Trends in Incident Varenicline Prescribing Among Veterans Following the US Food and Drug Administration Drug Safety Warnings

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ABSTRACT

Objective: To evaluate national trends in incident varenicline and nicotine replacement therapy (NRT) prescribing among Department of Veterans Affairs (VA) beneficiaries before and after US Food and Drug Administration (FDA) warnings regarding neuropsychiatric side effects with varenicline use.

Methods: All adult VA patients identified as smokers from 2007 to 2019 (N = 3,600,947) were determined and monthly counts of new varenicline and NRT users were calculated. An interrupted time-series analysis estimated the effect of the FDA warnings on varenicline and NRT prescribing overall and among Veterans with and without mental health disorders.

Results: The incident use rate of varenicline decreased from a peak of 6.2 per 1,000 veteran smokers in October 2007 to 1.0 by July 2009 following the first FDA warning (pre-warning monthly slope = –0.27; *P* = .03). New NRT use increased from 10.7 per 1,000 veteran smokers in October 2007 to a peak of 12.6 per 1,000 in July 2009 (slope change = 0.71; *P* = .01), suggesting potential substitution. Following removal of the FDA boxed warning in December 2016, varenicline prescribing increased but did not return to pre-warning levels by December 2019. Among veterans with and without mental health disorders, varenicline use decreased 90% and 88%, respectively, following the first FDA warning, and both groups had comparable rates of new NRT use.

Conclusions: Following the first FDA warning, incident use of varenicline declined significantly among veterans both with and without mental health disorders. Despite removal of the FDA boxed warning in December 2016, new use of varenicline had not returned to pre-warning levels 3 years following the removal.

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In February 2008, the US Food and Drug Administration (FDA) issued a drug safety warning regarding concerning changes in behavior associated with use of the smoking cessation medication varenicline. This FDA warning informed health care professionals that serious neuropsychiatric side effects including hostility, agitation, depressed mood, and suicidal ideation and behaviors had been found among varenicline users.[1] Due to these growing concerns, the FDA issued a boxed warning for varenicline in July 2009—the most stringent warning the FDA can issue for medications on the market.[2]

Following the boxed warning, several large observational studies failed to find significant neuropsychiatric side effects associated with varenicline use, including no change in rates of psychiatric hospitalizations, emergency department visits, depression, or suicidal behavior—including among patients with mental health disorders.[3–6] In April 2016, Pfizer, the manufacturer of varenicline, published the Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES)[7] demonstrating no significant neuropsychiatric side effects with use of varenicline compared to nicotine replacement therapy (NRT) or placebo. The study also found varenicline more effective than other smoking cessation medications such as NRT and bupropion in helping individuals to stop smoking. Additional studies[8–10] have demonstrated that varenicline is an effective and safe smoking cessation medication among patients with severe mental illness. In light of these findings, the FDA removed the boxed warning in December 2016.[11] The FDA concluded that benefits of stopping smoking outweighed risks of medication use. Nonetheless, the FDA continued to caution that risk of neuropsychiatric side effects including depression and suicidal behavior remained present, especially among individuals currently or previously receiving treatment for mental health disorders.[11]

To date, limited studies have evaluated the potential impact of the FDA warnings and subsequent removal on trends in prescribing varenicline and other smoking cessation medications. One study[12] utilizing data from the Medical Expenditure Panel Survey from 2007 to 2014 found significant declines in overall varenicline use that persisted following the first FDA warning. However, this study did not include the time period following the removal of the boxed warning in 2016. A 2001–2018 study[13] of Veterans Health Administration (VHA) and Medicaid data also found

Clinical Points

- US Food and Drug Administration (FDA) boxed warnings serve as the strongest labeling requirement for a high-risk medication. Little research has evaluated prescribing following the removal of FDA boxed warnings as safety information about a medication changes.
- Despite multiple trials demonstrating its safety, varenicline remains prescribed much less often in Veterans Health Administration patients than prior to the initial FDA warning.

significant declines overall in varenicline use following the first FDA warning in 2009, with increases in NRT prescribing during that time. Following the removal of the boxed warning in 2016, the authors observed a significant increase in use of varenicline among veterans, while a nonsignificant increase was observed in Medicaid prescribing.

