Real-World Adverse Reactions in COPD Patients on Inhaled Long-Acting Bronchodilators

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Abstract

Background: Inhaled bronchodilators are the mainstay of chronic obstructive pulmonary disease (COPD) pharmacotherapy, and several long-acting muscarinic antagonists (LAMA) and long-acting beta-2 agonists (LABA) are currently available. Recognizing real-life frequencies of adverse reactions enables clinicians to give appropriate counseling to COPD patients on these medications.

Objective: The main objective of this study was to assess frequencies of common adverse reactions of inhaled bronchodilators among COPD patients.

Design: This was a cross-sectional study.

Participants: Subjects registered in a database and followed up at pulmonary clinics for their COPD.

Main measures: Subjects were invited to complete a questionnaire regarding the frequency of common adverse reactions that can be associated with LAMA and LABA.

Key results: A total of 226 COPD patients were included and assigned to one of these three groups: LAMA + LABA (n = 182), LABA (n = 26), and LAMA (n = 18). The proportion of subjects in each group who reported to have experienced at least on adverse reaction in the week preceding the interview was 83.3%, 88.5%, and 95.6%, respectively. The most common adverse reaction that occurred "most of the time" or "always" in patients having LAMA and LABA was dry mouth (56%), followed by dry throat (32.4%) and muscle cramps (26.4%).

Conclusion: Adverse reactions in users of inhaled bronchodilators that are not necessarily attributed to the medication itself are common in real-life practice. In COPD, monitoring of adverse reactions is important as they influence quality of life and adherence to medication.

Résumé

Contexte : Les bronchodilatateurs inhalés sont le pilier de la pharmacothérapie de la maladie pulmonaire obstructive chronique (MPOC), et plusieurs antagonistes muscariniques à longue durée d'action (AMLA) et bêta-2 agonistes à longue durée d'action (BALA) sont actuellement disponibles. Reconnaître les fréquences

réelles des effets indésirables permet aux cliniciens de donner des conseils appropriés aux patients atteints de MPOC sur ces médicaments.
Objectif : L'objectif principal de cette étude était d'évaluer la fréquence des effets indésirables courants des bronchodilatateurs inhalés chez les patients atteints de MPOC.
Devis : Il s'agissait d'une étude transversale.
Participants : Sujets enregistrés dans une base de données et suivis dans des cliniques externes de pneumologie pour leur MPOC.
Principales mesures : Les sujets ont été invités à remplir un questionnaire concernant la fréquence des effets indésirables courants pouvant être associés à l'AMLA et au BALA.
Principaux résultats : Au total, 226 patients atteints de MPOC ont été inclus et répartis à l'un de ces trois groupes : AMLA + BALA (n = 182), BALA (n = 26) et AMLA (n = 18). La proportion de sujets dans chaque groupe qui ont déclaré avoir ressenti au moins un effet indésirable au cours de la semaine précédant l'entretien était de 83,3 %, 88,5 % et 95,6 %, respectivement. L'effet indésirable le plus fréquent survenu « la plupart du temps » ou « toujours » chez les patients sous AMLA et BALA était la sécheresse de la bouche (56 %), suivie de la sécheresse de la gorge (32,4 %) et des crampes musculaires (26,4 %).
Conclusion : Les effets indésirables chez les utilisateurs de bronchodilatateurs inhalés qui ne sont pas nécessairement attribués au médicament lui-même sont fréquents en pratique courante. Dans la MPOC, la surveillance des effets indésirables est importante car ils influencent la qualité de vie et l'adhésion au traitement.

