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Motor fluctuations in Parkinson's disease: Perceptions and treatment

Fabrizio Stocchi[1], Ricardo Oliveira[2], Francisco Rocha[2]

1. University San Raffaele Roma and IRCCS San Raffaele Pisana, Rome, Italy

2. Bial – Portela Co. SA, Trofa, Portugal

Abstract

Background: Levodopa is the gold standard of treatment for Parkinson's disease, but wearing off leads to motor fluctuations in most patients. Therapeutic strategy for motor fluctuation management relies heavily on physician judgement; however, real-world insight into physician attitudes towards detection and treatment of motor fluctuations is lacking.
Methods: Multinational qualitative online surveys were conducted among general neurologists and movement disorder specialists treating patients with Parkinson's disease in the UK, Germany, Italy, Spain, and Portugal in July 2020 (Wave 1) and September 2021 (Wave 2). The Perceptions and Attitudes questionnaire focused on attitudes towards detection and management of motor fluctuations by rating agreement with statements on a 7-point scale. The Treatment Landscape questionnaire involved completion of patient case reports (PCRs) for the four most recently treated patients with motor fluctuations.
Results: Respondents agreed that motor fluctuations place a heavy burden on patients (82%/85% in Wave1/2, respectively) and are underdiagnosed (64%/72%), but most do not routinely use screening tools known to increase their detection. Just 3% of neurologists agreed completely with being confident in fully resolving motor fluctuations to their patient's satisfaction. In contrast with the current evidence, most physicians perceive duration of levodopa treatment as a predictor of motor complications (72%/77%). Fractionating levodopa was the preferred first therapeutic strategy for motor fluctuation management versus adding an adjunct treatment. PCRs revealed that specialist neurologists used adjunct therapy more frequently than general neurologists, either as a first approach (31% versus 15%, respectively) or secondary to levodopa fractionating (62% versus 45%).
Conclusions: These surveys uncovered knowledge gaps around the predictors of motor fluctuations which could be addressed by future educational initiatives. Earlier detection of motor fluctuations and greater use of available adjunct treatments may help to reduce their burden in patients with Parkinson's disease.

Keywords

Adjunct, Detection, Levodopa, Motor fluctuations, Neurologist, Parkinson's disease, Perceptions, Real-world, Survey, Treatment

Corresponding author: Fabrizio Stocchi, Department of Neurology, University and IRCCS San Raffaele Pisana, Via della Pisana 235, 00163, Rome, Italy, Email: fabrizio.stocchi@uniroma5.it

Introduction

Parkinson's disease is a progressive neurodegenerative disease resulting from loss of dopaminergic neurons in the substantia nigra (1,2). It is one of the most common neurodegenerative movement disorders, with an estimated prevalence of 1 to 2 per 1000 population in Europe (3,4). Clinical diagnosis is primarily based on the cardinal motor symptoms of bradykinesia, resting tremor, and rigidity (2,5). Non-motor symptoms add to overall patient disability and can include cognitive and psychiatric symptoms, sleep disorder, olfactory loss, autonomic dysfunction, and pain (6,7). Levodopa has unrivalled efficacy for motor symptom improvement in early disease, providing near-normal patient function (8,9). It remains the gold standard of treatment for Parkinson's disease, required by virtually all patients during the course of the disease. However, long-term management with levodopa is complicated by the occurrence of the "wearing-off" phenomenon. Over time, the duration and reliability of therapeutic response is reduced with the emergence of "motor fluctuations", a term used to describe the transitions between periods when levodopa provides effective symptom control (ON time) and periods when signs and symptoms re-emerge (OFF time) (10). In addition to motor fluctuations, occurrence of dopamine-induced dyskinesia may further complicate management (11). Motor fluctuations and dyskinesia are observed in more than 50% of patients after 5 years of levodopa treatment (12,13). Some physicians prefer to use levodopa-sparing strategies to lower the incidence of motor complications, such as delaying levodopa for as long as possible, or using non-levodopa medications, such as dopamine agonists (DAs), early in disease and adding levodopa when symptom control fails (9). However, the potential lower risk of motor fluctuations must be balanced against the superior motor symptom control of levodopa and the increased potential for troublesome side effects with non-levodopa medications (9,14). Evidence suggests that motor complications are related to peaks and troughs in levodopa levels as the disease progresses (8,10). Progressive depletion of the nigrostriatal terminals disrupts the storage and slow release of dopamine required for continuous postsynaptic stimulation between doses of levodopa (8,10). Strategies for patients who develop dyskinesia and/or motor fluctuations aim to provide more continuous dopaminergic stimulation and reduction in OFF time. Interventions may include changes to levodopa dosing (fractioning or dose increases) and the use of adjunct therapies such as DAs, or monoamine oxidase (MAO)-B and catechol-O-methyl transferase (COMT) inhibitors to block peripheral metabolism of levodopa, extending the plasma half-life and availability to the brain. Treatment choice and combinations are determined by the individual's personal circumstances and the potential benefits and harms of the different drug classes (5).

Thus, management of Parkinson's disease and motor fluctuations relies heavily on physician judgement and shared decision-making with the patient. Physician perceptions of the burden of motor fluctuations and the risk-benefit of specific treatments will heavily influence clinical practice, but real-world insight into physician attitudes towards the management of motor fluctuations is lacking. This article reports findings from a series of surveys to explore physician perceptions of, as well as providing insights into, the clinical strategies currently used for motor fluctuation management in different European countries.

Methods

Survey design

A multinational qualitative survey was conducted among physicians treating patients with Parkinson's disease in the UK, Germany, Italy, Spain, and Portugal using standard market research methodology. The survey consisted of two online questionnaires: (1) *Perceptions and Attitudes*, and (2) *Treatment Landscape* and was conducted in July 2020 (Wave 1) and repeated in September 2021 (Wave 2), with minor adjustments to some questions.

A specialist market research company, Lumanity (London, UK; formerly Cello Health Insight) developed the questionnaires and Infocorp (London, UK) scripted and hosted the survey. All materials were translated by qualified translators specialized in the medical field and surveys were conducted in accordance with the EphMRA (European Pharmaceutical Market Research Association), ESOMAR (European Society for Opinion and Marketing Research), and Market Research Society (MRS) codes of conduct regarding anonymity and confidentiality. Ethics approval was not required according to local laws for observational questionnaire-based studies where all data is anonymized.

The *Perceptions and Attitudes* questionnaire focused on attitudes towards levodopa initiation, detection of motor fluctuations, confidence in their management, and the relative value of available treatments. Many questions in the *Perceptions and Attitudes* questionnaire employed a 7-point rating scale to assess agreement with statements. The *Treatment Landscape* questionnaire explored reasons for treatment choice in more detail and investigated the current therapeutic landscape by asking each participant to complete patient case reports (PCRs) to provide details for the four most recently treated patients with motor fluctuations. Participants were asked to refer to patient records, except for physicians in Germany where restrictions meant that physicians were required to recall the necessary information rather than refer directly to patient records. Written informed consent from patients was not sought given the anonymous nature of the collected data.

