Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

A Real-World Study on Unstable Parkinson's Disease: Levodopa Dosage Management and the Role of Nonmotor Symptoms

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Abstract: Background: Parkinson's disease (PD) is a neurodegenerative disorder associated with motor and nonmotor symptoms.

Objectives: This study assesses levodopa dose management, the therapeutic goals of clinicians, the factors that influence clinicians' choice of therapy, and the role of nonmotor symptoms using real-world evidence from Germany, Italy, and Spain.

Methods: To assess the management of unstable PD patients on levodopa-containing regimens, neurologists were asked to complete questionnaires (n = 181) and prospective electronic patient records (EPR) were collected (n = 2687). Neurologists were asked questions about their practice and approach to unstable PD patients. EPRs were completed by neurologists after each visit with patients, and the objectives of any changes to therapy were recorded.

Results: Seventy-four percent of neurologists cited "improving motor symptoms" as the main objective for increasing daily levodopa dose. This was also the main objective when starting an add-on (50%) and the main reason for selecting a new add-on therapy (29%). In comparison, reducing nonmotor symptoms, depression, and pain was rarely cited as either the main or secondary objective for a therapy selection (15%, 9%, and 9%, respectively) even when over 60% of unstable patients had pain or depression and 29% had both. When the importance of add-on therapy features was rated, "improve quality of life (QoL)" had the highest average score. Improving nonmotor symptoms, pain, and depression was among the lowest-rated therapy feature.

Conclusions: These findings suggest that improving motor symptoms is a key driver of therapeutic choice. In prioritizing motor symptoms, neurologists may unintentionally neglect nonmotor symptoms, despite most patients suffering from pain or depression.

Parkinson's disease (PD) is a neurodegenerative disorder most commonly characterized by the fundamental motor symptoms of tremor, rigidity, bradykinesia, and postural instability.[1] The disease is also associated with a variety of nonmotor symptoms that greatly affect patients' quality of life (QoL).[2,3] PD is the neurological condition with the fastest-growing population.[4] From 1990 to 2015, the number of people with PD worldwide doubled to over 6 million; it has been projected that in the next 20 years, cases could exceed 12 million.[4,5] These concerning epidemiological statistics and predictions underline the importance of efforts to improve the treatment of patients with PD.

Current treatment options attempt to replace the lost dopamine caused by the death of dopaminergic neurons in the substantia nigra.[6,7] The first line of treatment for dopamine

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replacement in PD is oral levodopa (L-dopa). The most significant side effects of L-dopa are on/off periods of effectiveness and dyskinesia.[6] Other medications (add-on therapies) are often given in conjunction with L-dopa, such as dopamine agonists, anticholinergics (rarely), monoamine oxidase-B (MAO-B) inhibitors, catechol-*O*-methyltransferase (COMT) inhibitors, and amantadine.[6,8,9]

Currently, there are no treatment options available to halt or slow the progression of the disease course, and the aim of treatment is to control symptoms.[6] Current management requires patients to stick to a strict, individualized, and timed regimen of medications to consistently alleviate symptoms.[7,10]

Nonmotor symptoms have largely been disregarded until recent years, and there remain considerable unmet needs in nonmotor symptom management.[11,12] These symptoms range from disorders of mood (eg, apathy, anhedonia, and depression) to cognitive dysfunction, hallucinations, pain, and cardiovascular, urogenital, gastrointestinal, complex behavioral, and sleep disorders.[2,13] Reports suggest about 90% to 100% of PD patients suffer from at least 1 nonmotor symptom.[13,14] The frequency of nonmotor symptoms tends to increase in more advanced stages of PD.[13,15,16]

Apathy, sad mood, decreased concentration, falls, anxiety, and pain have been found to have a negative correlation with health-related QoL (HRQoL).[3,14,16] A cohort study of 23,058 patients with PD found that, along with falls, the symptoms of PD most negatively associated with HRQoL were neuropsychiatric and that patients with moderate to severe depression were among the groups with the most substantially decreased HRQoL.[3] Moreover, in a cohort of 700 patients with PD and their care partners, 48% indicated that nonmotor symptoms pose greater challenges in life than motor symptoms.[14]

Whereas motor symptoms can be initially well controlled through dopamine replacement therapy, management of nonmotor symptoms requires intervention with non-dopaminergic treatments, typically as an add-on treatment.[6,17] Therefore, targeting symptomatic control of nonmotor symptoms in the treatment of PD may be key to optimizing patient HRQoL.

This study aims to better understand the impact of nonmotor symptoms in the management of PD, particularly doctors' therapeutic objectives, management of L-dopa dosages, and the reasons behind therapeutic choices, using real-world data collected through a questionnaire and a prospective chart review.

Patients and Methods

Neurologists from Germany, Italy, and Spain (N = 181) took part in this study between November 2020 and March 2021. The neurologists completed an online declarative questionnaire about their general approach to PD patients (full declarative questionnaire available in Supplementary Materials 1). They were also asked to review up to 20 prospective anonymous patient records and discuss how they would approach treatment in these cases. Considering the purely noninterventional nature of the study, neurologists were not asked to follow specific guidelines or procedure to change the treatment approach. Instead, they made treatment decisions based only on their clinical experience and usual practice, providing the main reasons behind their chosen approach. As patients' data were reported as aggregated data, ethical approval was not required. Consent for the questionnaire was obtained from the General Data Protection Regulation (GDPR).

