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## Utilization and effectiveness of pharmacotherapy for tobacco use following admission for exacerbation of COPD

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### Abstract

**BACKGROUND**—Patients admitted for chronic obstructive pulmonary disease (COPD) commonly continue to smoke. The utilization and effectiveness of tobacco cessation medications after discharge is largely unknown. We sought to examine whether pharmacologic treatment of tobacco use following admission for COPD was associated with smoking cessation at 6 to 12 months.

**METHODS**—Multivariable logistic regression analysis of a cohort of 1334 smokers, discharged from hospital with a COPD exacerbation between 2005 and 2012, identified administratively within the Veterans Affairs Veterans Integrated Service Network-20, adjusted for variables chosen *a priori*. Our primary exposure was treatment with any 1 or combination of smoking cessation medications within 90 days of discharge determined from pharmacy records, with the outcome of smoking cessation at 6 to 12 months after discharge.

**MEASUREMENTS AND MAIN RESULTS**—Four hundred fifty (33.7%) of the patients were dispensed a smoking cessation medication, with 53.4% receiving a nicotine patch alone. Overall, 19.8% of patients reported quitting smoking at 6 to 12 months. Compared to those not receiving medications, the odds of quitting were not greater among patients dispensed any single or combination of smoking cessation medications within 90 days of discharge (odds ratio [OR]: 0.88, 95% confidence interval [CI]: 0.74–1.04). Among patients treated with medications compared to nicotine patch alone, varenicline (OR: 2.44, 95% CI: 1.48–4.05) was associated with increased odds of cessation, and short-acting nicotine replacement therapy alone (OR: 0.66, 95% CI: 0.51–0.85) was associated with decreased odds of cessation.

**CONCLUSIONS**—Treatment was provided to a minority of subjects and was not associated with cessation, with potential differences observed in effectiveness between medications. Systems-based changes may improve delivery of this key intervention

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## Search Terms

tobacco; smoking; pulmonary disease; chronic obstructive; nicotine replacement therapy

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## Introduction

Up to 1/3 of the 700,000 patients admitted annually for an exacerbation of COPD continue to smoke tobacco.<sup>1, 2</sup> Smokers with COPD are at high risk for poor health outcomes directly attributable to tobacco related conditions, including progression of lung disease and cardiovascular diseases.<sup>3–5</sup> Treatment for tobacco addiction is the most essential intervention for these patients.

Hospital admission has been suggested as an opportune time for the initiation of smoking cessation.<sup>6</sup> Hospitalized patients are already in a smoke-free environment, and have access to physicians, nurses, and pharmacists who can prescribe medications for support.<sup>7</sup> Documenting smoking status and offering smoking cessation treatment during and after discharge are quality metrics required by the Joint Commission, and recommended by the National Quality Forum.<sup>8, 9</sup> Hospitals have made significant efforts to comply with these requirements.<sup>10</sup>

Limited data exist regarding the effectiveness and utilization of treatments known to reduce cigarette use among COPD patients in non-trial environments. Prescribing patterns of medications for smoking cessation in the “real world” following admission for COPD are not well studied. We sought to examine the utilization of inpatient brief tobacco counselling and post-discharge pharmacotherapy following discharge for exacerbation of COPD, as well as to 1) examine the association of post-discharge pharmacotherapy with self-reported smoking cessation at 6–12 months and 2) assess differences in effectiveness between cessation medications prescribed.

## Methods

We conducted a cohort study of current smokers discharged following a COPD exacerbation within the Veterans Affairs (VA) Veterans Integrated Service Network (VISN)-20. This study was approved by the VA Puget Sound Health Care System Institutional Review Board (#00461).

We utilized clinical information from the VISN-20 data warehouse that collects data using the VA electronic medical record, including demographics, prescription medications, hospital admissions, hospital and outpatient diagnoses, and dates of death, and is commonly used for research. In addition, we utilized “health factors,” coded electronic entries describing patient health behaviors that are entered by nursing staff at the time of a patient encounter, and the text of chart notes that were available for electronic query.

