RBFHSS
Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde

Original Paper

Open Access

Management of pharmacological treatment in patients with COPD and the direct cost of long-term anticholinergic therapy: real-world experience

Isabelle Viana BORGES, Priscilla Alves ROCHA, Karen Ramalho PALERMO, Andrea Pereira SFORSIN, Vanusa Barbosa PINTO, Rafael STELMACH

[1]Divisão de Farmácia, Instituto Central – ICHC – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil; [2]Divisão de Pneumologia, Instituto do Coração - InCor - Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil;

Corresponding author: Stelmach R, rafael.stelmach@incor.usp.br

Submitted: 23-10-2021 Resubmitted: 15-12-2021 Accepted: 17-12-2021

Peer review: Débora Rafaelli Carvalho and Tarcio de Almeida

Abstract

Objective: To describe the experience with the use of long-term anticholinergic therapy available in the public service. **Method:** A cross-sectional study with data collected in the real world. The sample consisted of SUS users who received inhaled LAMAs for the treatment of COPD between November 2019 and November 2020. Inclusion criteria were: diagnosis of COPD, being in clinical follow-up by the COPD health team, having record of anticholinergics dispensing by the pharmacy during the study period, having been using LAMA (tiotropium, glycopyrronium and umeclidenium) for at least 3 months. Patients with absence or insufficiency of data and without medical appointments for more than a year and a half from the final period of the study were excluded. Sociodemographic analysis, clinical assessment of patients and quality of life questionnaires were performed. Continuous variables were expressed as mean and standard deviation and analyzed by t Student, and categorical variables were expressed as absolute (n) and relative (%) frequency and analyzed by chi-square or Fisher, with confidence level <0.05. For direct costs, the analysis were performed in a simplified way, using the service's anticholinergics dispensing and stock data. **Results:** The study included 197 patients, 177 using anticholinergic tiotropium and 20 using glycopyrronium or umeclidenum. There was no significant difference when analyzing the groups regarding age (p=0.814), sex (p=0.780) and comorbidities (p >0.05). It was found that patients had polypharmacy (83.8%) and 74.1% of patients used 3 or more types of devices. We found in the population a predominance of patients classified as GOLD 3 and profile B, being represented by 45.2% (n = 89) and 66.5% (n = 131), respectively, showing a more severe population. In relation to the specific questionnaires, in both groups, we noticed an increase in the CAT value and a tendency towards a worsening in the mMRC. For the direct costs with the treatment, an annual expense of U$ 124.474,35 was estimated. Based on a drug dispensing strategy, we were able to predict savings of U$ 13.915,77/year for this treatment. **Conclusions:** Patients with severe COPD tend to use more inhalation devices. The availability of pharmacotherapeutic alternatives by the public service can contribute to the individualization of anticholinergic treatments and enable a more adequate assessment of therapy according to the patient's clinical profile, linked to possible economic strategies related to individualized treatment.

Keywords: chronic obstructive pulmonary disease; inhalation devices; pharmacist; pharmacoeconomics; anticholinergic; quality of life

Manejo do tratamento farmacológico em pacientes com DPOC e custo direto da terapia anticolinérgica: experiência de vida real

Resumo

Objetivo: Descrever a experiência com o uso da terapia anticolinérgica de longa duração disponível na rede pública de São Paulo, seus custos diretos inferidos e possíveis impactos econômicos. **Método:** Estudo transversal realizado em um ambiente de vida real. A amostra foi composta por usuários SUS que receberam os LAMAs inalatórios para tratamento da DPOC entre o período de novembro de 2019 a novembro de 2020. Os critérios de inclusão foram: diagnóstico de DPOC, acompanhamento clínico pelo grupo de DPOC, dispensação de anticolinérgicos durante o período de estudo e uso atual de LAMA (tiotrópio, glicopirrônio e umeclidínio) por pelo menos 3 meses. Foram excluídos os pacientes com ausência ou insuficiência de dados e sem consulta médica há mais de 1 ano e meio do período final do estudo. Foi feita a análise do perfil sociodemográfico, da evolução clínica e da qualidade de vida dos pacientes. As variáveis contínuas foram expressas por média e desvio padrão, e analisadas por t Student, e as variáveis categóricas foram expostas em frequência absoluta (n) e relativa (%), e analisadas por qui-quadrado ou Fisher, adotou-se um nível de confiança <0,05. Para os custos diretos, foi realizada uma análise simplificada, usando os dados de dispensação e estoque das terapias anticolinérgicas do serviço. **Resultados:** O estudo

