CMRO 12
Current Medical Research & Opinion

Taylor & Francis
Taylor & Francis Group

Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: https://www.tandfonline.com/loi/icmo20

Developing consensus among movement disorder specialists on clinical indicators for identification and management of advanced Parkinson's disease: a multi-country Delphi-panel approach

Angelo Antonini, A. Jon Stoessl, Leah S. Kleinman, Anne M. Skalicky, Thomas S. Marshall, Kavita R. Sail, Koray Onuk & Per Lars Anders Odin

To cite this article: Angelo Antonini, A. Jon Stoessl, Leah S. Kleinman, Anne M. Skalicky, Thomas S. Marshall, Kavita R. Sail, Koray Onuk & Per Lars Anders Odin (2018) Developing consensus among movement disorder specialists on clinical indicators for identification and management of advanced Parkinson's disease: a multi-country Delphi-panel approach, Current Medical Research and Opinion, 34:12, 2063-2073, DOI: 10.1080/03007995.2018.1502165

To link to this article: https://doi.org/10.1080/03007995.2018.1502165

Accepted author version posted online: 17 Jul 2018.
Published online: 20 Aug 2018.

CURRENT MEDICAL RESEARCH AND OPINION
2018, VOL. 34, NO. 12, 2063–2073
https://doi.org/10.1080/03007995.2018.1502165
Article FT-0310.R1/1502165

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Developing consensus among movement disorder specialists on clinical indicators for identification and management of advanced Parkinson's disease: a multi-country Delphi-panel approach

Angelo Antonini[a], A. Jon Stoessl[b], Leah S. Kleinman[c], Anne M. Skalicky[c], Thomas S. Marshall[d], Kavita R. Sail[d], Koray Onuk[d] and Per Lars Anders Odin[e,f]

[a]Department of Neuroscience, University of Padua, Padova, Italy; [b]Pacific Parkinson's Research Centre, Vancouver, BC, Canada; [c]Evidera, Bethesda, MD, USA; [d]AbbVie, North Chicago, IL, USA; [e]Department of Neurology, Lund University, Skåne University Hospital, Lund Sweden; [f]Klinikum-Bremerhaven, Bremerhaven, Germany

ABSTRACT

Background: Lack of a global consensus on the definition of advanced Parkinson's disease (APD) and considerations for timing of device-aided therapies may result in heterogeneity in care.

Objectives: To reach consensus among movement disorder specialists regarding key patient characteristics indicating transition to APD and guiding appropriate use of device-aided therapies in the management of PD symptoms.

Methods: A Delphi-panel approach was utilized to synthesize opinions of movement disorder specialists and build consensus.

Results: A panel was comprised of movement disorder specialists from 10 European countries with extensive experience of treating PD patients (mean $=24.8 \pm 7.2$ years). Consensus on indicators of suspected APD and eligibility for device-aided therapies were based on motor symptoms, non-motor symptoms, and functional impairments. Key indicators of APD included: (i) motor—moderate troublesome motor fluctuations, $\geq$1 h of troublesome dyskinesia/day, $\geq$2 h "off" symptoms/day, and $\geq$5-times oral levodopa doses/day; (ii) non-motor—mild dementia, and non-transitory troublesome hallucinations; (iii) functional impairment—repeated falls despite optimal treatment, and difficulty with activities of daily living. Patients with good levodopa response, good cognition, and $<$70 years of age were deemed as good candidates for all three device-aided therapies. Patients with troublesome dyskinesia were considered good candidates for both levodopa-carbidopa intestinal gel and Deep Brain Stimulation (DBS). PD patients with levodopa-resistant tremor were considered good candidates for DBS.

Conclusion: Identifying patients progressing to APD and suitable for device-aided therapies will enable general neurologists to assess the need for referral to movement disorder specialists and improve the quality of care and patient outcomes.

ARTICLE HISTORY
Received 14 May 2018
Revised 5 July 2018
Accepted 6 July 2018

KEYWORDS
Parkinson disease; Delphi technique; Patient identification; Motor fluctuations; Wearing-off; Dyskinesia; Levodopa-Carbidopa Intestinal Gel (LCIG); Deep brain stimulation (DBS); Continuous subcutaneous apomorphine infusion (CSAI)

Introduction

Effective management of Parkinson's disease (PD) at all stages requires individual customization of therapy as the disease progresses[1]. In the absence of cures or disease-modification therapies, oral therapies of levodopa-carbidopa administered with or without combination with dopamine agonists, Catechol-O-Methyl-Transferase (COMT) inhibitors, and Monoamine oxidase B (MAOB) inhibitors are used for symptom management[2,3]. However, advancing disease stage is generally associated with the development of potentially disabling motor complications (such as motor fluctuations and dyskinesia) and a narrowing therapeutic window, rendering additional limitation in the effectiveness of oral therapies[4,5]. Attempts have been made to chart the clinical progression of PD and define appropriate treatment and severity milestones[6]. As PD progresses, patients may become increasingly dependent on caregivers, and disability is dominated by motor symptoms (MS) and non-motor symptoms (NMS) that may be resistant to dopaminergic mediation and/or oral administration of medications[2,7–9]. Management of advanced PD (APD) symptoms, particularly motor fluctuations, dyskinesia and off-time, may require optimizing of oral therapies (including polypharmacy, dose fractioning, and dose tapering) or the use of advanced therapies such as deep brain stimulation (DBS), continuous subcutaneous apomorphine infusion (CSAI), or levodopa-carbidopa intestinal gel (LCIG) infusion[1,10–12]. Having reached a more severe stage of PD does not necessarily mean that a patient is suitable for advanced therapies; rather, patients suitable for advanced therapies are a sub-group of all PD patients. Gaps in clinical knowledge exist about when the various treatments should be initiated and what therapies are most suitable as the disease progresses to advanced stage[8,13,14].

One of the challenges in appropriate timing to optimize therapies for symptom control is the absence of a biomarker,

CONTACT Angelo Antonini angelo3000@yahoo.com Department of Neuroscience, University of Padua, Via Giustiniani 3, Padua, Italy

diagnostic test, or gold standard index resulting in no clear consensus on how to define the stage of advanced PD[11,15,16]. The lack of a unified disease progression understanding may result in heterogeneity in care. Recent attempts to determine the severity of chronic disease using objective markers have been elusive[15]. Uni- and multi-dimensional scales have been developed and validated for measuring the disease progression, but the link between scores on the scales and management is not always clear. For example, in clinical settings and clinical trials, the Hoehn and Yahr (H&Y) scale[12] is commonly used to classify a PD patient by disease progression based on disability; ranging from Stage 0 (no signs of disease) to Stage 5 (wheelchair-bound or bedridden, unless assisted)[17]. However, because of its focus on postural instability, H&Y captures neither motor fluctuations nor NMS, two key elements for understanding disease progression and the need of therapy optimization. Similarly, while the Unified Parkinson's Disease Rating Scale (UPDRS) was developed to determine levels of disease severity and has a more comprehensive assessment of PD symptoms[18], it has been acknowledged that linking UPDRS motor scores to a severity stage with precision may require a higher level of clinical expertise like movement disorder specialists[15]. In addition to simplicity, another key consideration for regular clinical practice by general neurologists and movement disorder specialists alike is the need for brevity due to busy clinical workflows.