Keywords: adverse reactions; chronic obstructive lung disease; inhaled bronchodilators; long-acting antimuscarinics; long-acting beta-agonists

Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent disease associated with significant morbidity.[1] Inhaled bronchodilators are the mainstay of pharmacotherapy, including long-acting muscarinic antagonists (LAMA) and long-acting beta-2 agonists (LABA).[1] Several LAMA and LABA are currently available and the selection between them is mostly based on patient's preference for an inhalation device. Newer long-acting bronchodilators have different pharmacokinetic properties, which might influence response to therapy (including adverse reactions), but this has not been studied specifically. Clinical trials report various incidences of adverse reactions to inhaled bronchodilators. For instance, dry mouth was reported in up to 8.9 % of patients having LAMA.[2–11] Probably, the prevalence of comorbidities is higher in practice than in randomized controlled trials (RCTs), which can influence the occurrence of adverse reactions (e.g., dry mouth in users of tricyclic antidepressants). For example, Scichilone et al. reported that more than 80% of COPD patients would not be eligible for inclusion in RCTs because of comorbidities, among other reasons, which underlines the importance of collecting "real-life" data.[12] Adverse reactions influence COPD outcomes such as quality of life, adherence to medication, and effectiveness of medication, and identifying the most common adverse events is important in the process of shared decision-making.[1] In a previous published study, we found that adverse reactions were frequent among 154 COPD patients having inhaled bronchodilators, but we did not describe polypharmacy, and the study included only a few patients on the more recent LAMA and LABA (e.g., only eight patients were having glycopyrronium, one patient had umeclidinium, and two patients were prescribed vilanterol).[13] In order to overcome previous limitations and increase the sample size, we pursued the study and combined results of previous and newly recruited patients. The main objective of this study was to describe the frequency of common adverse reactions in users of inhaled bronchodilators among COPD patients in the context of real-life clinical practice.

Methods

A cross-sectional study was conducted to describe the frequency of common adverse reactions in COPD patients. The methodology of this study was the same as adopted in Rodrigue et al.,[13] with the exception that we added

descriptive data on the number of different classes of medications prescribed to COPD patients.

Subjects

Subjects included in this study were selected from the *Registre de Données en Santé Pulmonaire* "RESP" database, which is a prospective registry of adults with a diagnosis of asthma and COPD confirmed by a respirologist, who are followed in two outpatients respiratory clinics in the province of Quebec, Canada. Data on demographic and clinical variables are collected in this database. Subjects who are registered have agreed to be contacted to participate in subsequent research projects. For some patients in the RESP database, information on medication dispensed in community pharmacies can also be collected from the "reMed" database. "reMed" database contains information related to drug prescription claims, updated every 2 weeks, and stored longitudinally for a sample of Quebec residents having a public (since 2016) or private (since 2008) drug insurance.

Subjects' inclusion criteria for this project were as follows: registration in the "RESP" database, having a diagnosis of COPD confirmed by a respirologist, and prescription of LAMA and/or LABA. Patients on other COPD medications (e.g., inhaled corticosteroids) were also included. Patients who were unable to provide their consent or who did not speak English or French were excluded from the study.

Course of the study

Eligible COPD patients received an invitation letter by mail to participate in this project. The letter included two consent forms: one to be kept by the subject and the other to be signed and returned by mail to the research team. After 1–2 weeks of sending the letter, subjects were contacted by phone to give further explanation on the project. Subjects who gave their verbal consent were invited to complete the questionnaire on adverse reactions at this time, or later (an appointment was provided). Only interviews of the subjects who returned the signed consent form were included in the analysis. The first part of the study was conducted between January and October 2015, included a sample of 154 patients, and published in 2016.[13] For the second part of the study, a sample of subjects was recruited from January to April 2019.

Questionnaire and other sources of data

The questionnaire included a list of adverse reactions commonly associated with the use of inhaled bronchodilators in COPD patients. It was pretested among five COPD patients to ensure the clarity of questions. First, the patients were asked to identify their current inhaler medications, and whether any changes were opted during the last 6 months. Then, we questioned subjects about the occurrence of common adverse reactions, most specifically tremors, nervousness, palpitations, muscle cramps, headache, constipation, unpleasant sensation in the mouth, dryness in the mouth, and dry throat during the previous week. We also asked about the occurrence of urinary retention and blurred vision during the last month. Subjects had to report the frequency of adverse reactions on a scale of 1 to 5 (1 = never, 2 = rarely, 3 = sometimes, 4 = most of the time, and 5 = always). Subjects were also asked in a simple open-ended question whether the occurrence of adverse reactions prevented them from completing daily activities.

