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ORIGINAL RESEARCH

Psychometric Properties of Clinical Indicators for Identification and Management of Advanced Parkinson's Disease: Real-World Evidence From G7 Countries

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ABSTRACT

Introduction: Standardized and validated criteria to define advanced Parkinson's disease (PD) or identify patient eligibility for device-aided therapy are needed. This study assessed the psychometric properties of clinical indicators of advanced PD and eligibility for device-aided therapy in a large population.

Methods: This retrospective analysis of the Adelphi Parkinson's Disease Specific Programme collected data from device-aided therapy-naïve people with PD in G7 countries. We assessed the presence of 15 clinical indicators of advancing PD and seven indicators of eligibility for device-aided therapy in patients classified with advanced PD or as eligible for device-aided therapy by the treating physician. Accuracy was assessed using area under the curve (AUC) and

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multivariable logistic regression models. Construct validity was examined via known-group comparisons of disease severity and burden among patients with and without each clinical indicator.

Results: Of 4714 PD patients, 14.9% were classified with advanced PD and 17.5% as eligible for device-aided therapy by physician judgment. The presence of each clinical indicator was 1.9- to 7.3-fold more likely in patients classified with advanced PD. Similarly, the presence of device-aided therapy eligibility indicators was 1.8- to 5.5-fold more likely in patients considered eligible for device-aided therapy. All indicators demonstrated high clinical screening accuracy for identifying advanced PD (AUC range 0.84–0.89) and patients eligible for device-aided therapy (AUC range 0.73–0.80). The Unified Parkinson's Disease Rating Scale (UPDRS) score, cognitive function, quality of life, and caregiver burden were significantly worse in indicator-positive patients.

Conclusion: Specific clinical indicators of advanced PD and eligibility for device-aided therapy demonstrated excellent psychometric properties in a large sample, and thus may provide an objective and reliable approach for patient identification and treatment optimization.

PLAIN LANGUAGE SUMMARY

Advanced Parkinson's disease (PD) refers to the stage of disease when motor complications are difficult to manage with standard therapy. Patients reaching this stage of the disease may benefit from a treatment change from pills to the so-called device-aided therapies. However, there is currently no unanimous definition of advanced PD, which makes it challenging to identify suitable candidates for device-aided therapies. There is urgent need to define specific features (or 'clinical indicators') to support healthcare professionals and patients in the identification of advanced PD as well as to define suitability for device-aided therapy. This study aimed to assess the accuracy of 15 clinical indicators and seven device-aided therapy eligibility criteria using information from a large database of 4714 patients in G7 countries. Physicians classified 14.9% of patients as having advanced PD and 17.5% were judged to be eligible for device-aided therapy. Each clinical indicator or device-aided therapy eligibility indicator was detected more frequently in patients classified as having advanced PD and in patients considered eligible for device-aided therapy, respectively. All indicators had high accuracy for identifying advanced PD and device-aided therapy-eligibility. These previously identified clinical indicators of advanced PD and device-aided therapy eligibility may provide an objective and reliable approach for patient screening and treatment optimization.

Keywords: Advanced Parkinson's disease; Clinical indicators; Device-aided therapy eligibility; Accuracy; Validity

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Key Summary Points

Why carry out this study?

Treatments for advanced Parkinson's disease (PD), including device-aided therapies, can improve symptom control, activities of daily living, and quality of life (QoL), but a lack of validated guidance on what defines advanced PD or when device-aided therapies are best indicated has hindered optimal and timely management for a proportion of patients.

Recently, 15 clinical indicators for suspected advanced PD and seven indicators for device-aided therapy eligibility were proposed by a Delphi consensus panel, and the current study aimed to evaluate the real-world clinical accuracy and validity of these specific indicators compared with the gold standard of physician assessment in a large, international sample of PD patients.

What was learned from the study?

All indicators demonstrated high clinical screening accuracy in identifying patients with advanced PD or identifying those who are candidates for device-aided therapy.

Specific indicators of advanced PD or device-aided therapy eligibility demonstrated strong validity in identifying patients with greater overall burden of disease, worse cognitive function, poorer PD-related QoL, and greater caregiver burden.

The identified specific clinical indicators provide objective, reliable, and validated tools to aid physicians in timely identification of patients with advancing PD, or who may benefit from device-aided therapies.

INTRODUCTION

The burden of Parkinson's disease (PD) increases as the disease progresses [1, 2], and advanced PD is characterized by a medley of non-motor and motor symptoms that cannot be managed with optimized oral therapy, including wearing off, an increased duration of 'off' time, and/or troublesome dyskinesia [3–6]. As PD advances, the higher burden of disease experienced by patients translates into reduced activities of daily living (ADL) and quality of life (QoL) [1, 7]. Caregivers of people with PD also see their burden increasing and QoL decreasing with disease progression [8–10].

Timely introduction of device-aided therapy may improve the QoL of some people with advanced PD whose symptoms are poorly controlled with oral therapy [11]. However, the absence of a biomarker or diagnostic test, or of uniform disease classification, hinders the identification of advanced PD and the selection of patients for device-aided therapies [5]. As a result, many patients with advanced PD who could benefit from device-aided therapy may not be considered, or referred, for this therapy option [1]. Improved and validated selection criteria and easy-to-use criteria for the identification of people with advanced PD would potentially help inform management decisions and improve communication with patients and carers [12, 13].

Some degree of consensus on how to define advanced PD has emerged in recent years [14–16]. A survey of 103 experts identified referral criteria for advanced PD of $\geq$ 5 oral levodopa doses/day with $>$ 1–2 h of troublesome 'off'-time/day despite optimal oral/transdermal levodopa or non-levodopa-based therapies [16]. A subsequent expert consensus used a Delphi process involving 17 movement disorder specialists from ten European countries that followed best practices [14]. The aim was to identify clinically important indicators that define advanced PD, and the group agreed ($\geq$ 70% agreement) on 15 specific clinical indicators of suspected advanced PD based on motor symptoms, non-motor symptoms and functional impacts. Independently of these 15

clinical indicators, seven patient characteristics that indicate eligibility for device-aided therapy were also developed [14]. There is now a need to assess the accuracy and validity of these indicators, both in controlled settings and, importantly, in current real-world settings. Therefore, we drew upon a large multi-country dataset to assess the psychometric properties of these consensus-based clinical indicators for identifying advanced PD and those patients eligible for device-aided therapy [14].