Given the lack of instruments linked to treatment management, developing indicators for clinical staging is important for routine clinical practice, especially since many PD patients are not seen by movement disorder specialists until later in the disease. Guidance is also lacking on the timing and use of device-aided therapies and when oral/transdermal medications are no longer effectively controlling symptoms[4,19–21]. Identifying the most appropriate management approach for patients in the advancing stage of PD is critical in providing improved health-related quality-of-life and stabilizing symptoms. The current study was aimed to achieve consensus among movement disorder specialists treating PD patients with regard to the following objectives: (i) identify the clinically important indicators that define APD, (ii) identify patient characteristics that indicate eligibility for device-aided therapy options in PD, and (iii) identify an appropriate patient profile for different device-aided therapy options in PD: CSAI, DBS, and LCIG. Identifying key indicators of patients transitioning to APD or with suspected APD is important for timely referral and intervention[4,8,22–24].

Our study adds to recent emerging literature which aims to generate consensus around identifying key symptoms of APD, and identifying indicators of when oral/transdermal medications are no longer effectively controlling symptoms to aid in practical management of the APD patients in clinical practice[4,16].

Methods

Study design

A modified Delphi study was conducted with a panel of movement disorder specialists. The Delphi methodology was selected as the approach for this study given the large body of published evidence of the use of Delphi methods in clinical practice and health research to explore topics in healthcare that have not been previously examined[25–27]. The Delphi is an iterative, structured consensus process which allows for eliciting and refining the opinions of a group[28]. The Delphi process has been widely used for achieving convergence of opinion from a panel of experts[29]. Consensus methods have been used previously in PD in the NAVIGATE-PD study[4] and the Spanish CEPA study[16], both of which used a modified approach to generate consensus.

For this study, the modified Delphi process consisted of four stages (Figure 1). Panelists were assigned a unique anonymous identifier and provided with an individualized web survey link (Delphi Round 1 and 2). Stage 1 involved

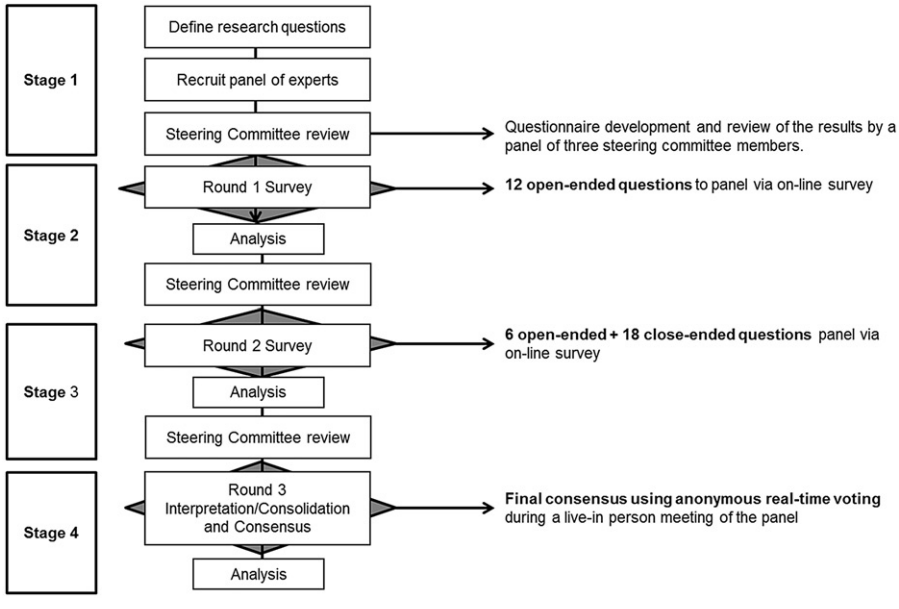

Figure 1. Delphi review process.

the recruitment of the Delphi panelists. In Stages 2 and 3 (the first two rounds of the Delphi consensus process), an anonymous web-based questionnaire was administered to the Delphi panelists. Stage 4 (Delphi Round 3) involved an in-person meeting to facilitate achievement of consensus through discussion, followed by anonymous, aggregated polling data and ranking activity. It is expected, during the Delphi process, that the group will converge more and more closely on consensus[30].

Stage 1: Recruitment of Delphi panelists

Leading movement disorder specialists from 10 EU countries (Austria, Belgium, Denmark, Germany, Italy, Netherlands, Norway, Spain, Sweden, and the UK) were recruited for this study. Per standard recommended practices, a sample of 10–15 panelists is considered sufficient if the background or expertise of the Delphi subjects is homogenous[31]. Panelists were chosen based on their recognized clinical expertise treating PD patients, breadth and depth of APD research, as well as their experience with the use of device-aided therapies for the treatment of APD patients. Movement disorder specialists rather than general neurologists or non-MD clinicians were chosen for this study because of their enhanced understanding of PD disease progression, their specialization in managing PD patients across the disease spectrum, and practical clinical experiences with the use of orals and device-aided therapies for the treatment of PD. A steering committee consisting of three senior movement disorder specialists provided clinical input into the development of each round of the Delphi survey questions and interpretation of the findings. Members of the steering committee and panelists were provided an honorarium for their participation in the Delphi study.

Stage 2: Round 1 Delphi survey

The Round 1 web-survey consisted of 12 open-ended questions designed to ascertain panelist opinion of attributes important in (i) identifying patients suspected to have APD, (ii) determining which patients are suitable for device-aided therapies, and (iii) selecting the appropriate device-aided therapies for patients. Questions were pre-tested by the study team with the Steering Committee for comprehension and feasibility for use as an online survey. An open-ended qualitative approach was taken in Round 1 to avoid pre-specifying indicators for consideration. In addition, general demographic and clinical practice information was requested from the panelists.

Stage 3: Round 2 Delphi survey

The Round 2 web-survey was based on Round 1 findings and consisted of a combination of six open-ended and 18 closed-ended questions (two of the 18 close-ended questions had multiple sub-questions) focused on documenting preliminary consensus on responses from Round 1 pertaining to motor, non-motor, and functional indicators of progression to APD. Round-2 and Round-3 questions are identical, except where noted in Table 3. A 4-point response scale was used for close-ended questions. Panelists were asked whether individual or combinations of indicators needed to be present to consider eligibility for device-aided treatment. Data on the survey questions were analyzed and were presented. The Round 2 Delphi survey also identified areas of agreement and levels of consensus regarding patient indicators for specific device-aided therapy and contraindications for device-aided therapies. As a final activity, panelists were asked to rank the most clinically relevant indicators per MS, NMS, and FI domain for suspected APD.