Electronic patient records (EPR) were prospectively collected for L-dopa-treated patients with unstable PD. According to the eligibility criteria, unstable patients are defined as subjects who do not adequately control the signs and symptoms of the disease. On the day of the visit, the neurologist decides to change the treatment and starts an add-on therapy, either as first add-on or as a switch from another add-on, or on top of another add-on therapy (second or third add-on). Their aggregated data were then declared by the neurologist after consultation. To be eligible for the research, neurologists were required to have 3 years' experience in treating PD and to be directly in charge of making therapeutic choices for their patients. Neurologists were invited by email, and their eligibility was verified using an unbiased online questionnaire. The full eligibility criteria for neurologists and patients are available in Supplementary Materials 2 (Tables S1 and S2).

In the EPRs and the questionnaire, treatment options were listed as individual molecules (except dopamine agonists and anticholinergics, which were listed as the class of drugs).

A descriptive summary of the sample is presented in Supplementary Materials 2 (Table S1). On average, participating neurologists had 18.8 years of postspecialization practice and visited 60.3 PD patients per month; 19.0% of their visits were new diagnoses, with the remaining 81.0% being follow-up visits. Doctors reported 35% of their PD patients to be in the early stages of the disease and 65% in the mid–late stages.

The neurologists spent 39% of their time managing PD, 15% other movement disorders, and 46% other neurological pathologies; 78.7% of the neurologists practiced in a public hospital, 13.1% in a private hospital/clinic, 8.2% in private offices, and 14.8% in a public office (some worked in multiple practices).

On average, each neurologist reported aggregated data from 15 patient records. The place of practice of the neurologists is presented in Supplementary Materials 2 (Tables S3 and S4).

The results were compared with those of a previous study of 187 neurologists conducted in the same countries between September and December 2019, with parallel objectives and methodology (details of these "wave 1" results can be found in Supplementary Materials 2).

Results

Current Treatment Patterns

Therapies Used in Current Management of Unstable Parkinson's Disease Patients

Among the 2687 EPRs of unstable PD patients receiving L-dopa therapy, over 60% are treated with MAO-B inhibitors, and

almost half are treated with dopamine agonists or (COMT) inhibitors. The individual molecules most commonly featured in treatment regimens were safinamide, the fixed combination of L-dopa/carbidopa/entacapone, rasagiline, and opicapone: 39%, 24%, 23%, and 22% of PD patients from the wave 2 sample, respectively (see Table 1). These therapy patterns were consistent with wave 1 (Supplementary Materials 2, Table S5).

The country-level results for Germany, Italy, and Spain showed that the use of dopamine agonists ranged from 44% to 51%, safinamide from 32% to 42%, and rasagiline from 17% to 21% (full details of the country analysis and wave 1 pooled analysis are presented in Supplementary Materials 2, Table S5).

MAO-B inhibitors were the most widely used class of drugs used as the first add-on therapy, selected for 40% of patients starting a first add-on. Dopamine agonists were also a popular choice, used as the first add-on therapy by neurologists for over a quarter of patients in the pooled analysis. Rasagiline was the common first add-on therapy, closely followed by safinamide (Table 1). MAO-B inhibitors were the most common class of drugs used as a first add-on therapy in Italy and Spain, whereas in Germany dopamine agonists were the most common. L-Dopa retard was a common first add-on therapy in Germany, where it was the second most popular behind dopamine agonists. However, there was a decline in the use of L-dopa retard as the first add-on therapy in Germany between waves 1 and 2 (24% and 16%, respectively; see Supplementary Materials 2, Table S5).

TABLE 1 *Therapies used in current management of Parkinson's disease in unstable patients on treatment regimens containing L-dopa*

	Molecules used in current therapy N = 2687 (%)	Molecules used as first add-on in current therapy N = 453 (%)
Dopamine agonists	48.1	26.9
Anticholinergics	3.5	1.3
COMT inhibitors	49.6	20.3
Opicapone	21.7	12.4
LCE	23.7	6.0
Other COMT inhibitors	4.2	1.9
MAO-B inhibitors	65.9	39.9
Safinamide	38.6	17.7
Rasagiline	23.0	18.6
Selegiline	4.3	3.6
L-Dopa (retard/gel/oral dispersible[a])	13.7	7.9
Melevodopa[a]	6.2	0.6
Amantadine	11.6	3.0

Note: Wave 2 results.
Abbreviations: L-dopa, levodopa; COMT, catechol-O-methyltransferase; LCE, levodopa/carbidopa/entacapone; MAO-B, monoamine oxidase-B.
[a]Only Italy had access to melevodopa and oral dispersible levodopa at the time of this project.

Treatment Discontinuation

Almost half of unstable patients did not discontinue any treatment in their current regimen when they started a new add-on therapy (see Table 2). This was consistent across waves 1 and 2 and in all countries. When at least 1 molecule was discontinued, the molecules with the highest discontinuation rates were selegiline (mainly used in Italy), anticholinergics, and rasagiline, with discontinuation rates of 67%, 52%, and 51%, respectively. L-Dopa, melevodopa, safinamide, and dopamine agonists had the lowest discontinuation rates, ranging from 6% to 19%. The full details of discontinued products are presented in Table 2 for wave 2; these were consistent with the wave 1 and country-specific results, which are presented in Supplementary Materials 2 (Table S5).

