Identification of wearing-off manifestations (reduction of levodopa effect) in Parkinson's disease using specific questionnaire and comparison of the results with routine ambulatory evaluations

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ABSTRACT

This study had the objective to verify if the presence of wearing-off phenomenon in patients with Parkinson's disease (PD) could be better identified by the administration of the "Wearing-off Questionnaire Card" (QC). The participant patients were first evaluated by resident doctors in neurology and then invited to answer the QC for detection of motor and nonmotor wearing-off manifestations. Seventy and nine patients were enclosed in the study. The questionnaire revealed that 63 patients (80%) presented wearing-off, whereas the consultation by the resident doctors only identified 33 subjects (41%) with this phenomenon. The motor wearing-off manifestations were more frequent then the nonmotor. We conclude that the administration of the QC in patients with PD may be a useful tool for the diagnosis of wearing-off phenomena.

Key words: Parkinson's disease, wearing-off, nonmotor fluctuations, screening.

Identificação de manifestações de wearing-off (redução do efeito da levodopa) em pacientes com doença de Parkinson utilizando questionário específico e comparação dos resultados com avaliações ambulatoriais de rotina

RESUMO

Este estudo teve como objetivo verificar se a presença do fenômeno wearing-off em pacientes com doença de Parkinson pode ser melhor identificada pela aplicação do cartão questionário wearing-off (QC). Os pacientes participantes foram avaliados pelos médicos residentes em neurologia e depois foram convidados a responder as questões do QC para detecção das manifestações motoras e não motoras do wearing-off. O número de pacientes estudados foi de 79. O questionário revelou que 63 pacientes (80%) apresentaram wearing-off, enquanto que a consulta dos residentes identificou apenas 33 indivíduos (41%) com este fenômeno. As manifestações motoras foram mais freqüentes do que as não motoras. Nós concluímos que a aplicação do QC em pacientes com doença de Parkinson pode ser uma ferramenta útil para o diagnostico do fenômeno wearing-off.

Palavras-chave: doença de Parkinson, wearing-off, flutuações não motoras, rastreamento.

The introduction of levodopa at the end of the sixties represented a milestone for the therapeutic management of Parkinson's disease (PD). But soon after, side effects were observed with the use of this drug such as fluctuations (dyskinesias and wearing-off phenomena)[1], and neuropsychiatric complications [2-4].

The wearing-off phenomenon, which is the reduction of the effect of levodopa or dopaminergic agonists, is one of the fluctuations manifestations and occurs when

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the benefit of the given dose of levodopa or dopaminergic agonists decay before the next intake[1]. In the early stage of the disease, the therapeutic effect of a single dose of levodopa is stable and long lasting, sometimes for more than four hours. This duration surpasses the plasmatic half-life of levodopa (approximately 60 to 90 minutes)[5].

The reasons for these complications are not completely well understood and they are possibly related to the reduction of dopaminergic cells and chronic use of levodopa or dopaminergic agonists. With the progression of the disease, the duration of the effect of each dose of levodopa is progressively reduced and reaches the plasmatic half-life of the drug, even though the pharmacodynamics zof the drug is unaltered during the course of the disease[6,7].

After ten years of levodopa intake, 80 to 100% of the patients develop wearing-off and dyskinesias[8,9], but these phenomena may appear after one or two years of the introduction of the medication in up to 50% of the patients[1,10]. Patients with earlier onset of PD are more susceptible to develop fluctuations[10]. Other risk factors for the development of wearing-off and dyskinesias are: severity of the disease, one daily intake of levodopa, and duration of levodopa therapy[10,3].

Although fluctuations are mainly recognized by the motor manifestations, they are not only restricted to the motor symptoms. Nonmotor fluctuations may also be identified and are classified into three categories: disautonomic, mental (cognitive and psychiatric), and sensorial/ painful[11].

Even though wearing-off is frequent, motor and nonmotor components may not be adequately recognized by the physicians. Besides, there are currently no tools to detect nonmotor symptoms. Therefore, we tested the Wearing-off Questionnaire Card (QC) adapted to Portuguese, an aid for the detection of these fluctuations, in PD patients[12].

The Wearing-off Questionnaire Card comprehends of 19 questions related to motor and nonmotor symptoms of wearing-off developed by Stacy and Hauser[12] and came from the original questionnaire with 32 symptoms[1]. This latter was designed by movement disorders specialists from Europe and United States, and based on reviews they came up with 32 symptoms and signs related to motor and nonmotor aspects of wearing-off phenomena[1].

Keeping the effort to guarantee the patient perception for some symptoms, some redundancies were allowed during the preparation of the original questionnaire. The wearing-off symptoms were listed randomically and their presentation to the patients were followed by succinct explanations with graphics which illustrated the temporal pattern of wearing-off phenomena in relation to levodopa intake.

