ORIGINAL ARTICLE

L-DOPA-induced dyskinesias, motor fluctuations and health-related quality of life: the COPARK survey

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Background and purpose: Studies assessing the correlations between L-DOPA-induced dyskinesias (LIDs) and motor fluctuations with health-related quality of life (HRQoL) in Parkinson's disease (PD) have yielded conflicting results. This study aimed to assess the relationship between LIDs and motor fluctuations with HRQoL in patients with PD, and to assess the relative contribution of their severity and duration in a large sample of patients with PD.

Methods: A total of 683 patients with PD from the COPARK survey were evaluated. HRQoL was assessed using the 39-Item Parkinson's Disease Questionnaire (PDQ-39) (primary outcome) and 36-Item Short Form Survey (SF-36). The daily duration and severity of LIDs were obtained from Unified Parkinson's Disease Rating Scale (UPDRS) IV items 32 and 33, respectively. The daily duration of motor fluctuations was obtained from UPDRS IV item 36 and severity was estimated as the difference between the UPDRS 2 (Activities of Daily Living) score in 'OFF' versus 'ON' condition.

Results: A total of 235 patients with PD (35%) experienced motor fluctuations and 182 (27%) experienced LIDs. The PDQ-39 total and SF-36 physical scores were significantly worse in patients with LIDs, after adjusting for the presence of motor fluctuations. The PDQ-39 total score and SF-36 physical and mental score were significantly worse in patients with motor fluctuations, after adjusting for the presence of LIDs. The severity of LIDs and the duration of motor fluctuations significantly and independently affected PDQ-39 scores. The SF-36 physical score was affected only by the severity of motor fluctuations, whereas the mental score was not affected by any of the aforementioned variables.

Conclusion: Our findings suggest that LIDs (mainly their severity) and motor fluctuations (mainly their duration) correlate independently with HRQoL in patients with PD.

Introduction

L-DOPA has remained the 'gold standard' treatment for Parkinson's disease (PD) motor symptoms since its introduction in the 1960s [1]. As documented in the placebo-controlled L-DOPA study in early PD (ELLDOPA), L-DOPA clearly improves parkinsonism

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and reduces Unified Parkinson's Disease Rating Scale (UPDRS) scores with a dose-related response, but also induces 'wearing-off' effects (30% of patients) and dyskinesia (17% patients) after only 40 weeks of treatment at the 600-mg daily dose [2,3]. Motor complications remain a major challenge in the long-term management of many patients with PD.

It is commonly suggested that OFF problems induce more disability than L-DOPA-induced dyskinesia (LIDs), and that most patients with PD when given a choice between (i) suffering from parkinsonian disability because of 'OFF' episodes or (ii) having fewer parkinsonian symptoms at the expense of more LIDs in the 'ON' condition, will choose the latter [4]. Indeed, some authors have even claimed that LIDs do not induce important clinical discomfort, and consequently should not be considered as an important issue, for example when defining therapeutic strategies to manage patients with PD in the short and long term. Nevertheless, it is also commonly observed in everyday clinical practice that many patients complain of LIDs, for functional or social reasons, to an extent that frequently limits the dose of antiparkinsonian medications required to optimally control OFF problems.

One way to address this issue is to assess to what extent motor fluctuations and LIDs correlate with health-related quality of life (HRQoL) in patients with PD suffering from L-DOPA-induced motor complications. There are a limited number of studies on this topic, and their results are controversial, some studies emphasizing the importance of motor fluctuations [5–9] and others emphasizing the importance of LIDs [10–13], showing similar correlations for both [14,15] or even showing that none of them displayed any relationship [16–18]. To the best of our knowledge, there has been no attempt to segregate potential differential effects of severity as opposed to duration of motor complications in such studies.

