Inhaled Medication Use in Smokers With Normal Spirometry

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BACKGROUND: The objective of our study was to identify variables associated with inhaled medication use in smokers with normal spirometry (GOLD-0) and to examine the association of inhaled medication use with development of exacerbations and obstructive spirometry in the future. METHODS: We performed a retrospective multivariable analysis of GOLD-0 subjects identified in data from the COPDGene study to examine factors associated with medication use. Five categories were identified: (1) no medications, (2) short-acting bronchodilator, (3) long-acting bronchodilator; long-acting muscarinic antagonists and/or long-acting β agonist, (4) inhaled corticosteroids (ICS) with or without long-acting bronchodilator, and (5) dual bronchodilator with ICS. Sensitivity analysis was performed excluding subjects with history of asthma. We also evaluated whether long-acting inhaled medication use was associated with exacerbations and obstructive spirometry at the follow-up visit 5 y after enrollment. RESULTS: Of 4,303 GOLD-0 subjects within the analysis, 541 of them (12.6%) received inhaled medications. Of these, 259 (6%) were using long-acting inhaled medications and 282 (6.6%) were taking short-acting bronchodilator. Female sex (odds ratio [OR] 1.47, $P = .003$), numerous medical comorbidities, radiographic emphysema (OR 2.22, $P = .02$), chronic bronchitis (OR 1.77, $P < .001$), dyspnea (OR 2.24, $P < .001$), asthma history (OR 15.56, $P < .001$), prior exacerbation (OR 8.45, $P < .001$), and 6-min walk distance (OR 0.9, $P < .001$) were associated with medication use. Minimal changes were noted in a sensitivity analysis. Additionally, inhaled medications were associated with increased total (incidence rate ratio 2.83, $P < .001$) and severe respiratory exacerbations (incidence rate ratio 3.64, $P < .001$) and presence of obstructive spirometry (OR 2.83, $P = .002$) at follow-up. CONCLUSIONS: Respiratory symptoms, history of asthma, and radiographic emphysema were associated with inhaled medication use in smokers with normal spirometry. These individuals were more likely to develop obstructive spirometry, which suggests that health care providers may be able to identify obstructive lung disease prior to meeting the current criteria for COPD. *Key words: COPD; empiric treatment; smoking; respiratory function tests; spirometry.* [Respir Care 2021;66(4):652–660. © 2021 Daedalus Enterprises]

Introduction

COPD diagnosis requires the presence of obstructive ventilatory defect. According to the GOLD guidelines, $FEV_1/FVC < 0.7$ confirms a diagnosis of COPD.[1] Among individuals who carry the COPD diagnosis, up to 61% have no obstructive ventilatory defect.[2,3] Obesity, congestive heart failure, depression, diabetes mellitus, obstructive sleep apnea, and hypertension are associated with the absence of

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obstructive ventilatory defect among those with COPD diagnosis.[4] Among veterans who received inhaled medications (such as bronchodilators and inhaled corticosteroids) for presumed COPD and had spirometry performed, only 62% had an obstructive ventilatory defect.[4]

Among individuals with normal spirometry, only 0–4% report a physician diagnosis of COPD.[3,5] The prevalence of inhaled medication use among those with normal spirometry and the factors associated with that are understudied. In a retrospective study at a small community hospital, inhaled medications were prescribed to 45% and 60% of individuals with normal spirometry and preserved ratio impaired spirometry (restrictive pattern), respectively.[6] In another single-center study among subjects undergoing a pulmonary function test for various clinical reasons (eg, dyspnea) and showing no obstructive defect, about one quarter of them continued to be prescribed inhaled medications at 6 months following the pulmonary function test. Increasing age and smoking history are factors associated with empiric use of inhaled medications.[7]

Apart from utilizing International Classification of Diseases, Clinical Modification (ICD-CM) codes based on chart review, previous studies evaluating inhaled medication use among individuals with normal spirometry were limited by the fact that they did not take into consideration other factors such as chest computed tomography (CT) findings.[4,6,7] A large proportion of smokers with normal spirometry have emphysema on chest CT, which potentially leads to inhaled medication use for COPD despite not being recommended by the current guidelines, which only recommend smoking cessation.[1,8] In addition, to our knowledge there are no studies evaluating the effect of inhaled medication use in high-risk populations. We hypothesized that certain clinical characteristics may predispose patients to inhaled medication use and that this is associated with improved outcomes. To investigate our hypothesis, we identified smokers with normal lung function in data from the COPDGene study. We compared characteristics between smokers who received inhaled medications and those who did not. We also examined the association between inhaled medication use among those with normal spirometry and respiratory exacerbations, as well as the presence of obstructive ventilatory defect in follow-up spirometry tests.