incluiu 197 pacientes, 177 em uso de tiotrópio e 20 em uso de glicopirrônio ou umeclidínio. Não houve diferença significativa quando analisados os grupos em relação a idade (p=0,814), sexo (p=0,780) e comorbidades (p >0,05). Os pacientes apresentavam polifarmácia (83,8%) e 74,1% dos pacientes tinham em uso 3 ou mais tipos de dispositivos. A população estudada predominantemente foi classificada como GOLD 3 e perfil B, representando 45.2% (n = 89) e 66.5% (n = 131) respectivamente, evidenciando uma população mais grave. Em ambos os grupos de tratamento percebemos um aumento no valor do CAT e uma tendência à piora do mMRC. Para os custos diretos do tratamento com os anticolinérgicos de longa ação, foi encontrado um gasto anual de U$ 124.474,35. Com base em estratégias de dispensação dos medicamentos, conseguimos prever uma economia de U$ 13.915,77/ano para este tratamento. **Conclusão:** Pacientes com DPOC grave tendem a usar mais dispositivos inalatórios. A disponibilização de alternativas farmacoterapêuticas pela rede pública pode contribuir para a individualização dos tratamentos anticolinérgicos e possibilitar uma avaliação mais adequada da terapia de acordo com o perfil clínico do paciente, atrelado a possíveis estratégias econômicas relacionadas ao tratamento individualizado.

Palavras-chave: doença pulmonar obstrutiva crônica; dispositivos inalatórios; farmacêutico; farmacoeconomia; anticolinérgicos; qualidade de vida.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a clinical condition that affects the respiratory system through a chronic obstructive process, which occurs due to prolonged inhalation exposure to risk factors and individual response.[1–4] According to the World Health Organization, it is the fourth leading cause of death in the world.[3,5] In Brazil, it is among the main 5 causes of death in the age group ≥40 years old.[3,4,6]

In Brazil, through the State Health Secretariat (*Secretaria Estadual de Saúde*, SES), the State of São Paulo incorporated a public therapeutic assistance protocol for patients with COPD.[7] Based on this protocol, the states of Espírito Santo, Minas Gerais, Ceará, Distrito Federal, Goiás, Maranhão and Pernambuco have also implemented specific protocols regulating the dispensation of tiotropium via the state secretariat.[8] A 2019 survey showed that exacerbation-associated mortality was higher in the 50-60-year-old age group in states without an anticholinergic dispensing protocol.[9]

Although long-acting anticholinergics (LAMAs) are widely recommended in the treatment of COPD, until 2012 the only representative available for inhaled use was tiotropium bromide. For this reason, despite the high cost, it was the recommended therapeutic option.[7,10] In Brazil, it was only in 2014 that the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA) approved a new drug for this condition: glycopyrronium bromide. Currently, in addition to the aforementioned, umeclidinium bromide is available, incorporated in the therapeutic options in 2016.[10,11] In the state of São Paulo, in 2019, Resolution No. 35, dated April 18th, was approved, which added the other two LAMAs to the COPD treatment protocol and made dispensing available by the Unified Health System (*Sistema Único de Saúde*, SUS).[12]

In view of the entire therapeutic arsenal for the treatment of the disease, in addition to the evaluation of the efficacy and safety of the therapies, another important assessment is about the types of devices available. In general, patients can use up to three different types of devices, which can cause the inhalers to be used incorrectly and impair patient compliance with the treatment proposed.[13]

In the treatment of COPD, the assessment of the patient's quality of life is an indispensable parameter.[4] One of the main symptoms associated to clinical deterioration is the report of dyspnea, as well as the presence of exacerbations. For monitoring the progression of COPD, the tools used are the modified Medical Research Council's (mMRC) dyspnea scale and the COPD Assessment Test (CAT) questionnaire, both of which help quantify the symptoms of the disease.[2,8,14,15]

This study aims at describing the experience of using long-term anticholinergic pharmacotherapy in COPD patients, available in the São Paulo public health network in a large health center, the direct costs of therapy, and possible economic impacts.