We therefore took the opportunity of the availability of the COPARK database to readdress this problem in a large population of patients with PD. The COPARK study enrolled several hundred ambulatory French patients with PD, all of them being assessed systematically for demographic characteristics, motor and non-motor PD features, including motor complications, medications, co-morbidities, co-therapies and HRQoL [19–22]. The main objective of this analysis was to assess the correlations of LIDs and motor fluctuations with HRQoL and the relative contribution of their severity and duration. We also took the opportunity of these analyses to explore as a secondary objective which factors were associated with the presence of LIDs or motor fluctuations in this population. This allowed us to (i) benchmark the COPARK sample against samples from other studies and check whether our findings were consistent with those previously reported, and (ii) explore whether novel correlations could be identified from the COPARK database, especially those referring to the use of non-parkinsonian medications as this information has not been collected and analyzed in most of the other published reports.

Methods

Population

The COPARK database includes 683 ambulatory patients with PD, without dementia (Mini Mental State Examination > 24), who have not undergone neurosurgical procedures for the treatment of PD or suffered from serious disease affecting life expectancy in the short term.

The study was approved by the French national authorities and was undertaken in accordance with international guidelines. Signed informed consent was obtained from all patients in accordance with the Institutional Ethics Committee Board.

Study procedures and assessment of motor complications

Each patient with PD was examined by a neurologist using a standardized and structured interview. A full description of study procedures can be found elsewhere [19–22]. Briefly, patients were evaluated by Mini Mental State Examination, a full UPDRS in the 'ON' condition, Hospital Depression and Anxiety Score, Pittsburg Sleep Quality Index, and two quality-of-life scores: a specific one, the 39-Item Parkinson's Disease Questionnaire (PDQ-39), and a generic one, the 36-Item Short Form Survey (SF-36). PDQ-39 [23] was regarded as the main outcome for this study and SF-36 as supportive information.

Severity of LIDs was assessed as the level of disability measured by UPDRS IV item 33 and the duration of LIDS was assessed as the proportion of the waking day during which they were present, according to item 32.

Proportion of the waking day with motor fluctuations was explored by means of UPDRS IV item 39. The severity of motor fluctuations was assessed indirectly, as there is no specific item in this version of the UPDRS directly addressing this parameter. Therefore, in order to provide an estimation of the severity of motor fluctuations, we calculated the magnitude of the difference in UPDRS 2 (Activities of Daily Living as assessed by the patients) scores between 'OFF' and 'ON' states.

Statistical analysis

The PDQ-39 and SF-36 scores were compared between patients with or without LIDs or motor fluctuations by *t*-tests. Logistic regression was then used to adjust HRQoL scale total scores for age, gender, duration of PD, UPDRS 2 + 3 score and presence of depression. In the model for LIDs, presence of motor fluctuation was included as a co-variate and vice versa. HRQoL scale total scores were rescaled to minimal clinically important differences [24].

The relative contribution of severity and duration of LIDs and motor fluctuations was then explored by ANCOVA. Three different ANCOVA models were built, each including one of the three HRQoL scores: PDQ-39 total score and SF-36 physical or mental component summary scores. Independent variables included in each model were similar: duration of LID (item 32) and severity of LID (item 33), and duration of motor fluctuations (item 39) and severity of motor fluctuations (UPDRS 2 scores in 'OFF' minus 'ON'). Co-variates included age, gender, duration of PD, UPDRS 2 + 3 score and presence of depression. Models only included main effects from independent variables and co-variates and not interactions. Partial η^2 statistic was used to assess the relative contribution from each of these factors to HRQoL scores in each ANCOVA model. Partial η^2 can be defined as the variance accounted for by a particular variable of interest, only considering that variable and the error term. Therefore, partial η^2 cannot be used to quantify the total contribution of each variable to HRQoL scores, but can be used to compare the size of the effect on HRQoL of the independent variables and co-variables included in the models.

Finally, demographic and clinical characteristics were compared between subjects with or without LIDs or motor fluctuations. Bivariate analyses were carried out with chi-square statistics or exact Fisher followed by logistic regression. Numerical variables were dichotomized to their medians to facilitate analyses. Only variables with significant differences at the bivariate comparisons were included in the stepwise logistic models. Hosmer–Lemeshow scores were used to assess model fit, which was higher than 0.8 in all cases. Multi-co-linearity was absent from all models.