QUICK LOOK

Current knowledge

A significant number of patients who are prescribed inhaled medication therapies and have a diagnosis of COPD are prescribed these medications empirically, despite lack of obstructive spirometry, which is currently not recommended. Smokers are at higher risk of developing COPD and are also prescribed these medications empirically.

What this paper contributes to our knowledge

In smokers with normal spirometry, respiratory symptoms, history of asthma, and radiographic emphysema were associated with inhaled medication use. They were also more likely to develop obstructive spirometry. Clinicians may be able to identify obstructive lung disease in such individuals before the criteria for COPD diagnosis are met.

Methods

Data Collection

We used data from the COPDGene study to conduct this analysis. COPDGene is an ongoing longitudinal cohort study that enrolled subjects in multiple clinical centers throughout the United States (http://www.copdgene.org, *Accessed December 4, 2020*). The institutional review boards at each participating center approved the study protocol (The University of Iowa Human Subjects Office #200710717). Details of the study protocol have been published previously.[9] Briefly, all subjects provided in-formed consent before participation in the study. Subjects self-identified as non-Hispanic whites or African-Americans between the ages of 45 and 80 y. Subjects completed a modified American Thoracic Society Respiratory Epidemiology questionnaire, St George Respiratory Questionnaire, and a 6-min-walk

Supplementary material related to this paper is available at http://www.rcjournal.com.

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test (6MWT) at the enrollment visit. Dyspnea was assessed using the modified Medical Research Council (mMRC) scale. At enrollment, individuals self-reported medication use, history of asthma, and respiratory exacerbations. Subjects also self-reported history of congestive heart failure, diabetes, obstructive sleep apnea, and hypertension. Subjects performed pre- and post-bronchodilator spirometry according to American Thoracic Society/European Respiratory Society guidelines.[9,10] Subjects underwent inspiratory CT scans using multidetector CT scanners as per protocol.[9,11,12] Approximately 5 y after the enrollment visit, a proportion of subjects had a repeat spirometry at a follow-up visit. Subjects were also contacted every 6 months and completed a validated questionnaire regarding respiratory exacerbations.

We included all subjects who enrolled in the COPDGene study with ≥ 10 pack-years of smoking and normal lung function at their baseline visit. We did not include subjects with any of the following: bronchiectasis, interstitial lung disease, or history of lung-volume-reduction surgery.

Definitions and Outcomes

Normal lung function was defined as post-bronchodilator $FEV_1/FVC \geq 0.7$ and FEV_1 percent predicted ≥ 80%. Medication use patterns were defined as: (1) no medications, (2) short-acting bronchodilator only, (3) any long-acting bronchodilator (LAB; either long-acting muscarinic antagonists or long-acting β agonists), (4) inhaled corticosteroids (ICS) or ICS combined with LABs (ICS/LAB), and (5) dual bronchodilator with ICS (ie, triple therapy with ICS/LABA and a long-acting muscarinic agonist). Long-acting inhaled medication use was defined as use of LAB, ICS or ICS/LAB, or triple therapy. We examined whether the presence and the severity of visual emphysema on chest CT imaging may have influenced that decision. Visual emphysema severity was defined based on the Fleischner Society grades[13] as no emphysema when both parenchymal emphysema severity grade and paraseptal grade were none, mild when parenchymal emphysema severity grade was trace or mild and/or paraseptal grade was none or mild, and substantial when either parenchymal emphysema severity grade was at least moderate and/or paraseptal grade was substantial. History of asthma was defined based on the answer to this question "Have you ever had asthma?." Chronic bronchitis was defined as productive cough for at least 3 consecutive months in the last 2 years. History of exacerbation was self-reported and was defined based on whether the subject had a history of acute bronchitis or prior exacerbation. History of acute bronchitis was defined as an answer of "yes" to the following question: "Have you ever had an attack of bronchitis?"[14] Subjects were also asked if they experienced COPD exacerbations in the past year, to quantify the number of episodes, and if they had been to the emergency department or hospitalized for an exacerbation in the past year. An exacerbation was defined as a flare-up of chest trouble consisting of increased cough, phlegm production, or shortness of breath lasting > 48 h and requiring treatment with antibiotics or steroids.[14,15] Severe exacerbations were defined as requiring an emergency department visit or hospitalization.[14] Obstructive ventilatory defect at the follow-up visit was defined as post-bronchodilator FEV_1 percent predicted < 0.7.