METHODS

This is a retrospective analysis of the Adelphi Parkinson's Disease Specific Programme (DSP) [17]. The Parkinson's DSP is a large, observational, non-interventional survey in G7 countries (France, Germany, Italy, Japan, Spain, UK and USA) of people with PD and the neurologists involved in their care. This analysis uses data collected from 2017 to 2020 (Wave VII and VIII of the Parkinson's DSP).

The data collected by Adelphi Real World (Bollington, Macclesfield, UK) was de-identified. No identifiable protected health information was extracted or accessed during the study, which is compliant with the Health Insurance Portability and Accountability Act (HIPAA). Therefore, Ethics Committee Review approval for the conduct of this study was not necessary.

Included Population

Qualified neurologists were identified from public lists of healthcare professionals and invited to participate if they were personally responsible for treatment decisions for at least 12 people with PD per week. The target recruitment of neurologists was 100 each from USA and Japan, 60 each from France, Germany, Italy, and Spain, and 58 from the UK, with the aim of including data from 4756 eligible patients. To avoid potential selection bias due to variable population densities in different areas of a given country, an appropriately larger sample of physicians was identified in densely populated areas than in more sparsely populated areas. Physicians were asked to recruit the next ten consecutive patients consulting with PD. Patients were eligible if diagnosed with PD on or before the date of their most recent consultation (i.e., the date they were included in the study), aged $\geq$ 18 years, receiving oral therapy, and device-aided therapy-naïve (i.e., naïve to levodopa/carbidopa intestinal gel, deep brain stimulation, and subcutaneous apomorphine infusion).

Data Collection

Data for each participant (and their physician) were collected at a single point in time. There were no follow-up visits. Disease severity was based on physician judgment and classified into early, intermediate and advanced PD (determined by the physician's answer to a single question: 'How would you describe this patient's overall condition currently?' Possible answers: Early stage PD [mild]; Intermediate stage PD [moderate to severe]; Advanced PD [late or severe]). Device-aided therapy eligibility was also based on the physician's global assessment of patients as candidates within the next 24 months (patients considered 'not candidate' or 'candidate for device-aided therapy in the next $\geq$ 3 years' were grouped as 'device-aided therapy ineligible patients' in this analysis). The presence of 15 clinical indicators of advanced PD and seven indicators of device-aided therapy eligibility defined by Antonini et al. [14] were derived for all patients (Electronic Supplementary Material [ESM] Tables S1, S2). Additional information collected included: patient characteristics (age, gender, duration of PD, number of comorbidities); Unified Parkinson's Disease Rating Scale (UPDRS; a measure of PD severity with a score ranging up to 199, with 199 indicating the worst possible disability) total score; Mini-Mental State Examination (MMSE; a measure of a person's cognitive function with a score ranging from 0 to 30, with lower scores indicating worse cognitive function) score; Parkinson's Disease Questionnaire (PDQ)-39 (a measure of PD-related QoL with scores ranging from 0 to 156, with higher scores indicating worse QoL); and Zarit Burden Interview (ZBI; a measure of caregiver burden, with a score

ranging from 0 to 88, with higher scores indicating a higher burden) total score.

Analyses

The psychometric properties of consensus clinical indicators were evaluated based on the screening accuracy and construct validity. Multivariable logistic regression models were run to evaluate screening accuracy and expressed as area under the curve (AUC) and the correct classification rate. The AUC was calculated from the sensitivity (i.e., presence of the indicator in patients with advanced PD or eligible for device-aided therapy according to physician's judgment) and specificity (i.e., absence of the indicator in patients with early/intermediate PD or ineligible for device-aided therapy according to physician's judgment). Correct classification rate was the percentage of patients with a given indicator who were classified by the physician as having advanced PD or assessed by the physician as being eligible for device-aided therapy. An AUC of ≥ 0.7 and correct classification rate $\geq 70\%$ were considered appropriate for screening performance. Odds ratios (OR) and 95% confidence intervals (CI) were computed to evaluate the association between each indicator as exposure and clinician assessment (advanced PD or device-aided therapy eligibility) as outcome. All logistic regression models were adjusted for country, age (< 65 years or ≥ 65 years), gender, time since diagnosis of PD and Charlson comorbidity index. Construct validity was evaluated using known-group comparisons of UPDRS score, cognitive function (MMSE score), Parkinson's disease-related QoL (PDQ-39), and caregiver burden (ZBI score) between patients with and without the clinical indicators. Group differences were assessed using Wilcoxon–Mann–Whitney, *t* test, chi-square, and Fisher's exact tests as appropriate.

RESULTS

The sample consisted of 563 physicians (France 58, Germany 60, Italy 60, Japan 88, Spain 62, UK 76, and USA 159,) and 6241 people with PD. Of this total sample, 1527 were excluded because they were not prescribed oral treatment or had received a device-aided therapy at the time of the sample, and 4714 were included in this analysis, of which 2051 (43.5%), 1961 (41.6%), and 702 (14.9%) were classified by the treating physician with early PD, intermediate PD, and advanced PD, respectively (Table 1). Of the 702 patients classified as having advanced PD, 418 (59.5%) were not considered candidates for device-aided therapy and 284 (40.5%) were candidates for device-aided therapy in the next 24 months.

According to the physician's opinion, 823 (17.5%) of the included population were considered to be eligible for device-aided therapy in the next 24 months (Table 1). Of these 823 patients, 57 (6.9%) were classified with early PD, 482 (58.6%) with intermediate PD, and 284 (34.5%) with advanced PD by the physician.

At least one of the 15 clinical indicators were reported in 3969 (84.2%) patients. The presence of each specific clinical indicator of suspected advanced PD was more likely in patients classified with advanced PD by the treating physician than in those with early/intermediate PD (Fig. 1a). For example, patients with ≥ 2 h 'off'-time per day were more than seven-times more likely to be classified as advanced PD than patients with less 'off'-time (OR 7.07; 95% CI 5.76, 8.68; Fig. 1a). The presence of multiple clinical indicators increased the probability of a patient being classified with advanced PD (ESM Table S3). For example, patients with ≥ 2 clinical indicators were more than 18-fold more likely to be classified with advanced PD than patients with 0 or 1 clinical indicators (OR 18.56; 95% CI 11.31, 30.46; ESM Table S3). Indicators of advanced PD that were reported most frequently in patients with early/intermediate PD were non-motor symptom fluctuations, moderate impaired mobility, and moderate/severe limitations in ADL.

