

ORIGINAL ARTICLE

Intercountry comparisons of advanced Parkinson's disease symptoms and management: Analysis from the OBSERVE-PD observational study

Alfonso Fasano^{1,2,3} | Victor S. C. Fung^{4,5} | Klaus Seppi⁶ | Zvezdan Pirtosek⁷ |
 Annamária Takáts⁸ | Ali Alobaidi⁹ | Koray Onuk⁹ | Lars Bergmann⁹ |
 Juan Carlos Parra⁹ | Bulent Elibol¹⁰

¹Edmond J Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN, Toronto, ON, Canada

²Division of Neurology, University of Toronto, Toronto, ON, Canada

³Krembil Research Institute, Toronto, ON, Canada

⁴Movement Disorders Unit, Westmead Hospital, Westmead, NSW, Australia

⁵Sydney Medical School, University of Sydney, Sydney, NSW, Australia

⁶Medical University Innsbruck, Innsbruck, Austria

⁷University Medical Center Ljubljana, Ljubljana, Slovenia

⁸Neurological Clinic of Semmelweis University, Budapest, Hungary

⁹AbbVie Inc., North Chicago, IL, USA

¹⁰Department of Neurology, Hacettepe University Hospitals, Ankara, Turkey

Correspondence

Alfonso Fasano, Chair in Neuromodulation and Multidisciplinary Care, Toronto Western Hospital, 399 Bathurst St, 7McL410, Toronto, ON, M5T 2S8, Canada. Email: alfonso.fasano@uhn.ca

Funding information This work was supported by AbbVie Inc., North Chicago, IL, USA.

Objectives: In the absence of widely accepted criteria, determining when a patient with Parkinson's disease (PD) may benefit from more advanced treatments such as device-aided therapy (DAT) so far remains a matter of physician judgment. This analysis investigates how classification of PD varies across countries relative to measures of disease severity.

Materials and Methods: The OBSERVational, cross-sectional PD (OBSERVE-PD) study included consecutive patients with PD at centers that offer DATs in 18 countries. In this subgroup analysis, we explore intercountry differences in identification of advanced versus non-advanced PD based on physician's clinical judgment, symptoms assessed using Delphi consensus criteria, use of DAT, motor and non-motor symptoms, and caregiver support. Demographic and clinical characteristics were obtained through review of medical records.

Results: Overall, 1342 of 2615 patients (51.3%) were assessed by physicians as having advanced PD. The proportion of patients in different countries identified as having advanced PD (24.4–82.2%) varied. In 15 of 18 countries, a greater proportion of patients with advanced PD, according to select Delphi criteria, were identified by physicians as having advanced PD than with non-advanced PD. There was a wide variability across countries in the proportion of patients with no dyskinesia, disabling dyskinesia, dyskinesia pain, and non-motor symptoms who were identified by physicians as having advanced versus non-advanced PD.

Conclusions: The proportion of patients identified with advanced PD symptoms varies widely across countries, despite differences on the patients' profiles, indicating a need for objective diagnostic criteria to help identify patients who may benefit from DAT.

KEYWORDS

apomorphine, deep-brain stimulation, Delphi study, infusion pump, intractable tremor, levodopa-carbidopa drug combination, Parkinson's disease

1 | INTRODUCTION

Patients with Parkinson's Disease (PD) often experience worsening motor and non-motor symptoms as the disease progresses.¹ As these symptoms advance, they often become disabling and severely impact patient quality of life and increase the burden on caregivers.² Patients with advanced PD may become refractory to initial oral levodopa therapy and require more advanced treatments, including deep-brain stimulation (DBS), levodopa-carbidopa intestinal gel (LCIG), or continuous subcutaneous apomorphine infusion (CSAI) to adequately manage symptoms.¹ However, determining the optimal timing for initiation of these advanced therapies is challenging, and physicians and their patients are left to make this decision with little guidance from well-designed clinical trials.¹ Among other challenges, the clinical course for patients with PD is variable, and the extent to which non-motor symptoms impact patients with advancing disease has only recently received increased consideration.³

A Delphi consensus panel has developed clinical criteria with a view to define the features of advanced PD to help clinicians identify patients that may benefit from more advanced therapies.⁴ An abbreviated version of these criteria, referred to as 5-2-1 criteria (≥ 5 doses of oral levodopa per day and/or ≥ 2 h of "Off" time, and/or ≥ 1 h of troublesome dyskinesia in a waking day), have since been applied to a group of patients identified as having advanced PD in the DUOGLOBE (DUOdopa/Duopa in Patients with Advanced Parkinson's Disease—a GLoBal Observational Study Evaluating Long-Term Effectiveness) study.⁵ In this study, 80 of 82 patients met at least one of the 5-2-1 criteria.

The international OBSERVE-PD (OBSERVational, cross-Sectional PD) study examined the characteristics of 2615 patients identified as having advanced or non-advanced PD in 18 countries.⁶ A little over half of patients (51.3%) were classified by physicians as having advanced PD, and the remainder as having non-advanced PD. Patients identified by physicians as having advanced PD in this study showed significantly greater disease burden in measures of activities of daily living, quality of life, motor symptom severity, duration of dyskinesia, and "Off" time than did patients identified as having non-advanced PD. There was a moderate correlation between physician-identified advanced PD, and advanced PD as identified by the Delphi criteria (correlation coefficient = 0.441; 95% confidence interval [95% CI], 0.408–0.473). Despite this correlation, there was wide variability across countries in the proportion of patients identified as having physician-identified advanced PD (24–82%). While patient characteristics from individual study countries have been explored,^{7–10} no studies have examined data between countries. This analysis of the OBSERVE-PD study data provides intercountry comparisons of patient clinical and demographic characteristics, treatment decisions, motor symptoms, non-motor symptoms, and caregiver support for patients identified as having advanced versus non-advanced PD.

2 | MATERIALS AND METHODS

2.1 | Study design and treatment

This is a subgroup analysis of the OBSERVE-PD study focusing on results from individual countries; primary results of this study and detailed methods have been published previously.⁶ Briefly, the OBSERVE-PD study was a multicenter, cross-sectional, non-interventional, observational study conducted across 128 movement disorders centers in 18 countries (Australia, Austria, Belgium, Canada, Croatia, Czech Republic, Germany, Greece, Hungary, Ireland, Israel, Italy, Romania, Russia, Slovakia, Slovenia, Switzerland, and Turkey).⁶ Study sites were selected based on the availability of DAT as offered by an expert or specialist team (Table S1). Data collection occurred between February 8, 2015, and January 14, 2016.

