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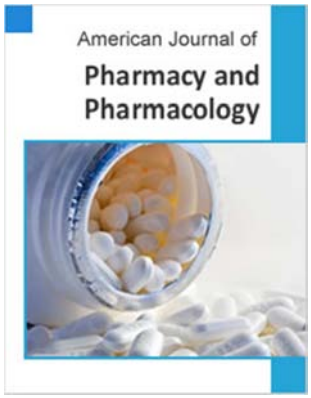

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Patient and Researcher Reported Outcomes in Parkinson's Disease Patients Treated with Brand or Generic Pramipexole

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Abstract
Generic drugs are widely considered to be cost-efficient substitutes for brand-name medications. The objective of this study is to compare patient-reported outcomes and investigator-rated outcomes in patients with PD treated with generic versus brand-name immediate-release pramipexole. For this purpose, a cross-sectional study was carried out. Patients on a stable dose of immediate-release pramipexole were divided in two groups (brand-name and generic drug). The MDS-UPDRS) part III and the Non-Motor Symptoms Scale were applied to all the participants. Also, PDQ-8 and MDS-UPDRS parts IB and II were completed by the patients. A total of 198 patients were included. No statistically significant difference was found in the motor evaluation. Health-related quality of life and motor experiences of daily living were significantly better in the group receiving the brand-name pramipexole. In conclusion, Subjects with Parkinson's disease treated with generic pramipexole scored worst in the self-reported motor experiences of daily living and quality of life.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease and is expected to impose an increasing social and economic negative impact on societies as population ages [1].

Levodopa remains the most effective symptomatic treatment in patients with PD, however, its relationship to the onset of motor complications, like motor fluctuations, places some limits on its use, especially in patients younger than 70 years. Dopaminergic agonist provides a safe and effective alternative to levodopa in younger patients and is associated with a lower incidence of motor fluctuations at the five-year mark [2].

Overall, generic drugs are widely considered to be cost-efficient substitutes for brand-name medications [3]. On the other hand, patients' beliefs and expectations towards the effectiveness of generic over brand-name drugs are gaining interest [4]. PD, along with pain, depression and apathy, is among the disorders in which the placebo effect can be

prominent. In PD, the placebo effect magnitude can range from 9% to 59% [5-7].

In addition, patient-reported outcomes may reflect more accurately the impact in daily activities in comparison to investigator-rated scales [8].

The aim of the study is to compare patient-reported outcomes and investigator-rated outcomes in patients with PD treated with generic versus brand-name pramipexole.

2. Methods

A cross-sectional study was carried out. Consecutive patients with PD based on the UK Parkinson's Disease Society Brain Bank Criteria attending the Movement Disorders outpatient clinic at the National Institute of Neurology and Neurosurgery in Mexico City were included [9]. Only patients on a stable dose of immediate-release pramipexole for at least six weeks, either as monotherapy or polytherapy, were included.

The study was approved by the Institutional Review Board. All the participant patients agreed with the study and gave full consent as dictated by the local Ethics Committee from the Institute. To minimize the risk of bias, patients were initially told that the objective of the study was to assess the effectiveness of their treatment; only after all the patient-reported instruments were completed, the main study objective was disclosed and patient informed consent was confirmed.

Clinical and demographic data was collected by a rater blinded to the patient's treatment. Data collected included age, gender, years of education, current employment, disease duration, and antiparkinsonian treatment. Levodopa equivalent daily dose (LEDD) was calculated as published elsewhere [10].

Socioeconomic status was determinate by a standardized evaluation performed by a social worker (being 1 the lowest and 6 the highest level) [11]. Patients were evaluated by a neurologist with expertise in movement disorders using the Spanish version of Movement Disorders Society Unified Parkinson's disease Rating Scale Part III (MDS-UPDRS Part III) [12]. Severity of the disease was evaluated using the Hoehn and Yahr (HY) staging scale [13].

Patient-reported outcomes were evaluated using the Spanish version of MDS-UPDRS Part IB and Part II. These two parts are designed as self-administered questionnaires and can be completed either alone or with their caregivers. Nevertheless, for the purposes of the present study only the patient-reported data were included.

MDS-UPDRS Part IB includes seven items regarding the non-motor experiences of daily living. Each item is scored according to the severity of the symptom (0, none to 4, severe) with a theoretical total score range of 0 to 28.

Conversely, the MDS-UPDRS Part II evaluates the motor experiences of daily living. This part has 13 items also scored according to the severity of the symptoms (0, none to 4, severe), with a theoretical range from 0 to 52.

In addition, the Parkinson's Disease Questionnaire 8 (PDQ-8) was applied [14]. The PDQ-8 is a disease-specific and self-administered instrument addressing aspects of functioning and well-being in the past month. The scale evaluates the health-related quality of life using eight questions, scored by frequency of problems (0, never to 4, always). A PDQ-8 single index is calculated resulting in a score ranging from 0 to 100 (0= no problem at all; 100= maximum level of problem).