Statistical significance was based in all cases on two-sided tests evaluated at a 0.05 level of significance. All analyzes were performed by SAS v.9.3 (Cary, NC, USA).

Results

Two patients had missing data, and thus the final sample size was 681 patients. Of these patients, 286 (42%) had motor complications: 235 (35%) experienced motor fluctuations and 182 (27%) experienced LIDs. Comparisons between patients with and without motor complications are shown in Table S1.

The PDQ-39 total score and SF-36 physical component summary scores were significantly and independently worse in patients with LIDs or motor fluctuations, after adjusting for confounding variables (Table 1).

Relative contributions of duration or severity of LIDs or motor fluctuations to PDQ-39 or SF-36 scores are shown in Table 2. Two factors, i.e. severity of LIDs and duration of motor fluctuations, correlated significantly and independently with PDQ-39 scores. The SF-36 physical component summary score correlated only with severity of motor fluctuations, whereas the mental component score did not correlate with any of the aforementioned variables.

Bivariate tests showed that patients with LIDs were more frequently treated with L-DOPA, entacapone, dopamine agonists and amantadine. They also showed higher L-DOPA daily dose, longer duration of L-DOPA therapy and higher dopamine agonist dose. Patients with LIDs were also younger at PD onset, had longer duration of PD, higher UPDRS 2 + 3 scores and subscores, higher UPDRS 1 score, suffered more frequently from anxiety or depression, and were more frequently exposed to antihypertensives, oral hypoglycemiant drugs and antidepressants. Full bivariate comparisons are shown in Table S2.

Table 1 Relationship between L-DOPA-induced dyskinesias (LIDs) or motor fluctuations and health-related quality of life (HRQoL)

	PDQ-39 total score[a]	SF-36 physical component summary[b]	SF-36 mental component summary[b]
LIDs			
No (n = 499)	33.1 ± 1.1	62.2 ± 0.8	60.6 ± 0.7
Yes (n = 182)	45.4 ± 2.1*	54.1 ± 1.3*	54.8 ± 1.3*
Multivariate OR (95% CI)	1.07 (1.01–1.13)	0.88 (0.78–0.99)	0.93 (0.85–1.01)
Motor fluctuations			
No (n = 446)	32.8 ± 1.1	63.2 ± 0.8	61.2 ± 0.8
Yes (n = 253)	43.3 ± 1.8*	53.8 ± 1.2*	54.7 ± 1.1*
Multivariate OR (95% CI)	1.08 (1.02–1.14)	0.79 (0.71–0.89)	0.88 (0.81–0.96)

Data are shown as means ± standard error of the mean. Bivariate comparisons were performed by *t*-test (*P < 0.01). Multivariate comparisons were performed by logistic regression. HRQoL total scores were adjusted by age, gender, duration of Parkinson's disease, Unified Parkinson's Disease Rating Scale 2 + 3 score, depression (Hospital Depression and Anxiety Score) and presence of motor fluctuations or LIDs. Units were rescaled to minimal clinically important differences [22]. CI, confidence interval; OR, odds ratio; PDQ-39, 39-Item Parkinson's Disease Questionnaire; SF-36, 36-Item Short Form Survey. [a]Missing data, 89 patients; [b]missing data, 28 patients.

Table 2 Relationship between the severity and duration of L-DOPA-induced dyskinesias (LIDs) and motor fluctuations and health-related quality of life scores

