Impact of FDA advisories on smoking cessation for Veterans with chronic obstructive pulmonary disease

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Abstract

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Many persons with chronic obstructive pulmonary disease (COPD) require medication to quit smoking. Few receive effective therapy with varenicline, partly due to reduced prescribing after the onset of Food and Drug Administration advisories for psychiatric risk. It is unknown whether prescribers responded differently for patients with high smoking related morbidity or low mental health risk. To inform future directives, we examined the association of advisories and varenicline dispensation among Veterans hospitalized for COPD who were currently smoking tobacco despite recent cessation medications. We compared varenicline dispensation within 3 months of admission between persons hospitalized before and after the first FDA advisory in February 2008. We estimated rate ratios using Poisson regression, stratified by the presence of any mental health disorder and adjusted for confounders of demographics and smoking related morbidity. Among 344 eligible Veterans, advisories were associated with lower varenicline dispensation (adjusted RR 0.47 [0.27–0.82]). Prevalent mental health disorders did not modify this association. Veterans who received varenicline versus other therapy were more likely to quit smoking at 12 months (adjusted RR 1.73, [1.07–2.78]). FDA safety advisories were thus associated with a nonspecific decrease in varenicline prescribing and lost opportunities for smoking cessation among persons with tobacco related morbidity.

Background and Significance

Chronic obstructive pulmonary disease (COPD) affects over 13 million U.S. adults, accounts for over $30 billion in annual healthcare costs, and is predominantly due to tobacco smoking [1]. Many persons diagnosed with COPD continue smoking after diagnosis, contributing to respiratory symptoms and progressive lung function decline [2-4]. This trend extends to those with severe COPD who are at highest risk of future disease exacerbations and associated morbidity, highlighting the need for effective smoking cessation interventions across the spectrum of illness severity.

Despite the broad benefits of smoking cessation, the delivery of smoking cessation therapy (SCT) remains suboptimal. Integrated health systems such as the Veterans' Health Administration (VHA) and Kaiser Permanente have made robust efforts to identify the majority of tobacco smokers and advise cessation. While up to 49% of all smokers accept cessation assistance, only 34% of smoking Veterans receive cessation medications after COPD hospitalization [5-7]. Fewer than 10% of these hospitalized Veterans receive varenicline, which is more effective for cessation than either nicotine replacement or bupropion among highly addicted groups [8, 9]. Increasing the use of varenicline among smokers who accept cessation assistance thus represents an opportunity to narrow the gap between tobacco use identification and cessation.

One likely contributor to infrequent varenicline use is psychiatric safety concerns. These evolved from post-marketing reports in late 2007, which yielded formal FDA advisories for psychiatric effects in February 2008 and eventually a black box warning by July 2009 [10]. Subsequent studies found no evidence of increased psychiatric harm from varenicline and advisories were removed in late 2016 [9]. National prescribing data from both Medicare and VHA found a significant fall in varenicline use after the onset of psychiatric advisories [10]. However, it remains unclear whether prescribers avoided varenicline among all smokers or if avoidance was limited to patients with an unfavorable balance of risks and benefits. Specifically, the association of advisories with prescribing has not been described among persistent smokers with COPD or other tobacco related morbidity, for whom varenicline's benefits to cessation might outweigh perceived risks. It is also unknown whether the fall in prescribing was limited to smokers with mental health disorders, who were specifically identified in the advisory as a high-risk

population. We sought to measure how FDA safety advisories affected SCT prescribing choice and subsequent cessation outcomes among these groups in order to inform future prescribing directives.

Methods

Study design, setting, and participants

We developed a nested cohort from among a larger cohort of Veterans over age 40 who were admitted for COPD exacerbation at five hospitals within VA Integrated Service Network (VISN)-20 [5]. All analyses used clinical information from the VISN-20 data warehouse, which aggregates electronic health record (EHR) data on demographics, hospitalizations, prescriptions, smoking status, inpatient and outpatient diagnoses, readmissions, and deaths.

