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Original Article

Excessive Short-acting Beta-agonists Prescriptions in COPD Treated with Triple Inhaler Therapy: A Possible Marker of Frequent Exacerbations. A Retrospective Cohort Study

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ABSTRACT

OBJECTIVE: Short-acting β2-agonists (SABA) are used both in asthma and in chronic obstructive pulmonary disease (COPD); SABA use appears to be associated with an increased risk of exacerbations. We evaluated whether COPD patients receiving regular treatment with single-inhaler triple therapy (SITT) used SABA and whether they experienced more exacerbations.

MATERIAL AND METHODS: Our single-center cohort study retrospectively included COPD patients who had been on SITT for 12 months and who were prescribed >7 inhaled corticosteroids/long-acting β2-agonists/long-acting muscarinic antagonist packages. Patients were divided into three groups based on the number of SABA boxes they received during the SITT year: no SABA (0 boxes/year), 1–2 boxes/year, and ≥3 boxes/year. Oral corticosteroids (OC) and antibiotic packs during the SITT year were considered outcomes for the SABA groups.

RESULTS: Five thousand one hundred and seven subjects were recruited, and 1,444 (28.3%) had at least one SABA prescription. Adherence to SITT treatment was similar across the three SABA groups: 10.7±2.8, 10.6±2.8, and 10.9±3.9 packages/year in the 0, 1–2, and ≥3 SABA groups, respectively. The number of OC/antibiotic packages increased progressively across SABA groups from 0 to 1-2 and ≥3 ($P < 0.0001$). When we applied logistic models, we also observed a progressively higher risk of taking OC and antibiotics among subjects who had taken 1-2 packs of SABA [odds ratio (OR): 2.299 (1.878-2.813) and 2.034 (1.621-2.551), respectively; $P < 0.0001$], and among those who had taken ≥3 packs of SABA [OR: 3.472 (2.871-4.200) and 2.714 (2.192-3.362), respectively; $P < 0.0001$].

CONCLUSION: A significant number of subjects were prescribed SABA despite SITT therapy. A relationship between SABA packages and the number of exacerbations, assessed by OC/antibiotic prescriptions, was observed. Excessive SABA use or prescription may indicate frequent exacerbations in patients with COPD despite receiving maximal inhaled therapy.

KEYWORDS: COPD, triple therapy, SABA, exacerbations, oral corticosteroids, antibiotics, real-life

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INTRODUCTION

Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines suggest using either short-acting β2-agonists (SABA) or short-acting muscarinic antagonists as reliever medications in chronic obstructive pulmonary disease (COPD) patients who are already receiving the recommended pharmacological maintenance treatment, which includes long-acting muscarinic antagonists (LAMAs), long-acting β2-agonists (LABAs), and inhaled corticosteroids (ICS), either in combination with LABAs or as LAMAs+LABAs.[1]

However, less is known about the effects of frequent SABA use in COPD. SABA therapy is classically considered a cornerstone in the management of asthma. Global Strategy for Asthma Management and Prevention guidelines[2] recommend using it only as a medication on demand and not as a regular therapy. The systematic use of salbutamol may have a pro-inflammatory effect, potentially increasing the risk of exacerbations, as noted by some researchers.[3-5]

High SABA use appears to be associated with worse outcomes, even in COPD. In fact, an association between a high level of SABA use and a low health status, as measured by the COPD assessment test, has been described.[6] Other researchers found that patients using high doses of SABA had more severe airflow limitation, were more symptomatic, and had worse health status compared with patients taking lower doses of SABA.[7] Furthermore, some authors reported that the level of SABA use during the first month of the study predicted exacerbation risk during the subsequent 10-month period.[8] This was also confirmed by another recent study, which observed that high SABA use is relatively common and associated with a higher risk of exacerbations and all-cause mortality.[9] However, these studies analyzed the effects of SABAs by considering all COPD patients together, regardless of disease severity (groups A, B, and E according to GOLD guidelines) or adherence to treatment. It is not clear whether patients in group E, who are frequent exacerbators, may have the highest SABA use. Furthermore, it is conceivable that high use of SABA may be associated with an elevated risk of exacerbations in this group of patients, despite regular treatment, including triple therapy. GOLD guidelines recommend ICS/LABA/LAMA therapy for subjects who have frequent moderate-to-severe exacerbations despite receiving LABA/LAMA therapy or who have blood eosinophils >300 cells/μL.[1] Triple therapy, especially when taken with a single-inhaler triple therapy (SITT), has been demonstrated to be effective in improving lung function, symptoms, health status, and in reducing moderate/severe COPD exacerbations compared to ICS, LABA, or LAMA monotherapies and LAMA/LABA and ICS/LABA combinations,[10-14] and even when compared to triple treatment with multiple devices.[15-17]