2.2 | Patients

The study included patients with PD who attended a routine visit in a participating clinic. To avoid selection bias, consecutive patients were offered the opportunity to participate. Eligible patients included adults diagnosed with PD who spoke the language of the respective country, could provide answers to the questionnaire written in the native language, and were willing to sign a patient authorization form or informed consent form. The study was conducted in compliance with local laws and regulations and followed Good Pharmacoepidemiology Practice for non-interventional studies. Patients were not included if they were in the "Off" stage at the time of the visit, if they were participating in another clinical study, or if there was significant uncertainty about the PD diagnosis (i.e., symptoms including early falls, early autonomic disturbances, or lack of responsiveness to levodopa).

2.3 | Assessments

Data were collected at a single study visit and from review of patient records. Patients were identified as having advanced or non-advanced PD according to physician judgment. The physician then assessed patients using the Delphi consensus criteria.⁴ While the 5-2-1 criteria mentioned above provides a simple and pragmatic screening approach for the identification of patients with PD whose symptoms were uncontrolled while receiving oral medications, select criteria to identify patients with advanced PD used in this study were derived from the second round of the Delphi consensus panel and included presence of moderate or severe motor fluctuations, occurrence of ≥ 2 h of "Off" time in a waking day, occurrence of ≥ 2 h of troublesome dyskinesia in a waking day, use of ≥ 5 doses of oral levodopa per day, and report of moderate or severe limitations on one or more activities of daily living.^{4,6}

Other assessments at the patient visit included a physician assessment of PD stage, demographics, current PD treatments, comorbidities, and scores on the Unified Parkinson's Disease Rating Scale (UPDRS) part IV (complications) and Non-Motor Symptom Scale (NMSS). All permissions were obtained. Patient demographic data, referral history, PD-related data, PD treatment history, and comorbidities were collected via interview with the patient and/or a review of patient records.

2.4 | Statistical analysis

This planned analysis evaluated intercountry differences in patient clinical characteristics, treatment patterns, motor symptoms, and non-motor symptoms. Data were summarized using descriptive statistics. The *p* values were generated using the binomial test or the chi-squared test. Analyses were performed using SAS version 9.2 or higher (SAS Institute).

3 | RESULTS

3.1 | Patients

Overall, 1342 of 2615 patients (51.3%) enrolled in the study had advanced PD, as assessed by physician clinical judgment. However, there was a wide intercountry range for the proportion of patients identified by physicians as having advanced PD (29 of 119 patients [24.4%] to 60 of 73 patients [82.2%]) or non-advanced PD (13 of 73 patients [17.8%] to 90 of 119 patients [75.6%]; [Table 1](#); [Figure 1](#)). There was also a large degree of intercountry variation in demographic data and clinical characteristics between those with advanced PD and those with non-advanced PD ([Table 1](#)).

Patients classified as having advanced PD were slightly older and had a longer time since PD diagnosis and a longer duration of motor fluctuations. Most patients in the advanced and non-advanced PD groups were receiving oral levodopa treatment in all countries; overall, 1227 of 1342 patients (91.4%) with advanced PD and 983 of 1273 patients (77.2%) with non-advanced PD were receiving oral levodopa/carbidopa or benserazide. As expected, greater proportions of patients with non-advanced PD versus advanced PD were receiving one or two drug classes for PD (906 of 1273 patients [71.2%] with non-advanced PD and 715 of 1342 patients [53.3%] with advanced PD), and greater proportions of patients with advanced PD versus patients with non-advanced PD were receiving three or four drug classes for PD (543 of 1342 patients [40.5%] with advanced PD and 306 of 1273 patients [24.0%] with non-advanced PD). These trends were consistent across almost all countries.

In 17 of 18 countries, 55 of 101 patients (54.5%) to 82 of 95 patients (86.3%) identified with advanced PD were receiving caregiver support at the time of assessment. Among patients with both

advanced and non-advanced PD receiving caregiver support in 17 of 18 countries, 13 of 25 patients (52.0%) to 29 of 34 patients (85.3%) were receiving support from their spouse or partner.

While 882 of 1342 patients (65.7%) identified as having advanced PD were eligible for DAT ([Table 1](#)), the proportion of all eligible patients who use DAT varied between all countries (2 of 62 patients [3.2%] to 42 of 62 patients [67.7%]). At the time of study visit, more than half of the patients who were receiving DAT were treated with deep-brain stimulation (DBS) in 12 of 18 countries, or levodopa-carbidopa intestinal gel (LCIG) in five of 18 countries ([Table 2](#)). Continuous subcutaneous apomorphine infusion (CSAI) was used only in seven countries based on local availability/approval and was never the most used DAT. At study visit, patients in 17 countries were planning to initiate DAT. The proportion of eligible patients planning to initiate DAT varied between countries (2 of 52 patients [3.8%] to 35 of 62 patients [56.5%]). Among patients planning to initiate DAT in a given country, over half were planning to initiate LCIG in five countries, or DBS in seven countries; fewer than half of patients in each country were planning to initiate CSAI ([Table S2](#)).

3.2 | Assessments based on Delphi criteria

Overall, 1968 of 2533 patients (77.7%) had advanced PD and 565 of 2533 patients (22.3%) had non-advanced PD, according to select Delphi criteria. Among those patients identified as having advanced PD by physicians, 1293 of 1340 (96.5%) had advanced PD according to select Delphi criteria, and 675 of 1193 patients (56.6%) with physician-identified non-advanced PD had advanced PD according to select Delphi criteria. A greater proportion of patients with advanced PD according to select Delphi criteria had been identified by physicians as having advanced PD versus non-advanced PD ([Figure 1](#)). Conversely, a greater proportion of patients with non-advanced PD according to select Delphi criteria were classified by physicians as having non-advanced PD than advanced PD; in two countries, no patients were regarded as having non-advanced PD according to select Delphi criteria.

When looking at patient characteristics according to advanced PD or non-advanced PD as assessed by select Delphi criteria ([Table S3](#)), there were no substantial deviations from the data shown in [Table 1](#).

