Original Investigation

Prevalence, Determinants, and Effect on Quality of Life of Freezing of Gait in Parkinson Disease

Santiago Perez-Lloret, MD, PhD; Laurence Negre-Pages, PhD; Philippe Damier, MD, PhD; Arnaud Delval, MD, PhD; Pascal Derkinderen, MD, PhD; Alain Destée, MD; Wassilios G. Meissner, MD, PhD; Ludwig Schelosky, MD; Francois Tison, MD, PhD; Olivier Rascol, MD, PhD

IMPORTANCE Freezing of gait (FOG) is a common axial symptom of Parkinson disease (PD).

OBJECTIVE To determine the prevalence of FOG in a large group of PD patients, assess its relationship with quality of life and clinical and pharmacological factors, and explore its changes from the off to on conditions in patients with motor fluctuations.

DESIGN, SETTING, AND PARTICIPANTS Cross-sectional survey of 683 patients with idiopathic PD. Scores for FOG were missing in 11 patients who were not included in the analysis. Patients were recruited from referral centers and general neurology clinics in public or private institutions in France.

EXPOSURE In all, 672 patients with FOG were identified as those with a score of 1 or greater on item 14 of the Unified Parkinson's Disease Rating Scale (UPDRS) in the on condition. Item 14 scores for FOG in the off condition were also collected in patients with fluctuating motor symptoms.

MAIN OUTCOMES AND MEASURES Quality of life (measured by the 39-item Parkinson's Disease Questionnaire and 36-Item Short Form Health Survey), anxiety and depression (Hospital Anxiety and Depression Scale), clinical features (UPDRS), and drug consumption.

RESULTS Of 672 PD patients, 257 reported FOG during the on state (38.2%), which was significantly related to lower quality of life scores ($P < .01$). Freezing of gait was also correlated with longer PD duration (odds ratio, 1.92 [95% CI, 1.28-2.86]), higher UPDRS parts II and III scores (4.67 [3.21-6.78]), the presence of apathy (UPDRS item 4) (1.94 [1.33-2.82]), a higher levodopa equivalent daily dose (1.63 [1.09-2.43]), and more frequent exposure to antimuscarinics (3.07 [1.35-6.97]) (logistic regression). The FOG score improved from the off to on states in 148 of 174 patients with motor fluctuations (85.1%) and showed no change in 13.8%. The FOG score improved by more than 50% in 43.7% of patients. Greater improvement in the on state was observed in younger patients ($r = -0.25$; $P < .01$) with lower UPDRS II and III scores ($r = -0.50$; $P < .01$) and no antimuscarinic use ($r = -0.21$; $P < .01$).

CONCLUSIONS AND RELEVANCE Freezing of gait in PD patients correlates with poor quality of life, disease severity, apathy, and exposure to antimuscarinics. Dopaminergic therapy improved FOG in most patients with motor fluctuations, especially younger ones with less severe disease and no antimuscarinic use. This finding suggests that quality of life is impaired in PD patients with FOG and that optimizing dopaminergic therapy and avoiding antimuscarinics should be considered.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Olivier Rascol, MD, PhD, Faculty of Medicine, Department of Clinical Pharmacology, University Hospital, University of Toulouse, 37 Allées Jules Guesde, 31000 Toulouse, France (olivier.rascol@univ-tlse3.fr).

Freezing of gait (FOG) is a sudden, variable, and often unpredictable transient break in walking, occurring at initiation of or during gait and especially while turning. Patients with Parkinson disease (PD) feel as if their feet are "glued" to the floor. Freezing of gait occurs during states of good mobility in response to dopaminergic therapy (on state) and/or impaired mobility with a poor response to dopaminergic therapy (off state) and is usually more common and severe in the off state.[1,2] Freezing of gait can reduce patients' independence and mobility profoundly.[3,4]

A few factors related to FOG have been identified, including male sex, severity of PD, lower cognitive performance, longer disease duration, higher depression scores, higher doses of dopaminergic medications, motor complications, and lower tremor scores.[5-10] Relationships of FOG with health-related quality of life and pharmacological factors, including exposure to dopaminergic and nondopaminergic antiparkinsonian medication and changes in the on or the off state have been poorly explored. The objective of this study was therefore to assess the prevalence of FOG and its relationship with quality of life and to determine the clinical and pharmacological factors related to its occurrence in a large French cohort of ambulatory PD patients.