Notably, neither study evaluated the impact of the FDA warnings on varenicline prescribing among individuals with mental health disorders—the population whom the FDA deemed at greatest risk for side effects associated with varenicline use. Further, these studies focused on overall varenicline prescribing without examining the impact of the FDA warnings on new (ie, incident) varenicline prescribing for smoking cessation, which may remain underutilized, despite the removal of the boxed warning.

This study aimed to evaluate the response of the VHA, the largest integrated health system in the US,[14] to the FDA drug safety warnings for varenicline. We sought to evaluate changes in prescribing of incident varenicline and NRT among veteran smokers with and without mental health diagnoses from 2007 to 2019 to identify potential differential changes in prescribing. We hypothesized, based on previous work,[13] that the initial drug safety warnings contributed to a significant decline in incident varenicline use and that these decreases in system-wide prescribing of varenicline would be associated with subsequent increase in prescriptions of other smoking cessation therapy. We hypothesized that these declines in prescribing would appear more pronounced among veterans with mental health disorders who may have greater risks of the neuropsychiatric side effects highlighted by the original FDA warning.

METHODS

We linked prescription data from the VA Pharmacy Benefits Management (PBM) with the VHA Corporate Data Warehouse (CDW) patient data and used an interrupted time-series design to examine changes in incident varenicline and NRT prescribing among veteran smokers after the FDA warnings.

Study Cohort

The study period ran from August 1, 2006 through December 31, 2019, which included varenicline prescribing at least 12 months before the first FDA advisory warning (February 2008) and 3 years after the removal of the FDA boxed warning (December 2016). We assembled a monthly rolling cohort of VA patients aged 18 years or older identified as current smokers utilizing health factor data from the VHA data. The VA Ann Arbor Healthcare System institutional review board approved this study.

Identification of Veteran Smokers

We identified veteran smokers using health factor data from the VHA CDW using previously validated methods.[15,16] VHA collects health factor data nationally using the clinical reminder process, in which providers receive automatic prompts by the electronic medical record to ask patients about their tobacco use. We classified veterans with entries assigned to standardized categories of "current smoker," "current tobacco user," and "tobacco cessation offered" as current smokers.[15] We computed the number of current veteran smokers monthly throughout the study period to serve as the monthly study denominator, defined as all veterans with at least one health factor smoking flag within the last 12 months without any mention of "quit." The computed number of veteran smokers appeared consistent with those from previous studies utilizing the same data sources.[17] We excluded veterans without health factor data from the study cohort.

Incident Varenicline and Nicotine Replacement Therapy Use

We compiled the number of veteran smokers with new prescriptions for varenicline and NRT monthly. Using the PBM data, we identified the date of the first varenicline or NRT prescription fill. No previous prescription claims in the 180 days before the first dispense date indicated incident varenicline and NRT use. For each monthly rolling cohort, we calculated the number of veterans with incident use of varenicline or NRT.