The 32 items questionnaire was then tested[1]. The working group which created the Wearing-off Questionnaire simplified it for a shorter version. Since the original extension could compromise its administration, a new 19 items card was developed[12].

The symptoms maintained in the new questionnaire were the ones considered to have sensitivity for the diagnosis all wearing-off phenomena. Sixteen out of thirty two original questions tested in 300 patients were present in all individuals with wearing-off[1] .Subtracting the redundant items, 13 in total, the remaining ones guaranteed the detection of these phenomena in all patients presenting fluctuations and consequently they were inserted in the new questionnaire. A regression analysis was performed to identify other symptoms, besides the 13 items already mentioned, which contributed for the patients discomfort in such intensity that they require treatment adjustments. After all this process, 19 symptoms were obtained[12]. In this present study we tested the 19 items Wearing-off Questionnaire Card translated into Portuguese in PD patients.

METHOD

Seventy and nine patients were randomly selected from the Clinic of Movement Disorders of the Department of Neurology of the University of São Paulo School of Medicine during the period of May to December of 2006. In total 81 patients were invited to participate but two could not answer the questionnaire for logistic reasons. The enrolled participants were older then thirty years, literate, in use of levodopa therapy, and signed the informed consent forms. The study was approved by the ethical committee of the Hospital das Clínicas of the University of São Paulo School of Medicine. The inclusion criteria for PD were in accordance to the United Kingdom Parkinson's Disease Society brain bank diagnostic criteria[13]. For rating the severity of PD, Hoehn and Yahr modified scale was adopted.

Although the questionnaire was designed to be self-rated, in this study it was administered by one examiner specialized in movement disorder. The enrolled patients indicated (when answering the QC) if one or more referred symptoms of PD listed in the questionnaire improved after taking a new dose of levodopa and if these variations were present routinely. Therefore, if the referred symptom improved after taking the medication, this indicated the presence of wearing-off phenomena. The patients were also asked to answer which symptoms were more disturbing in their daily life and if other symptoms not listed also bothered them.

Before the interview the patients went through routine follow-up with their doctors who were fellow residents at the Clinic of Movement Disorders of the Department of Neurology of Hospital das Clínicas of the University of São Paulo School of Medicine. These physicians were unaware of this study. When the residents fin-

ished their evaluation the following question was asked: *the patient you just saw presented wearing-off phenomena?* Their answer was compared to the data obtained by the questionnaire with the intention to verify if the card could help to better identify wearing-off phenomena.

RESULTS

Seventy nine patients were interviewed and the age ranged from 46 to 79 years old (mean=63.8, standard deviation=8.1). Twenty three patients were female (29%). The duration of the disease varied from 4 to 33 years (mean=12.4, standard deviation=6.8). The age of onset of the first symptom ranged from 30 to 70 years old (mean=51.5, standard deviation=10.1).

The education level of the interviewed patients was: nine patients had college degree (11%), four patients high-school degree (5.06%), eight (10%) elementary school degree, and fifty two (65.8%) patients did not complete the elementary school education. The duration for the completion of the questionnaire varied in accordance to the degree of the patient's education level and ranged from 3 to 10 minutes. The more educated the less it took to complete the card. Before the administration of QC a brief explanation was given about wearing-off.

Four patients (5%) were in Hoehn and Yahr stage 1.5; twenty and seven (34.1%) in stage 2; twenty and three (29.1%) in stage 2.5, and twenty and two in stage 3. Only 2 patients were on stage 4.

The result was later checked with the resident doctors and the presence or absence of wearing-off was congruent in 49 cases (62%). From the forty nine cases, 33 (41.8%) were congruent to the presence of wearing-off and 16 (20.25%) for the absence of this phenomenon. The card revealed that 63 (80%) of the 79 patients evaluated had wearing-off. All patients with wearing-off identified by the resident doctors were also detected by the questionnaire.

We calculated the sensitivity and specificity of the resident doctor's evaluation for the identification of wearing-off in comparison to the ones obtained with the QC. The sensitivity of the resident doctor's consultation was 52% and the specificity was 100% (confidence interval of 95%).

When the patients were asked about the symptoms not listed in the QC but which could also lead the discomfort, the most reported ones were dyskinesia, falls, and freezing (Table 1).

According to the patients, from all the symptoms related to the disease and the treatment included or not in the QC, the ones which most led to discomfort were: slowness, tremor, difficulty to move, and rigidity (Table 2).

All the patients with wearing-off presented at least one of the motor manifestations related to this complication. Forty and five (71%) presented at least one mental symptom (cognitive or psychiatric), forty two (66%) reported at least one sensory-painful manifestation, and eleven (17%) had at least one disautonomic manifestation included in the card (sweating).