At least one of the seven device-aided therapy criteria were reported in 2952 (62.6%) patients. The presence of each of the seven device-aided therapy criteria was more likely in patients considered to be a candidate for device-aided therapy within the next 24 months by physicians than in patients considered to be

Table 1 Characteristics of people with Parkinson's disease from the Parkinson's Disease Specific Programme included in this analysis

Characteristic	All patients (n = 4714)[a]
Physician's opinion of disease severity, n (%)	
Early	2051 (43.5)
Intermediate	1961 (41.6)
Advanced	702 (14.9)
Eligibility for device-aided therapy in the next 24 months, n (%)	
Eligible	823 (17.5)
Non-eligible	3891 (82.5)
Country, n (%)	
France	497 (10.5)
Germany	594 (12.6)
Italy	533 (11.3)
Japan	561 (11.9)
Spain	549 (11.6)
UK	586 (12.4)
USA	1394 (29.6)
Age, n (%)	
$<$ 65 years	1405 (29.8)
$\geq$ 65 years	3309 (70.2)
Gender, n (%)	
Male	2866 (60.8)
Female	1848 (39.2)
Mean (SD) time since PD diagnosis, years	4.3 (4.4) [n = 3712]
Hoehn and Yahr stage, n (%)	
1	1593 (33.8)
2	1545 (32.8)
3	932 (19.8)
4	457 (9.7)
5	187 (4.0)
Mean (SD) number of comorbidities	1.8 (1.8)
Number of comorbidities, n (%)	
0	1196 (25.4)
1	1252 (26.6)

Table 1 continued

Characteristic	All patients (n = 4714)[a]
2–3	1572 (33.3)
4 +	694 (14.7)
Mean (SD) UPDRS total score	30.6 (26.3) [n = 929]
Mean (SD) MMSE score	24.4 (4.9) [n = 1052]
Mean (SD) PDQ-39 summary index	26.9 (17.5) [n = 1425]
Mean (SD) ZBI total score	27.1 (18.0) [n = 644]

ADL Activities of daily living, *AUC* Area under the curve, *MMSE* Mini-Mental State Exam, *PDQ-39* Parkinson's Disease Questionnaire-39, *SD* standard deviation, *UPDRS* Unified Parkinson's Disease Rating Scale, *VAS* visual analogues scale, *ZBI* Zarit Burden Interview

[a]Unless otherwise stated

non-eligible (Fig. 1b). The presence of ≥ 2 device-aided therapy criteria increased the probability of a patient being considered a candidate for device-aided therapy compared with patients with 0 or 1 criteria (ESM Table S3). The device-aided therapy criteria most frequently reported in those not considered eligible for device-aided therapy were limited ADL and ≥ 2 h 'off' time/day.

Accuracy

All 15 clinical indicators demonstrated high diagnostic accuracy for advanced PD (all AUC > 0.80; Fig. 2). Likewise, the seven device-aided therapy criteria demonstrated high clinical accuracy for identifying patients eligible for device-aided therapy (all AUC > 0.70; Fig. 3). Accuracy was consistent regardless of the type of indicator or criterion (motor symptom, non-motor symptom, or functional impacts). The presence of multiple indicators or criteria also had a high accuracy for diagnosing advance PD or identifying patients eligible for device-aided therapy compared with the presence of fewer or no indicators/criteria (ESM Table S3).

Validity

All 15 clinical indicators demonstrated convergent and divergent validity in identifying patients with high disease burden based on the UPDRS score, cognitive function, QoL, and caregiver burden (Fig. 4). Disease burden based on these four measures also increased as the number of clinical indicators present increased to ≥ 2 or ≥ 4 (ESM Figure S1).

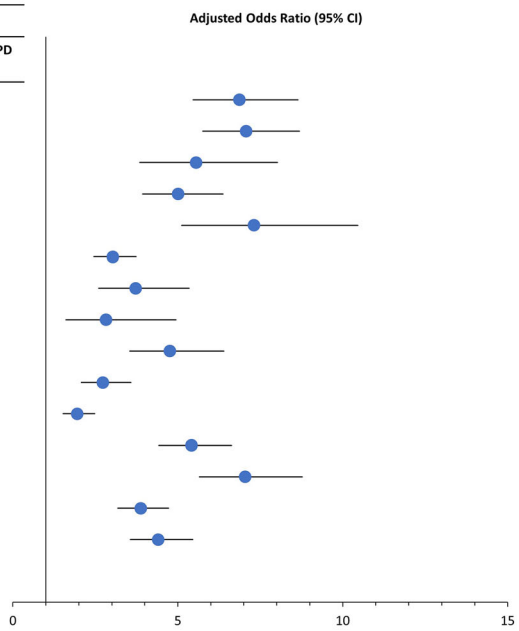
Similarly, patients with device-aided therapy eligibility criteria had a significantly higher burden than patients without criteria for device-aided therapy eligibility, and the presence of ≥ 2 criteria increased the burden even more than when one criterion only was present (Fig. 5; ESM Fig. S1).