Other data

Characteristics collected to describe participants were retrieved from the "RESP" database, and measured at the time of recruitment in the database. More specifically, the characteristics included age, gender, smoking status, body mass index (BMI), level of education, work status, drug insurance, prior participation in a rehabilitation program, oxygen supplementation, and level of dyspnea according to the Medical Research Council (MRC) dyspnea scale. From the "reMed" database, we measured the number of classes of medications filled during the 3 months preceding the interview by using the first four digits of the anatomical therapeutic chemical classification system (ATC) codes. We then calculated the number of patients who used at least five different classes of medications (including respiratory medications) based on previous definitions of polypharmacy or studies applying this definition.[14,15]

Statistical analysis

Descriptive statistics were estimated to report subjects' characteristics and frequency of adverse reactions. Number, percentage, and 95% confidence interval (CI) of subjects with adverse reactions "most of the time" or "always" were estimated for patients having LAMA+LABA, only LAMA without LABA, and only LABA without LAMA. Statistical analyses were completed by a statistician using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Ethical approval

The study was approved by the research and ethics committees of the *CIUSSS du Nord-de-l'Île-de-Montréal* and the *CIUSSS de l'Estrie-CHUS.*

Results

Overall, 360 subjects from the RESP database were eligible (242 in the first, and 118 in the second sample), and 226 patients were included in the present study (Figure 1). A total of 72 patients recruited in 2019 were added to the initial sample of 154 subjects.[13] In all, 54 of the 72 (75%) newly recruited patients were having a more recent LAMA and/or LABA (i.e., aclidinium, glycopyrronium, tiotropium by mist inhaler, umeclidinium, indacaterol, or vilanterol; data not shown). Characteristics of the participants are presented in Table 1. The mean age of 226 patients included in the project was about 70 years, most were ex-smokers, and less than 40% had participated in a rehabilitation program. Most of the participants were having LAMA+LABA (Table 1). Many subjects were also having an inhaled corticosteroid, and most of the patients filled at least five different classes of medications during the 3 months preceding the interview. Frequency of adverse reactions is presented in Table 2; dry mouth was the most common adverse reaction in 38–56% of patients, followed by dry throat, muscle cramps, and unpleasant sensation in the mouth. Palpitations and headache were less common but were present in about 20% of patients (Table 2). Almost all patients reported to have at least on adverse reaction during the week ahead of the interview, and about 10% outlined that it prevented them from completing daily activities (Table 2).

Discussion

Most COPD patients experienced adverse events and 10% of them reported that this limited their daily activities. When comparing results of this combined analysis to the ones published in 2016,[13] the findings were generally the same. However, the more recent results have demonstrated a slightly higher percentage of tremors (15.9% vs. 11.2%) and a lower percentage of unpleasant sensation in the mouth (24.7% vs. 29.3%).[13] These changes could be explained by a matter of chance rather than the inclusion of more recent long-acting bronchodilators. Our project was not intended to compare the prevalence of adverse reactions between medications of the same class. Combining the two samples had the advantages of increasing the sample size and generalization of results to the current practice, for which newer LAMA and LABA were prescribed.

The percentage of adverse reactions observed was higher than the estimates of previous RCTs. In fact, in clinical trials on LAMA, LABA, or both, the incidence of adverse effects was up to 6.7% for tremors,[2,3,16] 3.3% for nervousness,[2] 3.3% for palpitations,[17–19] 4.3% for muscle cramps,[7–11,19–23] 9% for headache,[3,5,7–9,11,19,20,21,23,24-26–33] 8.9% for dry mouth,[2–11] and less than 0.1% for urinary retention.[34] Deterioration of COPD was the most common adverse event in RCTs, occurring in up to 77.3% of patients, but we did not study the