## Study Cohort

We identified all smokers aged ≥ 40 years hospitalized between 2005–2012 with either a primary discharge diagnosis of COPD based on ICD-9 codes (491, 492, 493.2, and 496) or

an admission diagnosis from the text of the admit notes indicating an exacerbation of COPD. We limited to patients aged  $\geq 40$  to improve the specificity of the diagnosis of COPD, and we selected the first hospitalization that met inclusion criteria. We excluded subjects who died within 6 months of discharge (Figure 1).

To establish tobacco status, we built on previously developed and validated methodology,<sup>11</sup> and performed truncated natural language processing using phrases in the medical record that reflected patients' tobacco status, querying all notes from the day of admission up to six months prior. If no tobacco status was indicated in the notes, we identified the status encoded by the most recent health factor. We manually examined the results of the natural language processing and the determination of health factors to confirm the tobacco status. Manual review was undertaken by one of two trained study personnel. In the case of an ambiguous or contradictory status, an additional team member reviewed the information to attempt to make a determination. If no determination could be made, the record was coded to unknown. This method allowed us to identify a baseline status for all but 77 of the 3,580 patients admitted for COPD.

## Outcome and Exposure

The outcome was tobacco status at 6–12 months after discharge. Using the same methods developed for identification of baseline smoking status, we obtained a smoking status for each subject up to 12 months post-discharge. If multiple notes and encounters were available indicating smoking status, we chose the latest within 12 months of discharge. Subjects lacking a follow-up status were presumed to be smokers, a common assumption.<sup>12</sup> The 6–12 month time horizon was chosen as these are the most common time points used to examine a sustained change in tobacco status,<sup>13–15</sup> and allowed for adequate time for treatment and clinical follow-up.

Our primary exposure was any smoking cessation medication or combination dispensed within 90 days of discharge. This time horizon for treatment was chosen due to recent studies indicating this is a meaningful period for post-discharge treatment.<sup>14</sup> We assessed the use of: nicotine patch, short-acting nicotine, varenicline, bupropion, or any combination. Accurate data on the prescription and dispensing of these medications were available from the VA pharmacy record. Secondary exposure was the choice of medication dispensed among treated patients. We assessed additional exposures including receipt of cessation medications within 48 hours of discharge, treatment in the year prior to admission, and pre-discharge counselling. Pre-discharge counselling was determined as having occurred if nurses documented that they completed a discharge process focused on smoking cessation. Referral to a quit line is part of this process, however due to the confidential nature of these interactions, generally low use of this service, and lack of linkage to the VA electronic health record, it was not considered in the analysis.

## Confounders

Potential confounders were assessed in the year prior to admission up to discharge from the index hospitalization, with the use of mechanical or non-invasive ventilation assessed during the hospitalization. We adjusted for variables chosen *a priori* for their known or expected

association with smoking cessation including demographics, Charlson comorbidity index,<sup>16</sup> markers of COPD severity (need for invasive or non-invasive mechanical ventilation during index hospitalization, use of oral steroids, long-acting inhaled bronchodilators, and/or canister count of short-acting bronchodilators in the year prior to admission), history of drug or alcohol abuse, homelessness, depression, psychosis, post-traumatic stress disorder, lung cancer, coronary artery disease, and under or overweight status. Nurse-based counselling prior to discharge was included as a variable for adjustment for our primary and secondary predictors to assess the influence of pharmacotherapy specifically. Due to 3.1% missingness in body mass index, multiple imputation with chained equations was used to impute missing values, with 10 imputations performed. The imputation was performed using a linear regression model containing all variables included in the final model, grouped by facility.

### Statistical Analysis

All analyses were performed using Stata 13 (College Station, TX) software. Chi-squared tests and t-tests were used to assess for unadjusted bivariate associations. Using the pooled imputed datasets, we performed multivariable logistic regression to compare odds ratios for a change in smoking status, adjusting the estimates of coefficients and standard errors by applying combination rules to the 10 completed-data estimates.<sup>17</sup> We analyzed our primary and secondary predictors, adjusting for the confounders chosen *a priori*, clustered by facility with robust standard errors. Alpha level of <0.05 was considered significant.