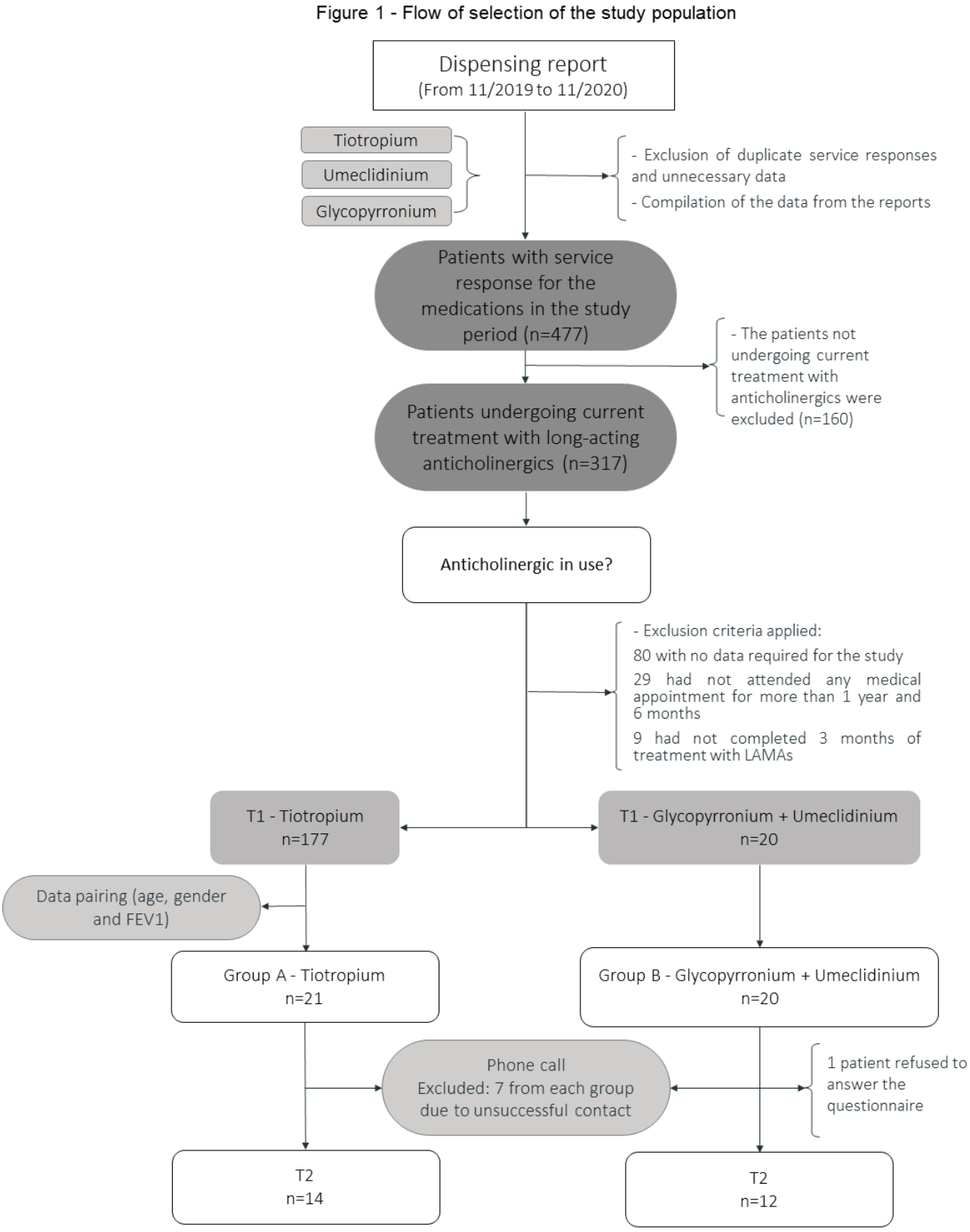
Methods

A cross-sectional study with data collected from patients treated at the Pulmonology outpatient clinic for the COPD group of an outpatient service linked to a hospital complex that attends to highly complex health conditions in São Paulo/SP. All the clinical data were collected through the REDCap 11.2.5 database projection software- © 2021 Vanderbilt University. The statistical analyses were performed in the GNU PSPP® program, version 1.4.1. The research was approved by the Committee of Ethics in Research with Human Beings of the Clinical Hospital of the Medical School at the University of São Paulo (CAAE No. 36998720.0.0000.0068).

The sample consisted of SUS users who received inhaled LAMAs for the treatment of COPD between November 2019 and November 2020 by the outpatient pharmacy attached to the hospital complex selected as the study locus. A dispensing report for the long-acting anticholinergics was generated to define the population. The inclusion criteria adopted were as follows: COPD diagnosis, clinical follow-up by the COPD group, pharmacy care of anticholinergics during the study period, and current use of LAMAs (tiotropium, glycopyrronium, and umeclidinium) for at least 3 months. Patients with missing or insufficient data and those without any medical appointment more than one and a half years prior to the end of the study period were excluded. The study design is shown in Figure 1.

The patients' initial information was collected from the electronic medical records referring to the medical appointments, and we called it T1 (Time 1). The patients were categorized by their sociodemographic profile, which included age, gender, comorbidities and smoking history. The variables on the patients' clinical evolution and quality of life were also extracted, being the CAT, mMRC and FEV_1 (Forced Expiratory Volume in 1 minute) values. The data on the number of inhalation devices, polypharmacy (characterized by the use of 5 or more drugs) and treatment lines (pharmacological classes to treat the pulmonary condition) were described to characterize the complexity of the patients' pharmacotherapy. After collecting the clinical data, the patients were classified according to the severity of the disease using the GOLD criteria.

Figure 1. Flowchart corresponding to the selection of the study sample.



To verify whether there were any clinical changes after initiating the treatment with the new long-acting anticholinergics, the tiotropium group was paired with patients taking glycopyrronium or umeclidinium. Equivalent samples, approximate mean age, gender distribution, and similar FEV_1 (liters) were recommended. This pairing was performed to allow for a comparative analysis of the data in two different moments of the study groups: before incorporating the new anticholinergics and after their standardization in the service.

At the second data collection moment, which we called T2 (Time 2), telephone contacts were made with the patients from the final sample, after pairing. The questionnaires for dyspnea (mMRC), CAT, exacerbations and satisfaction assessment about the inhalation device and treatment of COPD through the verbal numeric scale (ENV) were applied A specific form (Annex I) was prepared for this information, and the patient's authorization was verbally requested. The calls were recorded and the patients with whom it was not possible to make the telephone contacts and those who refused to answer the questionnaire were excluded from the sample.

