Time until modification of antiparkinsonian therapy in a group of patients from Colombia

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Introduction. The aim was to determine the time elapsed between the start of treatment with antiparkinsonian agents and the modification of the pharmacological therapy, and to establish its related factors, in a group of patients with Parkinson's disease from Colombia.

Patients and methods. Retrospective cohort study that collected information about the treatment of patients with Parkinson's disease who started drug therapy between June, 2011 and December, 2013; a five-year follow-up was performed. Survival analyses for time to therapy modification were generated, and factors related to these changes were determined using Cox regression models.

Results. A total of 3,224 patients (51.8% men) with a mean age of 73.1 ± 13.5 years started treatment with antiparkinsonian agents. After five years, 2,046 patients (63.5%) had modifications in drug therapy, in a mean time of 36.4 months (95% confidence interval: 35.7-37.1). A total of 1,216 patients (37.8%) required the addition of another active principle, while 830 (25.7%) had a switch to another drug. In the multivariate analysis, male sex, age over 65 years, and the start of amantadine were identified as factors that increased the likelihood of therapy modification. The use of bromocriptine, biperiden, and monotherapy as an initial treatment were associated with a reduction in this likelihood.

Conclusions. After five years of treatment, 63.5% of the patients with Parkinson's disease required modifications to their therapy, with a mean time of three years. Male sex, age over 65 years, and receiving initial therapy with amantadine affected the likelihood of switching therapy in these patients in Colombia.

Key words. Antiparkinsonian agents. Colombia. Drug utilization. Parkinson's disease. Pharmacoepidemiology. Survival analysis.

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The protocol was approved by the Bioethics Committee of the Universidad Tecnológica de Pereira in the category of 'risk-free research'. The principles established by the Declaration of Helsinki were respected. No personal data were collected from the patients. Institutional Review Board Code: CBE-SYR-202016.

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Introduction

Parkinson's disease is the second most frequent neurodegenerative disease worldwide, affecting 2-3% of the population over 65 years [1]. Its prevalence is higher in men and increases with aging, while its incidence has been reported between 10-18 cases per 100,000 inhabitants per year [1,2]. By 2016, Parkinson's disease was responsible for more than 210,000 deaths and the loss of 3.2 million disability-adjusted life years in the world [3]. In Colombia, a prevalence of 26,000 cases and 800 deaths were reported in 2016 [3]. The direct cost of the prescription of antiparkinsonian drugs for the Colombian health system in 2015, was USD 10.7 million [4].

The motor symptoms include, but are not limited to, the triad of bradykinesia, rigidity, and tremor, in association with a constellation of non-motor symptoms, which may precede the appearance of motor symptoms [5]. Antiparkinsonian drug therapy reduces the severity of motor symptoms and improves the quality of life of patients [6]. However, with the progression of the disease and the use of drug therapy, motor complications occur (motor fluctuations and dyskinesias) [7]. These are more frequent with the use of levodopa, so an attempt has been made to delay its onset using other antiparkinsonian drugs such as dopamine agonists or monoamine oxidase B inhibitors [8-10]. These therapeutic options allow dose modifications according to clinical improvement and adverse effects [5,11], but it should be noted that no strategy has delayed the evolution of the disease [8].

The Colombian health system offers universal coverage through two regimes, one contributory or paid by the employer and the worker, and another subsidized by the state that has a benefit plan with some of the useful drugs to treat Parkinson's disease. Identifying trends in the use of these drugs can increase the knowledge about the management of these patients. Therefore, the objective of this

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study was to determine the time elapsed from the start of treatment with antiparkinsonian drugs (with or without levodopa) until modification in therapy by adding or changing drugs, and the factors related to these modifications, in a group of patients with Parkinson's disease from Colombia.

