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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Do Parkinson's disease patients disclose their adverse events spontaneously?

Santiago Perez-Lloret · María Verónica Rey · Nelly Fabre · Fabienne Ory · Umberto Spampinato · Jean-Louis Montastruc · Olivier Rascol

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Abstract
Background Underreporting of adverse drug reactions is common but has been rarely studied in Parkinson's disease (PD).
Objective To compare the prevalence of adverse events (AEs) in relation to antiparkinsonian drugs in PD patients using two different data collection methods: patient's spontaneous reporting versus a predefined investigator-driven structured interview. Secondary objectives were to assess factors related to spontaneous reporting and to compare the rate of AE reporting in PD patients with that of a group of non-parkinsonian post-stroke patients.
Study design Cross-sectional study.
Patients Ambulatory, cognitively intact PD or post-stroke outpatients.
Interventions None.
Outcome measures Patients were first asked by means of an an open question to disclose any unpleasant effects in connection with their current medications that had occurred during the previous week. Afterwards, a predefined questionnaire listing the most common AEs known to be related to antiparkinsonian drugs was used to question the same patients in a systematic manner about the presence of any AE during the same week. Chronological and semiological criteria were used to classify the reported AEs as "unrelated" or "possibly/plausibly related" to the antiparkinsonian treatment.
Results A total of 203 PD and 52 post-stroke patients of comparable age and sex were recruited. Eighty-five PD and five post-stroke patients reported spontaneously at least one AE (42 vs. 10%, $p<0.01$), while 203 PD and 47 post-stroke patients reported at least one AE following the structured questionnaire (100 vs. 90%, $p<0.001$). In PD patients, there were a total of 112 spontaneously reported AEs as compared with 1,574 according to the structured questionnaire (7%). Spontaneous disclosure of AEs was associated with

S. Perez-Lloret · M. V. Rey · F. Ory · J.-L. Montastruc · O. Rascol
Laboratoire de Pharmacologie Médicale et Clinique, INSERM U 1027 Equipe de PharmacoEpidémiologie, Faculté de Médecine, Université de Toulouse,
Toulouse, France

S. Perez-Lloret · M. V. Rey · F. Ory · J.-L. Montastruc · O. Rascol
Service de Pharmacologie Clinique, Centre Midi-Pyrénées de PharmacoVigilance, de PharmacoEpidémiologie et d'Informations sur le Médicament, Centre Hospitalier Universitaire,
Toulouse, France

S. Perez-Lloret · M. V. Rey · O. Rascol
INSERM Centre d'Investigation Clinique CIC 9203,
Toulouse, France

N. Fabre
Service de Neurologie et Explorations Fonctionnelles du Système Nerveux, CHU Rangueil,
Toulouse, France

U. Spampinato
Department of Neurology,
University Hospital Bordeaux,
Bordeaux, France

U. Spampinato
INSERM U862, Neurocentre Magendie,
Bordeaux, France

S. Perez-Lloret (✉)
Department of Clinical Pharmacology, Faculty of Medicine,
University of Toulouse,
37 Allées Jules Guesde,
31000, Toulouse, France
e-mail: splloret@fleni.org.ar

experiencing>2 AEs [OR=1.2 (1.1–3.2)], logistic regression). Seventy-four percent of PD patients had ≥1 AE possibly/plausibly related to antiparkinsonian drugs.
Conclusions Results showed that only 7% of AEs were reported spontaneously by patients, thus underscoring the importance of systematically asking about AEs in PD patients.