Methods

Population

The present data refer to a French multicenter epidemiological survey (the COPARK study), including 683 ambulatory outpatients with PD who fulfilled the criteria of the UK Parkinson's Disease Society Brain Bank.[11] Patients were included prospectively as outpatients of public or private practicing neurologists with or without a special interest in movement disorders in 32 centers from 4 different regions of France (Midi-Pyrenees, Aquitaine, Pays de Loire, and Nord-Pas de Calais) (a list of all participating neurologists is given in the Additional Contributions section). Patients who were younger than 18 years, had a Mini-Mental State Examination[12] score of less than 24, were undergoing deep brain stimulation, had serious disease affecting life expectancy in the short term, or did not give consent were not included.

The study was approved by the French national authorities and was undertaken in accordance with Guidelines for Good Epidemiology Practices and recommendations from the Association des Epidémiologistes de Langue Française. Signed informed consent was obtained from all patients in accordance with the institutional ethics committee board.

Study Procedures

Each PD patient was examined by a neurologist using a standardized and structured interview. All investigators were trained during specific meetings.

Sociodemographic characteristics, clinical features of PD, cognitive function (assessed by the Mini-Mental State Examination),[12] medical history, and all drugs taken for PD at the time of the visit were recorded. The levodopa daily equivalent dose was calculated.[13]

We assessed scores on the Unified Parkinson's Disease Rating Scale (UPDRS)[14] parts I (Mood/Cognition), II (Activities of Daily Living), and III (Motor Examination) with patients in the on condition. In patients with motor fluctuations (score of ≥1 on UPDRS item 39), UPDRS part II was evaluated in the off state. The UPDRS II and III subscores were also calculated as follows: (1) gait impairment other than FOG (items 15 and 28-30); (2) tremor (items 16, 20, and 21); (3) daily chore impairments (items 8-13); (4) bradykinesia/rigidity (items 22-26 and 31); and (5) oropharyngeal symptoms (items 5-7, 18, and 19). Other outcomes included scores on the Hoehn and Yahr Scale,[15] the Hospital Anxiety and Depression Scale,[16] and the following 2 quality-of-life scores: the specific 39-item Parkinson's Disease Questionnaire (PDQ-39)[17] (range, 0-100, with lower scores indicating better perceived health state) and the generic 36-Item Short Form Health Survey (SF-36),[18] which includes the Mental Health Component and Physical Health Component summary scores. Higher SF-36 scores indicate better perceived health state.[19] Data were managed and analyzed by the Toulouse Center, including quality control and site monitoring.

FOG Evaluation

Freezing of gait was explored using item 14 (Freezing When Walking) of the UPDRS II. Patients were asked if they have felt that their feet were glued to the floor when trying to walk or if they had problems starting to walk or when turning. The following options were given: 0 indicates "no freezing"; 1, "rare freezing when walking; may have start hesitation"; 2, "occasional freezing when walking"; 3, "frequent freezing; occasionally falls from freezing"; and 4, "frequent falls from freezing."

The principal outcome of this study was FOG score in the on state (on-FOG), which was obtained in all patients who could undergo evaluation. In the subgroup of patients with motor fluctuations (scores of ≥1 on UPDRS item 39), FOG was also rated in the off condition (off-FOG). The on and off states were defined according to standard and validated international definitions.[20] In patients with an off-FOG score of greater than 0, an off-on difference was calculated in a way that positive scores reflected improved function in the on state, whereas negative scores reflected worsened function. The percentage of improvement was calculated as off/on scores × 100.

