 10.49 h (SD 3.63) of ONwoTD/day in the past week. Early-morning OFF time was common, with 66.11% of PwP experiencing it more than four times per week. Most participants reported having sleep problems in the past week, with 36.51% of respondents reporting sleep problems occurring 2–3 times and 34.21% experiencing them 4–6 times. Common comorbidities included depression/anxiety (30.92%) and arthritis (11.84%). All PwP reported being on an oral medication, with 10.86% currently also on a DAT (infusion therapy or DBS), and 84.54% had changed their medication at least once. Most participants (86.18%) reported taking pills for PD at least 3–4 times a day (Table 2) (see Tables S2–S5 in the Supplementary Materials for more on respondents' characteristics).

Main Preference Analysis

The estimated preference weights are presented in Fig. 2 (see also Table S6 in the Supplementary Materials). Preferences for most attribute levels followed the expected direction, and differences between most attribute levels were statistically significant at the 95% confidence level. Respondents preferred longer time of ONwoTD. Notably, the utility increase diminished as the ONwoTD increased. Regarding EMO time, "very often (7 times a week)" was unexpectedly preferred to "occasionally (once a week)" and "sometimes (3 times a week)." This would not represent a rationally correct preference (the levels for this attribute were not ordered as expected). ROA was the most important attribute (CRI 35.3), followed by ONwoTD (CRI 26.4); the CRIs of all other attributes were not statistically significantly different from one another, signaling their similar importance (Fig. 3).

Maximum Acceptable Risk

Table 3 shows the MARs estimated for the risks included in the study, namely for the risk of mild-to-moderate skin reaction and the risk of severe side effects requiring hospitalization, for various improvements. All else being equal, PwP were willing to accept high levels of risk for improvements in ONwoTD and for less invasive ROA. In particular, PwP were willing to accept any risk of mild-to-moderate skin reactions included in the survey (i.e., between 5% and 90%) to go from 3 to 6 h, a 69% increase in risk (from 5%) to go from 6 to 10 h, and 19% to go from 10 to 13 h, although the last of these was not statistically significant at the 95% confidence level. PwP would be willing to accept any risk of mild-to-moderate skin reactions (within the range included in the survey) to switch from surgical infusion to nonsurgical infusion and from electrostimulation to nonsurgical infusion. Reducing the frequency of taking

Table 2 Sociodemographic and clinical characteristics ($n = 304$)

Variable	Responses
Country of residence, *n* (%)	
USA	148 (48.68%)
UK	46 (15.13%)
Germany	110 (36.18%)
Age (years)	
Mean (SD)	65.73 (8.65)
Median (IQR)	67.00 (11)
Max–min	86–39
Duration of diagnosis (Parkinson's disease), years	
Mean (SD)	10.02 (4.22)
Median (IQR)	9 (4)
Max–min	32–6
Comorbid conditions, *n* (%)	
Depression, anxiety, or other psychiatric disorder	94 (30.92%)
Arthritis	36 (11.84%)
Cardiovascular disease (angina, heart failure, history of heart attack, or any other)	31 (10.20%)
Asthma, emphysema, or other pulmonary condition	26 (8.55%)
Type 2 diabetes	25 (8.22%)
Gastrointestinal disease	21 (6.91%)
History of stroke	13 (4.28%)
Multiple sclerosis	6 (1.97%)
OFF time per day in the past week, hours	
Mean (SD)	4.03 (2.40)
Median (IQR)	3.00 (2.125)
Max–min	16–2
ON time per day in the past week, hours	
Mean (SD)	10.49 (3.63)
Median (IQR)	12.00 (5)
Max–min	16–2
Frequency of early-morning OFF time, *n* (%)	
Never	6 (1.97)
Occasionally (once a week)	21 (6.91)