Stage 4: Round 3 Delphi meeting

An in-person meeting was conducted for Round 3 to facilitate interactive discussion before reaching final consensus. At the outset of the meeting, consensus definitions of terms pertaining to disease severity (e.g. mild, moderate, severe) or descriptions of the symptom(s) was established. The survey questions and responses from Round 2 were reviewed. The Round 3 consensus vote was conducted utilizing real-time, live, anonymous polling devices. At the conclusion of the polling exercise, panelists were asked to rank in order of clinical importance the indicators which had achieved consensus within three individual groups of symptoms: MS, NMS, and functional impacts.

Data analysis

Round 1 open-ended survey questions were categorized to allow for both qualitative and quantitative analysis. For Rounds 2 and 3, a priori definitions were used to determine different levels of reaching consensus: (i) consensus, (ii) combined consensus, (iii) nearing consensus, and (iv) no consensus (Table 1) on questions for indicators of suspected APD and patients eligible for device-aided treatment. Determination of consensus in a Delphi panel has been handled in a variety of ways, and depends on the nature of the questions and potential responses[31]. Setting an a priori percentage level for inclusion of items is common, although the determination of the level varies from study to study[27]. For this study, consensus in Rounds 2 and 3 was pre-defined as $\geq$70% agreement among the panelists on several types of 4-point numeric rating scale. A 70% level both provides the ability to interpret the results and has been used successfully in other Delphi panels[32].

Measures of central tendency (mean, median, and mode) and amount of dispersion (standard deviation [SD]) were calculated to examine the information concerning the collective judgments of the panelists. For categorical variables with ordinal or interval responses, the percentages of responses were examined to determine consensus level on single and combined responses[29]. For the ranking exercise, the mean rank was determined for each indicator.

Results

Stage 1: Panelist demographics

A total of 17 leading movement disorder specialists participated in the Delphi panel between February 2014 and January 2015; 15 (88%) participated in all three rounds. One panelist withdrew after the first round, and a second was not available to attend Round-3 in-person meeting. The panel included movement disorder specialists with extensive experience in treating patients across the PD severity spectrum based on: (i) the number of years working with PD patients [mean (SD) = 23.9 ± 6.4 years; median (range) = 25 (14–32) years], (ii) number of PD patients treated in their practice [mean (SD) = 84.7 ± 53.7 per month; median (range) = 80 (30–250) per month], (iii) the distribution of patients across PD severity, and (iv) the proportion of PD patients who are candidates for device-aided therapies (Table 2).

Stage 2: Round 1 survey

Nominations were made by the panelists of important attributes for indicators for advancing PD, good candidates and contra-indications for device-aided therapies. Panelists reported that, in general, PD progression could be staged based on: (a) MS including "wearing off", "on and off" periods, motor fluctuations, and dyskinesia; (b) NMS like cognitive impairment; and (c) functional status impairment, including the ability to perform activities of daily living (ADLs).

Identifying patients suspected to have APD

Panelists reported the need to evaluate a patient's response to oral treatment when considering the severity of a patient's disease. A unanimous view emerged on dyskinesia and motor features during "on/off periods", which were considered as critical indicators of symptom control by oral medications. The panelists reported that a patient could be suspected to have APD based on worsening MS (including tremors, dyskinesia) and NMS (including gait problems, cognitive function, depression, and apathy). MS and NMS appearing in later stages of PD included dementia, postural instability/rigidity, dyskinesia, off-time, speech problems, freezing of gait, repeated falls, non-transitory, troublesome hallucinations, and psychosis. The worsening of symptoms may impact the ability to independently perform ADLs.

Identifying patient characteristics that indicate eligibility for device-aided therapy options in APD. Overall, panelists reported MS as the most important characteristic for assessment of how well oral medications are controlling PD. DBS, LCIG, and CSAI were considered by panelists as the main options for device-aided treatment. Dyskinesia (71%), wearing on/off periods (76%), motor fluctuations despite optimal treatment (47%), freezing gait (35%), repeated falls (24%), and dystonia with pain, postural instability, and unresponsive tremors (18%) were reported as potential indicators which may be suitable for device-aided therapies. More than two-thirds (69%) of panelists consider the presence of Impulse Control Disorders (ICDs) and hallucinations as important NMSs for assessing the efficacy of oral medication therapy. About one third of the panelists viewed the degree of severity of ICDs, depression, and cognitive status as important clinical information for assessing the device-aided treatment decision-making. Lack of caregiver or family support (75%), level of support in a nursing care facility (24%), cost (17%), the patients' ability to travel to a treatment center for follow-up visits (17%), or whether a patient is still working (12%) were factors reported by panelists when considering recommending a patient for device-aided therapies (data not shown).

Table 1. Types of consensus.

Type of consensus	Definition
Consensus	≥70% of the panelists selecting a single option
Combined Consensus	≥70% of the panelists selecting two ordinal or interval responses that conceptually could be aggregated
Nearing consensus	60–69% of panelists selecting a single option
No consensus	≤59% of panelists selecting a single response option

Identifying patient profiles for different device-aided therapies

Key considerations for choosing the appropriate device-aided therapy in eligible patients included clinical MS like dyskinesia, levodopa-response, tremor, and NMS like impulse control disorders (ICDs), pain, and cognition. The panelists also identified additional patient characteristics like patient age, social and physical activity, and caregiver or nurse support as being important considerations in choosing the appropriate device-aided therapy (data not shown).

Stage 3: Round 2 survey

Results from the Round 2 survey provided a preliminary assessment of the level of consensus amongst the panelists on indicators for suspected APD and for device-aided therapies, as well as for selection of the appropriate device-aided therapy for eligible patients. Additional levels of specificity were added to the indicators identified in Stage 1 (e.g. moderate levels of motor fluctuations, 2–4 h of waking day with

Table 2. Characteristics of movement disorder specialist Delphi panelists.

Characteristic	*n* (%)
% male	10 (59%)
Delphi round	
Round 1	17 (100%)
Round 2	16 (94%)
Round 3	15 (88%)
Years working with PD patients	
Mean (SD)	23.9 ± 6.4
Median (range)	25 (14–32)
PD patients treated per month	
Mean (SD)	84.7 ± 53.70
Median (range)	80 (30–250)
Proportion of PD stages of patients seen in clinical practice	
Early-stage PD patients, Mean % (range)	21% (5–40%)
Mid-stage PD patients, Mean % (range)	43% (10–80%)
Late-stage PD patients, Mean % (range)	36% (10–85%)
Proportion of PD patients candidates for advanced therapies	
Oral medications	59% (10–85%)
Deep brain stimulation	19% (1–50%)
Apomorphine infusion	9% (0–30%)
Levodopa/carbidopa intestinal gel	13% (5–30%)

Abbreviations. PD, Parkinson's disease; SD, standard deviation.

Table 3. Round 3 final results on indicators for suspected APD.