The graphic in the Figure 1 compare the frequency of each wearing-off symptom between two groups. One sub-

Table 1. Symptoms not listed in the questionnaire, but also troublesome to the patient.

Manifestation	Frequency
Dyskinesia	15.18%
Falls	11.39%
Freezing	7.59%
Constipation	3.79%
Posture alterations	3.79%
Nightmares	2.53%
Erectile dysfunction	2.53%
Increase in libido	2.53%
Difficulties to move on bed	2.53%
Somnolence	2.53%
Festination	1.26%
Hallucinations	1.26%
Urinary dysfunctions	1.26%
Insomnia	1.26%
Depression	1.26%

Symptoms not listed in the questionnaire, but also bothering.

Table 2. Symptoms which lead to more discomfort.

Manifestation	Frequency
Slowness	41.77%
Tremor	30.37%
Difficulty to move	18.98%
Rigidity	12.65%
Pain	8.86%
Dyskinesia	6.32%
Falls	5.06%
Disabilities	3.79%
Anxiety	3.79%
Wearing off	3.79%
Weakness	2.53%
Cramps	2.53%
Dullness thinking	2.53%
Dependence	1.26%
Freezing	1.26%
Difficulties to move on bed	1.26%
Nausea	1.26%
Abdominal pain	1.26%
Repetitive speech	1.26%

Symptoms which lead to more discomfort.

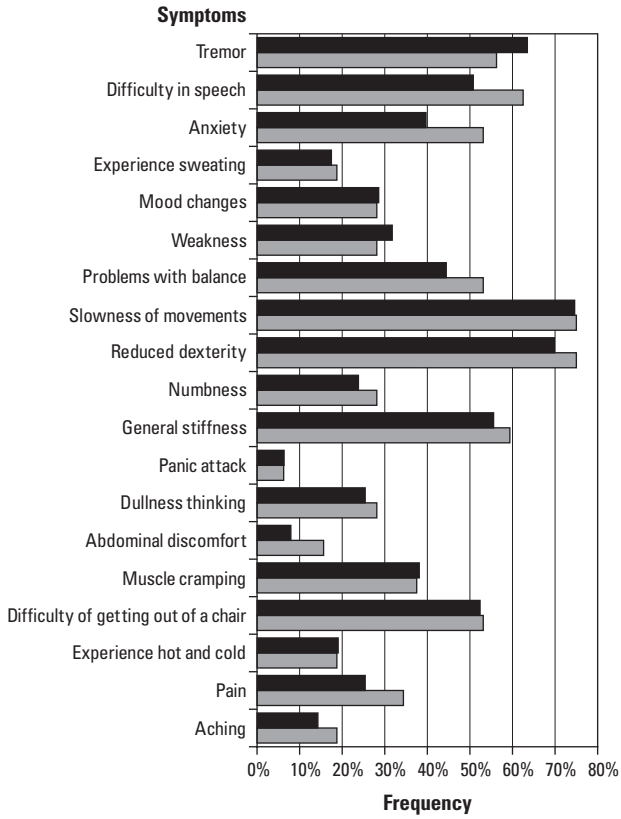

Figure. Frequency of wearing-off manifestations detected by resident doctors consultation (gray) and by the administration of the questionnaire (black).

group represents the patients whose wearing-off symptoms were diagnosed by the card administration, and the other subgroup the one in which the symptoms were identified during the routine consultation. The graphic reveals that the most common symptoms were the motor ones. From the nonmotor wearing-off manifestations, anxiety was the most frequent. After calculating the positive and negative predict values for each wearing-off manifestation, it was not possible to determine which symptom would help to identify the phenomena in the routine consultation ($p>0.05$), this fact may be due to the small number of patients selected for this study, although symptoms related as sensory-painful (such as pain and abdominal discomfort), and anxiety were more evident in the subgroup of patients in which the resident doctors made the diagnostic of wearing-off.

DISCUSSION

The main purpose of this study was to evaluate if the Wearing-off Questionnaire Card (QC) could be a good tool to identify the wearing-off phenomena. We considered wearing-off when at least one of the patient's listed symptoms improved after taking a new dose of dopamine agonist or levodopa. For the investigation of these fluctuations only patients taking at least levodopa were selected.

Using the QC, wearing-off phenomena were identified in 80% of patients meanwhile the anamnesis taken by the resident doctors only recognized fluctuations in 40.5% of cases. Therefore in the routine consultation the presence of these manifestations are less susceptible to be detected.

Stacy and cols[1], reported that the original questionnaire comprising 32 items, revealed that 57.1% of 300 PD patients evaluated had wearing-off symptoms while the routine interview performed by the movement disorder specialist detected them in 29.4% of the cases. The frequency of wearing-off was lower in their study in comparison to ours, independently of the interview methods chosen. This difference possibly occurred because our group of patients was more heterogeneous in duration and severity of the disease.