Participants

Accredited physicians, including general neurologists and movement disorder specialists, were recruited from multiple, well-established market research panels, built through many recruitment channels such as national and regional physician associations, member referrals, hospitals, private practices, and specialty-related associations. Participants were screened for the following criteria: 3–35 years since qualified; ≥50% professional time spent in direct patient care (personally responsible for initiating and switching treatments as part of their management of Parkinson's disease); ≥10 patients with Parkinson's disease treated in a typical month, with ≥4 patients currently receiving levodopa and experiencing motor fluctuations. Re-

cruitment was aimed at approximately 90 to 100 physicians per country per Wave (except Portugal which aimed to recruit about 20 to 30, since the total national population and therefore the potential pool of health care professionals is smaller than that for the other larger countries).

Data collection and analysis

Members of the market research panel were invited to complete each questionnaire in a separate email. Thus, each physician had the option to answer just one of the questionnaires or both and were renumerated per questionnaire. Respondents were re-invited to participate in Wave 2, together with a fresh sample of physicians. All respondents were assigned a unique ID to protect their identity and responses were tabulated using QPSMR software. Data was checked manually to remove outliers, speeders (respondents who complete in under a certain number of minutes), and flatliners (those answering the same for every question). Questions based on rating statements using a scale from 1=completely disagree to 7=completely agree, were interpreted as: 5, 6 or 7=agree to some extent; 4=neither agree nor disagree; 1,2,3=disagree to some extent**.** Results were analyzed descriptively and compared between Waves and by healthcare professional (HCP) type and country using standard *t* test with combined variance run at 95% confidence interval. Any difference between Portugal and the other countries was disregarded owing to the lower number of respondents in this country.

Results

Completed questionnaires and physician characteristics

A total of 761 physicians took part in the survey across the two waves with a fairly even split between general neurologists and movement disorder specialists overall (generalists n=375 and movement disorder specialists n=386, **Table 1**). Exceptions were Portugal, where almost all participants were generalists, and Italy, where three quarters of participants were movement disorder specialists. The most common setting was teaching hospitals and general public hospitals, and the mean number of years in practice among participants was 16. Overall, the estimated mean number of patients treated by participants per month was 55, with 39% of these estimated to be receiving levodopa. As outlined in the methods, physicians may have responded to one or both questionnaires and in one or both waves. The breakdown of respondents per q uestionnaire and overlap between questionnaires and waves is provided in **Table 2.**

Table 1. Characteristics of participating physicians (overall)

		Total	UK	Germany	Italy	Spain	Portugal
Total participants, N (%)		761 (100)	225 (100)	171 (100)	173 (100)	155 (100)	37 (100)
Years in practice	Median (min, max)	16 (3, 35)	15 (4, 26)	16 (6, 30)	20 (4, 35)	18 (3, 33)	7 (3, 35)
	Mean (SD)	16 (6.7)	15.2 (5.8)	17.1 (5.2)	18.8 (7.3)	18.5 (6.5)	9.6 (7.7)
Estimated number of patients treated previous month	Median (min, max)	40 (5, 650)	35 (5, 650)	40 (10, 420)	40 (5, 300)	45 (10, 410)	30 (10, 100)
	Mean (SD)	55.2 (58.7)	52.5 (74.6)	56.8 (54.7)	57.1 (47.9)	59.1 (47.9)	38.5 (26.6)
Physician type	n (%)						
Generalist		375 (49)	125 (56)	82 (47)	42 (24)	90 (58)	36 (97)
Movement disorder specialist		386 (51)	100 (44)	89 (52)	131 (75)	65 (42)	1 (3)
Estimated number of patients receiving levodopa (%)	Median (min, max)	30 (4, 350)	26 (4, 350)	30 (8, 320)	30 (5, 210)	35 (7, 300)	30 (7, 100)
	Mean (SD)	38.9 (35.6)	35.2 (39.0)	36.9 (30.2)	40.7 (36.0)	45.6 (37.1)	34.8 (24.6)
Setting	n (%)						
Teaching hospital		322 (42)	148 (66)	30 (18)	13 (8)	116 (75)	15 (41)
General public hospital		274 (36)	63 (28)	32 (19)	125 (72)	33 (21)	21 (57)
Private hospital		37 (5)	0	14 (8)	18 (10)	4 (3)	1 (3)
Public office		97 (13)	12 (5)	73 (43)	10 (6)	2 (1)	0
Private office		31 (4)	2 (1)	22 (13)	7 (4)	0	0

SD, standard deviation.

Table 2. Participating physicians by questionnaire in Wave 1 (July 2020) and Wave 2 (September 2021)

	Wave 1		Wave 2		Participant overlap		
	Attitudes and Perceptions	Treatment Landscape	Attitudes and Perceptions	Treatment Landscape	Across questionnaires**		Across waves***
	n	n (PCRs*)	n	n (PCRs*)	Wave 1 n (%)	Wave 2 n (%)	N (%)
Total	411	419 (1676)	379	394 (1576)	328 (65)	305 (61)	440 (44)
UK	88	96 (384)	78	90 (360)	61 (49)	40 (31)	26 (20)
Generalists	45	38 (152)	45	49 (196)			
Movement disorder specialists	43	58 (232)	33	41 (164)			
Germany	99	101 (404)	91	90 (360)	76 (61)	73 (68)	61 (56)
Generalists	58	55 (220)	46	51 (204)			
Movement disorder specialists	41	46 (184)	45	39 (156)			
Italy	101	102 (408)	90	91 (364)	83 (69)	71 (65)	57 (52)
Generalists	23	25 (100)	20	16 (64)			
Movement disorder specialists	78	77 (308)	70	75 (300)			
Spain	103	100 (400)	90	93 (372)	88 (77)	80 (78)	63 (61)
Generalists	56	59 (236)	52	52 (208)			
Movement disorder specialists	47	41 (164)	38	41 (164)			
Portugal	20	20 (80)	30	30 (120)	20 (100)	30 (100)	13 (43)
Generalists	19	19 (76)	29	29 (116)			
Movement disorder specialists	1	1 (4)	1	1 (4)			

* PCRs provided details from the medical records of the four most recently treated patients with motor fluctuations (except in Germany where there is restricted access to patient records. Information relied on physician recall).
** Participating physicians answering both questionnaires in each Wave.
*** Participating physicians answering at least one questionnaire in each Wave.
PCR, patient case report.