Table 2 continued

Variable	Responses	
Sometimes (2–3 times a week)	76 (25.00)	
Often (4–6 times a week)	110 (36.18)	
Very often (7 times a week)	91 (29.93)	
Frequency of sleep problems in the past week, *n* (%)		
Never	5 (1.64%)	
Occasionally (once a week)	38 (12.50%)	
Sometimes (2–3 times a week)	111 (36.51%)	
Often (4–6 times a week)	104 (34.21%)	
Very often (7 times a week)	46 (15.13%)	
Treatments, *n* (%)	Current	Previous
Oral medications (levodopa formulations, COMT, MAOB, etc.)	304 (100%)	200 (65.79%)
Inhaled (levodopa; Inbrijia)	5 (1.64%)	8 (2.63%)
Injection (apomorphine; Apokyn)	15 (4.93%)	23 (7.57%)
Infusion (levodopa formulations or apomorphine)	10 (3.29%)	8 (2.63%)
Oral film (apomorphine; Kynmobi)	5 (1.64%)	9 (2.96%)
Transdermal patch (rotigotine; Neupro)	17 (5.59%)	19 (6.25%)
Deep brain stimulation	23 (7.57%)	6 (1.97%)
Have not changed medication		47 (15.46%)
Frequency of taking oral pills for Parkinson's treatment, *n* (%)		
Once a day	6 (1.97%)	
Twice a day	36 (11.84%)	
3–4 times a day	125 (41.12%)	
5–6 times a day	81 (26.64%)	
7–8 times a day	41 (13.49%)	
More than 8 times a day	15 (4.93%)	
Ability to walk and get around, *n* (%)		
Walk without support from walking aids	81 (26.64%)	
Walk with walking aids (e.g., cane, walker) or support from another person	131 (43.09%)	
Walk with support from another person	51 (16.78%)	
Limited ability to walk, using wheelchair or support from another person	41 (13.49%)	

COMT catechol-O-methyltransferase, *MAOB* monoamine oxidase type B, *Max* maximum, *Min* minimum, *UK* United Kingdom, *USA* United States

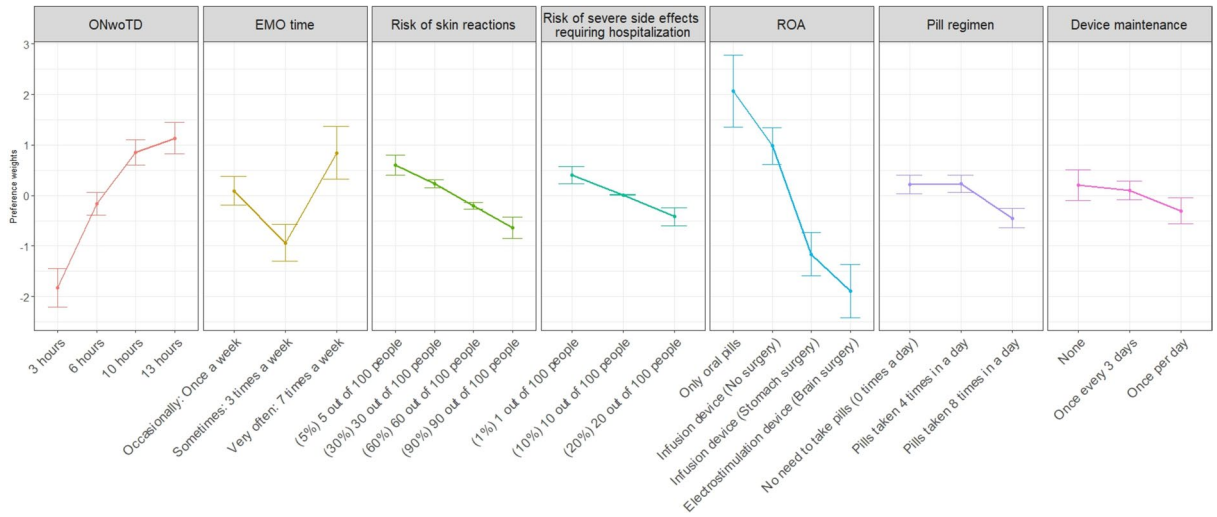

Fig. 2 Results from the random parameter logit model from the full sample ($N = 304$)—preference weights. The DCE data of the people with aPD and those who care for someone with aPD have been merged given that their preferences were demonstrated to be not statistically significantly different. We tested the statistical difference through a Louviere and Swait (1993) test. *aPD* advanced Parkinson's disease, *DCE* discrete choice experiment, *EMO* early-morning OFF time, *ONwoTD* ON time without troublesome dyskinesia, *ROA* route of administration