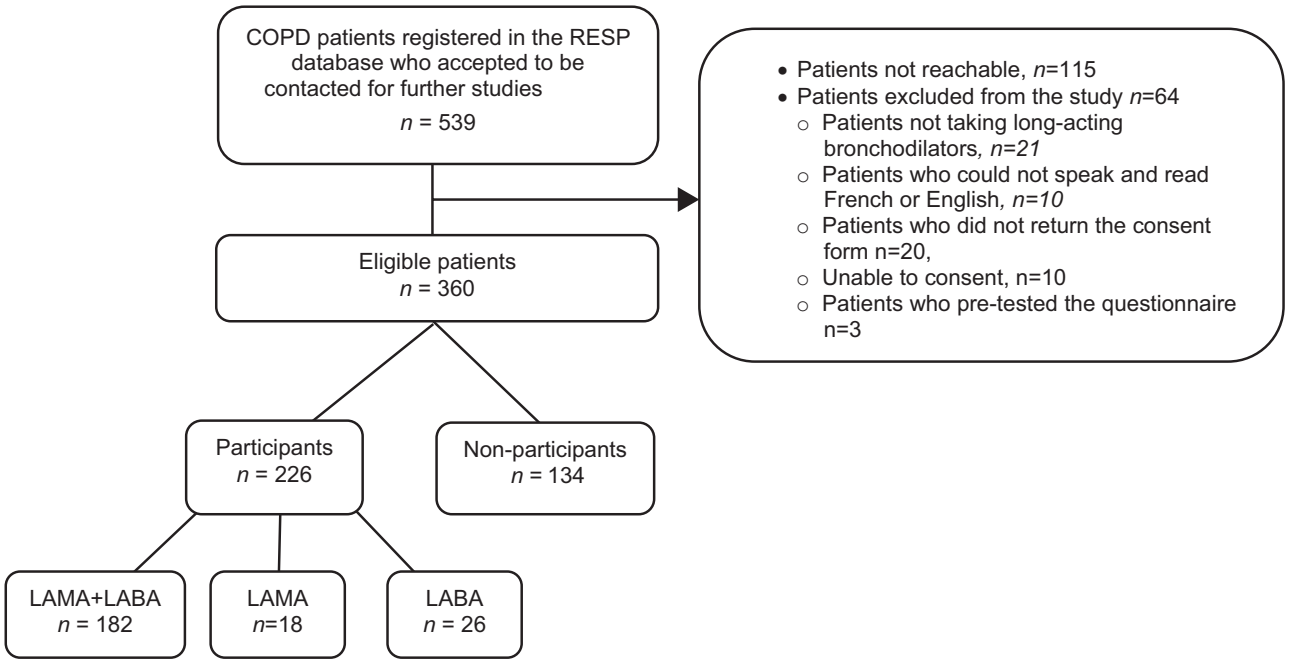

Figure 1. Selection of chronic obstructive pulmonary disease (COPD) patients.

Table 1. Characteristics of subjects treated with inhaled long-acting bronchodilators