Perception of motor fluctuations burden

Physician responses regarding the burden of motor fluctuations are summarized in **Figure 1**. Across the two waves, around 80% agreed to some extent (scored 7, 6 or 5) that motor fluctuations place a heavy burden on patients (16%/18% completely agreed in Wave 1/Wave 2, respectively, **Supplementary Table S1**) and that an effective treatment for motor fluctuations is an unmet need (19%/21% completely agreed in Wave 1/Wave 2). There was a tendency for less strong agreement with the other statements; (**Figure 1**) motor fluctuations are an inevitable part of Parkinson's (8%/6% completely agreed in Wave 1/2), most patients can tolerate some degree of motor fluctuations (5%/4% completely agreed), patients express the need for urgent management when motor fluctuations arise (5% completely agreed in both waves) (**Supplementary Table S1**). There was no significant difference in responses between countries or between the surveys in each wave.

Detection of motor fluctuations

Methods of detection

Most respondents rely on proactive questioning to detect motor fluctuations (**Figure 2**). Around a quarter of respondents (27%/24% in Wave 1/2) completely agreed with the statement "*I usually proactively ask specific questions to identify patients who are suffering from motor fluctuations*", while the proportion who completely agreed with the statement *"I use screening tools/standardized questionnaires (e.g. UPDRS, WOQ-19, WOQ-9, PDQ-8) to diagnose motor fluctuations"* was markedly less (6%/7% in Wave 1/2) (**Supplementary Table S2**). There was no significant difference in responses between countries or between the surveys in each wave.

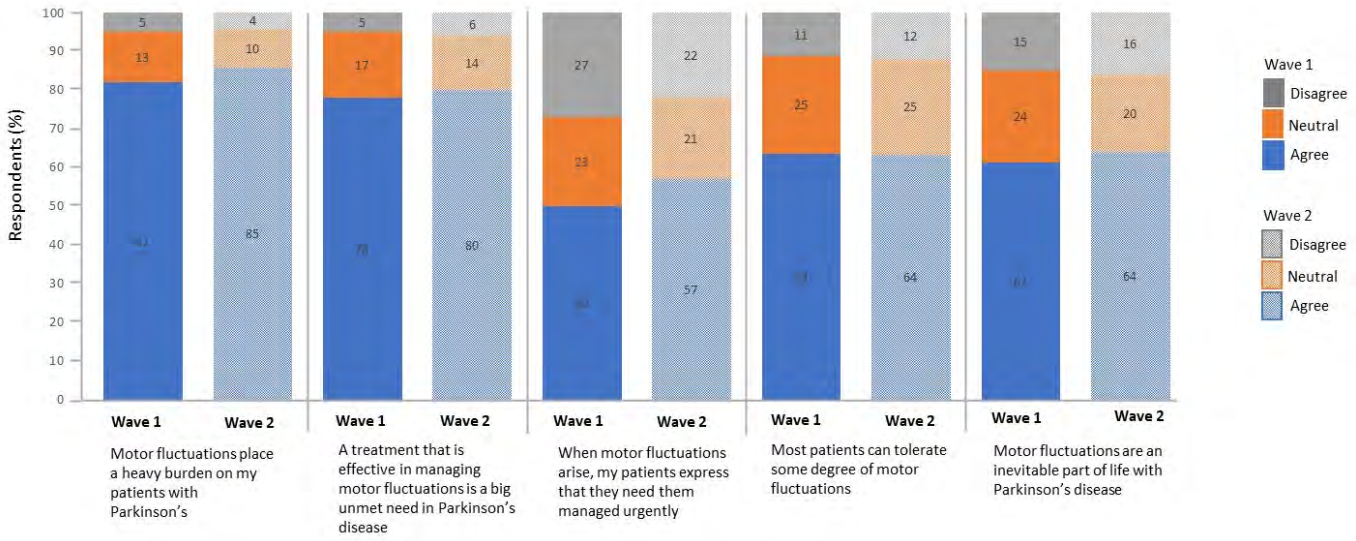

Figure 1. Perceived burden of motor fluctuations in Parkinson's disease

Question: Please indicate to what extent you agree or disagree with each of the following statements about motor fluctuations. Respondents indicated to what extent they agreed or disagreed with statements using a 7-point scale (1=completely disagree, 7=completely agree). Scores collapsed into 3 categories: 1,2,3 disagree; 4 neither agree nor disagree; 5,6,7 agree
Base: All HCPs answering Wave 1 (n=411), Wave 2 (n=394)
Raw data presented in Supplementary Table S1

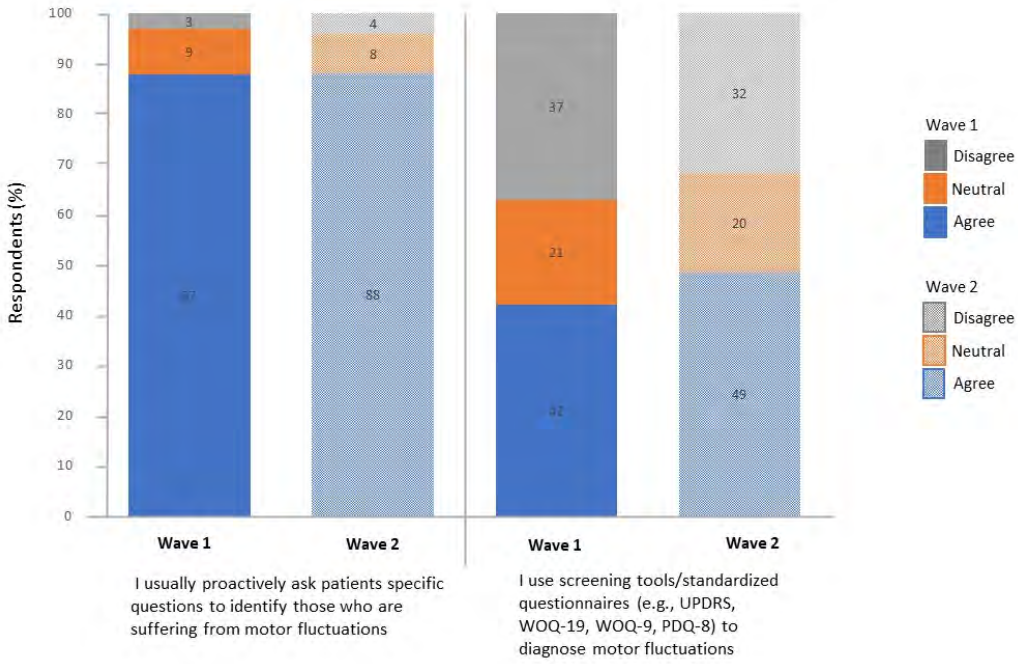

Figure 2. Detection of motor fluctuations in Parkinson's disease

Question: Please indicate to what extent you agree or disagree with each of the following statements about motor fluctuations. Respondents indicated to what extent they agreed or disagreed with statements using a 7-point scale (1=completely disagree, 7=completely agree). Scores collapsed into 3 categories: 1,2,3 disagree; 4 neither agree nor disagree; 5,6,7 agree
Base: All HCPs answering Wave 1 (n=411), Wave 2 (n=394). Raw data presented in Supplementary Table S2