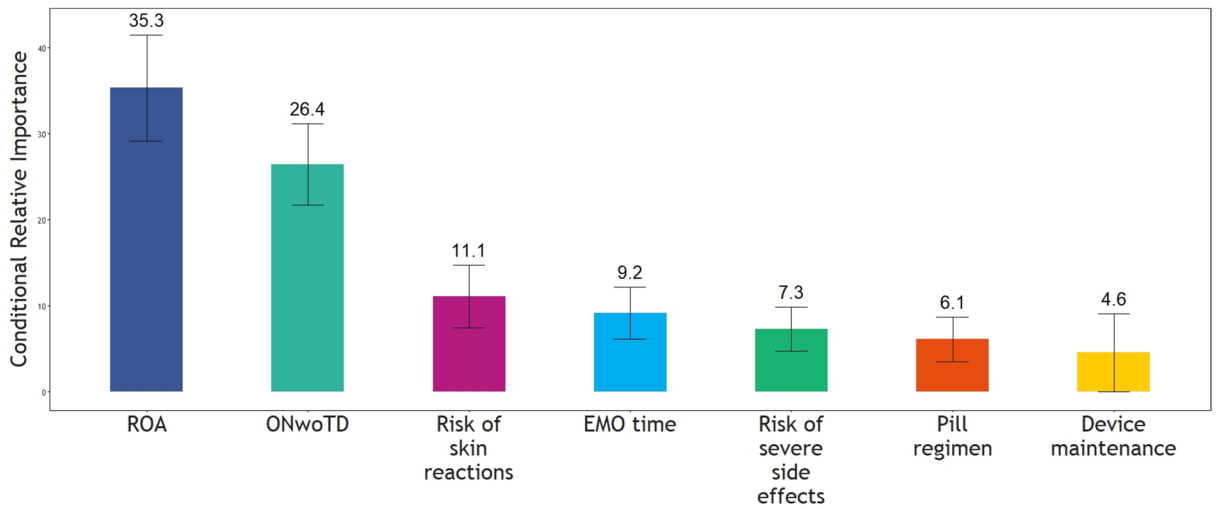

Fig. 3 Conditional relative importance. *EMO time* early-morning OFF time, *ONwoTD* ON time without troublesome dyskinesia, *ROA* route of administration

pills from eight times a day to four times a day is also considered a significant improvement, as respondents would be willing to accept a 47% increased risk of skin reactions.

Similar results are shown for the MAR of severe side effects requiring hospitalization, but with lower risk tolerance, as expected given the higher impact of this adverse event. On average, PwP were willing to accept any risk of severe side effects requiring hospitalization included in the survey instrument (i.e., between 1% and 20%) for increasing the hours of ONwoTD from 3 to 6 h, and from 6 to 10 h; to decrease from 3 days a week to once a week of EMO; and to change

Table 3 Maximum acceptable risk of mild-to-moderate skin reactions and of severe side effects requiring hospitalization

Improvement	Risk of mild-to-moderate skin reaction				Risk of severe side effects requiring hospitalization			
	Value	Confidence interval (95%)	Robust t-ratio	*P* value	Value	Confidence interval (95%)	Robust t-ratio	*P* value
Improvements in "ONwoTD"								
From 3 h of ONwoTD to 6 h of ONwoTD	> 85[a,b]	NA	4.31	< 0.001	> 19[a,b]	NA	4.52	< 0.001
From 6 h of ONwoTD to 10 h of ONwoTD	69.2[b]	35.6 to 102.8	4.0	< 0.001	> 19[a,b]	NA	3.6	< 0.001
From 10 h of ONwoTD to 13 h of ONwoTD	19.3	− 7.8 to 46.4	1.4	0.1615	6.6	− 2.6 to 15.7	1.4	0.162
Improvements in "Early morning OFF (EMO)"[c]								
From 3 days a week to once a week of EMO	70.4[b]	37 to 103.8	4.1	< 0.001	> 19[a,b]	NA	3.9	< 0.001
Improvements in "ROA"								
From electrostimulation to infusion device (with surgery)	49.7[b]	9.4 to 90	2.4	0.016	16.9[b]	2.8 to 30.9	2.4	< 0.001
From infusion device (with surgery) to infusion device (without surgery)	> 85[a,b]	NA	4.7	< 0.001	> 19[a,b]	NA	4.7	< 0.001
From infusion device (without surgery) to pills	74.3[b]	14.6 to 134	2.4	0.016	> 19[a,b]	NA	2.4	0.016
Improvements in "Frequency of pill regimen"[d]								
From pills taken 8 times a day to pills taken 4 times a day	46.9[b]	18.5 to 75.3	3.2	0.001	15.9[b]	6.3 to 25.6	3.2	0.001

from surgical infusion to nonsurgical infusion, and from nonsurgical infusion to oral pills. Risk tolerance for mild-to-moderate skin reactions and severe side effects requiring hospitalization was low when going from device maintenance once every 3 days to no maintenance.