Statistical Analysis

The subjects were categorized by medication usage as outlined above. We compared baseline characteristics of each group on medications with the group on no medications. We used the Student *t* test or Wilcoxon rank-sum test for normal and non-normal continuous variables, respectively, and the Fisher exact or chi-square test for categorical variables. We also examined variables associated with any medication use and variables associated with any long-acting inhaled medication use (ie, ICS, LABA, long-acting muscarinic antagonists) (see the supplementary materials at http://www.rcjournal.com). Variables with a univariate $P < .05$ were considered for a multivariable logistic regression model. Variables were selected for the final model using a stepwise backward variable elimination process to minimize the Akaike information criterion.[16] We assessed for variable multicollinearity using correlation matrices and variance inflation factor analysis.[17] Because we did not know whether health care providers had reviewed chest CT data, which may have influenced their decision to prescribe medication, we performed 2 separate multivariable analyses when appropriate, one without radiographic variables and one including radiographic variables. We performed multiple imputations to account for missing variables, and we repeated the multivariable analyses. As asthma patients may have normal lung function, we performed a sensitivity analysis excluding those with history of asthma.

We also examined the association of inhaled medication use with outcomes of total and severe exacerbations and presence of obstructive ventilatory defect at the follow-up visit. For this analysis, we included: subjects who were taking no medications at both enrollment and follow-up visit, subjects who were taking long-acting inhaled medications at both enrollment and follow-up visit, and subjects who were taking short-acting inhaled medications at both enrollment and follow-up visit.

For the exacerbation analysis, we created zero-inflated negative binomial models with long-acting inhaled medication use as the main independent variable (exposure) and total or severe exacerbations as the dependent variable (outcome) adjusted by age, current smoking status, gender, race, pack-years smoked, body mass index, chronic bronchitis, history of exacerbation prior to the enrollment, mMRC, history of asthma, and post-bronchodilator FEV_1 percent predicted at enrollment. There were no missing values in any of the covariates. Follow-up time was included as an offset in the models

Table 1. Characteristics of Subjects With Normal Spirometry Stratified by Medication Use

	No Medications	Short-Acting Bronchodilator	Long-Acting Bronchodilator	ICS or ICS/LABA	ICS/LABA/LAMA
Subjects, *n*	3,762	282	41	183	35
Age, y	56.7 ± 8.4	55.0 ± 7.6*	60.6 ± 9.4*	57.5 ± 8.9	58.0 ± 8.7
Female	1,666 (44.3)	184 (65.2)*	23 (56.1)*	117 (63.9)*	26 (74.3)*
African-American	1,506 (40.0)	141 (50.0)*	14 (34.1)	77 (42.1)	20 (57.1)
Body mass index, kg/m^2	28.7 ± 5.6	29.8 ± 6.6*	29.1 ± 6.2*	31.3 ± 6.9*	31.8 ± 7.5*
Pack-years	36.6 ± 19.5	39.4 ± 21.3*	54.6 ± 36.4*	39.0 ± 23.7	41.0 ± 19.5
Active smoking	2,225 (59.1)	203 (72)*	21 (51.2)*	95 (51.9)	16 (45.7)
Asthma	239 (6.4)	141 (50.0)*	6 (14.6)*	121 (66.1)*	14 (40.0)*
Chronic bronchitis	393 (10.4)	67 (23.8)*	10 (24.4)*	61 (33.3)*	5 (14.3)
History of prior exacerbation	161 (4.3)	91 (32.3)*	15 (36.6)*	80 (43.7)*	18 (51.4)*
Congestive heart failure	32 (0.9)	7 (2.5)*	4 (9.8)*	13 (7.1)*	3 (8.6)*
Diabetes mellitus	405 (10.8)	46 (16.3)*	9 (22.0)*	27 (14.8)*	7 (20.0)*
Obstructive sleep apnea	384 (10.2)	51 (18.1)*	9 (22.0)*	35 (19.1)*	14 (40)*
Hypertension	1,276 (33.9)	131 (46.5)*	26 (63.4)*	101 (55.2)*	22 (62.9)*
mMRC ≥ 2	695 (18.2)	147 (52.1)*	21 (51.2)*	97 (53.0)*	30 (85.7)*
FEV_1 percent predicted	97.8 ± 11.5	96.4 ± 11.5*	94.5 ± 10.0*	95.0 ± 11.4*	89.0 ± 6.2*
FVC percent predicted	96.7 ± 11.8	95.7 ± 12.5	96.3 ± 11.5	96.0 ± 12.0	90.5 ± 8.1*
6MWD, feet	1,521 ± 342	1,344 ± 351*	1,188 ± 349*	1,352 ± 340*	1,165 ± 358*
Emphysema severity					
None	1,524 (43.2)	92 (36.1)	9 (23.7)	70 (4.9)	6 (17.6)
Mild	1,402 (39.8)	103 (40.4)	21 (55.3)	63 (36.8)	17 (50.0)
Substantial	598 (17.0)	60 (23.5)	8 (21.1)	38 (22.2)	11 (32.4)
P		.01	.041	.21	.003

