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Implementation of guideline-based therapy for chronic obstructive pulmonary disease: Differences between men and women veterans

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Abstract

Chronic obstructive pulmonary disease (COPD) is common among both men and women, and guidelines recommend the same therapy for both sexes. While previous studies have identified gender differences in other chronic disease management, few studies have examined how implementation of COPD guidelines differs between men and women. We performed a cross-sectional study of veterans admitted to Veterans Affairs (VA) hospitals for COPD during October 1, 2008, to September 30, 2011. We collected information on baseline COPD medications during the 6 months prior to hospitalization and categorized therapies as "appropriate" or "inappropriate" based on current guidelines. We used multivariable logistic regression to examine the differences in COPD medications between men and women, after controlling for baseline patient characteristics. We also examined the differences in hospital outcomes, including length of stay and hospital readmission. We identified 33,558 veterans, including 1149 women and 32,409 men who were admitted to 130 VA hospitals. Women were significantly less likely to have received inhaler therapies prior to admission, with lower rates of short-acting beta agonists, short-acting muscarinic antagonists, long-acting beta agonists, and long-acting muscarinic antagonists compared to men. Women also received fewer appropriate inhaler combinations (odds ratio [OR] = 0.83, 95% confidence interval [CI] 0.74–0.93) and more inappropriate combinations (OR = 1.33, 95% CI 1.17–1.51). Women and men were prescribed similar rates of inhaled steroid and oral steroids. Hospital outcomes were also similar between the two groups. These findings highlight a potential gender disparity in appropriate outpatient COPD therapy. Improving the quality of care for patients with COPD should include equitable implementation of guideline-based COPD management.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease that is characterized by nonreversible airflow obstruction and is most commonly caused by exposure to inhaled pollutants, such as cigarette smoke.[1] Despite growing morbidity and mortality due to COPD, patients are often undiagnosed and untreated.[2] Historically, COPD has been viewed as a disease that primarily affects older men. As the prevalence of cigarette smoking rose among women during the last century, both the incidence of COPD and attributable mortality to COPD rose among women, and since the year 2000, COPD mortality among women has exceeded that of men.[3] While COPD is common among both sexes, few studies have examined differences in COPD management between men and women.[4–7]

Several studies have reported the influence of sex on the physiology and clinical presentation of COPD.[7] Women tend to develop COPD at younger ages and with a shorter smoking history.[8] Women also tend to have less radiographic emphysema and more exacerbations than men.[9,10] Increasingly, clinicians are recognizing that COPD is a heterogeneous disease and there are many different phenotypes that comprise the diagnosis. As researchers search for better ways to characterize COPD, sex may represent a driver of some of the differences in phenotype.

International societies, including the Global Initiative for Obstructive Lung Disease (GOLD) have published guidelines outlining appropriate pharmacologic treatment for COPD.[1] While differences exist in the presentation of COPD, guidelines for the management of COPD are the same for men and women. Short-acting bronchodilators and long-acting bronchodilators are the mainstays of therapy for COPD, and inhaled corticosteroids (ICSs) are reserved for patients with refractory or severe disease.[11] Long-term monotherapy with steroids, inhaled or oral, is not recommended. Studies that have examined pharmacologic treatment for COPD find similar efficacy of inhaled therapies for both men and women.[12,13]

While several studies have shown gender differences in therapy for other chronic diseases, there is limited research on how COPD management differs between men and women.[6,14] To identify possible gender differences in the implementation of guideline-based medications for COPD and highlight opportunities to improve the quality of COPD care, we examined differences in outpatient COPD management among patients admitted to Veterans Affairs (VA) hospitals with a primary diagnosis of COPD. We also investigated the differences in patient demographics, comorbidities, and hospital outcomes between men and women with COPD. Research on gender differences is lacking for COPD, and to our knowledge this has not been studied in a veteran population.