3.3 | Motor and non-motor symptoms

Most patients reporting a duration of dyskinesia (UPDRS IV question 32) for any amount of time during the day were identified by physicians as having advanced PD versus non-advanced PD (all countries, 837 of 1008 patients [83.0%] versus 171 of 1008 patients [17.0%], $p < .0001$; [Figure 2](#)). In all countries, a greater proportion of patients with dyskinesias that were mildly or moderately disabling (per UPDRS IV question 33) were identified as having advanced

TABLE 1 Intercountry range in demographics and clinical characteristics at study visit

Characteristic	Intercountry range	
	Advanced PD (n = 1342)	Non-advanced PD (n = 1273)
Physician-identified advanced or non-advanced PD, %	24.4–82.2	17.8–75.6
Age, years	64.1 (8.6)–71.3 (10.4)	62.4 (11.4)–70.4 (9.0)
Sex, %		
Male	24.7–81.8	18.2–75.3
Female	23.7–82.8	17.2–76.3
Education ^a , %		
No formal education	0–100	0–100
Primary school	25.0–83.3	16.7–75.0
Secondary school	20.0–86.5	13.5–80.0
Non-university professional education	14.3–92.7	7.3–85.7
University	16.7–78.9	21.1–83.3
Higher education than university	0–100	0–100
Time since PD diagnosis, years	7.5 (4.6)–14.3 (6.4)	2.8 (1.8)–6.6 (4.6)
Motor fluctuations, %	49.6–96.2	3.8–50.4
Duration of motor fluctuations ^b , years	3.3 (2.1)–8.6 (5.7)	1.0 (0.0)–4.1 (2.8)
Criteria-assessed advanced or non-advanced PD ^{c,d} , %		
Advanced PD	27.4–96.2	3.8–72.6
Non-advanced PD	0–40.0	60–100
Type of PD treatment ^e , %		
Any	92.0–100	85.2–100
Oral levodopa/carbidopa or benserazide	68.0–99.0	64.0–88.9
Oral dopamine agonist(s)	27.6–81.3	20.0–82.6
MAOB inhibitors	5.0–55.8	6.3–70.0
COMT inhibitors	11.0–50.0	0–34.6
Amantadine	9.1–51.4	0–47.8
Other	5.7–23.0	1.9–23.1
Number of current PD treatments, %		
1	13.6–100	0–86.4
2	18.2–80.0	20.0–81.8
3	38.9–96.3	3.7–61.1
4	42.9–100	0–57.1
5	0–100	0–100
Eligible for DAT, %	40.4–100	0–59.6
Caregiver support ^f		
Yes	46.0–86.3	0–48.9
No	12.0–54.0	46.7–100
Type of caregiver support ^f , %		
Partner/spouse	50.0–85.5	40.7–100
Family/friends	14.5–78.2	0–43.8
Hired home aide	0–42.9	0–37.0
Healthcare professional	0–25.0	0–33.3
Other	0–10.5	0–7.7

Note: Data are presented as the minimum–maximum values for intercountry range of mean (SD), unless otherwise specified. Percentages represent the proportion of patients with a given characteristic diagnosed with advanced versus non-advanced PD according to the physician. Patients were then assessed as having advanced or non-advanced PD determined by select Delphi criteria where advanced PD symptoms were defined as presence of moderate or severe motor fluctuations, occurrence of ≥ 2 h of “Off” time in a waking day, occurrence of ≥ 2 h of troublesome dyskinesia in a waking day, use of ≥ 5 doses of oral levodopa per day, and report of moderate or severe limitations on ≥ 1 activities of daily living.

Abbreviations: COMT, catechol-o-methyltransferase; DAT, device-aided therapy; MAOB, monoamine oxidase B; PD, Parkinson's disease.

^aData are for countries reporting $n \geq 1$ at the specified education level.

^bOnly includes patients with motor fluctuations at study visit.

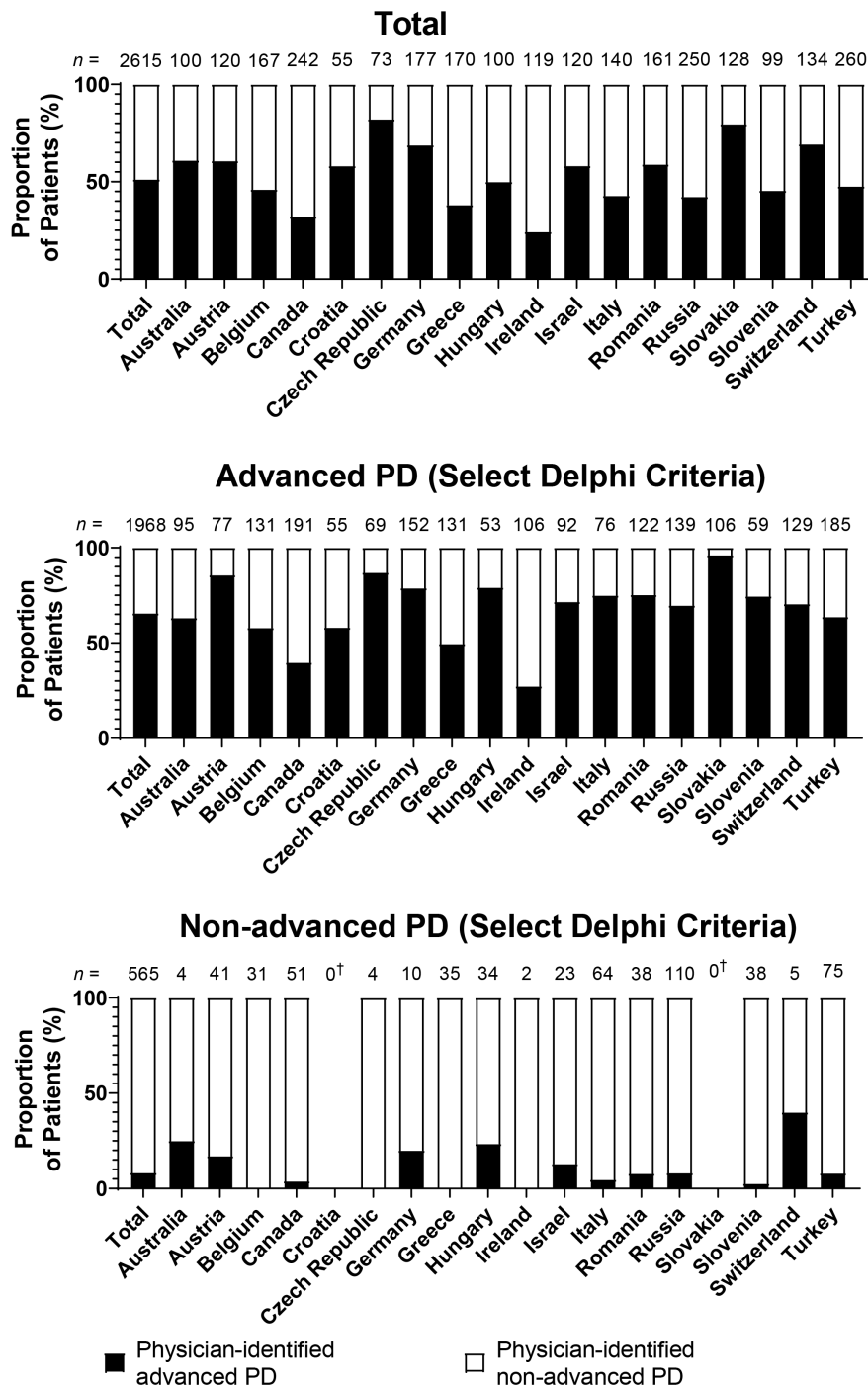
^cAs defined by select Delphi criteria.⁴