We studied Veterans who were eligible to receive varenicline after COPD hospitalization by restricting our cohort to those who were currently smoking tobacco on admission despite SCT dispensation in the prior year. This population met contemporary VHA prescribing guidelines for varenicline due to failure of previous therapy. We identified current tobacco smoking from review of free text health factors recorded at admission as per previously validated methods [11, 12]. We included patients who were admitted between January 1, 2007 and December 31, 2011 when varenicline was available from VHA pharmacies (Figure 1).

Exposures, outcomes, and covariates

For the primary analysis, the exposure was the presence of any FDA safety advisory or black box warning for varenicline on the date of admission. This was defined as admission after the first formal safety advisory on February 1, 2008. Admissions prior to this date were unexposed. The potential effect modifier of prevalent mental health disorder was defined by the presence of any ICD-9 diagnosis of depression, PTSD, or psychosis, or any dispensation of antidepressants or antipsychotics, within the 12 months prior to admission. The primary outcome was any varenicline dispensation from VHA occurring between hospital admission and 3 months after discharge, including dispenses during hospitalization, discharge, and outpatient visits. We collected exploratory data on dispensation of bupropion, sustained release nicotine patches, and short acting nicotine formulations in the same time frame, as these were the other forms of SCT available. We adjusted the primary analysis for likely confounders including age at

hospitalization, sex, intensive care during hospitalization, outpatient prescription of long-acting muscarinic antagonists, outpatient ICD-9 diagnosis of substance use disorder, and atherosclerotic cardiovascular disease (ASCVD) as defined by outpatient ICD-9 diagnoses of either coronary artery disease or cerebrovascular accident. All outpatient covariates were measured within the 12 months prior to admission.

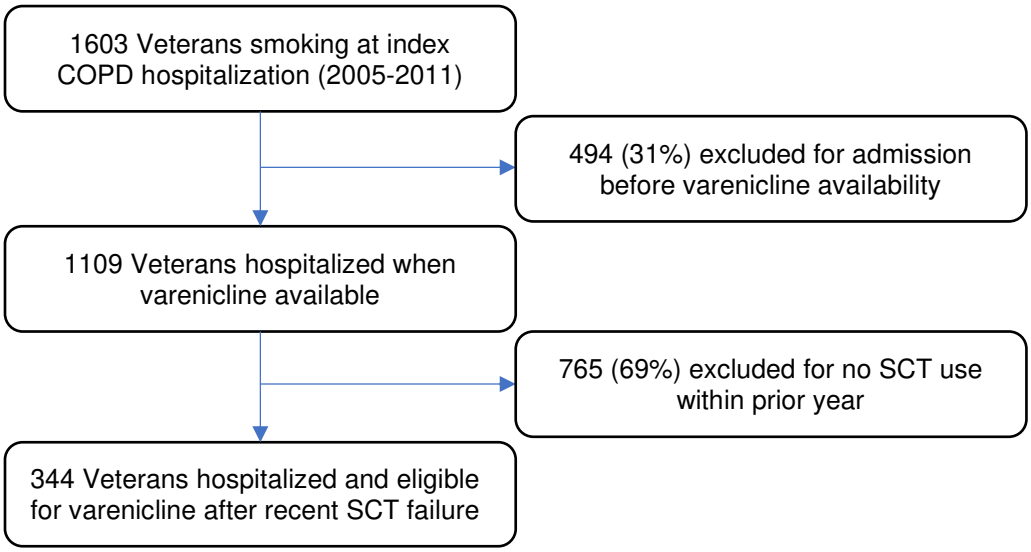
For the secondary analysis of varenicline effectiveness on smoking cessation, the exposure was any varenicline dispensation between admission and 3 months after discharge, including that dispensed in combination with other SCT. Unexposed subjects could have received other SCT medications or none. Smoking cessation was defined by a change in status to “former smoker” per the latest measured health factor in the 12 months after discharge. Patients surviving 12 months after discharge with no further smoking status records during this interval were assumed to continue smoking (last observation carried forward). The secondary analysis was adjusted for all confounders noted above and also for prevalent mental health disorder, as this was expected to confound the relationship between varenicline dispensation and smoking cessation.