### Sensitivity Analyses

We assumed that subjects missing a follow-up status were ongoing smokers. However, given the high mortality rate observed in our cohort, we were concerned that some subjects lacking a follow-up status may have died, missing the opportunity to have a quit attempt recorded. Therefore, we performed sensitivity analysis excluding subjects who died during 6–12 months of follow-up, repeating the imputation and analysis as described above. In addition, due to concern for indication bias in the choice of medication used for our secondary analysis, we performed propensity score matching for treatment with each medication in comparison to nicotine patch, using the *teffects* command, with 3 nearest neighbor matches. We included additional comorbidities in the propensity score matching.<sup>18</sup>

### Results

Among these 1,334 subjects at 6–12 months of follow-up, 63.7% reported ongoing smoking, 19.8% of patients reported quitting, and 17.5% of patients had no reported status and were presumed to be smokers. 450 (33.7%) patients were dispensed a smoking cessation medication within 90 days of discharge. Patients who were dispensed medications were younger and more likely to be female. Nearly all patients who received medications also received documented pre-discharge counselling (94.6%), as did the majority of patients who did not receive medications (83.8%). (Table 1)

Of patients dispensed a study medication, 246 (18.4% of patients, 54.7% of all medications dispensed) were dispensed medications within 48 hours of discharge. (Table 2) Of patients dispensed medication, the majority received nicotine patches alone (Table 3). 18.9%

received combination therapy, with the majority receiving nicotine patch and short-acting NRT or patch and bupropion. A significant number of patients were prescribed medications within 90 days of discharge, but did not have them dispensed within that timeframe (n=224, 16.8%).

### Association of treatment with study medications and quitting smoking

In adjusted analyses, the odds of quitting smoking at 6–12 months were not greater among patients who were dispensed a study medication within 90 days of discharge (OR 0.88, 95% CI 0.74–1.04). We found no association between counselling provided at discharge and smoking cessation (OR 0.95, 95% CI 0.66–1.), adjusted for the receipt of medications. There was no difference in quit rate between patients dispensed medication within 48 hours of discharge, or between patients treated in the year prior to admission, and again post-discharge (Table 2).

We then assessed differences in effectiveness between specific medications among the 450 patients who were dispensed medications. Using nicotine patch alone as the referent group, patients treated with varenicline demonstrated greater odds of smoking cessation (OR 2.44, 95% CI 1.48–4.05). Patients treated with short-acting NRT alone were less likely to report smoking cessation (OR 0.66, 95% CI 0.51–0.85). Patients treated with bupropion or combination therapy were no more likely to report cessation. (Table 3) When sensitivity analysis was performed using propensity score matching with additional variables included, there were no significant differences in the observed associations.

Our overall mortality rate observed at one year was 19.5%, nearly identical to previous cohort studies of patients admitted for COPD.<sup>19, 20</sup> Because of the possibility of behavioral differences on the part of patients and physicians regarding subjects with a limited life expectancy, we performed sensitivity analysis limited to the patients who survived to at least 12 months of follow-up. 106 patients (7.9%) died during 6–12 months of follow-up. There was no change in inference for our primary exposure (OR 0.95, 95% CI 0.79–1.14) or any of the secondary exposures examined.

## Discussion

In this observational study, post-discharge pharmacotherapy within 90 days of discharge was provided to a minority of high risk smokers admitted for COPD, and was not associated with smoking cessation at 6–12 months. In comparison to nicotine patch alone, varenicline was associated with a higher odds of cessation, with decreased odds of cessation among patients treated with short-acting NRT alone. The overall quit rate was significant at 19.8%, and is consistent with annual quit rates observed among patients with COPD in other settings,<sup>21, 22</sup> but is far lower than quit rates observed after admission for acute myocardial infarction.<sup>23–25</sup> While the proportion of patients treated at the time of discharge or within 90 days was low, our findings are in keeping with previous studies, which demonstrated low rates of pharmacologic treatment following hospitalization, averaging 14%.<sup>26</sup> Treatment for tobacco use is likely underutilized for this group of high risk smokers. However, a significant proportion of patients who were prescribed medications in the post-discharge period did not have medications filled. This likely reflects both the rapid changes in motivation that

characterize quit attempts,<sup>27</sup> as well as efforts on the part of primary care physicians to make these medications available to facilitate future quit attempts.

