ORIGINAL ARTICLE

The study of health-related quality of life using PDQ39 in patients with Parkinson’s disease treated with advanced therapies☆

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KEYWORDS
Parkinson’s disease; Quality of life; Deep brain stimulation; Duodopa; Apomorphine; PDQ39

Abstract Parkinson’s disease is a neurological chronic degenerative disorder which can lead to a progressive loss of quality of life and to incapacitation. Conventional treatment is effective in the first years of the disease, but other kinds of therapy should be considered upon the onset of motor and non-motor complications that are clearly impacting quality of life. At present we have three advanced therapies which have proven beneficial for these types of patients, namely: deep cerebral stimulation, subcutaneous apomorphine infusion pumps, and continuous intestinal levodopa infusion to the duodenum (Duodopa®).

Objectives: To assess the impact of advanced therapies on the quality of life of patients with Parkinson’s disease, measured using the PDQ39 scale.

Methods: Observational, prospective, non-randomized study. Three measurements (n = 20) using the PDQ39 scale were taken: the first before initiating advanced therapy, the second at 3–5 months, and the third at 6–10 months.

Results: Men who receive treatment with advanced therapies are younger and have fewer years of progression of the disease than women. There were significant differences between the three measurements in terms of emotional well-being, stigmatisation, cognitive state and overall assessment of PDQ39. Similarly, significant differences were found in pairs in the long term in these parameters. Social support deteriorated after entering advanced therapy.

Conclusions: Significant global improvements were observed in quality of life, measured using the PDQ39 scale, of patients with Parkinson’s disease, treated with advanced therapy in the Hospital of Navarre for 10 months.

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PALABRAS CLAVE
Enfermedad de Parkinson; Calidad de vida; Estimulación cerebral profunda; Duodopa; Apomorfina; PDQ39

Estudio de calidad de vida con la PDQ39 en pacientes con enfermedad de Parkinson tratados con terapias avanzadas

Resumen La enfermedad de Parkinson es una enfermedad neurodegenerativa que puede llevar progresivamente a la pérdida de calidad de vida y a la discapacidad. El tratamiento convencional es efectivo en los primeros años de evolución de la enfermedad, pero cuando aparecen complicaciones motoras y no motoras que repercuten claramente en su calidad de vida, es momento de plantearse otros tipos de terapias. En la actualidad disponemos de tres terapias avanzadas que han demostrado ser beneficiosas para este tipo de pacientes: la estimulación cerebral profunda, la terapia con bomba de apomorfina subcutánea y la terapia con bomba de Duodopa a través del duodeno.

Objetivos: Conocer el impacto de las terapias avanzadas en la calidad de vida de los pacientes con EP, medida con la escala PDQ39.

Método: Estudio observacional, prospectivo, no aleatorizado. Se realizaron tres mediciones (n=20) con la PDQ39 en diferentes momentos: 1.° previa al inicio de la TAV, 2.° a los 3-5 meses y 3.° a los 6-10 meses.

Resultados: Los hombres que se tratan con terapias avanzadas son menores y con menos años de evolución de la enfermedad que las mujeres. Existen diferencias significativas entre las tres medidas para el bienestar emocional, el estigma, el estado cognitivo y la valoración total de la PDQ39. Asimismo, hay diferencias significativas, por parejas, a largo plazo para los mismos. El apoyo social empieza al someterse a estas terapias.

Conclusiones: Se refleja la mejora, de manera global (PDQ39 total), en la calidad de vida medida con la escala PDQ39 en los pacientes sometidos a TAV en el Complejo Hospitalario de Navarra en un período de 10 meses.

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Introduction

Parkinson’s disease (PD) is a neurodegenerative disease belonging to a group of diseases termed movement disorders (MD). It affects the area in charge of coordinating activity, muscle tone and movements. It is the second most prevalent neurodegenerative disease after Alzheimer’s disease.

It comprises a progressive loss of neurones specific to the correct functioning of movements, which implies fewer connections with other nerve cells, which gradually leads to a loss of quality of life and incapacitation.