Statistical analysis

We performed a difference in difference analysis to assess the association between advisories and varenicline dispensation among Veterans with and without mental health diagnoses. We estimated incidence rate ratios for varenicline dispensation using Poisson regression with interaction between advisory status and mental health diagnosis, with robust standard errors clustered by hospital site. We adjusted a priori for all suspected confounders defined above. We reported estimates for both main effects and their interaction and estimated the incidence rate of varenicline prescription for each exposure combination. To explore the replacement of varenicline by alternative SCT we described the dispensation of bupropion and nicotine replacement therapy in the pre- and post-advisory periods.

In the secondary analysis, we measured the association between varenicline dispensation and cessation using Poisson regression with robust standard errors clustered by hospital site. Statistical significance was defined by Wald test using a two-sided alpha of 0.05. All participants had complete data on primary exposures, outcomes, and covariates. All analyses were performed with Stata/MP version 16.0 [13].

Figure 1: Cohort selection



Results

We identified 344 Veterans hospitalized between 2007 and 2011 who were currently smoking upon admission for COPD and eligible to receive varenicline. Of these, 279 (81%) were admitted after the FDA safety advisory. Like the base cohort, our subjects were predominantly male (N=324, 94%) and had a large burden of both medical and psychiatric comorbidities (Table 1). There was a high prevalence of ASCVD (N=99, 29%) or heart failure (N=69, 20%). Many Veterans had markers of severe COPD including recent systemic steroid use (N=146, 42%) and intensive care needs during admission (N=78, 23%). Mental health diagnoses and medications were highly prevalent (N=252, 73%), with a majority of the cohort receiving antidepressants, and concurrent substance use disorder was common (N=119, 35%).

In the primary analysis, the presence of an FDA safety advisory was associated with lower varenicline dispensation in both crude and adjusted models (crude IRR 0.45, 95% CI 0.33 – 0.61, Table 2). In the adjusted difference-in-difference analysis, the presence of mental health disorder was not significantly associated with dispensation (IRR 1.27, 95% CI 0.57 – 2.83), nor did it modify the association between advisory and dispensation (IRR for interaction 1.14, 95% CI 0.46 – 2.82). Among veterans with a mental health disorder, the onset of advisory corresponded to an absolute change in probability of varenicline dispensation from 18.7% to 10.1%, a decrease of 8.6% (95% CI 1.4% – 15.9%). Veterans

without a mental health disorder had a similar decrease in varenicline dispensation after the advisory (Table 3).

Table 1: Veteran characteristics by presence of varenicline advisory at hospitalization, 2007-2011				
	Advisory absent (n=65)		Advisory present (n=279)	
	N	%	N	%
Male sex	61	94%	263	94%
Age, years (μ, SD)	60.1	8.8	61.8	7.3
Charlson index (μ, SD)	2.5	2.1	2.4	1.8
Mental health disorder	45	69%	207	74%
Post-traumatic stress disorder	14	22%	62	22%
Depression	4	6%	24	9%
Psychosis	19	29%	74	27%
Antidepressant use	41	63%	188	67%
Antipsychotic use	14	22%	33	12%
Substance use disorder	18	28%	101	36%
Drug use	11	17%	57	20%
Alcohol use	14	22%	80	29%
Cardiovascular disease	17	26%	82	29%
Coronary artery disease	16	25%	71	25%
Stroke	3	5%	22	8%
Heart failure	15	23%	54	19%
Lung cancer	3	5%	15	5%
Long acting antimuscarinic use	7	11%	46	16%
Systemic steroid use	25	38%	121	43%
Intensive care during admission	14	22%	64	23%

Table 2: Incidence rate ratio (IRR) for varenicline dispensation by presence of advisory and mental health disorder		
	Crude IRR (95% CI)	Adjusted* IRR (95% CI)
Advisory present	0.45 (0.33, 0.61)	0.47 (0.27, 0.82)
Mental health disorder	-	1.27 (0.57, 2.83)
Advisory * Mental health	-	1.14 (0.46, 2.82)
* Adjusted for age, sex, intensive care, ASCVD, substance use disorder, long acting antimuscarinic use		