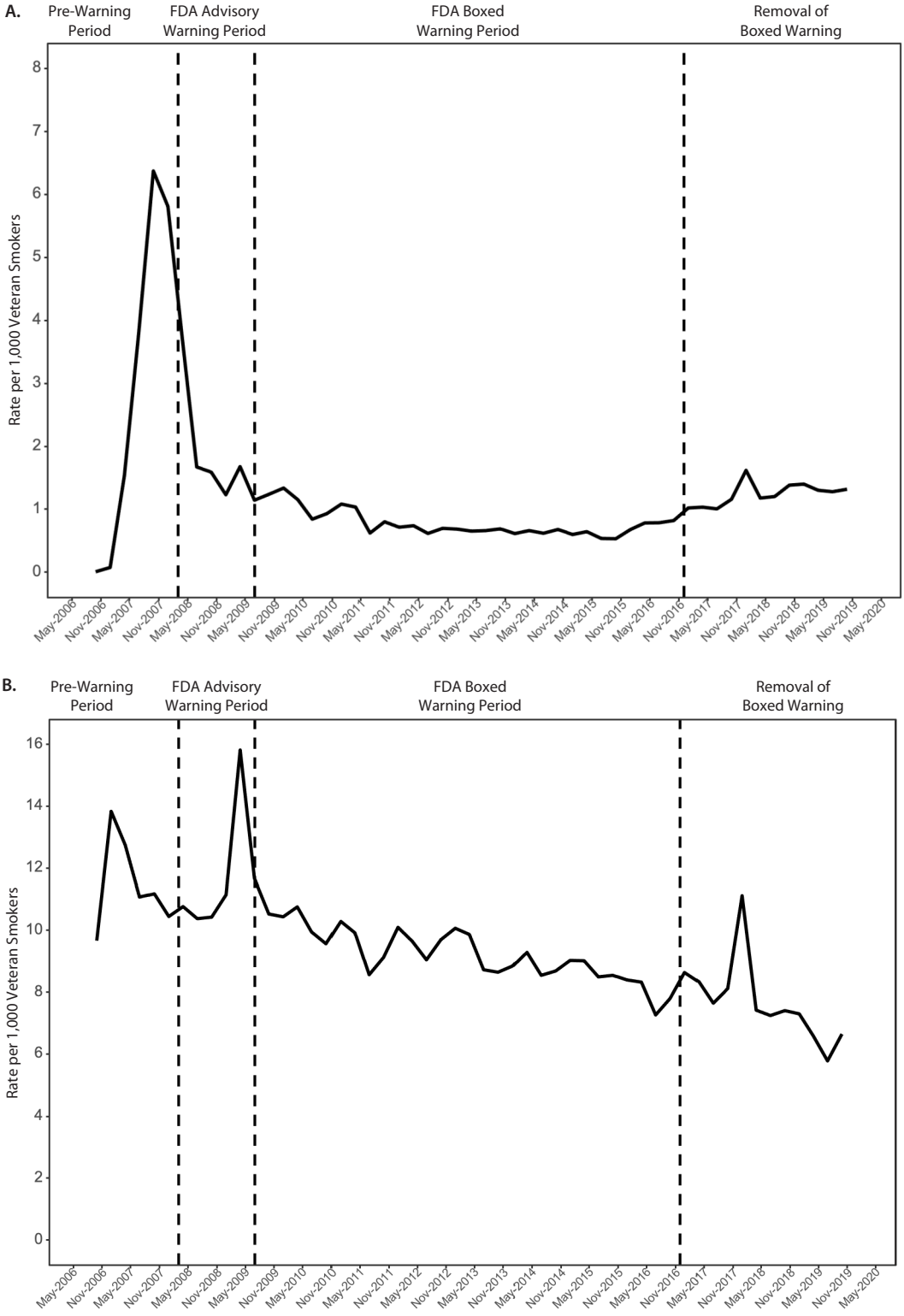
Mental Health Diagnoses

Among veterans with mental health disorders, we tested for differential rates of incident varenicline or NRT use following the drug safety warnings. Mental health diagnoses included a diagnosis of anxiety, bipolar disorder, depression, posttraumatic stress disorder, or psychosis/schizophrenia (*ICD-9* and *ICD-10* criteria). We identified diagnoses each month and classified patients into the mental health group if their diagnosis preceded their incident varenicline or NRT medication fill at each month.

