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Chronic pain in Parkinson's disease: The cross-sectional French DoPaMiP survey

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Abstract

Pain is a frequent, but poorly studied symptom of Parkinson's disease (PD). DoPaMiP survey aimed to assess the prevalence of chronic pain in PD, to describe PD patients with chronic pain, and to record analgesic consumption. About 450 parkinsonian patients underwent structured standardized clinical examination and completed self-reported questionnaires in a cross sectional survey. Pains related or unrelated to PD were identified according to predefined criteria. About 98 patients with other chronic disorders than PD were examined to assess if pain was more frequent in PD than in this population. Two thirds parkinsonian patients (278 of 450) had chronic pain. Twenty-five patients with non-chronic pain (<3-month duration) were excluded from subsequent analysis. Twenty six percent (111 of 425) parkinsonian patients had pain unrelated to PD ("non-PD-pain", caused mainly by osteoarthritis), while 39.3% (167 of 425) had chronic pain related to PD ("PD-pain"). In this last group, PD was the sole cause of pain in 103 and indirectly aggravated pain of another origin (mainly osteoarthritis) in 64. Parkinsonian patients with "PD-pain" were younger at PD onset, had more motor complications, more severe depressive symptoms than those without pain or with "non-PD pain." "PD-pain" was more intense ($P = 0.03$), but was less frequently reported to doctors ($P = 0.02$), and was associated with less frequent analgesic consumption than "non-PD-pain." Pain was twice more frequent in PD patients than in patients without PD after adjustment for osteo-articular comorbidities (OR = 1.9; 95% CI 1.2-3.2). Chronic pain is frequent but underreported in PD. Awareness of this problem should be increased and the assessment of analgesic strategies improved.

ARTICLE TEXT

Pain is underrecognized in Parkinson's disease (PD). Studies are rare, limited to small series of tertiary centers, without comparative group, and no standard definition nor systematic assessment of different types of chronic pain.[1-4] The aims of the DoPaMiP (Douleur et maladie de Parkinson en Midi-Pyrénées) survey were (1) to estimate chronic pain prevalence in a general PD population using a validated definition, (2) to compare PD patients with and without pain regarding symptoms and treatments, and (3) to assess if pain was more frequent in this population than in patients with other chronic disorders than PD.

METHODS

Study Design and Population

The first 25 consecutive Parkinsonian patients attending the outpatient clinics of 28 of the 95 neurologists of the Midi-Pyrénées Region were asked to participate in this cross-sectional survey. Inclusion criteria were: UK PD Society Brain Bank diagnosis,[5] age ≥ 18 years, Mini Mental State Examination (MMSE) score >24,[6] no deep brain stimulation, no serious, immediately life-threatening disease. Outpatients consulting GPs for other reasons than PD were recruited to compare pain prevalence.

Patient Assessment

Sociodemographic characteristics and PD history, comorbidities, and treatments were collected using structured interviews. Neurologists (pretrained for the survey) carried out detailed neurological examination, and identified patients with or without chronic pain (“no pain” group) according to the International Association for the Study of Pain (IASP) definition (unpleasant sensory and emotional experiences with actual or potential tissue damage or described in terms of such damage and lasting for more than 3 months).[7] Pain intensity was assessed with a 100-mm visual analog scale (0 = no pain, 100 = worst pain imaginable).[8] Specific predefined information on pain characteristics were collected based on DoPaMiP experts consensus: patient's opinion about the relationship between pain and PD, topography, duration, frequency, aggravating factors, temporal and topographical relationship with PD symptoms (onset and location), influence of motor complications (fluctuations, OFF dystonia, ON dyskinesia), and antiparkinsonian medications. Neurologists used this information and their best clinical judgment to separate chronic pain into two categories: “non-PD-pain” (pain related to another cause than PD and not aggravated by PD) and “PD-pain” (pain that was caused or aggravated by PD). In this last category, pain was considered to be (1) directly related to PD (“PD-Pain direct”) if it could not be attributed to any other health problem according to medical history, clinical examination, laboratory test, or imaging results, or (2) indirectly related to PD (“PD-pain indirect”) if another diseases caused pain (e.g. osteoarthritis) but PD aggravated pain intensity because of rigidity, abnormal posture, or movements. Patients reporting more than one pain described their most severe pain first.

