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Development of a Patient Questionnaire to facilitate recognition of motor and non-motor wearing-off in Parkinson's disease

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Summary We previously reported that the use of a specifically designed Wearing-Off Questionnaire (WOQ) identified symptoms of wearing-off more frequently than standard assessments conducted by movement disorder specialists during a routine office visit. In the previous study we used a WOQ of 32 symptoms; however this tool was not designed for daily use. In this paper we describe the retrospective development of a simpler, 19-symptom WOQ more suitable for routine clinical use.

Keywords: Parkinson's disease, wearing-off, non-motor fluctuations

Introduction

The first few years of medical therapy for Parkinson's disease (PD) are often referred to as the 'honeymoon phase' because patients generally enjoy sustained, reliable symptomatic relief with dopaminergic therapy. Although the choice of initial therapy varies depending on the age and health of the patient, it is generally agreed that the most effective treatment for the symptoms of PD is levodopa (Agid et al., 2000; Goetz et al., 2005).

However, within 2–5 years of dopaminergic therapy, whether with levodopa alone or levodopa and a dopamine agonist, many patients begin to notice a decline in the duration of benefit with each medication dosing cycle, a phenomenon termed 'wearing-off.' When this occurs, rather than experiencing a smooth and sustained response to medication, patients often notice predictable 'motor fluctuations' – from 'on' time, when parkinsonian symptoms are minimized, to 'off' time, when symptoms recur. Typically, patients report a predictable return of motor or non-motor symptoms occurring before their next dose of medication is due, which usually means 2 or more hours after the last dose of medication. These symptoms then improve 15–45 minutes after the next dose of medication.

While it is clear that long-term levodopa therapy is associated with the emergence of these complications, there is wide variability in the literature regarding the incidence of these potentially troublesome symptoms (Ahlskog and Muenter, 2001). For many years it has been held that 50–80% of PD patients develop motor complications within 5–10 years of therapy (Marsden and Parkes, 1977). However, more recent studies report that 38–50% of patients develop symptom re-emergence within only 2 years of therapy (Parkinson Study Group, 1996, 2000). Importantly, the symptoms of wearing-off are neither well established nor the same for all patients, and therefore may not be readily recognized. For some patients, wearing-off is characterized by a return of motor symptoms, such as tremor, rigidity, or bradykinesia. However, wearing-off symptoms frequently also include non-motor symptoms such as anxiety, fatigue, mood changes, difficulty in thinking, restlessness, sweating or increased salivation. Indeed, a recent study reported that 100% of patients with motor fluctuations also experienced fluctuations of non-motor symptoms (Witjas et al., 2002).

In a comprehensive review of PD literature concerned with motor complications, Ahlskog and Muenter determined that there is no uniform agreement regarding the optimal methodology for ascertaining levodopa-related

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complications (dyskinesia and motor fluctuations) (Ahlskog and Muenter, 2001). When one considers that the emergence of motor complications not only impacts patients condition but also directly increases healthcare utilization costs (Dodel et al., 2001), it is important that physicians recognize the development of these symptoms in a timely manner in order to treat and manage them effectively. More over, recent advances in our understanding of the development of treatment complications have helped develop new strategies to reduce or delay them (Olanow and Stocchi, 2004).

We have previously reported that the use of a specifically designed wearing-off questionnaire (WOQ) identified symptoms of wearing-off more frequently than standard assessments (including UPDRS) conducted by movement disorder specialists during a routine office visit (Stacy et al., 2005). In the previous study we used a WOQ of 32 symptoms (WOQ-32), however this tool was developed to evaluate the study hypotheses and was not designed for daily use. In this paper we describe the retrospective development of a simpler, 19-symptom WOQ more suitable for routine clinical use.

Methods

Design of the WOQ-32

A panel of ten movement disorder specialists (A. Bowron, M. Guttman, R. Hauser, J.P. Larsen, P. LeWitt, W. Oertel, N. Quinn, K. Sethi, M. Stacy, and F. Stocchi) from Europe and North America met in person on three occasions and participated in one conference call to develop a prototype Patient Questionnaire based on a review of the literature and a consensus view of the most common motor and non-motor symptoms associated with wearing-off.