DISCUSSION

These data show that the specific clinical indicators of advanced PD assessed in this large dataset demonstrated robust psychometric properties and diagnostic accuracy in identifying patients classified as having advanced PD. Likewise, the device-aided therapy indicators proved accurate for identifying patients who were considered eligible for device-aided therapy in the next 24 months. The clinical indicators may be useful for timely and accurate identification of patients whose PD symptoms are suboptimally controlled while on an oral regimen, and the device-aided therapy indicators may help identify patients who may benefit

a

Clinical indicator of suspected advanced PD	Physician assessment: Advanced PD (n=702)	Physician assessment: Early/intermediate PD (n=4012)
1: Moderate/severe troublesome motor fluctuations	292 (54.3%)	246 (45.7%)
2: ≥2hrs 'off'-time/day	494 (40.9%)	713 (59.1%)
3: ≥1hr troublesome dyskinesia/day	111 (62.0%)	68 (38.0%)
4: At least moderate level of dyskinesia	228 (50.7%)	222 (49.3%)
5: Troublesome dysphagia	138 (66.7%)	69 (33.3%)
6: Has at least 5 times oral levodopa/day	289 (36.1%)	511 (63.9%)
7: Has at least mild dementia	155 (66.2%)	79 (33.8%)
8: Non-transitory troublesome hallucinations	31 (47.7%)	34 (52.3%)
9: Moderate/severe psychosis	173 (56.0%)	136 (44.0%)
10: Has non-motor symptom fluctuations	626 (17.9%)	2874 (82.1%)
11: Moderate/severe sleep disturbances	159 (27.3%)	424 (72.7%)
12: Falls most/all of the time	404 (42.3%)	550 (57.7%)
13: Moderate/severe limitations with activities of daily living	556 (37.4%)	932 (62.6%)
14: Not able to perform complex tasks at least some of the time	452 (35.1%)	835 (64.9%)
15: At least moderate impaired mobility	549 (29.4%)	1318 (70.6%)



b

Indicator of device-aided therapy eligibility	Physician assessment: Eligible (n=823)	Physician assessment: Non-eligible (n=3891)
1: Troublesome dyskinesia and 'off'-periods	188 (53.3%)	165 (46.7%)
2: ≥2hrs 'off'-time/day	504 (41.8%)	703 (58.2%)
3: 'Off'-period postural instability	62 (38.3%)	100 (61.7%)
4: Dystonia with pain	41 (40.6%)	60 (59.4%)
5: Freezing of gait during 'off'	287 (44.3%)	361 (55.7%)
6: Night-time sleep disturbances	162 (27.8%)	421 (72.2%)
7: Limited activities of daily living	595 (23.8%)	1903 (76.2%)

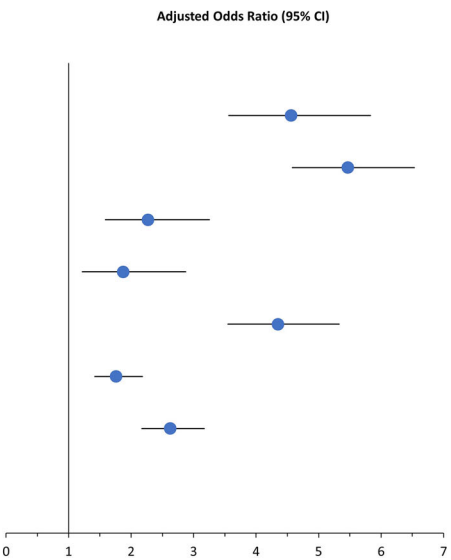


Fig. 1 Multivariable logistic regression models evaluating the relationship between the 15 clinical indicators and physician assessment of advanced Parkinson's disease (PD) (**a**) and the seven device-aided therapy criteria and provider assessment of device-aided therapy eligibility (**b**). Odds ratio (*OR*) was adjusted to account for differences by country, age, gender, PD stage, years since PD diagnosis, and number of comorbidities. *CI* Confidence interval

from advanced treatment options, such as device-aided therapy.

The presence of each specific clinical indicator of suspected advanced PD demonstrated good construct validity on outcomes measuring PD status, PD-related QoL, cognitive function, and care partner burden. While other studies have assessed disease burden in patients with a

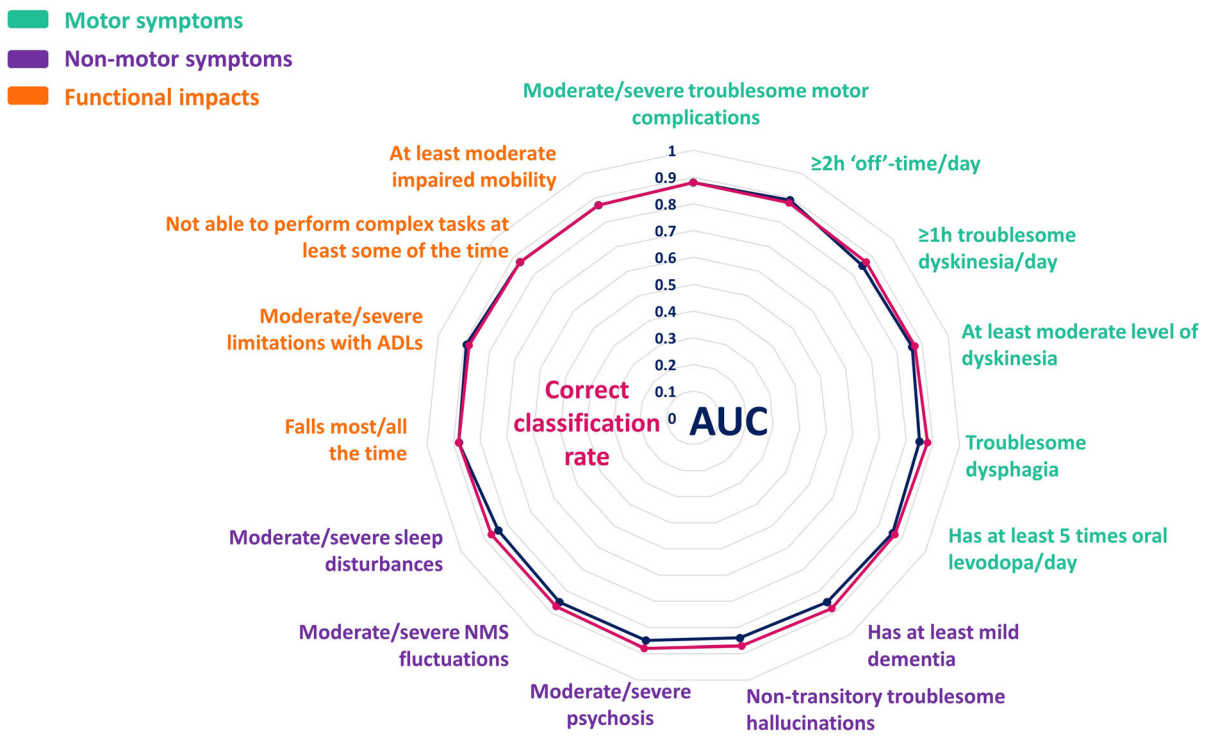


Fig. 2 Diagnostic accuracy of the 15 Delphi clinical indicators of suspected advanced PD. The area under the curve (AUC; blue line) was calculated from the sensitivity (i.e., presence of the indicator in patients with advanced PD according to physician's judgment) and specificity (i.e., absence of the indicator in patients with early/intermediate PD according to physician's judgment). Correct classification rate (pink line) was the percentage of patients with a given indicator who were classified as having advanced PD by the physician (expressed above as percentage/100). An AUC $\geq$ 0.7 and correct classification rate $\geq$ 70% were considered appropriate for screening performance. AUC model was adjusted to account for differences by country, age, gender, PD stage, years since PD diagnosis, and number of comorbidities. *NMS* Non-motor symptom