Statistical Analysis

We calculated prevalence with 95% CIs. Demographic and clinical characteristics are presented as frequencies and proportions or means (SEM). Bivariate analysis was performed with χ^2 statistics or Fisher exact test and 2-sided *t* test according to the type of variable undergoing analysis. Bivariate tests were followed by logistic regression. Only variables with significant differences at the bivariate comparisons were included in the stepwise logistic models. Hosmer-Lemeshow goodness-of-fit scores were used to assess model fit. In all cases, model fit was higher than 0.8. Multicolinearity was absent from all models.

The on-off change in FOG scores was correlated with other variables by the Spearman rank correlation ρ coefficient. A mul-

Table 1. Characteristics of Patients With or Without FOG in the On State

Characteristic	No. (%) of Patients[a]			Multivariate OR (95% CI)[b]
	Study Population (n = 672)	FOG Score of 0 (n = 415)	FOG Score ≥1 (n = 257)	
Age ≥68 y	341 (50.7)	196 (47.2)	142 (55.3)[c]	NR
Female sex	291 (43.3)	192 (46.3)	91 (35.4)[d]	NR
Age at end of studies >18 y	300 (44.6)	186 (45.1)	107 (42.0)	NR
Age at PD onset >62 y	341 (50.7)	223 (53.7)	114 (44.5)[c]	NR
PD duration >5 y	341 (50.7)	165 (39.8)	172 (67.2)[d]	1.92 (1.28-2.86)
Help with daytime activities	170 (25.3)	87 (21.0)	80 (31.1)[d]	NR
MMSE score <29	17 (2.5)	10 (2.4)	7 (2.7)	NR
HADS score >7				
Anxiety	336 (50.0)	194 (48.6)	136 (55.1)	NR
Depression	211 (31.4)	113 (28.0)	96 (38.7)[d]	NR
UPDRS part I score				
Hallucination (item 2)	182 (27.1)	96 (23.1)	84 (32.7)[d]	NR
Apathy (item 4)	383 (57.0)	196 (47.2)	182 (70.8)[d]	1.94 (1.33-2.82)
Score				
UPDRS part I total >2	291 (43.3)	148 (35.7)	143 (55.6)[d]	NR
UPDRS parts II and III total >26	331 (49.3)	138 (33.3)	190 (73.9)[d]	4.67 (3.21-6.78)
Subcategories				
Bradykinesia/rigidity >11	333 (50.0)	161 (38.8)	169 (65.8)[d]	NR
Tremor >0	523 (77.8)	331 (79.8)	183 (71.2)	0.67 (0.43-1.00)
Impairment in daily chores >5	282 (42.0)	117 (28.2)	164 (63.8)[d]	NR
Gait impairment (other than FOG) >4	333 (50.0)	98 (23.6)	197 (76.7)[d]	4.09 (2.79-5.98)
Oropharyngeal symptoms >3	321 (47.8)	151 (36.4)	169 (65.8)[d]	1.54 (1.02-2.33)
LDED >500 mg/d	330 (49.1)	164 (39.5)	166 (64.6)[d]	1.63 (1.09-2.43)
UPDRS part IV				
Dyskinesias	183 (27.2)	87 (21.0)	96 (37.4)[d]	NR
Wearing off	235 (35.0)	126 (30.4)	109 (42.4)[d]	NR
Antiparkinsonian medication				
Antimuscarinics	34 (5.1)	14 (3.4)	20 (7.8)[c]	3.07 (1.35-6.97)
Levodopa	545 (81.1)	323 (77.8)	221 (86.0)[d]	NR
Dopamine agonists	423 (62.9)	255 (61.4)	167 (65.0)	NR
MAO-B inhibitors	98 (14.6)	68 (16.4)	30 (11.7)	NR
Entacapone	123 (18.3)	81 (19.5)	42 (16.3)	NR
Amantadine hydrochloride	61 (9.1)	27 (6.5)	34 (13.2)[d]	NR

Abbreviations: FOG, freezing of gait; HADS, Hospital Anxiety and Depression Scale; LDED, levodopa daily equivalent dose; MAO-B, monoamine oxidase type B; MMSE, Mini-Mental State Examination; NR, not retained; OR, odds ratio; PD, Parkinson disease; UPDRS, Unified Parkinson's Disease Rating Scale.