Patients and methods

A retrospective cohort study was conducted with survival analysis to determine the time elapsed between the start of treatment with antiparkinsonian drugs and the modification of pharmacological therapy in patients with a diagnosis of Parkinson's disease affiliated to the Colombian health system. Patients with Parkinson's disease of either sex, aged 18 years or older, who started therapy with antiparkinsonian drugs for the first time in the period between June, 2011 and December, 2013 and had a continuous prescription of at least three months, were included. A monthly follow-up of the received prescriptions was subsequently performed for a period of five years until the time they presented any modification (addition or switch) in the therapy with antiparkinsonian drugs.

Information was obtained from the dispensing records of a company which delivers drugs to six health insurance companies, corresponding to approximately 17.3% of the Colombian population (30% of the active affiliated population of the contributory regime and 6% of the subsidized regime, without differences in drug access between regimes). The database and the information were verified by a pharmacologist and a neurologist, and the following groups of variables were included:

- Sociodemographic: age, sex, and city.
- Pharmacological: antiparkinsonian drugs included:
  - Dopamine precursor: levodopa-carbidopa, etc.
  - Anticholinergics: biperiden, etc.
  - Dopamine receptor agonists: pergolide, pramipexole, etc.
  - Catechol-o-methyltransferase inhibitors: entacapone.
  - N-methyl-D-aspartate receptor antagonist: amantadine.
  - Mono-aminoxidase-B inhibitor: selegiline and rasagiline.
- Comedication: the main comedications were identified, considering the following groups of drugs: a) antihypertensives (inhibitors of the renin angiotensin aldosterone system, β-blockers, thiazide diuretics, calcium channel antagonists); b) lipid-lowering drugs; c) antiplatelet drugs; d) antidiabetics and insulins; e) psycho-neurotropic drug (anxiolytics and hypnotics, antidepressants, antipsychotics, antiepileptics); f) thyroid hormone.

Data analysis was conducted using SPSS 24.0 version for Windows. The start of follow-up was considered as the moment when the patient with Parkinson's disease began antiparkinsonian drug therapy (time $0 - t_0$). A monthly time scale was used and any modification (switch or addition of any medication) in therapy was defined as the outcome (time $k - t_k$). A Kaplan-Meier survival analysis was performed to assess the time elapsed from t_0 to t_k. A separate analysis was performed for the group of patients who did not start their treatment with levodopa, and the time elapsed until the use of this drug was determined (it is understood as the moment at which levodopa was added to the background therapy or the initial drug was switched to levodopa). Patients that never presented any switch in therapy were categorized as censored, and those who withdrew before the completion of the follow-up time were categorized as lost in follow-up.

The differences among groups were estimated through a log rank test, and the risk of modification in therapy (switch or addition) and the start of levodopa were estimated using logistic regression analysis. $p < 0.05$ was considered statistically significant.

The protocol was reviewed by the Bioethics Committee of the Universidad Tecnológica of Pereira (Pereira, Colombia); it was approved as 'research without risk' and guaranteed the anonymity of the patients, following the principles of the Declaration of Helsinki.

Results

During the observation period, 3,224 patients who started treatment with antiparkinsonian drugs were found; 51.8% were men and the mean age at the beginning of the observation period was 73.1 years (range:30.3-95 years) (Table I). During the five-year follow-up, 2,046 (63.5%) patients presented modifications in their pharmacological treatment, of which 1,216 (37.8%) required the addition of another active ingredient, while 830 (25.7%) switched to another drug. At the beginning of follow-up, 1,854 (57.5%) patients used levodopa in any of its presentations, associated with dopa-decarboxylase inhibitors.

When a switch of therapy to levodopa was required during the observation period, 236 patients (7.3%) were modified (switched or added) to levodopa with a decarboxylase inhibitor, while 562 patients (17.4%) needed the modification to levodopa-carbidopa-entacapone. A total of 2,377 (73.7%) patients used levodopa in any of its presentations at some point in the study.

The most frequently used combinations at the end of the follow-up period were levodopa-carbidopa-entacapone in 521 (16.2%) patients, levodopa-decarboxylase inhibitors (carbidopa, benserazide) + amantadine in 334 (10.3%) patients, levodopa-carbidopa-entacapone + amantadine in 90 (2.8%) patients, levodopa-decarboxylase inhibitors + biperiden in 74 (2.2%) patients, levodopa-decarboxylase inhibitors + pramipexole in 59 (1.8,%) patients, levodopa-decarboxylase inhibitors + rasagiline in 37 (1.1%) patients, and levodopa-decarboxylase inhibitors + rotigotine in 31 (0.96%) patients. Table II shows the proportions of antiparkinsonian drugs used during the five years of follow-up.