^dData are for countries reporting $n \geq 1$ for non-advanced PD or advanced PD as assessed by select Delphi criteria.

^eProportions are calculated from the total number of patients with advanced PD or non-advanced PD receiving a particular therapy.

^fProportions are calculated from the total number of patients with advanced PD or non-advanced PD receiving a particular type of caregiver support.

FIGURE 1 Classification of advanced or non-advanced PD according to select Delphi criteria among patients with physician-assessed advanced or non-advanced PD by country. Total numbers of patients with physician-assessed advanced versus non-advanced PD for each country have been reported previously.⁶⁻¹⁰ Advanced PD according to select Delphi criteria were defined as presence of moderate or severe motor fluctuations, occurrence of ≥ 2 h of "Off" time in a waking day, occurrence of ≥ 2 h of troublesome dyskinesia in a waking day, use of ≥ 5 doses of oral levodopa per day, and report of moderate or severe limitations on ≥ 1 activities of daily living.[†]No enrolled patients in Croatia or Slovakia had non-advanced PD as identified by select Delphi criteria. PD, Parkinson's disease



versus non-advanced PD (573 of 657 patients [87.2%] versus 84 of 657 patients [12.8%], $p < .0001$; Figure S1). All patients with dyskinesias that were completely disabling ($n = 9$) were identified as having advanced PD, while in 15 of 18 countries, most patients with dyskinesias that were not disabling were identified as having non-advanced PD.

In 16 of 18 countries, 30 of 47 patients (63.8%) to 100% (multiple n's) of patients who reported dyskinesia pain (per UPDRS IV question 34) that was slight, moderate, or severe were identified as having advanced PD (Figure S2). All patients with marked dyskinesia pain ($n = 7$) were identified as having advanced PD.

The mean NMSS total and domain scores were higher for patients identified as having advanced PD than for patients with non-advanced PD in all countries (NMSS total score, 58.6 versus 34.4, $p < .0001$), indicating a greater burden of non-motor symptoms among patients identified as having advanced PD (Figure S3, Table S4). NMSS domain scores varied by country, with the highest intercountry ranges for patients with advanced PD reported for the domains of mood/cognition and sleep/fatigue (Table S4). Overall, most patients with non-motor symptoms that were mild (NMSS, 1-20) were identified as having non-advanced PD versus advanced PD (389 of 578 patients [67.3%] versus 189 of 578 patients [32.7%],

TABLE 2 Type of DAT at study visit by country

Country	LCIG, n (%)	DBS, n (%)	CSAI, n (%)	Total patients using DAT, n
Australia ^a	11 (26.2)	27 (64.3)	9 (21.4)	42
Austria	5 (16.1)	21 (67.7)	5 (16.1)	31
Belgium	8 (28.6)	20 (71.4)	0 (0)	28
Canada	4 (22.2)	14 (77.8)	0 (0)	18
Croatia ^a	5 (100)	1 (20.0)	0 (0)	5
Czech Republic	2 (10.5)	17 (89.5)	0 (0)	19
Germany ^a	5 (20.0)	19 (76.0)	5 (20.0)	25
Greece ^a	4 (33.3)	9 (75.0)	0 (0)	12
Hungary	15 (62.5)	9 (37.5)	0 (0)	24
Ireland ^{a,b}	3 (30.0)	7 (70.0)	3 (30.0)	10
Israel	5 (50.0)	5 (50.0)	0 (0)	10
Italy	7 (36.8)	12 (63.2)	0 (0)	19
Romania	29 (100)	0 (0)	0 (0)	29
Russia	0 (0)	2 (100)	0 (0)	2
Slovakia	26 (72.2)	7 (19.4)	3 (8.3)	36
Slovenia	8 (61.5)	5 (38.5)	0 (0)	13
Switzerland	6 (15.4)	32 (82.1)	1 (2.6)	39
Turkey ^a	10 (27.0)	22 (59.5)	7 (18.9)	37

Note: Overall patient numbers for Australia, Hungary, Italy, and Switzerland have been previously reported.^{7,9-11}

The percent of patients reported is the proportion of patients in a country using a particular DAT out of the total patients using DAT in that country.

Abbreviations: CSAI, continuous subcutaneous apomorphine infusion; DAT, device-aided therapy; DBS, deep-brain stimulation; LCIG, levodopa-carbidopa intestinal gel.

^aPatients in this country have more than one type of DAT.

^bOne patient received invasive treatment other than LCIG, DBS, or CSAI.

$p < .0001$; Figure S4). Overall, most patients with very severe non-motor symptoms (NMSS, >70) were identified as having advanced PD versus non-advanced PD (338 of 446 patients [75.8%] versus 108 of 446 patients [24.2%], $p < .0001$).

4 | DISCUSSION

This analysis highlights the regional differences in the classification of PD, as well as patient characteristics, disease symptoms, disease management, and caregiver support among patients with physician-identified advanced versus non-advanced PD. While detailed patient characteristics and assessments for some individual countries from the OBSERVE-PD study have been published,⁷⁻¹¹ data presented here provide additional important insight into the intercountry variability within the OBSERVE-PD study. Patients with advanced PD generally exhibited greater disease burden, but there was wide intercountry variability in the proportions of patients with advanced versus non-advanced PD exhibiting

individual clinical characteristics and symptoms, including age, sex, and time since diagnosis.