Statistical Analysis

Varenicline became available on formulary in the VA in January 2007 with a steep increase in use in the following 9 months. To identify changes in incident varenicline and NRT prescribing after the varenicline-related FDA warnings, we used data from the period after which varenicline use reached its peak in the VA in October 2007. We first divided the study into 4 periods: (1) October 2007–February 2008 (before the FDA advisory warning: pre-warning period),

Figure 1. Trends in Incident (A) Varenicline and (B) Nicotine Replacement Therapy Use Among Veteran Smokers



Abbreviation: FDA = US Food and Drug Administration.

Table 1. Descriptive Characteristics of Veteran Smokers Overall and Veterans With Incident Varenicline and Nicotine Replacement Therapy (NRT) Use During 2007[a]

Characteristic	Veteran Smokers Overall (N = 1,068,710)	Veteran Smokers With Incident Varenicline Use (n = 43,336)	Veteran Smokers With Incident NRT Use (n = 155,095)
Age, mean (SD), y	57.2 (12.8)	55.8 (10.2)	55.0 (10.9)
Sex			
Male	1,013,756 (94.9)	39,590 (3.7)	145,445 (13.6)
Female	54,950 (5.1)	3,746 (0.4)	9,649 (0.9)
Race/Ethnicity			
White	721,786 (67.5)	34,949 (3.3)	104,728 (9.8)
Black	198,091 (18.5)	4,023 (0.4)	32,765 (3.1)
Hispanic	28,262 (2.6)	526 (0.05)	3,792 (0.4)
Other	27,515 (2.6)	962 (0.09)	3,852 (0.4)
Unknown	39,531 (3.7)	1,667 (0.2)	5,467 (0.5)
Mental Health Disorder[b,c]			
Any	493,414 (46.2)	24,082 (2.3)	83,800 (7.8)
Anxiety	92,490 (8.7)	4,787 (0.4)	16,195 (1.5)
Bipolar disorder	17,948 (1.7)	1,040 (0.1)	3,794 (0.4)
Depression	29,7945 (27.9)	15,493 (1.5)	53,562 (5.0)
PTSD	99,350 (9.3)	5,259 (0.5)	18,287 (1.7)
Psychosis/schizophrenia	52,787 (4.9)	1,691 (0.2)	8,453 (0.8)

[a]Unless otherwise noted, values are shown as n (% among veteran smokers overall).
[b]*ICD-9* codes for specific mental health diagnoses are as follows: anxiety (300.00, 300.02), bipolar disorder (296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8), depression (296.2, 296.3, 301.12, 300.4, 293.83, 298.0, 301.1, 311, 312, 296.9, 296.99, 309.0, 309.19), PTSD (309.81), psychosis/schizophrenia (295.0, 295.1, 295.2, 295.3, 295.4, 295.6, 295.7, 295.8, 295.9, 297.0, 297.1, 297.2, 297.3, 297.8, 297.9, 298.0, 298.1, 298.2, 298.3, 298.4, 298.8, 298.9).
[c]*ICD-10* codes for specific mental health diagnoses are as follows: anxiety (F45.20, F45.21, F45.29, F06.4, F41.0, F41.3, F41.8, F41.9, F40, F42, F41.1), bipolar disorder (F30, F301, F302, F303, F304, F308, F309, F310–F3178, F318, F3181, F3189, F319), depression (F32, F33, F32.8, F33.8), PTSD (F43.10, F43.11, F43.12), psychosis/schizophrenia (F20, F200, F201, F202, F203, F205, F208, F2081, F2089, F209, F25, F250, F251, F258, F259, F060, F062, F22, F23, F24, F28, F29, F53, F531).
Abbreviation: PTSD = posttraumatic stress disorder.