Confidence in detecting and treating motor fluctuations

Ranking of agreement with statements concerning ease of detection and treatment of motor fluctuations are shown in **Figure 3.** Most respondents (64%/72% in Wave 1/2, respectively) agreed with the statement "*Motor fluctuations are underdiagnosed within the Parkinson's community*", and around one fifth gave a neutral response (score=4; 22%/16% in Wave 1/2). Overall, responses indicate physicians are not entirely confident about being able to effectively treat motor fluctuations. Around a quarter of respondents (26%/30% in Wave 1/2) agreed to some extent with the statement *"once identified, motor fluctuations are usually easy to treat"* and just 3% of respondents completely agreed with the statement *"I am confident in being able to fully resolve motor fluctuations to my patient's satisfaction"* (**Supplementary Table S3**). No significant differences in responses were detected between countries.

Perceptions around levodopa introduction and predictors of motor complications

Around three quarters of respondents (73%/79% in Wave 1/2) agreed with the statement that levodopa at diagnosis improves patients' quality of life compared with delaying (just 1% in each wave completely disagreed with this statement, **Supplementary Table S4**) and around two thirds (66%/73%) agreed to some extent with the statement, *"The overall benefit/risk balance favours levodopa initiation over levodopa-sparing therapy and leads to better patient-rated quality of life and mobility in the short term than initiation with DAs or MAOB inhibitors alone"* (**Figure 4**). However, when responding to statements about predictors of motor complications, around 60% in each wave agreed that early levodopa is associated with higher rates of dyskinesia and motor fluctuations (**Figure 4**). More than 80% of respondents agreed that duration of disease predicts motor complications (although significantly more respondents from the UK disagreed with this statement; 14% versus 6% overall), while >70% agreed that duration of levodopa and dose of levodopa are predictors of motor complications (**Figure 4**). There was also significant agreement (42%/41% in Wave 1/2) with the statement, "*Patients with a fear of initiating treatment with levodopa is a problem that I encounter in daily practice*" (**Supplementary Table S4**).

Around 40% of patients are reportedly initiated on levodopa within a month of diagnosis (35%/39% in Wave 1/2), a similar proportion within 1 year (42%/41%), and around 20% within 2 years (23%/20%). There was no significant difference in the timing of levodopa initiation between specialist and general neurologists, although there was a tendency for neurologists

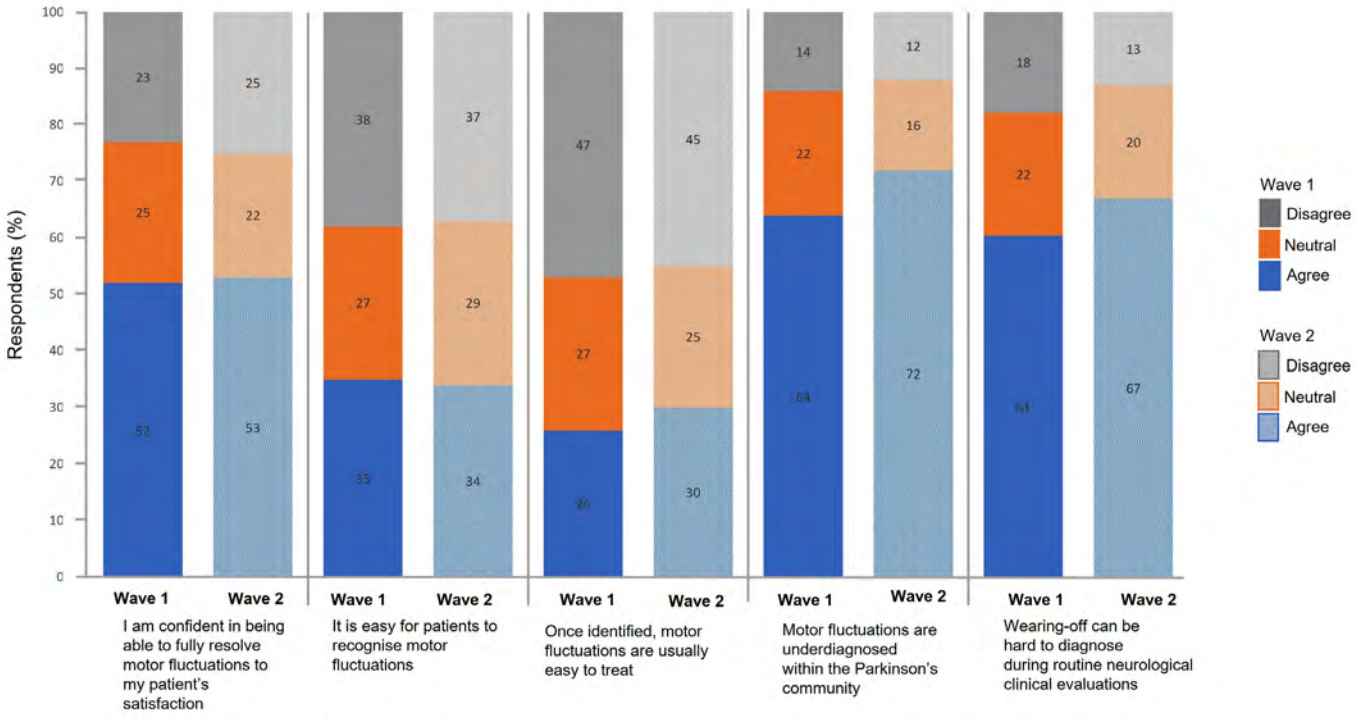

Figure 3. Confidence in detecting and treating motor fluctuations

Question: Please indicate to what extent you agree or disagree with each of the following statements about motor fluctuations. Respondents indicated to what extent they agreed or disagreed with statements using a 7-point scale (1=completely disagree, 7=completely agree). Scores collapsed into 3 categories: 1,2,3 disagree; 4 neither agree nor disagree; 5,6,7 agree

Base: All HCPs answering Wave 1 (n=411), Wave 2 (n=394). Raw data presented in Supplementary Table S3