[a] Owing to missing data, patient numbers do not equal totals for all categories.

[b] All variables with significant differences at the bivariate analyses were entered in the multivariate stepwise logistic regression model. Variables not retained in the final model are indicated. Multivariate significance of UPDRS subscores was tested in an independent logistic model also including all previously significant correlates.

[c] $P < .05$ vs PD without FOG (χ^2 test).

[d] $P < .01$ vs PD without FOG (χ^2 test).

tivariate ordinal regression analysis, which is an extension of logistic regression used for outcome variables with multiple levels, was then applied. For this analysis, the on-off change was categorized as 0 indicating no; 1, improvement from 1% to 50%; and 2, improvement from 51% to 100%. Only variables significantly correlated with the outcome were introduced in the model.

Statistical significance was based on a 2-sided test evaluated at a .05 level of significance. All analysis was performed using commercially available software (SAS, version 9.3; SAS Institute Inc).

Results

Population Characteristics

We included 683 patients in the study (**Table 1**). Of these, 39.1% were followed up by movement disorder specialists and 60.9% by general neurologists.

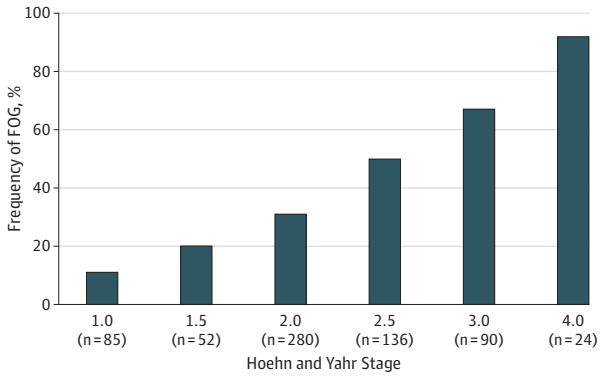
On-FOG Prevalence

Eleven patients had missing data and were excluded from this analysis. On-FOG point prevalence was 38.2% (95% CI, 34.5%-41.9%). Distribution across on-FOG scores was as follows: 415 patients (61.8%) had 0; 176 (26.2%), 1; 66 (9.8%), 2; 14 (2.1%), 3; and 1 (0.1%), 4. Prevalence of on-FOG scores across the Hoehn and Yahr Scale stages is shown in **Figure 1**.

Relationship of On-FOG With Quality of Life

Patients with on-FOG showed worse total scores and several subscores of the PDQ-39 and SF-36 (**Figure 2**). A multivariate logistic regression showed that on-FOG was still significantly related to an increased PDQ-39 total score (odds ratio, 1.32 [95% CI, 1.04-1.67]) and reduced Physical (0.68 [0.54-0.87]) and Men-

Figure 1. Frequency of Freezing of Gait (FOG) by Hoehn and Yahr Scale Stages in the On State



A significant linear trend across stages was disclosed by results of a χ^2 test ($P < .001$). No patient had a stage 5.0 rating.

tal (0.71 [0.57-0.88]) Component summary scores on the SF-36 after adjusting for disease severity, duration, and motor complications. The relationship between the on-FOG score and the PDQ-39 total score and SF-36 Physical and Mental Component summary scores is shown in **Figure 3**.