* Data are shown as *n* (%) or mean ± SD. $P < 0.05$ compared to no medication use
ICS = inhaled corticosteroids
LABA = long-acting β agonist
LAMA = long-acting muscarinic antagonist
mMRC = modified Medical Research Council scale
6MWD = 6-min walk distance

as previously described.[18] For progression to obstructive ventilatory defect over time, we created a multivariable logistic regression model with the presence of obstructive ventilatory defect at the follow-up visit as the dependent variable (outcome), and medication use as the main independent variable (exposure). Age, current smoking status, gender, race, pack-years smoked, body mass index, chronic bronchitis, history of exacerbation prior to the enrollment, mMRC, history of asthma, and post-bronchodilator FEV_1 percent predicted at enrollment were included in the model as covariates. We repeated the progression to obstructive ventilatory defect analysis in smokers with a pre-bronchodilator FEV_1/FVC and $FEV_1 \geq$ lower limit of normal, and we defined obstructive ventilator defect as FEV_1/FVC < lower limit of normal at the follow-up visit. There were no missing values in any of the covariates. We used the R software package (http://www.r-project.org, *Accessed December 4, 2020*) for all statistical analysis.

Results

Of 4,409 GOLD-0 participants, we excluded 6 subjects with bronchiectasis, 14 subjects with interstitial lung disease, and 1 subject with lung-volume-reduction surgery. There were 85 individuals with incomplete medication histories who were also excluded. Of the remaining 4,303 individuals, 541 (12.6%) were taking medications for obstructive lung disease. There were 259 (6%) individuals taking at least one long-acting inhaled medication: 41 on LAB, 183 on ICS or ICS/LAB, and 35 on triple therapy. There were 282 subjects (6.6%) taking short-acting inhaled medications alone. Table 1 shows characteristics of the subjects. Supplemental Tables 1 and 2 show characteristics of subjects with any medication and long-acting inhaled medication use; Supplemental Table 3 shows medication use at 5-y follow-up visit stratified by medication use at enrollment (see the supplementary materials at http://www.rcjournal.com).