All 32 of the motor and non-motor symptoms (Table 1) identified by the panel were incorporated into a four-page prototype WOQ that included a brief set of instructions and definitions, as well as a representative graph illustrating a classic pattern of wearing-off fluctuations. For the purposes of evaluating this tool, the group defined wearing-off as any ($\geq$1) of the 32 symptoms that the patient currently experienced during their normal day and which improved or resolved following a dose of antiparkinsonian medication.

Patients

The utility of the WOQ-32 was evaluated in 300 male and female patients with idiopathic PD who were at least 30 years of age and had a duration of illness of less than 5 years (60 months). The questionnaire was only evaluated in specialist Movement Disorder centers participating in the Ali Project. These centers routinely use a systematized Parkinson's disease data evaluation tool to capture clinical data for research purposes (Thomas et al., 2002). Participating centers in the present evaluation were the Muhammad Ali Parkinson Research Center in Phoenix, Arizona, USA and the Boca Raton Parkinson Center in Boca Raton, Florida, USA. All participating subjects gave written informed consent regarding participation in Ali Project database studies prior to initial subject enrollment, according to the St. Joseph's Hospital Institutional Review Board, Phoenix, Arizona, USA. All subject visits and WOQ-32 evaluations were completed between December 2, 2002 and March 24, 2003.

Table 1. *Wearing-off symptoms in Parkinson's disease*

Number	Symptom
1	Reduced dexterity
2	Tiredness
3	Difficulty in getting out of the chair
4	Muscle cramping
5	Cloudy mind or dullness in thinking
6	Difficulty in speech
7	Pain
8	Slowness
9	General stiffness
10	Panic attacks
11	Chest discomfort
12	Abdominal discomfort
13	Sweating
14	Tremor
15	Slowness in the early morning
16	Slowness of movement
17	Slowness during the night time
18	Restlessness
19	Problems with balance
20	Slowness of thinking
21	Bladder problems – problems passing urine
22	Early morning muscle cramps in the feet or legs
23	Stiffness in the early morning
24	Stiffness in the afternoon
25	Anxiety
26	Mood changes
27	Weakness
28	Stiffness during the night time
29	Difficulty in swallowing
30	Abnormal sensation of hot and cold
31	Abnormal sensation of aching
32	Abnormal sensation of numbness

Evaluation protocol

The WOQ-32 was completed by the subject after the routine clinician visit without any assistance from their physician. Within the questionnaire, subjects were asked to indicate whether they experienced any of the 32 symptoms during a normal day, and whether these symptoms improved with anti-parkinsonian medication dosing. Subjects were also asked how troublesome these symptoms were in their daily routine, and whether the symptoms had been discussed with the clinician. In addition, subjects were queried regarding the importance (troublesomeness) of these symptoms in a daily routine, and whether the symptoms identified in the survey were sufficiently bothersome that the patient would like to discuss a different treatment option with their physician.

Immediately after completion, an administrative assistant reviewed the questionnaire with the subject to assess whether the explanations, visuals and questions were easily understood and to ensure that the questions were answered completely. The primary investigator reviewed all survey data prior to entry into the question database.

Development of the WOQ-19

It was pre-determined by the panel that the prototype WOQ of 32 symptoms would not be suitable for general use, and that the symptom list should be

shortened on the basis of the results of the WOQ-32 evaluation. It was agreed that this procedure should also include reduction of any redundancies in the list of 32 symptoms included in the prototype. Thus, for the purposes of developing the questionnaire into the final WOQ-19, the primary retrospective analyses were:

- Frequency of subjects with 'wearing-off'
- Ranked identification of the types of wearing-off symptoms included in the Patient Questionnaire
- Identification of the most troublesome wearing-off symptoms by subject survey

WOQ-32 data were entered and quality checked, then merged on a patient by patient basis with data from the Ali Project database. An initial exploratory analysis was performed by tabulating the data to identify the symptoms included in the WOQ-32 reported most frequently as wearing-off. Canonical discriminant analysis was then performed to identify the symptoms that were best predictors of wearing-off in those patients not identified as experiencing wearing-off by the clinician.