Methods

Study design and population

We performed a retrospective observational study of patients admitted to 130 VA hospitals for COPD during 3 fiscal years (October 1, 2008, to September 30, 2011). We identified 38,128 unique COPD admissions by a primary ICD-9 discharge diagnosis of COPD (491.2, 492.8, 493.2, and 496). Previous studies have validated the use of a principal ICD-9 discharge diagnosis to identify COPD patients.[15] To ensure stability of practice patterns impacting medication prescriptions, we excluded patients who were admitted to hospitals that discharged fewer than 25 patients for COPD during the study period ($n = 11$ patients). We also excluded patients who died during hospitalization ($n = 518$), were discharged to a nursing facility ($n = 683$), were transferred to a non-VA hospital ($n = 2773$), had a length of stay (LOS) <1 day ($n = 502$), or had an LOS greater than 30 days ($n = 83$). The institutional review board of VA Puget Sound and VA Connecticut Healthcare Systems approved the study.

Outcome variables

Outpatient medications. Our primary outcomes of interest were prescriptions for baseline COPD medications. We used the VA outpatient pharmacy file to identify any outpatient prescription for COPD

medications (yes/no), including short-acting beta agonists (SABAs), short-acting muscarinic antagonists (SAMAs), long-acting beta-agonists (LABAs), long-acting muscarinic antagonists (LAMAs), ICSs, and oral steroids in the 6 months prior to hospitalization. Medications were extracted based on pharmacological identity, and we do not have information on brand names, mechanism of delivery, or whether medications were prescribed as combination inhalers.

We also categorized "appropriate" and "inappropriate" combinations of medication based on GOLD society recommendations.[1] These guidelines recommend short-acting bronchodilators for all patients with COPD, long-acting bronchodilators as second-line therapy, and ICS therapy reserved for patients with frequent exacerbations (defined as two or more exacerbations per year) or high risk based on severe airflow obstruction. In our analysis, appropriate combinations of medications included (1) short-acting bronchodilators only (SABA and/or SAMA), (2) short-acting bronchodilators and one or more long-acting bronchodilators (LABA and/or LAMA), or (3) one or more short-acting bronchodilators, one or more long-acting bronchodilators, and an ICS. Inappropriate combinations included (1) no short-acting bronchodilators and (2) ICS without a concurrent long-acting bronchodilator (LABA or LAMA). All patients who received COPD medications in the baseline period were classified as having either appropriate or inappropriate combinations.

Hospital outcomes. Secondary outcomes incorporated severity of disease based on hospital outcomes, including LOS and 30-day readmission. LOS was treated as a continuous variable. We identified all-cause 30-day readmission and COPD-specific 30-day readmission using the VA patient treatment file and Medicare claims.

Covariates

We controlled for baseline patient characteristics including age, race, health insurance, number of home ZIP codes in the year prior to index hospitalization (1 vs. >1) as a measure of housing instability, and discharge against medical advice in the prior year. We identified comorbidities based on any inpatient or outpatient ICD-9 codes from the year prior to index hospitalization based on a validated risk score.[16] Diagnosis of asthma was included as a separate covariate. Number of VA hospitalizations and clinic visits in the prior year was also included in the analysis.

Statistical analyses

We conducted unadjusted analyses to compare baseline characteristics, prescribed medications, and hospital outcomes between men and women in the study. We then used multivariable logistic regression to examine the differences in prescribed COPD medications between men and women, after controlling for baseline patient characteristics. We also used multivariable regression to compare appropriate and inappropriate combinations of therapy. While the multivariable analysis controlled for the diagnosis of asthma, we performed an additional sensitivity analysis, excluding patients with the diagnosis of asthma, to account for differences in recommended medications for this comorbidity.

To examine differences in hospital outcomes between men and women, we used multivariable regression, including a generalized linear model to examine the association with LOS and logistic regression to examine the association with readmission. All statistical analyses were performed using Stata version 14.1.[17]

Results

We identified 33,558 unique veterans admitted to 130 VA facilities for COPD during the study period, consisting of 1149 women (3.4%) and 32,409 men (96.6%). Compared with men, women were younger (63.1 vs. 68.9 years, $p < 0.01$), less likely to be married (27.2% vs. 48.2%, $p < 0.01$), and less likely to be White (67.4% vs. 74.7%, $p < 0.01$) (Table 1). While women had fewer hospitalizations in the year prior to index admission (1.1 vs. 1.3, $p = 0.04$), they had more face-to-face outpatient encounters (5.7 vs. 5.3, $p = 0.04$). Comorbidities differed between the two groups: Women were more likely to have depression (32.8% vs. 19.9%, $p < 0.01$) and asthma (34.6% vs. 17.5%, $p < 0.01$) but were less likely to have other medical comorbidities such as ischemic heart disease, heart failure, chronic kidney disease, and cerebrovascular disease.