Main Points

- Excessive use of short-acting β2-agonists (SABA) was associated to chronic obstructive pulmonary disease (COPD) exacerbations.
- There was a relationship between SABA packages and number of COPD exacerbations.
- Excessive SABA prescriptions may be used as a marker of possible disease exacerbation.

Given the uncertainties on this matter, we evaluated, in a group of patients continuously treated with SITT, the prevalence of SABA use and whether high SABA use was associated with an increased risk of COPD exacerbations compared with low SABA use, despite optimal adherence to SITT.

MATERIAL AND METHODS

Study Design

We retrospectively extracted from the pharmaceutical prescriptions archive database patients who had received triple therapy from a single dispenser (SITT) with fluticasone furoate/vilanterol/umeclidinium [dry powder inhaler (DPI)] or beclometasone dipropionate/formoterol fumarate/glycopyrronium [metered dose inhaler (MDI)] for 1 year. Among them, we considered only those prescribed more than seven triple-therapy per year. Packages of systemic corticosteroids [Anatomical Therapeutic Chemical Classification (ATC) code: H02], antibiotics (ATC code: J01), and salbutamol (SABA; ATC code: R03AC02) prescribed during the year of SITT were considered for each patient, identified using tax codes. Only MDI formulations of SABA were considered. In Italy, a medical prescription is required to obtain SABA at pharmacies. The number of SABA packages prescribed for each individual during the year of SITT therapy was used to divide patients into three groups: 0, 1-2, and ≥3 packs/year. In each group, the number of oral corticosteroids (OC) and antibiotic boxes (commonly used for COPD exacerbations) prescribed during the year of treatment with SITT was evaluated and compared across the three groups. In this study, COPD exacerbation was defined as the prescription of at least one package of OC, with or without concomitant antibiotics.

Setting and Participants

The USL SUDEST-Tuscany pharmaceutical database for the period 2019-2023 was consulted. As already said, we extracted from this database all patients on SITT therapy who got more than 7 boxes of ICS/LABA/LAMA during a year of triple treatment.

Prescribing SITT allowed us to identify only those subjects affected by COPD. In Italy, a pulmonary specialist is authorized and required to prescribe SITT with a therapeutic plan after establishing a correct COPD diagnosis. In Italy, SITT is considered only for patients diagnosed with COPD who have had at least two moderate-to-severe exacerbations in the previous year despite LAMA/LABA or ICS/LABA therapy (group E, according to GOLD guidelines). Therefore, our selection from the database of patients treated only with SITT allowed us to identify those with a definite COPD diagnosis classified as group E according to GOLD guidelines.[1] For each patient, a 12-month period of treatment was considered from the month they started through the twelfth month thereafter.

The study was approved by Area Vasta Sudest Ethical Committee (C.E.A.S.V.E.), Azienda Ospedaliera Universitaria Senese, and Azienda USL Toscana Sud-Est (Protocol TRIPLECOPD, ID:

19196; determination: N° 358, 16/02/2021) on the basis that it complied with the Declaration of Helsinki and that the protocol followed existing Good Clinical Practice guidelines.

Inclusion Criteria

We included patients who got more than 7 boxes of SITT during a year of observation, who were >40 years old and who never underwent any changes to other triple therapies during the year considered. SITT prescriptions of >7 boxes/year confirmed the diagnosis of COPD (in Italy, until the end of 2023, the prescription of SITT was exclusive to patients with COPD diagnosed by a pulmonologist with spirometry and clinical features suggestive of the disease).

The study period was 2019-2023. For each patient, a 12-month treatment period was considered, from the month they started therapy through the twelfth month thereafter.