For the analysis of the direct costs, a medical prescription report was generated for the three medications. The report discriminates the group and medical specialty in which the prescription was made, as well as data related to the prescription, validity and prescribed dosage. From this report, the number of units of each medication ordered per prescription was counted. To analyze the stock of the service, a movement sheet was generated, with the inputs and outputs of the supply center for the period from 11/2019 to 11/2020.

Based on the demand generated by the medical prescriptions and with the cost of each medication, the total expenditure for all three medications was estimated. The medication values were extracted from the CMED table, which regulates the maximum price charged by manufacturers and/or distributors and is updated monthly. The 18% factory price (FP) was used for the study calculation, which identifies the regulated values for the state of SP; the table was consulted in the November 2021 update. The values presented were converted into dollars to express the direct costs of the treatments, using a rate of 5.6118 reais to 1 dollar; data extracted from the Central Bank of Brazil with November 29th, 2021, as quotation date. For this analysis, only the COPD group within the Pulmonology specialty was selected from the report, these being the patients who make up our study population. From this consumption estimation, a possible change in the distribution of the medications was proposed, following the recommendation of the SES in partnership with the institution's pharmacology commission. The project aimed at structuring a care where 20% of the treatments would be with glycopyrronium, 20% with umeclidinium, and 60% with tiotropium. This recommendation takes into consideration that the vast majority of the population on inhaled LAMAs already used tiotropium therapy and the goal of the protocol was to gradually incorporate the new standardized medications. With these data, possible savings generated by the CPOD outpatient service with the prescriptions of the anticholinergics were estimated.

The descriptive statistical analysis was expressed as mean and standard deviation for the continuous variables, and absolute (n) and relative (%) frequencies were used for the categorical variables. The statistical tests employed were Pearson's Chi-Square and Fisher's Exact for the categorical data, and Student's t for the continuous variables. A confidence level <0.05 was adopted for this univariate analysis.

Results

The study included 197 patients, of which 177 (89.9%) were undergoing anticholinergic therapy with tiotropium and 20 (10.1%) were in use of glycopyrronium or umeclidinium. In Table 1 we can verify the results found in relation to the total population and the characterization of the groups regarding the patients' sociodemographic profile. The patients' clinical data are also represented in Table 1, where we can find the values referring to the total population and to the study groups. When we classify the patients in relation to severity, according to the GOLD recommendation, we can state that the population is predominantly GOLD 3 with a B profile, being represented by 45.2% (n=89) and 66.5% (n=131), respectively. The same profile was observed between the groups, with 44.6% (n=79) of the tiotropium group classified as GOLD 3, 41.2% (n=73) as GOLD 4, 13.6% (n=24) as GOLD 2, and only 0.6% (n=1) as GOLD 1. Regarding the glycopyrronium + umeclidinium group, a similar distribution was observed, with 50.0% for GOLD 3, 25.0% (n=5) classified as GOLD 4, 20.0% (n=4) as GOLD 2, and only 5.0% (n=1) as GOLD 1. On the other hand, for the patients' clinical profile, when we analyzed the questionnaires and exacerbations, we notice a small difference in distribution of the patients. In the tiotropium group there is 66.7% (n=118) of patients with profile B, 26.0% (n=46) classified as D, 5.6% (n=10) with profile A, and only 1.7% (n=3) as C. In the glycopyrronium and umeclidinium group, the B profile continues to predominate with 65.0% (n=13), but followed by the A profile ahead of the D and C profiles, with 20.0% (n=4), 10.0% (n=2) and 5.0% (n=1), respectively.

In the characterization of pharmacotherapy, it was found that the patients predominantly have polypharmacy; 165 patients, that is, 83.8% used more than 5 continuous use medications. In addition, 74.1% of the patients were using 3 or more types of different devices (n=146). Among the predominant types, the nebulimeter and inhalation capsule models were among the most frequent, with 73.6% and 71.6% (n=145 and n=141) respectively, second only to the respimat® model, which presented 89.8% (n=177). Reasserting the previous result, there were 181 (91.9%) patients on long-acting β2 adrenergic agonist associated with inhaled corticosteroid and 129 patients on short-acting β2 adrenergic agonist (65.5%). Only 13 patients used long-acting β2 adrenergic agonist alone and 2 patients used inhaled corticosteroid alone (n=6.6% and 1.0%, respectively).