(2) February 2008–July 2009 (between the FDA advisory warning and FDA boxed warning: FDA advisory warning period), (3) July 2009–April 2016 (between the FDA boxed warning and the removal of the FDA boxed warning: FDA boxed warning period), and (4) December 2016–December 2019 (from the removal of the FDA boxed warning to the end of the study period: removal of FDA boxed warning) (Figure 1). To examine the effect of the varenicline-related drug safety warnings on incident prescriptions for varenicline and NRT, we fit interrupted time-series regression models with first-order autoregressive errors separately among current veteran smokers overall, veteran smokers with mental health diagnoses, and veteran smokers with no mental health diagnoses. We used the model to describe the change in level (intercept) and trend over time (slope) in incident varenicline and NRT prescribing during the study period, controlling for pre-warning level and trend. We conducted all statistical analyses using the SAS 9.4 statistical software package (SAS Institute Inc; Cary, NC).

RESULTS

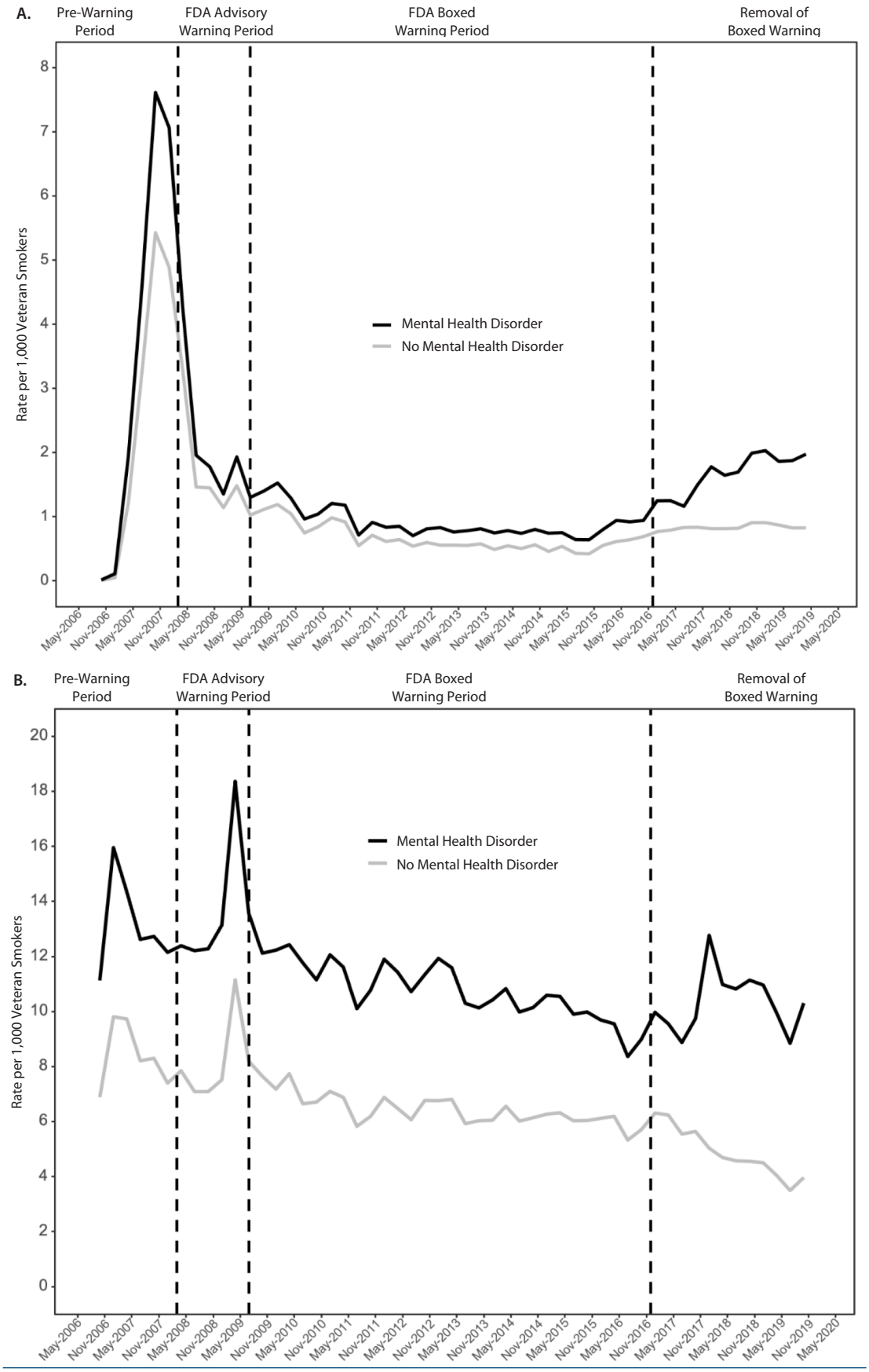
Study Cohort Characteristics

The study identified VA outpatient service users aged 18 years or older during 2007–2019 (N = 10,272,467). We excluded the 10% of the study sample who did not have health factor data. In this cohort, the study identified 3,600,947 VA service users as current smokers between 2007 and 2019. Table 1 presents descriptive characteristics of the study cohort and those with incident use of varenicline and NRT in 2007. A total of 43,336 VA smokers (4.1%) newly received varenicline prescriptions and 155,095 (14.5%) newly received NRT prescriptions during 2007.

Trends in Varenicline and Nicotine Replacement Therapy Among Veteran Smokers Overall

Figure 1 demonstrates the monthly rate of incident (no previous prescription within the past 180 days) varenicline and NRT use per 1,000 veteran smokers throughout the study period. Table 2 depicts changes in the level and slope of incident varenicline and NRT prescribing during the 4 study periods for veterans identified as current smokers. At the peak of varenicline use in October 2007, 6.2 per 1,000 veteran smokers had new varenicline prescriptions. Even during the pre-warning period prior to the first drug safety communication in February 2008, incident varenicline use