Question ($n = 22$)[a,b]	Domain	Consensus result (total questions)		
		Final Round 3 result[c]	Consensus	Clinically important (Yes/No)
Does troublesome dysphagia make you suspect APD?	MS	Definite	93%	Yes[h]
For optimally treated patients, how many hours of the waking day with "off" symptoms indicate a patient is suspected to have APD?	MS	At least 2 h	86%	Yes[h]
In your opinion, how many hours of the day with troublesome dyskinesia indicate a patient is suspected to have APD?	MS	At least 1 h	84%	Yes[h]
What level of troublesome motor fluctuations indicates a patient is suspected to have APD?	MS	Moderate	81%	Yes[h]
What is the frequency of daily oral levodopa dosing that indicates suspected to have APD?	MS	At least 5-times/day	79%	Yes[h]
Does a good "on" response to medication indicate a stable stage of PD?	MS	Yes	79%	No
For optimally treated patients, what level of troublesome dyskinesia indicates that a patient is suspected to have APD?	MS	Moderate	77%	Yes[h]
What is the frequency (in hours) of "off" symptoms that indicates that a patient is suspected to have APD?	MS	Every 3 h	75%	Yes[f]
Would non-transitory troublesome hallucinations make you suspect APD?	NMS	Presence	100%	Yes[h]
What level of non-transitory psychosis indicates that a patient is suspected to have APD?	NMS	Mild-to-moderate	94%	Yes[h]
What level of dementia indicates that a patient is suspected to have APD?	NMS	Mild	86%	Yes[h]
What level of night-time sleep disturbances[d] indicate a patient is suspected to have APD?	NMS	Moderate	81%	Yes[h]
What level of apathy indicates that a patient is suspected to have APD?	NMS	Mild to moderate	75%	No
Do you consider NMS fluctuations as an indicator that a patient is suspected to have APD?	NMS	Probable	71%	Yes[h]
Despite optimal treatment, would troublesome excessive daytime sleepiness make you suspect APD?	NMS	Yes	57%	No
Despite optimal treatment, would repeated falls[e] make you suspect APD?	FI	Presence	100%	Yes[h]
How often does needs help with ADLs indicate a patient is suspected to have APD?	FI	At least some of the time	100%	Yes[h]
How often does not able to perform complex tasks indicate a patient is suspected to have APD?	FI	At least some of the time	94%	Yes[h]
How often does limitation in performing one or more ADLs indicate that a patient is suspected to have APD?	FI	Some to most of the time	88%	Yes[g]
How often does not able to work part-time indicate a patient is suspected to have APD?	FI	At least some of the time	81%	No
What level of impaired mobility indicates that a patient is suspected to have APD?	FI	Moderate	75%	Yes[h]
How often does not able to work full-time indicate a patient is suspected to have APD?	FI	At least some of the time	69%	No

Abbreviations. FI, functional impairment; NMS, non-motor symptoms; MS, motor symptoms; ADL, activities of daily living; APD, advanced Parkinson's disease.
[a]Question concept indicates minimum accepted level of concept.
[b]Same questions were presented in Round 2.
[c]Severity definitions were provided by the panelists. Mild: Detectable to clinician but not interfering with daily life (minimally troublesome to the patient or not troublesome at all). Moderate: Detectable to clinician and influences daily life (troublesome to the patient). Severe: Detectable to clinician and significantly influences daily life (very troublesome to the patient).
[d]"Sleep disturbance" defined as sleep initiation and sleep maintenance problems related to PD.
[e]"Repeated falls" was defined as more than one fall.
[f]Indicator overlaps with the clinically more informative consensus item: "For optimally treated patients, how many hours of the waking day with "off" symptoms indicate a patient is suspected to have APD".
[g]Indicator overlaps with the clinically more informative consensus item: "How often does needs help with ADLs indicate a patient is suspected to have APD?"
[h]Indicators achieving consensus carried forward to ranking exercise.

"off" symptoms). Items which did not reach consensus based on the a priori defined threshold (Table 1) were discarded. In total, 22 items were identified as indicators of suspected APD.

Stage 4: Round 3 survey

In the process of developing consensus on the indicators, the panelists also developed consensus on the definition and levels of severity measuring the indicators. In addition, the

process of a priori consensus on the terminology of the indicators (e.g. non-transitory psychoses, defined as non-acute event psychoses, including hallucinations and delusions), levels of severity (e.g. mild features are those that are detectable to a clinician but are minimally troublesome to the patient) and ways to clinically measure symptoms (e.g. measuring dementia)[33] further standardized and increased the robustness of the indicators and the level of consensus achieved for the key objectives.

Definitions of mild/moderate/severe

Panelists concluded that mild symptoms are those that are detectable to a clinician, but may not interfere with a patient's daily life, and are either minimally troublesome to the patient or not troublesome at all. Moderate features were defined as detectable to the clinician, interfering with daily life, and troublesome to the patient. Severe features were determined to be detectable to the clinician, interfere significantly with daily life, and are troublesome for the patient.

Definition of cognitive function and dementia

In identifying patient stages of dementia, the panelists discussed the standard Mini-Mental State Exam definitions of dementia severities[33]. Panelists noted the importance of determining whether a patient's dementia is related to PD or attributable to another condition.

Final consensus on clinical indicators of suspected APD and eligibility for device-aided therapies. Overall, consensus was reached on 15 clinically relevant indicators (six MS, five NMS, and four functional impairments), as indicators for suspected APD (Table 3). The panelists noted that, for this preliminary consensus building activity, it was premature to determine combinations of motor and NMS indicators that need to be present for identifying suspected APD. The panelists acknowledged that the consensus is based on the extent to which an individual indicator needs to be present in order for suspected APD to be present or a patient is a good candidate for device-aided treatment. Panelists reached consensus that individual MS or NMS alone may be considered as clinically relevant indicators of APD but not functional impact. The panelists also reached consensus onseven indicators which described characteristics of APD patients eligible for device-aided therapies. The majority of the consensus indicators of APD patients eligible for device-aided therapies include MS (Figure 2).

Ranking of questions by clinical relevance. Based on clinical importance, panelists ranked the relative priority of the 15 consensus indicators of suspected APD within MS, NMS, and functional impact domains (Table 4). Panelists determined that the most clinically important MS indicators (in order of importance) were: (i) moderate level of troublesome motor fluctuations; (ii) $\geq$ 2 h of the waking day with "off" symptoms; (iii) $\geq$ 1 h of the day with troublesome dyskinesia; (iv) moderate level of dyskinesia; (v) troublesome dysphagia; and (vi) $\geq$ 5-times oral levodopa doses/day. The most clinically important NMSs (in order of importance, using Round-3 definitions) were: (i) mild level of dementia (due to PD); (ii) non-transitory troublesome hallucinations; (iii) moderate level of non-transitory psychosis; (iv) NMS fluctuations; and (v) moderate level of nighttime sleep disturbances (i.e. problems with sleep initiation or maintenance). The most clinically important functional impact indicators (in order of importance) were: (i) repeated falls despite optimal treatment; (ii) needs help with ADLs at least some of the time; (iii) not able to perform complex tasks at least some of the time; and (iv) moderate impaired mobility.