There are several possible explanations for the findings in our study. Pharmaceutical therapies were not provided at random. The provision of pharmacotherapy and the ultimate success of a quit attempt reflects a complex interaction of patient beliefs concerning medications, level of addiction and motivation, physician behavior and knowledge, and organizational factors. Organizational factors such as the structure of electronic discharge orders and the availability of decision support materials may influence a physician's likelihood of prescribing medications, the choice of medication prescribed, and therefore the adequacy of control of withdrawal symptoms. NRT is often under dosed to control ongoing symptoms,<sup>28</sup> and needs to be adjusted until relief is obtained, providing an additional barrier to effectiveness during the transition out of the hospital. Because most smokers with COPD are highly addicted to nicotine,<sup>29</sup> high-dose NRT, combination therapy, or varenicline would be necessary to adequately control symptoms.<sup>30</sup> However a significant minority of patients received short-acting NRT alone.

Despite a high observed efficacy in recent trials,<sup>31, 32</sup> few subjects in our study received varenicline. This may be related to both secular trends and administrative barriers to the use of varenicline in the VA system. Use of this medication was limited among patients with psychiatric disorders due to safety concerns. These concerns have since been largely disproven, but may have limited access to this medication.<sup>33–35</sup> Although we adjusted for a history of mental illness, patients who received varenicline may have had more past quit attempts and less active mental illness, which may be associated with improved cessation rates. Despite the high prevalence of mental illness we observed, this is typical of the population of smokers, with studies indicating nearly 1/3 of smokers overall suffer from mental illness.<sup>36</sup>

While the majority of our patients received a brief, nurse-based counselling intervention, there is considerable concern about the overall effectiveness of a single pre-discharge interaction to produce sustained smoking cessation among highly addicted smokers.<sup>37–40</sup> The Joint Commission has recently restructured the requirements for smoking cessation treatment for hospitalized patients, and it is now up to hospitals to implement treatment mechanisms that not only meet the national requirements, but also provide a meaningful clinical effect. Though the optimum treatment for hospitalized smokers with COPD is unknown, previous positive studies of smoking cessation among hospitalized patients underscore the need for a higher intensity counselling intervention that begins during hospitalization and continues after discharge.<sup>13, 41</sup> Cessation counselling services including tobacco cessation groups and quit lines are available through the VA, however the use of these services is typically low and requires the patient to enroll independently after discharge, an additional barrier. The lack of association between medications and smoking cessation found in our study could reflect poor effectiveness of medications in the absence of a systematic counselling intervention. Alternatively, the association may be explained that patients who were more highly addicted and perhaps less motivated to quit received tobacco cessation medications more often, but were also less likely to stop tobacco use, a form of indication bias.



Our study has several limitations. We do not have addiction or motivation levels for a cessation attempt, a potential unmeasured confounder. While predictive of quit attempts, motivation factors are less predictive of cessation maintenance, and may therefore have an unclear effect on our outcome.<sup>42, 43</sup> Our outcome was gathered as part of routine clinical care, which may have introduced bias if patients over reported cessation because of social desirability. In healthcare settings, however, this form of assessing smoking status is generally valid.<sup>44</sup> Exposure to counselling or medications obtained outside of the VA system would not have been captured. Given the financial incentive, we believe it is unlikely that many patients admitted to a VA medical center obtained medications elsewhere.<sup>45</sup> The diagnosis of COPD was made administratively. However, all subjects were admitted for an exacerbation, which is associated with more severe COPD by GOLD stage.<sup>46</sup> Patients with more severe COPD are often excluded from studies of smoking cessation due to concerns of high dropout and lower prevalence of smoking among patients with GOLD IV disease,<sup>47, 48</sup> making this a strength of our study. Subjects who died may have quit only in extremis, or failed to document their quit attempts. However, our sensitivity analysis limited to survivors did not change the study results. There may have been some misclassification in the use of bupropion which may also be prescribed as an antidepressant. Finally, while representative of the Veterans who seek care within the VISN-20, our patients were primarily white and male, limiting the ability to generalize outside of this group.

