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Epidemiology of major depression in Belgian parkinsonian patients

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Abstract

Background: Epidemiological data concerning the prevalence of major depression in PD patients in Belgium is very scarce.

Methods: A total of 1086 patients with idiopathic Parkinsons disease were included in the analysis. The neurological evaluation of the patients was made by the Hoehn and Yahr Staging of Parkinsons disease, the Unified Parkinson Disease Rating Scale (UPDRS), and the Schwab and England Activities of Daily Living. The psychiatric evaluation was based on the Mini-International Neuropsychiatric Interview (MINI) and the Montgomery Asberg Depression Rating Scale (MADRS).

Results: Based on the MINI questionnaire, the overall proportion of PD patients presenting a current major depressive episode was 15.6%. Interestingly, 30% of all patients included had a history of mood disorder and 46% received either an anxiolytic, an antidepressant or an atypical neuroleptic or a combination of them. The characterisation of the profile of depressed parkinsonian patients shows very few patient's parameters (demographics or motor symptoms) to be associated with a higher risk for major depression.

Conclusions: The PARKIDEP survey confirms a high prevalence of major depression in PD patients in Belgium. A careful follow up of PD patients with a poor functionality, a history of mood disorder or with a complaint of depression or anxiety during the "off" state would help towards a better treatment of the Parkinson's disease associated depression and should improve the quality of life of PD patients.

Key words: depressive symptoms; Parkinson's disease, depression, MINI, antidepressant; prevalence.

Introduction

It is currently well accepted that motor symptoms are only one aspect of the idiopathic Parkinson's disease (PD). A growing body of evidence shows that non-motor symptoms are numerous and frequently encountered in PD, and that their occurrence may even precede the appearance of motor symptoms and PD diagnosis (Bodis-Wollner, 2003). Among those non-motor symptoms, depression is one of the most common in PD but still remains largely underestimated (GPDSSC, 2002; Shulman *et al.*, 2002). According to the literature, the prevalence of depression in PD varies between 2.7% and 70% depending on the population studied (Schuurman *et al.*, 2002). A prevalence of at least 40% is more commonly reported (Cummings, 1992; Cummings and Masterman, 1999; Okun and Watts, 2002). Moreover, depression in PD is also pointed out as one of the most important factors impacting the quality of life of patients and of their caregivers (Schrag *et al.*, 2000; GPDSSC, 2002; Schrag, 2006; Muslimovic *et al.*, 2008).

The reported prevalence of depression in PD varies greatly from one publication to another partly due to the definition used, from depressive symptoms or depressive disorder to minor or major depression according to the DSM-IV (Lieberman, 2006). Diagnosing depression in the course of PD can be difficult because of the large overlap of symptoms between depression and the motor

manifestations of PD, including for example, the inexpressive face, slowness of movement, sexual and sleep disturbances… Fatigue, lassitude and decreased initiative in PD are often caused by an unrecognised depression which would be revealed by a structured interview. The prevalence of depression in PD may also be influenced by the diagnostic tool used for its diagnosis. Among the many depression scales available, a few like the BDI and GDS have been validated for the screening of depression in PD patients and the HAM-D and MADRS for the assessment of severity of depression in the same context (Miyasaki *et al.*, 2006, Schrag *et al.*, 2007).

The high but under-recognised prevalence of depression in PD patients coupled with its impairing effect on their quality of life justify the need to rapidly detect symptoms of depression and to find associated factors which could help diagnose depression in the context of PD.

There is currently only sparse epidemiological data available concerning the PD population in Belgium. A previous survey on Belgian PD patients had pointed out depression as well as social isolation as major risk factors for resistant tremor (Vanderheyden *et al.*, 2009). For these reasons, this current national survey (PARKIDEP) was designed to assess the prevalence of major depression in PD patients in Belgium, and to look at its relationship with the characteristics of the patients (demographic, motor symptoms and treatment).

Methods and Materials

The PARKIDEP survey was a multicentre, non-interventional, cross-sectional, epidemiologic, naturalistic survey, carried out in Belgium between January 2006 and December 2007. A total of 51 neurologists was involved in the survey. Data from a total of 1086 consecutive outpatients has been collected during one visit to their respective neurologist.

