Acta neurol. belg., 2006, **106**, 137-141

Detection of motor and non-motor symptoms of end-of dose wearing-off in Parkinson's disease using a dedicated questionnaire : a Belgian multicenter survey

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Abstract

In this report the usefulness of a dedicated questionnaire to detect end-of-dose wearing-off (EODWO) fluctuations in PD was studied. One hundred and sixty patients were administered an 18-item questionnaire encompassing both motor and non-motor phenomena. One hundred and eight (86%) reported EODWO, defined as the occurrence of at least one symptom improving by drug intake. Motor phenomena were significantly more frequent and non-motor phenomena never occurred in isolation. This questionnaire was deemed useful by most participants.

Introduction

Long-term treatment of Parkinson's Disease (PD) with levodopa is complicated by the development of motor complications, such as end-of-dose wearing-off phenomena, on-off fluctuations and dyskinesia. It is generally assumed that motor fluctuations occur in about 50 percent of patients after 5 years of levodopa treatment, and this proportion increases to 70 percent among patients treated for 15 years or more (1, 2), although in some reports higher proportions have been mentioned with shorter treatment duration. The evidence from both fundamental pharmacological research and from large-scale studies investigating the therapeutical effects of different dopaminergic agents indicates that the short-lasting and pulsatile action of levodopa is an important factor in the development of motor fluctuations (3).

Usually the first response fluctuation occurring during long-term levodopa treatment is the end-of-dose wearing-off phenomenon (EODWO). This phenomenon has classically been described as the recurrence of motor features of parkinsonism before the next levodopa intake. However, it is becoming more and more obvious that other, non-motor, phenomena may indicate EODWO. These non-motor features vary substantially from one patient to another, may occur as isolated phenomena (i.e. without motor symptoms), and be even more incapacitating than motor fluctuations (4-7). Non-motor features may include autonomic symptoms (perspiration, flushing, alterations of body temperature, abdominal discomfort, changes in blood pressure and heart rate, dry mouth), mental problems (bradyphrenia, anxiety, mood alterations, panic attacks) as well as sensory dysfunctions (pain, paresthesia). They are frequently missed as EODWO symptoms. Moreover, non-motor symptomatology may also appear during on-episodes, suggesting that adequate motor control not necessarily implies an adequate medication regimen.

Therefore a prospective, observational survey was started among movement disorder specialists in Belgium. The primary objective of this survey was to evaluate the usefulness and efficacy of a specially designed patient questionnaire to enhance early detection of motor and non-motor EODWO. Secondary objectives were to estimate the proportion of fluctuators in the total population of PD patients and to estimate within the group of fluctuators the proportion of patients suffering from motor and non-motor fluctuations.

Patients and methods

Twelve Belgian movement disorder specialist centres participated in this observational survey. Patients treated with levodopa in monotherapy or combined with other anti-parkinsonian medications could liberally be included, as far as they were on a stable drug regimen for at least 6 months. Although originally inclusion criteria limited the maximum daily dose of levodopa to 600 mg, enrolment of patients with higher daily doses was allowed later, although separate analyses for this subgroup were performed. The only formal exclusion criterion was previous or concomitant use of entacapone. This survey was approved by a central Committee for Medical Ethics, and written informed consent was obtained from all included patients.

The survey was performed during a single visit, and consisted of demographic data registration, Hoehn and Yahr staging and PD history. Subsequently a specifically designed questionnaire for motor and non-motor EODWO symptoms was collected (8). Patients were considered to suffer from wearing-off if at least one of the registered symptoms improved after the next dose intake. A subjective level of usefulness of the questionnaire was rated by the participating neurologist. Finally, neurologists were asked if clinical impression and EODWO questionnaire led to modifications of the treatment.

All registered data were analyzed by means of descriptive statistics. Statistical procedures were performed in SAS.

Results

A total of 160 PD patients were included in the survey. Daily levodopa doses were below or equal to 600 mg in 128 patients (subgroup 1). The remaining 32 patients received daily doses of levodopa above 600 mg (subgroup 2). Demographic data, as well as data of the medical history are presented in table 1. As expected, the patients of subgroup 2 had longer disease duration and longer duration of levodopa treatment than subgroup 1.