Parkinsonism was assessed in the ON condition, using the Unified Parkinson's Disease Rating Scale (UPDRS)[9] and the Hoehn and Yahr scale.[10]

PD patients completed questionnaires rating (1) depressive and anxious symptoms (Hospital Anxiety and Depression Rating Scale - HADS),[11] (2) sleep quality (Pittsburgh Sleep Quality Index - PSQI),[12] and (3) health-related quality of life (PD Questionnaire - PDQ-39).[13] The Brief Pain Inventory items concerning pain interference (from 0: does not interfere, to 10: complete interference) were used to measure the impact of chronic pain on general activity, mood, walking ability, normal working, relations with other people, sleep and enjoyment of life in these patients.[14] The French version[15] of the McGill Pain Questionnaire short form[16] was used to measure the sensory and affective dimensions of pain. Finally, patients with chronic pain were asked whether they had reported this pain to a doctor and which analgesics they had taken for this pain.

Patients with other disorders than PD were assessed in the same way by the GPs, except for PD-specific outcomes. They were recruited at the end of the survey, to include patients of the same age range (mean = 70 years) and sex ratio (55% males) than in the PD group.

Data Management and Quality Control

Data were stored by the Toulouse Clinical Pharmacology Unit. Random independent monitoring was performed in 10% of the sample. Missing values or inconsistencies were discussed with investigators. Two PD experts (OR, WR) reviewed all cases for consistency. The protocol was approved by the French regulatory authorities, including data protection committees. The study was undertaken in accordance with Guidelines for Good Epidemiology Practice and ADELF (*Association Française des Epidémiologistes de Langue Française*) recommendations. All patients provided informed written consent.

Variables Studied

Different UPDRS scores were used to assess PD symptoms: total score [Part II (activities of daily living) + Part III (motor examination), (most severe score = 108)]; "dopa-responsive" subscore [tremor (item 20) + akinesia (items 23 - 26 + 31) + rigidity (item 22), maximal score = 76]; and "axial" subscore [falling, freezing, speech, posture, postural stability (items 13 + 14 + 18 + 28 + 30), maximal score = 20]. Two HADS subscores (one for depressive and one for anxious symptoms, most severe score for each = 21) were used, with subscores >7 indicating patients with possible or probable anxiety or depression symptoms.[11][17] PSQI score >5 was used to define patients with "poor sleep quality."[12] Health-related quality of life was evaluated using total score and each dimension subscores of the PDQ-39 scale.[13]

Comorbidities were classified into six WHO categories (cardiovascular, metabolism, osteoarticular, sleeping, mood, and "others").[18] Concurrent medication use during the previous month was analyzed, using the drug coding system of the anatomical therapeutic

chemical (ATC) classification.[19] Analgesics were classified according to the WHO three-level classification system.[20] Patients' levodopa equivalent daily dose (accounting for dopamine agonists, COMT and MAO-B inhibitors) was calculated as previously described.[21]

Statistical Analysis

Demographic and clinical characteristics are presented as frequencies, proportions or means ± standard deviation (SD) with 95% confidence intervals (CI).

A sample size of 385 PD patients allowed detecting a chronic pain prevalence of 50% (precision = 0.05) - an hypothesis in line with the literature[2] - and showing an odds ratio (OR) of 2 on associated factors for which the prevalence in patients with no pain was estimated to be 20% (alpha = 5%; beta = 80%). A sample size of 90 subjects per group allowed detecting a difference in pain prevalence between 2 different groups (patients and without PD), assuming that pain would be present in 30% of non PD patients[22] and twice more frequent in the PD group (alpha = 5%, beta = 80%). Based on these estimations, we planned to include 450 patients in the PD group and 100 patients in the non PD chronic disorder group, ensuring power in spite of possible missing data.

Analysis was restricted to the most severe and troublesome pain in patients reporting more than one chronic pain (n = 93). Patients suffering from non chronic pain (lasting <3 months; n = 25) were included only in the initial global population description. They were excluded from subsequent analyses, as some of these cases may have corresponded to a short-term acute syndrome, whereas others may have corresponded to the early phase of a chronic syndrome. The different parkinsonian groups (no pain, non-PD-pain, PD-pain - including direct or indirect) were compared, using ANOVA and Student's *t* tests. Bivariate Chi-squared analyses were carried out, with the level of significance set at 0.05. A backward logistic regression analysis was performed to identify the factors best predicting the occurrence of PD-pain, by comparison with patients with no pain, with a *P*-value threshold of 0.05 used to exclude factors.[23] Correlates identified as significant were included in the model as explanatory variables. These variables were categorized using the median value or cutoff points. Hosmer and Lemeshow tests and likelihood ratio tests were used to check the quality of the models. We assessed potential interactions in these two models, but found no such interactions.

Statistical analyses were carried out with SAS software version 9.1 for Windows.

Role of the Funding Source

The survey was funded by the French Programme Hospitalier Regional de Recherche Clinique and unrestricted grants from pharmaceutical companies None of these had any input into study design, data analysis, or manuscript preparation.