declined to a low of 3.4 incident users per 1,000 veteran smokers by February 2008 (pre-warning period monthly slope = −0.27; $P = .03$). Incident use of varenicline remained low throughout the FDA advisory and boxed warning periods, with roughly 1 new varenicline prescription per 1,000 veteran smokers following the FDA boxed warning from July 2009 to December 2016. Following the removal of the FDA boxed warning in 2016, incident use of varenicline rose by 0.01 additional new users per 1,000 veteran smokers per month; however, this was a nonsignificant increase (slope change = 0.01, $P = .05$). Rates of incident use of varenicline overall remained low at 1.3 per 1,000 smokers at the end of the study period. On the other hand, after the first FDA drug safety warning in February 2008 as use of incident varenicline declined, new prescriptions for NRT increased by 0.23 (slope change = 0.71, $P = .01$) per 1,000

Figure 2. Trends in Incident (A) Varenicline and (B) Nicotine Replacement Therapy Use Among Veterans Smokers With Mental Health and No Mental Health Diagnoses



Abbreviation: FDA = US Food and Drug Administration.

Table 2. Rates per 1,000 Veteran Smokers and Trends of Incident Varenicline and Comparison Nicotine Replacement Therapy Among Veteran Smokers Overall

	Varenicline		Nicotine Replacement Therapy	
Milestone and Variable	Coefficient (SE)	95% CI	Coefficient (SE)	95% CI
Pre-Warning Period				
Rate of use at peak (October 2007)	6.23 (0.22)	5.81 to 6.66	10.74 (0.51)	9.74 to 11.74
Slope during pre-warning period	−0.27 (0.12)	−0.51 to −0.03**	−0.48 (0.28)	−1.03 to 0.07
FDA Advisory Warning (February 2008)				
Rate of use at start of warning period 1	3.36 (0.14)	3.09 to 3.63	9.02 (0.32)	8.39 to 9.65
Slope change during warning period 1	0.11 (0.12)	−0.13 to 0.35	0.71 (0.28)	0.15 to 1.26*
FDA Boxed Warning (July 2009)				
Rate of use at start of warning period 2	1.00 (0.08)	0.85 to 1.16	10.49 (0.20)	10.10 to 10.89
Slope change during warning period 2	0.16 (0.02)	0.12 to 0.20***	−0.26 (0.03)	−0.34 to −0.16***
Removal of the Boxed Warning (December 2016)				
Rate of use at start of post-warning period	1.09 (0.12)	0.85 to 1.32	9.03 (0.31)	8.42 to 9.64
Slope change during post-warning period	0.01 (0.01)	0 to 0.02	−0.06 (0.02)	−0.09 to −0.03***
Rate of use at end of post-warning period	1.3 (0.12)	1.07 to 1.54	5.68 (0.31)	5.08 to 6.29