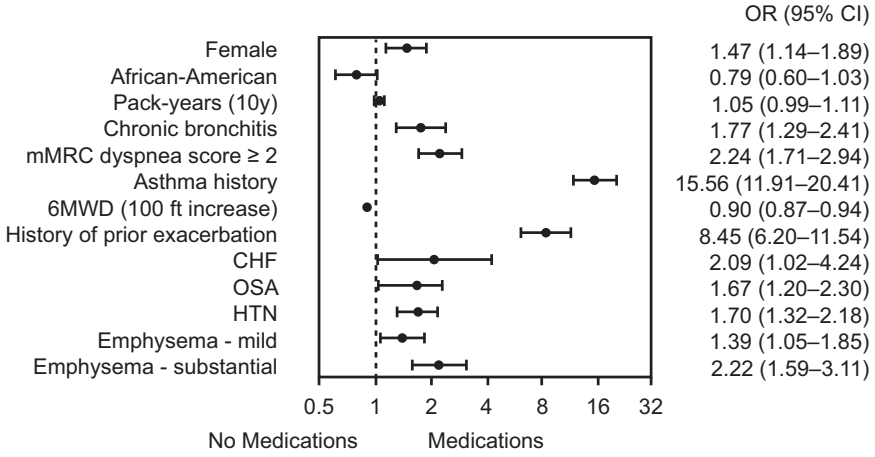

Fig. 1. Factors associated with any medication use. 6MWD = 6-min walk distance, CHF = congestive heart failure, OSA = obstructive sleep apnea, HTN = hypertension.

Factors Associated With Any Medication Use

In the multivariate analysis taking into consideration radiographic variables (Fig. 1 and Supplemental Table 4), female sex (odds ratio [OR] 1.47, 95% CI 1.14–1.89, $P = .003$), history of congestive heart failure (OR 2.09, 95% CI 1.02–4.24, $P = .047$), obstructive sleep apnea (OR 1.67, 95% CI 1.20–2.30, $P = .002$), hypertension (OR 1.70, 95% CI 1.32–2.18, $P < .001$), and evidence of emphysema were all associated with medication use. More significant factors included chronic bronchitis (OR 1.77, 95% CI 1.29–2.41, $P < .001$), increased mMRC dyspnea scores (OR 2.24, 95% CI 1.71–2.94, $P < .001$), asthma history (OR 15.56, 95% CI 11.91–20.41, $P < .001$), and history of prior exacerbation (OR 8.45, 95% CI 6.20–11.54, $P < .001$). Additionally, greater 6MWT distances (OR 0.9, 95% CI 0.87–0.94, $P < .001$, per 100 ft) were associated with less medication use. Similar results were seen when radiographic variables were excluded. A sensitivity analysis was performed excluding subjects with history of asthma ($n = 3,782$) showing similar results to the original analysis except that female sex, obstructive sleep apnea, and congestive heart failure became statistically insignificant factors (see the supplementary materials at http://www.rcjournal.com).

Factors Associated With Long-Acting Inhaled Medication Use

In the multivariate analysis taking into consideration radiographic variables (Fig. 2 and Supplemental Table 6), chronic bronchitis (OR 2.36, 95% CI 1.54–3.57, $P < .001$), increased mMRC scores (OR 2.51, 95% CI 1.73–3.64, $P < .001$), asthma history (OR 16.94, 95% CI 11.87–24.34, $P < .001$), and history of prior exacerbation (OR 10.66, 95% CI 7.22–15.79, $P < .001$) were strongly associated with long-acting inhaled medication (LAB, ICS, ICS/LAB, or triple therapy)

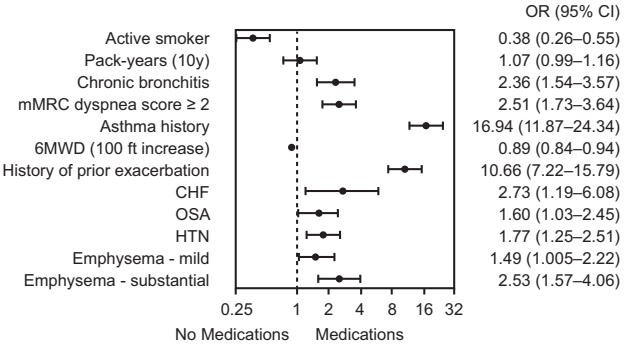

Fig. 2. Factors associated with inhaled corticosteroid, long-acting bronchodilator, or a combination. 6MWD = 6-min walk distance, CHF = congestive heart failure, OSA = obstructive sleep apnea, HTN = hypertension.

use, while history of congestive heart failure (OR 2.73, 95% CI 1.19–6.08, $P = .02$), obstructive sleep apnea (OR 1.60, 95% CI 1.03–2.45, $P = .034$), hypertension (OR 1.77, 95% CI 1.25–2.51, $P = .001$), and evidence of emphysema on imaging were also associated with medication use. Increasing 6MWD (OR 0.9, 95% CI 0.84–0.94, $P < .001$, per 100 ft) were again associated with less medication use. Similar results were seen when radiographic variables were excluded. A sensitivity analysis was performed after excluding subjects with history of asthma ($n = 3,782$), with results similar to the original analysis except that female obstructive sleep apnea and congestive heart failure became statistically insignificant factors (see the supplementary materials at http://www.rcjournal.com).