RESULTS

A total of 450 patients with PD and 98 with non-PD disorders were included. Their main sociodemographic profiles were comparable. Non-PD patients had more frequent somatic comorbidities [cardiovascular disease (hypertension and arrhythmia), metabolic disorders (dyslipidemia) and osteoarthritis] as expected from recruitment strategy (they visited GPs for another disease than PD). PD patients had more severe, sleep quality, anxiety and depression scores, as previously reported (Table 1).

Table 1. Principal demographic and clinical characteristics of parkinsonian patients and patients with disorders other than PD

	Parkinsonian patients (n = 450)	**Patients with disorders other than PD (n = 98)**	***P* value**
Age (years)	68.8 ± 9.7	70.3 ± 9.3	0.17
Sex (% male)	254 (56.4%) [52-61]	53 (54.1%) [44-64]	0.67
Age at which left education (years)	17.5 ± 5.9	16.9 ± 4.3	0.21
PSQI score	7.6 ± 4	6.1 ± 3.8	0.002
HADS-D score	6.6 ± 3.8	3.9 ± 3.2	<0.0001
HADS-A score	8.2 ± 3.9	6.5 ± 3.2	<0.0001
Comorbidities (%)	364 (80.9%) [77-85]	93 (94.9%) [91-99]	0.0007
Cardiovascular	178 (39.6%) [34-44]	62 (63.3%) [54-73]	<0.0001
Metabolic	145 (32.2%) [28-37]	54 (55.1%) [45-65]	<0.0001
Osteoarticular	111 (24.7%) [21-29]	43 (43.9%) [34-54]	<0.0001

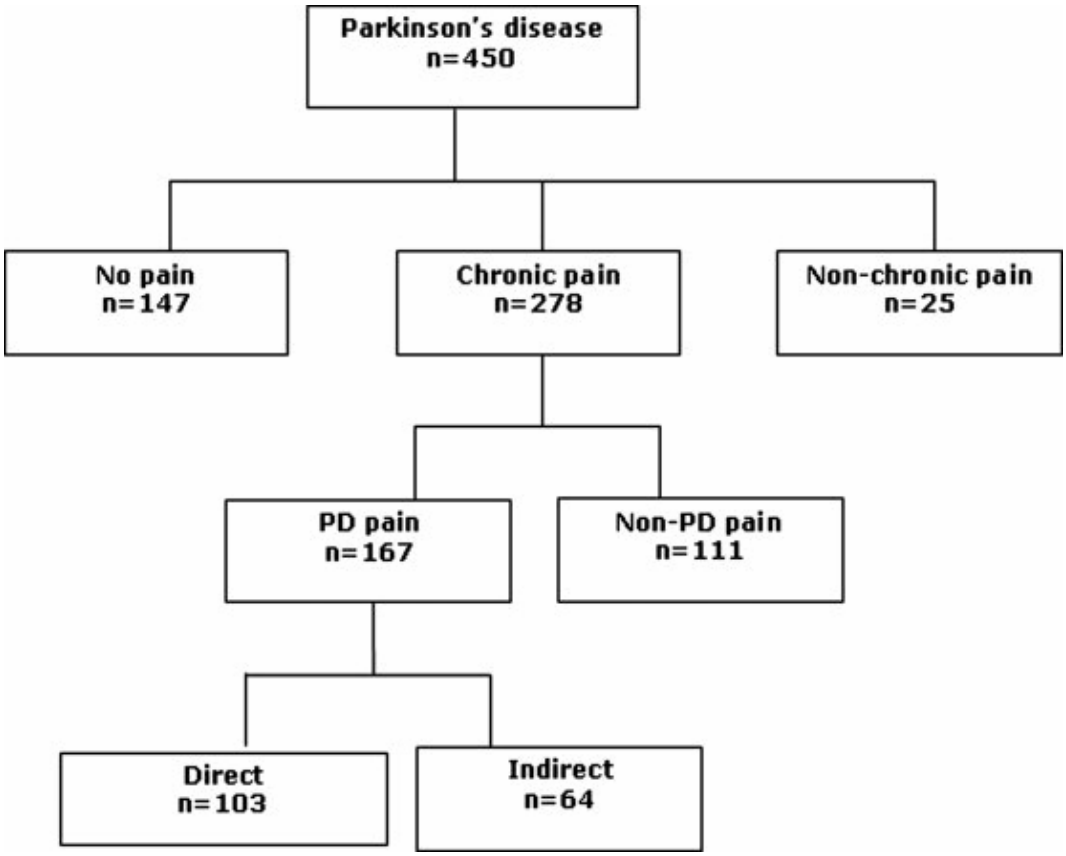
Data are means ± SD or number (percentage) [95% CI].