Exclusion Criteria

Patients aged and with fewer than 7 boxes/year of SITT were excluded from the study. Changes to other triple therapies during the year of treatment were another exclusion criterion. The association of Montelukast with SITT was also considered one more reason to exclude patients as it is a drug prescribed for asthma which could have altered the results.

Variables and Measurements

Age, gender, comorbidities associated with COPD, and the number of SITT packages, OC packages, and antibiotic packages during the year of triple treatment were considered for each patient. The systemic corticosteroids considered in this study, which can be used in COPD exacerbations, were betamethasone, dexamethasone, methylprednisolone, prednisolone, prednisone, and deflazacort. Antibiotics, such as penicillins with an extended spectrum of activity, combinations of penicillins with beta-lactamase inhibitors, cephalosporins, macrolides, fluoroquinolones, combinations of sulphonamides and trimethoprim, and some aminoglycosides, were considered for this research because they can also be used to treat COPD exacerbations.

The dispensing of >7 packages of maintenance inhaler medications (SITT) was the cut-off used to identify proper adherence to treatment. Individuals taking fewer than 7 ICS/LABA/LAMA packs per year were excluded from the study because they were either poorly adherent or had their therapy changed (i.e., switched to other inhaler treatments) during the year under consideration.

Prescriptions for drugs indicated for other diseases were also reviewed for each patient to identify comorbidities affecting the individuals examined in this study. Comorbidities were identified by searching for medications taken by each patient for various COPD-related diseases during triple treatment. The criterion for identifying comorbidities was the use of at least three boxes per year of each medication taken for non-COPD diseases. The following ATC codes of drugs used together with the triple A02 were identified: A07, A10, A11/A12/H05/M05, B01/C01/C03C/C03D/C03E/C08D, B03, B03X, C02/C03A/C03B/C07/C08/C09, C10, G04, H03, L01/L02/L03/N02, L04/M01/M04AC01/P01, M04, N03/N04, N05/N06/N07, S01. Such codes identified the following conditions: gastroesophageal reflux/dyspepsia, intestinal disorders, diabetes, osteoporosis, and cardiovascular diseases, including heart failure, cardiac arrhythmias, and coronary artery disease. cerebrovascular diseases (considered all together), anemia, renal failure, hypertension, dyslipidemia, prostatic hypertrophy, thyroid disorders, oncology pathologies, autoimmune disorders, hyperuricemia, neurological disorders, psychiatric disorders, and glaucoma.

Unavailable Variables

Patients' lung function and other clinical data (smoking status, body mass index, blood eosinophils) were unavailable because subjects came from different parts of southeastern Tuscany and the data had been archived in various local databases that were not readily accessible. However, for a triple therapy prescription, as previously stated, a diagnosis of symptomatic moderate-to-severe COPD with a history of frequent and/or severe exacerbations (according to GOLD guidelines)[1] was required. Such a prescription had to be made exclusively by a pulmonologist (not by a GP) and accompanied by a written treatment plan, as indicated by the Italian Drug Agency. In addition, the diagnosis of COPD had to be made by spirometry, as recommended by GOLD guidelines.[1] However, the absence of the aforementioned data did not affect the objectives of our study.

Statistical Analysis

Chi-square tests were used to compare categorical variables. The Kruskal-Wallis test was used to compare continuous variables among the different groups.

Multivariate analysis was also performed. Linear and logistic regression models were applied to test whether there was a relationship between the number of SABA packages and the number of OC/antibiotics prescriptions. All models adjusted for sex, age, adherence to treatment with SITT (number of packages per year), and comorbidities. P values < 0.05 were considered statistically significant.