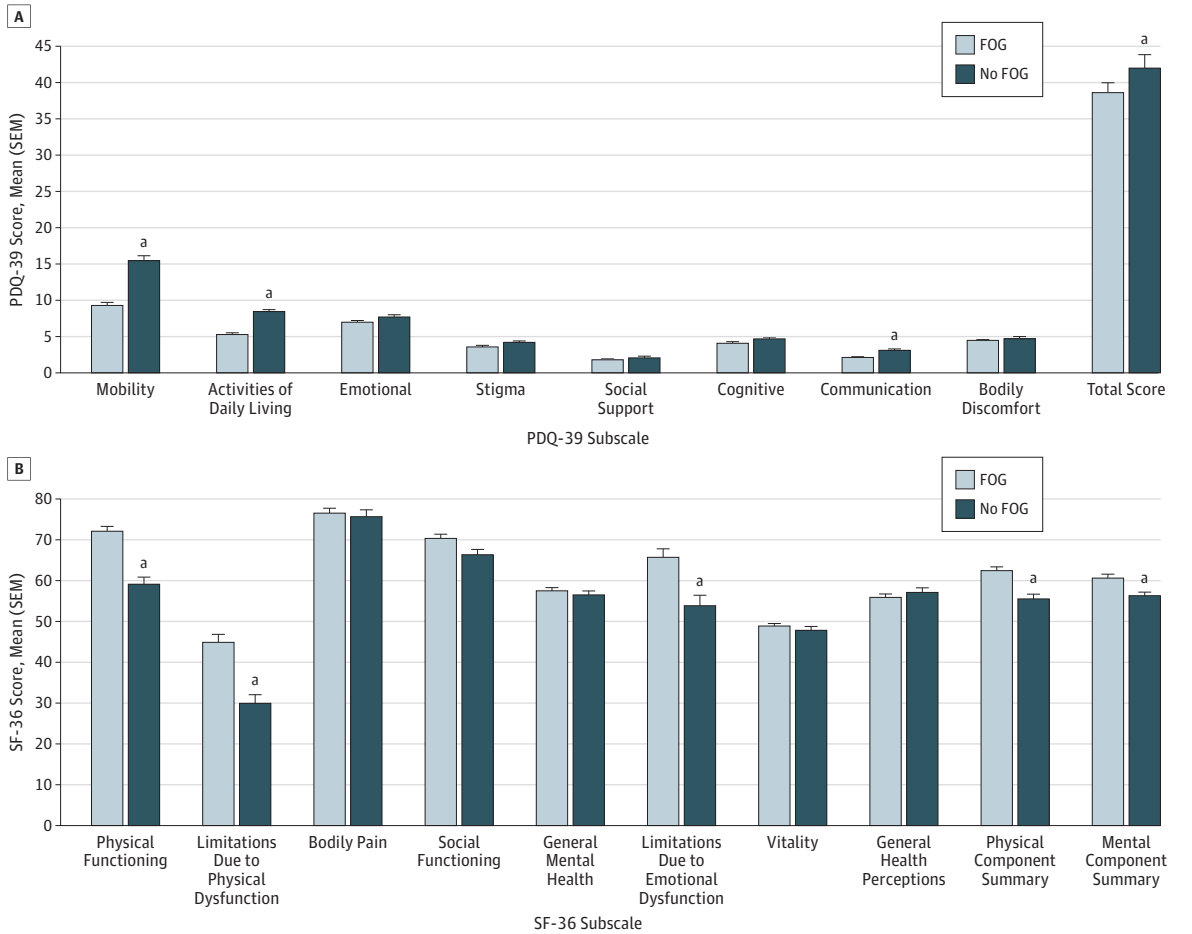
Factors Related to On-FOG

Patients reporting on-FOG had a significantly longer PD duration, higher apathy item and UPDRS II and III scores, and a higher levodopa daily equivalent dose and were exposed more frequently to antimuscarinics (logistic regression) (Table 1). Exposure to antipsychotics, opioids, antidepressants, anxiolytics, or hypnotics was not associated with FOG (data not shown). In a logistic regression model including factors from the previous logistic model and UPDRS subscores, worse gait impairment, oropharyngeal symptoms, and absence of tremor were related to on-FOG (Table 1).