To evaluate the presence of depressive mood and apathy, the nonmotor symptoms scale (NMSS) was used [15]. The NMSS evaluates the frequency and severity of 30 nonmotor symptoms in patients with PD, scored by frequency (1, less than 1 day per week to 4 very frequently) and severity (0, none to 3, severe). For this study, depressive mood and apathy were considered present with a score >0.

Statistical analysis

Demographic data were reported in terms of percentage, mean and standard deviation. The analysis of quantitative variables between the two groups (brand-name pramipexole versus generic pramipexole) was performed using an independent two sample t-test. Differences in proportions of categorical variables were analyzed using chi-square test. The 95% confidence interval is reported through-out. A level of $p < 0.05$ was set for statistical significance. All statistical analyses were performed with SPSS software version 17.

3. Results

A total of 198 patients (116 males and 82 females) with PD and treated with a stable dose of immediate-release pramipexole were included. The mean of age was 61.72 ± 11.53 [95% CI 60.11 to 63.34] years, with a mean disease duration of 7.91 ± 5.37 [95% CI 7.14 to 8.68] years. The duration of the dopamine agonist treatment was 3.70 ± 3.01 [95% CI 3.27 to 4.13] years; 52% of the sample was receiving the brand-name pramipexole. The complete sociodemographic characteristics of the sample are summarized in Table 1.

Table 1. *Sociodemographic characteristics of the study sample.*

Variable	N=198
Male gender (n,%)	116 (58.6)
Current age in years (mean ± SD)	61.72 ± 11.53
Years of education (mean ± SD)	8.3 ± 5.03
Currently employed (n,%)	56 (28.2)
Social security (n,%)	105 (53.0)
Disease duration in years (mean ± SD)	7.91±5.37
Years on dopamine agonist (mean ± SD)	3.70 ± 3.01
On brand-name pramipexole (n,%)	103 (52.0)
On generic pramipexole (n,%)	95 (48.0)

SD. Standard deviation.

Comparison of patients treated with brand-name pramipexole with those receiving the generic dopaminergic agonist is shown in Table 2. To be highlighted, no statistically significant differences between groups were

found for age (Mean difference of 2.49 ± 1.63, 95% CI -0.73 to 5.73, p=0.129), disease duration (Mean difference of 1.10 ± 0.77, 95% CI -0.39 to 2.60, p=0.146), LEDD (Mean difference of -68.61 ± 58.34, 95% CI -183.78 to 46.55, p=2.41), pramipexole daily dose (Mean difference of -0.28 ± 0.18, 95% CI -0.64 to 0.07, p=0.123), and MDS-UPDRS part III (Mean difference of -4.65 ± 2.40, 95% CI -9.40 to 0.83, p=0.54), In addition, no statistically significant difference was found in the frequency of depressive mood (p=0.850) or apathy (p=0.138).

Table 2. *Comparison between patients with Parkinson's disease treated with brand-name or generic immediate-release pramipexole.*

	Brand-name pramipexole (n=103)	***Generic pramipexole (n=95)***	***p***
Age (years) [1]	62.95±11.50	60.45±11.54	0.129
Male gender *	57 (55.3)	59 (62.1)	0.334
Currently employed *	25 (24.2)	31 (32.6)	0.192
Socioeconomic status [1]	2.34±1.08	2.06±1.22	0.128
Disease duration [1] (years)	8.42±6.02	6.81±4.65	0.146
MDS-UPDRS Part III [1]	27.75±17.06	32.40±16.64	0.055
Hoehn and Yahr stage[1]	2.41±.942	2.41±8.31	0.186
Antiparkinsonian polytherapy *	91 (88.3)	78 (82.1)	0.214
Pramipexole daily dose[1]	2.16±1.26	2.45±1.33	0.123
LEDD[1]	811.28±404.52	879.89±365.13	0.241
Depressive symptoms *	48 (46.6)	43 (45.2)	0.850
Apathy *	36 (34.9)	24 (25.2)	0.138

[1] Mean ± Standard deviation. Independent two-sample t-test.
* N (%). Chi square test.

Table 3 compares the patient-reported outcomes between groups treated with the brand-name versus generic pramipexole. No statistically significant differences in the MDS-UPDRS IB score were found (Mean difference of -1.15 ± 0.75, 95% CI -2.63 to 0.32, p= 0.126), On the other hand, MDS-UPDRS part II score was higher in the group receiving the generic drug (Mean difference of -3.33 ± 1.41, 95% CI -6.13 to -0.54, p=0.20). Likewise, patients with PD treated with the generic pramipexole reported a worst quality of life (Mean difference of -4.33 ± 1.94, 95% CI -8.20 to -0.51, p=0.26).