The presence of dyskinesia generally resulted in a diagnosis of advanced PD, highlighting the importance of this symptom in determining the severity of PD. In most countries in this study, more than half of patients with no dyskinesia duration (UPDRS part IV question 32) or disability (question 33) were identified as having non-advanced PD. All patients in the study with marked dyskinesia pain (UPDRS part IV question 34) and with dyskinesia that was completely disabling (question 33) were identified by physicians as having advanced PD. It is possible that any differences in dyskinesia burden observed across countries among patients with advanced PD may be due to higher levels of levodopa and lower dopamine agonist use. This underscores the need for treatment that adequately manages symptoms in patients with advanced PD.

As with dyskinesia, the severity of non-motor symptoms generally aligned with physician identification of advanced versus non-advanced PD. Patients diagnosed with advanced PD had higher mean NMSS total scores in all countries studied, and overall, patients with advanced PD had significantly higher NMSS subdomain scores. In most countries, over half of the patients with an NMSS score of "very severe" (NMSS >70) were identified as having advanced PD, while more than half of patients with "mild" scores (NMSS 1-20) were identified as having non-advanced PD. Non-motor symptoms are an important, but often overlooked aspect of PD,¹² and the intercountry variation in non-motor symptom burden in our study may reflect this.

More than half of those patients identified by physicians as having non-advanced PD had advanced PD as identified by select Delphi criteria, suggesting that many patients identified by physicians as having non-advanced PD are not receiving adequate symptom control. This, therefore, suggests a need for validated universal criteria to identify patients who may benefit from optimized treatment regimens including more advanced therapies.

To our knowledge, the OBSERVE-PD study represents the first observational analysis of intercountry difference in identifying patients as having an advanced or non-advanced disease. As anticipated, analysis of the entire study population indicates significant differences between these two groups.⁶ We would expect clinical characteristics of patients identified as having advanced PD or non-advanced PD to generally be similar across countries. However, it is clear from our analysis that there are differences as to how physicians identify advanced and non-advanced PD in different regions, resulting in intercountry differences in the clinical characteristics of these patients. Regional variations in the epidemiology of PD have been well documented, with higher prevalence in North America, Eastern Europe, and Australia.^{13,14} Another observational study, conducted entirely within Romania with the aim of characterizing patients with advanced PD and examining suitability for DAT, found large variability in symptoms and characteristics between patients, even within the same country, driven at least in part by the availability of DAT at different centers (DBS was available at only one

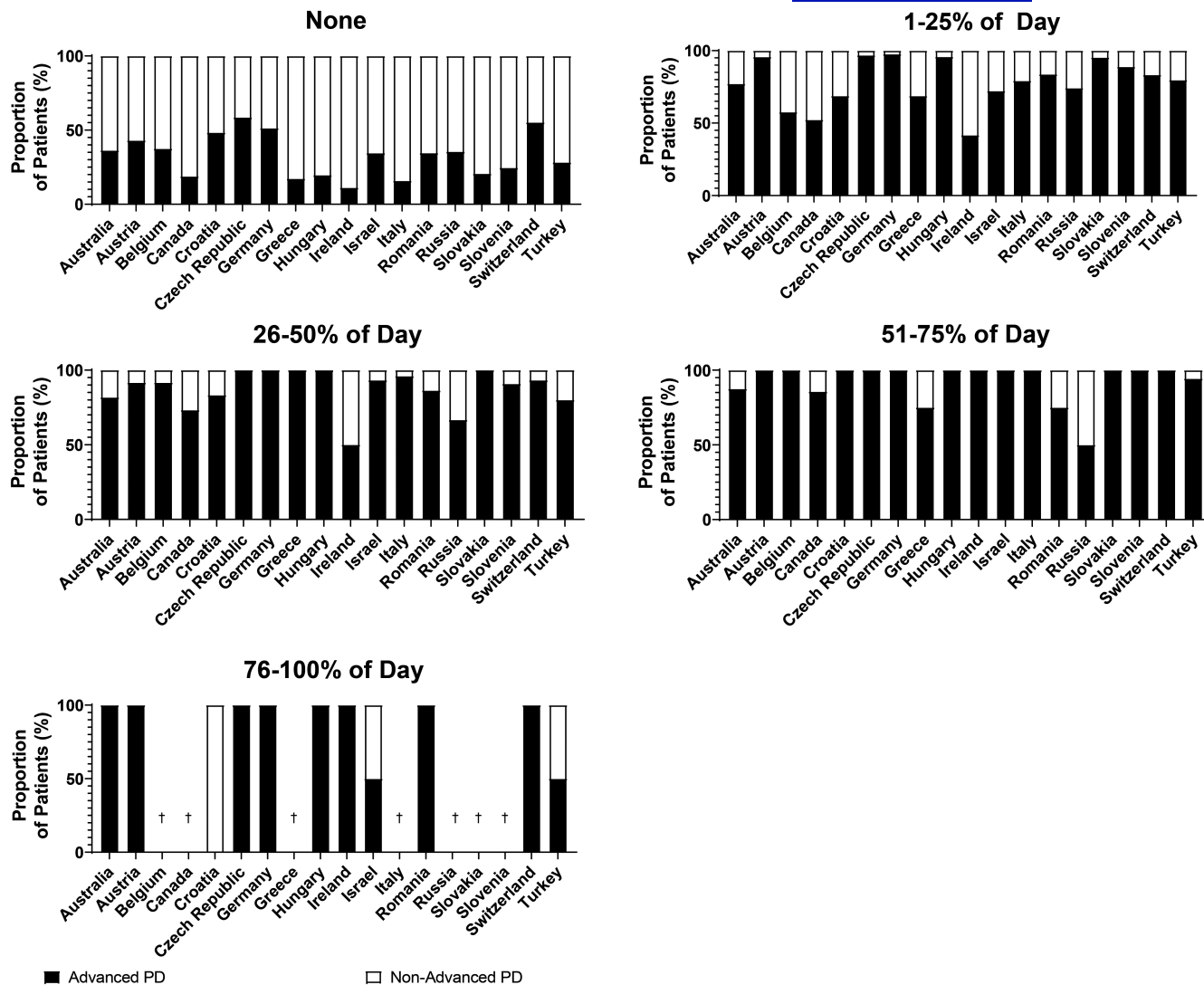


FIGURE 2 Dyskinesia duration by country. Values are based on question 32 from the UPDRS part IV. †Indicates no patients matched the criteria for a given country. Overall patient numbers for Hungary and Switzerland have been previously reported.^{9,10} PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale

center).¹⁵ Although the study does not provide the same cross-country insights observed here, it does highlight the potential for regional variation.