Management of L-dopa

During the wave 2 period, 453 unstable patients (previously on L-dopa monotherapy) started their first add-on therapy. On average, these patients spent 4 years on L-dopa monotherapy (3.95 and 3.65 years in wave 2 and wave 1, respectively).

TABLE 2 *Discontinuation rate of treatments in unstable Parkinson's disease patients on treatment regimens containing L-dopa*

	Wave 2 (N = 2687)
Unstable patients who did not discontinue current treatment when starting a new add-on therapy, n (%)	1324 (49.3%)
Unstable patients who discontinued any current treatment when starting a new add-on therapy, n (%)	1363 (50.7%)
Discontinuation rate when discontinuing at least 1 molecule (%)	
Dopamine agonists (n = 1122)	18.9%
L-Dopa (all types) (n = 2704)	6.0%
Melevodopa (n = 136)	10.3%
LCE (n = 575)	28.5%
Opicapone (n = 161)	30.4%
Amantadine (n = 308)	40.3%
Safinamide (n = 324)	16.4%
Rasagiline (n = 676)	50.6%
Selegiline (n = 135)	66.7%
Anticholinergics (n = 123)	52.0%

Note: Sample number for wave 2 is in parentheses. Melevodopa was available only in Italy at the time of this project.
Abbreviations: L-dopa, levodopa; LCE, levodopa/carbidopa/entacapone.

Figure 1A shows the length of time that patients being prescribed their first add-on therapy had previously spent on L-dopa monotherapy. Patients in Italy spent the longest on L-dopa: over 40% of Italian patients spent at least 5 years on L-dopa monotherapy before starting an add-on therapy. In Spain, patients with PD spent on average 3.5 years on L-dopa monotherapy, whereas in Germany the average was similar to the pooled sample (Supplementary Materials 2, Table S6).

Most patients in wave 2 (38.2%) were receiving L-dopa doses exceeding 500 mg/day when the first add-on therapy was started (see Fig. 1B). This represents an increase from wave 1, where 36% and 33.3% of patients received L-dopa doses between 400 and 500 mg/day and >500 mg/day, respectively. At wave 2, in Germany more than 75% of patients with PD took >400 mg/day (48.6% took 400–500 mg/day and 27.5% >500 mg/day), in Spain about 68% (27.6% took 400–500 mg/day and 40.1%