After pairing, the tiotropium group was reduced to a number approximating the glycopyrronium and umeclidinium group (n=21 and n=20); the mean age between the groups showed no significant differences, being 67.8 years old for tiotropium and 67.6 years old for glycopyrronium and umeclidinium (p=0.928). The distribution by the sex was similar between the two groups with 10 female and 11 male patients in the tiotropium group, a similar proportion found for the glycopyrronium and umeclidinium group, with 10 female and 10 male patients (p=0.563). FEV_1 (liters), which indicates the patients' severity, also presented no significant difference between the two groups after pairing, with the mean for the tiotropium group being 1.15 liters and 1.19 liters for glycopyrronium and umeclidinium (p=0.787). The data found after interviewing the patients at time T2 are described in Table 2, where we can see the patients' clinical data at the two moments of the study. In both groups, an increase in the CAT value and a tendency for the mMRC to become worse is noticed. When looking at the exacerbations, we notice that the patients started to exacerbate more, but the number of episodes did not increase.

RBFHSS
Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde

Table 1. Sociodemographic and clinical characterization according to use of the medications.

Information	Total (n=197)	Tiotropium (n=177)	Glycopyrronium + Umeclidinium (n=20)	p-value
Sociodemographic				
Male gender[1] n (%)	107 (54.3)	97 (54.8)	10 (50.0)	0.814
Age (years old) Mean (SD)	68.1 (8.6)	68.2 (8.7)	67.6 (7.66)	0.780
Clinical conditions n (%)				
Smoking[1]	188 (95.5)	169 (95.5)	19 (95.0)	0.928
Systemic Arterial Hypertension	112 (56,9)	103 (58.2)	9 (45.0)	0.341
Other pulmonary diseases	77 (39.1)	71 (40.1)	6 (30.0)	0.472
Acute Coronary Syndrome	37 (18.8)	32 (18.1)	5 (13.5)	0.547
Heart Failure	26 (13.2)	25 (14.1)	1 (5.0)	0.483
Diabetes Mellitus	46 (23.4)	40 (22.6)	6 (30.0)	0.577
Dyslipidemia	44 (22.3)	39 (22.0)	5 (25.0)	0.780
Gastroesophageal Reflux	44 (22.3)	41 (23.2)	3 (15.0)	0.574
Obesity	21 (10.7)	19 (10.7)	2 (10.0)	0.639
Anxiety / Depression	16 (8,1)	15 (8.5)	1 (5.0)	0.499
Osteoporosis	13 (6,6)	11 (6.2)	2 (10.0)	0.626
Cancer (except lung nodules)	12 (6,1)	12 (6.8)	-	0.615
Others	79 (40.1)	71 (40.1)	8 (40.0)	0596
FEV_1 n (SD)				
FEV_1 (liters) Mean (SD)	0.97 (0.39)	0.94 (0.36)	1.19 (0.58)	0.007
FEV_1 (predicted%) Mean (SD)	35.75 (13.25)	34.94 (12.49)	42.95 (17.45)	0.009
CAT				
CAT Mean (SD)	19.88 (7.46)	20.44 (7.40)	14.95 (6.15)	0.002
CAT $\geq$ 10[1] n (%)	179 (90.0)	164 (92.7)	15 (75.0)	0.023
mMRC Mean (%)				
mMRC $\geq$ 2[1] n (%)	171 (86.8)	157 (88.7)	14 (70.0)	0.049
Exacerbations n (%)				
No exacerbations[1] n (%)	110 (55.8)	96 (54.2)	14 (70.0)	0.180
3 or more exacerbations[1] n (%)	23 (26.4)	22 (27.2)	1 (16.7)	0.853

[1]Dichotomous variable for which information of only one of the categories was presented.

Table 2 Clinical data of the patients who were interviewed at T2, shown together with the values obtained at T1.

Information	**Tiotropium** (n=14)		**Glycopyrronium + Umeclidinium** (n=12)	
	T1	T2	T1	T2
CAT				
CAT Mean (SD)	15.29 (8.88)	21.14 (6.43)	16.08 (6.50)	18.50 (6.68)
CAT $\geq$ 10[1] n (%)	9 (64.3)	14 (100.0)	2 (16.6)	11 (91.7)
mMRC				
mMRC $\geq$ 2[1] n (%)	12 (85.7)	12 (85.7)	9 (75.0)	12 (100.0)
Exacerbations				
No exacerbations[1] n (%)	10 (28.6)	8 (42.9)	8 (33.3)	6 (50.0)
3 or more exacerbations[1] n (%)	1 (25.0)	1 (16.7)	1 (25.0)	-

[1]Dichotomous variable for which information of only one of the categories was presented.

On patient satisfaction regarding the inhaler device and treatment of the lung disease as a whole, we found that, for the tiotropium group, the mean was 9 (±1.5) for the inhaler device, whereas it was 9.4 (±0.79) for the overall treatment. In turn, in the glycopyrronium + umeclidinium group we had mean values of 8.4 (±1.9) for the device and of 8.9 (±1.6) for the treatment of the pulmonary disease.

Table 3 shows the response capacity, which indicates the number of medications that the hospital was able to supply with the current stock in the study period. The response capacities for glycopyrronium, tiotropium and umeclidinium were found to be 48.1%, 83.91%, and 168.36%, respectively. It can be then inferred that glycopyrronium and tiotropium did not have enough stock to meet the demands, only umeclidinium presented enough stock to meet the demands.