Inclusion criteria: male or female outpatients suffering from idiopathic PD based on the United Kingdom PD Society Brain Bank Criteria (Gibb and Lees, 1988), sporadic form and examined during the "on" state.

Exclusion criteria: incapacity of the patient to answer the question. This survey was approved by the local ethics committees and patients included gave their informed consent to participate.

Demographic and clinical information about the disease and treatment history were obtained from the patient's records. Data about the "off" state neuropsychiatric non-motor symptoms was collected with a structured interview of the patient. The neurological evaluation performed by the neurologist classified the patients according to the Unified Parkinson Disease Rating Scale (UPDRS) (Fahn and Elton, 1987), modified Hoehn and Yahr scale (Hoehn and Yahr, 1967) and Schwab and England Activities of Daily Living scale (Schwab and England, 1969). In order to simplify the interview, the examiner employed only a few items of the UPDRS III and IV (items 20-22, 31-33, 35, 39) for motor assessment. These items were giving a specific subscore on tremor, rigidity, bradykinesia and also on motor complications like dyskinesia, dystonia and motor fluctuation.

Similarly, the neurologist performed the Mini International Neuropsychiatric Interview (M.I.N.I.) (Sheehan *et al.*, 1998) to evaluate the psychiatric state of the patient at the time of the visit. The M.I.N.I. allows the diagnosis of major depression according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV, 1994). The M.I.N.I. is considered the structured psychiatric interview of choice for psychiatric evaluation in epidemiological studies. It has been validated against the Composite International Diagnostic Interview for ICD-10 (CIDI) and expert opinion (Sheehan *et al.*, 1997 and 1998; Lecrubier *et al.*, 1997). Severity of the depression was measured by the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979; Snaith *et al.*,1986) if the diagnosis of major depression according to the MINI was positive.

The *primary objective* was to define the proportion of PD outpatients with major depression according to the MINI and the severity of this depression according to the MADRS. The *secondary objectives* were to assess the profile of the PD patient with major depression in order to detect potential epidemiological and clinical risk factors and to study the relationships between presence and/or severity of depression with demographic, neurological and treatment parameters.

For statistical analysis, results were expressed as means ± standard deviations (SD) for quantitative variables and as counts and proportions (%) for categorical variables. Patients with major depression according to the M.I.N.I. were compared to those without depression by means of the Student t-test (corrected for unequal variances if necessary), analysis of variance (ANOVA) or by the Krustal-Wallis test for quantitative variables, whereas the classical chi-square test was used for comparing proportions. Logistic regression was applied to analyse the relationship between the prevalence of depression (outcome variable) and a set of covariates. The odds ratio (OR) with 95% CI was used to measure the association between the outcome variable and the covari-

ates. All statistical calculations were performed using the SAS (version 9.1. for Windows) and S-Plus (version 6.2) statistical packages.

Results

Description of the PARKIDEP survey population

Demography and disease history

A usual slight predominance of males was noted but no age difference was observed between men and women (data not shown) (Table 1). There was a mean elapsed time of one year between the symptom appearance and the diagnosis of PD.

Data collected from the patient records and interviews, showed that 30% of the patients reported a history of mood disorder. Neuropsychiatric non-motor symptoms in the "off" state were reported by 61.1% of the patients.

The frequency of neuropsychiatric non-motor symptoms occurrence in the "off" state and improvement after treatment with antiparkinsonian drugs are presented in Table 2. Despite the treatment, patients reported being relieved of them in only 30 to 50% of the cases. Most of the patients suffered from more than one non-motor symptom in the "off" state.

Neurological evaluation

Figure 1 displays the classification of patients based on the three predominant motor-symptoms at the time of diagnosis and at the time of survey visit. With time, a clear inversion of the proportions was seen between tremor and bradykinesia while rigidity remained low.