subset of these 15 clinical indicators [7, 18], and determined the frequency of these indicators in patients initiating device-aided therapy [19], the current study benefits from a larger, and current real-world population of PD patients receiving care in seven countries and across three continents. However, there is an absence of a 'gold standard' for advanced PD diagnosis to compare these findings with; indeed, there is no widely accepted definition of advanced PD. This is illustrated by the finding that the majority of patients with many of the clinical indicators were classified as having early/intermediate PD (e.g., 82.1% of those with non-motor symptom fluctuations were classified by the physician as having early/intermediate PD) and 44% of patients with moderate/severe psychosis (1 of the 15 clinical indicators, and a symptom that is generally accepted to occur later in the disease course [20]) were assessed as having early/intermediate PD (Fig. 1).

As a practical proposal, it may be best to view the 15 clinical indicators developed by the Delphi panel [14] as indicators that the patient is moving towards, or already has, advanced PD. The more of these indicators that are present in a patient, the greater the burden on the patient and their caregiver and, therefore, the greater the need to try and improve treatment. The results of the current analysis illustrate that the burden of disease becomes greater with an increase in the number of indicators present from 0 or 1 to $\geq$ 4, but further studies are needed to assess if specific combinations/clusters of

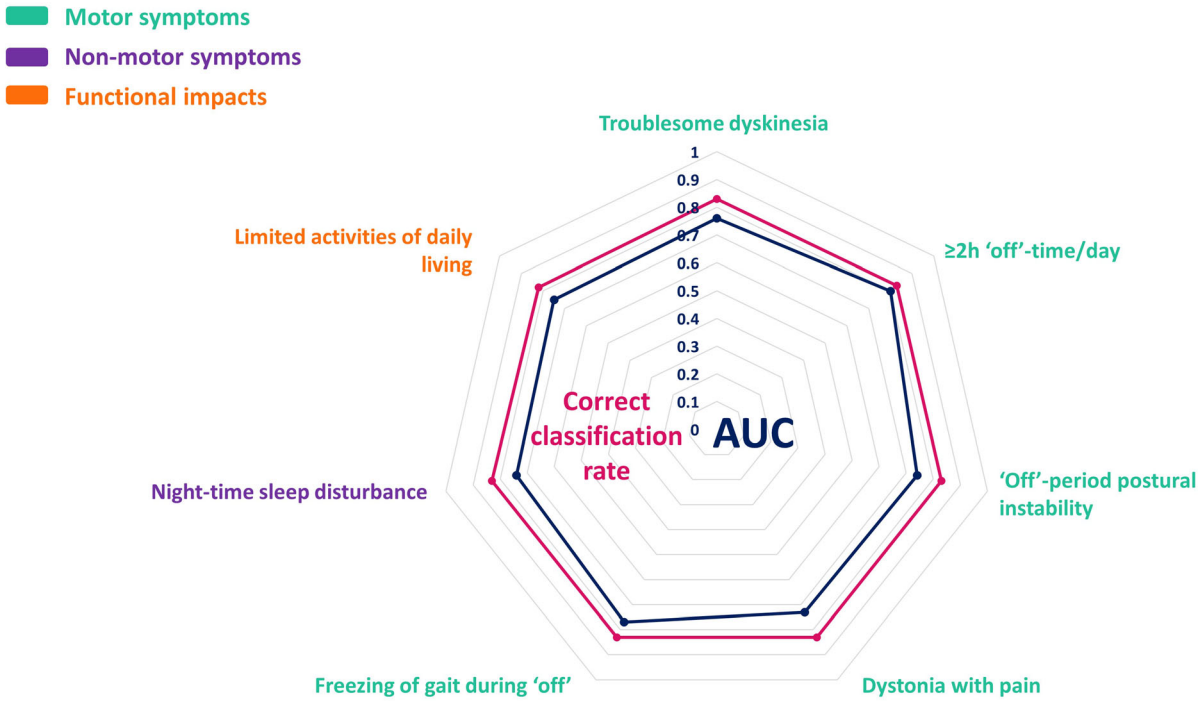


Fig. 3 Clinical accuracy of the seven device-aided therapy indicators for identifying patients eligible for device-aided therapy. The area under the curve (AUC; blue line) was calculated from the sensitivity (i.e., presence of the indicator in patients eligible for device-aided therapy according to physician's judgment) and specificity (i.e., absence of the indicator in patients ineligible for device-aided therapy according to physician's judgment). Correct classification rate (pink line) was the percentage of patients with a given indicator who were classified as being eligible for device-aided therapy by the physician (expressed above as percentage/100). An AUC $\geq$ 0.7 and correct classification rate $\geq$ 70% were considered appropriate for screening performance. AUC model adjusted to account for differences by country, age, gender, PD stage, years since PD diagnosis, and number of comorbidities

clinical indicators conferred higher disease burden and acted as the most accurate markers of advanced PD. For example, the presence of clinical indicators for motor symptoms combined with indicators of functional impairment could spotlight a particular need for improved management. From the data presented in this study, there is no indication that any one clinical indicator has the most robust psychometric properties and diagnostic accuracy in identifying advanced PD, or if the type of indicator (motor symptom, non-motor symptom, or functional impact) is more important in this respect.