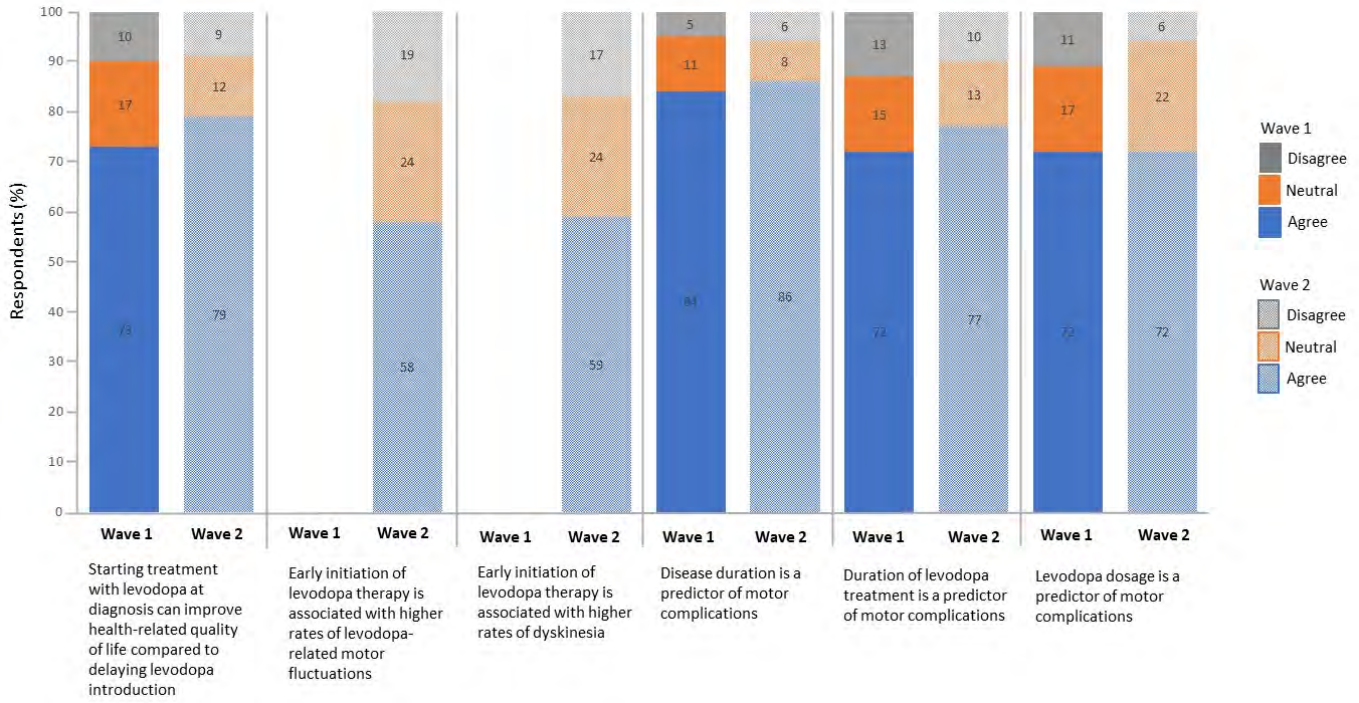

Figure 4. Perceptions around levodopa introduction and predictors of motor complications

Question: Please indicate to what extent you agree or disagree with each of the following statements about motor fluctuations. Respondents indicated to what extent they agreed or disagreed with statements using a 7-point scale (1=completely disagree, 7=completely agree). Scores collapsed into 3 categories: 1,2,3 disagree; 4 neither agree nor disagree; 5,6,7 agree

Base: All HCPs answering Wave 1 (n=411), Wave 2 (n=394). Raw data presented in Supplementary Table S4

in Germany to initiate levodopa later than in other countries. For example, in Wave 2, 23% of patients in Germany were initiated within a month compared with 37% in Spain, 36% in Italy, 48% in the UK, and 66% in Portugal (although low base in this country makes comparison difficult).

Management of motor fluctuations

In general, there does not appear to be a high level of satisfaction with available treatments for the management of motor fluctuations; there was an even spread of agreement (35%/40%) and disagreement (41%/35%) with the statement *"I am happy with the treatments I have available to me to treat motor fluctuations"* (**Supplementary Table S5**). Fractionating levodopa is the preferred first strategy versus adding an adjunct (68%/69% agreed in Wave 1/2; **Figure 5**). The treatment strategies recorded in the PCR forms of the most recent survey (Wave 2; **Figure 6**) show that the immediate addition of adjunct therapy is a more common first strategy used by specialists than general neurologists (31% of cases versus 15%, respectively), with MAOB and COMT inhibitors the most frequently used treatments (**Figure 6**). When levodopa change is used as a first treatment strategy by generalists, most patients have no subsequent change in therapy (55% versus 38% of those treated by specialists), whereas specialists are more likely to add an adjunct later (62% versus 45%). The three most important priorities reported for choosing an adjunct treatment were (1) level of ON time/reduced OFF time, (2) tolerability, and (3) impact on non-motor symptoms.

When respondents were asked about potential barriers to choosing specific treatments, it was reported that there were greater restrictions imposed on the use of newer COMT and MAOB inhibitors (e.g., opicapone, safinamide) compared with generic treatments. Compared with other countries, significantly more physicians in the UK reported budget restrictions and non-inclusion on hospital formulary as reasons for non-prescribing of these products.

Discussion

This series of surveys explored physician perceptions around motor fluctuations in levodopa-treated patients with Parkinson's disease and provided insight into the clinical strategies currently used for their management. In line with the current evidence base, almost half of physicians strongly or completely agreed that levodopa treatment at diagnosis improves patients' quality of life (5,14,15). However, the proportion who agreed strongly or completely (score of 6 or 7) that the benefit/risk balance favors levodopa initiation over levodopa-sparing was only around one third, despite growing evidence that this is the case. In an open-label trial (PD MED study) of newly diagnosed patients with Parkinson's disease randomized to levodopa-sparing therapy (DAs or MAOB inhibitors) or levodopa alone, the overall benefit/risk balance favoured levodopa initiation over levodopa-sparing therapy, leading to persistently better patient-rated quality of life and mobility in both the short