On- vs Off-FOG Comparisons

Two hundred thirty-eight patients reported motor fluctuations and were included in this analysis (mean age, 66 [1] years;

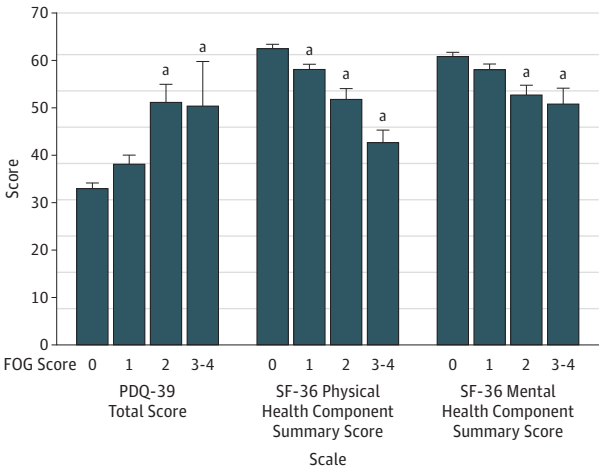
Figure 2. Quality-of-Life Scores in Patients With or Without Freezing of Gait (FOG) in the On State



A, Scores on the 39-item Parkinson's Disease Questionnaire (PDQ-39). B, Scores on the 36-Item Short Form Health Survey (SF-36). Higher PDQ-39 scores and lower SF-36 scores reflect worse quality of life. Error bars indicate SEM.

[a]$P < .01$, 2-sided t test with step-down Holms correction for multiple comparisons.

Figure 3. Relationship Between Freezing of Gait (FOG) Severity and Quality of Life



Quality of life was measured by the 39-item Parkinson's Disease Questionnaire (PDQ-39) total score and the 36-Item Short Form Health Survey (SF-36) Physical and Mental Component scores according to FOG severity. Error bars indicate SEM. The FOG scores are described in the FOG Evaluation subsection of the Methods section.

[a]$P < .05$ compared with patients without FOG (Dunnet post hoc test after an analysis of variance test[21]).

40.9% female; mean PD duration, 8.8 [0.3] years; mean UPDRS II + III score, 33.6 [1.1]; mean levodopa daily equivalent dose, 834 [28] mg/d). Antiparkinsonian medications used included levodopa in 95.7%, a dopamine agonist in 68.9%, a monoamine oxidase type B inhibitor in 16.2%, entacapone in 31.9%, and an antimuscarinic in 5.5%. Off-FOG affected 167 of 238 patients (point prevalence, 70.2% [95% CI, 64.2%-76.0%]), whereas on-FOG affected only 116 (48.7% [42.2%-55.2%]).

Frequency of FOG in the on and off states in this group of patients is shown in **Table 2**. Change in FOG scores from the on to off states was calculated in the 174 patients with FOG scores greater than 0 in the off state. The FOG score did not show any changes in 24 (13.8%) patients and improved by 50% or less in 72 (41.4%) and by 51% to 100% in 76 (43.7%). Finally, 2 patients (1.1%) showed worsening in the on state.

The magnitude of FOG improvement from the off to on states correlated negatively with older age ($r = -0.25$; $P < .01$), UPDRS II and III scores ($r = -0.50$; $P < .01$), the Hospital Anxiety and Depression Scale depression score ($r = -0.17$; $P = .045$), the UPDRS apathy score ($r = -0.20$; $P < .01$), and exposure to antimuscarinics ($r = -0.21$; $P < .01$). The magnitude correlated positively with exposure to dopamine agonists ($r = 0.18$; $P = .03$) or entacapone ($r = 0.21$; $P < .01$). A multivariate ordinal regression model showed that variables independently associated with improvement in FOG scores were younger age ($P = .02$), lower UPDRS II and III scores ($P < .01$), and exposure to entacapone ($P = .05$).