RESULTS

A total of 5,107 patients were enrolled in SITT therapy for 1 year. Among these, 1,444 (28.3%) had at least one SABA prescription; in particular, those who had 1-2 boxes were 651 (12.8%), while 793 (15.5%) had ≥3 (Figure 1). Patient characteristics are described in Table 1. Females tend to have more SABA prescriptions than males (626/1,844 - 34% vs. 818/3,263-25%; P = 0.0001), while older subjects used fewer packages of short-acting bronchodilators. The number of comorbidities appeared to be significantly higher in subjects with a higher number of SABA box prescriptions (Table 1). Over 60% of patients have ≥4 comorbidities. Adherence to SITT (number of triple-therapy boxes per year) did not differ among the three groups (means ± standard deviation: 10.7±2.8, 10.6±2.8, and 10.9±3.9 for subjects using 0, 1-2, and ≥3 SABA packages per year, respectively; P = 0.310; Table 1). Instead, the number of OC/antibiotic packages per year increased progressively with the number of SABA packs prescribed during the year of SITT treatment (Figure 2A and 2B).

Table 1. Baseline demographics and clinical characteristics of COPD patients subdivided into 3 groups on the basis of SABA prescriptions

	SABA packages/year			*P*
	0	**1-2**	**≥3**	
Sex				
Males	2445 (66.7%)	387 (59.4%)	431 (54.4%)	0.0001
Females	1218 (33.3%)	264 (40.6%)	362 (45.6%)	
Age				
≤70 years	964 (26.3%)	184 (28.3%)	301 (38%)	0.0001
71-79 years	1404 (38.3%)	242 (37.2%)	310 (39.1%)	
≥80 years	1295 (35.4%)	225 (34.6%)	182 (23%)	
Comorbidities				
0-1	437 (11.9%)	65 (10%)	100 (12.6%)	0.040
2-3	956 (26.1%)	144 (22.1%)	214 (27%)	
≥4	2270 (62%)	442 (67.9%)	479 (60.4%)	
SITT packages/year	10.7±2.8	10.6±2.8	10.9±3.9	0.310

COPD: chronic obstructive pulmonary disease, SABA: short-acting β2-agonists, SITT: single-inhaler triple therapy

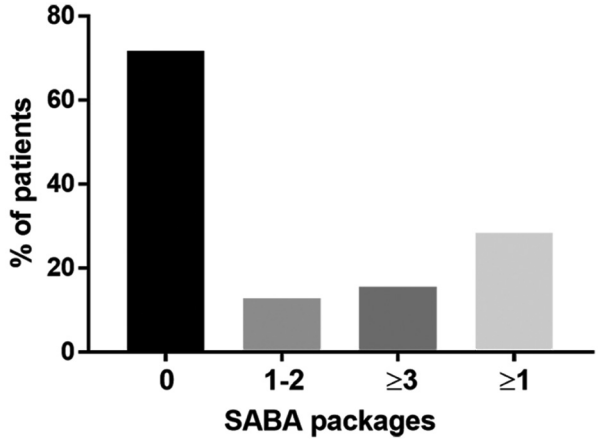

Figure 1. Prevalence of subjects who had SABA prescriptions

SABA: short-acting β2-agonists

When we applied multivariate analysis (linear regression models) adjusted for all confounding variables, we found that the groups with 1-2 and ≥3 SABA prescriptions per year received higher numbers of OC (β: 0.905±0.238 and β: 1.698±0.222, respectively) and of antibiotic packages (β: 1.256±0.287 and β: 1.853±0.269, respectively; $P < 0.0001$) than subjects who had never taken SABA during the year of SITT therapy (Figure 3A and 3B).

Even when we applied logistic models, we observed a progressively higher risk of taking OCs and antibiotics among subjects who had taken 1-2 packets of SABA [odds ratios (OR): 2.299 (1.878-2.813) and 2.034 (1.621-2.551), respectively; $P < 0.0001$] and ≥3 packets of SABA [ORs: 3.472 (2.871-4.200) and 2.714 (2.192-3.362), respectively; $P < 0.0001$] (Figure 4A and 4B).