HADS-A = Hospital Anxiety and Depression Scale - Anxiety subscore; HADS-D = Hospital Anxiety and Depression Scale - Depression subscore; MMSE = Mini-Mental State Examination; PSQI = Pittsburgh Sleep Quality Index; UPDRS = Unified Parkinson's Disease Rating Scale.

Different Types of Chronic Pain Observed in PD Patients (see Fig. 1)

About 147 of the 450 parkinsonian patients (32.6%) reported no pain while chronic pain was present in 278 (61.8%). Twenty-five patients were excluded from subsequent analyses because pain did not fulfill the IASP definition (last <3 months).

Figure 1. Types of pain reported by PD patients in the DoPaMiP survey.



Among the 278 PD patients with chronic pain, 167 (60.1%) did so, at least partly, because of PD (PD-pain group). In these, no other cause of pain than PD could be identified in 103 (PD-pain direct group), whereas PD aggravated a pain of other origin (mainly osteoarthritis) in 64 (PD-pain indirect). The PD-pain direct group was heterogeneous according to pain description, pain being associated with abnormal movements ("OFF" dystonia) in 20 patients, resembling neuropathic pain in 14 others - although sensory examination was normal- and being associated with akathisia in 4. Pain was less precisely described in many other cases including various sensations such as deep aching, myalgia, cramps, stiffness or articular or abdominal discomfort (n = 63).

The other 111 PD patients with chronic pain (39.9%) had so because of another disorder than PD (osteoarthritis in 88/111) with no influence of PD on pain expression according to the patient and the neurologist.

Comparison of Parkinsonian Patients With No Pain, PD-Pain, and Non PD-Pain

The mean VAS and SF-McGill scores were significantly greater in PD-pain than in non PD-pain patients (Table 2). Overall, patients with PD-pain were younger than those without pain (no pain) or with non-PD pain. They were also younger at PD onset with indices of more severe PD (longer duration and dopatherapy exposure, more severe UPDRS and Hoehn and Yahr scores, more frequent motor complications, higher L-DOPA daily dose) (Table 2). Conversely, sleep quality scores were not different.

Table 2. Demographic and clinical characteristics of parkinsonian patients with no pain, chronic pain related to PD (PD-pain) or chronic pain unrelated to PD (non-PD-pain)

	No pain (n = 147)	**PD-pain (n = 167)**	**Non-PD-pain (n = 111)**	***P* value**
Pain intensity (VAS)	-	6.5 ± 2.0 [6.2-6.8]	6.0 ± 2.2 [5.6-6.4]	0.03
SF-McGill score	_	16 ± 9.4 [14.4-17.5]	12.3 ± 8.3 [10.8-13.9]	0.002
Sensory score	_	6.9 ± 4.1 [6.3-7.6]	6.3 ± 4.3 [5.5-7.1]	0.25
Emotional score	_	9.1 ± 6.8 [8-10.1]	6.2 ± 5.1 [5.2-7.2]	0.0003
Sex (% male)	61.2% [53-69]	53.9% [46-61]	51.4% [42-61]	0.24
Age (years)	69.7 ± 10.4 [68-71.4]	66.4 ± 9.8 [64.9-67.9]	71.7 ± 7.7 [70.3-73.1]	<0.0001‡‡, ◊◊◊
MMSE score	28.0 ± 2.2 [27.6-28.3]	27.9 ± 2.6 [27.5-28.3]	28.0 ± 1.8 [27.6-28.3]	0.98
PD duration (years)	5.1 ± 5.5 [4.2-6.0]	7.1 ± 4.9 [6.3-7.8]	5.0 ± 4.4 [4.2-5.9]	0.0004‡‡‡, ◊◊◊
Age at PD onset (years)	65.1 ± 11.5 [63.2-67]	59.8 ± 10.1 [58.3-61.4]	67.2 ± 8.7 [65.6-68.9]	<0.0001‡‡, ‡, ◊◊◊
UPDRS (II+III) ON score	25.6 ± 13.9 [23.2-27.9]	32.3 ± 16.4 [29.7-34.9]	26.5 ± 13.5 [23.8-29.1]	0.0002‡‡‡, ◊◊
UPDRS axial subscore	3.8 ± 3.3 [3.2-4.4]	4.9 ± 3.4 [4.4-5.5]	3.9 ± 3.0 [3.4-4.5]	0.006‡‡