Table 2. Frequency of FOG During On and Off States in Patients With Motor Fluctuations

	State, No. (%) of Patients (n = 238)	
FOG Score	On	Off
0 (No freezing)	126 (52.9)	64 (26.9)
1 (Rarely, start hesitation)	66 (27.7)	42 (17.6)
2 (Occasional)	35 (14.7)	83 (34.9)
3 (Frequent, some falls)	7 (2.9)	40 (16.8)
4 (Frequent falls)	1 (0.4)	7 (2.9)

Abbreviation: FOG, freezing of gait.

Discussion

The present study is one of the largest available on FOG in PD focusing on quality of life, correlations with patients' medications, and scores in the on and off states to identify factors related to dopaminergic responsiveness. We used UPDRS item 14 to define FOG, and this item correlates strongly with specific FOG questionnaires developed more recently.[8] Our survey involved ambulatory patients recruited prospectively in the outpatient clinic of neurologists with or without special interest in movement disorders, thus minimizing potential recruitment bias of previously published clinical surveys or trials generally conducted in specialized tertiary movement disorder centers.

The observed 38.2% FOG prevalence reflects a mixed population of patients with early and advanced disease who were still ambulatory, with or without motor fluctuations. They underwent assessment when symptoms were improved by dopaminergic medications. Such prevalence would have been greater if patients had undergone assessment in the off state or if more severe cases had been included. Prevalence of FOG has varied from 7% in PD patients with a recent diagnosis[7] to 47% in studies not restricted to de novo patients.[9] Prevalence of FOG was strongly correlated with Hoehn and Yahr Scale scores, emphasizing that future prevalence studies should stratify by disease severity to provide accurate results.

The presence of FOG correlated with worse quality of life, which probably reflects the fact that patients feel loss of control, restriction in mobility, exposure to the risk of falling, and therefore the loss of an important part of their mobility and independence.[3,7] However, few studies have addressed this question directly.[22] The correlation between FOG and 2 different health-related quality of life scales, one generic (SF-36) and the other disease specific (PDQ-39), combined with the fact that quality of life decreased proportionally with the severity of FOG scores emphasizes the link between FOG and the patients' perceptions of everyday life.

Our findings confirm some correlations previously reported between FOG and PD duration and between severity and motor and nonmotor symptoms, thus reinforcing the consistency of these pilot findings.[5-10,23] We observed no correlations with other dopa-responsive symptoms such as bradykinesia and rigidity, possibly because our patients underwent assessment in the on state. Conversely, tremor was inversely

correlated with FOG, suggesting that both symptoms may have different mechanisms.[7] Freezing of gait also correlated with an oropharyngeal subscore; speculation about its cause is difficult, but the finding is consistent with the long-lasting concept of axial symptoms in advanced PD.[24] The observed independent correlation between FOG and gait impairment also warrants further research because gait can be impaired by different factors, including FOG, bradykinesia, balance, or cognitive problems. Various neuropsychological traits, such as cognitive impairment and depression, have been connected to FOG in the past.[7,25] In line with such reports, we observed univariate correlations between the presence of FOG and worse scores on the UPDRS I, the depression component of the Hospital Anxiety and Depression Scale, and the UPDRS apathy item score, but these findings were significant in the multivariate analysis for the apathy component only. The exclusion of patients with dementia combined with the limits of the used scales and the common comorbidity of different neuropsychiatric symptoms in PD patients might have reduced the sensitivity of our approach. Nevertheless, the fact that apathy was more pronounced in our patients with FOG is consistent with the hypothesis that FOG mechanisms may involve upper-level cortical dysfunction, as suggested by imaging studies.[26-28]