Our study had several strengths. We examined a large cohort of patients admitted to a complete care organization, including patients from a diverse group of VA settings comprising academically and non-academically affiliated centers. We performed an unbiased collection of patients, including all smokers discharged for COPD. We had access to excellent completeness of medications prescribed and filled as collected within the VA system, enabling us to observe medications dispensed and prescribed at several time points. We also had near complete ascertainment of outcomes including by using natural language processing with manual confirmation of smoking status.

In summary, we found that provision of medications to treat ongoing tobacco use among patients discharged for COPD was low, and receipt of medications was not associated with a reduction in smoking tobacco at 6–12 months post-discharge. However, among those treated, varenicline appears to be superior to the nicotine patch, with short-acting nicotine replacement potentially less effective, a biologically plausible finding. The motivation to quit smoking changes rapidly over time. Providing these medications in hospital and during the time after discharge is a potential means to improve quit rates, but medications need to be paired with counselling in order to be most effective. Collectively, these data suggest that systems based interventions are needed to increase the availability of intense counselling and the use of tailored pharmacotherapy to these patients.

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Dr. Melzer conceived of the research question, performed background reading, analyses, primary drafting and final revision of the manuscript. Drs. Collins and Feemster participated in finalizing the research question, developing the cohort, and performing data collection, and revising the manuscript. Dr. Au provided the database for analysis, helped finalize the research question, assisted in interpretation of the data, and revision of the manuscript. Dr. Au has personally reviewed the data, understands the statistical methods employed, and confirms an understanding of this analysis, that the methods are clearly described and that they are a fair way to report the results.

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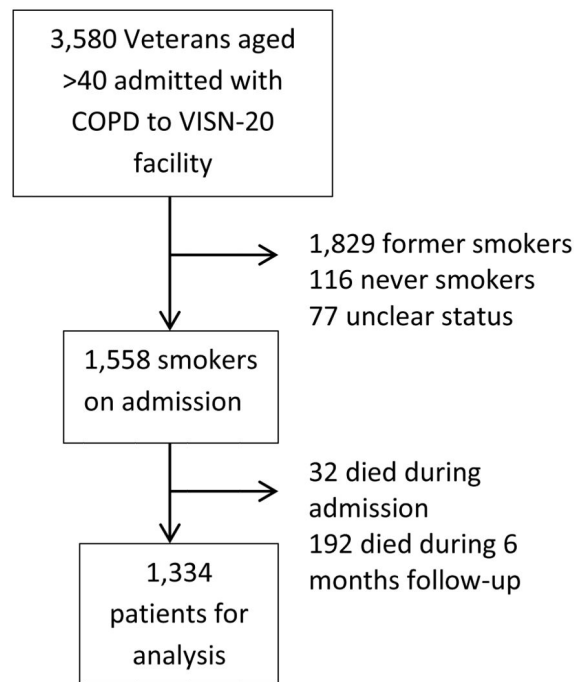
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**Figure 1.**

Results of cohort selection among Veterans admitted to the VA Veterans Integrated Service Network 20 for exacerbation of COPD from 2005–2012

**Table 1**

Characteristics of Veterans by smoking cessation medications dispensed from discharge to 90 days following admission for exacerbation of COPD from 2005–2012 (N=1,334)