Keywords Parkinson's disease · Adverse drug reactions · Pharmacological treatment · Levodopa · Dopamine agonists · Underreporting · Non-motor symptoms · Motor fluctuations

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative condition [1] affecting 1% of people aged>60 years [2]. The current treatment for PD is based on symptomatic medications including levodopa and other drugs such as dopamine agonists, monoamine oxidase-B inhibitors, catechol-O-methyl transferase inhibitors, antimuscarinics, or amantadine [3]. Pharmacological strategies to treat PD usually combine multiple drugs for prolonged periods of time. Therefore there is a high risk for potential adverse events [4–6]. Spontaneous reporting of adverse events (AEs) by patients is a common method to detect safety problems in clinical trials. Similarly, most pharmacovigilance systems are based on physicians' spontaneous reports of adverse drug reactions [7]. However, this method suffers from limitations related to underreporting, which can be as high as 95% in the general population [8] or in patients suffering from chronic disorders such as epilepsy [9]. There are no data about AE or adverse drug reaction underreporting in PD. Thus, our goal for this study was primarily to compare the prevalence of the most common AEs to antiparkinsonian drugs when evaluated by two different means: patients' spontaneous reports or a predefined structured interview. The secondary objectives of this study were to assess factors related to AE spontaneous reporting and to compare the rate of AEs in PD patients and in post-stroke patients used as "controls."

Methods

Population

Consecutive PD patients were recruited from two tertiary Movement Disorders outpatient clinics at the Neurological Departments of the Toulouse and Bordeaux University Hospitals (France). Patients were included if they fulfilled the United Kingdom PD Society Brain Bank criteria for PD [10] and had been receiving at least one antiparkinsonian drug for at least 1 month. Patients with previous neurosurgical interventions for PD or with cognitive impairment preventing the collection of data in a reliable manner were excluded. Age- and sex-matched ambulatory neurovascular patients who had recovered from a stroke without cognitive impairment or aphasic sequelae preventing data collection in a reliable manner and who were receiving at least one drug were also recruited from the outpatient clinic of the same neurological departments. This control group was used as an internal comparator to assess the rates and types of reported AEs.

The study was approved by the local ethics committee. Informed consent was obtained from all patients after full information on the study was provided and prior to inclusion.

Procedures

PD patients and post-stroke controls were approached and interviewed by one of the authors (S.P.L.L., M.V.R.) while waiting for their regular medical consultation. Both investigators used the same standard process and had been trained to collect data in a similar way. After collecting a medical history, including demographics and a detailed medication inventory, patients and controls were asked by the investigators to disclose spontaneously all AEs of which they were aware; the following standard open question was used: "Have you noticed any unpleasant effects of your medications during the previous week?" The question did not refer specifically to antiparkinsonian medications but to any drug. Once their responses had been collected, the subjects were questioned again by the same investigator using a predefined list of AEs (i.e., a structured questionnaire). Only AEs that were present during the previous week were considered, irrespective of their date of onset.

The predefined list of AEs contained the most common adverse reactions to levodopa, dopamine agonists, monoamine oxidase-B (MAO-B) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, antimuscarinics, and amantadine. This list was first developed from a literature search in Pubmed, drug reference manuals, and PD treatment textbooks [11–13]. It was then critically reviewed by a group of PD and pharmacovigilance specialists and a consensus was reached to establish the final version. The list included six classes of AEs: (1) general (weight loss, appetite loss, allergic reactions, fatigue); (2) cardiovascular (orthostatic hypotension, arrhythmia, leg edema); (3) gastrointestinal (dry mouth, nausea and vomiting, constipation, diarrhea); (4) urinary (incontinence, retention, discolored urine); (5) neuropsychiatric (hallucinations, delirium, delusions, confusion, memory loss, depression, anxiety, somnolence, sleep disorders, nightmares, headache, vertigo, impulse-control disorders, and dyskinesias or wearing-off); and (6) dermatologic (skin dryness, livedo reticularis, dermatitis ochre, lipodystrophia). For each AE, the date of onset and

response to dechallenge or rechallenge, when available, were registered.

Finally, PD was evaluated by means of the Unified Parkinson's Disease Rating Scale (UPDRS) [14].

Adverse events evaluation

An AE was defined as any untoward medical occurrence in a patient who is under any pharmacological treatment; the AE does not necessarily have to have a causal relationship with this treatment [15]. Although the standard open question refers to "unpleasant effects of medications," it is recognized that patients may wrongly connect some events with medications when in fact they are not related to them. Therefore it was decided to treat these events initially as if they were AEs.