	PDQ-39 total	SF-36 physical	SF-36 mental
LIDs			
Duration	0.4% ($P = 0.63$)	0.3% ($P = 0.79$)	0.7% ($P = 0.37$)
Severity	1.3% ($P < 0.04$)	0.5% ($P = 0.42$)	0.3% ($P = 0.55$)
Motor fluctuations			
Duration	3.0% ($P < 0.01$)	1.4% ($P = 0.07$)	0.5% ($P = 0.55$)
Severity[a]	0.1% ($P = 0.64$)	2.0% ($P < 0.01$)	0.6% ($P = 0.06$)
Co-variates			
Age	0.6% ($P = 0.05$)	0.2% ($P = 0.30$)	0.1% ($P = 0.56$)
Female gender	3.0% ($P < 0.01$)	3.2% ($P < 0.01$)	0.8% ($P < 0.02$)
Duration of PD	0.3% ($P = 0.16$)	0.3% ($P = 0.17$)	0.5% ($P = 0.07$)
UPDRS 2 + 3	4.2% ($P < 0.001$)	3.1% ($P < 0.01$)	0.1% ($P = 0.63$)
Depression (HADS)	15.3% ($P < 0.001$)	14.5% ($P < 0.01$)	29.3% ($P < 0.01$)

Data were analyzed by ANCOVA. Data are shown as η^2-values and *P*-values for each factor. [a]Calculated as the differences between Unified Parkinson's Disease Rating Scale (UPDRS) 2 in OFF and ON states. HADS, Hospital Depression and Anxiety Score; PD, Parkinson's disease; PDQ-39, 39-Item Parkinson's Disease Questionnaire; SF-36, 36-Item Short Form Survey.

Variables independently and significantly related to LIDs, as shown by logistic regression, were L-DOPA daily dose and dopamine agonist equivalent dose, duration of L-DOPA therapy, age at PD onset, UPDRS tremor score, anxiety and exposure to oral hypoglycemiant drugs (Table S2).

Patients manifesting motor fluctuations were more frequently on L-DOPA, entacapone, dopamine agonists and amantadine. They also had higher L-DOPA daily dose, duration of L-DOPA therapy and daily L-DOPA equivalent dose from dopamine agonists. They were also younger at PD onset, had longer duration of PD, higher UPDRS 2 + 3 score, higher UPDRS 1 score, anxiety and depression scores, and were more frequently exposed to antihypertensives. Full bivariate comparisons are shown in Table S3. Variables independently and significantly related to motor fluctuations, as shown by logistic regression, were L-DOPA daily dose, duration of L-DOPA therapy and age at PD onset (Table S3).

Discussion

The main finding of the present analysis is that both motor fluctuations and LIDs were significantly and independently correlated with HRQoL indices as measured by PDQ-39 and SF-36 in the French COPARK survey. Moreover, we identified that the severity of LIDs and the duration of motor fluctuations might be important factors to consider.

The relationship between motor complications and HRQoL, and the respective association of LIDs and fluctuations with HRQoL impairment have been explored previously in several studies that provided controversial conclusions [5–18]. In many studies, methodological differences and limitations may explain such divergences. For example, motor complications have been sometimes assessed by means of non-validated and/or non-standard methods. Other studies have involved a limited number of subjects, reducing the power of the analyses. The COPARK survey offered the opportunity to assess this issue in a large cohort of several hundreds of patients with PD. Data were collected by neurologists practicing in a broad spectrum of outpatient clinics including academic or non-academic centers, public or private centers, tertiary movement disorder reference centers or non-specialized general neurological centers. The COPARK database includes a large number of demographic, clinical and therapeutic information relevant for the analysis of L-DOPA-induced complications, including international validated scales such as a disease-specific (PDQ-39) and a generic (SF-36) HRQoL scale, together with the UPDRS, which are the reference tools used to assess PD symptoms and disability by the Movement Disorders Society for such purposes [25–27]. The UPDRS also gives the opportunity to assess separately the duration of LIDs and motor fluctuations, and the severity of LIDs. However, it does not include any specific item referring to the severity of motor fluctuations. Consequently, we had to estimate this parameter indirectly, and we used the difference in UPDRS Activities of Daily Living scores in 'OFF' and 'ON' condition (both scores being available in the COPARK database) as an indicator of the magnitude of change between the two conditions. This approach has the advantage of using Activities of Daily Living scores that reflect the patients' perception of their own condition, but it has not been validated, and this is a limitation of the present study. Another limitation is that COPARK has been conducted in French centers only, and that socioeconomic and cultural factors influencing patients' perception of HRQoL and motor complications might be different in different countries.