UPDRS dopa-responsive subscore	13 ± 7.6 [11.7-14.3]	15 ± 8.6 [13.6-16.3]	12.1 ± 7.3 [10.7-13.5]	0.01‡◇◇
Hoehn and Yahr stage	2.1 ± 0.8 [2.0-2.3]	2.4 ± 0.8 [2.3-2.5]	2.1 ± 0.7 [2.0-2.3]	0.002‡‡,◇◇
Patients with motor fluctuations	19.1% [13-25]	44.9% [37-52]	19.8% [12-27]	<0.0001‡‡‡,◇◇◇
Patients with dyskinesia	16.3% [10-22]	38.3% [31-46]	16.2% [9-23]	<0.0001‡‡‡,◇◇◇
PSQI score	7.6 ± 3.9 [6.8-8.3]	7.8 ± 3.8 [7.2-8.4]	7.7 ± 4.3 [6.7-8.6]	0.89
Levodopa equivalent dose (mg/day)	771 ± 657 [661-882]	1175 ± 877 [1038-1311]	819 ± 674 [687-950]	<0.0001‡‡‡,◇◇◇
Dopatherapy duration (years)	4.7 ± 4.6 [3.9-5.6]	6.1 ± 4.5 [5.4-6.8]	4.5 ± 4.2 [3.7-5.4]	0.01‡,◇◇

Data are means ± SD [95% CI] or percentages [95% CI].

‡ $P < 0.05$;

‡‡ $P < 0.01$;

‡‡‡ $P < 0.001$; PD-pain versus no pain.

$P < 0.05$;

◇◇ $P < 0.01$;

◇◇◇ $P < 0.001$; PD pain versus non-PD pain. No statistical significance observed between non-PD pain versus no pain.

MMSE = Mini-Mental State Examination; PSQI = Pittsburgh Sleep Quality Index; UPDRS = Unified Parkinson's Disease Rating Scale.

Several health-related quality of life items related to PD (PDQ-39) or chronic pain (BPI) as well as anxiety/depression scores indicated significant alteration in patients with PD-pain with respect to the others (Table 3). In multivariate logistic regression analysis, factors associated with PD-pain were younger age at PD onset, presence of motor fluctuations and depressive symptoms (HADS-D >7) (Table 4).

Table 3. Anxiety and depression HADS scores and quality of life related to PD or chronic pain in PD patients

	No pain (n = 147)	PD-pain (n = 167)	Non-PD-pain (n = 111)	*P* value
PDQ-39 total score	24 ± 14 [21-26]	32 ± 14 [30-34]	27 ± 13 [25-30]	<0.0001‡‡‡,◊◊
Mobility	27 ± 26 [22-31]	38 ± 25 [34-42]	32 ± 25 [27-37]	0.0005‡‡‡
Activities of daily living	24 ± 23 [20-28]	34 ± 23 [30-37]	29 ± 21 [25-33]	0.0006‡‡‡
Emotional well being	26 ± 20 [23-29]	37 ± 21 [33-40]	31 ± 22 [27-35]	<0.0001‡‡‡,◊
Stigma	24 ± 24 [20-27]	27 ± 24 [24-31]	22 ± 24 [17-26]	0.14
Social support	9 ± 17 [7-12]	12 ± 18 [10-15]	8 ± 16 [5-12]	0.14
Cognitive impairment	26 ± 18 [23-29]	31 ± 19 [28-34]	29 ± 18 [25-32]	0.03‡‡
Communication	24 ± 21 [21-28]	29 ± 21 [26-32]	22 ± 21 [18-26]	0.02‡,◊◊
Bodily discomfort	30 ± 20 [27-34]	49 ± 18 [46-52]	44 ± 18 [40-47]	<0.0001‡‡‡,§§§,◊
BPI scores				
General activity	-	3.7 ± 3.1 [3.2-4.2]	2.7 ± 2.8 [2.2-3.2]	0.007
Mood	-	2.7 ± 2.8 [2.3-3.2]	1.7 ± 2.6 [1.2-2.2]	0.004
Walking ability	-	3.1 ± 3.1 [2.6-3.6]	2.8 ± 3.3 [2.2-3.5]	0.47
Normal working	-	3.6 ± 3.1 [3.1-4.1]	3.3 ± 3.1 [2.7-3.8]	0.39
Relations with other people	-	2.2 ± 2.8 [1.8-2.7]	1.4 ± 2.4 [1.0-1.9]	0.02
Sleep	-	2.1 ± 3.0 [1.6-2.5]	1.6 ± 2.7 [1.1-2.1]	0.15

Enjoyment of life	-	2.6 ± 3.0 [2.1-3.1]	1.2 ± 2.2 [0.8-1.6]	<0.0001
HADS-D score	5.9 ± 4 [5.2-6.5]	7.5 ± 3.7 [6.9-8.1]	6.8 ± 3.6 [6.0-7.5]	0.002‡‡‡
HADS-A score	7.3 ± 3.9 [6.7-8.0]	9.1 ± 3.8 [8.5-9.7]	8.0 ± 3.6 [7.3-8.7]	0.0003‡‡‡ ◊

Data are mean ± SD [95% CI].