In relation to the costs, Table 6 represents the expenses for each medication considering the prices indicated in the CMED table. Current spending was assumed based on the demand for each medication, considering only the Pulmonology prescriptions of the COPD group, as umeclidinium and glycopyrronium are only prescribed by this group of physicians. Performing this selection by prescribing specialty, we were able to calculate that the COPD outpatient clinic of the Pulmonology team accounts for 26.76% of the tiotropium requests. Based on the total expenditure, 20%, 60% and 20% predicted consumptions were estimated for glycopyrronium, tiotropium and umeclidinium, respectively. From this projection, we managed to predict savings, only by the COPD outpatient service, of nearly US$ 13,915.77/year, considering the period analyzed.

Table 3. Total outpatient stock response capacity in relation to requests for medications through medical prescriptions.

Consumption analysis	Tiotropium[1]	Glycopyrronium	Umeclidinium
Outpatient stock n (%)	6,386 (93.9)	160 (2.3)	248 (3.6)
Patients' requests n (%)	7,610.3 (94.1)	332.3 (4.1)	147.3 (3.1)
Response capacity of the service[2] (%)	83.9	48.1	168.4

[1] 1 prescription that generated a 120 mcg/day for tiotropium was excluded. [2] Response capacity = Number of units in outpatient stock of each medication/number of patients' requests X 100%

Table 4. Cost projection in relation to the medications analyzed and requests from the COPD outpatient clinic by the Pulmonology team.

Information	Tiotropium	Glycopyrronium	Umeclidinium	Total costs
Cost analysis				
Price according to the CMED table[1], dated 11/10/2021 - FP18%[2]	US$ 53.22	US$ 32.30	US$ 24.97	
Patients' requests n (%)	2,068.70 (81.1)	332.3 (4.1)	147.3 (3.1)	
Cost for the service	US$ 110,096.21	US$ 10,700.06	US$ 3,678.08	US$ 124,474.35
Consumption projection considering standardization of the technologies in the 20%-60%-20% proportion, respectively				
Consumption predicted by the SES[3] n (%)	1,528.90 (60.0)	509.7 (20.0)	509.7 (20.0)	
Proportional costs	US$ 81,368.06	US$ 16,463.31	US$ 12,727.21	US$ 110,558.58
Predicted annual savings	US$ 28,728.15	US$ -5,763.25	US$ -9,049.13	US$ 13,915.77

[1] CMED: ***Câmara de Regulação do Mercado de Medicamentos*** (Medication Market Regulation Chamber). [2] FP: Factory Price. [3] SES: ***Secretária Estadual de Saúde*** (State Health Secretariat).

Discussion

The study characterized our population as more severe patients, as the vast majority of the patients were classified as GOLD 3 and 4. Due to this severity profile, the relationship with the use of a more complex pharmacotherapy is coherent, with frequent use of associations of 3 therapeutic classes.[14,16] Although they are a more severe population, they are mostly non-exacerbating patients. We can infer low occurrence of exacerbations to the use of several control therapies. Regarding disease control, most of the patients do not have the disease controlled and are classified as GOLD B or D, despite the widespread use of triple therapy.

Several clinical studies show the benefit of the anticholinergic therapy in the treatment of COPD; the use of tiotropium has been associated with improved lung function, quality of life, and reduced exacerbations, as well as when analyzing the benefits of umeclidinium and glycopyrronium in monotherapy or in association with LABAs.[17–19] Considering that it has already been proven that there is no superiority between treatments with different LAMAS,[11] this study reflects the same findings in real life, and it is not possible to show better or worse clinical efficiency between the studied groups.

It is known that, in a real life environment, other factors can influence effectiveness of the treatment, for example, the correct use of inhaled medications and adherence to the treatment. Inhaling devices are associated with greater difficulty for the effective use of the medications. A study that assessed errors when using inhaling devices found a prevalence of 50% to 100% of general errors. When the critical errors were analyzed, this percentage varied from 14% to 92% regardless of device type, i.e., most of the patients have difficulty using their inhalation devices.[20,21] In patients with polypharmacy and mostly using 3 or more devices, as in this study, a barrier to the efficacy of inhaled therapies can be speculated. Patients with moderate to severe COPD who require more complex therapies with the use of several devices may have impaired compliance, as each inhaler requires a different and appropriate use technique, impacting on treatment efficacy.[10,13,22]

Our study is innovating as it describes a population in use of different anticholinergic agents in patients treated exclusively by the SUS. In the state of São Paulo, a COPD protocol is currently in effect that makes other anticholinergic agents besides tiotropium available free of charge. As the protocol is still recent (2020), in this study it was not possible to recruit a significant sample to perform statistical analyses comparing the clinical evolution of patients on different anticholinergic therapies, as few patients were using glycopyrronium or umeclidinium. It is worth noting other intrinsic study limitations, such as the fact that the retrospective observational data collection caused a large number of patients to be excluded due to the absence of important data for the study. In addition, the medications under study were in short supply for a certain period of the study, which contributed to the restriction in the dispensing of the group of new anticholinergics. Likewise, due to the current pandemic which started in 2020, access to the hospital was restricted and many patients refrained from attending the appointments.