The neurological evaluation of the patients was performed in the "on" state, according to three different scales. More than 60% of the patients were in the stages 1 to 2 of the modified Hoehn and Yahr scale with no significant difference between men and women. The UPDRS scores obtained in the "on" state for the selected items were respectively of

Table 1

Demographic characteristics of the 1086 PD patients

Variable		N (%)	Mean ± SD
Age (years)		1086	71.4 ± 8.5
Gender	Male	592 (54.5)	
	Female	494 (45.5)	
Age at time of PD symptoms appearance (years)		1012	65.2 ± 10.0
Age at time of PD diagnosis (years)		1058	66.2 ± 9.8
Duration of the disease (years)		1057	5.19 ± 5.02
History of mood disorder (N=1048)		314 (30.0)	

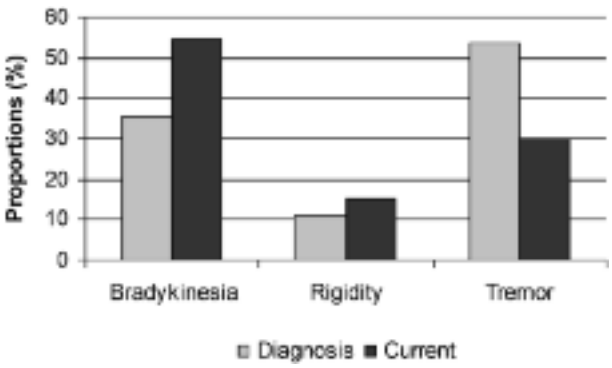

Fig. 1. — Predominant motor symptoms at diagnosis and at the time of the survey (current) in the survey sample (N = 1086).

Table 2

Occurrence of non-motor symptoms during the "off" state and improvement by antiparkinsonian drugs

Symptoms	Number (%) (N = 1010)	Improvement by antiparkinsonian treatment (%)
Patients presenting non-motor symptoms in the "off" state	617 (61.1)	NA
Bradyphrenia	322 (31.9)	53.9
Depression/anxiety	290 (28.7)	45.7
Cognitive impairment	217 (21.5)	27.6
Pain /Sensitive impairment	223 (22.1)	53.7
Sleep rhythm disorders	245 (24.3)	34.5

Table 3

Classes of antiparkinsonian drugs taken as initial and current therapies

	Initial antiparkinsonian treatment N = 1025 n (%)	**Current anti-parkinsonian treatment N=1055 n (%)**
L-dopa monotherapy	684 (66.7)	268 (25.4)
	93.4%	34.4%
Dopamine agonists monotherapy	152 (14.8)	74 (7.01)
Others monotherapies	121 (11.8)	21 (1.99)
Combinations L-Dopa + dopamine agonist	18 (1.8)	495 (46.9)
Other combinations	50 (4.9)	199 (18.9)

11.8 ± 6.8 for the men and 10.9 ± 6.7 for the women (p = 0.026). The distribution of patients according to their score on the Schwab and England scale showed that almost half of them (49.8%) were totally or completely independent (score 100% or 90%); the mean score was 81.1% with no significant difference between men and women.

Initial and current treatments

The initial antiparkinsonian treatment was mostly L-dopa monotherapy (66.7%) (Table 3). Dopamine agonists were prescribed as initial therapy to 16.6% of the patients (in monotherapy or in combinations). At the time of the visit, around 98% of the patients received at least one antiparkinsonian drug, and the proportion of monotherapies had fallen from 93.4% (initial) to less than 40%. In parallel, the proportion of combination of L-dopa and a dopamine agonist increased to 46.9%. Non-medicated treatments were also prescribed to a large proportion of patients (40%) with a predominance of physical therapy (37%) (Table 4).

Globally, 46 % of the patients were treated with at least one psychotropic drug, classified between: anxiolytics, atypical neuroleptics and antidepressants (Fig. 2).

Table 4

Current non-drug antiparkinsonian treatments (N = 1086)

Current non medicated treatment	**n (%)**
Physiotherapy	405 (37.3)
Patient advocacy groups	40 (3.7)
Speech therapy	32 (2.9)
Work therapy	23 (2.1)
Deep Brain Stimulation (DBS)	22 (2.1)
Psychotherapy	16 (1.5)

Overall, 34.1% of the survey patients were taking an anxiolytic drug (mainly alprazolam or clonazepam) and 26.4% received at least one antidepressant. No information was collected on the indication for prescription of those antidepressant preventing the assessment of the proportion of patients with previous episode of major depression. The antidepressants were divided into three classes: SSRI (51.9%, mainly escitalopram), non-selective monoamine reuptake inhibitor (41.3%, mainly trazodone) and tricyclic or related (6.4%, mainly amitryptiline). An atypical neuroleptic was given to merely 8% of the patients (mainly quetiapine or clozapine). Only 2% of the patients were following a psychotherapy. In this survey, more than 15% of the patients received two or more classes of psychotropic agent.