Association of Long-Acting Inhaled Medication Use With Exacerbations

For exacerbations analysis, there were available data for 2,197 subjects. Among individuals who used no long-acting

inhaled medication, 23.3% ($n = 487$) of them had ≥ 1 exacerbation, and 9% ($n = 189$) of them had ≥ 1 severe exacerbation. Among subjects who used a long-acting inhaled medication (LAB, ICS, ICS/LAB, or triple therapy), 68.6% ($n = 72$) of them had ≥ 1 exacerbation, and 41% ($n = 43$) of them had ≥ 1 severe exacerbation. After adjusting for demographics, body mass index, chronic bronchitis, history of prior exacerbation, dyspnea, history of asthma, and post-bronchodilator FEV_1 percent predicted, long-acting inhaled medication use was associated with increased total (incidence rate ratio 2.83, 95% CI 1.69–4.73, $P < .001$) and severe exacerbations (incidence rate ratio 3.64, 95% CI 1.70–7.81, $P < .001$) (Table 2).

Table 2. Association of Empiric Treatment With Inhaled Medication Use and Progression to COPD Over Time

	Incidence Rate Ratio (95% CI)	*P*
Inhaled medication use*		
Total exacerbations	2.83 (1.69–4.73)	< .001
Severe exacerbations	3.64 (1.70–7.81)	< .001
Progression to COPD at 5 y ($n = 2,185$)†	Odds Ratio (95% CI)	*P*
No medications	Reference	Reference
Short-acting inhaled medications	2.01 (0.84–4.48)	.10
Long-acting inhaled medications	2.83 (1.46–5.42)	.002

$N = 2,291$.
*For exacerbation analysis, we used only long-acting inhaled medications ($n = 2,197$ subjects with data available) and created zero-inflated negative binomial models adjusted by age, current smoking status, gender, race, pack-years smoked, body mass index, chronic bronchitis, history of exacerbation, modified Medical Research Council scale, asthma, and FEV_1. Follow-up time was included as an offset in the models.
†For progression to COPD at 5-y follow-up visit ($n = 2,185$ subjects with data available), we created a multivariable logistic regression model adjusted by age, current smoking status, gender, race, pack-years smoked, body mass index, chronic bronchitis, history of exacerbation, modified Medical Research Council scale, asthma, and FEV_1.

Association of Medication Use With Obstruction at 5-Y Follow-Up Spirometry

There were 2,185 subjects who had a 5-y follow-up spirometry. At the follow-up visit, 10.4% (210 of 2,022) of subjects who took no medication, 16.7% (10 of 60) of subjects taking a short-acting bronchodilator, and 24.3% (25 of 103) of subjects who took long-acting inhaled medication had an obstructive ventilatory defect (Fig. 3).

After adjusting for demographics, body mass index, chronic bronchitis, history of prior exacerbation, dyspnea, history of asthma, and post-bronchodilator FEV_1 percent predicted, long-acting inhaled medication use was associated with an obstructive ventilatory defect at the 5-y follow-up visit (OR 2.83, 95% CI 1.46–5.42, $P = .002$), while short-acting bronchodilators were not associated (OR 2.01, 95% CI 0.84–4.48, $P = .10$) (Table 2). In smokers with pre-bronchodilator FEV_1/FVC and FEV_1 above the lower limit of normal, we observed similar results (see the supplementary materials at http://www.rcjournal.com).

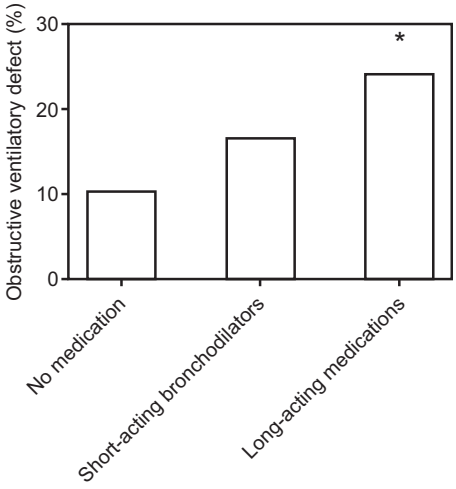

Fig. 3. Presence of obstructive ventilatory defect at 5-y follow-up visit in subjects who took no medication, only short-acting bronchodilators, or long-acting inhaled medications ($n = 2,185$). *$P < .001$ using chi-square test versus no medication.