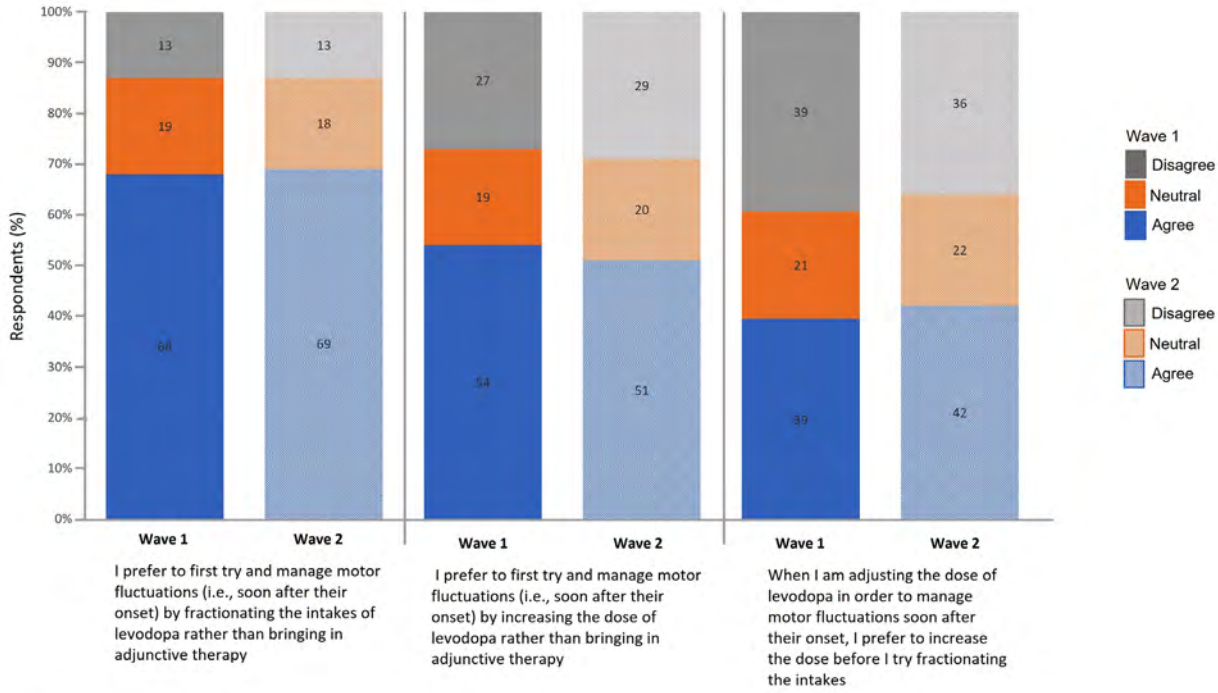

Figure 5. Levodopa treatment strategies

Question: Please indicate to what extent you agree or disagree with each of the following statements about motor fluctuations. Respondents indicated to what extent they agreed or disagreed with statements using a 7-point scale (1=completely disagree, 7=completely agree). Scores collapsed into 3 categories: 1,2,3 disagree; 4 neither agree nor disagree; 5,6,7 agree
Base: All HCPs answering Wave 1 (n=411), Wave 2 (n=394). Raw data presented in Supplementary Table S5

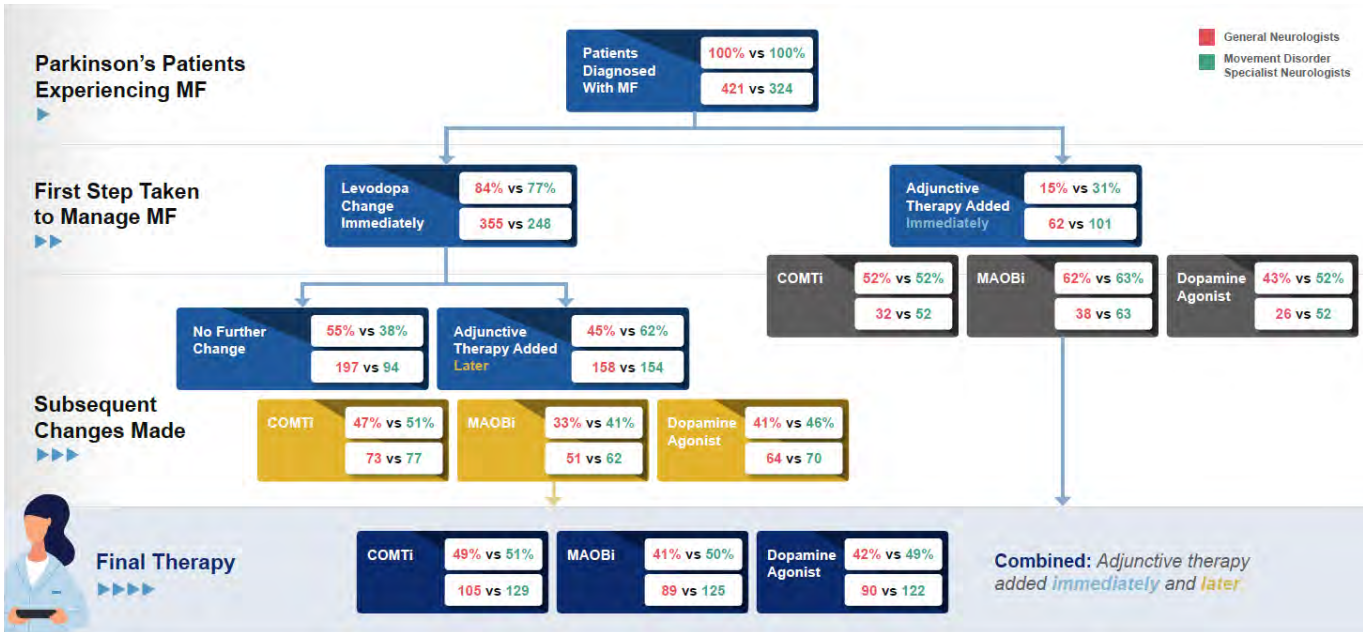

Figure 6. Treatment strategies in patients with motor fluctuations receiving levodopa (Wave 2)

and long term than treatment with DAs or MAOB inhibitors alone (14). In addition, during 7 years' follow up, there was no indication of cumulative adverse effects or loss of benefit over time. This was also observed in another placebo-controlled, delayed-start trial where early levodopa-carbidopa treatment for 80 weeks was not associated with higher rates of dyskinesia or levodopa-related motor fluctuations compared with delayed initiation of levodopa–carbidopa therapy (40 weeks placebo, 40 weeks levodopa–carbidopa) (15). Furthermore, discontinuation of treatment owing to side effects in the PD MED study was significantly less among patients treated with levodopa, occurring in 179 (28%) of 632 patients allocated DAs, 104 (23%) of 460 patients allocated MAOB inhibitors, and 11 (2%) of 528 patients allocated levodopa (p<0·0001) (14).

Studies in levodopa-treated patients with Parkinson's disease have demonstrated that use of screening tools leads to greater detection of wearing off symptoms compared with neurologist assessment alone. However, while most respondents in the current survey believe that motor fluctuations are underdiagnosed, responses reveal that screening tools are not used routinely to detect motor fluctuations, with physicians relying on proactive questioning of patients. A non-interventional study in levodopa-treated patients with Parkinson's disease found that wearing-off symptoms were detected in 66.7% of patients by neurologists' assessment compared with 90.6% of patients using the WOQ-9 questionnaire, with the biggest discrepancy between neurologists' assessment and WOQ-9 evaluation found in Parkinson's disease patients treated with levodopa for <2 years (16). The observational, cross-sectional, multicentre DEEP study also demonstrated that the use of the self-assessed 19-question tool, WOQ-19, doubled the proportion of patients (with a <2.5-year disease duration) in whom wearing off was detected versus neurologist assessment (13). The most frequent symptoms of wearing-off in this study were slowness of movements and reduced dexterity. Factors predicting the development of motor complications identified in this and other studies include younger age, female gender, higher levodopa dose, and greater disability, measured by the Unified Parkinson's Disease Rating Scale (UPDRS) part II score (13,17). Low body weight was found to be predictive of dyskinesia but not wearing off (17).