The relationship of AEs to antiparkinsonian drugs was assessed by means of the imputation method proposed by Begaud and colleagues [16]. Briefly, based on chronological and semiological criteria, a causality score was assigned as 0 (excluded), 1 (possible), 2 (plausible), 3 (likely), or 4 (very likely). Due to limited available information, events could only by classified as "unrelated" or as "possibly/plausibly" related to antiparkinsonian medications. A conservative approach was taken during causality assessment, thus when data were missing, events were classified as unrelated.

AE intensity was evaluated subjectively by a common scale: "mild" if the AE had no effect on the patient's activities or wellbeing, "moderate" if it perturbed daily activities, or "severe" if daily functioning was impaired [15]. AEs were considered "serious" when they required hospital admission or prolongation of existing hospital stay, resulted in persistent or significant disability/incapacity, or were life threatening [15].

Statistical analysis

It was determined that 200 PD patients would be needed to detect a difference of at least 10% between the frequency of AEs identified by spontaneous reporting as opposed to those detected using the structured questionnaire with an 80% power and an α error of 1/1,000. It was calculated that, using the same parameters, 50 nonparkinsonian control patients were needed to detect differences in AE frequencies with regard to PD patients.

Demographic data of PD and post-stroke patients were compared by unpaired *t*-test or chi-squared test.

The number of patients reporting at least one AE and the total number of AEs collected using the two different methods (spontaneous reporting and structured questionnaire interviews) is reported for both groups of patients (PD and post-stroke).

These numbers were then compared in each group using the chi-squared test (primary objective). Secondly, for each particular AE, the rate (in %) of underreporting (that is the number of cases with a given AE reported spontaneously divided by the number of cases with the same AE identified following the structured questionnaire) and their 95% confidence intervals were calculated in the PD group. Binomial test was used to check if rates differed from 0% (i.e., the null hypothesis). No adjustment for α error inflation resulting from multiple pairwise comparisons was performed as this was planned as an exploratory study. Nonetheless, in an attempt to limit the number of such comparisons only AEs affecting more than 10% of the patients, regardless of the recollection method (spontaneous or questionnaire), were analyzed.

Unpaired *t*-test or chi-squared test was employed for comparing numerical or categorical variables between subjects who reported their AEs spontaneously and those who did not. Forward logistic regression was used to identify independent factors related to spontaneous reporting of AEs by the patients. The independent variables tested were age, gender, UPDRS I or II+III scores, PD duration, total number of drugs consumed, number of antiparkinsonian meds consumed, number of AEs, presence of AEs causally related to any given antiparkinsonian medication, and AE severity. The model's goodness of fit was explored by using the Hosmer and Lemeshow score. Potential interactions and multicollinearity were found to be absent. Numerical independent variables were dichotomized to their median values to facilitate results interpretation. Only variables attaining significance in the bivariate comparisons were included in the multivariate models.

Subsequently the number of events "unrelated" or "possibly/plausibly" related to antiparkinsonian medications was explored. Binomial tests were used to classify each AE as (1) "possibly/plausibly" related to antiparkinsonian medications in more than 50% of cases, (2) not related to antiparkinsonian medications in more than 50% of cases, or (3) undefined (i.e., in between cases 1 or 2).

Finally, the frequency of each particular AE recorded after the full questionnaire was compared between PD and post-stroke patients by chi-squared test.

Results

A total of 52 post-stroke and 203 PD outpatients were included in the study. As shown in Table 1, subjects were similar in terms of age, sex, and total number of administered drugs. However, as expected, PD patients received antihypertensive, antilipidemic, and antithrombotic drugs less frequently, and antidepressants and domperidone more frequently than post-stroke patients.