Discussion

In a cohort of current and former smokers with normal spirometry, 12.6% of subjects were prescribed inhaled medications. Overall, 7% were using short-acting inhaled medications, while 6% were using LABs. The variables most prominently associated with inhaled medication use were respiratory symptoms (ie, chronic bronchitis, increased dyspnea), asthma history, and presence of exacerbation in the year prior to enrollment, while several variables (ie, female sex, congestive heart failure, obstructive sleep apnea, hypertension, presence of radiographic emphysema) had a less significant association with medication use. A sensitivity analysis excluding asthma revealed persistent use of inhaled medications despite lack of an asthma diagnosis. Inhaled medication use was associated with increased exacerbations and obstructive spirometry at the follow-up visit.

In a study conducted within the Veterans Health Administration health system, nearly 40% of individuals on COPD medications had no obstructive ventilatory defect[4]; > 40% of smokers with normal spirometry were prescribed inhaled bronchodilators, and 23% were prescribed inhaled corticosteroids.[19] These findings are similar to those of Sator et al,[3] who reported that 60% of individuals with a diagnosis of COPD had no obstructive ventilatory defect, and, of these, 35% remained on bronchodilator therapy despite the absence of an obstructive spirometry. In our study, we noted lower rates of inhaled medication use relative to

these prior Veterans Health Administration-based and community-based studies; however, we assessed individuals at risk for COPD (ie, smokers) who had normal lung function, while the aforementioned studies evaluated individuals with a diagnosis of COPD who were found to have no obstructive defect on spirometry.

The most significant variables associated with medication use were self-reported asthma history, history of prior respiratory exacerbations, and presence of chronic bronchitis. ICS use occurs in 30% of patients with an empiric diagnosis of asthma, and up to half (49.5%) of these individuals remain on ICS despite spirometry showing no obstruction,[20] which is a similar finding to those prescribed bronchodilators.[3] However, up to 50% of asthma patients may have no obstructive spirometry.[21] In addition, 21% of smokers in the United States have a diagnosis of asthma[22] and are more likely than their nonsmoking counterparts to experience exercise limitation, respiratory exacerbations, and poorer quality of life.[23] Smoking in patients with asthma is also associated with a more precipitous decline in lung function compared to nonsmokers.[24-27] This is even more pronounced in those who develop adult-onset asthma compared to those with childhood-onset asthma.[28]

Chronic bronchitis can also be present without obstructive spirometry and is itself associated with exacerbations; further studies are needed to elucidate whether bronchodilators are beneficial in this population.[8,29,30] Additionally, individuals who present with exacerbations requiring hospitalization may be prescribed bronchodilators despite lack of objective data, which may be in hopes of preventing future exacerbations or worsening lung function.[15,29]

A subset of active smokers with normal spirometry have emphysema on CT scans, and some of these patients are treated with bronchodilators[19] despite a lack of evidence to support treatment without evidence of obstruction.[8,30] In early stage COPD (GOLD 1 or 2), use of tiotropium can mitigate the decline in FEV_1[31]; however, this has not been shown in smokers without obstructive ventilatory defect. Current ongoing studies are investigating the effect of LABs on smokers with no obstructive ventilatory defect.[32]

Obesity was not a significant factor in our final analysis, which is likely due to its association with poor exercise capacity and nonobstructive pathology. Increasing body mass index is also associated with increased respiratory complaints that improve with bariatric surgery[33]; nevertheless, obese individuals tend to be prescribed bronchodilators.[6,7] We have contributed to the literature by showing that other factors associated with poor exercise capacity like congestive heart failure, obstructive sleep apnea, and hypertension are associated with empiric treatment.

Female sex may be associated with medication use given that they seek health care at a higher rate than males[34] and report a greater burden of medical symptoms in general,[35] even when controlling for smoking history and disease severity in COPD.[36-38]

Increasing pack-year history and age were associated with long-acting inhaled medication use. Patients report more symptoms as they age,[35] and increased pack-years are associated with increased respiratory symptoms and worsening functional status.[19,38,39] This increasing symptomatology likely translates into concern for obstructive airway disease and may be a reason for non-guideline-directed therapy.