Even though the study has the limitations cited for a more robust analysis, the comparison of patients on glycopyrronium and umeclidinium shows better FEV_1, CAT and mMRC values than in those on tiotropium. It can be stated that the major difference between the anticholinergics studied in this paper is the way in which the drugs are made available by the devices, as tiotropium uses SMI release and glycopyrronium/umeclidinium resort to the DPI system.[10,12] Associated with efficacy of the treatments, choice of the ideal inhaling device must be individualized. It is important to consider the evaluation of the individual's peak lung flow (inspiratory and expiratory) in the clinical follow-up, as some device models require an adequate inspiratory flow to overcome resistance of the device and allow the drug to reach its action site. There are also recommendations on the use of devices in dry powder for patients with better clinical and functional parameters.[23] In this direction, the results found in this study signal an opportunity for criteria to indicate the type of therapy (drug and device) provided to the patients according to their clinical evaluation.

Structuring a methodology of choice for the appropriate treatment of patients with COPD should be a priority in health services, as this is a condition sensitive to primary care. In our service, the Pulmonology specialty only accounts for 26% of the prescriptions for tiotropium for COPD, which shows that many more patients could benefit from the new treatments incorporated, potentially increasing the savings simulated in this study.

Conclusion

In conclusion, patients with severe COPD tend to use more inhaling devices. Availability of pharmacotherapeutic alternatives by the public health system can contribute to the individualization of anticholinergic treatments and allow for a more adequate evaluation of the therapy according to the patient's clinical profile, coupled with possible economic strategies related to individualized treatment. With the incorporation of the new drugs in the public health network of the state of São Paulo, migration between the anticholinergic therapies was possible, according to clinical criteria, and may stimulate savings for the service. Reducing the number of inhaling devices per patient and improving adherence are guiding actions to optimize this treatment. When used to rationalize therapy and the benefits for the patient, the therapeutic arsenal is a determinant factor for comprehensive health care.

Funding source

The authors declare that the research did not receive funding for its conduction.

Collaborators

Borges, IV: conception and design or data analysis and interpretation; writing of the article or relevant critical review of the intellectual content; approval of the final version. Rocha, PA: relevant critical review of the intellectual content; approval of the final version. Palermo, KR: data analysis and interpretation; approval of the final version. Pinto, VB: relevant critical review of the intellectual content; approval of the final version. Sforsin, AP: relevant critical review of the intellectual content; approval of the final version. Stelmach, R: conception and design of the paper; relevant critical review of the intellectual content; approval of the final version.

Acknowledgments

I would like to thank the Pharmacy Division of the Instituto Central" "Hospital das Clínicas of the Medical School at the University of São Paulo for making this study possible, as well as the Pulmonology team at the Instituto do Coração (Incor-HCFMUSP) for their support and for sharing the diverse knowledge that added to the development of this study.

Conflict of interest statement

The authors declare that there is no conflict of interest in relation to this article.

References

1. II Consenso Brasileiro sobre Doença Pulmonar Obstrutiva Crônica: Caracterização da Doença Pulmonar Obstrutiva Crônica (DPOC) – Definição, Epidemiologia, Diagnóstico e estadiamento. J Bras Pneumol. 2004; 30 (5):S1-5. Available in: https://cdn.publisher.gn1.link/jornaldepneumologia.com.br/pdf/Suple_124_40_DPOC_COMPLETO_FINALimpresso.pdf. Accessed in: May 27, 2020.
2. Menezes AMB, Perez-Padilla R, Jardim JB, *et al*. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. The Lancet. 2005; 366(9500):1875–81. DOI: 10.1016/S0140-6736(05)67632-5.
3. Brasil. Ministério da Saúde. Protocolo Clínico e Diretrizes Terapêuticas: Doença pulmonar obstrutiva crônica. Portaria SAS/MS no 609, June 6, 2013, amended on June 14, 2013. Available in: https://portalarquivos2.saude.gov.br/images/pdf/2014/abril/02/pcdt-doenca-pulmonar-obs-cronica-livro-2013.pdf. Accessed on: May 27, 2020.
4. Câmara, KJC. *et al.* Caracterização da qualidade de vida de indivíduos com DPOC e sua associação com variáveis sociodemográficas e clínicas. 2019. Artigo (Graduação em Fisioterapia)- Faculdade de Medicina, Universidade Federal do Ceará, Fortaleza, 2019. Available in: http://www.repositorio.ufc.br/handle/riufc/48690. Accessed on: May 27, 2020
5. Global Initiative for Chronic Obstructive Lung Disease: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease; Available in: https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf. Accessed on: May 27, 2020.
6. Bagatin E, Jardim JRB, Stirbulov R. Doença pulmonar obstrutiva crônica ocupacional. J Bras Pneumol. 2006; 32(2):S35–40. DOI: 10.1590/S1806-37132006000800007.
7. São Paulo. Secretaria de Estado da Saúde. Resolução no 278 de 26 de julho de 2007. Diário Oficial do Estado. 2007 Jul 27; Seção I. p. 27-9. 2007 p. 3.
8. Carvalho-Pinto RM, Silva IT, Navacchia LYK, *et al.* Exploratory analysis of requests for authorization to dispense high-cost medication to COPD patients: the São Paulo "protocol". J Bras Pneumol. 2019; 45(6):e20180355. DOI: 10.1590/1806-3713/e20180355.
9. Bispo, NS. Nery, TCS. Stelmach, R. Diferença de taxa mortalidade por dpoc em estados do brasil com e sem protocolos específicos de dispensação de medicamentos, segundo faixa etária, no período 2014 a 2017: análise exploratóriapreliminar de banco de dados públicos pelos cid- j44.0 e j44.1. J Bras Pneumol. 2019; 45(2):R1-R224. Available in: https://issuu.com/jornalbrasileirodepneumologia/docs/completo_v45n6_pt. Accessed in: May 27, 2020.
10. Rogliani P, Calzetta L, Coppola A, *et al*. Optimizing drug delivery in COPD: The role of inhaler devices. Respir Med. 2017; 124:6–14. DOI: 10.1016/j.rmed.2017.01.006.
11. Ismaila AS, Huisman EL, Punekar YS, *et al*. Comparative efficacy of long-acting muscarinic antagonist monotherapies in COPD: a systematic review and network meta-analysis. Int J Chron Obstruct Pulmon Dis. 2015; 10:2495–517. DOI: 10.2147/COPD.S92412.
12. São Paulo. Resolução SS n°35, de 18 de abril de 2019. Aprova