Figure 1 illustrates the results of the questionnaire and presents the percentage of patients reporting the presence of the individual symptoms as well as the percentage of patients improving after the next intake. The most frequently reported motor symptom was slowness of movement (81,9%). However the proportion of patients improving with the next intake was highest for tremor (76%). Anxiety, mood changes and dullness of thinking were the most frequently reported non-motor symptoms. Mood changes were the non-motor phenomena with the highest proportion of patients improving with drug intake. Calculated from these data the percentage of patients suffering from EODWO in the total population was 86,2%.

The distribution of EODWO patients roughly followed the distribution of the Hoehn and Yahr stages in the entire population as presented in table 1.

Although the number of subjects differed largely between both subgroups as defined above, an attempt was made to compare the frequency of motor and non-motor phenoma between subgroups. This was done by non-parametric tests. As expected the relative frequency of motor symptoms was higher in subgroup 2 ($p = 0.01$). However, there was no significant difference between both subgroups in the occurrence of non-motor symptoms ($p = 0.11$). In subgroup 1, motor symptoms responded significantly more frequently to the next levodopa intake than non-motor symptoms ($p = 0.01$). This was not the case in subgroup 2 ($p = 0.14$). As a whole motor symptoms improved to levodopa intake equally well in both subgroups ($p = 0.77$), but the improvement of non-motor symptoms to medication administration was significantly higher in subgroup 2 ($p = 0.01$).

Table 2, illustrating the co-occurrence of motor and non-motor symptoms, demonstrates that in most patients both motor and non-motor symptoms occurred simultaneously. About 10% of the patients only had motor symptoms. None of the patients in this sample reported non-motor symptoms in the absence of motor symptoms.

Principal component analysis was performed in order to reduce the number of items representative of the entire questionnaire. From this study a significant reduction of items was deemed not possible as the use of nine components explained only 70% of the variation in the questionnaire.

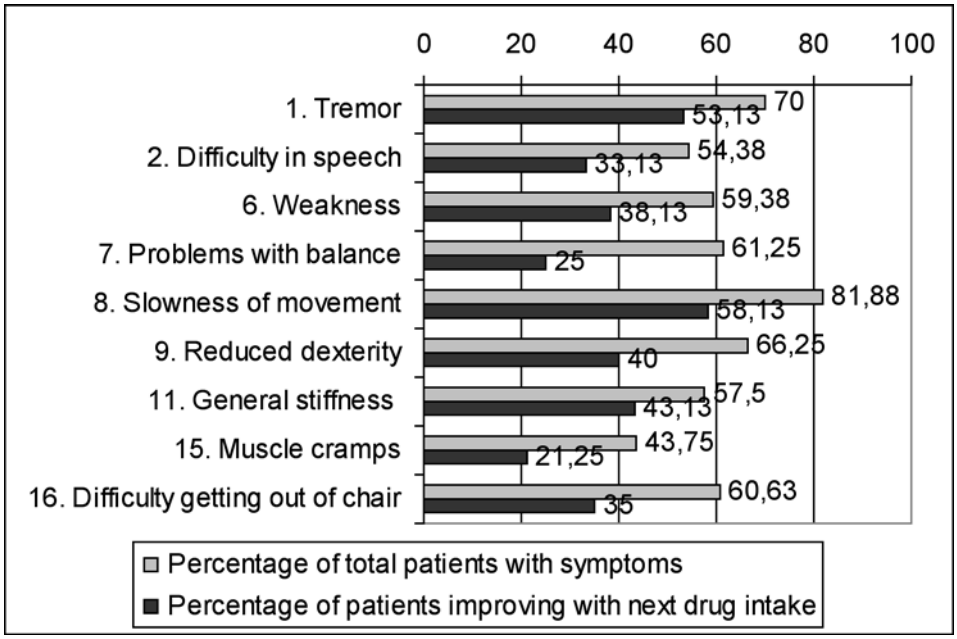
From fig. 2 it is clear that a majority of the participating neurologists considered the questionnaire as useful or very useful in detecting EODWO, more so for non-motor phenomena (61%) than for motor symptoms (56%).

The participating neurologists intended a change of treatment in 60,6% of the patients. In 34,4% of patients the questionnaire urged the neurologist to alter the treatment.