Table 3 continued

Improvement	Risk of mild-to-moderate skin reaction				Risk of severe side effects requiring hospitalization			
	Value	Confidence interval (95%)	Robust t-ratio	*P* value	Value	Confidence interval (95%)	Robust t-ratio	*P* value
Improvements in "Device maintenance"								
From maintenance once per day to maintenance once every 3 days	27.8[b]	2.9 to 52.8	2.2	0.028	9.4[b]	1.1 to 17.8	2.2	0.028
From maintenance once every 3 days to no maintenance	7.0	− 22.5 to 36.6	0.5	0.617	2.4	− 7.6 to 12.4	0.5	0.617

EMO early-morning OFF time, *MAR* maximum acceptable risk, *ONwoTD* ON time without troublesome dyskinesia, *ROA* route of administration

[a]85 and 19 were the largest risk of mild-to-moderate skin reactions and of severe side effects requiring hospitalization variation value included in the survey. As the estimated MAR was greater than 100, we can assume the respondents would accept any level of risk for this improvement

[b]Significantly different from zero at 95% confidence level

[c]Disordered improvement in attribute levels. The level transitions EMO from 7 to 3 times a week

[d]Disordered improvement in attribute levels. Frequency of pill regimen from no need to take pills to pills taken 4 times in a day

Minimum Acceptable Benefit

Table 4 presents the MAB in terms of additional ONwoTD hours to accept a less preferred ROA, EMO time, pill regimen, and device maintenance frequency. On the basis of the preferences elicited, all else being equal on average, PwP would require more than 10 additional daily hours of ONwoTD (starting from the lowest level of 3 h) to accept either a change from pills to electrostimulation or from pills to surgical infusion. However, PwP would only require two additional daily hours of ONwoTD to accept a change from pills to a nonsurgical infusion. On average, PwP would require more than 10 additional daily hours of ONwoTD (starting from a baseline of 3 h) to accept EMO occurring more frequently, more burdensome pill regimen, and higher device maintenance frequency.

Direct Elicitation Questions

Respondents preferred hypothetical treatment A (subcutaneous) over treatment B (oral therapy) (49.34% vs. 41.45%), with a small proportion opting for neither (9.21%).

When adding the sleep problems attribute, we observed an increased preference for treatment A (60.53%) compared with treatment B (25.00%). This change was likely driven by the additional consideration of sleep problems, which occur occasionally with treatment A and very often with treatment B. However, more people chose "Neither" compared with the first elicitation question. Figure S2 in the Supplementary Materials presents the responses to the direct elicitation exercise adding a sleep problems attribute. The Fisher and the Wilcoxon tests found no significant difference in response distributions between the two

Table 4 Minimum acceptable benefit in terms of additional ON time without troublesome dyskinesia hours from 3 (minimum level) to accept a change in the route of administration (ROA), in early-morning off (EMO) time, pill regimen, and device maintenance frequency

Expression	Value	Robust SE	95% CI	t-ratio (0)
ROA				
From pills to nonsurgical infusion	2.0	0.80	0.42–3.58	2.44
From pills to surgical infusion	> 10	–		–
From pills to electrostimulation	> 10	–		–
From nonsurgical infusion to surgical infusion	4.9	1.20	2.58–7.22	4.09
From nonsurgical infusion to electrostimulation	9.0	4.39	0.38–17.62	2.05
From surgical infusion to electrostimulation	1.3	0.52	0.28–2.32	2.52
EMO time frequency				
From occasionally (once a week) to sometimes (3 times a week) of EMO time	> 10	–	–	–
Pill regimen frequency				
From 4 times a day to 8 times a day	> 10	–	–	–
Device maintenance frequency				
From once every 3 days to once per day	> 10	–	–	–
From none to once every 3 days	8.38	1.59	5.27–11.49	5.27

CI confidence interval, *EMO* early-morning OFF time, *ROA* route of administration, *SE* standard error

choice tasks (Table S7 in the Supplementary Materials).