Final consensus on patient profiles for device-aided therapies. Movement disorder specialists determined that, in general, patients who had a good levodopa response, patients

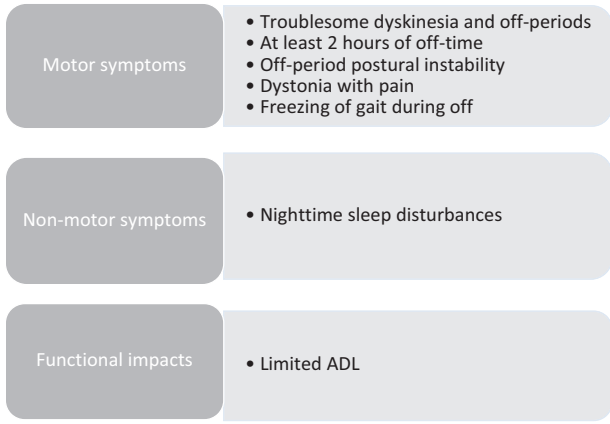

Figure 2. Consensus characteristics of APD patients eligible for device-aided treatments. Abbreviations. ADL, activities of daily living.

Table 4. Round 3 ranking of most clinically important indicators of patients with suspected APD.[a]

Ranking	Clinically important indicators ($n = 15$)[b]
Motor symptom	
1	Moderate level of troublesome motor fluctuations
2	At least 2 h of the waking day with "off" symptoms
3	At least 1 h of the day with troublesome dyskinesia
4	Moderate level of dyskinesia
5	Troublesome dysphagia
6	Daily oral levodopa doses "At least 5 times a day"
Non-motor symptom	
1	Mild level of dementia
2	Non-transitory troublesome hallucinations
3	Moderate level of psychosis
4	NMS fluctuations
5	Moderate level of nighttime sleep disturbances
Functional impacts	
1	Repeated falls[c] despite optimal treatment
2	Needs help with ADLs at least some of the time
3	Not able to perform complex tasks at least some of the time
4	Moderate impaired mobility

Abbreviations. ADL, activities of daily living; APD, advanced Parkinson's disease; NMS, non-motor symptoms.
[a]Signs and/or symptoms described in the table are inclined towards lower levels of severity to obtain indicators for suspected APD.
[b]Severity definitions were provided by the panelists. Mild: Detectable to clinician but not interfering with daily life (minimally troublesome to the patient or not troublesome at all). Moderate: Detectable to clinician and influences daily life (troublesome to the patient). Severe: Detectable to clinician and significantly influences daily life (very troublesome to the patient).
[c]"Repeated falls" was defined as more than one fall.

Table 5. Patient profiles—good candidates for device-aided treatments.

Characteristics	Domain	CSAI	DBS	LCIG
Good levodopa response	MS	++	++	+++
Levodopa resistant tremor	MS	–	+++	–
Troublesome dyskinesia	MS	+	++	++
Pain[a]	MS	+	+	+
Good cognitive function	NMS	++	++	++
Nighttime sleep disturbances	NMS	+	+	+
Impulse control disorder	NMS	–	+	+
Troublesome hallucinations	NMS	–	–	–
Depression	NMS	+	–	+
Apathy	NMS	+	–	+
Anxiety	NMS	–	+	+
Dysarthria	NMS	–	–	–
Repeated falls	FI	+	–	–
Limitation with ADLs	FI	+	–	+
Younger age (<70)	PC	++	++	++
Patients own values	PC	–	++	+
Lack of caregiver/nurse support	PC	–	+	–

Abbreviations. FI, functional impairment; NMS, non-motor symptoms; MS, motor symptoms; PC, patient characteristic.
[a]Panelists clarified that pain is from dystonia
+++Definitely good candidate (considered as absolute determinant); ++Probable good candidates (considered as sufficient determinant); +Possible candidates (considered as potential determinant); –Not a Candidate

Table 6. Patient profiles—contraindications for device-aided treatments.

Characteristics	Domain	CSAI	DBS	LCIG
Dysphagia	MS	–	+	–
Freezing of gait during "off" time	MS	–	+	–
Dysarthria	NMS	–	++	–
Non-transitory psychosis	NMS	+++	++	+
Severe dementia	NMS	+++	+++	++
Moderate dementia	NMS	++	+++	+
Mild dementia	NMS	–	+++	–
Impulse control disorder	NMS	++	+	+
Depression	NMS	+	+++	+
Troublesome hallucinations	NMS	+	++	+
Repeated falls	FI	+	++	+
Older age (>70)	PC	–	++	–
Patient fear of side-effects	PC	+	+	+
Living in a nursing home	PC	–	+	+
Lack of caregiver/family support	PC	+	+	+
Access to a hospital or treatment center	PC	+	+	+
Patient expectations	PC	+	+	+

Abbreviations. FI, functional impairment; NMS, non-motor symptoms; MS, motor symptoms; PC, patient characteristic.
+++ Definite: Considered as an absolute contraindication; ++ Probable: Considered as a sufficient contraindication; + Possible: Considered as a potential contraindication; – Not a contraindication.

70 years of age or younger, and patients who had good cognitive function were considered generally definite or probable good candidates for all three device-aided therapies. Patients with troublesome dyskinesia were considered probable good candidates for both LCIG and DBS. Panelists reported that patients with levodopa-resistant tremors were probable good candidates for DBS. Patients with limitations with ADLs were considered by panelists to be good candidates for CSAI and LCIG. For patients having non-motor symptoms, panelists viewed that the use of device-aided treatments may be a possible therapy choice but may vary with the underlying symptom, such as nighttime sleep disturbances, pain, ICDs, depression, apathy, and anxiety (Table 5).

Given the heterogeneity in the PD symptoms and the data on the safe and efficacious use of the three device-aided therapies, it was deemed important to also consider the contraindications for the use of the treatments. For patients older than 70 years, there was no consensus reached for CSAI nor LCIG, whereas DBS was deemed as a probable contraindication. Having non-transitory psychosis was a "definite" contraindication for CSAI and "probable" contraindication for DBS, while severe cognitive impairment was a "definite" contraindication for both CSAI and DBS and "probably" contraindication for LCIG. In addition to clinical factors, patient factors like patient fear of side-effects, access to a treatment center, and lack of caregiver/family support were also considered as "possible" contraindications for all three device-aided therapies. Living in a nursing home was a "possible" contraindication for DBS and LCIG, depending on the patients' level of ADL impairment and support provided with ADLs. The addition of the patient factors was considered important to decide the best way to ensure patient-centered decision-making in the choice of appropriate device-aided therapies (Table 6).

Discussion

The results from this study add to the emerging literature on developing consensus on indicators of advanced PD patients. The study results provide a preliminary spectrum of indicators for identifying patients transitioning to APD, to identifying patients requiring non-orals/device-aided therapies, to clinical choices between the most widely available device-aided therapies[34]. To our knowledge, this is the first study to provide ranking of clinically important motor, non-motor, and functional impact indicators for suspected APD based on a list of items identified by a multi-national panel of movement disorder specialists. Such information can be very valuable for pragmatically addressing patient screening and identification and reducing heterogeneity of care by facilitating the provision of the right treatment to the appropriate patients in a timely manner.