Table 1 Sample population characteristics

	PD patients (n=203)	Post-stroke patients (n=52)	p-value
Age	66.7±0.7	69.1±1.8	0.7
Males	124 (62%)	28 (54%)	0.3
PD duration (years)	9.0±0.4	–	–
UPDRS II+III score	37.2±1.4	–	–
Dyskinesias	83 (41%)	–	–
Wearing-off	80 (39%)	–	–
Number of drug treatments	5.0±0.2	5.4±0.4	0.6
Antimuscarinics	12 (6%)	1 (2%)	0.4
Dopaminergic therapy			
No	3 (1%)	52 (100%)	0.001
Only DAs	22 (11%)	0	–
Only LD	37 (18%)	0	–
LD+DAs	141 (69%)	0	–
MAOB-I	17 (8%)	0	0.01
COMT-I	47 (23%)	0	0.01
Amantadine	31 (15%)	0	0.01
Hypnotics	28 (14%)	5 (10%)	0.5
Antidepressants	50 (25%)	4 (8%)	0.01
Domperidone	45 (22%)	0	–
Antihypertensives	26 (13%)	33 (64%)	0.001
Antilipidemics	21 (10%)	34 (68%)	0.001
Antithrombotics	22 (11%)	29 (69%)	0.001

Shown are mean ± standard error of the mean or number of subjects (percentages). *p<0.05, **p<0.01 vs controls (t-test or chi-squared test)

DAs Dopamine agonists, *LD* levodopa, *MAOB-I* monoamine oxidase B inhibitors, *COMT-I* catechol-O-methyltransferase inhibitors

Number of patients reporting at least one AE and mean number of AEs per patient in PD or post-stroke groups using spontaneous and questionnaire-based reporting

Significantly more PD patients spontaneously reported at least one AE (85/203, 42%) than post-stroke patients (5/52, 10%; p<0.01). Similarly, following the structured questionnaire, there were more patients with at least one AE in the PD group (203/203, 100%) than in the post-stroke group (47/52, 90%; p<0.001) (Fig. 1). In both groups, there were significantly more AEs identified using the questionnaire than using the spontaneous report (p<0.05). There were also a greater mean number of AEs reported per PD patient than per post-stroke patient, both spontaneously (0.55±0.05 vs. 0.12±0.05; mean ± SEM; p<0.001) and according to the structured questionnaire (7.75±0.23 vs. 3.21±0.32; mean ± SEM; p<0.001).

Spontaneous reporting versus questionnaire-based identification of each particular AE in PD patients

The proportion of PD patients reporting each AE spontaneously or after systematic questioning is shown in Table 2. In all instances, the proportion of cases identified with the questionnaire was greater than the proportion identified based on spontaneous reporting. A number of AEs (namely appetite loss, allergic reactions, arrhythmia, diarrhea, urinary retention, delirium, delusions, confusion, vertigo, livedo reticularis, dermatitis ochre, and lipodystrophia) were recorded in<10% of the patients and were not further analyzed statistically (see Methods). Only dry mouth, nausea/vomiting, constipation, and diurnal somnolence were reported spontaneously with rates differing from 0% (i.e., the null hypothesis).

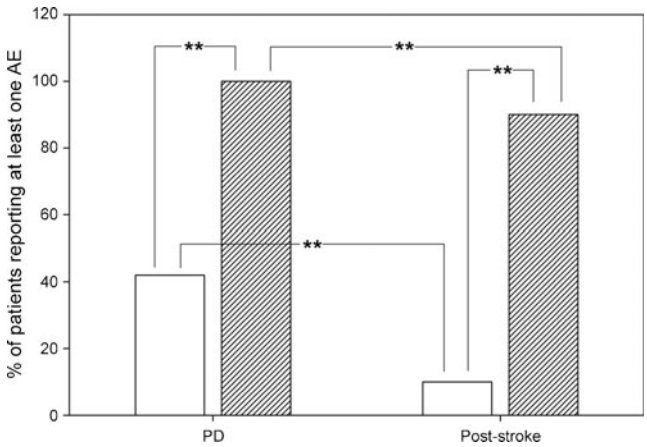

Fig. 1 Percentage of patients reporting at least one adverse event (AE) after the standard open question "Have you noticed any unpleasant effects of your medications during the previous week?" or after the predefined structured interview . **p<0.01 (chi-squared test)