The presence of each of the eligibility criteria for device-aided therapy also demonstrated good construct validity on measurements of PD burden. The number of patients with at least one of the device-aided therapy criteria (n = 2952; 62.6%) far exceeded the number considered to be eligible for device-aided therapy in the next 24 months (n = 823; 17.5%) by physician judgment (of the latter only 180 [3.8%] were considered to be eligible for device-aided therapy in the next 6 months). The disparity between these numbers is probably due to the decision on whether a patient is eligible or not often being a complicated decision-making process that relies on a number of factors, including the likely responsiveness of patient's symptoms to device-aided therapy, indications and contraindications for each of the device-aided therapies, and the patient's general health status or age. Such complexity may partly explain why, for example, > 50% of the patients with $\geq$ 2 h of 'off'-time/day were

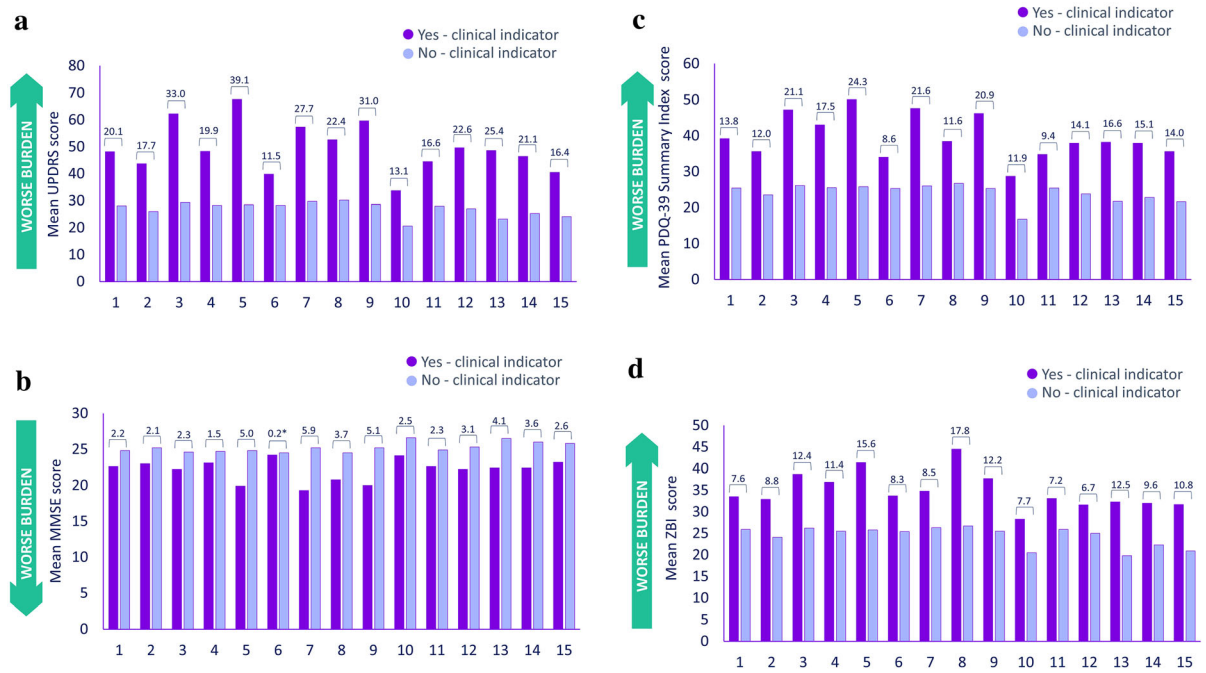


Fig. 4 Construct validity of the 15 Delphi clinical indicators of advanced PD based on: **a** UPDRS total score, **b** MMSE score, **c** PDQ-39 Summary Index score, **d** ZBI score. All differences between presence and absence of a clinical indicator were statistically significantly different ($p < 0.01$, t test)—except where marked with an asterisk. Numbers under each graph represent the following indicators: *1* Moderate/severe troublesome motor fluctuations, *2* $\geq$ 2 h 'off'-time/waking day, *3* $\geq$ 1 h troublesome dyskinesia/waking day, *4* at least moderate level of dyskinesia, *5* troublesome dysphagia, *6* at least 5 times oral levodopa/day, *7* has at least mild dementia, *8* non-transitory troublesome hallucinations, *9* moderate/severe psychosis, *10* moderate/severe non-motor symptom fluctuations, *11* moderate/severe sleep disturbances, *12* falls most/all the time, *13* moderate/severe limitations with activities of daily living, *14* not able to perform complex tasks at least some of the time, *15* at least moderate impaired mobility. *MMSE* Mini-Mental State Examination, *PDQ-39* 39-item Parkinson's Disease Questionnaire, *UPDRS* Unified Parkinson's Disease Rating Scale, *ZBI* Zarit Burden Interview

not considered eligible for device-aided therapy. We may expect that $\geq$ 2 h of 'off'-time/day would highlight the need for treatment optimization in most patients, but this dataset does not provide enough information to ascertain why device-aided therapy was not considered appropriate for most of these patients. If the device-aided therapy criteria are considered to be reliable indicators, then limited ADL is one criterion that seems to be particularly 'overlooked' by physicians—i.e., 1903 of 3891 patients (48.9%) considered to be non-eligible for device-aided therapy had limited ADL, and only 23.8% of those with limited ADL were considered to be eligible for device-aided therapy (Fig. 1b). The difficulties in interpreting the above numbers may highlight the need to consider, as with the clinical indicators, specific combinations of these criteria to accurately identify patients eligible for device-aided therapy. Certainly, the burden of disease appears to worsen when there are $\geq$ 2 device-aided therapy criteria present.