In addition, a stepwise approach was undertaken to determine which symptoms were the best predictors in order of usefulness. Starting from the most important three symptoms, then the most important six symptoms, the list of key symptoms was extended in stages, until optimal lists containing between nine and 20 symptoms were obtained. At each stage, the principle used was to look at frequency counts of symptoms indicating wearing-off amongst those not yet identified by the previous list of symptoms. The one symptom that could maximally increase the number of patients identified as experiencing wearing-off was then chosen for inclusion. Finally, multiple linear regression analysis was undertaken to see which symptoms, when present, contributed most to the perception that symptoms were particularly troublesome.

Table 2. *Patient demographic information*

	Total population ($n = 289$)	Subjects with wearing-off* ($n = 181$) (% total population)
Male/female (N)	174/115	105/76
Age (years)	72.0 ± 9.6	70.1 ± 9.9
Total UPDRS score	36.3 ± 19.7	38.8 ± 20.9
% receiving levodopa	87.5	91.2
Hoehn and Yahr		
Stage 1	7	5 (71.4%)
Stage 1.5	16	10 (62.5%)
Stage 2	77	46 (59.7%)
Stage 2.5	84	52 (61.9%)
Stage 3	84	52 (61.9%)
Stage 4	14	9 (64.3%)
Stage 5	7	5 (71.4%)
Years on levodopa therapy		
0	63	33 (52.4%)
1	41	24 (58.5%)
2	50	33 (66.0%)
3	52	32 (61.5%)
4	36	32 (88.9%)
5	11	11 (100%)
not on levodopa	36	16 (44.4%)

Results

Demographics

Three hundred subjects completed the WOQ-32 between December 2, 2002 and March 23, 2003. Eleven subjects were subsequently excluded, because they were determined to have been diagnosed with PD for >5 years. Therefore, a total of 289 subjects were included in the final analysis. Demographics for total study population and for patients identified as experiencing wearing-off by the WOQ-32 are presented in Table 2.

Results of the overall Patient Questionnaire evaluation

Overall, 165 patients (57.1%) were identified as experiencing wearing-off by the WOQ-32. The most common wearing-off symptom reported using the questionnaire was tremor and the most common non-motor symptom was tiredness. The mean number of wearing-off symptoms reported by the subjects was 6.25 (SD, ±5.44). Eighteen subjects reported only one symptom, while six subjects reported at least 20 of the 32 symptoms listed. When the subjects with wearing-off were queried regarding the difficulties associated with wearing-off symptoms, 37% of subjects indicated that the symptoms were very troublesome and 55.2% indicated they were slightly troublesome.

Development of the Patient Card

Nineteen of the 32 symptoms were found to be statistically relevant for inclusion into the final WOQ-19 (Fig. 1).

Predictive symptoms of wearing-off

Sixteen out of the original 32 symptoms were required to capture all subjects reporting wearing-off (Table 3). These included two references to stiffness (stiffness in the morning, stiffness in the afternoon) and three references to slowness (slowness of movement, slowness in the early morning and slowness in the night) which were subsequently simplified into general stiffness and slowness of movement, respectively. Thus, 13 of the 16 symptoms required to capture 100% of patients in this population were included in the final WOQ-19.