Table 2 Frequencies of adverse events in Parkinson's disease patients

	Patients spontaneously reporting AEs (n=203)	Patients reporting AEs during the questionnaire (n=203)	Percentage of spontaneously reported AEs out of total AEs (95% CI)
Total general[a]	4 (3%)	127 (63%)	3% (0–6%)
Weight loss	0 (0%)	28 (14%)	0% (0–0%)
Fatigue	3 (1%)	111 (55%)	3% (0–6%)
Total cardiovascular[a]	5 (4%)	122 (60%)	4% (0–8%)
Orthostatic hypotension	4 (2%)	59 (29%)	7% (0–13%)
Leg edema	0 (0%)	78 (38%)	0% (0–0%)
Total gastrointestinal[a]	41 (26%)	157 (77%)	26% (19–33%)**
Dry mouth	12 (6%)	103 (51%)	12% (5–18%)*
Nausea/vomiting	24 (12%)	42 (21%)	57% (42–72%)**
Constipation	12 (6%)	97 (48%)	12% (6–19%)*
Total urinary[a]	5 (6%)	79 (39%)	6% (0–12%)
Incontinence	4 (2%)	34 (17%)	12% (0–23%)
Discolored urine	1 (0%)	47 (23%)	2% (0–6%)
Total neuropsychological[a]	43 (23%)	190 (94%)	23% (17–29%)**
Hallucinations	2 (1%)	30 (15%)	7% (0–16%)
Memory loss	2 (1%)	60 (30%)	3% (0–8%)
Depression	0 (0%)	71 (35%)	0% (0–0%)
Anxiety	2 (1%)	60 (30%)	3% (0–8%)
Diurnal somnolence	22 (11%)	103 (51%)	21% (13–29%)**
Vivid dreams	3 (1%)	74 (36%)	4% (0–9%)
Sleep troubles	5 (2%)	88 (43%)	6% (0–11%)
Headache	1 (0%)	26 (13%)	4% (0–11%)
Impulse-control disorders	4 (2%)	54 (27%)	2% (0–6%)
Dyskinesias	0 (0%)	83 (41%)	0% (0–0%)
Wearing-off	0 (0%)	80 (39%)	0% (0–0%)
Total dermatological[a]	0 (0%)	95 (47%)	0% (0–0%)
Dry skin	0 (0%)	87 (43%)	0% (0–0%)

AE Adverse event

*p<0.05, **p<0.01 vs 0% (i.e., the null hypothesis)

[a] Total figures include AEs that were not further analyzed as they were reported by less than 10% of patients (see Methods)

Factors related to spontaneous reporting of AEs were further explored. In most instances, the low numbers of spontaneous reports prevented them from being studied individually, and this analysis was thus performed globally on the basis of the patients reporting at least one AE spontaneously versus those reporting no AEs spontaneously. As shown in Table 3, the sole factor related to spontaneous reporting of at least one AE was the fact that the PD patient reported>2 AEs after the systematic questionnaire [OR=1.2 (1.1–3.2)].

Causality assessment of AEs in PD patients

Out of the 1,547 AEs reported by PD patients, none could be classified as "likely" or "very likely" related to antiparkinsonian medications because data on dechallenge and rechallenge were missing in all cases. A total of 754 (47%) AEs were considered "not related" and 793 (53%) were "possibly/plausibly" related to antiparkinsonian medications. No serious AEs were detected. Causality assessments for each AE are shown in Table 4. Binomial tests showed that dry mouth, nausea/vomiting, discolored urine, hallucinations, diurnal somnolence, impulse-control disorders, and motor fluctuations were possibly/plausibly related to antiparkinsonian medications in more than 50% of cases. Conversely, AEs such as weight loss, leg edema, memory loss, depression, anxiety, and dry skin were not thought to be related to antiparkinsonian drugs in more than 50% of cases. Finally, similar proportions of cases of fatigue, orthostatic hypotension, constipation, vivid dreams, sleep troubles, or headache cases were considered not related vs. related to antiparkinsonian medications.