While the survey responses indicated that physicians perceive motor fluctuations to impose a heavy burden on their patients, this does not align with the fact that patients are not generally perceived to be demanding urgent management. This may be due to patient fear of initiating levodopa treatment. Around 40% of respondents reported encountering patients in daily practice who fear initiating treatment with levodopa.

Around one third of respondents in our survey strongly/completely agreed that levodopa duration (35–40%) predicts motor complications, with a similar proportion strongly/completely agreeing that levodopa dose (33–35%) is a predictor. However, evidence suggests that, while motor fluctuations and dyskinesia are associated with a longer duration of disease and higher doses of levodopa, they are not associated with duration of levodopa treatment (15,17,18). For example, when patients with and without wearing off were compared in the DEEP study (13), the duration of treatment with levodopa did not differ between patients with and without wearing off (3.70 y ± 3.58 vs 3.42 y ± 2.55; p = 0.3104), while the mean daily levodopa dosage was significantly higher in patients in whom wearing off was detected (439.4 mg ± 217.0 vs 370.6 mg ± 179.3; p = 0.0002). Logistic regression analysis confirmed that the time since initiation of levodopa did not predict occurrence of wearing off (13).

Among both general neurologists and movement disorder specialist neurologists who completed PCRs, fractionating levodopa was the preferred initial approach to managing motor fluctuations. However, adjunct treatments were used more frequently among specialists. The proportion of patients treated with levodopa in combination with an adjunct treatment as a first approach was doubled for those managed by specialists compared with general neurologists (31% vs 15% in Wave 2). Furthermore, more than half of those treated initially with levodopa changes by general neurologists had no adjunct added to their therapy at a later stage, whereas 62% of those treated by a specialist neurologists had an adjunct added later.

As wearing off represents the time between doses when the therapeutic benefit of the levodopa begins to deteriorate, one of the most important goals in long-term levodopa therapy is to prolong the duration of symptomatic efficacy per dose (8). A key factor in the prevention of motor complications is avoidance of peaks and troughs in levodopa plasma levels, but pharmacokinetic analysis suggests that profound trough levels may still exist despite fractionating or increasing the dose of levodopa. Even when levodopa is administered hourly, low plasma trough levels are not avoided (8). The use of adjuncts can help prevent fluctuations in plasma levodopa levels, but our findings suggest there may be a reluctance to use them, especially among general neurologists. Better understanding of levodopa pharmacokinetics and the reasons for drug-associated motor complications among physicians and patients, may lead to improved adherence and build confidence in the use of adjuncts to achieve a more consistent levodopa effect. Another barrier that may be contributing to the lack of adjunct therapy use is that more recently approved medications, with improved efficacy and safety profiles (e.g., the COMT inhibitor opicapone (18)), were reported as being less accessible than generic versions. This was especially the case in the UK where significantly more physicians reported budget restrictions and non-inclusion on hospital formulary as reasons for non-prescribing, compared with other countries.

This study has some limitations which are inherent to the market research methodology. The perceptions and practices of the selected respondents may not be generally representative of neurologists treating patients with Parkinson's disease. There was no data verification of patient records and some questions relied on estimates or recall. Furthermore, many questions involved rating agreement with statements rather than allowing physicians to respond or elaborate in their own words. Despite these limitations, the major strengths of the study are the real-word and multinational aspects, giving insight into current perceptions, challenges, and practices for the routine management of motor fluctuations in patients with Parkinson's disease across Europe. The similarity in results between the surveys conducted in Wave 1 and Wave 2 (when compared overall and only in participants responding to both surveys) adds to the credibility of the findings. This qualitative research has identified potential knowledge gaps between neurologists' perceptions and the evidence base that could be addressed through future educational intervention.

Conclusions

The "real-world" insights into the experience and perceptions of physicians treating motor fluctuations reveals several unmet needs in current practice. Screening tools that could increase the detection and early treatment of motor fluctuations are not routinely used and confidence in the ability to fully resolve motor fluctuations is lacking. Increased physician and patient understanding of the causes and predictors of motor fluctuations and greater accessibility and use of currently available adjunct treatments may help optimize management and improve the quality of life for patients with Parkinson's disease.

Abbreviations

COMT, catechol-O-methyl transferase
DA, dopamine agonists
EphMRA, European Pharmaceutical Market Research Association
ESOMAR, European Society for Opinion and Marketing Research
HCP, healthcare professional
MAOB, monoamine oxidase-B
MRS, Market Research Society
PCR, patient case report
UPDRS, Unified Parkinson's Disease Rating Scale

Declarations

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions

RO and FR were responsible for study conception and design, data analysis, interpretation of the data, and drafting of the manuscript. FS contributed to the analysis and interpretation of the data and drafting of the manuscript.

Declaration of conflicting interests

FS has served as a paid consultant for BIAL, Sunovion, Abbvie, Luosofarmaco, Kjowa, Synegile, Lundbeck, TEVA, UCB, Zambon, Blue Rock, Neuroderm, and Contera and has received honoraria for educational activities from BIAL, Sunovion, Abbvie, Luosofarmaco, Kjowa, Synegile, Lundbeck, TEVA, UCB, and Zambon. FR is an employee of Bial and RO was an employee of Bial at the time of the study.

Compliance with Ethics Guidelines

Surveys were conducted in accordance with the EphMRA (European Pharmaceutical Market Research Association), ESOMAR (European Society for Opinion and Marketing Research) and Market Research Society (MRS) codes of conduct regarding anonymity and confidentiality. Ethics approval was not required according to local laws for observational questionnaire-based studies where all data are anonymized.

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available. Researchers may request data from Francisco Rocha at francisco.rocha@bial.com.