Predicted Choice Probabilities

Figure 4 presents the predicted choice probabilities across five pairwise choice scenarios in which the EMO, risk of severe side effects, frequency of pill regimen and device maintenance attributes were held constant across alternatives. This approach ensured that preferences were assessed under equal conditions, isolating the impact of ONwoTD and ROA. Please note that these choice probabilities were predicted based on the RPL model output, and were not directly elicited from the participants. Therefore, results are conditional to the assumptions, the construction of the scenarios, and the survey design. In scenario 1, alternative B (6 h of ONwoTD) was strongly preferred over alternative A (3 h of ONwoTD, keeping all else equal), receiving the vast majority of predicted choices (84% vs. 16%). This suggests that participants placed high value on extended ONwoTD.

In scenario 2, where both alternatives offered 6 h of ONwoTD but alternative B required a electrostimulation device, alternative A (infusion without surgery) was preferred (95% vs. 5%). In scenario 3, alternative B consisted of surgical infusion, and alternative A (infusion without surgery) was also preferred (89% vs. 11%). This indicates that, while ONwoTD was an important factor, participants were less willing to accept a treatment requiring brain or stomach surgery when a nonsurgical option with equivalent efficacy and safety was available.

In scenario 4, alternative A (6 h of ONwoTD, infusion without surgery) was overwhelmingly favored (98% vs. 2%) compared to B (3 h of ONwoTD, infusion with surgery), confirming

	Scenario 1		Scenario 2		Scenario 3		Scenario 4		Scenario 5	
	Alternative A	Alternative B	Alternative A	Alternative B	Alternative A	Alternative B	Alternative A	Alternative B	Alternative A	Alternative B
ONwoTD	3 hours	6 hours	6 hours	6 hours	6 hours	6 hours	6 hours	3 hours	6 hours	3 hours
Early Morning OFF Time	3 days	3 days	3 days	3 days	3 days	3 days	3 days	3 days	3 days	3 days
Risk of Mild Skin Reaction	30%	30%	30%	30%	30%	30%	30%	30%	60%	30%
Risk of Severe Side Effects	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
ROA	Infusion (without surgery)	Infusion (without surgery)	Infusion (without surgery)	Electro stimulation	Infusion (without surgery)	Infusion (with surgery)	Infusion (without surgery)	Infusion (with surgery)	Infusion (without surgery)	Infusion (with surgery)
Frequency of Pill Regimen	4 times per day	4 times per day	4 times per day	4 times per day	4 times per day	4 times per day	4 times per day	4 times per day	4 times per day	4 times per day
Device Maintenance	No maintenance	No maintenance	No maintenance	No maintenance	No maintenance	No maintenance	No maintenance	No maintenance	No maintenance	No maintenance

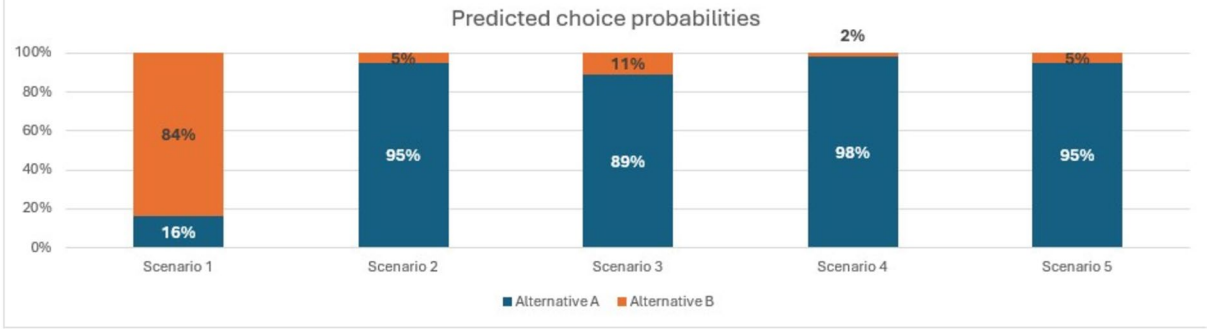

Fig. 4 Predicted choice probabilities (profiles and outcomes). *ONwoTD* ON time without troublesome dyskinesia, *ROA* route of administration

that improved efficacy and non-invasive treatment option drive treatment preferences.

In scenario 5, with the risk of having skin reactions increased from 30% to 60% in alternative A compared with scenario 4, alternative A would be still preferred over B (95% vs. 5%).