Table 3 Factors related to spontaneous reporting of at least one adverse event (AE) in patients with Parkinson's disease (PD)

	PD patients with no spontaneously reported AEs (n=118)	PD patients with at least 1 spontaneously reported AE (n=85)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Males	72 (62%)	52 (62%)	1.0 (0.6–1.8)	–
Age>68 years	57 (48%)	40 (47%)	1.1 (0.6–1.9)	–
PD duration>9 years	51 (43%)	37 (44%)	0.9 (0.5–1.6)	–
UPDRS I>3	34 (29%)	34 (41%)	1.7 (0.9–3.1)	–
UPDRS II+III>33	56 (48%)	42 (51%)	1.1 (0.6–2.0)	–
Total number of drugs>6	41 (35%)	27 (32%)	0.8 (0.5–1.6)	–
Number of antiPD drugs>3	40 (34%)	36 (42%)	1.4 (0.8–2.5)	–
Number of AEs>2	51 (43%)	48 (56%)*	1.9 (1.3–3.1)	1.8 (1.1–3.2)
AEs related to antiPDs	100 (85%)	77 (91%)	1.7 (0.7–4.1)	–
AE severity > median	67 (57%)	53 (62%)	1.2 (0.7–2.2)	–

Values shown are n (%). *p<0.05 vs. patients not spontaneously reporting their AEs (chi-squared test)

Variables not included in the forward logistic regression models as they did not show significance in the bivariate tests are indicated with *a dash*

Comparison of AEs recorded after the structured questionnaire in PD or post-stroke patients

As shown in Table 5, dry mouth, nausea/vomiting, constipation, discolored urine, hallucinations, delusions, anxiety, somnolence, vivid dreams, sleep troubles, impulse-control disorders, motor fluctuations, and dry skin were more frequent in the PD group as compared with the post-stroke one.

Discussion

Clinical evaluation of PD patients relying on spontaneous reporting of symptoms is the most common strategy to assess AEs in clinical trials in PD. This has however important limitations connected to underreporting. Indeed, our data confirm that less than 10% of AEs were spontaneously reported by patients, suggesting that evaluation of tolerability to antiparkinsonian medications should not rely exclusively on patients' spontaneous reports of their symptoms.

We have studied in this cross-sectional survey 203 PD patients attending two movement disorders outpatient clinics. This method has some limitations. The number of patients who were interviewed was limited, which provided limited power for the study of rare AEs. A selection bias may also be possible as such patients were attending tertiary units specializing in PD. Moreover, some patients may have discontinued some drugs before being recruited because of past AEs. Imperfect recall of dates of AEs or antiparkinsonian therapy onset could have also generated some protopathic bias.

Moreover, AEs were evaluated by means of a structured interview based on a questionnaire that had not been validated previously and did not use specific scales referring to each item. Considering that patients were questioned on more than 30 possible AEs, the use of specific tools was not considered acceptable from a pragmatic perspective because of the duration of the visit and the patients' fatigability, which is an important parameter in PD. A non-motor-symptoms questionnaire, such as the one recently developed by Chaudhuri et al. [17], could have been considered for screening purposes, but several relevant adverse reactions to antiparkinsonian drugs are not covered by such surveys (most notably, impulse-control disorders) and no information regarding AE causality would have been recorded. On the other hand, we must admit that although a valid imputation method was used, it is still possible that a number of AEs could have been wrongly classified as related to antiparkinsonian drugs when they were not or vice versa. Moreover, our structured questionnaire had been designed to interview patients receiving antiparkinsonian medications, and thus its use in non-PD post-stroke patients was in some ways artificial. Finally, it must be acknowledged that events requiring laboratory examinations for diagnosis, such as fibrotic events requiring chest x-ray or echocardiographic studies, could not be addressed in our survey.