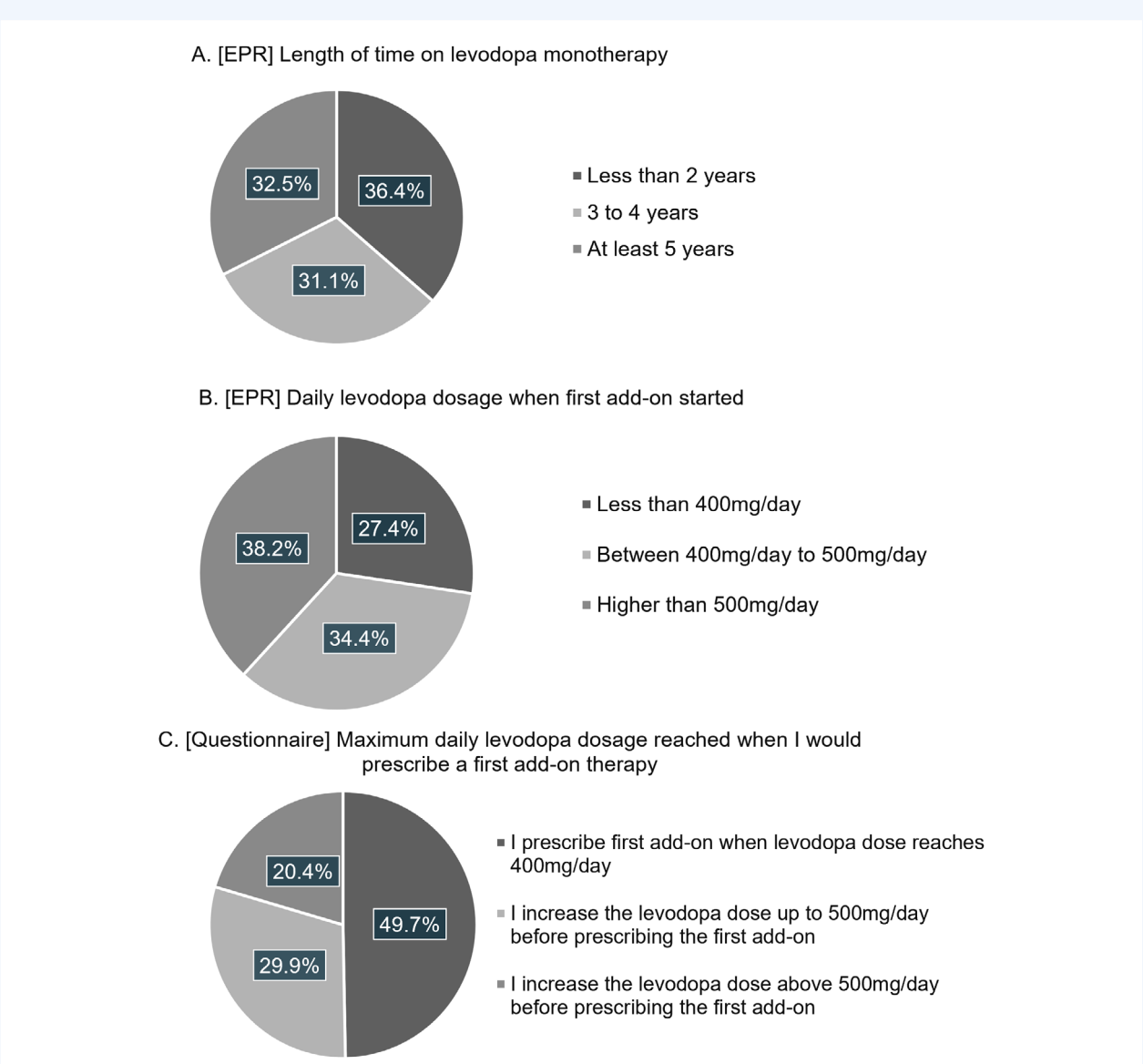

FIG. 1. Management of levodopa: actual practice versus neurologist opinion. (**A**) Time spent on levodopa (L-dopa) monotherapy by patients with Parkinson's disease (PD) when starting add-on therapy. The length of time on L-dopa monotherapy was calculated based on when L-dopa therapy was initiated in patients (n = 453) at the point of prescribing the first add-on therapy. (**B**) Daily L-dopa dose in unstable patients with PD when starting first add-on therapy. Daily L-dopa dosage was calculated based on unstable patients' (n = 453) daily L-dopa dose at the point of prescribing the first add-on therapy. (**C**) Neurologists' stated opinion: the maximum daily L-dopa dose before starting an add-on therapy. Question to neurologists (N = 181) asked in questionnaire: "Now considering your patients on L-dopa monotherapy that are unstable and whose signs and symptoms are not adequately controlled, you have decided to prescribe the first add-on therapy. Can you please split them in percentage according to the maximum daily dosage of L-dopa they achieved before receiving their first add-on therapy?"

>500 mg/day) and in Italy about 77% (29.4% took 400–500 mg/day and 47.2% >500 mg/day; Supplementary Materials 2, Table S6).

Objectives of L-Dopa Monotherapy

As part of the questionnaire, neurologists were asked to split their patients into groups based on the maximum daily L-dopa dose they would allow them to reach before opting to start an add-on therapy. The results of the pooled analysis are shown in Figure 1C and are consistent across waves 1 and 2 within each country (Supplementary Materials 2, Table S6). When compared to what actually occurs in clinical practice, data suggest that neurologists underestimate the maximum daily L-dopa dose they allow patients to reach before prescribing a first add-on; 50% of neurologists estimated their patient would be prescribed an add-on therapy when the L-dopa dose reached 400 mg/day; in reality, 73% of PD patients' daily L-dopa dose exceeds 400 mg when they first start an add-on therapy, as shown in Figure 1B.

Neurologists were also asked how they would manage unstable patients with PD (ie, those for whom symptoms of the disease are not adequately controlled) currently receiving L-dopa monotherapy. In this scenario, neurologists can either increase the daily L-dopa dose or start an add-on therapy. The neurologists were asked to select and rank the main objectives pursued when increasing L-dopa dose if they chose to do so, and the reasons why they opted to increase the daily L-dopa dose over starting an add-on (ie, reason for not choosing an add-on). A summary of responses is presented in Table 3 and Supplementary Materials 2, Table S7.

The most common objective for increasing daily L-dopa dosage was to improve PD cardinal motor symptoms: 74% of neurologists cited this as 1 of their objectives (main and secondary objective), and 55% cited it as their primary objective (Table 3). Other main objectives commonly given by neurologists were to reduce or control motor symptoms (31.5%), to support patient compliance (30.9%), or to reduce or avoid side effects (29.8%) (Table 3). This was consistent with the wave 1 results and the country-level results (see Supplementary Materials 2, Tables S7 and S8).

When asked why they would increase L-dopa dose rather than starting an add-on therapy, almost half (49.7%) of neurologists

TABLE 3 *Neurologists' stated reasons when changing L-dopa therapy according to their clinical experience*

Main objectives when increasing L-dopa dosage	**Main objective★ (%)**	**Primary objective (%)**	**Secondary objective (%)**
Improve PD cardinal motor symptoms	74.0	55.3	18.8
Reduce/control motor complications	31.5	14.4	17.1
Support patient compliance	30.9	11.1	19.9
Reduce/avoid side effects	29.8	8.3	21.6
Satisfy patient requests	11.1	2.8	8.3
Obtain better cost–benefit balance	6.6	3.9	2.8
Achieve a good synergy between treatments	4.4	4.4	0.0
Other[a]	0.6	0.0	0.6
Main reasons for opting to increase L-dopa dosage over starting an add-on therapy	**Main reason★**	**Primary reason**	**Secondary reason**
Confidence in using higher doses of L-dopa[b]	49.7	30.4	19.3
Do not trust efficacy of the available add-on options	7.2	3.3	3.9
Control motor functions only	10.4	4.4	6.6
In the long term, postponing add-on initiation is a winning strategy	14.7	6.1	7.7
To contain costs	13.8	6.1	7.7
Do not trust this patient's compliance to multitreatments	26.5	14.4	12.2
Patients do not like taking additional drugs	34.3	12.7	21.6
Tolerability concerns about the available add-on options	37.0	22.1	14.9
Other[b]	49.7	5.0	5.0