Another important aspect that influences choice of treatment is the individual preferences and circumstance of patients and carers, and these may have influenced the classification of patients as eligible or non-eligible, irrespective of the presence of device-aided therapy criteria. We cannot determine from this dataset whether patients and caregivers find such clinical indicators and device-aided therapy

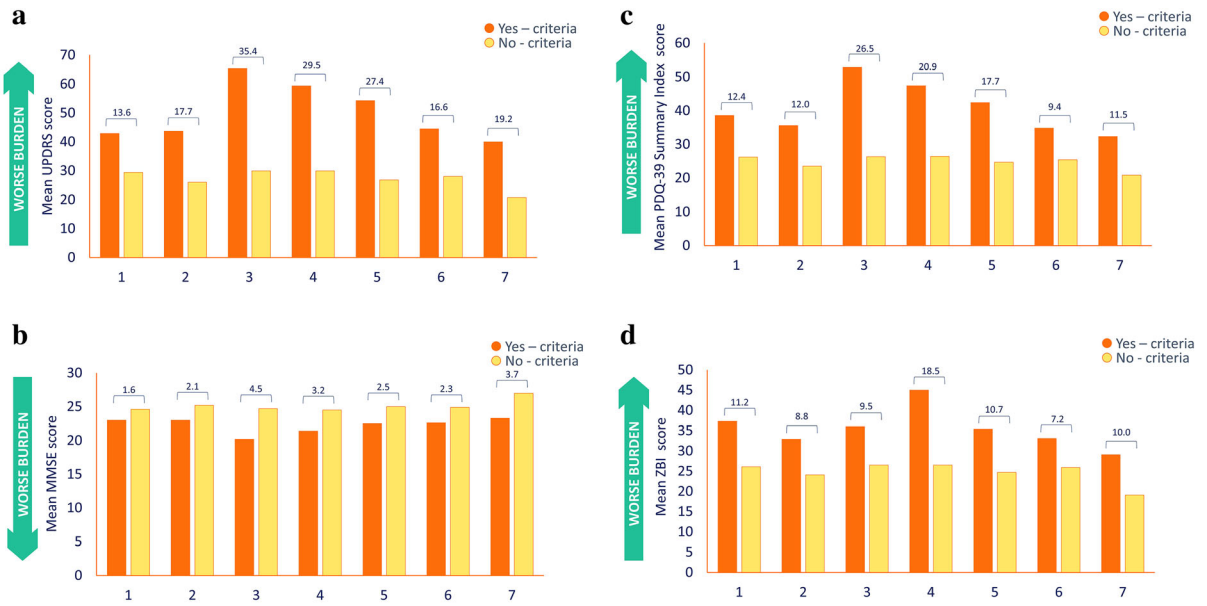


Fig. 5 Construct validity of the seven device-aided therapy criteria based on: a UPDRS total score, b MMSE score, c PDQ-39 Summary Index score, d ZBI score. All differences between presence and absence of device-aided therapy criteria were statistically significantly different ($p < 0.01$, t test). Numbers under each graph represent the following indicators: *1* Troublesome dyskinesia, *2* $\geq$ 2 h 'off'-time/waking day, *3* 'Off'-period postural instability, *4* dystonia with pain, *5* freezing of gait during 'off', *6* nighttime sleep disturbances, *7* limited activities of daily living

eligibility criteria useful or not. A subset of indicators (or indeed other indicators not included in the Delphi panel list) could have a particular resonance with patients and carers, and identifying these could also help in refining joint treatment–management decisions. The involvement of patients and carers in the refinement of device-aided therapy criteria should be included in future research.

Irrespective of the clinical indicators and device-aided therapy eligibility criteria, these data showed that physician assessment of disease severity and device-aided therapy eligibility does not appear to overlap as much as would be expected. Only 284 of the 702 patients with advanced PD (40.5%) were also classified by the physician as being eligible for device-aided therapy. Not all patients with advanced PD will be eligible for device-aided therapy, and in the absence of a uniform definition of advanced PD, it is difficult to estimate the proportion of these 702 advanced PD who would be good candidates for any of the device-aided therapies.

Similarly, physician assessment of device-aided therapy eligibility and disease status does not appear to be consistent, with most of those considered device-aided therapy eligible in the next 24 months having intermediate PD (and even 6.9% having early PD). This inconsistency may reflect some overlap between the definitions of intermediate and advanced PD (in the answers that physicians gave, intermediate PD was also classed as 'moderate to severe', while advanced PD was classed as 'late or severe'), but it would not explain why 57 people with early PD would be considered eligible for device-aided therapy by the treating physician. As the Parkinson's DSP did not collect information to explain physician assessment, we can only postulate on the reasons for people with early PD being eligible for device-aided therapy. It is possible that subcutaneous apomorphine infusion is prescribed at earlier stages of disease in some countries and that this treatment option could explain this apparent disparity. The disconnect between physician assessment of advanced PD and device-aided therapy eligibility may accurately reflect the proportion of patients with advanced PD who are eligible for device-aided therapy, or may suggest different

levels of awareness of advanced disease assessment and device-aided therapy eligibility. Thus, these observations may illustrate exactly why there is an urgent need for accurate and objective diagnostic criteria.

Inclusion of such criteria in clinical pathways and guidelines may facilitate timely and more accurate identification of patients who need treatment optimization and, when appropriate, referral of those patients who are eligibile for device-aided therapy to optimize treatment and improve their QoL. Such indicators for patient assessment may be used in some expert centres, but the efficacy of tools used currently by neurologists are likely to differ depending on their level of experience. This may be reflected in some of the findings in the current analysis and provides a strong rationale for further validating and refining clinical indicators that could be used uniformly. Future assessment may determine whether all 15 criteria are of equal importance; for example, the '$\geq$ 2 h 'off'-time/waking day' and 'at least 5 times oral levodopa/day' indicators along with any dyskinesia may be sufficient to identify patients who may have advanced PD or are eligible for advanced therapies [16]. Intensified therapy (consisting of a levodopa equivalent daily dose of $\geq$ 1000 mg/day or $\geq$ 5 oral levodopa doses/-day) alone may also identify patients who would benefit from treatment optimisation [21].

The 15 advanced PD and seven device-aided therapy indicators assessed in this study stem from a robust consensus [14], and the Parkinson's DSP is validated for capturing large, statistically robust samples of global real-world evidence. The data collected, therefore, reflect current clinical practice, providing objective and impartial data from physicians and from people with PD and their caregivers. However, there are inherent limitations in such observational studies: although physicians are requested to collect data on a series of consecutive patients to avoid selection bias, the absence of randomization could introduce some bias; and the quality of data depends, to a large extent, on the accurate reporting of information by physicians and patients, which may be subject to recall bias. Similarly, the information collected differs from patient-to-patient; for example, the UPDRS total score was collected for only 26.3% of the population; however, while missing data may result in an unrepresentative picture of the whole population, the number of observations is still large enough (e.g., 929 patients had data on UPDRS total score) to draw meaningful conclusions on accuracy and validity of the clinical indicators. Inevitably, the proportion of patients included from each country varied from the original target (with almost 30% of patients from the USA), but all G7 countries were well represented ($>$ 10% of the total sample); as such, the patients can be considered to be a broad international sample. The 'gold standard' used in this analysis was physician assessment of device-aided therapy eligibility in the next 24 months, which may not be as useful as using current eligibility, as has been used with assessments of other tools, such as MANAGE PD [22]. Also, with all 15 clinical indicators demonstrating good accuracy and validity, future research should focus on the accuracy of more concise combinations of these indicators to help physicians with their assessment of people with advancing PD.