ICS are the guideline therapy for patients with asthma to improve bronchial hyper-responsiveness, reduce symptoms, and reduce the risk of exacerbations. ICS use in COPD is off-label and is usually reserved for those in the GOLD guidelines Group D or those with eosinophilia. ICS potentially help improve exacerbation rates, but the effect of ICS on progression of lung disease and mortality is unclear.[1]

Short-acting bronchodilators are critical as rescue medications and short-term therapy in patients with COPD and asthma and are the most basic component of treatment for both conditions. LABs (ie, long-acting muscarinic antagonists and LABAs) are approved for use in patients with COPD and are the cornerstone of therapy for those with persistent symptoms or recurrent exacerbations based on GOLD guidelines (Groups B–D).[1] Both help reduce bronchial hyper-responsiveness and lead to improved FEV_1, symptoms, and quality of life. It should be noted that much of the GOLD guidelines focus on treatment of symptoms and exacerbations as opposed to FEV_1 values; our results may provide insight into why providers often provide inhaled therapies despite a lack of current evidence to do so.

From a cost and patient safety standpoint, prescribing bronchodilator therapy can be associated with adverse events[40] and tends to be more prevalent in higher-income countries.[3] Inhaled medication use in individuals with normal spirometry is a financial strain on our health care system. Yearly medication costs for individuals can range from \$500 for albuterol to $>$ \$2,500 for tiotropium or combination ICS/LABA medications.[41] There is also some risk of adverse effects (albeit small): anticholinergics increase the risk of cardiovascular death,[42] β agonists can cause tachycardia or tremors and are associated with higher mortality in African-Americans,[43] and inhaled/systemic corticosteroids are associated with numerous complications (eg, adrenal insufficiency, infections, diabetes, hypertension). However, emerging evidence indicates that smokers without obstructive ventilatory defect based on the traditional criteria may be at risk for respiratory symptoms, hospitalizations, and death due to "obstructive lung disease."[19,44] A recent publication by the COPDGene group suggested that the definition of COPD should expand to include not only spirometry but also symptoms and radiographic measurements.[45] Further study is

warranted in this patient population to determine the potential efficacy of empiric use of inhaled medications.

In this study, we noted that inhaled medication use was associated with increased respiratory exacerbations and the presence of obstructive ventilatory defect (as defined by $FEV_1/FVC < 0.7$) over a 5-y follow-up period. These findings suggest that health care providers identified smokers at risk of developing obstructive ventilatory defect prior to meeting the current spirometric criteria for COPD. However, as there is lack of access to specific provider thought processes, the rationale or answer for why this occurs is an important question to evaluate moving forward.

Our study has several limitations. First, we recorded medication use at only 2 time points (ie, at enrollment and at the follow-up visit). Second, we have no data regarding the frequency of medication use and adherence. Third, we do not know whether health care providers who prescribed those medications had obtained and were aware of chest CT scans. Fourth, we have no data for other tests (eg, methacholine challenge test), especially for individuals with asthma who may have normal spirometry. Another limitation is that we do not have data regarding the socioeconomic status, access to health care, timing of initiation of bronchodilator therapy, or other medications that were prescribed to our population. These limitations do not undermine the strengths of our study, which are the large cohort of subjects and the stringent quality control of the data.

Conclusions

Of smokers with normal spirometry, 12.6% were prescribed inhaled medications: 7% were prescribed short-acting bronchodilators, while 6% were prescribed long-acting inhaled medications like ICS and LABs. The presence of respiratory symptoms, evidence of emphysema on imaging, asthma history, and history of prior respiratory exacerbations were all associated with empiric treatment, whereas medical comorbidities (eg, congestive heart failure, hypertension, obstructive sleep apnea) played a less significant role. Individuals are regularly prescribed these medications, likely in hopes of providing relief from debilitating symptoms. Additionally, we report for the first time that individuals who smoke but had normal spirometry and received inhaled medications were more likely to develop obstructive spirometry, which suggests that health care providers may be able to identify obstructive lung disease prior to meeting the current criteria for COPD.

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