o Protocolo para Tratamento dos portadores de Doença Pulmonar Obstrutiva Crônica – DPOC, atendidos pelo Sistema Único de Saúde – SUS, do Estado de São Paulo e da providências correlatas. Diário Oficial, São Paulo, SP, v.129, n. 75, April, 19 2019. Sessão I, p 32.

13. Lai C-C, Chen C-H, Lin CYH, *et al*. The effects of single inhaler triple therapy vs single inhaler dual therapy or separate triple therapy for the management of chronic obstructive pulmonary disease: a systematic review and meta-analysis of randomized controlled trials. Int J Chron Obstruct Pulmon Dis. 2019. 14:1539–48. DOI: 10.2147/COPD.S200846.

14. Riley CM, Sciurba FC. Diagnosis and Outpatient Management of Chronic Obstructive Pulmonary Disease: A Review. JAMA. 2019; 321(8):786. DOI: 10.1001/jama.2019.0131.

15. Kovelis D, Segretti NO, Probst VS, *et al*. Validation of the Modified Pulmonary Functional Status and Dyspnea Questionnaire and the Medical Research Council scale for use in Brazilian patients with chronic obstructive pulmonary disease. J Bras Pneumol. 2008; 34(12):1008–18. DOI: 10.1590/S1806-37132008001200005.

16. Celli BR, Wedzicha JA. Update on Clinical Aspects of Chronic Obstructive Pulmonary Disease. Drazen JM, organizador. N Engl J Med. 2019; 381(13):1257–66. DOI: 10.1056/NEJMra1900500.

17. Tashkin DP, Celli B, Senn S, et al. A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease. N Engl J Med. 2008; 359(15):1543–54. DOI: 10.1056/NEJMoa0805800.

18. Donohue JF, Kalberg C, Shah P, *et al*. Dose response of umeclidinium administered once or twice daily in patients with COPD: A pooled analysis of two randomized, double-blind, placebo-controlled studies. J Clin Pharmacol. 2014; 54(11):1214–20. DOI: 10.1002/jcph.340.

19. Bateman ED, Ferguson GT, Barnes N, *et al*. Dual bronchodilation with QVA149 *versus* single bronchodilator therapy: the SHINE study. Eur Respir J. 2013; 42(6):1484–94. DOI: 10.1183/09031936.00200212.

20. Gregoriano C, Dieterle T, Breitenstein A-L, *et al*. Use and inhalation technique of inhaled medication in patients with asthma and COPD: data from a randomized controlled trial. Respir Res. 2018; 19(1):237. DOI: 10.1186/s12931-018-0936-3.

21. Chrystyn H, van der Palen J, Sharma R, *et al*. Device errors in asthma and COPD: systematic literature review and meta-analysis. Npj Prim Care Respir Med. 2017; 27(1):22. DOI:10.1038/s41533-017-0016-z.

22. López-Campos JL, Quintana Gallego E, Carrasco Hernández L. Status of and strategies for improving adherence to COPD treatment. Int J Chron Obstruct Pulmon Dis. 2019; (14):1503–15. DOI: 10.2147/COPD.S170848.

23. Haidl P, Heindl S, Siemon K, *et al.* Inhalation device requirements for patients' inhalation maneuvers. Respir Med. 2016; 118:65–75. DOI: 10.1016/j.rmed.2016.07.013.