*$P < .05$.
**P < .01.
***$P < .001$.

Table 3. Rates per 1,000 Veteran Smokers and Trends of Incident Varenicline and Comparison Nicotine Replacement Therapy Among Veterans Smokers With Mental Health and No Mental Health Diagnoses

	Mental Health Diagnosis				No Mental Health Diagnosis			
	Varenicline		Nicotine Replacement Therapy		Varenicline		Nicotine Replacement Therapy	
Milestone and Variable	Coefficient (SE)	95% CI	Coefficient (SE)	95% CI	Coefficient (SE)	95% CI	Coefficient (SE)	95% CI
Pre-Warning Period								
Rate of use at peak (October 2007)	7.42 (0.27)	6.89 to 7.95	12.19 (0.58)	11.04 to 13.33	5.32 (0.18)	4.96 to 5.69	8.04 (0.40)	7.25 to 8.83
Slope during pre-warning period	−0.30 (0.15)	−0.59 to −0.01*	−0.49 (0.32)	−1.12 to 0.15	−0.24 (0.10)	−0.44 to −0.04*	−0.44 (0.22)	−0.87 to 0.00*
FDA Advisory Warning (February 2008)								
Rate of use at start of period	3.96 (0.17)	3.62 to 4.29	10.51 (0.36)	9.79 to 11.23	2.91 (0.11)	2.69 to 3.14	6.34 (0.25)	5.84 to 6.83
Slope change from prior period	0.10 (0.15)	−0.19 to 0.39	0.75 (0.32)	0.11 to 1.38*	0.10 (0.10)	−0.10 to 0.30	0.59 (0.22)	0.15 to 1.03***
FDA Boxed Warning (July 2009)								
Rate of use at start of black box warning	1.12 (0.09)	0.94 to 1.31	12.33 (0.24)	11.85 to 12.80	0.91 (0.07)	0.78 to 1.05	7.18 (0.15)	6.88 to 7.47
Slope change from prior period	0.19 (0.02)	0.15 to 0.23***	−0.29 (0.06)	−0.40 to −0.18***	0.13 (0.02)	0.10 to 0.16***	−0.17 (0.04)	−0.24 to −0.10***
Removal of the Boxed Warning (December 2016)								
Rate of use at start of period	1.29 (0.14)	1 to 1.57	10.28 (0.37)	9.54 to 11.01	0.82 (0.1)	0.61 to 1.02	6.54 (0.23)	6.08 to 7
Slope change from prior period	0.02 (0.01)	0.01 to 0.03***	0.01 (0.02)	−0.03 to 0.05	0.01 (0.01)	0 to 0.02	−0.08 (0.01)	−0.1 to −0.06***
Rate of use at end of post-warning period	1.95 (0.14)	1.67 to 2.23	9.48 (0.37)	8.75 to 10.22	0.82 (0.1)	0.61 to 1.03	3.13 (0.23)	2.67 to 3.59

*$P < .05$.
***$P < .001$.

smokers per month during warning period 1, suggesting potential substitution.