Discussion

EODWO fluctuations were extremely frequent (86%) in the cohort of PD patients studied in this report. They were reported in all stages of the disease. The population however may have been biased by the restriction of this study to movement disorder specialists, leading to inclusion of more advanced cases. Moreover attrition bias may have resulted in increased reporting of patients already mentioning EODWO symptoms in informal history. However, it is clear from the existing literature that EODWO is under-recognised in routine clinical practice. Moreover, most participating neurologists found the use of the dedicated questionnaire useful or very useful, indicating that at least a number of cases would have been missed in everyday consultation. Furthermore, the questionnaire may urge the neurologist to change the patient's treatment, which indicates the potential impact on patient management.

Both motor and non-motor phenomena occurred in a large proportion of patients. By the use of this questionnaire motor symptoms were reported slightly more frequently than non-motor phenomena, with non-motor phenomena never occurring in isolation. This contradicts previous reports mentioning the presence of isolated non-motor phenomena as EODWO symptoms. Overall the response of motor phenomena to drug intake was higher than that of non-motor phenomena. A clear explanation for the latter finding is lacking. Perhaps the



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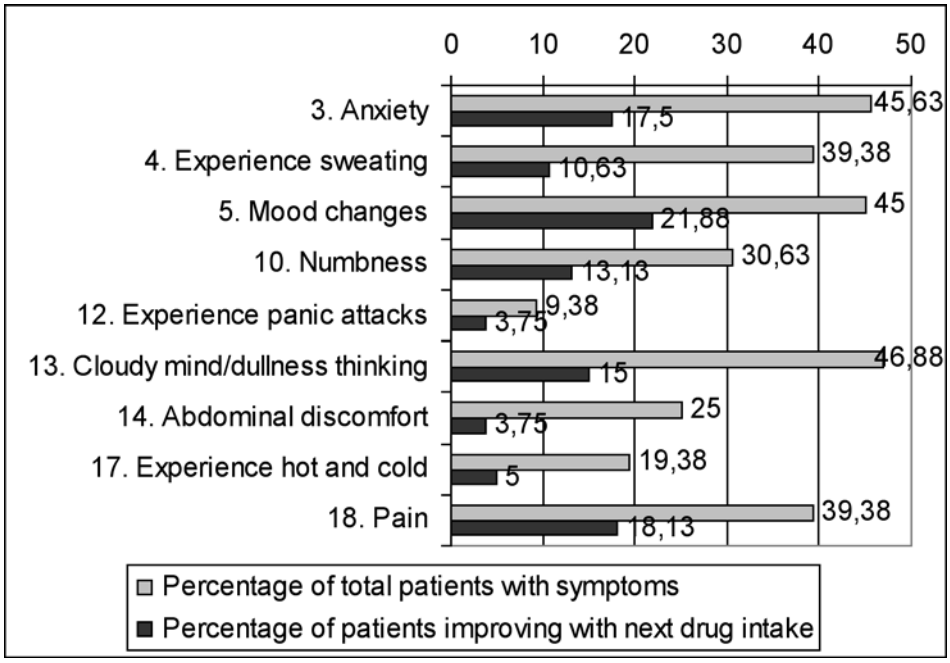

B

FIG. 1. — Results of the questionnaire : item per item illustration of the percentage of patients suffering from individual symptoms and of the percentage demonstrating improvement of the symptom after the next intake of antiparkinson medication. A : Motor symptoms. B : Non-motor symptoms.

improvement of non-motor phenomena is less well appreciated by patient or examiner than a clear motor improvement. An alternative hypothesis might be that non-motor phenomena respond less rapidly to medication administration, so that a clear relation with medication intake would be less straightforward. Finally, as mentioned above, the motor-defined on-status might not be totally representative of an optimal situation.

Although the interpretation of our results is hampered by the difference in sample size of both subgroups, it seems that motor symptoms respond to levodopa administration in all stages of the disease, while non-motor symptoms are reported to respond more frequently in later stages of PD. Indeed, our results suggest that non-motor symptoms in more advanced PD improve equally well to medication intake than motor symptoms.