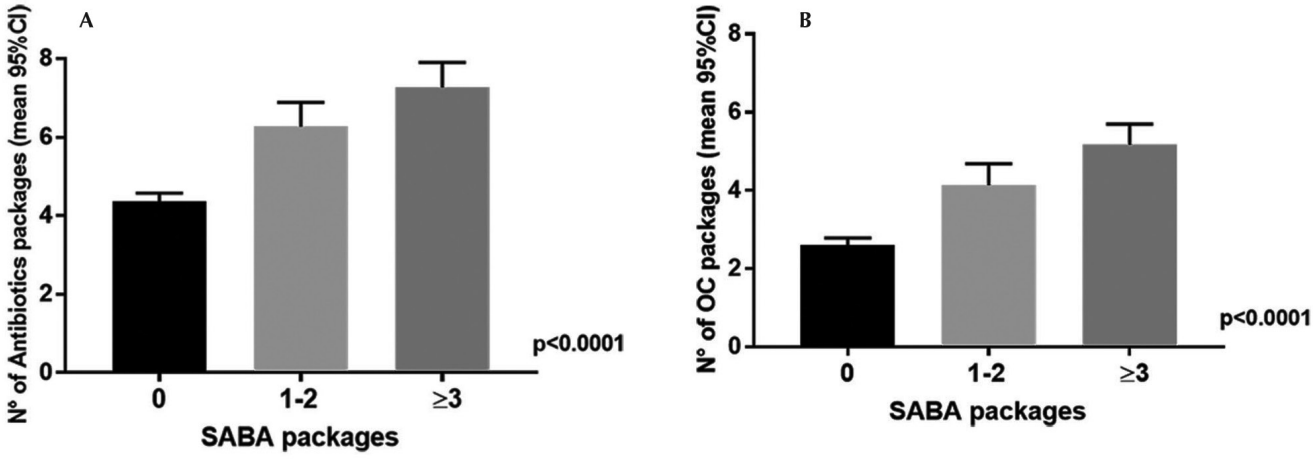

Figure 2. Number of oral corticosteroid and antibiotic packages used in the different SABA groups

SABA: short-acting β2-agonists, OC: oral corticosteroids, CI: confidence interval

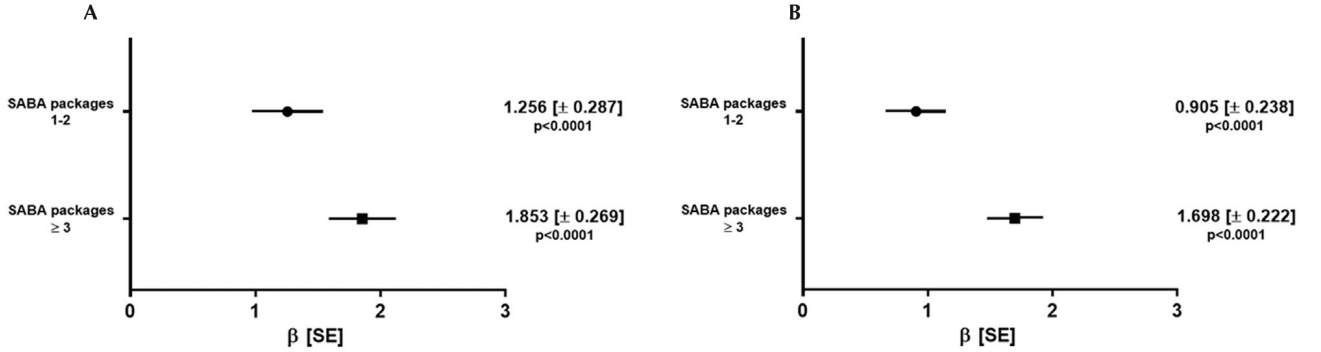

Figure 3. Number of additional OC (A) and antibiotic (B) boxes prescribed in the groups of subjects who had 1-2 or >3 boxes of SABA compared to those who never took SABA, calculated with a linear regression model adjusted for sex, age, comorbidities and number of SITT boxes used in the year of follow-up considered

SABA: short-acting β2-agonists, OC: oral corticosteroids, SITT: single-inhaler triple therapy, SE: standard error

