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ORIGINAL ARTICLE

# The PRIAMO study: background, methods and recruitment

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**Abstract** PRIAMO (PaRkinson And non Motor symptOms) is an epidemiology study aimed to assess the prevalence and incidence of non-motor symptoms (NMS) in patients with parkinsonism. PRIAMO consists of two phases: (1) a transversal assessment of the prevalence of NMS and (2) a longitudinal observation with two follow-up visits at 12 and 24 months to establish the incidence of NMS. A secondary aim of PRIAMO is to study the relationship between NMS and quality of life. Patients with parkinsonism have been evaluated in 59 Neurology Centres widely distributed throughout Italy. PRIAMO has analysed a total of 1307 patients (out of 1325 initially enrolled). We expect that PRIAMO will substantially help to quantify the burden of NMS in patients with parkinsonism.

**Keywords** Epidemiology · Incidence · Parkinsonism · Prevalence

*The members of the PRIAMO study group are listed in Appendix 1

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## Introduction

Treatment of Parkinson's disease (PD) has traditionally focused on the improvement of motor symptoms [1]. More recently, treatment has widened to include non-motor symptoms (NMS) such as neuropsychiatric, autonomic, sensory and sleep disturbances [2]. Despite the fact that NMS worsen quality of life (QOL) and increase management costs, they go undetected in 50% of PD patients [3–5]. In a recent series, every PD patient had at least one NMS and most had two NMS [6]. Moreover, there is evidence that the number and severity of NMS grow with increasing PD duration. Current knowledge about NMS in PD derives from studies performed in small series of patients and allows only limited inferences on the relationship between NMS and the severity of the underlying disease [7]. The PRIAMO study aims to fill this gap by studying prevalence as well as one- and two-year incidence of NMS in a large sample of patients with parkinsonism. A secondary aim of PRIAMO is to assess the relationship between NMS and QOL.

## Methods

### Study design

PRIAMO is a longitudinal study performed in 59 Neurological Centres widely distributed throughout Italy. It consists of two phases: (1) a transversal phase aimed to

assess the prevalence of NMS and (2) a longitudinal phase, consisting of two follow-up visits at 12 and 24 months, aimed to assess the incidence of NMS. The study protocol was approved by local ethical committees and participants gave written informed consent. Participating centres were selected not only on the basis of excellence in the treatment of PD but also on previous participation in clinical studies and proven ability in the administration of the study questionnaires (see next section).

## Subjects

Consecutive subjects of either gender aged ≥18 who had a diagnosis of parkinsonism based on UK Brain Bank criteria (namely presenting with bradykinesia with or without rigidity, tremor or postural instability) [8], independent of disease duration, were referred to the study centres between July 2005 and June 2006 and were eligible for the study.

The subjects could have other neurological symptoms in addition to parkinsonism provided they had appeared at least one year after the onset of the movement disorder. We did not include patients with essential tremor.

## Methods

Questionnaires were used to collect demographic, clinical and lifestyle data. NMS were assessed by means of a purposely developed structured interview exploring 12 types of symptoms (gastrointestinal symptoms, pain, urinary symptoms, postural hypotension and related symptoms, sleep disorders, fatigue, apathy, attention and memory, skin disorders, psychiatric symptoms, respiratory symptoms, other symptoms). Each symptom domain comprises from 2 to 10 questions with dichotomous (yes/no) answers. Symptoms assessed by neurologist were considered "present" according to patient response and clinical opinion. The NMS was developed on the basis of the available literature [2, 4, 7, 9] and the clinical experience of the PRIAMO researchers. For more detailed information about the NMS interview, see Table 1. Motor Symptoms were evaluated using part III of the Unified Parkinson's Disease Rating Scale (UPDRS), cognitive abilities using the Mini-Mental State Examination (MMSE) [10], frontal functions using the Frontal Assessment Battery (FAB) [11], depression using the Hamilton Rating Scale for Depression (HAM-D) [12] and DSM-IV, QOL using the EuroQOL-5D [13] questionnaire and the Parkinson's Disease Questionnaire (PDQ-39) [14] and anhedonia using the Snaith-Hamilton Pleasure Scale (SHAPS) [15]. Linguistic and psychometric validation of the SHAPS was performed during the PRIAMO study. PD patients were evaluated in three conditions: "untreated" (without dopaminergic treatment), treated but in stable motor conditions as well as treated assessed in the "on" state if they presented motor fluctuations. The centres adopted the same diagnostic criteria for the diagnosis of PD [16], mul-

**Table 1** Non-motor symptoms included in the Structured Interviewa

| Type | Characterisation | Number of items per domain |
|---|---|---|
| Gastrointestinal symptoms | Dribbling of saliva, difficulty in swallowing, nausea/vomiting, constipation, lowered number of evacuations (<3 times/week), bowel emptying incomplete, faecal incontinence | 7 |
| Pain | Undefined pain, pain to the inferior limbs, abdominal pain, pain related to intake of drugs (e.g., levodopa), experience of pain in shoulders during the night | 5 |
| Urinary symptoms | Urgency, frequency (voiding every 2 h), nocturia | 3 |
| Instability symptoms related to postural hypotension | Lightheadedness/dizziness during the postural changes, fall because of syncope | 2 |
| Sleep disorders | Behavioural sleep disturbances(REM), insomnia, falling asleep unintentionally during the day, urgency to move the legs that improves with movement | 4 |
| Fatigue | Fatigue limiting the patient's day activities | 1 |
| Apathy | Loss of interest in surrounding matters, lose of interest in activities of daily living, awareness deficit | 3 |
| Attention/memory | Difficulties in holding concentration, forgetting things or conversations done a short time ago, forgetting to do daily things | 3 |
| Skin disorders | Seborrhoea, hyperhydrosis | 2 |
| Psychic symptoms | Anhedonia, anxiety, panic attacks, aggressive behaviour, suicidal ideas, nervousness, frightened without reason, sadness/depression, delirium, hallucinations | 10 |
| Respiratory symptoms | Dyspnoea, cough, stridor | 3 |
| Miscellaneous | Olfactory disturbances, taste disturbances, diplopia, weight variation, sexual dysfunction | 5 |

[a] Copies of the Case Record Forms (CRF) are available from the authors upon request

tiple system atrophy [17], progressive supranuclear palsy [18], dementia with Lewy bodies [19] and corticobasal degeneration [20]. No attempt was made to standardise the diagnosis of secondary parkinsonism, nevertheless the identification of these patients was suggested to be made according to criteria proposed by Morgante et al. [21].