Our data is based on a robust study design and a panel whose composition meets or exceeds best practices and recommendations from other published Delphi panel studies[27,28,35–37]. A recent systematic review of over 80 Delphi panel studies focused on healthcare quality indicators by Boulkedid *et al.*[36] found that the median size of the panel was 17 (which is consistent from the recommended size of 10–18 members[35]), with ~56% of the studies choosing panelists based on expertise and number of years or expertise. The median years of experience of the panelists was 15 years. Another review of a random sample of 100 Delphi studies by Diamond *et al.*[27] found that over 90% of the studies had up to three rounds of iterations.

Our panel of movement disorder specialists determined that moderate levels of troublesome motor fluctuations and dyskinesia are indicators that are detectable to the clinician, troublesome to the patient, and interfere significantly with daily life[38]. Development of motor fluctuations and dyskinesia are well recognized and characterized in PD as signs of progressing disease[24,39]. However, the specific descriptive indicators identified in this study by the Delphi panel of

leading movement disorder specialists, such as "at least two hours of the waking day with 'off' symptoms" and "at least one hour of the day with troublesome dyskinesia", and "at least 5 times oral levodopa doses per day" provides objective information on indicators of patients inadequately controlled on oral PDs who may be transitioning to APD. In a study by Luquin *et al.*[16] defining patients with APD MS related to dopaminergic treatment, such as presence of motor fluctuations, functional limitations, such as patient requiring help, or experiencing limitations with daily activities were considered sufficient or absolute determinants of APD. Other motor limitations, such as moderate-to-severe dysphagia or moderate and/or severe dysarthria and NMS, such as dementia and hallucinations without insight, were also considered determinants of APD[16].

The panelists in this study determined that treatment with oral levodopa tablets five or more times per day indicates suspected APD. Five was selected as a cut-off because dose fractioning beyond five or more times per day may signal that motor features are not controlled on the current oral therapeutic regimen. As the disease progresses, the need for symptomatic treatment grows, resulting in an increase in both total and number of levodopa doses per day[40–42]. Similarly, in a web-survey study by Odin *et al.*[4], levodopa greater than 5-times daily for patients with severe, troublesome "off" periods (>1–2 h/day) despite optimal oral/transdermal levodopa treatment was identified as a critical indicator to the management of PD and referral to movement disorder specialists. It is important to consider the balance between an increase/decrease in dose fractioning and impact on "off" periods (e.g. total duration in day, frequency of period) and (troublesome) dyskinesia (e.g. duration in a day, treatment induced dyskinesia).

Research indicates that PD in later stages is dominated by the emergence of new—or exacerbation of existing—motor features and NMS that may not be responsive to levodopa. These symptoms play a substantial role in patient quality of life (QoL), are a major source of disability, and are risk factors for institutionalization and death[7]. The high incidence of falls in APD (40–70%) leads to injuries and fractures that further reduce patient independence[24]. Behavioral disorders, especially hallucinations and other psychotic signs and/or symptoms, are also frequent in APD (25–30%)[24]. Results from this study have pointed out certain signs and/or symptoms as being indicative of APD: mild level of dementia, non-transitory troublesome hallucinations, moderate level of psychosis, and repeated falls. Research has indicated that the most troublesome and distressing complications in APD are usually those NMS that significantly increase patients' need for supportive care, yet are frequently neglected in clinical practice[24]. Given the slow progression of PD, NMS or motor fluctuations may be missed by general neurologists who treat the majority of PD patients[43]. There is a finite treatment timeframe for treating patients with DBS due to specific motor and cognitive eligibility considerations, while a wider timeframe is often available for CSAI and LCIG treatments.

Having consensus definitions and definitive indicators of suspected APD from movement disorder specialists may enable those general neurologists to earlier identify patients with APD and refer them to movement disorder specialists or specialized centers for optimization of their current treatment regimens and/or consideration of optimization using advanced-stage treatment options, which could improve patients' QoL and reassure caregivers that everything possible is being done.

The consensus generated in this study addresses key questions for the clinical management of the patients with PD in real-world settings. The indicators of suspected APD and patients eligible for device-aided therapies may aid in development of robust screening and identification tools which will aid in timely initiation of appropriate treatments for the patients. Comprehensive patient profiles based on clinical and demographic characteristics of the patient and not necessarily the characteristics of advanced PD patients only (e.g. age, magnitude of levodopa responsiveness) may add expert consideration to local guidelines and best medical practices for the use of appropriate device-aided therapies in the treatment of APD patients. In addition, initiation of device-aided therapies should also consider patients' preferences for treatment attributes and risks[34,44], as well as overall living conditions (e.g. the presence of caregiver/family support, access to a treatment center). The findings add to emerging literature on selection on device-aided therapies[42,45] by providing a multi-national expert view through a robust Delphi consensus process.

Despite multiple evidence-based guidelines for PD, there remain clear gaps in knowledge of clinical practice that are being addressed through expert judgment and experience[4,14]. Current guidelines provide recommendations for PD treatment, which are based on randomized placebo-controlled studies. Such evidence, while of the highest quality, is often not available for sub-groups of patients (e.g. those also having non-motor issues) who may have been excluded in the trials. Additional challenges in the identification of "advanced" PD patients further hinder timely initiation of appropriate treatments and sharing of relevant information in a timely manner[9,41,46]. Recently published systematic reviews and consensus articles acknowledge that there is a growing need to establish guidelines and pragmatic clinical management approaches for the different treatment choices for PD patients requiring device-aided interventions[47–50]. Despite the potential clinical advantages, the total number of patients treated with device-aided therapies is still limited, due to the complexity of the procedure, difficulties in long-term patient management, and poor characterization of suitable candidates[45]. Our data complements the recent efforts, like in the NAVIGATE-PD (an educational program to supplement existing guidelines and provide recommendations of PD refractory to oral/transdermal therapies to understand clinical questions related to device-aided management of PD)[4], which further the understanding of practical implications of managing PD patients inadequately controlled on oral medications. The evidence in this study through the consensus of a global panel of leading movement disorder specialists brings the perspective from clinical practice to complement guidelines. A combination of available evidence,

with practical clinical experience and patient's preferences, can improve care[14,51].

Strengths and limitations

The findings from this Delphi study represent the consensus of movement disorder specialists from multiple countries in Europe with geographic variation in clinical practice and is not necessarily representative of movement disorder specialists practicing in other countries. However, additional data from a panel including US healthcare practitioners has shown concordance in the items and concepts from this study[52]. While any one of the indicators could be a possible marker for eligibility for suspected APD or device-aided therapy, further work on testing the diagnostic properties of these indicators is ongoing (data to be presented at a future meeting in 2018)[34,52]. This study follows a robust Delphi process, adhering to the best practices in terms of number of iterations (using a combination of open and closed ended questions), anonymity of responses, controlled feedback, group statistical response, an a priori definition of consensus based on a high threshold ($\geq$70%), and the selection of an homogeneous panel (based on sample size, level of expertise, and years of experience)[35–37]. While generating expert consensus, there may still be individual exceptions which are possible. Our high cut-off may also have resulted in not capturing all different points of view about appropriate indicators or treatment profiles.