CONCLUSIONS

Specific clinical indicators of advanced PD and device-aided therapy eligibility demonstrated robust screening accuracy and validity in a large, real-world sample of PD patients across G7 countries. While a large proportion of patients with PD are evaluated in centres where treating specialists have extensive experience of recognizing advanced features, many people with PD are not, which may result in a delay in considering potentially beneficial therapies. Recognizing advanced PD is critical to provide patients with access to potentially beneficial treatments, which may include device-aided therapy in a timely manner. These clinical indicators provide an objective and standardized approach to aid physicians in the timely identification and treatment optimization of patients with high unmet needs who are suboptimally controlled while on oral medications.

Inclusion of such criteria in clinical pathways and guidelines may help optimize PD symptom and treatment management. Future studies should evaluate the potential impact of timely PD treatment optimization on alleviating the burden of patients and care partners with PD.

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Data Availability. All authors have full control of all primary data. Restrictions may apply to the availability of these data, which were used under license for this study.

REFERENCES

1. Fasano A, Fung VSC, Lopiano L, et al. Characterizing advanced Parkinson's disease: OBSERVE-PD observational study results of 2615 patients. BMC Neurol. 2019;19:50.

2. Findley LJ, Wood E, Lowin J, Roeder C, Bergman A, Schifflers M. The economic burden of advanced Parkinson's disease: an analysis of a UK patient dataset. J Med Econ. 2011;14:130–9.

3. Brooks DJ. Optimizing levodopa therapy for Parkinson's disease with levodopa/carbidopa/entacapone: implications from a clinical and patient perspective. Neuropsychiatr Dis Treat. 2008;4:39–47.

4. Giugni JC, Okun MS. Treatment of advanced Parkinson's disease. Curr Opin Neurol. 2014;27:450–60.

5. Kulisevsky J, Luquin MR, Arbelo JM, et al. Advanced Parkinson's disease: clinical characteristics and treatment. Part II Neurologia. 2013;28:558–83.

6. Olanow CW, Obeso JA, Stocchi F. Drug insight: continuous dopaminergic stimulation in the

treatment of Parkinson's disease. Nat Clin Pract Neurol. 2006;2:382–92.

7. Santos-Garcia D, de Deus Fonticoba T, Suarez Castro E, Aneiros Diaz A, McAfee D. 5–2–1 Criteria: a simple screening tool for identifying advanced PD patients who need an optimization of Parkinson's treatment. Parkinsons Dis. 2020;2020:7537924 https://doi.org/10.1155/2020/7537924.

8. Tessitore A, Marano P, Modugno N, et al. Caregiver burden and its related factors in advanced Parkinson's disease: data from the PREDICT study. J Neurol. 2018;265:1124–37.

9. Schrag A, Hovris A, Morley D, Quinn N, Jahanshahi M. Caregiver-burden in parkinson's disease is closely associated with psychiatric symptoms, falls, and disability. Parkinsonism Relat Disord. 2006;12:35–41.

10. Oh YS, Lee JE, Lee PH, Kim JS. Neuropsychiatric symptoms in Parkinson's disease dementia are associated with increased caregiver burden. J Mov Disord. 2015;8:26–32.

11. Timpka J, Nitu B, Datieva V, Odin P, Antonini A. Device-aided treatment strategies in advanced Parkinson's disease. Int Rev Neurobiol. 2017;132:453–74.

12. Lokk J. Lack of information and access to advanced treatment for Parkinson's disease patients. J Multidiscip Healthc. 2011;4:433–9.

13. Titova N, Martinez-Martin P, Katunina E, Chaudhuri KR. Advanced Parkinson's or "complex phase" Parkinson's disease? Re-evaluation is needed. J Neural Transm (Vienna). 2017;124:1529–37.

14. Antonini A, Stoessl AJ, Kleinman LS, et al. Developing consensus among movement disorder specialists on clinical indicators for identification and management of advanced Parkinson's disease: a multi-country Delphi-panel approach. Curr Med Res Opin. 2018;34:2063–73.

15. Luquin MR, Kulisevsky J, Martinez-Martin P, Mir P, Tolosa ES. Consensus on the definition of advanced Parkinson's disease: a neurologists-based Delphi study (CEPA study). Parkinsons Dis. 2017;2017:4047392.

16. 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.

17. Anderson P, Benford M, Harris N, Karavali M, Piercy J. Real-world physician and patient behaviour across countries: disease-specific programmes—a means to understand. Curr Med Res Opin. 2008;24:3063–72.

18. Tsuboi Y, Nakagawa R, Ishido M, et al. The quality of life burden in advanced Parkinson's disease applying "5–2–1" diagnosing criteria: subgroup analyses of the JAQPAD (Japanese QOL survey of Parkinson's disease) study. Eur J Neurol. 2019;26 (Suppl. 1) 316.

19. Aldred J, Anca-Herschkovitsch M, Antonini A, et al. Application of the "5–2–1" screening criteria in advanced Parkinson's disease: interim analysis of DUOGLOBE. Neurodegener Dis Manag. 2020;10(5):309–23. https://doi.org/10.2217/nmt-2020-0021.

20. Levin J, Hasan A, Hoglinger GU. Psychosis in Parkinson's disease: identification, prevention and treatment. J Neural Transm (Vienna). 2016;123:45–50.

21. Barer Y, Gurevich T, Chodick G, et al. Advanced stage of Parkinson's disease: from identification to characterization and disease burden assessment using a nationwide database. Mov Disord. 2019;34(Suppl. 2):S739.

22. Antonini A, Odin P, Schmidt P, et al. Validation and clinical value of the MANAGE-PD tool: A clinician-reported tool to identify Parkinson's disease patients inadequately controlled on oral medications. Parkinsonism Relat Disord. 2021;92:59–66.