Conventional oral and transdermal treatment principally based on the combination of levodopa and dopamine agonists is beneficial for at least 3-5 years of disease progression. After 5-10 years of treatment with these drugs, motor and non-motor fluctuations start to appear in 50-70% of patients, which impact their quality of life. This phenomenon causes periods of good mobility and other periods of poor motor function when adjustments need to be made to their oral medication, which achieve reasonable control of symptoms for most patients. However, there are patients, although continuing to respond well, whose duration of response is insufficient, meaning that they spend a large part of their day (considered by consensus >25% of their waking hours) with poor motor function. This phase of the disease is termed advanced Parkinson’s disease (APD), for which we have three different strategies to improve the management of these patients’ clinical situation, using advanced therapies (AT):

- Surgery with deep brain stimulation (DBS) in the subthalamic nucleus/pallidum.
- Therapy with continuous subcutaneous apomorphine infusion delivered via a pump.
- Therapy with continuous duodenal infusion of levodopa gel, Duodopa.

Since PD is an essentially motor disease it is reasonable to assume that controlling the symptoms of the disease will have an impact on quality of life. There is a relationship between the Unified Parkinson’s Disease Rating Scale (UPDRS) and quality of life and duration of off-time, the higher the score on the Unified Parkinson’s Disease Rating Scale and longer off-time, the poorer the patient’s quality of life. We should not ignore the fact that non-motor symptoms also occur which can cause great suffering, and accelerate the progression of disability. The AT shorten off-time, and this results in improved quality of life.

The choice of AT, candidates and time it should be started falls to the neurologists who are experts in MD, and is made according to the clinical practice guidelines of the Spanish Neurology Society and expert consensus. Patients are selected by determining the balance between the predictable benefit and risks and disadvantages of each; therefore not all patients are candidates for all the AT.
In the nineties, Dr. Martínez-Martín studied the quality of life of patients with PD and found a clear need for instruments to measure it. In one of his studies he validated the Spanish version of the Parkinson's Disease Questionnaire (PDQ39) to assess quality of life, which we used in our article. The PDQ39 evaluates physical, emotional and psychosocial aspects of quality of life.\textsuperscript{18}

According to García-Ramos et al. statistically significant improvements are found in the PDQ39 in patients who undergo DBS, and they highlight the importance of the pre and postoperative assessment of patients with PD.\textsuperscript{19}

Santos-García et al. demonstrate improvements in motor fluctuations and dyskinesia with a reduction in off-time/day and time with dyskinesia after a period of 3–31 months, in patients treated with Duodopa.\textsuperscript{6} It also improves the PDQ39 and Schwab & England scales.\textsuperscript{10}

According to Kulisevsky, treatment with subcutaneous apomorphine improves patients' quality of life, although it seems that therapy is being initiated late.\textsuperscript{9}

According to Marti and Kulisevsky, 52% of patients and caregivers consider that they might have benefited earlier from apomorphine infusion, since this therapy is less invasive, completely reversible, easy to deliver and lower cost.\textsuperscript{12}

Hypothesis

Patients with advanced PD treated with AT show improvements in motor and non-motor response, which has a favourable impact on their quality of life, measured using the PDQ39 questionnaire.

Objectives

To discover the impact of AT on the quality of life of patients with APD measured using the PDQ39 questionnaire.

To assess and compare the quality of life measured with the PDQ39 questionnaire of patients with APD before initiating treatment with an AT, at 3–5 months and at 6–10 months.

Methods

An observational, prospective, case series study with a conditional sample. The study was conducted in the neurology specialist care clinics of the Hospital Complex of Navarre. The study population comprised all the patients diagnosed with PD who received treatment with any of the three abovementioned advanced treatment types within the recruitment period. Selection of patients started in May 2014 and ended in June 2016. Assuming a 95% confidence level, with a mean dimension score of 40 for the PDQ39 and a standard deviation of 20, the sample size of 20 enabled detection of a change in the PDQ39 dimensions of 12 points, with 80% power, after starting AT. The calculations were undertaken with the "sample size" library of the R programme, version 2.13.2.

The patients were asked to collaborate in completing the first measurement of the PDQ39 questionnaire when the MD expert neurologist considered them good candidates for starting an AT. The second measurement coincided with the medical visit to the hospital in a period of 3–5 months after starting the AT. A third measurement was taken, also to coincide with the visits to the hospital at 6–10 months, in order to observe long-term progress. The patients were asked to sign their informed consent. The study was approved by the healthcare ethics committee of the Hospital Complex of Navarre.