Subgroup Analysis

Subgroup analyses (Tables S8–S25 and Figs. S3–S14 in the Supplementary Materials) revealed varying preferences across different participant characteristics. ONwoTD was statistically more important in the UK/Germany group than in the US one (RI 31.4 vs. 19.9). In the USA, ROA was viewed twice as important as ONwoTD (RI 37.2 vs. 19.9). US respondents also valued the risk of skin reactions more than their UK/Germany counterparts (RI 15.5 vs. 8.5). Both subsamples showed willingness to accept the highest risk of skin reactions (90%) for switching to a less invasive ROA. Both groups would consider switching from oral pills to nonsurgical infusion for a gain of two additional ONwoTD hours (considering 3 h of ONwoTD as the starting point).

Participants taking more than 5 pills a day prioritized ONwoTD (RI 27.3) more than those taking fewer pills (RI 23.1), with no differences in other attributes. Participants taking fewer than 5 pills a day were willing to accept a higher risk of skin reactions in exchange for additional ONwoTD hours and a lower EMO frequency than the high pill regimen group.

CPs valued ONwoTD (RI 35.8) significantly more than PwP (RI 22.8), while PwP prioritized minimizing risks of skin reactions compared with CPs (RI 14.6 vs 6.9). CPs were willing to accept any risk of mild-to-moderate skin reactions (within the range included in the survey) to have gains in ONwoTD and EMO, and to switch from nonsurgical infusion to oral pills.

Younger participants placed slightly more importance on ROA (RI 37.8 vs 34.3), while older participants prioritized ONwoTD (RI 29.4 vs 23.5). Older participants were willing to switch from oral pills to nonsurgical infusion for less than one additional hour of ONwoTD, while younger participants would require almost eight

additional hours of ONwoTD to accept the same change. Older participants were willing to accept a higher risk of skin reactions to gain hours of ONwoTD. No significant differences were found in the OFF time hours subgroup.

When comparing preferences between the sample consisting of participants with current or past experience with DATs and the total sample, no major differences were observed. In fact, the preference weights across all levels were not statistically different between samples (Figs. S15–S16 in the Supplementary Materials).

DISCUSSION

This study elicited preferences of PwP and CPs of PwP for aPD treatment options. By employing a DCE, we sought to understand the CRI of various treatment attributes, such as hours of ONwoTD, frequency of EMO time, risk of mild-to-moderate skin reactions, risk of severe side effects requiring hospitalization, ROA, pill regimen, and device maintenance frequency. We found that PwP and CPs prioritized ROA, with a clear preference for nonsurgical options (oral pills and subcutaneous infusion devices) over surgical options (infusion devices requiring gastric surgery and electrostimulation). This aligns with findings from previous studies, which often showed a preference for noninvasive ROAs—including oral, sublingual, and inhaled options—over more invasive procedures (intraduodenal pump, electrostimulation) [10, 11, 14, 20, 25]. These preferences likely reflect a desire to minimize surgical risks, avoid recovery burdens, and reduce the (perceived) complexity of certain treatments. Some studies have documented that the real-world uptake of DATs remains low, despite their potential benefits [44, 45]. The emergence of less invasive options, such as subcutaneous infusions, offers promising alternatives. Ensuring that PwP are informed about these nonsurgical options, particularly when oral medications become less effective, is crucial.

ONwoTD was consistently prioritized in prior PD preference studies [8, 10, 11, 16, 18, 19], and emerged as the second most important attribute in this study. Improvements in ONwoTD were highly valued; however, the utility gained from each additional hour of ONwoTD diminished with increasing duration, suggesting diminishing utility returns beyond a certain threshold. This pattern likely reflects that PwP assign the greatest value to achieving enough ONwoTD to complete essential daily activities—like personal care, meals, or light exercise—rather than maximizing ONwoTD beyond functional needs. In addition, PwP experiencing only 3 h of ONwoTD—often due to narrowing of the therapeutic window on oral medications over time—may be more willing to switch to subcutaneous infusions, as their utility gain would be higher.

The two risks included in the survey based on the literature and qualitative interviews (namely risk of mild-to-moderate skin reaction and severe side effects requiring hospitalization) were important to respondents, but secondary to efficacy and ROA (and specifically avoiding surgery), with participants willing to accept certain risks for improving these outcomes. This aligns with other preference studies [8, 16, 19] demonstrating that PwP were willing to tolerate significant risks—such as depression, anxiety, diarrhea, and brain hemorrhage—for more daily ONwoTD. These findings highlight that for many PwP, the burden of PD symptoms may outweigh concerns about treatment side effects. However, this should be approached with caution. In our study, only two safety-related attributes were included—selected based on qualitative interviews, and common adverse events reported in clinical trials—while other risks were held constant (and not directly included in the design). This simplification, also needed considering the target population and the already complex study design, may underrepresent the weight of other severe complications in real-world decisions and should be considered a limitation.