The main finding of this study is that only 7% of AEs were spontaneously disclosed by PD patients. Interestingly, some gastrointestinal events (including dry mouth, nausea/vomiting, and constipation) and diurnal somnolence were reported spontaneously by a proportion of patients significantly higher than 0%. This may suggest that patients might find these events more distressing or might associate them more easily with antiparkinsonian drugs. In contrast, other AEs that are commonly caused by antiparkinsonian drugs, including cardiovascular and neuropsychiatric ones, were dramatically spontaneously underreported. This figure has

Table 4 Adverse events reported by PD patients categorized by causality score

	Not related	Possibly/plausibly related
General		
Weight loss	28 (100%)[a]	0 (0%)
Fatigue	62 (56%)	49 (44%)
Cardiovascular		
Orthostatic hypotension	32 (54%)	27 (46%)
Leg edema	57 (73%)[a]	21 (27%)
Gastrointestinal		
Dry mouth	40 (39%)	63 (61%)[b]
Nausea/vomiting	9 (21%)	33 (79%)[b]
Constipation	55 (57%)	42 (43%)
Urinary		
Incontinence	26 (76%)[a]	8 (24%)
Discolored urine	5 (11%)	42 (89%)[b]
Neuropsychological		
Hallucinations	8 (27%)	22 (73%)[b]
Memory loss	57 (95%)[a]	3 (5%)
Depression	68 (96%)[a]	3 (4%)
Anxiety	41 (68%)[a]	19 (32%)
Diurnal somnolence	31 (30%)	72 (70%)[b]
Vivid dreams	42 (57%)	32 (43%)
Sleep troubles	52 (59%)	36 (41%)
Headache	15 (58%)	11 (42%)
Impulse-control disorders	9 (17%)	45 (83%)[b]
Dyskinesias	0 (0%)	83 (100%)[b]
Wearing-off	0 (0%)	80 (100%)[b]
Dermatological		
Dry skin	85 (98%)[a]	2 (2%)

[a] AE was related to antiparkinsonian medications in less than 50% of cases (binomial test)

[b] AE was related to antiparkinsonian medications in more than 50% of cases (binomial test)

Table 5 Frequencies of adverse events recorded after the structured questionnaire in PD and post-stroke patients

	PD (n=203)	Post-stroke (n=52)	p-values
General			
Weight loss	28 (14%)	4 (8%)	0.7
Fatigue	111 (55%)	21 (40%)	0.07
Cardiovascular			
Orthostatic hypotension	59 (29%)	14 (27%)	0.8
Leg edema	78 (38%)	13 (25%)	0.08
Gastrointestinal			
Dry mouth	103 (51%)	14 (27%)	0.002
Nausea/vomiting	42 (21%)	1 (2%)	0.001
Constipation	97 (48%)	7 (13%)	0.001
Urinary			
Incontinence	34 (17%)	6 (12%)	0.4
Discolored urine	47 (23%)	0 (0%)	0.001
Neuropsychological			
Hallucinations	30 (15%)	0 (0%)	0.003
Memory loss	60 (30%)	18 (35%)	0.5
Depression	71 (35%)	14 (27%)	0.3
Anxiety	60 (30%)	4 (8%)	0.001
Diurnal somnolence	103 (51%)	8 (15%)	0.001
Vivid dreams	74 (36%)	1 (2%)	0.001
Sleep troubles	88 (43%)	7 (13%)	0.001
Headache	26 (13%)	4 (8%)	0.3
Impulse-control disorders	54 (27%)	0 (0%)	0.001
Dyskinesias	83 (41%)	0 (0%)	0.001
Wearing-off	80 (39%)	0 (0%)	0.001
Dermatological			
Dry skin	87 (43%)	14 (27%)	0.04

*p<0.05, **p<0.01 vs controls (chi-squared test)

been rarely specifically explored in PD, but is in line with previous studies in the general population [8, 18] and in epileptic patients [9, 19]. It is possible that studying a larger sample of patients might have provided more significant results from a statistical perspective, but the contrast between spontaneous and questionnaire results is already so spectacular in the present survey that we believe physicians should be aware of such figures for their everyday practice, even if spontaneous reporting reduces the time spent in assessing the patients. In line with previous data [20], our results support the concept that an approach based on spontaneous reporting of symptoms has limited reliability, especially for treatment tolerability, although patients suffering from more than two AEs might be more prone to disclose their AEs spontaneously.