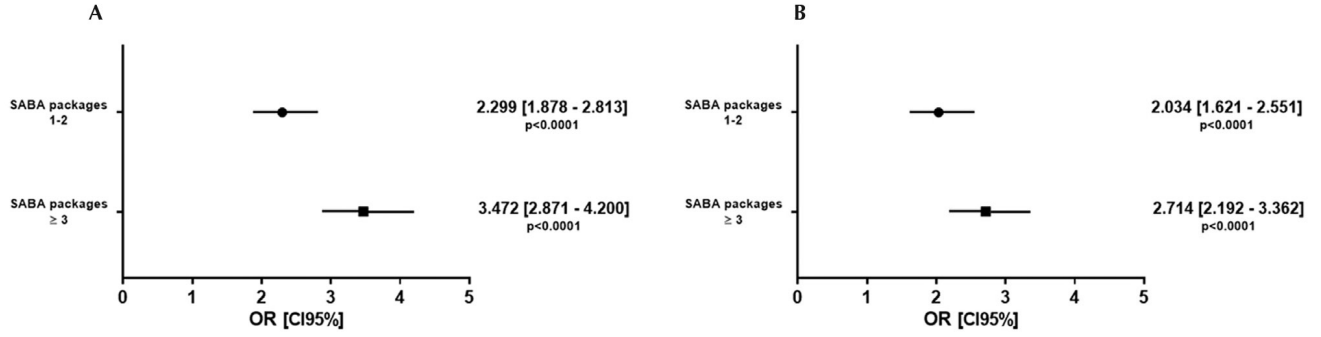

Figure 4. Risk (odds ratios) of using OC (A) and antibiotics (B) in subjects who took 1-2 or >3 boxes of SABA compared to those who never had any SABA prescription calculated with logistic models adjusted for sex, age, comorbidities and number of boxes of SITT taken during the year of follow-up considered

SABA: short-acting β2-agonists, OC: oral corticosteroids, SITT: single-inhaler triple therapy, CI: confidence interval, OR: odds ratios

DISCUSSION

This study highlighted that, in a very large COPD population in group E, despite receiving maximized SITT treatment, about 28% of patients had at least one SABA prescription. Furthermore, we observed an association between the number of SABA packages prescribed and COPD exacerbations in patients regularly treated with SITT, as evaluated by OC/antibiotic use. In fact, as SABA prescriptions increased, OC/antibiotic prescriptions also showed a progressive increase. Our study examines only patients with optimal adherence to triple treatment (approximately 11 packs/year of SITT), unlike other studies[8,9] that considered all COPD patients treated with mono-, dual, and triple therapies regardless of their level of adherence. This highlights that despite maximum and regular SITT, many individuals still use SABA because they remain symptomatic and are therefore susceptible to exacerbations. Moreover, patients receiving SITT (group E according to GOLD guidelines) have substantially more severe COPD than patients in GOLD groups A and B and are therefore more difficult to treat.[18] In our analysis, we considered OC/antibiotic prescriptions as outcomes of exacerbations. When they are at least moderate in severity, they should be treated with OCs and/or antibiotics according to guidelines.[1] Therefore, the outcome of OC/antibiotics prescriptions analyzed in our study during the year of SITT should be considered to correspond to COPD exacerbations.

A recent study found that 30.1% of patients used SABAs during the 12-month baseline period,[9] which is comparable to what we observed. Our study only included patients belonging to group E according to GOLD guidelines,[1] i.e., those with more severe COPD characterized by frequent exacerbations (more precisely, a distinct COPD phenotype). In fact, according to another study, these subjects use more SABA than patients with less severe disease do, namely those belonging to groups A and B according to GOLD recommendations.[9] Excessive use of SABA indicates that patients, despite regular treatment with ICS/LABA/LAMA (SITT), remain symptomatic and are therefore at increased risk of disease exacerbations. Subjects who use SABA excessively may be patients with very severe COPD, for which even regular triple therapy fails to control the disease, suggesting that high SABA use is a marker of more severe disease. A recent study highlighted that patients with high SABA use had more severe airflow limitation, were more symptomatic, and had worse health status than patients with lower SABA use.[7] Therefore, these patients should receive additional treatments, such as roflumilast and/or azithromycin, as recommended by guidelines.[1] Dupilumab should also be considered because recent evidence has shown significant efficacy in reducing exacerbations in COPD patients receiving triple therapy who have blood eosinophils <300 cells/microliter.[19] Conversely, using high doses of ICS does not appear to be effective. A recent meta-analysis has shown that high doses of ICS, compared

with medium doses, do not appear to further reduce COPD exacerbations and mortality.[20] Also, rehabilitation interventions and the best possible management of comorbidities must always be considered; in particular, management of comorbidities remains an important determinant of health in COPD.[1,21]