The present analyzes show that LIDs and motor fluctuations were both correlated with an impaired HRQoL, as captured by the specific PDQ-39 and SF-36 scales. The fact that we used a logistic regression model to analyze our data, and included motor fluctuations and LIDs as co-variates, allows us to conclude that both LIDs and motor fluctuations were independently associated with HRQoL impairment. Therefore, both rather than one or the other should

be considered as important when managing patients with PD, which is in line with empirical clinical practice. Interestingly, our results suggest that the severity rather than the duration of LIDs might be the most important contributing factor, whereas the opposite was observed for motor fluctuations. These results should be considered with caution, due to power limitations and the fact that we measured the severity of fluctuations indirectly, using a non-validated definition. However, based on such observations, it is not illogical to speculate that mild LIDs may not have a major impact on patients' HRQoL, even if present for long periods of time during the day, whereas severe LIDs do, even if present only during brief moments.

Our data do not allow a conclusion as to whether LIDs or motor fluctuations contributed more to HRQoL impairment. A recent survey concluded that patients with LIDs, when given the choice, would prefer to endure the former rather than experiencing increased parkinsonian symptoms as, for example, during OFF periods [4]. Nevertheless, it is clear that the impact of motor fluctuations and LIDs varies greatly from one subject to another, according to many different individual demographic, educational, sociocultural, professional and economic factors, which cannot be easily captured and analyzed on the basis of a group analysis. This illustrates the fact that a personalized approach with a careful case-by-case analysis is crucial when considering the impact of the different L-DOPA-induced motor complications in a given patient with PD.

Finally, as a secondary objective we analyzed the factors correlated to LIDs and motor fluctuations. We observed that the main factors correlated with the presence of LIDs and motor fluctuations in the COPARK survey were consistent with previous findings, including a greater daily dose and a longer duration of L-DOPA therapy and a younger age at disease onset. Such correlations, although not original [28–31], can be considered as a way to benchmark the results obtained in our sample with those from other studies, reinforcing the assumption that the COPARK sample is representative of the PD population in general. However, we also identified a few novel and more original correlations. Patients exposed to oral hypoglycemic agents suffered from LIDs less frequently than non-exposed patients. This association might not have been reported in previous surveys as, with large cohorts of patients with PD, the different co-medications prescribed for diseases others than PD are rarely collected and analyzed. This correlation remains to be confirmed and replicated in future studies as numbers were limited and, at this point, its interpretation still remains speculative. Interestingly, however, recent pre-clinical experimental and pilot clinical trials conducted with oral hypoglycemic agents suggested that such medications might reduce nigrostriatal damage and might have disease-modifying effects [32–34]. We also observed in the COPARK population that greater tremor scores were associated with a lower risk of dyskinesia. The influence of clinical phenotypes on the risk of developing LIDs has been a matter of debate, but tremor-dominant forms of PD are often considered as more 'benign'. In one recent case-control study, patients with PD with a tremor-dominant phenotype at the time of parkinsonian symptom onset had a lower risk of LIDs [35]. Our results as well as those of previous studies in smaller cohorts support this conclusion [28, 36]. Finally, the COPARK data showed that the presence of LIDs tended to be correlated with higher anxiety ratings. We are not aware of similar epidemiological observations, but this correlation is consistent with the common clinical observation that the severity of LIDs worsens when patients with PD are stressed [37]. Experimental studies in 6-hydroxydopamine-lesioned rats failed to demonstrate a relationship between anxiety and LIDs [38], but further studies are needed before drawing firm conclusions.

In summary, we found that LIDs and motor fluctuations were both significantly and independently correlated with impaired HRQoL as measured with disease-specific and generic HRQoL scales. This demonstrates that both types of L-DOPA-induced motor complications are important when managing patients with PD.

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Disclosure of conflicts of interest

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. COPARK Study Group.
Table S1. Characteristics of the studied sample.
Table S2. Factors related to L-DOPA-induced dyskinesias.
Table S3. Factors related to motor fluctuations.

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