HADS-A = Hospital Anxiety and Depression Scale - Anxiety subscore; HADS-D = Hospital Anxiety and Depression Scale - Depression subscore; BPI = Brief Pain Inventory.

‡ $P < 0.05$;

‡‡ $P < 0.01$;

‡‡‡ $P < 0.001$; PD-pain versus no pain.

◊ $P < 0.05$;

◊◊ $P < 0.01$;

$P < 0.001$; PD pain versus non-PD pain.

$P < 0.05$;

$P < 0.01$;

§§§ $P < 0.001$; non-PD pain versus no pain.

Table 4. Logistic regression model of factors significantly associated with PD-pain, with parkinsonian patients with no pain used as the control group

	OR [95% CI]	**Adjusted OR[95% CI]***
Age at PD onset		
≤65 years	3 [1.9-4.8]	3 [1.7-5.4]
>65 years	1	1
Motor fluctuations		
Presence	3.5 [2.1-5.8]	2.8 [1.5-5.1]
Absence	1	1
Depressive symptoms (HADS-D > 7)		
Yes	2.1 [1.3-3.4]	2 [1.1-3.6]
No	1	1

Adjusted *R*-square value 0.23.

Goodness of fit, Hosmer and Lemeshow[19] - Pr > Chi^2: 0.8039.

* OR adjusted for age at onset, PD duration, motor fluctuations, dyskinesia, UPDRS II+III, dopatherapy duration, HADS-A and HADS-D.

HADS-D = Hospital Anxiety and Depression Scale - Depression subscore; HADS-A = Hospital Anxiety and Depression Scale - Anxiety subscore; UPDRS = Unified Parkinson's Disease Rating Scale; OR = odds ratio.

Analgesic consumption was reported by fewer patients with PD-pain than non-PD-pain and than patients with other disorders than PD exhibiting chronic pain (57 of 98) (Table 5).

Table 5. Analgesic consumption (yes/no) during the month preceding assessment in parkinsonian patients with chronic pain related to PD (PD-pain) or unrelated to PD (non-PD-pain) and in patients with disorders other than PD and chronic pain

	PD-pain (n = 167)	Non-PD-pain (n = 111)	Patients with disorders other than PD and chronic pain (n = 57)	*P* value
Any analgesic	50.3% [43-58]◊◊,€€	67.6% [59-76]	70.2% [58-82]	0.003
Level I[a]	34.1% [27-41]◊,€€€	48.6% [39-58]	61.4% [49-74]	0.0007
Level II[a]	9.6% [5-14]	15.3% [9-22]	10.5% [3-19]	0.33
Level III[a]	0.6% [0-2]	0	0	-
Co-analgesic[a]	10.8% [6-16]	16.2% [9-23]	15.8% [6-25]	0.36

Data are percentages [95% CI].

WHO three-level classification system (Level I - non-opioids; Level II - weak opioids; Level III - strong opioids; co-analgesic - tricyclic antidepressants, antiepileptics, hypnotics/anxiolytics).[20] Medications are listed in this table only if they have been consumed by the patient in order to treat chronic pain and not for other purposes

◊ $P < 0.05$;

◊◊ $P < 0.01$; PD pain versus non PD-pain.

€€ $P < 0.01$;
€€€ $P < 0.001$; PD pain versus patients with disorders other than PD and chronic pain.

Comparison of PD Patients With Different Subtypes of Chronic Pain: PD-Pain Direct, PD-Pain Indirect, or Non-PD Pain

PD-pain direct (considered as being caused only by PD) differed from the two other pain subtypes in many aspects (Table 6): it was more recent, occurred less frequently before PD onset, was less frequently worsened by physical effort, worsened more frequently during OFF episodes and was better improved by antiparkinsonian drugs. It was also more frequently located in the lower limbs and was less frequently reported to doctors.

Table 6. Comparison of chronic pain characteristics among parkinsonian patients with chronic pain unrelated to PD (non-PD-pain), chronic pain indirectly related to PD (PD-pain-indirect) and chronic pain directly related to PD (PD-pain-direct)

	Non-PD-pain (n = 111)	**PD-pain indirect (n = 64)**	**PD-pain direct (n = 103)**	***P* value**
Pain duration (years)	10.2 ± 12.7 [7.8-12.6]	9.3 ± 11 [6.6-12.0]	3.7 ± 3.8 [3.0-4.5]	<0.0001£££,µµµ
Patients with pain onset preceding PD diagnosis	60.4% [51.3-69.5]	48.4% [36.2-60.7]	10.7% [4.7-16.6]	<0.0001£££,µµ
Pain activating factor				
Effort	69.4% [60.8-77.9]	67.2% [55.7-78.7]	48.5% [38.9-58.2]	0.004££,µ
Anxiety	11.7% [5.7-17.7]	26.6% [15.7-37.4]	30.1% [21.2-39]	0.003£££†
Emotions	9.0% [3.7-14.3]	25% [14.4-35.6]	29.1% [20.4-37.9]	0.0007£££,††
Pain worsened during off episodes	0.9% [0-2.7]	18.8% [9.2-28.3]	24.3% [16.0-33.2]	<0.0001£££,†††µ