In unadjusted analyses, women were significantly less likely to have received COPD inhaler therapy prior to admission when compared with men: with lower rates of SABA (74.6% vs. 78.0%, $p < 0.01$), SAMA (42.1% vs. 49.0%, $p < 0.01$), LABA (41.4%

Table 1. Differences in baseline characteristics between women and men with COPD.

Characteristic	Women $n = 1149$	Men $n = 32,409$
Age (mean, SD)[c]	63.1 (12.3)	68.9 (10.3)
Married (%)[c]	27.2	48.2
White race (%)[c]	67.4	74.7
Black race (%)	13.5	12.6
Other race (%)[c]	19.2	12.7
Medicare FFS (%)[c]	54.4	64.1
Medicare MA (%)[c]	7.0	10.8
Medicare Part D (%)[a]	15.6	18.3
Medicaid (%)	5.9	5.6
Distance to VA (mean, SD)[b]	31.2 (30.1)	34.1 (31.1)
History of AMA (%)	1.6	1.4
>1 ZIP code (%)	22.2	20.4
Prior hospitalizations (mean, SD)[a]	1.1 (2.2)	1.2 (2.2)
Prior clinic encounters (mean, SD)[a]	5.7 (7.9)	5.3 (7.1)
Depression (%)[c]	32.8	19.9
Asthma (%)[c]	34.6	17.5
Hypertension (%)[c]	63.8	73.7
Ischemic heart disease (%)[c]	19.7	37.4
Heart failure (%)[c]	16.8	28.0
Arrhythmia (%)[c]	14.4	26.6
Uncomplicated DM (%)	20.5	21.4
Complicated DM (%)[a]	10.4	13.0
Chronic kidney disease (%)[c]	6.4	14.3
Cerebrovascular disease (%)[b]	10.5	13.2
Pulmonary vascular disease (%)	7.2	8.5

COPD: chronic obstructive pulmonary disease; SD: standard deviation; FFS: fee for service; MA: Medicare Advantage; VA: Veterans Affairs; AMA: against medical advice; DM: diabetes mellitus.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.

vs. 44.5%, $p = 0.04$), and LAMA (16.8% vs. 21.2%, $p < 0.01$) (Table 2). Of note, women and men were prescribed similar rates of ICS (53.6% vs. 54.2%, $p = 0.72$) and oral steroids (29.5% vs. 27.6%, $p = 0.15$) prior to admission. These findings persisted in multivariable analysis, after controlling for patient characteristics. Examining appropriate and inappropriate inhaler medication combinations revealed that women were less likely to receive appropriate combinations (odds ratio [OR] = 0.83, 95% confidence interval [CI] 0.74–0.93) and more likely to receive inappropriate inhaler combinations (OR = 1.33, 95% CI 1.17–1.51) (Table 3).

In sensitivity analyses, excluding patients with asthma yielded similar findings, with lower rates of SABA (68.2% vs. 75.3%, $p < 0.01$), SAMA (41.1%

Table 2. Association of gender with baseline COPD medication prescriptions among veterans hospitalized for COPD.

Medication	Women, $n = 1149$	Men, $n = 32,409$	Adjusted OR (95% CI) Reference = men
SABA (%)	74.6	78.0	0.83 (0.72–0.95)
SAMA (%)	42.1	49.0	0.76 (0.67–0.86)
LABA (%)	41.4	44.5	0.87 (0.77–0.99)
LAMA (%)	16.8	21.2	0.74 (0.63–0.87)
ICS (%)	53.6	54.2	0.96 (0.85–1.09)
Oral steroids (%)	29.5	27.6	1.01 (0.88–1.16)

COPD: chronic obstructive pulmonary disease; OR: odds ratio; CI: confidence interval; SABA: short-acting beta-agonist; SAMA: short-acting muscarinic antagonist; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroid.