Our study demonstrated a strong association between the number of SABA prescriptions and OC/antibiotics packages dispensed. This suggests that increased SABA use is associated with a higher number of COPD exacerbations. This appears to be in line with observations by other authors.[7-9] As further confirmation, a systematic review reported that reducing the number of rescue puffs per day proportionally decreased the rate of moderate-to-severe COPD exacerbations.[22] High SABA use often indicates COPD deterioration, characterized by declining lung function and worsening symptoms such as dyspnoea, sore throat, and cough, which usually precede disease exacerbations.[23-25] Another randomized clinical trial showed that increased SABA use related to symptom deterioration is common and contributes to negative outcomes in patients with COPD.[26] Thus, the use of SABA in COPD, even with optimal continuous treatment, may predict a subsequent exacerbation.

Another possible explanation for excessive SABA use is the presence of marked bronchial hyperreactivity (BHR) in some patients with COPD. Airway hyperresponsiveness is a hallmark of obstructive airway disorders, such as asthma and COPD.[27] Bronchospasm events in COPD may be related to the presence of BHR. The reported prevalence of BHR in COPD patients was consistently higher than in the general population, reaching values of 63% in men, and 87% when assessed with the methacholine challenge test using a dose of 25 mg/mL as a cut-off to identify it.[28] Airway hyperresponsiveness significantly increases the frequency of exacerbations in COPD, regardless of airway eosinophilia.[29,30] SITT, which also includes ICS treatment, may not effectively reduce airway hyperresponsiveness in all patients. In fact, ICS therapy does not always appear to reduce BHR in patients with COPD.[29] High SABA use has been associated not only with increased bronchial responsiveness but also with the development of tolerance to the bronchodilating effect of β2-agonists.[31] A reduced efficacy of LABAs in patients with COPD who are high SABA users has also been reported.[7] Prolonged or repeated use of β2-agonists leads to the loss of some of their effects, a pervasive phenomenon termed tachyphylaxis, refractoriness, or desensitization.[32] Regular β2-agonist use can induce tolerance to their bronchoprotective effects and reduce bronchodilator responsiveness to β2-agonists.[33] Moreover, a study observed that salmeterol might be subject to tachyphylaxis because the duration of action and the peak effect decreased over time.[34] Prolonged use of LABAs may therefore lead to receptor tachyphylaxis and reduced therapeutic efficacy of these drugs, which may consequently justify greater use of SABA in COPD patients even if treated with SITT. It is also possible that excessive and continuous SABA use could be responsible for down-regulation of β2-agonist receptors (tachyphylaxis), thus leading to a consequential and progressive reduction in the efficacy of LABAs when taken with triple therapy, thereby predisposing the patient to exacerbations.

Another aspect to consider is that comorbidities can influence disease exacerbations.[35] In fact, real-world data confirm that, in patients with COPD, they also affect their frequency and their COPD-related health care resource utilization.[36] According to recent studies, COPD patients receiving SITT were older and had more comorbidities, especially cardiovascular diseases, than patients receiving LABA/LAMA or other treatments.[37] In our study, subjects with more SABA packages had more comorbidities, confirming that these comorbidities could be associated with greater SABA use and, consequently, with an increased number of COPD exacerbations. As we have already said, in addition to inhaled treatment, it is necessary to optimize all available therapies for the various comorbidities associated with COPD.

Another aspect to consider is that some patients on triple therapy may make critical errors during various phases of inhalation therapy, such as performing inhalations incorrectly. Some studies report that, even with triple therapy in both MDI and DPI, 10-15% of patients make critical errors with the device.[38,39] This could compromise the effectiveness of the therapy, thus pushing them to use SABA more often and thereby increasing the risk of disease exacerbations.

In summary, excessive SABA prescriptions could be a marker of poor treatment efficacy even in patients receiving regular SITT. These subjects should be identified and re-evaluated, with improved management of comorbidities, optimization of inhalation technique to the greatest extent possible, and addition of therapies to achieve optimal disease control. It is also necessary to investigate whether asthma coexists with COPD, as this can occur in between 4.2% and 66% of individuals identified as having COPD.[40] This might allow us to consider additional therapies currently used solely for the treatment of asthma.