Pain improved by antiparkinsonian drugs	3.6% [0-7]	12.5% [4.0-21.2]	47.6% [38.1-57.0]	<0.0001£££,†††,µµµ
Pain topography				
Head	12.6% [6.4-18.8]	10.9% [3.3-18.6]	8.7% [3.3-14.2]	0.66
Back	44.1% [34.9-53.4]	60.9% [49-72.9]	12.6% [6.2-19]	<0.0001£££,†††,µµµ
Upper limbs	23.4% [15.5-31.3]	14.1% [5.6-22.6]	21.4% [13.4-29.3]	0.32
Lower limbs	31.5% [22.9-40.2]	29.7% [18.5-40.9]	67% [57.9-76.1]	<0.0001£££,µµ
Pain mentioned to GP or neurologist	85.6% [79.1-92.1]	82.8% [73.6-92.1]	68.0% [59-77]	0.004£,µ

Data are means ± SD [95% CI] or percentages [95% CI].
VAS = Visual Analog Scale.
† $P < 0.05$;
†† $P < 0.01$;
††† $P < 0.001$; PD-pain indirect versus non-PD pain.
£ $P < 0.05$;
£ $P < 0.01$;
£ $P < 0.001$; PD-pain direct versus non-PD pain.
µ $P < 0.05$;
µ $P < 0.01$;
µµµ $P < 0.001$; PD-pain direct versus PD pain indirect.

Both PD-pain direct and indirect subtypes were more frequently worsened by anxiety/emotions, were more frequently aggravated during OFF episodes and improved by antiparkinsonian drugs than non PD-pain subtype.

Comparison of the Prevalence of Chronic Pain in PD Patients and Patients With Other Disorders Than PD

Chronic pain occurred in 278 of 450 Parkinsonian patients (61.8%) and in 57 of 98 patients with other disorders than PD (58.2%) ($P = 0.51$). Osteoarthritis was an important cause of pain in both groups and was significantly more prevalent in patients with other disorders than PD. After adjustment for osteo-articular comorbidity, parkinsonian

patients were found to be twice as likely to suffer from chronic pain as patients with non-PD disorders [OR = 1.9; 95% CI 1.2-3.2].

DISCUSSION

DoPaMiP is the first cross-sectional survey to investigate chronic pain in a large population of Parkinsonian patients seen in general neurological practice. Our estimate of the prevalence of chronic pain in PD (61.8%) is within the range of previous reports, which have varied from 30 to 85%.[1][2][24-28] This variability may be accounted for by differences in chronic pain definitions, a lack of distinction between pain related and unrelated to PD or recruitment bias in specialized tertiary centers.

This survey was not population-based but our patients were recruited consecutively by 30% of the neurologists in the Midi-Pyrénées area. More than 80% of patients diagnosed with PD in France are managed by a neurologist. The DoPaMiP population included 6% of the entire parkinsonian population of the area,[29][30] and its demographic characteristics were similar to those of ambulatory parkinsonian populations reported in other studies.[31] Therefore, we assume that our patients were representative of the general PD population and that a figure of 2 of 3 parkinsonian patients suffering from chronic pain is a reasonable estimation.

One can discuss the fact that we recruited patients visiting GPs for other reasons than PD to compare pain prevalence in another population. Comparing parkinsonian patients with their spouses would have been biased by the burden carried out by caregivers, while recruiting 70-year-old subjects free of chronic disorders would have created a too artificial group of comparison. We had therefore to adjust for painful co-morbidity (osteoarthritis) when comparing the groups to show that chronic pain is more frequent in patients with PD than without.

There are no validated tools to establish whether pain should be considered or not as part of PD features in a given patient. Many parkinsonian patients may suffer because of disorders other than PD, such as osteoarthritis, while other may suffer specifically because of PD. It is important to separate these entities. We addressed this issue by asking the neurologists who assessed our patients to classify pain regarding this issue according to careful examination, specific questions based on experts' consensus and best clinical judgment. This approach may lead to selection bias. However, neurologists concluded that ~25% of DoPaMiP Parkinsonian patients suffered from chronic pain for another cause than PD, and this is consistent with previous surveys in the general population.[32-34] Conversely, they concluded in almost 40% of the Parkinsonian population that chronic pain was related to PD. The fact that these 2 groups (PD- and non-PD pain) had different age at onset, prevalence of motor complications, quality of life and affective scores suggests that this separation is clinically meaningful and that PD-pain is indeed a specific entity.