It is worth pointing that the routine consultation identified fluctuations in only half of the cases identified by the questionnaire in both situations, either using the 32 questions card or, as in our case,the 19 questions one.

Stacy et al utilized a broaden questionnaire containing 32 questions which was the basis and adaptation for the 19 items questionnaire adopted in our study. Although there are no studies comparing both the complete and shorten version of the QC, the last one does not seem to alter the sensitivity in comparison to the larger version, since the reduction was accomplished after meticulous statistical methodological analysis[12]. Moreover the questionnaire could be shorten even more without loosing its sensitivity according to what we have seen in our study. If only the motor wearing-off symptoms items were asked they would have detect all the patients with wearing-off. The reduction would simplify and fasten the administration of the questionnaire. But a reduction in the number of questions may reduce attention for the nonmotor symptoms of wearing-off, which also bother some patients, as could be noted in the Table 2 and in the Figure.

The higher sensitivity revealed by the administration of the questionnaire in our study may be attributed to the variety of listed symptoms and to the application method in which the examiner participated directly asking the questions as opposed to Stacy's study[1] in which the questionnaire was self-administered. This procedure was adopted because the education level of our patient was low and the patients could face some difficulty to answer to the questionnaire.

The doctor may apply the QC either choosing the self-administration or questioning method. We could have stratified the patients into subgroups according to their level of education. The patients with higher degree could self-administer the QC, meanwhile to the lower ones it could be administered by the examiner doctor. This practice could measure the impact of the doctor's participation in the sensitivity of the questionnaire. At the same it

could measure how the education level would influence on the identification of wearing-off phenomena.Once the purpose of this study was to answer the question if QC is a useful tool to identify wearing-off phenomena, we chose to not stratify the patients in subgroups since this would only measure the sensitivity and specificity of the administration method in accordance to patient's education level. Therefore we could consider the use of the questionnaire as an aiding tool to detect the presence of wearing-off phenomena and correlated manifestations, including nonmotor symptoms.

The routinely consultation performed by the resident doctors is broaden and has to carry for all the other aspects of PD so, the attention for wearing-off symptoms may be diluted during their interview (Table 2). Another detail is that the resident's evaluation only screened the more impacting wearing-off symptoms but the questionnaire lists all symptoms including the milder ones since it was design to detect the presence of wearing-off phenomena, not the severity. Duration, frequency and the relevance of wearing-off were not the scope of this questionnaire.

The correct detection of wearing-off must be performed in inward patients. It must correlate the fluctuation symptoms and the intake of levodopa. This procedure is very expensive but it is the only way to test the real sensitivity of the QC. According to Stacy et al.[1], the develop QC is the most sensible method for the detection of wearing-off in outpatients and has a good reliability.

Since it is very easy to use the questionnaire, it may be administered in routine consultation as a tool to improve the quality of the interview. Besides, to detect the wearing-off symptom it is necessary to have positive answer in two questions referring to a specific symptom. This process is easy for the patient to comprehend and may avoid duplicities and misunderstandings.

The importance of nonmotor symptoms of wearing-off was demonstrated in many studies[1,11,14,15,17] and it is important to emphasize that for some patients they cause more discomfort than the motor complications[15]. Besides, these symptoms may manifest independently of motor fluctuation[1] however, their frequency tends to increase according to the worsening of motor symptoms[1]. In the present study nonmotor wearing-off symptoms was only found in patient with motor complications. The Figure depicts the high frequency of some nonmotor wearing-off symptoms such as cramps and anxiety. It is also important to mention that cramps are probably related to dystonia caused by the reduction of plasmatic level of levodopa.

In Table 1 and 3 we can observe that the motor manifestations are more frequently mentioned as the main cause for the decline in patient's quality of life. Table 2 shows that many of the symptoms which bother PD patients could be related to wearing-off phenomena. This table also demonstrates indirectly the impact and significance of wearing-off in the quality of life of the patients.

Although the QC is not validated in Portuguese language and our translation could potentially hinder the understanding of certain items of the questionnaire for the Brazilian patients, it has not affected the sensitivity and specificity of the QC since the patients reported no difficulty to comprehend the symptoms listed in our version of the questionnaire.

This study showed that wearing-off phenomena was under recognized by the resident doctors. This result is similar to the one obtained by Stacy et al.[1] in multicenter study which revealed smaller detection of wearing-off by the movement disorder trained neurologist during routine consultation. The Wearing-off Questionnaire Card is a tool of easy administration for the identification of wearing-off manifestations and takes approximately 5 minutes for its completion. A better recognition of wearing-off complications may improve patient's quality of life since it will lead to better identification of patient's symptoms and therapeutic changes. This is the first study conducted in Brazil for this purpose. We may conclude that the questionnaire card helps to diagnose the wearing-off phenomena in PD patients.

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