Table 3: Adjusted incidence rate of varenicline dispense by presence of advisory, stratified by mental health disorder				
Mental health disorder	Adjusted incidence rate* (%)		Rate Difference (95% CI)	Rate ratio (95% CI)
	Advisory absent	Advisory present		
Absent	14.8	7.0	-7.8 (-15.5, -0.2)	0.47 (0.27, 0.82)
Present	18.7	10.1	-8.6 (-15.9, -1.4)	0.54 (0.33, 0.87)
* Adjusted for age, sex, intensive care, ASCVD, substance use disorder, long acting antimuscarinic use				

In exploratory analysis of substitutions for varenicline, the advisory onset was accompanied by a slight increase in the proportion of Veterans dispensed no SCT (43% to 46%) or short acting nicotine (5% to 11%). There was no apparent change in dispensation of bupropion (15% to 15%) or long acting nicotine (31% to 32%).

In the secondary effectiveness analysis, varenicline dispensation was associated with a higher 12-month cessation rate when compared with other therapies (adjusted IRR 1.73, 95% CI 1.07 – 2.78). This corresponded to a cessation rate of 25.6% with varenicline versus 14.8% with any other therapy, a difference of 10.8% (95% CI 1.1% – 20.4%, Table 4).

Table 4: Smoking cessation at 12 months post-hospitalization by type of SCT dispensed				
	Crude		Adjusted*	
	Cessation rate (95% CI)	Rate ratio (95% CI)	Cessation rate (95% CI)	Rate ratio (95% CI)
Varenicline	31.5% (23.9, 39.3)	2.2 (1.45, 3.32)	25.6% (19.4, 31.8)	1.73 (1.07, 2.78)
Other therapy	14.4% (11.7, 17.0)	ref	14.8% (11.1, 18.5)	ref
* Adjusted for mental health disorder, age, sex, intensive care, ASCVD, substance use disorder, long acting antimuscarinic use				

Discussion

In this study of Veterans who were current smokers and hospitalized for COPD, we found that FDA drug safety advisories were associated with a twofold decrease in varenicline dispensation. We found no evidence to suggest the decrease in varenicline use differed between Veterans with or without

mental health disorders, as might be expected from the advisories' specific reference to suicide and other psychiatric risks. Our estimated decline in varenicline dispensation for these Veterans with smoking-related morbidity is similar to the 69% decrease found among all smokers in VHA [10]. These findings suggest that the onset of FDA advisories was associated with a substantial and nonspecific reduction in varenicline dispensation which extended to Veterans with smoking-related morbidity, even in the absence of concurrent high-risk mental health disorders.

Several mechanisms might explain the nonspecific decrease in varenicline dispensation associated with advisories. One likely mediator was the VHA prescribing directive for varenicline, which was issued within 3 months of the first FDA advisory. This directive was intended to enhance screening for psychiatric risk before varenicline dispensation, instructing prescribers to screen all patients for symptoms and potentially involve mental health care before ordering varenicline [14]. While this could improve recognition of latent mental health risks, it also added to prescribers' workload and thus could have discouraged consideration of varenicline. We could not assess the degree of mediation in this analysis given the very short time interval between these two exposures and the lack of an unexposed comparator group after the directive was issued.

We found varenicline to be significantly more effective than other agents in this population of Veterans with severe COPD, persistent tobacco addiction, and substantial rates of mental health comorbidity. The efficacy of varenicline in this group is similar to other populations, including those with mild COPD or isolated mental health disorders (4,7,8). Our estimated efficacy corresponds to a number needed to switch of nine; one additional Veteran was reported to be tobacco free at 12 months for every nine Veterans who were dispensed varenicline instead of another agent. From the observed efficacy and decrease in varenicline dispensation, we estimate that the FDA advisory was associated with one less tobacco cessation per hundred smokers with severe COPD. The exact difference in cessation depends on which SCT medications were dispensed in lieu of varenicline, as bupropion and nicotine patches are more effective than short acting nicotine alone [4].