One explanation for the regional variation observed in this study could involve cultural factors related to patient self-perception, use of healthcare resources, caregiving, and treatment practices for patients with PD. Findings from studies have shown intercountry differences in caregiver demographics, the amount of burden, and time spent caregiving, possibly because of differences in the availability of social support and cultural attitudes toward familial caregiving.^{16,17} Likewise, cultural differences have been attributed to different outcomes in cognitive testing.¹⁸ Furthermore, there could be differences in medical practice that determine how and when patients are referred to a unit that offers DAT,¹⁹ where all the patients in this study were assessed. Regional differences in healthcare costs and availability could also contribute to the variability observed in this study. Healthcare costs related to PD have shown considerable

intercountry variation, due in part to differences in the number of specialist visits, and differences in prescribing patterns.²⁰ Access to healthcare resources, driven by both geography and the structure of the healthcare system itself, is another potential barrier to efficient diagnosis and symptom management. The relative number and location of movement disorder centers that offer DAT in each country may have an important impact on which patients are referred to such clinics. This contention is supported by findings in an earlier study that observed that patients in an urban area had more physician visits were more likely to have DAT and used a significantly higher daily levodopa equivalent dose than did those patients from a rural area.²¹ Finally, the centers and clinics within each country that participated in this global study could have introduced some variability.

Another possible reason for regional variation may lie in the specific differences of participating centers. The observational OBSERVE-PD study was prospectively designed to assess patients

identified as having advanced versus non-advanced PD, with planned analysis within each participating country to allow regional evaluation of over 2500 patients. However, the study was only conducted at select movement disorder centers in each country. As a result, the OBSERVE-PD study is not a comprehensive epidemiologic study, and site geography and patient access may be sources of variability. Although the movement disorder centers included in the study gave access to a greater number of patients with advanced PD, general neurology practices were not included, allowing for possible selection bias. Another potential source of regional variability is the availability of select DATs in each country. In this study, CSAI use was documented in only seven of 18 countries, suggesting that the availability of this treatment modality varies across countries.

Reasons patients with advanced PD were not using DAT in the OBSERVE-PD study have been reported previously, with the most common being "patient needs more time to decide," and "patient refusal."⁶ Reimbursement was not reported as a reason not to use DAT among any of the patients with advanced PD. However, the rationale and decision-making to implement DAT, as well as selection of DAT type (DBS, CSAI, or LCIG) were at the discretion of patients and physicians, and not captured in this analysis. Therefore, the full impact of patient and physician preference versus reimbursement on treatment decisions is unclear.

The individual factors that influenced physician judgment of advanced PD or non-advanced PD were not captured in this analysis and may represent an additional source of variability. Even so, the OBSERVE-PD study includes a real-world application of the Delphi consensus criteria. The overall data from the OBSERVE-PD study indicate that the Delphi criteria were moderately correlated with physician judgment, with two of 11 of the criteria having a statistically significant correlation.⁶ While the OBSERVE-PD study used the benchmarked second-round criteria rather than the final Delphi consensus criteria, most items applied in the OBSERVE-PD study remained unchanged from the published criteria.⁴

The 5-2-1 criteria, derived from the Delphi consensus panel, provides an abbreviated and effective screening tool to identify patients whose symptoms are uncontrolled on oral therapy. A post hoc analysis of an interim DUOGLOBE study analysis found that 80 of 82 patients with advanced PD were correctly classified using the 5-2-1 criteria.⁵ However, the 5-2-1 criteria does not differentiate between patients who would benefit from optimized oral therapy versus DAT. Given the need for validated universal criteria to help optimize treatment regimens for patients who would benefit from more advanced therapies, the Making Informed Decisions to Aid Timely Management of Parkinson's Disease (MANAGE PD) tool was developed to assist in identifying patients who are not receiving optimized treatment.²² Many of the criterion in the final MANAGE PD tool align with the select Delphi criteria for advanced and non-advanced PD investigated in our analysis.

In this analysis of the OBSERVE-PD study, we saw large inter-country variation in the proportion of patients identified as having advanced PD versus patients with non-advanced PD. Overall, more than half of patients identified by physicians as having non-advanced

PD have advanced PD according to select Delphi criteria, indicating a need for optimized therapy in these patients. The broad differences in patient characteristics, symptoms, and treatment decisions underscore the need for unified criteria and/or guidelines to help identify those patients who may benefit from more advanced therapy to achieve their treatment objectives.

AUTHOR CONTRIBUTIONS

A.F. contributed to conceptualization (lead), methodology (lead), writing original draft (equal), and review and editing (equal). V.S.C.F. contributed to the investigation (supporting), writing original draft (equal), and review and editing (equal). K.S. contributed to the investigation (supporting), writing original draft (equal), and review and editing (equal). Z.P. contributed to the investigation (supporting), writing original draft (equal), and review and editing (equal). A.T. contributed to the investigation (supporting), writing original draft (equal), and review and editing (equal). A.A. contributed to conceptualization (equal), methodology (equal), writing original draft (equal), and review and editing (equal). K.O. contributed to conceptualization (lead), formal analysis (lead), methodology (lead), writing original draft (equal), and review and editing (equal). L.B. contributed to conceptualization (equal), methodology (lead), writing original draft (equal), and review and editing (equal). J.C.P. contributed to the formal analysis (equal), writing original draft (equal), and review and editing (equal). B.E. contributed to the investigation (supporting), writing original draft (equal), and review and editing (equal).

ACKNOWLEDGMENTS

AbbVie Inc. participated in the study design; study research; collection, analysis, and interpretation of data; and writing, reviewing, and approving this manuscript for submission. AbbVie provided writing support for this manuscript. Medical writing assistance, funded by AbbVie, was provided by James Street, PhD, Alicia Salinero, PhD, ISMPP CMPP, Kersten Reich, MPH, ISMPP CMPP, and Marion France, PhD, of JB Ashtin.