Note: Sample size (N = 181) refers to neurologists who completed questionnaires.
Abbreviations: L-dopa, levodopa; PD, Parkinson's disease.
★Indicated by neurologists as either the most important or second most important objective/reason for changing current therapy.
[a]Other: improve nonmotor symptoms.
[b]Main reasons in "other": contraindications of add-on therapies, elderly patients, willingness to use L-dopa monotherapy as long as possible.

cited "confidence in using higher doses of L-dopa" (ie, confidence it would maintain efficacy while minimizing adverse events) as a main reason. Other reasons related to patient compliance and tolerability concerns with the available add-on therapies, although each of these was chosen by less than 25% of neurologists as the primary reason (Table 3; Supplementary Materials 2, Table S9).

Treatment Objectives

Deciding to Start a New Add-On Therapy

Neurologists were asked to select 2 objectives pursued when selecting a new add-on therapy and to rank them by importance. The summary of their responses in wave 2 is presented in Table 4. Half of neurologists selected "improve motor

TABLE 4 *Main objective pursued when starting a new add-on therapy and reasons for selecting a new add-on therapy in unstable Parkinson's disease patients treated with L-dopa (N = 2687)*

Main objective when starting an add-on therapy	Main objective*	Primary objective	Secondary objective
Improve motor symptoms	50.4	34.4	16.0
Reduce/control motor complications	41.2	24.4	16.9
Achieve a good synergy between treatments	31.6	13.7	17.9
Improve nonmotor symptoms	25.0	12.3	12.7
Reduce/avoid side effects	14.1	6.6	7.5
Support patient compliance	9.7	3.5	6.2
Satisfy patient requests	6.4	2.5	3.9
Obtain better cost–benefit balance	4.0	1.7	2.2
Other[a]	1.3	0.8	0.5
Reason for selecting a new add-on therapy	**Cited as a reason**	**First reason**	**Second reason**	**Third reason**
Efficacy in improving motor function	28.7	15.2	8.1	5.4
Increasing daily ON time	27.9	12.3	9.6	6.1
Decreasing daily OFF time	25.6	10.8	10.0	4.9
Improve QoL	21.5	7.5	8.3	5.8
Control motor functions	21.3	8.8	8.3	4.1
Overall good tolerability	17.1	4.5	7.7	4.8
Improvement in nonmotor symptoms	14.7	5.4	5.5	3.8
Control dyskinesia	13.8	6.9	4.4	2.6
Possibility of L-dopa dose reduction	11	3.3	4.1	3.7
Once-daily dose/compliance	10	3.2	4.1	2.7
Long-term efficacy	9.5	3.5	3.8	2.2
Positive effect on depression	9.0	3.1	3.1	2.8
Familiarity with medication	8.9	3.2	3.2	2.5
Positive effect in pain	8.6	2.8	3.5	2.2
Other[b]	24.7	9.4	7.9	7.5

Note: Wave 2 results (N = 2687).
Abbreviations: L-dopa, levodopa; QoL, quality of life.
*Indicated by neurologists as either the most important or second most important objective for changing current therapy.
[a]Objective includes reduction in dysphagia, reduction in dyskinesia, reduction in tremors, avoiding increasing/reducing L-dopa, enlarge Mechanism of action (MoAs), improvement in night symptoms, contrast to depression, neuroprotection, improvement in other symptoms (eg, dystonia), and improvement in cognitive symptoms.
[b]Reasons include new mode of action, neuroprotective effect, good cost–benefit balance, and a few interactions with other treatments. Cost–benefit balance was not strictly defined in questionnaire; however, the questionnaire reported better cost option for patients in other similar questions. Cost–benefit could be considered as the measurement of both the health outcomes and direct costs associated with a particular treatment or intervention; percentages add up to more than 100% because participants were permitted to select multiple answers for each question.

symptoms" as either the primary or secondary objective when starting a new add-on therapy. This was the most popular objective in each country, consistent with wave 1 results (see Supplementary Materials 2 for full details, Tables S10 and S11).

Other frequently stated objectives of starting an add-on therapy were "reduce/control motor complications" (41%), "achieve a good synergy between treatments" (31%), and "improvement in nonmotor symptoms" (25%) (Table 4).

Choosing a New Add-On Therapy

When choosing a new add-on therapy, neurologists were also asked to select up to 3 reasons they chose the product as an add-on, ranked by importance. A summary of the reasons chosen is presented in Table 4. "Efficacy in improving motor function," "increasing daily ON time," and "decreasing daily OFF time" were all stated as reasons for selecting the new add-on therapy at least in 25% of cases. The results were similar in wave 1 and within each country (see Supplementary Materials 2, Tables S12 and S13 for full details).

Stated Importance of Add-On Therapy Features

Neurologists were presented with a list of potential features a therapy might have and asked to score them from 1 to 7 based on how important they would be when choosing an add-on therapy for unstable patients with PD (1–3, not important/unimportant; 4 and 5, rather important; 6 and 7, very/extremely important). A summary of the stated importance of add-on therapy features is presented in Table 5.