Consistent with prior research [8, 18], PwP in our study preferred less frequent pill regimens and lower device maintenance. While taking pills up to four times daily was acceptable, eight times per day was significantly less preferred, indicating a threshold beyond which medication regimens may become too burdensome. In addition, findings from the pill regimen subgroup

analysis suggest that as pill burden increases, PwP may become more focused on gaining additional efficacy benefits. Device maintenance frequency also played a role in shaping preferences. Compared to other DATs such as DBS, infusion therapies—particularly subcutaneous infusions—require more frequent handling and hygienic procedures to ensure proper administration and prevent local complications. This added burden may influence real-world acceptability and adherence, especially among patients with limited dexterity or caregiver support.

EMO was reported to be highly prevalent, which also emerged as a concern for PwP. Existing literature shows that the therapeutic effect of oral medications often wanes overnight, leaving PwP to wake up in a debilitated OFF state, which delays or impairs their ability to initiate morning activities such as getting out of bed, dressing, and eating [46, 47]. PwP in our study preferred treatments that reduced the frequency of EMO episodes. This underscores the value of considering therapies that provide 24-h continuous dopaminergic stimulation, maintaining therapeutic levels overnight, such as subcutaneous infusions of foslevodopa/foscarbidopa or apomorphine formulations [5, 48–50] and levodopa/carbidopa intestinal gel [51–53].

Sleep-related data were included to explore whether overnight symptom control—particularly through continuous infusion therapies—might influence treatment preferences in aPD. Although sleep disturbance was numerically less influential in decision-making, its high prevalence among PwP highlights its potential importance. In our study, most PwP reported experiencing sleep problems more than two nights/week. When faced between two hypothetical treatments, PwP preferences shifted toward treatments that minimized sleep disturbances.

CPs acted as proxies, reflecting their perception of PwP preferences rather than direct PwP input. CP-reported PwP demographics suggested an older, more advanced PD population with more OFF time, indicating greater dependency. These likely influenced preferences: CPs placed greater importance on increased ONwoTD than PwP (RI 35.8 vs. 22.8) and showed more willingness to accept risks, such as skin reactions, in exchange for improvements in ONwoTD and EMO, and to switch from nonsurgical infusion to oral pills. In contrast, PwP prioritized minimizing skin reaction risks (RI 14.6 vs. 6.9). These findings highlight CPs' supportive role in treatment management and suggest that their perspectives may be valuable to consider alongside PwP preferences in shared decision-making.

This study has some limitations. As in many similar studies, the data collected were based on responses to hypothetical choice profiles and might not fully reflect actual real-world decisions; thus, differences can arise between stated and actual choices. Real-life factors such as cost, side effects, access, and daily use burden may or may not be fully known to respondents. The marginal rate of substitution derived from the DCE—i.e., the MAB or MAR—should not be interpreted as values reflecting clinically attainable or realistic treatment outcomes. These values are derived from the preference-elicitation model, and are conditional to the assumptions underlying the selection and definition of attributes and levels, as well as on the structure of the experimental design. In these settings, MAB and MAR represent how respondents traded off attribute levels within the hypothetical scenarios they were presented with in the survey, not what they would expect to receive or achieve in real-world clinical practice. These results are intended as a starting point for discussion among clinical experts, policymakers, regulators, payers, and patients. Interpretation of MAR estimates also warrants caution. In several cases, the estimated MAR exceeded the highest increase in risk level presented in the survey (i.e., 85% for skin reaction and 19% for severe adverse event). While this suggests a strong willingness to accept high risk for certain improvements, it does not imply that respondents would accept any level of risk. In this experiment we only tested MAR within the risk ranges included in the survey (i.e., between 5% and 90% for the risk of mild-to-moderate skin reaction and between 1% and 20% for the risk of severe side effects requiring hospitalization). Therefore, results should be interpreted as indicative of high risk tolerance within the tested range, rather than an unqualified acceptance of any risk. High MAR values should be understood as indicating strong preference for less invasive options within the risk ranges tested, rather than tolerance for risks