Follow-up analysis

The mean time to modification (addition or switch) of antiparkinsonian drug treatment in the five years of follow-up was 36.4 months (95% confidence interval: 35.7-37.1) (Figure a). Men presented a shorter mean time compared to women (33.9 versus 39.2 months; $p < 0.001$). On the other hand, patients older than 65 years (n = 2,344, 72.7%) presented a mean time of 34 months until the switch or addition, while it was 45.3 months in those younger than 65 years ($p < 0.001$) (Figure b).

In patients who did not receive levodopa as initial treatment (n = 1,370, 42.5%), a mean time of 42.1 months was observed to start this drug (95% confidence interval: 40.8-43.3). In this subgroup of patients, men started levodopa earlier compared to women (mean: 39 ± 1 versus 44.9 ± 0.9 months; $p < 0.001$). The mean time to start levodopa in those older than 65 years was 35.4 months (95% confidence interval: 33.7-37.2).

Multivariate analysis for therapy modification

The multivariate analysis showed that being male, being over 65 years of age, and receiving initial therapy with amantadine were statistically associated with an increased likelihood of modifications in antiparkinsonian drug therapy, while initiating therapy with biperiden or bromocriptine, and anti-

Table I. Sociodemographic characteristics and comedication in patients treated with antiparkinsonian drugs, Colombia, 2013-2018.

	Frequency n = 3,224	%
Age (years) - mean ± SD	73.1 ± 13.5	
Male sex	1,670	51.8
Departments		
Valle del Cauca	1,547	48.0
Cundinamarca	664	20.6
Atlántico	192	6.0
Risaralda	190	5.9
Cauca	112	3.5
Santander	97	3.0
Nariño	85	2.6
Others	337	10.4
Comedication	2,174	67.4
Antihypertensives	1,407	43.6
Analgesics	1,087	33.7
Antiulcer drugs	972	30.1
Antiplatelet drugs	915	28.4
Statins	848	26.3
Antidepressants	841	26.1
Diuretics	812	25.2
Levothyroxine	394	12.2
Antiepileptics	360	11.2
Antidiabetics	330	10.2
Inhaled bronchodilators	311	9.6
Other lipid-lowering drugs	203	6.3
Anxiolytics	174	5.4
Antipsychotics	154	4.8
Antidementia drugs	84	2.6

SD: standard deviation.

Table II. Profile of antiparkinsonian drugs use during the follow-up period, Colombia, 2013-2018.

	Mean age	Male sex (%)	Start of follow-up		End of follow-up	
			n	%	*n*	%
Levodopa[a]	77.4	55.3	1,854	57.5	1,750	54.3
Levodopa + ID			1,605	49.8	1,234	38.3
Entacapona/levodopa/carbidopa			249	7.7	516	16
Amantadine	76	54.2	910	28.2	704	21.8
Biperiden	69	52.2	732	22.7	548	17
Bromocriptine	63.5	36.4	327	10.1	192	6
Pramipexole	71.3	58.6	251	7.8	418	13
Rotigotine	73.5	70.4	27	0.8	201	6.2
Selegiline	72.7	66.7	6	0.2	9	0.3
Rasagiline	57.5	66.7	3	0.1	218	6.8
Entacapone	N/A	0	1	0	1	0
Monotherapy	71.5	49.7	2,260	70.1	2,133	66.1

DI: decarboxylase inhibitors (carbidopa, benserazide). [a] Any presentation.

parkinsonian monotherapy were associated with a reduced risk of modifications (Table III).