### Statistical analysis

Data management and statistical analysis is performed by MEDIDATA (Modena, Italy) using internal procedures and respecting Italian privacy legislation. Sample size calculation was based on the reported prevalence and incidence of selected NMS in PD and our expectation that 70% of PRIAMO patients would have PD. The least frequent NMS reported in PD is REM sleep behaviour disorder (9.7%). During the planning phase, sample size was estimated in order to have a relative error ≤20%. We calculated that 1800 patients with parkinsonism – corresponding to 1253 PD patients – were sufficient to detect a prevalence of 9.7±1.6% with 95% confidence interval. At the end of the enrolment period data from 1325 patients were gathered, of which 1307 were suitable for analysis. This sample size was considered to be satisfactory. In fact, 1307 patients with parkinsonism – corresponding to 910 PD patients – allow detection of a prevalence of 9.7±1.9% with 95% confidence interval (the relative error is still <20%).

The four-year incidence of dementia in PD is reported to be 23%. Assuming a linear trend, we estimated that 11.5% of our PD patients would develop dementia in 2 years. Nine hundred and ten patients with parkinsonism – corresponding to 435 PD patients – allow detection of an incidence of 11.5±3.0% with 95% confidence interval assuming a drop-out rate of 30% for every year of the study.

The prevalence of NMS at baseline and follow-up visits will be calculated and stratified by the underlying diagnosis. Incidence rates at one and two years will also be calculated and stratified by diagnosis. EuroQOL-5D and PDQ-39 scores will be compared between patients with and without NMS using Student' s *t*-test if variables are normally distributed and homoskedastic or by a Wilcoxon test if otherwise. Linear or rank-based correlation coefficients will be used to quantify the association between QOL, HAM-D and SHAPS scores. A generalised linear model (GLM) will be used to study the cross-sectional and longitudinal relationship between NMS (outcome) and questionnaire scores (predictors). Another GLM will be used to assess the relationship between MS (outcome, as detected by UPDRS III) and NMS (predictors). A comparison of patients with incident and remitting NMS will be performed regarding QOL.

## Current status

PRIAMO has analysed a total of 1307 of 1325 enrolled patients. Four of the 59 participating centres have withdrawn participation from the study. Data quality is high: 99% of patients were valuable for statistical analysis, physician- and self-compiled questionnaire availability ranged from 71 to 98% of enrolled patients. Most patients (60%) are men, with a mean (SD) age of 67 (9) years. Women (40%) have a mean (SD) age of 68 (9) years; 60% of patients have a low degree of education; 68% are retired; 76% are married or share their household with a partner; and 17% are widow or widower. Table 2 shows the distribution of clinical diagnoses as determined at the baseline visit. As expected, the most frequent disorder was idiopathic PD.

## Conclusions

PRIAMO is the first epidemiological study of NMS performed in a large sample of patients with parkinsonism. The use of multiple validated instruments to assess NMS is another strong point of PRIAMO as compared to available studies. The high rate of compliance to questionnaire compilation (≥71%) indicates great interest in this study from both patients and physicians. We expect that PRIAMO will substantially help to understand and quantify NMS in patients with parkinsonism.

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**Table 2** Clinical diagnosis distribution at the baseline visit

| Diagnosis | n | % |
|---|---|---|
| Idiopathic PD | 1130 | 86.46 |
| Vascular parkinsonism | 83 | 6.35 |
| Multiple system atrophy | 34 | 2.60 |
| Progressive supranuclear palsy | 30 | 2.30 |
| Dementia with Lewy bodies | 14 | 1.07 |
| Cortico-basal degeneration | 11 | 0.84 |
| Drug-induced parkinsonism | 3 | 0.23 |
| Parkinsonism related to other neurological disorders | 1 | 0.08 |
| Post-encephalitic parkinsonism | 1 | 0.08 |
| Total | 1307 | 100.00 |

***Sommario*** *PRIAMO (PaRkinson And non Motor symptOms) è uno studio epidemiologico con l'obiettivo di valutare prevalenza e incidenza dei sintomi non motori (NMS) in pazienti con parkinsonismi. Lo studio PRIAMO si compone di due fasi: (1) la prima prevede una valutazione trasversale della prevalenza dei NMS e (2) la seconda prevede un'osservazione longitudinale con due visite di follow-up a 12 e 24 mesi per stabilire l'incidenza dei NMS. Obiettivo secondario di PRIAMO è studiare la relazione tra i NMS e la qualità di vita dei pazienti che ne sono affetti. I pazienti con parkinsonismo sono stati valutati da 59 Centri Neurologici distribuiti su tutto il territorio italiano. In totale nello studio PRIAMO sono stati analizzati 1307 pazienti (rispetto ai 1325 arruolati dai centri). Da questi primi risultati ci aspettiamo che PRIAMO possa aiutarci a quantificare l'impatto dei sintomi non motori in pazienti con parkinsonismo.*

**Appendix 1** The PRIAMO study group

| | | |
|---|---|---|
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