The in-person meeting allowed for discussion, but did not sacrifice the anonymity of final voting. The anonymous feedback at all stages of the study allowed for strengthening the conclusions and achieving consensus across movement disorder specialists from 10 EU countries. The role of the non-voting steering committee members was pivotal in reviewing interim results and facilitating the Round 3 consensus process. To our knowledge, this is the first study to identify and rank the relevance of objective clinical measures to define suspected APD. The comprehensiveness of the study approach, along with a multinational consensus, further aides in a holistic management of advanced PD patients through appropriate identification and patient selection.

The Delphi approach is not without limitations. One potential limitation of the Delphi process is that it may represent a compromise position or a middle-of-the-road consensus, due to a tendency to eliminate extreme positions[53]. During the Delphi process, we did not assess hierarchy or combinations of symptoms that may demonstrate movement to APD. Due to multiple rounds of review with the goal of synthesizing consensus of PD experts were encouraged to consider and possibly revise their earlier answers in light of the replies of other members of their panel. Each panelist, however, was evaluating the discussion and subsequent indicator questions based on his/her clinical practice and experience and voting anonymously using the electronic polling device. In future phases of work, clinical meaningfulness of indicators, including their sensitivity/specificity to identify advanced PD patients and hierarchy of utility for clinical-decision making, will be further explored. Other treatments (dopamine agonists, COMT, MAOB inhibitors) that may be used before advanced therapies were not discussed with the assumptions that device-aided therapies will not be used if oral therapies can adequately control the PD symptoms. The lack of direct comparison between the three device-aided therapies in randomized clinical trials may have led to broader, rather than more specific consensus. Future studies should evaluate if there are combinations of symptoms that can impact clinical evaluation, especially given the context of heterogeneity in clinical practice and the differences in availability of the treatments in different countries.

Conclusion

Since many PD patients are not seen by movement disorder specialists, it is important for physicians in clinical practice to be able to timely identify PD patients in their progression to advanced-stage disease (where oral medications may not adequately control the symptoms). With timely detection, patients could benefit from interventions (appropriate treatment and/or involvement of appropriate multi-disciplinary team) resulting in improved QoL and prolonged function. A consensus definition to identify patients who are potentially reaching an APD stage could be beneficial to clinical practice, treatment trials, and epidemiological prevalence studies.

Consensus was reached among a group of movement disorder specialists with regards to the key motor, non-motor, and function indicators of PD patients who may be suspected to be APD and a preliminary characteristics profile of PD patients who could be considered for device-aided therapies. Agreement on the patient profiles who may be appropriate for different device-aided therapies complements the emerging literature by providing robust multi-country expert opinion based on clinical practice. Given that the determination of advancing disease depends on the nature and severity of the symptoms, identifying consensus guidelines for patient profiles needing treatment is critical. Further development of screening and identification approaches based on clinical indicators observable in a clinical visit could aid in improving the homogeneity of care and patient outcomes. Understanding key indicators of disease progression and choice of appropriate interventions (based on timing and patient profiles) could aid in development of tools and clinical practice pathways which are focused on better management of the PD symptoms. Future research should focus on developing guidance for general neurologists, not only for optimizing dopaminergic therapy for PD patients, but also for defining indicators and timing of CSAI, DBS, and LCIG device-aided treatments.

Transparency

Declaration of funding

This study and manuscript were funded by AbbVie. The design, study conduct, and financial support for the study were provided by AbbVie. AbbVie participated in the study design, research, interpretation of data, writing, reviewing, and approving the manuscript.

Declaration of financial/other relationships

AA, PO, and JS have received honoraria from AbbVie for participation in the Delphi Steering Committee. KS, TM, and KO are employees of AbbVie, and may own AbbVie stock or stock options. LK and AS are employees of Evidera, which has received study funding from AbbVie for conducting the Delphi Study. The authors have no other relevant affiliations or financial involvement with any organization or entity with financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. A CMRO peer reviewer on this manuscript has declared consulting fees from Abbvie, ACADIA, Acorda, Adamas, Cynapsus, Global Kinetics, Ionis, Lundbeck, Neurocrine, St Jude Medical, Teva Neuroscience, UCB and US World Meds. They have also received research grants from Acorda, Adamas, Avid, Boston Scientific, Cala Health, Cynapsus, Kyowa, National Parkinson Foundation, NIH/NINDS, Parkinson Study Group, Pfizer and US WorldMeds. Other CMRO reviewers on this manuscript have no disclosures.

Acknowledgments

The authors thank Christina Vernon (Evidera) and Gemma Al-Jassar (Evidera) for their assistance during the study, and the movement disorder specialists who participated in the Delphi Panel. Financial support for their services was provided by AbbVie. The authors would also like to thank Yash J. Jalundhwala (AbbVie) for support with the manuscript development. The datasets associated with this paper are available upon request to the corresponding author.