The improvement in QoL, efficacy in improving motor symptoms, increasing ON time without dyskinesia, control of motor complications, decreasing OFF time, and good overall tolerability were the main drivers for add-on choice for a regimen containing L-dopa. Positive effects on pain or depressive symptoms, and in general on nonmotor symptoms, were rarely considered to be strong drivers of choice (Table 5). Wave 1 and country-specific results were consistent with the wave 2 results (see Supplementary Materials 2, Tables S14–S16).

Nonmotor Symptoms: Depression and Pain in Patients with Parkinson's Disease

Prevalence of Depression and Pain in Patients with Parkinson's Disease

Pain and depression are 2 common nonmotor symptoms of PD, with their prevalence in unstable L-dopa-treated PD patients being 46% (Fig. 2). According to the EPR, over 60% of patients

TABLE 5 *Neurologists' stated importance of add-on therapy features when selecting for unstable patients receiving L-dopa*

Add-on therapy feature	Average score	Proportion rated		
		Very important	Rather important	Not important
Improve QoL	6.3	84.0	15.5	0.6
Control of motor complications	6.1	79.0	20.4	0.6
Efficacy in improving motor symptoms	6.1	77.4	21.6	1.1
Decreasing daily OFF time	6.0	77.4	22.1	0.6
Increasing daily ON time without dyskinesia	6.1	76.8	21.6	1.7
Good overall tolerability	6.1	76.2	23.2	0.6
Long-term efficacy	5.8	64.1	34.8	1.1
Favoring patients' compliance/easy therapy management	5.5	56.4	43.1	0.6
Product supported by solid clinical trials' data	5.5	52.5	45.9	1.7
Product supported by RWE data	5.4	50.3	47.0	2.8
Possibility of L-dopa dose reduction	5.1	39.8	58.0	2.2
Improve other nonmotor symptoms (different from pain/mood)	5.2	39.2	59.7	1.1
Positive effect on pain	4.9	29.3	68.0	2.8
Two mechanisms of actions	4.5	26.0	64.6	9.4
Positive effect on depressive symptoms	4.7	24.9	71.3	3.9
Neuroprotective effect	4.15	21.6	59.7	18.8

Note: Sample consists of 181 neurologists.
Abbreviations: L-dopa, levodopa; QoL, quality of life.

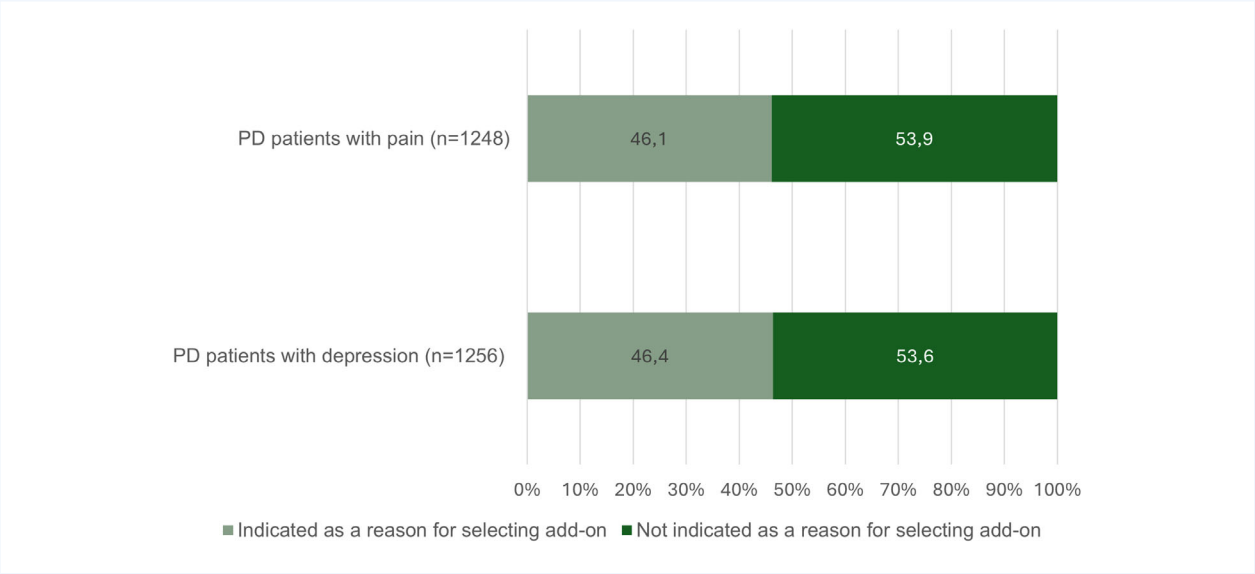

FIG. 2. Proportion of unstable patients with pain or depression who indicated that a positive effect on their pain/depression was a driver of their choice of add-on therapy. Within the subsample of patients with PD who suffer from pain or depression, the reasons for selecting any add-on therapy were analyzed to find how often "improvement in nonmotor symptoms," "positive effect on pain" (for patients with pain), or "positive effect on depression" (for patients with depression) was selected as a driver of treatment choice. PD, Parkinson's disease.

suffered from either depression or pain, and almost 30% had both depression and pain (Table 6). In Italy, the rates of patients with either pain or depression were higher than those in the pooled sample (72%). The German and Spanish results aligned with the pooled sample (full details are presented in Supplementary Materials 2, Tables S17 and S18).