beyond what is clinically plausible. In addition, the attribute describing 'mild-to-moderate skin reactions' condensed the range of dermatological complications, and should be interpreted as a simplified representation designed for preference elicitation, not as a comprehensive depiction of real-world clinical experience. Notably, the two safety attributes were selected to reflect different types of adverse events—namely, a high-probability but generally low-impact event (mild-to-moderate skin reactions) and a low-probability but potentially high-impact event (severe side effects requiring hospitalization). This conceptual distinction was intentional to support respondents in making meaningful trade-offs during the preference tasks; however, it also represents a simplification of the broader safety profiles of aPD therapies. In real-world clinical practice, the nature, severity, and cumulative burden of adverse events may differ from the simplified way these two risks were operationalized within the survey design. We did not assess cultural or healthcare system factors (e.g., access to DATs by country) due to sample size constraints. Future studies should examine these influences using larger, country-specific samples. The online survey administration may have introduced selection bias, as individuals without internet access or familiarity with digital platforms were not included. The sample was predominantly white, highly educated, and younger than expected based on real-world epidemiology, which limits the generalizability of the findings. Recall bias is another potential concern, as participants self-reported disease and treatment history, potentially leading to inaccuracies in the data. Diagnosis of PD was self-reported and not clinically verified, which may introduce uncertainty in participant eligibility. Inclusion criteria aimed to approximate aPD, but misclassification is possible, especially among CPs responding as proxies. Additionally, potential confusion between correlated attributes—EMO and ONwoTD—may have introduced noise and resulted in disordered levels (from 7 days a week to 3 days a week of EMO), although no concerns were raised during qualitative interviews and pretesting. Since ONwoTD and EMO both relate to motor symptom control and daily functioning, respondents may have interpreted them as partially redundant or conflated their meanings during the choice tasks.

Despite these limitations, this study has significant strengths in the methodology adopted, which adhered to best practice recommendations by ISPOR [37, 43, 54, 55], ensuring rigor and relevance. Extensive qualitative research involving PwP and CPs informed the development of attributes that reflected real-world experiences, enhancing the study's validity [35, 56, 57]. Pretesting of the survey through cognitive interviews further improved clarity and comprehension, minimizing potential sources of confusion and strengthening the reliability of the data [58].

Future research should explore how prior experience with specific therapies, such as infusion devices or surgical interventions, may shape preferences. Individuals with positive outcomes (e.g., improved symptom control) may express greater openness to similar treatments, whereas those who experienced complications (e.g., skin reactions or infections) may be more hesitant. Understanding how lived experiences influence trade-offs and risk tolerance could help tailor treatment discussions and improve shared decision-making in aPD. By continuing to prioritize PwP preferences, we can develop more effective and personalized treatment strategies for aPD, ultimately improving PwP outcomes and quality of life. However, identifying preferences alone is not sufficient; physicians must also act on them by appropriately referring patients for advanced therapies when indicated. Tools such as MANAGE-PD can support healthcare providers in recognizing patients inadequately controlled on oral medication and in need of timely referral [59]. In addition, digital solutions like MY PD-CARE can further facilitate preference-sensitive care by enhancing communication and symptom tracking [60]. Together, these approaches can help ensure that patient preferences translate into actionable treatment decisions in clinical practice.

CONCLUSION

This study highlights that PwP and CPs prioritize treatment efficacy—specifically, increased ONwoTD—and ROA, with a clear preference for nonsurgical options. These findings underscore the importance of incorporating PwP and

CP preferences into treatment discussions, particularly when considering transitions from oral therapies to DATs. Notably, CPs acting as proxies, emphasized the value of including their perspectives in shared decision-making. To support informed and personalized care, healthcare professionals should provide comprehensive education that addresses both patient and CP priorities, especially when evaluating more complex or invasive treatment options. Incorporating PwP preferences into care decisions fosters more personalized treatments for aPD and contributes to better outcomes and quality of life.

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Data Availability. AbbVie studies that are available for data sharing are listed on Vivli. Data requestors should use the Vivli Data Request Form to request data package(s). Access to data is determined based on the business feasibility to support the request and the scientific merit of the research proposal.

Declarations

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Ethical Approval. Centralized ethics approval was obtained from SALUS IRB, USA, on 20 September 2023 (Reference number 21091). All procedures in this study followed the guidelines outlined in the Declaration of Helsinki (1964) and its later amendments, along with good clinical practice of the International Council for Harmonisation. All subjects provided informed consent to participate in the study.

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