Unfortunately, our exploratory analysis suggests that decreases in varenicline use after FDA advisory were not offset by substantial increases in the use of other highly effective SCT medications. It is possible that varenicline and other medications were avoided in favor of alternatives such as formal

cessation counseling, but this is unlikely given that only 4% of Veterans utilized these services in subsequent years [15]. Together, these findings support the idea that reduced varenicline dispensation in the face of FDA advisories represented a lost opportunity for smoking cessation among Veterans with severe tobacco-related morbidity.

This study has potential limitations. We restricted our study to Veterans within a single VISN who had previously failed SCT, resulting in a small sample with limited power to detect interactions between mental health and smoking cessation therapy choices. However, this restriction likely improved internal validity by reducing site to site variations in dispensing and excluding smokers who had shown no recent intention to quit. We also did not have data on prescriber characteristics to help distinguish individual prescribers' SCT choices from the broader effect of VHA prescribing directives. Despite the absence of prescriber information, our study conclusions are strengthened by the detailed and complete records on participants' medical diagnoses, mental health diagnoses, and medication history. Future studies of smoking cessation therapy using national cohorts of Veterans with linked prescriber information would add to our understanding of barriers to effective cessation.

References

1. Guarascio, A.J., et al., *The clinical and economic burden of chronic obstructive pulmonary disease in the USA.* Clinicoecon Outcomes Res, 2013. **5**: p. 235-45.
2. Au, D.H., et al., *The effects of smoking cessation on the risk of chronic obstructive pulmonary disease exacerbations.* J Gen Intern Med, 2009. **24**(4): p. 457-63.
3. Scanlon, P.D., et al., *Smoking Cessation and Lung Function in Mild-to-Moderate Chronic Obstructive Pulmonary Disease.* Am J Respir Crit Care Med, 2000. **161**: p. 381-390.
4. van Eerd, E.A., et al., *Smoking cessation for people with chronic obstructive pulmonary disease.* Cochrane Database Syst Rev, 2016(8): p. CD010744.
5. Melzer, A.C., et al., *Utilization and effectiveness of pharmacotherapy for tobacco use following admission for exacerbation of COPD.* J Hosp Med, 2016. **11**(4): p. 257-63.
6. Tonnesen, P., *Smoking cessation and COPD.* Eur Respir Rev, 2013. **22**(127): p. 37-43.
7. Quinn, V.P., et al., *Tobacco-Cessation Services and Patient Satisfaction in Nine Nonprofit HMOs.* American Journal of Preventive Medicine, 2005. **29**(2): p. 77-84.
8. Hoogendoorn, M., et al., *Long-term effectiveness and cost-effectiveness of smoking cessation interventions in patients with COPD.* Thorax, 2010. **65**(8): p. 711-8.
9. Anthenelli, R.M., et al., *Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial.* The Lancet, 2016. **387**(10037): p. 2507-2520.
10. Desai, R.J., et al., *Varenicline and Nicotine Replacement Use Associated With US Food and Drug Administration Drug Safety Communications.* JAMA Netw Open, 2019. **2**(9): p. e1910626.
11. McGinnis, K.A., et al., *Validating smoking data from the Veteran's Affairs Health Factors dataset, an electronic data source.* Nicotine Tob Res, 2011. **13**(12): p. 1233-9.
12. Melzer, A.C., et al., *Validating the use of veterans affairs tobacco health factors for assessing change in smoking status: accuracy, availability, and approach.* BMC Med Res Methodol, 2018. **18**(1): p. 39.
13. StataCorp, *Stata Statistical Software: Release 16*. 2019, StataCorp LLC College Station, TX.
14. *Varenicline Criteria for Prescribing*. 2008, VA Center for Medication Safety.
15. Kelly, M.M., H. Sido, and R. Rosenheck, *Rates and correlates of tobacco cessation service use nationally in the Veterans Health Administration.* Psychological Services, 2016. **13**(2): p. 183-192.