Impact of Depressive Symptoms and Pain on Treatment Objectives and Selection of New Add-On Therapy

Table 6 presents the proportion of therapy changes (ie, starting any new add-on therapy) that featured "improving nonmotor symptoms" as a treatment objective. "Improving nonmotor symptoms" was most often stated as a treatment objective in PD patients who suffer from both pain and depression (38.1%); in this population, it was a primary objective in 20% of therapy changes. However, only 25% of patients suffering from pain and not depression and 31% suffering from depression and not pain had this as a treatment objective. This result was consistent in all 3 countries (Supplementary Materials 2, Table S19).

The effect of an add-on therapy on pain was a treatment objective for 46% of patients with pain (n = 1248) (Fig. 2). Similarly, the positive effect of a treatment on depression was indicated as a driver for choosing an add-on therapy for 46% of patients with PD who suffer from depression (n = 1256) (Fig. 2).

TABLE 6 *Prevalence of depression and pain in unstable PD patients and the proportion of therapy changes with "improving nonmotor symptoms" as a main objective in those patients*

	Sample n (%)	Main objective*	Primary objective	Secondary objective
All patients with PD	2687 (100)	25	12.3	12.7
PD patients with either pain or depression	1721 (64)	32.5	16.3	16.3
PD patients with both depression and pain	783 (29.1)	38.1	20.4	17.6
PD patients with only depression	473 (17.6)	31.1	14.6	16.5
PD patients with only pain	465 (17.3)	24.7	11.0	13.8
PD patients without depression or pain	966 (36)	11.6	5.2	6.4

Note: Wave 2 results only—questions on prevalence of depressive symptoms and pain added only in wave 2.
Abbreviation: PD, Parkinson's disease.
*Indicated by neurologists as either the most important or second most important objective for changing current therapy.

Discussion

The Undervaluation of Nonmotor Symptoms in Neurologists' Treatment Decisions

The high prevalence of pain and depression found in PD patients in this study supports the previously published literature on the prevalence of nonmotor symptoms.[13,16] In PD patients, depression is a key contributor to decreased QoL and poor health outcomes. Depression is linked to increased disability, accelerated cognitive decline, higher mortality rates, and a greater burden on families and caregivers.[18] Additionally, pain in these patients tends to fluctuate throughout the day and is generally associated with motor fluctuations and wearing off. Therefore, effectively managing pain in PD patients is essential for improving their overall well-being.[19] Dopamine agonists, including L-dopa, are effective options for addressing both depression and pain related to PD.[18,19] L-Dopa serves as the first pharmacological treatment for managing PD-related pain.[19] Despite this, in this study, the most important objective of neurologists when deciding to increase L-dopa dosage was to improve motor symptoms (>50%), whereas less than 1% cited "improvement in nonmotor symptoms."

Similarly, when selecting an add-on therapy, improving symptoms was twice as likely to be a driver of choice of therapy than improvement in nonmotor symptoms. The expected efficacy of an add-on therapy on motor symptoms was the strongest driver in the choice of therapy among neurologists. Furthermore, a positive effect on depression, pain, and other nonmotor symptoms was ranked among the lowest importance among features of an add-on therapy. The relatively low importance neurologists place on improving nonmotor symptoms is clear even when focusing on patients suffering from depressive symptoms and/or pain.

Although the treatment of motor symptoms is the basis of PD treatment and is thus expected to be the main treatment objective, the importance of nonmotor symptoms is perhaps underestimated by neurologists given the impact they have on patients, as cited throughout the literature.[3,15,16,20] Of note, improvement in QoL was the highest-scoring add-on feature, rated as "very important" by 84% of neurologists when selecting an add-on therapy. This suggests that neurologists may be unaware of the level of impact that nonmotor symptoms such as pain and depression have on patient QoL and psychological well-being.

Respondents indicated that nonmotor symptoms had a negative impact on daily activities such as running errands, completing household chores, completing self-care, and socializing.[14] Furthermore, it has previously been found that psychological well-being as assessed using the Psychological Wellbeing Scale is not correlated with motor symptoms but is inversely correlated with nonmotor symptoms, in particular depression.[20] A greater consideration in treating nonmotor symptoms like pain and depression is key to enhancing patient QoL in PD and should therefore hold more weight when determining treatment patterns.