Multivariate analysis for adding or switching therapy to levodopa

Within the group of patients who did not initially start treatment with levodopa, the multivariate analysis showed that being male, being older than 65 years, receiving initial therapy with pramipexole, and having cardiovascular disease were associated with a higher probability of adding or switching to levodopa in any of its presentations, whereas the initiation of therapy with bromocriptine and monotherapy with antiparkinsonian drugs was associated with a reduction of this risk (Table III).

Discussion

This study identified the time elapsed between the initiation of antiparkinsonian drug therapy and its modification (addition or switch of medications) after a five-year follow-up. These data have not been described before in Colombia and may be the starting point for carrying out complementary analyses, after the entry of therapies such as apomorphine or safinamide into the Colombian market.

During the follow-up period, more than 60% of patients presented modifications in antiparkinsonian drug therapy, with 37.7% of patients requiring an addition; a proportion higher than the 12.2% found in the United States (2012-2017) and the 28% reported in the United Kingdom (2004-2015) [12]. On the other hand, the switch from the initial antiparkinsonian drugs occurred in about a third of patients in Colombia, and these results are also higher than the 4.6% shown in the United States and the 17.2% noted in the United Kingdom [12]. These modifications may be explained by different reasons, some specific to the patient, such as age, ethnicity, duration of the disease (presence of motor fluctuations and dyskinesias), comorbidities, economic situation, and geographic location [13,14], and others that are not inherent to the patients, such as variability in prescription patterns and drug use trends among different populations, which may even be related to factors specific to the prescriber [13].

Figure. a) Time to modification (switch or addition) of antiparkinsonian therapy in the total cohort (*n* = 3,224). b) Time to modification (switch or addition) of antiparkinsonian therapy according to age group (over 65 years). Censored patients corresponded to those who never presented any switch in therapy during follow-up.

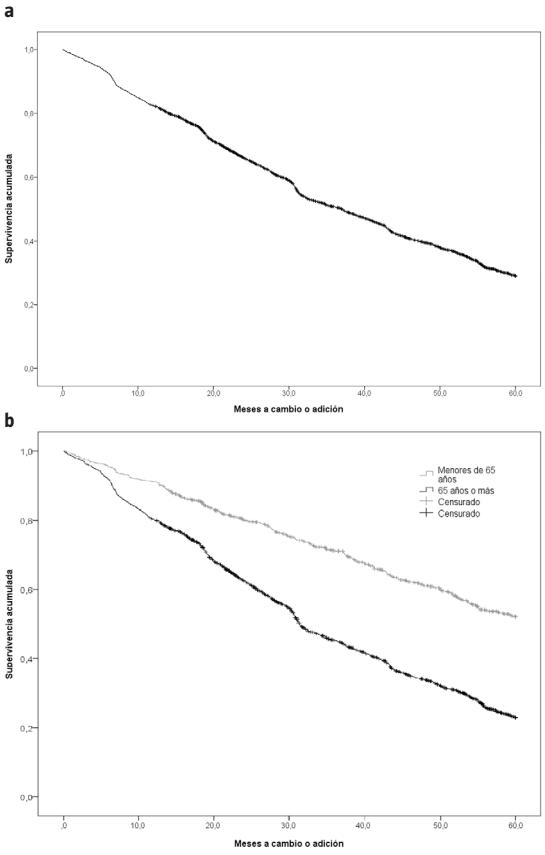

Table III. Multivariate analysis on modification of antiparkinsonian drug therapy in the total cohort (*n* = 3,224) and on the initiation of levodopa in antiparkinsonian drug therapy (*n* = 1,370).