It is important to revisit such underreporting of AEs in PD in light of the disabling adverse drug reactions that were underestimated or even ignored for a long period in PD, such as daytime somnolence or impulse-control disorders [21, 22]. Our findings of a limited number of impulse-control disorders spontaneously reported by patients may explain why they remained unrecognized for many years [21, 22]. In contrast, considering that underreporting was not so poor for daytime somnolence, this should reinforce our efforts to listen to patients' complaints. In view of the psychosocial or physical consequences of such events, all efforts should be made to recognize them, which can probably only by achieved by systematically questioning patients, as is now legally required for daytime somnolence and impulse-control disorders when prescribing a dopamine agonist.

Several pieces of evidence suggest that the frequency of some AEs, such as somnolence and impulse-control disorders,

is higher when they are systematically evaluated. For example, impulse-control disorders are seldom reported in clinical trials [5] but were found to affect about 13% of patients in a recent cross-sectional study [23]. Similarly, somnolence has been reported by 2.5 or 17% of patients on ergolinic or non-ergolinic dopamine agonists in clinical trials [23] but has been found to affect 33–48% of patients recruited in recent cross-sectional studies where somnolence was systematically explored [24, 25]. Thus, clinical trials of antiparkinsonian drugs should always include systematic measures of somnolence and impulse-control disorders, such as Epworth Sleepiness Scale [26] and the Modified Minnesota Impulsive Disorders Interview [27].

Causality assessment was difficult in our sample as in previous reports [28]. Lack of information on dechallenge and rechallenge made impossible the classification of AEs as "likely" or "very likely" related to drug therapies. Nonetheless some interesting findings deserve further discussion. Several AEs were classified as "possibly/plausibly" related to antiparkinsonian medications, including dry mouth, nausea/vomiting, discolored urine, hallucinations, diurnal somnolence, impulse-control disorders, and levodopa-related motor complications, such as wearing-off or dyskinesias. These represent "type A" adverse drug reactions [15], which have well known connections to antiparkinsonian drugs, are relatively easy to establish, and are usually not observed in untreated patients. It is therefore not surprising that such AEs were more frequently observed in PD patients than in post-stroke ones, confirming the validity of our method. Some of these AEs could still however be partly related to PD per se and not exclusively to its treatments.

Other AEs were classified as unrelated to antiparkinsonian drugs in the majority of cases (i.e., weight loss, leg edemas, incontinence, memory loss, depression, anxiety, dry skin) or as seldom related to antiparkinsonian drugs (i.e., fatigue, orthostatic hypotension, constipation, vivid dreams, sleep troubles, and headache). Some of these AEs were more common in PD than post-stroke patients, thus pointing out that factors other than antiparkinsonian medications may be suspected. In contrast, other AEs such as weight loss, fatigue, orthostatic hypotension, leg edemas, incontinence, memory loss, depression, and headache were also relatively commonly observed in the post-stroke group. While this may call into question a specific relationship with PD or its treatment for some of them, others, such as the lack of significant differences in orthostatic hypotension or leg edema frequency, may be related to different medication use in post-stroke patients.

In summary, our study suggests that assessment of tolerability to drug treatments in PD by spontaneous reporting of symptoms has many limitations. Patients showed a greater tendency to disclose their AEs spontaneously when they were affected by more than two events. Taking into consideration the disease burden imposed by AEs in PD, active surveillance is recommended.

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