CONFLICT OF INTEREST

A.F. is a study investigator and an external study consultant who has served as an advisor for AbbVie, and a consultant for Abbott, UCB Pharma, Medtronic, Boston Scientific, and AbbVie. He has received research support from Medtronic, Boston Scientific, University of Toronto, Michael J. Fox Foundation for Parkinson's Research, and honoraria for serving as a speaker from UCB, Medtronic, Novartis, Chiesi, Boston Scientific, AbbVie, and Teva. V.S.C.F. receives a salary from NSW Health. He has received unrestricted research grants from AbbVie and Merz; is on advisory boards and/or has received travel grants from AbbVie, Allergan, Cavion, Ipsen, Merz, Praxis, Seqirus, Stada, Teva, and UCB; and receives royalties from Health Press Ltd. K.S. reports personal fees from Teva, UCB, Lundbeck, AOP Orphan Pharmaceuticals AG, Roche, Grünenthal, Stada, Licher Pharma, Biogen, BIAL and AbbVie, honoraria from the International Parkinson and Movement Disorders Society, research grants from FWF Austrian Science Fund, Michael J. Fox Foundation, and AOP

Orphan Pharmaceuticals AG, outside the submitted work. Z.P. was a study investigator and has received compensation from AbbVie for speaker-related activities. A.T. was a study investigator and has served as an advisor for AbbVie. She has also served as a consultant for UCB pharma, Ever Pharma, TEVA, and AbbVie, and has received honoraria from UCB, MERZ, AbbVie, and Teva for serving as speaker. A.A., K.O., L.B., and J.C.P. are employees of AbbVie and may hold AbbVie stock and/or stock options. B.E. was a study investigator, has served as a local advisor for AbbVie, and has received honoraria from AbbVie for serving as a speaker.

ETHICAL APPROVAL

The study was conducted in compliance with local laws and regulations and followed Good Pharmacoepidemiology Practice for non-interventional studies. The local ethics committees that provided approval included those in Austria (Ethik Kommission des Landes Oberösterreich, Ethikkommission der Medizinischen Universität Innsbruck, Ethik Kommission des Bundeslandes Niederösterreichs), in Belgium (Universitair Ziekenhuis Antwerpen), in Canada (REB of Centre intégré de santé et de services sociaux de Chaudière-Appalach [MSSS pour les centres du Québec], Health Research Ethics Boards [UofA], Western University Health Science REB [HSREB], MSSS [authorized by MUHC], Ottawa Health Science Network REB, Conjoint Health Research Ethics Board of the University of Calgary, Queen's University Health Sciences & Affiliated teaching hospitals REB [HSREB], University Health Network REB, IRB Services [Advarra], REB Horizon Health Network, MSSS [authorized by JGH], IRB Services [Advarra]), in Switzerland (Ethikkommission Ostschweiz Kantonsspital), in Germany (Ethikkommission der Universität zu Köln, Ethikkommission der Landesärztekammer Brandenburg, Ethikkommission Ärztekammer Niedersachsen, Ethikkommission der Landesärztekammer Thüringen, Ethik-Kommission Landesärztekammer Baden-Württemberg, Ethik-Kommission Albert-Ludwigs-Universität Freiburg, Ethik-Kommission der Ärztekammer Berlin, Ethikkommission Ärztekammer Nordrhein, Ethik-Kommission der Bayerischen Landesärztekammer, Ethikkommission der Ärztekammer Hamburg, Ethikkommission Ärztekammer Niedersachsen, Ethik-Kommission Rheinische Friedrich-Wilhelms-Universität Medizinische Fakultät, Ethikkommission Ärztekammer Sachsen-Anhalt, Ethikkommission Ärztekammer Niedersachsen, Ethikkommission Ärztekammer Nordrhein), in Greece (Ethics Committee of General Hospital of Thessaloniki "G. Papanikolaou", Ethics Committee of General Hospital of Thessaloniki "Papageorgiou", Ethics Committee of 251 Airforce General Hospital, Ethics Committee of Naval Hospital of Athens, Ethics Committee of University General Hospital "Attikon", Ethics Committee of University General Hospital of Heraklion, Ethics Committee of University General Hospital of Patras, Ethics Committee of Mediterraneo Hospital, Ethics Committee of University General Hospital of Alexandroupoli, Ethics Committee of HYGEIA Hospital, Ethics Committee of General Hospital of Athens "G. Gennimatas", Ethics Committee of University General Hospital of Thessaloniki "Axepa", Ethics Committee of University General Hospital of Ioannina, Ethics Committee of 417 Nursing Institution of Partecipial Army Fund [NIMTS]), in Ireland

(Education and Research Committee St Vincent's University Hospital, Joint Research Ethics Committee SJH/AMNCH, Clinical Research Ethics Committee of the Cork Teaching Hospitals, Galway research ethics committee), in Israel (E. Wolfson Medical Center Helsinki Committee, IRB Committee Sheba Medical Center Israel, Tel Aviv Sourasky Medical Center Institutional Review Board, Ethics committee of Rabin Medical Center), in Italy (Comitato Etico delle Aziende Sanitarie dell'Umbria di Perugia, Comitato Etico Regional [CER] delle Marche c/o AUO Ospedali Riuniti, Comitato Etico AOU di Cagliari, Comitato Etico Indipendente Azienda Ospedaliero Universitaria Policlinico Consortiale di Bari, Comitato Etico Interaziendale AOU Città della Salute e della Scienza di Torino AO Ordine Mauriziano - ASL TO1, Comitato Etico Interaziendale della Provincia di Messina AOU Policlinico "G Martino", Comitato Etico Area Vasta Centro c/o AOU Careggi, Comitato Etico Indipendente dell'Azienda Ospedaliera Universitaria Policlinico Tor Vergata di Roma, Comitato Etico Seconda Università degli Studi di Napoli Azienda Ospedaliera Universitaria SUN-AORN "Ospedali dei Colli"), in Turkey (Kocaeli University Medical Faculty Ethics Committee), in the Czech Republic (Ethics Committee of the General Hospital of Charles University in Prague, Ethics Committee of the St Anna Hospital of Masaryk University in Brno), in Slovakia (the local legislation valid at that time of 2015 did not impose an obligation to approve epidemiological observational studies by the ethics committee; therefore, the opinions of the two ethics committees in the Czech Republic can be used to comply with the ethical principles in both countries), in Russia (Advisory Council on Ethics St Petersburg State Budgetary Healthcare Institution City Hospital No 40, Ethics Committee of the Federal State Budgetary Institution State Research Center, Independent Interdisciplinary Committee for Ethical Review of Clinical Studies [125,468, Moscow, Leningradskiy prospect 51]), in Romania (National Commission of Bioethics [Comisia Nationala de Bioetica a Medicamentului si a Dispozitivelor Medicale]), in Hungary (Ethics committees of the Medical Research Council of Hungary [ETT] Egészségügyi Tudományos Tanács Klinikai Farmakológiai Etikai Bizottsága), in Slovenia (Republic of Slovenia Medical Ethics Committee, Institute of Clinical Neurophysiology, University Medical Centre Ljubljana [Komisija Republike Slovenije Za Medicinsko Etiko]), in Croatia (Drug Committee of Clinical Hospital Center Zagreb [Povjerenstvo za lijekove Kliničkog Bolničkog Centra Zagreb], Drug Committee of Clinical Hospital Center Osijek [Povjerenstvo za lijekove Kliničkog Bolničkog Centra Osijek], Drug Committee of Clinical Hospital Center Split [Povjerenstvo za lijekove Kliničkog Bolničkog Centra Split]), and Australia (Belberry Human Research Ethics Committee, Royal Brisbane and Women's Hospital Human Research Ethics Committee).