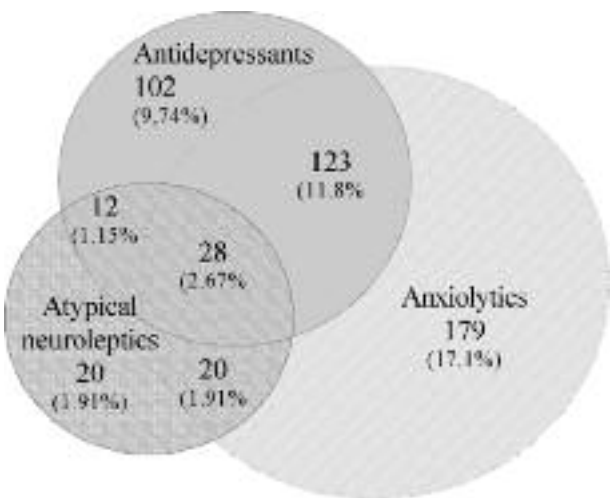

Fig. 2. — Distribution of PD patients taking psychotropic drugs: anxiolytics, antidepressants and/or atypical neuroleptics in the survey sample (N = 1057).

Table 5

Relationship of the prevalence of major depressive disorder (MINI) according to PD patient's neurological evaluation

Scales	N	Current depression		p-value
		Yes Mean ± SD	No Mean ± SD	
Hoehn and Yahr (max = 5)	1082	2.07 ± 0.92	1.82 ± 0.87	0.0008
UPDRS subscore (max = 65)	1081	13.1 ± 7.30	1.0 ± 6.60	0.0002
Schwab and England ADL (%)	1083	74.3 ± 19.3	82.4 ± 15.	<0.0001

Prevalence of major depression (primary objective)

To assess the prevalence of major depression in the survey population, patients had to answer during "on" state, the MINI questionnaire based on the DSM-IV. On the 1084 patients tested, 169 were diagnosed with a current episode of major depression leading to an overall prevalence of major depression of 15.6 % (95% CI: 13.4 – 17.8%).

Patients having been diagnosed as depressed with the M.I.N.I. underwent the MADRS questionnaire in order to assess the severity of their depression. More than half of them (54%) presented a moderate depression, 39% had a mild depression and only 7% presented a severe depression. Depression was significantly more frequent among women (18.7%) than men (13.0%) (p = 0.011) but the severity of the depression was not related to gender (means score 22.4 ± 7.0 for men *vs* 22.0 ± 8.1 for women, p = 0.76).

Relation between depression (prevalence/severity) and other parameters (secondary objectives)

Demography and disease history

No difference was seen between depressed and non-depressed PD patients for the mean age at time of symptoms appearance or of PD diagnosis nor for the predominant motor symptom at time of PD diagnosis. The small difference in duration of the PD disease between depressed and non-depressed patients (respectively 6.1 ± 5.2 years *vs* 5.0 ± 5.0 years) was statistically significant (p = 0.0009). However, no correlation was found between this duration and the severity of the depression (p = 0.87).

Neurological status

The scores of neurological evaluation were systematically worse in PD patients diagnosed with a major depressive episode (Table 5). For the Schwab and England ADL, the correlations between the scores and the severity of the depression were also significant (p = 0.005).

Treatments

Globally, the PD patients diagnosed with major depression in this survey received significantly more psychotropic drugs that the non-depressed PD patients. Antidepressants and anxiolytics were both used by more than 50% of the depressed PD patients (Table 6). From this table, it has been calculated that the proportion of major depression among patients already receiving an antidepressant was 34.6%. There was a trend between the use of an antidepressant and the severity of the depression (p = 0.06).