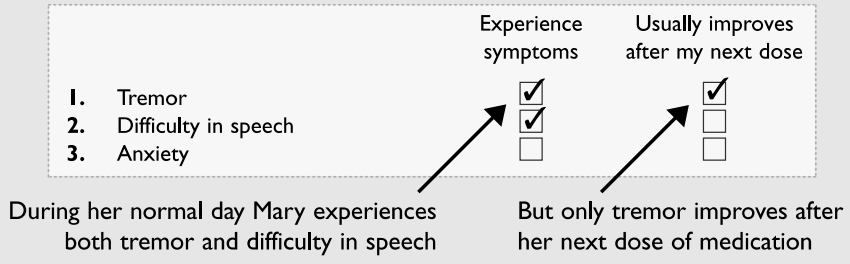
Symptoms found to be most troublesome

Analysis of troublesome symptoms found that, in addition to the 13 symptoms identified above as predictive, difficulty with speech and pain were also significant contri-

butors. Regression analysis was performed to identify whether any other symptoms were correlated with being troublesome or a wish to change treatment. This further analysis identified an additional four symptoms for inclusion into the final WOQ-19: sweating, hot and cold, panic attacks and aching.

Please tick in column 1 any symptoms that you currently experience during your normal day. Please also tick the box in column 2 if this symptom usually improves or disappears after you take a dose of your Parkinson's medication.

Mary's example



		Experience symptoms	Usually improves after my next dose
1.	Tremor	☐	☐
2.	Difficulty in speech	☐	☐
3.	Anxiety	☐	☐
4.	Experience sweating	☐	☐
5.	Mood changes	☐	☐
6.	Weakness	☐	☐
7.	Problems with balance	☐	☐
8.	Slowness of movement	☐	☐
9.	Reduced dexterity	☐	☐
10.	Numbness	☐	☐
11.	General stiffness	☐	☐
12.	Experience panic attacks	☐	☐
13.	Cloudy mind / dullness thinking	☐	☐
14.	Abdominal discomfort	☐	☐
15.	Muscle cramping	☐	☐
16.	Difficulty getting out of the chair	☐	☐
17.	Experience hot and cold	☐	☐
18.	Pain	☐	☐
19.	Aching	☐	☐