The PDQ39 contains 39 items in 8 different domains covering mobility (10 items), activities of daily living (6 items), emotional well-being (6 items), stigma (4 items), social support (3 items), cognitive status (4 items), communication (3 items), bodily discomfort (3 items).

Mobility measurements: difficulty in doing leisure activities, difficulty looking after the home, difficulty carrying bags of shopping, problems walking short distances, concerns about falling in public. Activities of daily living measure difficulties in washing, dressing unaided, cutting up food, holding a drink and problems doing up buttons or shoe laces. Emotional well-being evaluates feelings of depression, loneliness, anger or anxiety. Stigma covers feeling a need to conceal the disease, avoiding eating or drinking in public, and feeling embarrassed due to the disease and worried about other people's reactions. Social support evaluates problems with close personal relationships, lacking support from family members in the ways needed. Cognitive status evaluates problems with concentration, feeling that memory is bad, experiencing hallucinations and/or distressing dreams. Communication measures: difficulty with speech, communicating properly with people, feeling ignored by people. Bodily discomfort covers: muscle cramps, joint pains, feeling unpleasantly hot or cold.

In each item of each domain, patients are asked how often they have experienced the problem in the past month, and the possible response options are: 0 (never), 1 (occasionally), 2 (sometimes), 3 (often), 4 (always or cannot do at all). The domain score is calculated adding together the scores obtained in each of the items and dividing them by the maximum possible score in this domain. The result represents the percentage of problems, and therefore the higher the number the greater the amount of problems.

The sample was described using descriptive statistics such as mean, median, standard deviation and interquartile range, according to the type of variable. We studied the possible association of the types of treatment applied over each of the domains examined by the PDQ39 questionnaire. In a stage before the study we used the Shapiro–Wilks test to analyse the normality of the data in the three measurements of the variables. If we obtained normality in the data, we used the repeated measures ANOVA, and we used Friedman's non-parametric test to compare paired samples in the event of non-normality. In addition, to determine when the differences occurred we performed a pairwise comparison of the means with the Bonferroni test, in the event of normality, and compared the medians with the Wilcoxon test, in the event of non-normality. A $p < .05$ was considered significant. SPSS software version 20 was used for the entire process.

Results

Of the 20 patients who started AT, 11 were male and 9 female. The mean age was between 67.5 ± 7.67, and we
observed that the men who had undergone DBS were younger than the women who had undergone the procedure, with a mean age of 60.88 ± 7.18 compared to 66 ± 5 years for the women (Table 1). The men who had started treatment with Duodopa® or apomorphine pump were also younger than the women who had started these treatments. According to the Hoehn and Yahr scale, the patients treated with DBS had less disease progression, and it was less in the men than the women. There were no differences in staging in those treated with apomorphine infusion therapy. Of those treated with Duodopa® the men had more disease progression than the women (Table 2).

We had 1 smoker and 5 ex-smokers in the study, and 14 had never smoked.

The domains where the highest percentages of problems prior to starting AT were observed in order of importance are (Table 2): mobility, followed by bodily discomfort, emotional well-being and activities of daily living, those that showed fewer problems were social support, stigma and communications. There were statistically significant intra-subject differences in emotional well-being, stigma, cognitive status and the total score of the scale.

We then focussed on determining the time that the differences occurred. In the total score of the PDQ39 scale, there were improvements (p = .029), between the baseline measurement and at more than 6 months after starting the AT. We found significant changes in emotional well-being, between the first and second measurement (p = .034), and they were maintained over time between the first and final measurement (p = .004). In cognitive status we found differences between the first and the final assessment (p = .013).

When we analysed the data of the patients who had undergone DBS separately, we found improvements in emotional well-being, bodily discomfort (p = .033, p = .027), stigma, cognitive status (p = .025, p = .004), and the total PDQ39 score (p = .017). And by pair, we found that the improvement in emotional well-being and bodily discomfort presented between the first and second measurements (p = .001 and p = .010), and were not maintained over time. We observed that the differences were found between the first and the final measurement of cognitive status (p = .004). With regard to the total PDQ39 score, they were found between the first and second measurement (p = .007) and also between the first and final measurement (p = .013), showing that the overall improvement in quality of life was maintained over time.