References

1. Antonini A, Isaias IU, Rodolfi G, et al. A 5-year prospective assessment of advanced Parkinson disease patients treated with subcutaneous apomorphine infusion or deep brain stimulation. J Neurol 2011;258:579-85
2. Antonini A, Chaudhuri KR, Martinez-Martin P, et al. Oral and infusion levodopa-based strategies for managing motor complications in patients with Parkinson's disease. CNS Drugs 2010;24:119-29
3. Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006;66:983-95
4. Odin P, Ray Chaudhuri K, Slevin JT, et al. Collective physician perspectives on non-oral medication approaches for the management of clinically relevant unresolved issues in Parkinson's disease: consensus from an international survey and discussion program. Parkinsonism Relat Disord 2015;21:1133-44
5. Worth PF. When the going gets tough: how to select patients with Parkinson's disease for advanced therapies. Pract Neurol 2013;13:140-52
6. Evans JR, Mason SL, Williams-Gray CH, et al. The natural history of treated Parkinson's disease in an incident, community based cohort. J Neurol Neurosurg Psychiatry 2011;82:1112-18
7. Coelho M, Ferreira JJ. Late-stage Parkinson disease. Nat Rev Neurol 2012;8:435-42
8. Fox SH, Katzenschlager R, Lim SY, et al. The Movement Disorder Society evidence-based medicine review update: treatments for the motor symptoms of Parkinson's disease. Mov Disord 2011;26(Suppl 3):S2-S41
9. Antonini A, Moro E, Godeiro C, et al. Medical and surgical management of advanced Parkinson's disease. Mov Disord 2018. doi:10.1002/mds.27340 [Epub ahead of print]
10. Macleod AD, Taylor KS, Counsell CE. Mortality in Parkinson's disease: a systematic review and meta-analysis. Mov Disord 2014;29:1615-22
11. Riedel O, Klotsche J, Wittchen HU, et al. Motor impairment, depression, dementia: which forms the impression of disease severity in Parkinson's disease? Parkinsonism Relat Disord 2014;20:1365-70
12. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427-42
13. Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and pharmacological management of Parkinson's disease: a national clinical guideline. SIGN; 2010; NHS Scotland. Available at: http://www.sign.ac.uk/pdf/sign113.pdf [Last accessed 7 August, 2018]
14. Rodriguez R, Green T, Rossi F, et al. Suggested criteria for patient selection for therapy with carbidopa/levodopa enteral suspension (cles) [absract]. Mov Disord 2016;S627-8
15. Martinez-Martin P, Rodriguez-Blazquez C, Mario A, et al. Parkinson's disease severity levels and MDS-Unified Parkinson's Disease Rating Scale [Multicenter Study]. Parkinsonism Relat Disord 2015;21(1):50-4
16. Luquin MR, Kulisevsky J, Martinez-Martin P, et al. Consensus on the definition of advanced Parkinson's disease: a neurologists-based Delphi Study (CEPA study). Parkinsons Dis 2017;2017:4047392
17. Jankovic J. Parkinson's disease: Clinical features and diagnosis. J Neurol Neurosurg Psychiatry 2008;79:368-76
18. Goetz CG, Poewe W, Rascol O, et al. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. Mov Disord 2004;19:1020-8
19. Ferreira JJ, Katzenschlager R, Bloem BR, et al. Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease. Eur J Neurol 2013;20:5-15
20. Kruger R, Hilker R, Winkler C, et al. Advanced stages of PD: interventional therapies and related patient-centered care. J Neural Transm (Vienna) 2016;123:31-43
21. National Collaborating Centre for Chronic Conditions (UK). Parkinson's disease: national clinical guideline for diagnosis and management in primary and secondary care. London, UK: Royal College of Physicians; 2006
22. Brettschneider C, Leicht H, Bickel H, et al. Relative impact of multimorbid chronic conditions on health-related quality of life—results from the MultiCare Cohort Study. PLoS One 2013;8:e66742
23. Forsaa EB, Larsen JP, Wentzel-Larsen T, et al. Predictors and course of health-related quality of life in Parkinson's disease. Mov Disord 2008;23:1420-7
24. Varanese S, Birnbaum Z, Rossi R, et al. Treatment of advanced Parkinson's disease. Parkinsons Dis 2011;2010:480260
25. Dujardin K, Auzou N, Lhommee E, et al. French consensus procedure for assessing cognitive function in Parkinson's disease. Rev Neurol (Paris) 2016;172:696-702
26. Ferreira JJ, Santos AT, Domingos J, et al. Clinical parameters and tools for home-based assessment of Parkinson's disease: results from a Delphi study. J Parkinsons Dis 2015;5:281-90
27. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol 2014;67:401-9
28. Dalkey N, Helmer O. An experimental application of the DELPHI method to the use of experts. Manag Sci 1967;9:458-67
29. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs 2000;32:1008-15
30. von der Gracht HA. Consensus measurement in Delphi studies. Technol Forecast Soc Change 2012;79:1525-36
31. Hsu C-C, Sandford BA. The Delphi technique: making sense of consensus. Pract Assess Res Eval (PARE) 2007;12:1-8
32. Sereda M, Edmondson-Jones M, Hall DA. Relationship between tinnitus pitch and edge of hearing loss in individuals with a narrow tinnitus bandwidth. Int J Audiol 2015;54:249-56
33. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98
34. Titova N, Martinez-Martin P, Katunina E, et al. Advanced Parkinson's or "complex phase" Parkinson's disease? Re-evaluation is needed. J Neural Transm (Vienna) 2017;124:1529-37
35. Okoli C, Pawlowski SD. The Delphi method as a research tool: an example, design considerations and applications. Inform Manag 2004;42:15-29

36. Boulkedid R, Abdoul H, Loustau M, et al. Using and reporting the Delphi method for selecting healthcare quality indicators: a systematic review. PLoS One 2011;6:e20476
37. Landeta J. Current validity of the Delphi method in social sciences. Technol Forecast Soc Change 2006;73:467-82
38. Mathur S, Mursaleen L, Stamford J, et al. Challenges of improving patient-centred care in Parkinson's disease. J Parkinsons Dis 2017;7:163-74
39. Nutt JG. Motor fluctuations and dyskinesia in Parkinson's disease. Parkinsonism Relat Disord 2001;8:101-8
40. Cenci MA, Ohlin KE, Odin P. Current options and future possibilities for the treatment of dyskinesia and motor fluctuations in Parkinson's disease. CNS Neurol Disord Drug Targets 2011;10:670-84
41. Lokk J. Lack of information and access to advanced treatment for Parkinson's disease patients. J Multidiscip Healthc 2011;4:433-9
42. Abbruzzese G, Barone P, Bonuccelli U, et al. Continuous intestinal infusion of levodopa/carbidopa in advanced Parkinson's disease: efficacy, safety and patient selection. Funct Neurol 2012;27:147-54
43. Stocchi F, Antonini A, Barone P, et al. Early detection of wearing off in Parkinson disease: the DEEP study. Parkinsonism Relat Disord 2014;20:204-11
44. Marshall T, Pugh A, Fairchild A, et al. Patient preferences for device-aided treatments indicated for advanced Parkinson disease. Value Health 2017;20:1383-93
45. Antonini A, Tolosa E. Apomorphine and levodopa infusion therapies for advanced Parkinson's disease: selection criteria and patient management. Expert Rev Neurother 2009;9:859-67
46. ?>Antonini A, Yegin A, Preda C, et al. Global long-term study on motor and non-motor symptoms and safety of levodopa-carbidopa intestinal gel in routine care of advanced Parkinson's disease patients; 12-month interim outcomes. Parkinsonism Relat Disord 2015;21:231-5
47. Ray Chaudhuri K, Rojo JM, Schapira AH, et al. A proposal for a comprehensive grading of Parkinson's disease severity combining motor and non-motor assessments: meeting an unmet need. PLoS One 2013;8:e57221
48. Kulisevsky J, Luquin MR, Arbelo JM, et al. Advanced Parkinson's disease: clinical characteristics and treatment. Part II. Neurologia 2013;28:558-83
49. Kulisevsky J, Luquin MR, Arbelo JM, et al. [Advanced Parkinson's disease: clinical characteristics and treatment (part 1)]. Neurologia 2013;28:503-21
50. von Campenhausen S, Bornschein B, Wick R, et al. Prevalence and incidence of Parkinson's disease in Europe. Eur Neuropsychopharmacol 2005;15:473-90
51. Nijhuis FA, van Heek J, Bloem BR, et al. Choosing an advanced therapy in Parkinson's disease; is it an evidence-based decision in current practice? J Parkinsons Dis 2016;6:533-43
52. Antonini A, Schmidt P, Odin P, et al., editors. Development of a clinician-reported screening tool to identify patients with Parkinson's disease inadequately controlled on oral medications. Vancouver, BC, Canada: International Parkinson's Disease Movement Disorder Society; 2017
53. Mitroff I, Turoff M. Philosophical and methodological foundations of Delphi. In: Linstone H, Turoff M, editors. The Delphi method: Techniques and applications. Reading, MA: Addison-Wesley; 1975. p. 17-35