Table 3. *Comparison of patient-reported outcome scales between patients with PD treated with brand-name or generic immediate-release pramipexole.*

Patient-reported scale	**Brand-name pramipexole**	**Generic pramipexole**	**p-value[1]**
	n= 103	**n= 95**	
MDS-UPDRS IB	7.68 ± 5.16	8.84 ± 5.37	0.126
MDS-UPDRS II	12.88 ± 9.27	16.22 ± 10.56	0.020*
PDQ-8 SI	15.96 ± 12.55	20.32 ± 14.52	0.026*

MDS-UPDRS. Movement Disorder Society – Unified Parkinson's Disease Rating Scale. PDQ-8. Parkinson's disease questionnaire 8 simplified index. [1]Independent two-sample t-Test. * Statistical significant.

4. Discussion

In the present study we analyzed the presence of differences between patient-reported outcomes and investigator-rated outcomes in subjects with PD treated with either generic or brand-name pramipexole. No differences were found in the main clinical and demographic characteristics between patients treated with the brand-name or generic pramipexole. Moreover, no difference was found in disease severity. Motor impairment as assessed by the rater using the MDS-UPDRS motor part failed to show a statistically significant difference, although a trend was observed. On the other hand, patient-reported scales assessing motor experiences of daily living scored significantly better in the group of patients treated with the brand-name drug.

There are few reports in the literature comparing the use of brand-name versus generic antiparkinsonian drugs. Pahwa et al conducted an open label study in 86 patients with PD on brand-name carbidopa/levodopa who were switched to the generic drug. Although almost three quarters of the patients either preferred generic drug or had no preference, patients with a more advanced disease or with motor complications did preferred the brand-name carbidopa/levodopa [16]. In addition, two other studies comparing the pharmaceutical quality of levodopa formulations have been published, but no clinical data was collected [17, 18]. A third pharmacokinetic study in Chilean population also comparing branded and generic carbidopa/levodopa only assessed the motor state on their "best on" and "worst off" without reporting any differences [19].

Regarding dopamine agonists, a recent study evaluated 21 patients with PD switching from brand-name to generic ropirinole, an extended-release dopamine agonist [20]. In regards to the motor function, patients reported a decrease in the "on" time without dyskinesia when receiving the generic drug ($p<0.01$). Furthermore, no difference was found in the UPDRS part III (motor scale) score as assessed by a rater. These findings are in line with our results.

On the other hand, our study did not find a statistically significant difference on nonmotor experiences of daily living according to the MDS-UPDRS part Ib. Additionally, no difference in the frequency of depressive mood or apathy as assessed by the NMSS was found between groups. This is important due to the fact that these two factor are known to impact on the self-perceived quality of life. On this matter, health-related quality of life was also better in patients treated with the brand-name drug. The ropinirole study did not find any differences in quality of life scales between the branded and generic dopamine agonist administration.

Since no differences between groups were found in terms of demographical data, disease duration, disease severity, LEDD and use of antiparkinsonian polytherapy, a placebo effect related to the drug cost cannot be ruled out. Numerous mechanisms contribute to placebo effects, including the patient's expectations; moreover, it has been suggested that placebo effect can be seen in clinical practice, even if no placebo is actually given [21]. A recent study assessed the effect of cost in the response of motor symptoms in PD. Espay et al conducted a cross-over, double-bind, clinical trial

in which patients with PD were randomized to a "expensive" or to a "cheap" novel dopamine agonist, being placebo in both cases. The authors reported an improvement in motor function with both placebos, but greater when patients were receiving the "expensive" placebo [22]. Since our study was open-label, the perception of cost may have had an impact on the placebo response which reflected in the patient-reported motor symptoms and quality of life.

The study has limitations. First, the study was cross-sectional. Although the patients were on a stable dose of pramipexole, thus minimizing the risk of bias resulting from escalating dosage, a prospective study would provide better evidence. Second, the design was an open-label study. In this matter, the study main objective was only disclosed to the patient after the self-reported instruments were completed. On the other hand, the rater was blinded to the patients' treatment. Again, a randomized, double-blind, crossover study would be advisable. Third, a patients' beliefs about prescribed drugs and adherence was not assessed. Finally, the pharmaceutical equivalence was not assessed in the present study. Nevertheless, the Federal Commission for the Protection against Sanitary Risk (COFEPRIS), Mexico´s drug regulatory authority, uses almost the same parameters as the European Medicines Agency or the Food and Drug Administration [23]. Consequently, the drawbacks of considering pharmaceutical equivalence as a surrogate of bioequivalence and therapeutic effect also holds for Mexico, as is the case of not considering antiparkinsonians as narrow therapeutic index drugs. These issues are beyond the scope of our study, and have been addressed extensively elsewhere [24].

5. Conclusion

In conclusion, patients treated with brand-name pramipexole reported better scores in the motor experiences of daily living and the quality of life in comparison to those receiving the generic drug. On the other hand, no statistically significant difference in the motor evaluation was found between groups. It should also be pointed out that the MDS-UPDRS part III minimal clinically important difference has been reported to be -3.25 points for detecting improvement and 4.63 points for observing worsening [25]. In our study, the difference between groups was 4.65 points, suggesting this difference may be in fact clinically meaningful. A prospective study is still needed to better address this important issue which has both clinical and economical effects.

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