Table 2 shows that there are no differences in mobility, activities of daily living, social support, communication and bodily discomfort. In the cases of mobility, activities of daily living and bodily discomfort the tendencies show a marked decrease when AT was started, and this smooths out between the second and third measurement. However, communication drops rapidly from the first and second measurement to then increase again, reaching very similar levels to those found at the first measurement. In contrast, in social support, the problems increased when AT was started and remained practically the same until the final measurement. It can be observed from these variables studied using

### Table 1  Baseline characteristics of the sample.

<table>
<thead>
<tr>
<th></th>
<th>DBS</th>
<th>Apomorphine</th>
<th>Duodopa®</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td>F 3 (15%)</td>
<td>2 (10%)</td>
<td>4 (20%)</td>
<td>.121</td>
</tr>
<tr>
<td></td>
<td>M 8 (40%)</td>
<td>1 (5%)</td>
<td>2 (10%)</td>
<td>.121</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>F 66 ± 5</td>
<td>73.50 ± .71</td>
<td>74.25 ± 4.11</td>
<td>.200</td>
</tr>
<tr>
<td></td>
<td>M 60.88 ± 7.18</td>
<td>69 ± .01</td>
<td>71.50 ± 3.57</td>
<td>.200</td>
</tr>
<tr>
<td>Years of progression</td>
<td>F 11.5 ± 3.54</td>
<td>12 ± 2.83</td>
<td>10.25 ± 3.78</td>
<td>.718</td>
</tr>
<tr>
<td></td>
<td>M 8.38 ± 3.07</td>
<td>8 ± 0</td>
<td>10.50 ± 3.54</td>
<td>.834</td>
</tr>
<tr>
<td>Hoehn and Yahr</td>
<td>F 2.83 ± .17</td>
<td>4 ± 0</td>
<td>3.5 ± .71</td>
<td>.978</td>
</tr>
<tr>
<td></td>
<td>M 2.67 ± .58</td>
<td>3.5 ± .71</td>
<td>3.5 ± .56</td>
<td>.978</td>
</tr>
</tbody>
</table>

SD: standard deviation; DBS: deep brain stimulation; M: male; F: female.

### Table 2  Multivariate contrast results of PDQ39.

<table>
<thead>
<tr>
<th>PDQ39</th>
<th>1st visit</th>
<th>2nd visit</th>
<th>3rd visit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility (mean ± SD)</td>
<td>54.03 ± 5.03</td>
<td>46.97 ± 6.68</td>
<td>46.25 ± 6.82</td>
<td>.299*</td>
</tr>
<tr>
<td>Activity (mean ± SD)</td>
<td>41.65 ± 5.37</td>
<td>37.03 ± 6.69</td>
<td>37.04 ± 6.47</td>
<td>.557*</td>
</tr>
<tr>
<td>Well-being (median, IQR)</td>
<td>50.00 (30.21–65.62)</td>
<td>29.17 (12.5–70.83)</td>
<td>33.34 (16.67–51.04)</td>
<td>.002*</td>
</tr>
<tr>
<td>Stigma (median, IQR)</td>
<td>15.63 (1.56–42.19)</td>
<td>12.50 (.00–25.00)</td>
<td>6.25 (.00–23.44)</td>
<td>.034*</td>
</tr>
<tr>
<td>Support (median, IQR)</td>
<td>8.33 (.00–22.92)</td>
<td>8.33 (.00–33.33)</td>
<td>10.17 (.00–25.00)</td>
<td>.864*</td>
</tr>
<tr>
<td>Cognitive (median, IQR)</td>
<td>31.25 (12.50–50.00)</td>
<td>37.50 (6.25–43.75)</td>
<td>18.75 (.00–37.50)</td>
<td>.005*</td>
</tr>
<tr>
<td>Communication (mean ± SD)</td>
<td>33.33 ± 4.67</td>
<td>30.55 ± 3.57</td>
<td>32.85 ± 6.27</td>
<td>.874*</td>
</tr>
<tr>
<td>Discomfort (mean ± SD)</td>
<td>48.61 ± 6.40</td>
<td>38.42 ± 6.40</td>
<td>37.96 ± 5.61</td>
<td>.368*</td>
</tr>
<tr>
<td>Total (mean ± SD)</td>
<td>39.18 ± 3.20</td>
<td>33.05 ± 4.16</td>
<td>29.38 ± 3.79</td>
<td>.037*</td>
</tr>
</tbody>
</table>