	LAMA+ LABA n = 182	LAMA n = 18	LABA n = 26
Mean age (years) at the time of recruitment in RESP database ± SD	71.1 ± 8.7	72.6 ± 8.8	75.2 ± 7.5
Males, n (%)	86 (47.2)	7 (38.9)	11 (44.4)
Smoking status at the time of recruitment in RESP database, n (%)			
Current smoker	40 (22.0)	3 (16.7)	4 (15.4)
Ex-smoker	134 (73.6)	13 (72.2)	20 (76.9)
Nonsmoker	8 (4.4)	2 (11.1)	1 (3.8)
Missing	0 (0.0)	0 (0.0)	1 (3.9)
Body mass index at the time of recruitment in RESP database, n (%)			
Underweight (≤18.5 kg/m^2)	7 (3.9)	1 (5.6)	2 (7.7)
Normal (18.6–24.9 kg/m^2)	61 (33.5)	2 (11.1)	6 (33.5)
Overweight (25.0–29.9 kg/m^2)	54 (29.7)	11 (61.1)	6 (23.1)
Obesity (≥30.0 kg/m^2)	53 (29.1)	4 (22.2)	11 (42.3)
Missing	7 (3.8)	0 (0.0)	1 (3.8)
Level of education at the time of recruitment in RESP database, n (%)			
No diploma	60 (33.0)	6 (33.3)	10 (38.5)
High school	57 (31.3)	8 (44.4)	7 (26.9)
CEGEP	31 (17.0)	0 (0.0)	3 (11.5)
University	31 (17.0)	4 (22.2)	5 (19.2)
Missing	3 (1.6)	0 (0.0)	1 (3.8)
Work status at the time of recruitment in RESP database, n (%)			
Worker	32 (17.6)	3 (16.7)	2 (7.7)
Retired	125 (68.7)	15 (83.3)	19 (73.1)
Other	24 (13.2)	0 (0.0)	4 (15.4)
Missing	1 (0.6)	0 (0.0)	1 (3.8)
Drug insurance at the time of recruitment in RESP database, n (%)			
Public	42 (23.6)	6 (33.3)	4 (15.4)
Private	137 (75.3)	12 (66.7)	21 (80.8)
Missing	2 (1.1)	0 (0.0)	1 (3.8)
Participated in a respiratory rehabilitation program in the year before recruitment in RESP database, n (%)			
Yes	52 (28.6)	5 (27.8)	10 (38.5)
No	114 (62.6)	11 (61.1)	14 (53.8)
Missing	16 (8.8)	2 (11.1)	2 (7.7)
Oxygen supplementation at the time of recruitment in RESP database, n (%)			
Yes	28 (15.4)	0 (0.0)	2 (7.7)
No	139 (76.4)	16 (88.9)	22 (84.6)
Missing	15 (8.2)	2 (11.1)	2 (7.7)
MRC dyspnea scale at the time of recruitment in RESP database, n (%)			
Grade 0	14 (7.7)	2 (11.1)	3 (11.5)
Grade 1	55 (30.2)	8 (44.4)	5 (19.2)
Grade 2	31 (17.0)	2 (11.1)	5 (19.2)
Grade 3	23 (14.6)	2 (11.1)	6 (23.1)
Grade 4	43 (23.6)	1 (5.6)	4 (15.4)
Missing	16 (8.8)	3 (16.7)	3 (11.5)

(*continues*)

Table 1. (Continued)

	LAMA+ LABA n = 182	LAMA n = 18	LABA n = 26
Mean FEV_1, % of predicted pre-bronchodilator therapy in the year before recruitment in RESP database ± SD			
(n, available number)	52.1 ± 16.3 (164)	67.7 ± 11.4 (18)	63.3 ± 29.7 (22)
Treatment regimen at the interview, n (%)			
LABA	16 (8.8)	NA	7 (26.9)
Salmeterol	3 (1.7)	NA	4 (15.4)
Formoterol	11 (6.0)	NA	2 (7.7)
Indacaterol	2 (1.1)	NA	1 (3.8)
LAMA	175 (96.1)	18 (100.0)	NA
Tiotropium	145 (79.7)	15 (83.3)	NA
Glycopyrronium	14 (7.7)	3 (16.7)	NA
Aclidinium bromide	12 (6.6)	0 (0.0)	NA
LAMA/LABA	7 (3.8)	NA	NA
Umeclidinium/vilanterol	4 (2.2)	NA	NA
Glycopyrronium/indacaterol	3 (1.7)	NA	NA
Any ICS†	168 (92.3)	2 (11.1)	23 (88.5)
ICS/LABA/LAMA	1 (0.6)	NA	0 (0.0)
Fluticasone/uméclidinium/vilantérol	1 (0.6)	NA	0 (0.0)
ICS/LABA	161 (88.5)	NA	20 (76.9)
Fluticasone/salmeterol	91 (50.0)	NA	8 (30.8)
Budesonide/formoterol	54 (29.7)	NA	9 (34.6)
Mometasone/formoterol	11 (6.0)	NA	1 (3.8)
Fluticasone/vilanterol	7 (3.9)	NA	2 (7.7)
ICS	15 (8.2)	2 (11.1)	4 (15.4)
Budesonide	1 (0.6)	1 (5.6)	1 (3.8)
Fluticasone	7 (3.9)	0 (0.0)	1 (3.8)
Ciclesonide	7 (3.9)	1 (5.6)	2 (7.7)
Other respiratory medications‡	76 (41.8)	7 (38.9)	12 (46.2)
Prescription filled in the 3 months preceding the interview (n patients with available data), n (%)	178	18	25
LAMA+LABA	156 (87.6)	2 (11.1)	5 (20.0)
LAMA (without LABA)	10 (5.7)	15 (83.3)	0 (0.0)
LABA (without LAMA)	3 (1.7)	0 (0.0)	18 (72.0)
Without LABA and LAMA	9 (5.1)	1 (5.6)	2 (8.0)
Number of classes of medication filled in the 3 months preceding the interview, n (%)			
0–4	22 (12.4)	1 (5.6)	6 (24.0)
≥5	156 (87.6)	17 (94.4)	19 (76)
Mean delay between recruitment in RESP database and the interview, days ± SD	641 ± 683	378 ± 342	399 ± 290
Subjects reporting a change in their inhaled bronchodilator therapy in the last 6 months, n (%; 95% CI)	28 (15.4; 10.1–20.6)	4 (22.2; 3.0–41.4)	4 (15.4; 1.5–29.3)