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Supplementary tables

Table S1. Burden of motor fluctuations

	A treatment that is effective in managing motor fluctuations is a big unmet need in Parkinson's disease		Motor fluctuations are a heavy burden for my Parkinson's patients		Motor fluctuations are an inevitable part of life with Parkinson's disease		Most patients can tolerate some degree of motor fluctuations		When motor fluctuations arise, my patients express that they need them managed urgently	
	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2
7 Completely Agree	19%	21%	16%	18%	8%	6%	5%	4%	5%	5%
6	28%	33%	30%	33%	21%	21%	19%	22%	18%	20%
5	31%	26%	35%	35%	33%	37%	40%	38%	27%	32%
4	17%	14%	13%	10%	24%	20%	25%	25%	23%	21%
3	4%	6%	4%	4%	10%	11%	10%	10%	20%	17%
2	1%	0%	1%	1%	4%	4%	1%	2%	7%	4%
1 Completely Disagree	0%	0%	0%	0%	1%	1%	0%	0%	0%	1%

Table S2. Method of detection of motor symptoms

	I usually proactively ask patients specific questions to identify patients who are suffering from motor fluctuations		I use screening tools / standardized questionnaires (e.g. UPDRS, WOQ-19, WOQ-9, PDQ-8) to diagnose motor fluctuations	
	Wave 1	Wave 2	Wave 1	Wave 2
7 Completely Agree	27%	24%	6%	7%
6	34%	38%	15%	17%
5	27%	26%	21%	24%
4	9%	8%	21%	20%
3	3%	3%	13%	13%
2	0%	1%	17%	11%
1 Completely Disagree	0%	0%	8%	8%

Table S3. Ease of detection of motor symptoms

	I find it easy to diagnose motor fluctuations in my patients		I am confident in being able to fully resolve motor fluctuations to my patient's satisfaction		It is easy for patients to recognize motor fluctuations		Once identified, motor fluctuations are usually easy to treat	
	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2
7 Completely Agree	6%	6%	3%	3%	3%	2%	2%	2%
6	19%	17%	14%	17%	11%	10%	6%	9%
5	38%	39%	35%	34%	21%	22%	17%	20%
4	23%	23%	25%	22%	27%	29%	27%	25%
3	10%	10%	14%	15%	25%	23%	28%	27%
2	4%	4%	7%	7%	10%	11%	15%	15%
1 Completely Disagree	0%	1%	2%	3%	2%	3%	4%	3%

	The time it takes for motor fluctuations to be identified and treated can be a lengthy process		Motor fluctuations are underdiagnosed within the Parkinson's community		Wearing-off can be hard to diagnose during routine neurological clinical evaluations		Symptoms of motor fluctuations can be hard to spot		It's more challenging to identify motor fluctuations early in a patient than it is to treat them effectively	
	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2
7 Completely Agree	11%	9%	9%	11%	6%	8%	7%	7%	4%	4%
6	25%	27%	24%	22%	20%	20%	18%	20%	14%	15%
5	36%	38%	32%	40%	35%	39%	31%	37%	28%	24%
4	18%	16%	22%	16%	22%	20%	22%	21%	27%	30%
3	8%	8%	9%	8%	14%	10%	16%	11%	14%	18%
2	2%	1%	3%	2%	3%	2%	5%	4%	10%	7%
1 Completely Disagree	0%	1%	1%	1%	1%	1%	2%	1%	2%	2%

Table S4. Perceptions around levodopa introduction and predictors of motor complications

	Starting treatment with levodopa at diagnosis can improve health-related quality of life compared to delaying levodopa introduction		The overall benefit/risk balance favours levodopa initiation over levodopa-sparing therapy and leads to better patient-rated quality of life and mobility in the short term than initiation with Das or MAOB inhibitors alone		The overall benefit/risk balance favours levodopa initiation over levodopa-sparing therapy and leads to better patient-rated quality of life and mobility in the long term than initiation with Das or MAOB inhibitors alone		Levodopa-sparing strategies provide delaying benefits to the eventual onset of motor fluctuations		Early initiation of levodopa therapy is associated with higher rates of levodopa-related motor fluctuations		Early initiation of levodopa therapy is associated with higher rates of dyskinesia	
	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2
7 Completely Agree	14%	14%	8%	8%	6%	7%	0%	9%	0%	4%	0%	8%
6	30%	34%	25%	30%	23%	28%	0%	21%	0%	22%	0%	17%
5	30%	31%	33%	36%	35%	32%	0%	36%	0%	31%	0%	34%
4	17%	12%	21%	16%	23%	22%	0%	20%	0%	24%	0%	24%
3	6%	6%	9%	7%	8%	6%	0%	9%	0%	13%	0%	9%
2	2%	2%	4%	3%	4%	4%	0%	5%	0%	5%	0%	7%
1 Completely Disagree	1%	1%	0%	1%	0%	1%	0%	1%	0%	1%	0%	1%

	Disease duration is a predictor of motor complications		Duration of levodopa treatment is a predictor of motor complications		Levodopa dosage is a predictor of motor complications		Concerns about levodopa neurotoxicity are supported by scientific evidence		Patients with a fear of initiating treatment with levodopa is a problem that I encounter in my daily practice	
	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2
7 Completely Agree	20%	25%	10%	11%	9%	9%	3%	5%	4%	4%
6	35%	33%	25%	29%	24%	26%	13%	15%	12%	15%
5	28%	28%	37%	37%	38%	37%	25%	23%	26%	22%
4	11%	8%	15%	13%	17%	22%	25%	27%	23%	22%
3	4%	6%	9%	7%	7%	4%	14%	12%	15%	15%
2	1%	0%	4%	3%	3%	2%	15%	11%	14%	15%
1 Completely Disagree	0%	0%	0%	1%	1%	0%	5%	6%	6%	7%

Table S5. Levodopa treatment strategies

	I prefer to first try and manage motor fluctuations (i.e. soon after their onset) by fractionating the intakes of levodopa rather than bringing in adjunctive therapy		Increasing the peripheral bioavailability of levodopa plays an important role in the choice of adjuncts (not including DDCI) that I consider for patients first experiencing motor fluctuations		Increasing the peripheral bioavailability of levodopa plays an important role on my choice of adjuncts (not including DDCI) that I consider for patients who have been experiencing motor fluctuations for some time (in whom I may have already tried)		I prefer to first try and manage motor fluctuations (i.e. soon after their onset) by increasing the dose of levodopa rather than bringing in adjunctive therapy		When I am adjusting the dose of levodopa in order to manage motor fluctuations soon after their onset, I prefer to increase the dose before I try fractionating the intakes		I'm happy with the treatments I have available to me to treat motor fluctuations in my patients	
	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2	Wave 1	Wave 2
7 Completely Agree	8%	10%	5%	7%	5%	8%	3%	4%	3%	3%	2%	2%
6	28%	26%	23%	28%	26%	26%	19%	21%	16%	14%	9%	10%
5	32%	33%	42%	38%	39%	37%	31%	26%	21%	26%	25%	29%
4	19%	18%	22%	20%	24%	23%	19%	20%	21%	22%	24%	25%
3	9%	9%	6%	6%	5%	5%	15%	15%	19%	19%	24%	25%
2	4%	4%	2%	2%	1%	1%	10%	10%	16%	11%	13%	9%
1 Completely Disagree	0%	1%	0%	0%	0%	0%	2%	4%	4%	6%	3%	1%