Fig. 1. The Patient Card: Available for download from www.parkinsonpoly.com

Please list any other symptoms that you find troublesome

Please list the symptoms that you find the most troublesome

Typical pattern of wearing-off during the day

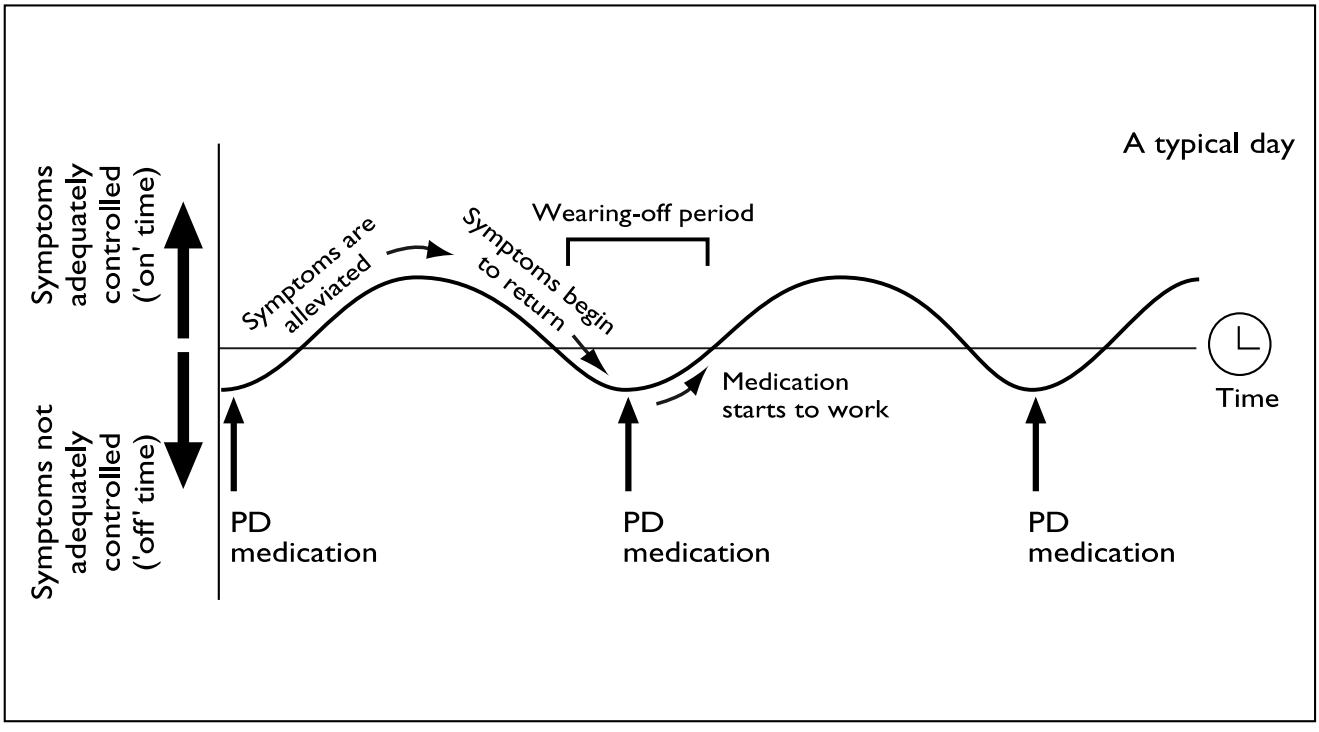


Fig. 1 (*continued*)

Discussion

Wearing-off is often defined as the re-emergence of parkinsonian symptoms before the next scheduled dose of antiparkinsonian medication. At present, although many physicians recognize wearing-off when it is associated with the return of obvious motor symptoms (e.g. tremor, bradykinesia and

Table 3. *Symptoms needed to capture patients with wearing-off*

Tremor Slowness in early morning Anxiety	1st 3 explain 75.2%
Slowness during night Mood changes Weakness	+ next 3 explain 78.7%
Problems with balance Slowness of movement Reduced dexterity	+ next 3 explain 93.3%
Numbness Stiffness in the afternoon Stiffness in the morning	+ next 3 explain 97.5%
Cloudy mind/dullness thinking Abdominal discomfort Slowness, muscle cramping Difficulty getting out of the chair	+ next 4 explain 100%

stiffness), the importance of more subtle signs such as non-motor symptoms is probably under-recognized. Our aim was to develop a tool to facilitate the recognition of the full range of these signs and symptoms in routine clinical practice.

We previously reported the results of the prospective comparison of the proportion of patients who reported the symptoms of wearing-off using the prototype (32-symptom) WOQ with the proportion identified by the physician (at the same visit). In support of the utility of the tool, patients using the prototype WOQ-32 reported the wearing-off significantly more often than was recognized by their physician (57.1 vs. 29.4%, respectively) (Stacy et al., 2005). In addition to the direct questioning for the presence of wearing-off, it is also probable that the specific inclusion of a wide range of both motor and non-motor symptoms contributed to the greater sensitivity of the WOQ-32. The presence of non-motor symptoms and their temporal relationship to the patients dosing regimens may not be easily detected during the brief time available in a normal office visit. Indeed, the importance of non-motor symptoms and how to incorporate them in PD rating scales, such as the UPDRS, is the focus of much research (UPDRS Taskforce, 2003; Welsh et al., 2003; Chaudhuri et al., 2005).

It is important to recognize that the WOQ-32 was specifically developed as a study tool for investigators and was not intended for use by physicians in routine practice. As such, it was designed to include some redundancy in the questions with four descriptions of slowness and four of stiffness in order to capture the fullest range of patient perceptions. When designing the shorter tool, we used statistical methods to reduce and simplify the number of symptoms. Throughout this process, our aim was to ensure that the shorter tool would capture the majority of patients in the original population. In this respect, although six subjects reported at least 20 of the 32 symptoms listed in the original study, this was mainly due to the built-in redundancy in symptoms.