This 18-item questionnaire seems useful for the early detection of EODWO in general practice. Its administration is easy and completes the routine history taking of patients with PD. The results of this study prompt its use in a wider range of patients and neurological practices. For this purpose abbreviated versions of this questionnaire are being tested. In the population studied here, a

Table 1

Demographic data of the included patients

	Total group (N = 160)	Subgroup 1 (N = 128)	Subgroup 2 (N = 32)
Age (years)			
Mean (SD)	67.7 (9.3)	67.5 (9.2)	68.8 (9.9)
Range	32-88	32-88	46-84
Duration of PD (years)			
Mean (SD)	8.5 (5.5)	7.4 (4.9)	12.9 (5.8)
Range	1.0-26.0	1.0-6.4	3.0-26
Hoehn and Yahr Stage (%)			
I	2.5	3.1	0
II	37.5	42.2	18.7
III	38.1	35.1	50
IV	16.2	13.3	28.1
V	0	0	0
Unknown	5.6	6.2	3.1
Time since start levodopa (years)			
Mean (SD)	8.2 (6.0)	6.7 (5.1)	13.5 (6.0)
Range	0-26	0-24	3-26
Daily dosage of levodopa (mg)			
Mean	470.7 (236.2)	376.4 (135.0)	848.3 (166.4)
Range	0-1200	0-600	650-1200
Number of pts treated with			
Agonist (%)	96 (60)	76 (59.4)	20 (62.5)
Anticholinergics (%)	7 (4.4)	7 (5.5)	0 (0)
Amantadine (%)	13 (8.1)	10 (7.8)	3 (9.4)
Selegiline (%)	20 (12.5)	17 (13.3)	3 (9.4)

Table 2

Cross-tabulations of motor by non-motor symptoms

Cross tabulation of motor by non-motor symptoms : % occurrence All patients			
	Non-motor symptoms		
Motor symptoms	Not Present	Present	Total
Not present	1.25	0.00	1.25
Present	9.38	89.38	98.75
Total	10.63	89.38	100.00

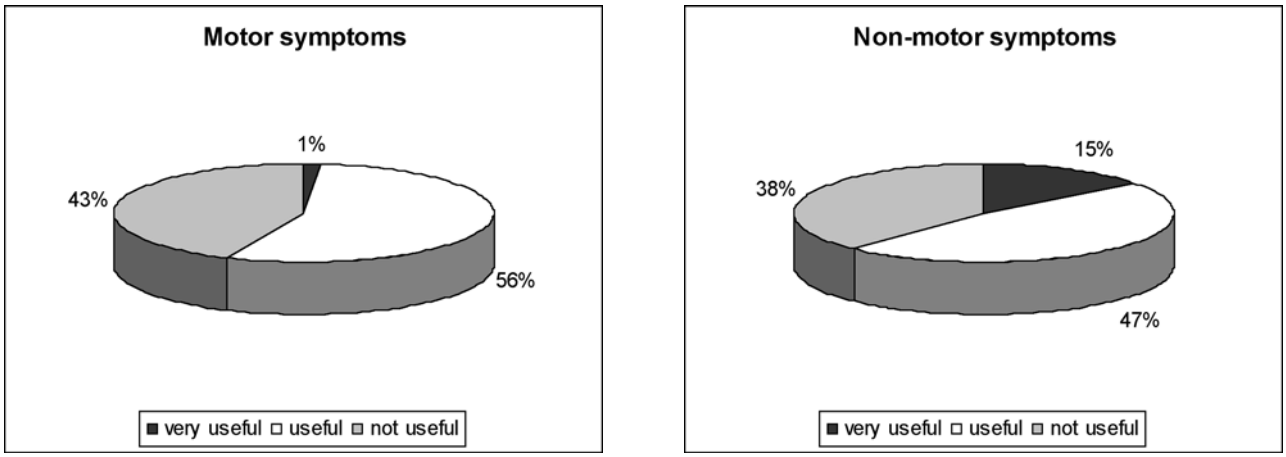

FIG. 2. — Subjective impression of the usefulness of the questionnaire as reported by the participating neurologists

reduction of items was not possible by means of principal component analysis. This, however, should not automatically lead to the conclusion that abbreviated versions are less reliable in a general neurological consultation. Indeed, the patients in this study were selected from movement disorder specialist sites, which may have led to the inclusion of more advanced patients. The issue is therefore a matter of further investigation. However, the role of introducing a dedicated questionnaire in raising the awareness of EODWO in PD seems undoubted.

Acknowledgement

The study was supported by Novartis Pharma, who provided the questionnaires and organized a consensus meeting for the EODWO study group. Statistical analysis was performed by G.Byttebier, GBSC, Oostakker.

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Appendix

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