Another issue to consider is the differential influence of gender on aspects of the disease, with possible repercussions for differences in treatment efficacy between males and females. Notably, in our study we observed a higher frequency of SABA prescriptions in female patients compared with males, a pattern already observed in asthma.[5] The explanations for this could be multifactorial: differences in types of airway inflammation; a higher prevalence of obesity in females; greater BHR, which may lead to greater symptom perception; and greater anxiety and mood disturbances[5] when females are compared with males. Other explanations are also possible, but this aspect should be investigated further by designing an appropriate study to analyze it.

Study Limitations

The major limitation of our study is that clinical data, such as lung function measurements, smoking status, and symptoms, were not available in our dataset; the strength of our analysis is the large number of subjects enrolled and their strong adherence to SITT. It should also be noted that the drug prescriptions referenced in our study may not always correspond to actual use of the drug in question. For example, not all prescribed SABAs may have been used by patients. In fact, physicians often prescribe SABAs for possible emergencies, which, in many

cases, do not occur. In other circumstances, patients want to feel secure that the drug will be available if needed. Therefore, SABA prescriptions may not always correspond to their actual use. However, our analysis considered drug prescriptions rather than actual drug use because the study was conducted using a database.

OCs administered may also not correspond to the actual number of exacerbations. Some OC packages may cover multiple exacerbation treatments and therefore lead to underestimation of their intake. On the other hand, it is possible that the prescription of OCs and antibiotics does not always correspond to their use. This may not accurately capture all true exacerbation events, potentially leading to misclassification.

However, we believe that the large number of patients studied may mitigate such biases. Furthermore, our study evaluated drug prescriptions dispensed directly by pharmacies, that is, drug packages taken from the pharmacy by them. Therefore, we believe that prescribed drugs are frequently used.

Some SABA prescriptions may have been given during exacerbations in our study. However, as we have previously stated, our study only considered prescriptions for SABA in MDI formulations. It should also be noted that in Italy, COPD exacerbations are commonly treated with OCs combined with antibiotics, and in some cases with the addition of SABA, primarily via nebulized formulations rather than using MDI devices. Furthermore, two similar studies confirm that COPD patients use SABA primarily to control symptoms despite ongoing maintenance therapies, among those with more severe disease.[7,9]

CONCLUSION

In a significant number of COPD patients belonging to group E SABA was prescribed despite SITT therapy. This means that, despite such treatment, they still did not demonstrate complete disease control. Furthermore, there is a significant relationship between SABA use and OC and antibiotic prescriptions commonly used during disease exacerbations. In other words, an increase in SABA use is associated with an increased risk of COPD exacerbations.

Therefore, excessive SABA use could be a marker of frequent exacerbations in patients with COPD despite maximal inhaled therapy. Other therapies, in addition to SITT, should be considered for them.

Ethics

Ethics Committee Approval: The study was approved by Area Vasta Sudest Ethical Committee (C.E.A.S.V.E.), Azienda Ospedaliera Universitaria Senese, and Azienda USL Toscana Sud-Est (Protocol TRIPLECOPD, ID: 19196; determination: N° 358, 16/02/2021) on the basis that it complied with the Declaration of Helsinki and that the protocol followed existing Good Clinical Practice guidelines.

Informed Consent: Due to the retrospective nature of the study and the exceptionally large sample size, reaching each individual participant was deemed unfeasible. All data were processed in a pseudonymized form to ensure the highest level of privacy protection in accordance with the Italian laws. No patients were identifiable at any time during the entire study period. Informed consent was obtained only in those patients in whom it was possible to acquire it.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.S., Concept: B.S., Design: B.S.,L.G.L., E.P., A.S., Data Collection or Processing: B.S.,L.G.L., E.P., A.S., Analysis or Interpretation: B.S., L.G.L., E.P., A.R., A.C., P.B., A.S., C.M., M.D.T., A.P., V.A., S.C., M.S., Literature Search: B.S., A.R., A.C., P.B., M.D.T., A.P., V.A., S.C., M.S., Writing: B.S., A.R., A.C., P.B., M.D.T., A.P., V.A., S.C., M.S.

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