A descriptive analysis was performed to look at the prevalence of major depression in PD patients classified according to their current antiparkinsonian treatment. Figure 3 shows that the lowest prevalence was seen in the subgroup of patients receiving a

Table 6

Distribution of major depression according to patient's current psychotropic treatment

Treatment	Current depression		p-value
	Yes n (%)	No n (%)	
Antidepressant			
Yes (n=280)	97 (59.2)	183 (20.4)	< 0.0001
No (n=781)	67 (40.9)	714 (79.6)	
Anxiolytic			
Yes (n=365)	93 (55.0)	272 (30.2)	< 0.0001
No (n=705)	76 (45.0)	629 (69.8)	
Atypical neuroleptic			
Yes (n=85)	26 (16.1)	59 (6.60)	< 0.0001
No (n=971)	136 (84.0)	835 (93.4)	

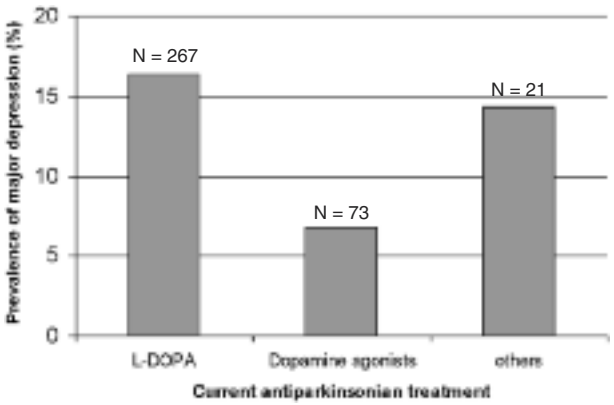

Fig. 3. — Prevalence of major depression regarding current antiparkinsonian treatment: levodopa in monotherapy, dopamine agonists in monotherapy or other monotherapies (N = 1055).

dopamine agonist in monotherapy (N = 73) and the highest prevalence was observed in those (N = 267) receiving levodopa alone. The survey was not powered to perform statistical comparison on these results.

Neuropsychiatric "off" non-motor symptoms

The predominant neuropsychiatric non-motor symptom in the "off" state in PD patients diagnosed with current major depression was depression/anxiety (81.9%). Similarly, presence of depression/anxiety in the "off" state was related to a higher prevalence (43 %) of major depression compared to other non-motor symptoms (24 to 27 %), and this despite a high rate of antidepressant use (61.1%).

Predictive factors of major depression in PD patients

Multiple logistic regression was applied to the data to uncover potential risk factors associated with depression in PD patients (Table 7). No association was found between the episode of major depression and demographic characteristics of the patient. In particular, disease duration and gender did not turn out to be risk factors. By contrast, antidepressant treatment, history of mood disorder and feeling of depression or anxiety during the "off" state were highly associated with a current episode of major depression.

Discussion

In our large scale survey, the prevalence of major depression according to the MINI questionnaire was found to be 15.6%. This percentage is similar to that of 17% found by the systematic review from Reijnders (Reijnders *et al.*, 2008) and slightly higher than the 9.9% observed in the PRODEST-PD study and using stricter criteria (Barone *et al.* poster MDS 2007). The prevalence of major depression in the PARKIDEP population is more than twice as high as that observed in primary care in Belgium and Luxembourg, measured with the same tool (6.3%) in 2002 (Ansseau *et al.*, 2005). In our survey, 30% of the patients had a history of mood disorder, which is close to the 27.8% observed with a history of depression in the PRODEST-PD population (Barone *et al.* poster EFNS 2007).

About half of the patients in our survey were receiving a psychotropic treatment at the time of the visit with a predominance of anxiolytics (34%) of which some might have been prescribed for Restless Legs Syndrome (e.g. clonazepam). The lower rate of atypical neuroleptics is explained by their controversial use in PD patients due to their dopamine antagonist effect. They might have been prescribed to treat drug-induced hallucinations (e.g. clozapine). A quarter of the patients (25.4%) received antidepressants, which is again in line with the 20.8% from the

Table 7

Relationship between presence of major depression and potential risk factors as derived from logistic regression analysis (N = 761)

Variable	Coefficient ± SE	Odds ratio	95% CI
Age (years)	0.02 ± 0.02	1.02	0.98-1.05
Gender (Men *vs.* Women)	-0.13 ± 0.13	0.77	0.46-1.30
Duration of the disease (years)	-0.03 ± 0.03	0.97	0.91-1.03
History of mood disorder (Yes *vs.* No)	0.44 ± 0.14	2.40*	1.41-4.10
Current antidepressant drugs (Yes *vs.* No)	0.48 ± 0.14	2.59*	1.50-4.48
Depression/Anxiety in "off" state	1.19 ± 0.15	10.9*	5.99-19.7