SD: standard deviation; IQR: interquartile range.

a ANOVA.
b Friedman.
Discussion and conclusions

This paper shows the overall improvement (total PDQ39) in quality of life measured with this scale for patients given AT in the Hospital Complex of Navarre over a period of 10 months.

In terms of epidemiological features, it is interesting to observe that the men started all the AT at a younger age, with fewer years of disease progression and at a lower stage than the women, except for those treated with Duodopa® who were found to be at similar stages. The mean age of the patients who underwent DBS was greater compared with other studies.21-24 We bore in mind exclusion criteria for DBS over the age of 70–72 years.10

We also noticed that the patients who started treatment with Duodopa® were older in our study, in line with other studies.3,25-27

For apomorphine pump therapy, it was also the women who started AT later, which again contrasted with other studies.18,23

Although PD affects men by around 50% more than women,10 our selection of candidate patients (9 women and 10 men) did not reflect this proportion because this was not a randomised sample, and it was also undertaken in a single centre.

We can highlight in this study that there was an impact (improvement) on the perception of quality of life for the patients with DBS, at more than 6 months from starting the AT. When we compared intrasubject, considering that the first assessment referred to patients undergoing conventional therapy, who were going to start an AT for better control of their symptoms, and the second and third measurements corresponded to the same patients when AT had been started, we found that they perceived an improvement medium term, even when the disease was chronic neurogen- erative and progressive.

In the sample, 95% of the patients were non-smokers. We should point out that smoking is associated with a higher risk of PD coinciding with Campdelacreu.31

The only domain where there was no improvement was social support, because these patients have greater demand for social support when starting the AT. This finding is in line with other studies we consulted.32,33

With regard to communications, a mild short-term decrease in speech problems occurred after starting the AT, which was not maintained medium term. This effect might be explained by the fact that more than half the sample had undergone DBS and, according to Kulisevky et al.,9 speech problems that do not improve with levodopa, do not improve with surgery either.

We found a confirmed improvement short and medium term in bodily discomfort. The lowest percentage of problems was associated with patients treated with Duodopa® and DBS, as reflected in the literature.10,13

Future lines of investigation might be to enlarge the sample size, diversify the type of patients and extend the study to other referral hospitals. Relevant data on sociodemographic characteristics could be gathered to gain a broader view of the sample. And the features of the study population could be studied: comorbidities, previous treatments, educational and psychological factors. The quality of life of Parkinson’s patients could be measured from a different perspective: UPDRS, impaired gait, Swang & England, non-motor symptoms, memory complaints, associated psychotic symptoms. And other factors could be identified that influence the HRQL of these patients and their caregivers.

Because they are started later in Navarre than in other national and international hospitals, the effects of early therapeutic intervention with AT and on the HRQL of patients with Parkinson’s disease could be analysed.

Limitations

This study has some important limitations. On the one hand, the methodology used did not enable conclusions to be reached beyond a description of the sample participants, and on the other hand, other important variables in the associations were not considered, such as those described previously or those relating to socioeconomic status, or with caregiver overload, etc., which are very relevant to the comprehensive assessment of patients using a biopsychosocial model.

The limitation of a small sample size should also be highlighted.

We consider that the lack of statistical significance in the Duodopa® pump therapy group, despite the marked tendency to improvement, could be due to the small sample size.

Bearing in mind the type of population from which the sample came (patients with advanced chronic disease, with high morbidity and mortality and a major percentage having undergone intracranial surgery), it is interesting to note that there were only two losses. The loss of these two patients did not significantly affect the power of the study and therefore does not invalidate its results and conclusions.

Conflict of interests

The authors have no conflict of interests to declare.

References