Table 3. Risk of appropriate and inappropriate COPD therapy by gender.

	Women, $n = 1149$	Men, $n = 32,409$	Adjusted OR (95% CI) Reference = men
Appropriate therapy combinations			
Short-acting BD only (%)	5.8	4.7	1.47 (1.14–1.91)
Short-acting BD + long-acting BD (%)	7.9	8.0	1.04 (0.84–1.30)
Short-acting BD + long-acting BD + ICS (%)	33.8	37.1	0.74 (0.65–0.84)
Any appropriate therapy	47.5	49.8	0.83 (0.74–0.93)
Inappropriate therapy			
No short-acting BD (%)	24.3	21.1	1.40 (1.21–1.62)
ICS without long-acting BD (%)	17.0	15.1	1.12 (0.96–1.32)
Any inappropriate (%)	39.3	34.6	1.33 (1.17–1.51)

COPD: chronic obstructive pulmonary disease; OR: odds ratio; CI: confidence interval; BD: bronchodilator; short-acting BD: short-acting beta-agonist and/or short-acting muscarinic antagonist; long-acting BD: long-acting beta-agonist and/or long-acting muscarinic antagonist; ICSs: inhaled corticosteroids.

Table 4. Risk of hospital outcomes by gender.

Medication	Women, $n = 1149$	Men, $n = 32,409$	Adjusted estimate (95% CI)
LOS in days, mean (SD)[a]	3.8 (3.0)	3.9 (3.1)	−0.1 (−0.2–0.1)
COPD-specific 30-day readmission, %[b]	8.2	8.4	1.0 (0.8–1.3)
All-cause 30-day readmission, %[b]	15.4	18.3	0.9 (0.8–1.1)

LOS: length of stay; SD: standard deviation; COPD: chronic obstructive pulmonary disease.
[a]Adjusted analysis using linear regression, reporting regression estimate.
[b]Adjusted analysis using logistic regression, reporting odds ratios.

vs. 48.0%, $p < 0.01$), LABA (41.4% vs. 48.0%, $p < 0.01$), LAMA (16.1% vs. 20.4%, $p < 0.01$), and ICS (44.2% vs. 50.3%, $p < 0.01$) compared to men. Women and men were still prescribed similar rates of oral steroids (21.9% vs. 24.0%, $p = 0.20$). These findings persisted in multivariable regression, which also revealed that women were less likely to have been prescribed appropriate inhaler combinations (OR = 0.79, 95% CI 0.68–0.92) and more likely to have been prescribed inappropriate combinations (OR = 1.36, 95% CI 1.17–1.58).

Hospital outcomes were similar between men and women, with similar hospital LOS (3.8 vs. 3.9 days, $p = 0.15$) and COPD-specific 30-day readmission (8.2% vs. 8.4%, $p = 0.81$) (Table 4). While women had significantly fewer all-cause 30-day readmissions in unadjusted analysis (15.4% vs. 18.3%, $p = 0.05$), in multivariable analysis, there was no difference in any of the hospital outcomes examined.

Discussion

Despite growing awareness of gender differences in patient care, women continue to receive disparate health care for many common conditions.[18] While some of this variance stems from differences in disease prevalence, presentation, and therapeutic response, several studies have also demonstrated gender bias leading to systemic mistreatment of women.[4,18,19] An important step in overcoming this bias is identifying the presence of gender differences in patient care.

Despite available treatment guidelines for COPD, women veterans hospitalized with COPD exacerbations were less likely to have received appropriate outpatient therapy prior to their hospitalization. This relationship persisted even after controlling for differences in baseline patient characteristics. While women tended to be younger and had fewer comorbidities, hospital outcomes were not significantly different between the two groups. As we search for ways to improve COPD management, equitable implementation of guideline-based treatment for both women and men could improve the overall quality of care.