	p	HR	95% CI	
			Lower	Upper
Modification of antiparkinsonian drug therapy (*n* = 3,224)				
Male sex	<0.001	1.327	1.213	1.453
>65 years	<0.001	1.619	1.415	1.853
Cardiovascular disease	0.419	1.04	0.946	1.142
Amantadine	0.034	1.118	1.009	1.239
Bromocriptine	0.013	0.811	0.687	0.958
Biperiden	<0.001	0.583	0.513	0.661
Levotiroxine	0.108	0.887	0.766	1.027
Antiepiléptics	0.271	0.917	0.786	1.07
Start with monotherapy	<0.001	0.576	0.521	0.637
Initiation of levodopa in antiparkinsonian drug therapy (*n* = 1,370)				
Male sex	0.003	1.31	1.095	1.568
>65 years	<0.001	2.757	2.138	3.555
Biperiden	0.065	0.608	0.359	1.031
Amantadine	0.13	1.499	0.888	2.53
Bromocriptine	0.024	0.498	0.273	0.91
Pramipexole	0.024	1.838	1.084	3.116
PPI	0.551	0.933	0.744	1.171
Antidepressants	0.653	1.052	0.843	1.314
Analgesics	0.892	0.985	0.788	1.231
Cardiovascular disease	0.004	1.364	1.107	1.681
Start with monotherapy	<0.001	0.3	0.153	0.586

CI: confidence interval; HR: hazard ratio; PPI: proton pump inhibitors.

At the time of recruitment, 57.5% of patients used levodopa. There is a trend towards high initiation of levodopa among different populations, varying between 49.6% and 85.1% [15-17]. This may be related to a high prevalence of Parkinson's disease in the elderly, because levodopa is the drug of choice to initiate treatment in this population, or to the search for the control of motor symptoms as the primary objective of therapy, according to international guidelines [6,18].

The results of the modification (addition or switch) of antiparkinsonian drug therapy during follow-up are consistent with those reported in other countries, such as Japan, the United States, and the United Kingdom, in which monotherapy decreases, whereas combined treatment increases, mainly with levodopa and entacapone, amantadine, dopamine agonists, or mono-aminoxidase-B inhibitors in different proportions, as well as a decrease in the use of ergot-derived dopamine agonists and anticholinergic drugs [12,15,16,19]. These modifications in therapy are not only explained by various factors (inherent to the patient or not), as men-

tioned above, but are also related to the treatment options of international guidelines regarding motor complications that occur in the course of the disease [6,18]. It should be mentioned that there is a correlation between the time of evolution of the disease and the number of antiparkinsonian drugs used, which can reflect the need to control motor complications [7].

The mean time to addition or switch of antiparkinsonian treatment (36.4 months) may be explained by the substantial increase in the frequency of motor complications requiring treatment (around three years) that has been reported in other populations. In a follow-up study in a hospital in Spain, a frequency of motor fluctuations at three years of treatment of 10% and dyskinesias of 16% were reported, increasing to 35% and 32%, respectively, at 5 years [20].

The mean time to addition of levodopa (42.1 months) in patients who did not receive it as the initial treatment (42.5%) is a prolonged time that may reflect an attempt to delay its use, due to evidence of the association of early use with motor complications [20]. In this regard, an observational study in Estonia in patients who initiated levodopa therapy reported a frequency of motor fluctuations in 4.8% and dyskinesias in 3.4% of those with a time of use less than 2.5 years; but these increased in the usage group between 2.5 and 5 years, to 21.2% and 16.7%, respectively [21]. This result may reflect the delay in the presentation of motor complications in patients using other groups of drugs that are less effective in controlling motor symptoms, when compared with levodopa. In contrast, the mean time to therapy modification and the start of levodopa were shorter in patients older than 65 years; a finding that has been consistent, given the correlation of older age with motor fluctuations [22]. However, the results regarding age are variable among different studies [20,21].

In the multivariate analyses for the modification of antiparkinsonian drug therapy and the initiation of levodopa, most of the studies on trends in use are limited to descriptive analysis, and the variables in the treatment cohorts are far from those included in this study, which limits the comparison of results [23,24]. It was considered that the variables associated with a greater probability of requiring modifications in antiparkinsonian drug therapy and with the initiation of levodopa, such as being older than 65 years or having cardiovascular disease, may be related to a longer time of evolution of the disease and the possible high incidence of motor complications. In the same way, there is increasing evidence of neurodegeneration with Lewy bodies that affects the peripheral and enteric nervous systems, far from the classic Braak staging; and in this context, cardiovascular disease or symptoms could serve as a measure of this underlying neurodegeneration and its expected progression [25-27].