Our findings regarding relationships between FOG and dopaminergic and nondopaminergic medications and between FOG and the on vs off conditions are novel. Freezing of gait can be divided into "off freezing," which is improved by dopaminergic stimulation, and "on freezing," which is resistant to dopaminergic replacement therapy.[29] This aspect has been seldom studied in the past.[29] The empirical observation that most cases of FOG respond at least partially to dopaminergic therapies is consistent with our finding that FOG scores were less severe in the on than off states in patients with fluctuations. Freezing of gait did not disappear entirely during the on state in most patients. Dopaminergic medications may not have been fully optimized in all patients, or FOG may only incompletely respond to levodopa. Indeed, 15% of our patients did not report any benefit in the on vs off conditions. Furthermore, FOG worsened during the on condition in 2 patients (<1% of the sample), as previously reported.[30] We also identified factors related to a better FOG sensitivity to levodopa, including younger age, less severe disease, and exposure to entacapone, in line with a previous small series.[31] Other studies[32,33] suggested that monoamine oxidase type B inhibitors could display a protective effect toward FOG. We did not find such inverse correlations, perhaps because of insufficient power. Together, these results reinforce the practical concept that dopaminergic treatment optimization is the first-line strategy to be tried in most patients before any further pharmacological option, although the result is likely to be incomplete, especially in older patients and/or those with more severe disease.[29,34]

We also observed that exposure to antimuscarinics was more frequent in patients with FOG and in those with less improvement from the off to on states. This finding is original because little attention is given to such medications. Cholinergic mechanisms have been linked to gait impairment in PD. Cholinergic neurons of the pedunculopontine nucleus play a role in the control of gait and posture,[35] and deep brain stimulation of the pedunculopontine nucleus may display some antifreezing effects.[36] Antimuscarinics are known to induce cognitive impairment,[37] a syndrome that correlates with the presence of FOG in PD patients (see above).[10] Recent pilot studies have suggested that anticholinesterase medications may reduce falling in PD patients.[38] In practical terms, these data might be interpreted as an alert to avoid antimuscarinics in PD patients with FOG.

Conclusions

Freezing of gait correlates in PD patients with poor quality of life, disease severity, cognitive deficit, and exposure to antimuscarinics. Dopaminergic therapy improves FOG in most patients with motor fluctuations, especially younger ones with less severe disease who do not use antimuscarinics. This finding suggests that quality of life is impaired in PD patients with FOG and that optimizing dopaminergic therapy and avoiding antimuscarinics should be considered in such patients.

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Author Affiliations: Department of Clinical Pharmacology, Faculty of Medicine, University Hospital, University of Toulouse, Toulouse, France (Perez-Lloret, Rascol); Department of Neurosciences, University Hospital, University of Toulouse, Toulouse, France (Perez-Lloret, Rascol); Clinical Investigation Center 1436, University Hospital Toulouse, Institut National de la Santé et de la Recherche Médicale (INSERM), Toulouse, France (Perez-Lloret, Rascol); LN Pharma, Toulouse, France (Negre-Pages); Department of Neurology, Hôpital Laënnec, Centre Hospitalier Universitaire (CHU) Nantes, Nantes, France (Damier, Derkinderen); NS-Park Network, INSERM, Toulouse, France (Damier, Derkinderen, Destée, Tison, Rascol); Department of Neurology, CHU Lille, Lille, France (Delval, Destée); INSERM U 837 Eq6, Lille, France (Destée); Institut des Maladies Neurodégénératives, Université de Bordeaux, Bordeaux, France (Meissner, Tison); Centre National de la Recherche Scientifique, Institut des Maladies Neurodégénératives, Bordeaux, France (Meissner, Tison); Service de Neurologie, CHU de Bordeaux, Bordeaux, France (Meissner, Tison); Neurology Department, Kantonsspital Münsterlingen, Münsterlingen, Switzerland (Schelosky).

Author Contributions: Dr Rascol had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Negre-Pages, Tison, Rascol.
Acquisition, analysis, or interpretation of data: Perez-Lloret, Negre-Pages, Damier, Delval, Derkinderen, Destée, Meissner, Schelosky, Rascol.
Drafting of the manuscript: Perez-Lloret, Schelosky, Rascol.
Critical revision of the manuscript for important intellectual content: Negre-Pages, Damier, Delval, Derkinderen, Destée, Meissner, Schelosky, Tison, Rascol.
Statistical analysis: Perez-Lloret, Negre-Pages.
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Study supervision: Negre-Pages, Rascol.

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