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/ane.13648>.

DATA AVAILABILITY STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual,

and trial-level data (analysis data sets), as well as other information (e.g., protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and statistical analysis plan and execution of a data sharing agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: <https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html>.

REFERENCES

- Clarke CE, Worth P, Grosset D, Stewart D. Systematic review of apomorphine infusion, levodopa infusion and deep brain stimulation in advanced Parkinson's disease. *Parkinsonism Relat Disord*. 2009;15(10):728-741. doi:10.1016/j.parkreldis.2009.09.005
- Rajiah K, Maharajan MK, Yeen SJ, Lew S. Quality of life and caregivers' burden of Parkinson's disease. *Neuroepidemiology*. 2017;48(3-4):131-137. doi:10.1159/000479031
- 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(12):1529-1537. doi:10.1007/s00702-017-1799-3
- Antonini A, Stoessel 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(12):2063-2073. doi:10.1080/03007995.2018.1502165
- 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):309-323. doi:10.2217/nmt-2020-0021
- 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(1):50. doi:10.1186/s12883-019-1276-8
- Evans A, Fung VSC, O'Sullivan JD, et al. Characteristics of advanced Parkinson's disease patients seen in movement disorder clinics - Australian results from the cross-sectional OBSERVE study. *Clin Park Relat Disord*. 2021;4:100075. doi:10.1016/j.prdoa.2020.100075
- Szász JA, Jianu DC, Simu MA, et al. Characterizing advanced Parkinson's disease: Romanian subanalysis from the OBSERVE-PD study. *Parkinsons Dis*. 2021;2021:6635618. doi:10.1155/2021/6635618
- Möller JC, Baumann CR, Burkhard PR, et al. Characterisation of advanced Parkinson's disease: OBSERVE-PD observational study - results of the swiss subgroup. *Swiss Med Wkly*. 2021;151:w20419. doi:10.4414/smw.2021.20419
- Takáts A, Aschermann Z, Vécsei L, et al. Az előrehaladott Parkinson-kór jellemzői a klinikai gyakorlatban: az OBSERVE-PD vizsgálat eredményei és a magyarországi alcsoport elemzése [Advanced Parkinson's disease characteristics in clinical practice: results from the OBSERVE-PD study and sub-analysis of the Hungarian data]. *Ideggyogy Sz*. 2020;73(7-8):261-268. doi:10.18071/isz.18073.10261.10.18071/isz.73.0261
- Stefani A, Tessoro A, Tambasco N, et al. Criteria for identification of advanced Parkinson's disease: the results of the Italian subgroup of OBSERVE-PD observational study. *BMC Neurol*. 2022;22(1):41. doi:10.1186/s12883-022-02554-z
- Todorova A, Jenner P, Ray CK. Non-motor Parkinson's: integral to motor Parkinson's, yet often neglected. *Pract Neurol*. 2014;14(5):310-322. doi:10.1136/practneurol-2013-000741
- GBD 2016 Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2018;17(11):939-953. doi:10.1016/s1474-4422(18)30295-3
- Muangpaisan W, Mathews A, Hori H, Seidel D. A systematic review of the worldwide prevalence and incidence of Parkinson's disease. *J Med Assoc Thai*. 2011;94(6):749-755.
- Szász JA, Constantin VA, Orbán-Kis K, et al. Profile of patients with advanced Parkinson's disease suitable for device-aided therapies: retrospective data of a large cohort of Romanian patients. *Neuropsychiatr Dis Treat*. 2019;15:3187-3195. doi:10.2147/ndt.S230052
- Smith ER, Perrin PB, Tyler CM, Lageman SK, Villaseñor T. Cross-cultural differences in Parkinson's disease caregiving and burden between the United States and Mexico. *Brain Behav*. 2020;10(9):e01753. doi:10.1002/brb3.1753
- Tanji H, Koyama S, Wada M, et al. Comparison of caregiver strain in Parkinson's disease between Yamagata, Japan, and Maryland, The United States. *Parkinsonism Relat Disord*. 2013;19(6):628-633. doi:10.1016/j.parkreldis.2013.02.014
- Statucka M, Cohn M. Origins matter: culture impacts cognitive testing in Parkinson's disease. *Front Hum Neurosci*. 2019;13:269. doi:10.3389/fnhum.2019.00269
- Corallo AN, Croxford R, Goodman DC, Bryan EL, Srivastava D, Stukel TA. A systematic review of medical practice variation in OECD countries. *Health Policy*. 2014;114(1):5-14. doi:10.1016/j.healthpol.2013.08.002
- von Campenhausen S, Winter Y, Rodrigues e Silva A, et al. Costs of illness and care in Parkinson's disease: an evaluation in six countries. *Eur Neuropsychopharmacol*. 2011;21(2):180-191. doi:10.1016/j.euroneuro.2010.08.002
- Lubomski M, Rushworth RL, Lee W, Bertram K, Williams DR. A cross-sectional study of clinical management, and provision of health services and their utilisation, by patients with Parkinson's disease in urban and regional Victoria. *J Clin Neurosci*. 2013;20(1):102-106. doi:10.1016/j.jocn.2012.05.015
- 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. doi:10.1016/j.parkreldis.2021.10.009

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Fasano, A., Fung, V. S., Seppi, K., Pirtosek, Z., Takáts, A., Alobaidi, A., Onuk, K., Bergmann, L., Parra, J. C. & Elibol, B. (2022). Intercountry comparisons of advanced Parkinson's disease symptoms and management: Analysis from the OBSERVE-PD observational study. *Acta Neurologica Scandinavica*, 146, 167-176. <https://doi.org/10.1111/ane.13648>