Although we believe that the range of symptoms included in the original list of 32 make it unlikely that truly important items were missed in the original study, we cannot exclude the possibility that additional symptoms may contribute to wearing-off in individual patients. We also note that it was not our intention to develop a diagnostic instrument, but rather we aimed to develop a tool to increase recognition of the signs and symptoms of wearing-off and aid communication between physicians and their patients. Further validation of the WOQ-19 in new populations is important and the WOQ-19 is currently being tested in new samples in the Netherlands, Spain and Australia.

It should also be noted that because the WOQ-32 was tested in a specific set of patients who had PD for less than 5 years, we cannot say with certainty that this card will help identify patients with wearing-off fluctuations who have been diagnosed with PD for greater than 5 years. However, we anticipate that patients at this more advanced stage of their disease experience many of the same problems as those observed in the current group.

In conclusion, it is clear from the final WOQ-19 development process that the signs and symptoms of wearing-off are varied. Close monitoring of the patient's response for several hours following administration of the patient's standard levodopa dose can be informative. However this is usually too expensive and time-consuming to be performed in daily clinical practice and does not address the re-emergence of non-motor fluctuations. Failure to recognize wearing-off may lead to delayed management, thereby limiting effective treatment of the patient. It is important to recognize these symptoms in order to take full advantage of the range of strategies now available to treat wearing-off. Thus, we believe that the development of this 19-symptom questionnaire, which specifically questions the patient about potential symptoms of wearing-off, may aid the physician in their clinical assessment. It is hoped that better recognition of wearing-off will permit the physician to make treatment modifications in a more timely manner and enable the patient to maintain optimal symptomatic control throughout the day.

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References

Agid Y, Olanow CW, Mizuno Y (2002) Levodopa: why the controversy. Lancet 360: 575

Ahlskog JE, Muenter MD (2001) Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord 16: 448–458

Chaudhuri KR, Yates L, Martinez-Martin P (2005) The non-motor symptom complex of Parkinson's disease: a comprehensive assessment is essential. Curr Neurol Neurosci Rep 5: 275–283

Dodel RC, Berger K, Oertel WH (2001) Health-related quality of life and healthcare utilisation in patients with Parkinson's disease: impact of motor fluctuations and dyskinesias. Pharmacoeconomics 19: 1013–1038

Goetz CG, Poewe W, Rascol O, Sampaio C (2005) Evidence-based medical review update: pharmacological and surgical treatments of Parkinson's disease: 2001 to 2004. Mov Disord 20: 523–539

Marsden CD, Parkes JD (1977) Success and problems of long-term levodopa therapy in Parkinson's disease. Lancet 1: 345–349

Olanow CW, Stocchi F (2004) COMT inhibitors in Parkinson's disease: can they prevent and/or reverse levodopa-induced motor complications? Neurology 62 [Suppl 1]: S72–S81

Parkinson Study Group (1996) Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients not requiring levodopa. Ann Neurol 39: 29–36

Parkinson Study Group (2000) Pramipexole vs. levodopa as initial treatment for Parkinson disease: A randomized controlled trial. JAMA 284: 1931–1938

Stacy M, Bowron A, Guttman M, Hauser R, Hughes K, Larsen JP, et al. (2005) Identification of motor and nonmotor wearing-off in Parkinson's disease: Comparison of a patient questionnaire versus a clinician assessment. Mov Disord 20: 726–733

Thomas K, Samanta J, Mahant P, Williamson K, Stacy M (2002) The Ali Project: A web-based database for Parkinson's disease. Mov Disord 17 [Suppl 5]: S141

UPDRS Taskforce (2003) The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. Mov Disord 18: 738–750

Welsh M, McDermott MP, Holloway RG, Plumb S, Pfeiffer R, Hubble J (2003) Development and testing of the Parkinson's disease quality of life scale. Mov Disord 18: 637–645

Witjas T, Kaphan E, Azulay JP, Blin O, Ceccaldi M, Pouget J, et al. (2002) Nonmotor fluctuations in Parkinson's disease: frequent and disabling. Neurology 59: 408–413