	No medication dispensed n=884	Medication dispensed n=450	
Variable	n (%)	n (%)	p value
Not smoking at 6–12 months	179 (20.2)	85 (18.9)	0.56
Brief counselling at discharge	<b>742 (83.8%)</b>	<b>424 (94.6%)</b>	<b>&lt;0.001</b>
Age *	<b>64.4 +/- 9.13 (40–94)</b>	<b>61.0 +/- 7.97 (41–85)</b>	<b>&lt;0.001</b>
Male	<b>852 (96.3)</b>	<b>423 (94.0)</b>	<b>0.05</b>
Race			0.12
White	744 (84.2)	377 (83.8)	
Black	41 (4.6)	12 (2.7)	
Other/Unknown	99 (11.1)	61 (13.6)	
BMI *	28.0 +/- 9.5 (12.6–69.0)	28.9 +/- 10.8 (14.8–60.0)	0.15
Homeless	68 (7.7)	36 (8.0)	0.84
Psychiatric conditions/substance abuse:			
History of alcohol abuse	205 (23.2)	106 (23.6)	0.88
History of drug abuse	110 (12.4)	72 (16.0)	0.07
Depression	39 (4.4)	29 (6.4)	0.11
Psychosis	201 (22.7)	88 (19.6)	0.18
PTSD	146 (16.5)	88 (19.6)	0.17
Comorbidities:			
Coronary artery disease	254 (28.7)	110 (24.4)	0.10
Cerebrovascular accident	80 (9.0)	28 (2.2)	0.86
Obstructive sleep apnea	42 (4.8)	23 (5.1)	0.77
Lung cancer	21 (2.4)	10 (2.2)	0.86
Charlson comorbidity index *	2.25 +/- 1.93 (0–14)	2.11 +/- 1.76 (0–10)	0.49
Markers of COPD severity:			
Mechanical ventilation during admission	28 (3.2)	14 (3.1)	0.96
NIPPV during admission	97 (11.0)	51 (11.3)	0.84
Oral steroids prescribed in the past year	334 (37.8)	154 (34.2)	0.20
Treatment with tiotropium in the past year	97 (11.0)	55 (12.2)	0.50
Treatment with LABA in the past year	264 (29.9)	155 (34.4)	0.09
Canisters of SABA used in past year *	6.63 +/- 9.8, (0–84)	7.46 +/- 9.63 (0–45)	0.14
Canisters of ipratropium used in past year *	6.45 +/- 8.81 (0–54)	6.86 +/- 9.08 (0–64)	0.42
Died during 6–12 months of follow-up	78 (8.8)	28 (6.6)	0.10

\* values presented are mean, SD and range. 3.3% missing in BMI.

Bold indicates statistical significance.

Abbreviations used: BMI: body mass index, PTSD: post-traumatic stress disorder, LABA: long-acting beta agonist, SABA: short-acting beta agonist

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**Table 2**

Adjusted odds ratios of quitting smoking at 6–12 months among Veterans admitted for exacerbation of COPD<sup>\*</sup> (n=1334)

Medication dispensed:	n (%)	% Quit (unadjusted)	OR (95% CI)	p-value
No medications dispensed	884 (66.3)	20.2	referent	
Any medication from:				
Discharge to 90 days	450 (33.7)	18.9	0.88 (0.74–1.04)	0.137
Within 48 hours of discharge	246 (18.4)	18.3	0.87 (0.66–1.14)	0.317
Treated in the year prior to admission	221 (16.6)	19.6	referent	
Treated in the year prior to admission + 0–90 days post-discharge	152 (11.4)	18.4	0.95 (0.79–1.13)	0.534
No nurse-provided counselling prior to discharge <sup>‡</sup>	169 (12.7)	20.5	referent	
Nurse-provided counselling prior to discharge	1165 (87.3)	19.5	0.95 (0.66–1.36)	0.774

<sup>\*</sup> Model adjusted for age, gender, race, underweight or obese, alcohol use, homelessness, comorbidities, history of mental illness, markers of COPD severity, and receipt of counselling prior to discharge.

<sup>‡</sup> Model adjusted for above confounders and for receipt of medications



**Table 3**

Adjusted odds ratios of quitting smoking at 6–12 months among Veterans admitted for exacerbation of COPD who were treated with cessation medications after discharge. \* (n=450)

Medication dispensed:	n (%)	% Quit (unadjusted)	OR (95% CI)	p-value
Nicotine patch	242 (53.8)	18.6	referent	
Monotherapy with:				
Varenicline	36 (8.0)	30.6	2.44 (1.48–4.05)	0.001
Short-acting NRT	34 (7.6)	11.8	0.66 (0.51–0.85)	0.001
Bupropion	55 (12.2)	21.8	1.05 (0.67–1.62)	0.843
Combination therapy	85 (18.9)	15.7	0.94 (0.71–1.24)	0.645

\* Model adjusted for age, gender, race, underweight or obese, alcohol use, homelessness, comorbidities, history of mental illness, markers of COPD severity, and receipt of counselling prior to discharge.

NRT=nicotine replacement therapy