*Two patients from the LAMA+LABA group were treated with tiotropium soft mist inhaler.

†Patients can be prescribed more than one ICS.

‡Includes respiratory medications such as phosphodiesterase-4 inhibitors, leukotriene receptor antagonists, and oral corticosteroids.

LAMA, long-acting muscarinic antagonists; LABA, long-acting beta-2 agonists; ICS, inhaled corticosteroids; CI, confidence interval; CEGEP, *Collège d'enseignement general et professionnel*; FEV1, Forced Expiratory Volume; MRC, Medical Research Council.

Table 2. Frequency of adverse reactions, N = 226

	LAMA+LABA N = 182	LAMA N = 18	LABA N = 26
AEs in the week before the interview			
Any AE, n (%, 95% CI)	174 (95.6; 92.6–98.6)	15 (83.3; 66.1–100.0)	23 (88.5; 76.2–100.0)
Any AE according to the number of classes of medications, n/n evaluable* (%; 95% CI)			
0–4 classes	34/37 (91.9; 83.1–100.0)	5/5 (100; 100.0–100.0)	6/8 (75.0; 45.0–100.0)
Five and more classes	140/145 (96.6; 93.6–99.5)	10/13 (76.9; 54.0–99.6)	17/18 (94.4; 83.9–100.0)
Dry mouth, n (%; 95% CI)	102 (56.0; 48.8–63.3)	7 (38.9; 16.4–61.4)	13 (50.0; 30.8–69.2)
Dry throat, n (%; 95% CI)	59 (32.4; 25.6–39.2)	5 (27.8; 7.1–48.5)	10 (38.5; 19.8–57.2)
Muscle cramps, n (%; 95% CI)	48 (26.4; 20.0–32.8)	2 (11.1; 0.0–25.6)	5 (19.2; 4.1–34.4)
Unpleasant sensation in the mouth, n (%; 95% CI)	45 (24.7; 18.5–31.0)	4 (22.2; 3.0–41.4)	5 (19.2; 4.1–34.4)
Nervousness, n (%; 95% CI)	33 (18.1; 12.5–23.7)	1 (5.6; 0.0–16.1)	4 (15.4; 1.5–29.3)
Constipation, n (%; 95% CI)	28 (15.9; 10.6–21.3)	2 (11.1; 0.0–25.6)	4 (15.4; 1.5–29.3)
Tremors, n (%; 95% CI)	29 (15.9; 10.6–21.2)	0	5 (19.2; 4.1–34.4)
Palpitations, n (%; 95% CI)	22 (12.1; 7.4–16.8)	0	4 (15.4; 1.5–29.3)
Headache, n (%; 95% CI)	22 (12.1; 7.4–16.8)	1 (5.6; 0.0–16.1)	3 (11.5; 0.0–23.8)
AE during the last month			
Any AE, n (%; 95% CI)	176 (96.7; 94.1–99.3)	15 (83.3; 66.1–100.0)	23 (88.5; 76.2–100.0)
Patients with AE that prevents them from completing a daily activity, n (%; 95% CI)	23 (12.6; 7.–17.5)	0	2 (7.7; 0.0–17.9)
Blurred vision, n (%; 95% CI)	21 (11.5; 6.9–16.2)	1 (18.0; 0.0–16.1)	6 (23.1; 6.9–39.3)
Urinary retention, n (%; 95% CI)	15 (8.2; 4.2–12.1)	2 (11.1; 0.0–25.6)	2 (7.7; 0.0–17.9)

LAMA, long-acting muscarinic antagonists; LABA, long-acting beta-2 agonists; AE, adverse reaction; CI, confidence interval.