On the other hand, the initiation of monotherapy, which was associated with a lower likelihood of switches or initiation of levodopa, may be related to shorter times of evolution of the disease and less severity of motor symptoms [20,22]. In addition, it should be considered that amantadine as an initial monotherapy was associated with a greater likelihood of modification, because its role in treatment is fundamentally related to the control of dyskinesia and not the control of motor symptoms [1-3].

The data shown in this study represents local treatment practices; therefore, interpretation should be within the context of this population and others with similar healthcare conditions or availability and access to treatments, which may also vary during time. In addition, the data include information from outpatients with Parkinson's disease and are therefore not applicable to hospital care.

The limitations of this study include a lack of clinical data, such as the stage or severity of the disease, the presence and characteristics of motor and non-motor complications, as well as the presence of the only advanced therapy available in the country at the time of the study (deep brain stimulation), which can determine switches in therapy.

Furthermore, we have no information on the specific reasons that led to the modification of antiparkinsonian drug therapy, nor the specialty of the prescribing physician. However, there are also strengths to this study, including the relatively large number of patients with Parkinson's disease followed in the cohort who started drug therapy in different cities in Colombia and the follow-up period of five years, which provide valuable information for continuous monitoring of antiparkinsonian drug therapy.

Conclusions

This study showed that 63.5% of patients with Parkinson's disease required modifications in antiparkinsonian therapy during the five-year observation period, and the mean time of these switches was three years. Patients older than 65 years required these modifications earlier than younger patients. The drug combinations were carried out in accordance with the possibilities established in the inter-

national recommendations for the control of symptoms and the management of complications typical of advanced Parkinson's disease. Knowledge of the time elapsed until modifications in antiparkinsonian drug therapy provides valuable information that can be used by health administrators to make decisions aimed at improving the healthcare of patients with Parkinson's disease in Colombia.

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Tiempo hasta la modificación de la terapia antiparkinsoniana en un grupo de pacientes de Colombia

Introducción. Se buscó determinar el tiempo transcurrido desde el inicio del tratamiento con fármacos antiparkinsonianos hasta la modificación en la terapia y establecer sus factores relacionados en un grupo de pacientes con enfermedad de Parkinson de Colombia.

Pacientes y métodos. Estudio de cohorte retrospectiva que recolectó información sobre el tratamiento de pacientes con enfermedad de Parkinson que iniciaron terapia farmacológica entre junio de 2011 y diciembre de 2013; se realizó seguimiento a cinco años. Se generaron análisis de sobrevida para el tiempo trascurrido hasta la modificación de la terapia y se determinaron los factores relacionados con estos cambios utilizando modelos de regresión de Cox.

Resultados. Un total de 3.224 pacientes (51,8%, hombres), con edad media de 73,1 ± 13,5 años, iniciaron tratamiento con fármacos antiparkinsonianos. Después de cinco años, 2.046 pacientes (63,5%) tuvieron modificaciones en la terapia farmacológica, con un promedio de tiempo de 36,4 meses (intervalo de confianza al 95%: 35,7-37,1). Un total de 1.216 pacientes (37,8%) requirió adición de otro principio activo, mientras que 830 (25,7%) tuvieron un cambio por otro medicamento. En el análisis multivariado, el sexo masculino, la edad mayor de 65 años y el inicio de amantadina se identificaron como factores que aumentaron la probabilidad de modificar la terapia. El uso de bromocriptina y biperideno, y la monoterapia como tratamiento inicial redujeron dicho riesgo.

Conclusión. Después de cinco años de tratamiento, el 63,5% de los pacientes con enfermedad de Parkinson requirió modificaciones de la terapia, con un tiempo promedio de tres años. El sexo masculino, la edad mayor de 65 años y recibir terapia inicial con amantadina afectaron a la probabilidad de cambio de terapia en estos pacientes en Colombia.

Palabras clave. Análisis de supervivencia. Fármacos antiparkinsonianos. Colombia. Enfermedad de Parkinson. Farmacoepidemiología. Utilización de medicamentos.