* $p<0.05$

PRODEST-PD study (Barone *et al.* poster EFNS 2007). This proportion increased to about 50% in those diagnosed with episode of major depression. One third of the PD patients receiving an antidepressant were still diagnosed with a major depression at the time of the visit. Background information on the start of treatment with antidepressants is lacking, therefore, the possibility of other indications or more severe depressive symptoms cannot be ruled out. Insufficient efficacy of antidepressant therapy in those PD patients however, cannot be excluded. With the exception of amitriptyline, which is not necessarily the first choice in parkinsonian patients, there is currently a lack of evidence to make recommendations regarding treatments for depression in PD (Miyazaki *et al.*, 2006). On the other hand, the high rate of patients with major depression who are not receiving an antidepressant (> 50%) might reflect the underestimation of depressive symptoms by the treating physician as well as by the patient him/herself. These underestimations were already observed in previous studies (GPDSSC, 2002; Shulman *et al.*, 2002). However, the question can be asked whether usual antidepressants remain the most appropriate treatment for mood disorders in the frame of PD (Weintraub *et al.*, 2005).

Interestingly, the prevalence of major depression increased only slightly with the score of Hoehn and Yahr. Both the Hoehn and Yahr and the UPDRS scores were slightly higher in patients with major depression. However, the difference in neurological status between the depressed and non-depressed patients was probably not clinically significant and no relation was found between the severity of the neurological status and the severity of the depression. The functional score of Schwab and England Activity of Daily Living (ADL) was significantly and clinically lower in patients with depression and a direct correlation was found between this score and the severity of depression. However, a conclusion about the causality relationship between depression and the loss of independence is not yet determined.

The results from the motor scales are in accordance with the results from previous studies (Celesia and Wanamaker, 1972; Starkstein *et al.*, 1990), where no relationship was seen between the prevalence of major depression or its severity and the severity of motor symptoms. These results are in favour of a biological etiology of depression in PD (Lieberman, 2006).

Major depression and other depressive disorders in the frame of Parkinson's disease have most probably a biological origin and cannot be fully attributed to a reactive phenomenon. There are several publications supporting a dopaminergic direct involvement in the depression of the PD patients (Starkstein *et al.*, 1990; Cummings, 1992; McDonald *et al.*, 2003; Lieberman, 2006). A depletion in dopamine neurotransmitter but not in serotonin neurotransmitter was previously measured in spinal fluid of depressive PD patients (Vanderheyden et al. 1980). More recently, a degeneration of the dopaminergic neurons projecting to the limbic and cortical structures from the ventral mesencephalon has been observed in PD patients with depression (Mann et Kapur, 1995, Remy *et al.*, 2005). Dopaminergic receptors D_3 are highly distributed in the limbic system (Willner, 1997) which is well described to play an important role in apathy, anhedonia and depression (Cummings, 1993). In PD, a decrease of dopamine in the limbic system might be the origin of depressive symptoms. Observations made in our survey that prevalence of depression was lower in subgroups of patients receiving a drug treatment mainly based on dopamine agonist as current treatment, supports this specific etiology. However, the analysis of potential confounding factors such as concomitant use of antidepressant or neurological status was not performed.

Despite a significant difference of prevalence between genders or in relation to duration of the disease, the characterisation of the profile did not show any of the patient's demographics nor of the three predominant motor symptoms to be associated with a higher risk for major depression. This result confirms previous observation (Lieberman, 2006). Impact of the various classes of antiparkinsonian initial and current treatment was not included in the regression analysis and should be further studied in view of our preliminary results.

Conclusions

The large scale PARKIDEP survey , shows that the prevalence of major depression is high in parkinsonian patients suffering from Parkinson's disease in Belgium. These results should draw physician's attention to the need to carefully follow up PD patients with a history of mood disorder or with a complaint of depression or anxiety during the "off" state because they are probably at higher risk of presenting major depression. Because depression in PD seems to have a common etiology with the motor symptoms, PD patients with poorer functionality should also be closely watched. A more rapid recognition of the symptoms and a specific treatment (preferably dopaminergic) of the Parkinson's disease associated depression would improve the quality of life of the PD patient.

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Ethical Approval

This observational survey has been submitted to and approved by ethics committees in all recruiting centres.

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