*n/n, number of subjects that match the characteristic over the number of evaluable subjects.

occurrence of this outcome in our study.[2,3,5,7–11,16,19,20–29,31,32,34–36] Considering "dry mouth" as an example, its frequency in our study was up to 56%, which was about six times more frequent than what was observed in clinical trials. The higher incidence of adverse effects in our study could be explained by the fact that participant characteristics were different compared to the characteristics found in RCTs in terms of comorbidities and use of concomitant medication. Furthermore, our design did not include a control group. In addition, there was a probability of having responder bias, since patients who experienced adverse reactions were more likely to participate in the study. Probability of a confirmation bias was also encountered because we specifically asked about the occurrence of adverse reactions. Users of both LAMA and LABA had more severe disease, which could have also influenced the frequency of adverse reactions.

Our study was limited by the measurement of some characteristics (i.e., age, smoking status, BMI, level of education, work status, drug insurance, participation in a rehabilitation program, oxygen supplementation, level of dyspnea, and forced expiratory volume (FEV1)) at the time of recruitment in the RESP database, which does not necessarily reflect current status. Furthermore, we included patients having other COPD medications, such as inhaled corticosteroids, that could have influenced the incidence of adverse reactions. In addition, we did not compare users of additional anticholinergics or adrenergic drugs with nonusers, which could have influenced the incidence of adverse effects. There was also a response bias, since participants were given a set list of adverse reactions to choose from, which naturally lead to higher percentage. Strengths of this study were the inclusion of COPD patients with a diagnosis confirmed by a respirologist, use of a pretested questionnaire, and access to drug claims data and its conduct under real-life conditions.

Adverse reactions are very common in COPD patients on inhaled bronchodilators for which many of them are on at least five different classes of medications, which could impact their daily activities. Even if adverse reactions were frequent, the patients were still using the prescribed medication at the time of completing the questionnaire. Further studies could investigate association between occurrence of adverse reactions, adherence to medication, and quality of life in COPD patients.

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Prior Presentations

The first part of the study was presented at the following meetings:

1. Rodrigue C, Beauchesne MF, Savaria F, Forget A, Lemière C, Larivée P, Blais L. Effets secondaires des bronchodilatateurs à longue action chez les patients souffrant de la MPOC. Congrès Québécois en Santé Respiratoire (CQSR), November 13, 2015, Lévis, Canada.
2. Rodrigue C, Beauchesne MF, Savaria F, Lemière C, Larivée P, Blais L. Effets secondaires des agents anticholinergiques et des bêta-2 agonistes à longue action chez les patients souffrant de Maladie Pulmonaire Obstructive Chronique. Rendez-vous de la Recherche, Université de Montréal, Décember 3, 2015, Montréal, Canada.
3. Rodrigue C, Savaria F, Beauchesne MF, Larivée P, Lemière C, Blais L. Effets secondaires des agents anticholinergiques et des bêta-2 agonistes à longue action chez les patients souffrant de maladie pulmonaire obstructive chronique. Colloque Annuel 2015 du Réseau Québécois de Recherche sur les Médicaments (RQRM), June 2, 2015, Québec, Canada.

Author Contributions

All authors contributed to the designing of the project, analysis of the results, and writing of this paper. Hajar Kalakeche, Claudie Rodrigue, and Amélie Forget were more specifically involved in data collection and statistical analyses.

Conflict of Interest

Hajar Kalakeche, Claudie Rodrigue, and Amélie Forget had no conflict of interest to declare.

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