These results suggest that neurologists choose to increase L-dopa doses and delay starting an add-on therapy when patients become unstable (patients receive L-dopa monotherapy for an average of 4 years, with 73% taking daily doses exceeding 400 mg/day). This does not align with the treatment plans of neurologists: according to neurologists' forward-looking estimates, approximately 50% of patients would take over 400 mg/day of L-dopa. High L-dopa doses may increase risk to patients, and the risk of developing dyskinesia is closely linked to L-dopa dosage.[21,22] Additionally, previously published literature has recommended initiating an add-on therapy to manage complications that may result from prolonged L-dopa therapy and reducing "off time" rather than increasing L-dopa dose.[21,23]

Patient Outcomes

Motor symptoms have been described as "just the tip of the iceberg."[16] Nonmotor symptoms are a significant clinical burden for patients with PD and can significantly impact their QoL and psychological well-being.[20] In some cases, nonmotor symptoms can be more disabling than motor symptoms,[24] and they typically pre-date the emergence of motor symptoms.[2,6,12]

Neurologists typically prioritize motor symptoms when treating and assessing patients. By foregoing the opportunity to address the effect of nonmotor symptoms on a patient's QoL, focusing only on motor symptoms may disadvantage the patient and potentially contribute to further functional decline.[16]

A 2022 systematic literature review found that selegiline, rasagiline, and safinamide can improve depression, sleep disturbances, and pain, when prescribed as add-on therapies, in patients with PD.[11] Rasagiline and safinamide have clinically demonstrated efficacy in improving pain, particularly in advanced PD patients. Safinamide significantly reduced on average the individual use of concomitant pain treatments by approximately 24%, with a direct effect on pain accounting for about 80% apart from the effect on motor fluctuations and dyskinesia. These results might be explained by the non-dopaminergic mechanism of action of safinamide and its modulation of glutamate hyperactivity.[23] Adding these drugs to L-dopa when symptom control appears insufficient, instead of increasing the dose of L-dopa beyond 400 mg, could be a better strategy to prevent long-term motor complications.[25]

Perhaps the largest limitation of this study is the method in which the data were collected. Sampling bias and self-selection bias must be acknowledged when interpreting these results: the study's sample consisted of neurologists who agreed to participate, which might introduce bias and limit the generalizability of the findings to all neurologists treating PD patients. Those who chose not to participate could have different management approaches.

The questionnaire did not ask neurologists to specify the treatment plans they apply when nonmotor symptoms occur, as this was beyond the study's scope. Nevertheless, given the relevance of this topic, future research could explore it in depth.

The Movement Disorder Society (MDS) provides evidence-based recommendations for managing nonmotor symptoms in PD. However, the MDS highlights the importance of integrating

recommendations with clinicians' experience, patient preferences, and economic factors in daily clinical practice, all of which are essential for determining the most appropriate treatment approach. Furthermore, personalized treatment, acknowledging patients' unique clinical characteristics and needs, should be prioritized.[26]

Although the study reported that improvement in all nonmotor symptoms is crucial, the questionnaire addressed the most common psychiatric disorders, that is, depression and pain. These symptoms have a major impact on patients' QoL and can be effectively managed by antiparkinsonian therapy, such as dopamine agonists. In contrast, this research did not focus on frequent nonmotor symptoms such as sleep disturbances and constipation. The impact of insomnia and constipation will have to be further investigated in the future. However, these are the symptoms most likely to improve with adjuvant treatments.[14–16] Data collection took place across different countries and various settings, including public and private hospitals and offices. However, this study did not include a subgroup analysis to evaluate whether differences or similarities in PD management existed across different clinical settings and/or countries. This analysis could be considered for future research.

This study supports previous research and demonstrates the high prevalence of nonmotor symptoms that exist in PD. To the best of our knowledge, it is the first study to document the treatments patterns and treatment goals of neurologists for unstable PD patients using real word evidence (RWE).

The results from our data suggest that neurologists may underestimate the importance of nonmotor symptoms when designing a treatment regimen, as well as the impact that these symptoms have on a patient's QoL. A more holistic view of the disease, and a greater consideration of nonmotor symptoms such as pain and depression, may be key to maximizing patient outcomes.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript preparation: A. Writing of the first draft, B. Review and critique.

F.S.: 1A, 1C, 2C, 3A, 3B

J.K.: 1A, 1C, 2C, 3A, 3B

W.H.J.: 1A, 1C, 2C, 3A, 3B

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Supporting Information

Supporting information may be found in the online version of this article.

Data S1. IG925M13—study on Parkinson's disease—database reference book.

Table S1. Description of project sample.

Table S2. Eligibility criteria.

Table S3. Sample description (waves 1 and 2).

Table S4. Place of practice of neurologists included in the sample.

Table S5. Current management of Parkinson's disease in unstable patients on treatment regimens containing levodopa: pooled wave 1 and country-specific results.

Table S6. Breakdown of levodopa management: pooled wave 1 and country-specific results.

Table S7. Main objectives and reasons for levodopa therapy changes: wave 1 results.

Table S8. Main objectives when increasing levodopa dosage.

Table S9. Main reasons for opting to increase levodopa dosage over starting an add-on therapy.

Table S10. Main objective when starting an add-on therapy: wave 1 results.

Table S11. Main objective when starting an add-on therapy: country-specific results.

Table S12. Main reasons for selecting an add-on therapy: wave 1 results.

Table S13. Main reasons for selecting an add-on therapy: country-specific results.

Table S14. Average rated importance of features of add-on therapies: wave 1 results.

Table S15. Average scored importance of add-on therapy features: country-specific results.

Table S16. Stated importance of add-on therapy features: country-specific results.

Table S17. Prevalence of depressive symptoms and pain in Parkinson's patients: Country-specific results.

Table S18. Proportion of patients with positive effect on depression/pain and/or improvement in nonmotor symptoms as a treatment objective: country-specific results.

Table S19. The proportion of therapy changes with "improving nonmotor symptom" as a main objective in patients with depression and/or pain: country-specific results.