Women in our study were younger than men, which may influence the perceived severity of disease and associated medication prescriptions. The population of women veterans tends to be younger than their male counterparts.[20] The age discrepancy that we identified is also consistent with prior research that shows women develop COPD at younger ages and with lower cumulative cigarette smoke exposure.[8] Women's increased susceptibility to COPD may be related to anatomic and physiologic differences; compared with men, women tend to have smaller lungs, smaller airways, and generate lower airflow rates.[21] These differences can lead to higher airway concentration of cigarette toxins among women who smoke. Even childhood exposure to tobacco smoke or environmental air pollution causes girls to experience a larger reduction in lung function than boys.[22]

Women in our study were also less likely to be married when compared to men and may have less available social support. In a study of patients with COPD, greater subjective social support and greater self-efficacy were independently associated with better overall functioning.[23] These investigators highlighted the importance of subjective social support and self-efficacy in the context of improving health management and adherence to the treatment regimen by COPD patients.

Comorbidities differed between men and women in our study. Women were more likely than men to be depressed. Depression can decrease medication adherence and may impact prescribing patterns by clinicians.[24] Women were also more likely to have a concurrent diagnosis of asthma, which is consistent with previous studies that have demonstrated higher prevalence of asthma among adult women.[25] Recommended inhaler therapies differ for asthma and COPD, with ICS being an initial therapy for asthma and being reserved for resistant disease in COPD.[26] Because of differences in recommended therapies, we conducted a sensitivity analysis excluding patients with a concurrent diagnosis of asthma, and we found similar results.

We identified significant differences in outpatient COPD medications between men and women, with systematically fewer inhaler medications, less appropriate therapies, and more inappropriate therapies for women. The etiology of these differences is unclear. It is possible that women had less severe COPD than men, leading to differences in prescribing patterns. Unfortunately, we do not have spirometric data, and we cannot control for the severity of airflow obstruction. We also do not have baseline symptoms, which can be a driver for stepping up inhaler therapies.[1] However, it is notable that men and women had similar rates of ICS and oral steroid prescriptions, which are recommended for more severe COPD. Furthermore, hospital outcomes were similar between the two groups, with no significant difference in LOS or hospital 30-day readmissions in multivariate analysis.

Previous studies have demonstrated gender bias in the diagnosis of COPD. In a randomized study of primary care providers who were given clinical vignettes of patients with COPD, the correct diagnosis was more common if the vignette included a man than a woman.[4] Furthermore, a study of patient with a chart diagnosis of COPD found that women were less likely to have been appropriately diagnosed with spirometry.[5] Few studies have examined gender differences in prescriptions for COPD medications. Dales et al. conducted a study of clinical presentation and management of 130 patients with airflow obstruction and found that women with mild to moderate obstruction were more likely to have been prescribed inhaler medications than men, though this finding did not persist among patients with severe obstruction, and they did not examine specific types of inhaler medications.[6]

Our study represents a larger and more detailed examination of differences in inhaler therapies between men and women with COPD. In contrast to the study by Dales et al., we found that women tended to receive fewer inhaler therapies, which may reflect underrecognition of disease severity, inattentiveness to guidelines, and misinterpretation of respiratory symptoms. Somatic symptoms are more often attributed to psychological disorders for women than men, which could contribute to mismanagement of COPD.[27] More equitable implementation of guideline-based care could help overcome potential gender bias in COPD management.

Our study has several limitations. We did not have access to key risk factors and diagnostic criteria for COPD, including smoking status, spirometry, and respiratory symptoms. Absence of these variables limits the ability to draw definitive conclusions on differences in COPD management. Furthermore, there was no difference in severity of disease between men and women in our study based on hospital outcomes. We also did not have information on medication adherence or the adverse effects that patients experienced with different classes of medications, and we cannot determine whether these factors may have influenced our results. We studied the VA population, which is comprised of notably fewer women than men. Less experience in treating women could contribute to a gender bias in disease management, and our findings may not generalize to non-VA settings.

Conclusions

Guidelines are available for COPD management, and recommended treatments do not differ for treating men and women. Nevertheless, we identified systematic differences in COPD therapy, with less appropriate therapy for women than men. These differences persist after controlling for potential confounding factors and may imply an underlying gender bias in COPD care. Future studies are needed to understand why differences in COPD medications exist and how to effectively improve guideline-based care. As health systems search for ways to improve the quality of COPD care, specific attention should be directed to promoting equitable treatment of men and women with COPD.

Author note

The views expressed here are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the US Government.

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