The subdivision of PD-pain into direct and indirect PD-pain was also based on specialists' clinical judgment. The numerous differences in the clinical features between these two

subtypes (onset, topography, activating factors, effect of antiparkinsonian drugs, mentioning to doctors by the patient...) suggest that this categorization may also have clinical relevance, with PD pain direct representing a separate entity. It is important to emphasize, however, that the PD-pain direct group was not homogeneous regarding pain description. Several subcategories of PD pain reported in this survey were consistent with previous studies, including pain associated with OFF dystonia or described as abnormal sensations similar to neuropathic pain syndromes, in spite of no objective sensory deficit.[2][8] Most cases, however, did not correspond to well define syndromes and were reported as vague painful sensations. This heterogeneity deserves further investigations and probably reflects the multiplicity of the underlying mechanisms.

Peripheral mechanical factors, such as muscular contraction, dystonia or abnormal posture, may play a role in certain patients, accounting for the analgesic efficacy of botulinum toxin in these cases.[35] However, several anatomical, electrophysiological and pharmacological arguments also link PD-pain to the central dopaminergic deficit[36-40] while central non dopaminergic mechanisms cannot be excluded.[41] Some findings of the DoPaMiP survey are compatible with the dopaminergic hypothesis: PD-pain worsened during OFF episodes and improved on antiparkinsonian drugs. Moreover, PD-pain patients were younger at PD onset, had a more severe "dopa-responsive" UPDRS subscore and more frequent motor fluctuations, such factors indicating a more severe dopamine deficit. Being younger (but not earlier age at onset) and motor complications have already been shown to be associated with pain in PD.[2][4]

DoPaMiP showed that pain was associated with higher scores for depression and health-related quality of life in PD. Depression has already been reported to be more severe in Parkinsonian patients with pain, although the overall prevalence of depression in these patients was not higher than that in patients without pain.[4][42] Sleep problems are commonly reported in patients with PD with and without pain.[42] We found no overall difference in sleep quality between the 3 groups of Parkinsonian patients, although Parkinsonian patients generally slept less well than non PD patients. This suggests that factors other than pain may have a more profound impact on sleep quality in PD. Conversely, after adjustment for other factors, possible/probable depressive symptoms were found to be significantly correlated with the presence of PD-pain when patients with no pain were used as the control group. Whether pain is a contributing factor for depression or vice-versa remains to be explored.

Finally, DoPaMiP was the first study to assess analgesic consumption in PD patients. Almost 50% of parkinsonian patients with PD-pain took at least one analgesic during the previous month. This analgesic consumption was lower than that of patients with non-PD-pain (and of patients with other disorders than PD), despite greater indices of PD-pain intensity and impact on health-related quality of life. This lower level of analgesic consumption may reflect the lower frequency with which patients reported PD-pain to their physicians, as opposed to non-PD-pain. Memorization bias may explain this observation, but this seems unlikely considering the large number of patients interviewed. It is possible that a poor understanding of the mechanisms underlying pain raised doubts about analgesics efficacy in this situation, or that other types of management, such as

dopaminergic drug adjustment, were preferred. This issue merits further investigation. The efficacy of analgesics has never been assessed specifically in Parkinsonian patients, and assessments of the effects of these drugs in this population appear to be required, given that almost 50% of Parkinsonian patients with PD-pain consumed analgesics. Such assessments would help to determine whether Parkinsonian patients benefit from analgesic treatment and, therefore, whether as many as half of all PD patients are missing out on a potentially useful treatment.

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Competing interest: L Nègre-Pagès owns a start-up company that has worked with Boehringer Ingelheim, Eisai, Faust Pharmaceuticals, Fertizin, GlaxoSmithKline, Pierre Fabre Médicaments, and Solvay Pharma. O Rascol has acted as an expert advisor for pharmaceutical companies, including Boehringer Ingelheim, Eisai, Euthérapie, GlaxoSmithKline, Pierre Fabre Médicaments, and Solvay Pharma. D Bouhassira has acted as advisor to Pfizer and Eli Lilly. H Grandjean has no conflicts of interest.

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Contributions

L Nègre-Pagès and O Rascol drafted the protocol for this study, managed the survey, contributed to data collection and analysis, and were responsible for manuscript preparation and submission. M Aristin and C Hurault from Toulouse University Hospital conducted the statistical analysis under the supervision of L Nègre-Pagès and O Rascol. H Grandjean and D Bouhassira participated in data analysis, and in preparation of the manuscript.

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