Trends in Varenicline and Nicotine Replacement Therapy by Veteran Smokers With Mental Health Diagnoses

Veteran smokers with mental health diagnoses (ie, anxiety, bipolar disorder, depression, posttraumatic stress disorder, or psychosis/schizophrenia) had higher incident use of varenicline prior to the first FDA drug safety warning (7.4 per 1,000 veterans) compared to veteran smokers without mental health disorders (5.3 per 1,000 veterans; Table 3). We observed higher rates of incident varenicline use among veteran smokers with mental health disorders than among those without mental health disorders throughout the entire study period, but the changes in the patterns of incident use in the two groups over the study period appeared similar. Incident varenicline prescribing declined among veteran smokers with mental health disorders, with a monthly slope during the pre-warning period of −0.30 ($P = .04$) per 1,000

veteran smokers with mental health disorders and −0.24 ($P = .02$) in veteran smokers without mental health disorders (Table 3, Figure 2). Following the removal of the FDA boxed warning in December 2016, incident varenicline use began to increase significantly only among those with mental health disorders (slope change = 0.02, $P < .001$) but not among veterans without mental disorders (slope change = 0.01, $P = .20$). At the end of the study period, the overall use of varenicline remained significantly lower compared to pre-warning levels among both groups. For incident NRT use, following the first FDA advisory warning, rates increased significantly among both groups with a slope of 0.26 (slope change = 0.75, $P = .02$) in those with mental health disorders and 0.15 (slope change = 0.59, $P = .008$) in those without mental health disorders, suggesting substitution.

DISCUSSION

In this large, national sample of veterans in VA care who smoked tobacco, we found that trends in incident varenicline prescribing declined significantly leading up to and following the 2008 FDA warning. Rates of new varenicline use remained low from 2008 to 2019 and began to increase slightly following the removal of the FDA warning. At the end of the study period in 2019, incident varenicline use had declined 79% to 1.3 per 1,000 veteran smokers compared to pre-warning levels of 6.2 per 1,000 veteran smokers.

Among veteran smokers with mental health conditions, who would likely have the highest risk for the neuropsychiatric side effects listed by the FDA warning, incident use of varenicline remained higher throughout the study compared to varenicline use among veterans without mental health disorders. Rates of new varenicline use decreased significantly among veterans both with and without mental health disorders; however, those with mental disorders experienced a steeper rate of decline. Following the removal of the boxed warning, incident varenicline use increased significantly only for those with mental health disorders. Higher incident use may reflect previous failure of first-line NRT among veterans with mental health disorders and increased comfort in monitoring neuropsychiatric side effects given comprehensive psychiatric treatment services available within the VHA. Following the initial declines in varenicline initiation, we observed concomitant increases in NRT prescriptions among all groups after the 2008 FDA warning, suggesting potential substitution of NRT for varenicline.

The designation of a boxed warning serves as the FDA's strongest labeling requirement for high-risk medications. Studies evaluating health system responsiveness to FDA drug safety warnings have found that these warnings often have variable, and at times limited, effects in influencing changes in prescribing practices.[18,19] A 2006 study[20] evaluating over 200 boxed warnings among nearly 1 million patients found that over 40% of patients still received medications potentially contraindicated based on the boxed warning. In the case of varenicline, the FDA warning led to substantial and sustained reductions in the use of this medication among veterans.[13] Studies finding significant intended effects of FDA warnings have cited the importance of communication efforts in changing prescribing practices.[21]

The VA took several steps to clearly communicate concerns following the initial FDA warning to both providers and veterans. The VA Center for Medication Safety (VAMedSafe) within the VA PBM Services directed such communications through its role in managing dissemination of national directives regarding medication use and safety.[22,23] The VAMedSafe issued prescribing criteria for varenicline that recommended against its use in veterans with suicidal or assaultive behaviors within the past 12 months until they are evaluated by a mental health professional.[24] The VA further recommended that prescribing providers complete a brief suicide and violence risk assessment with patients as well as inquire regarding mental health treatment prior to initiating treatment with varenicline. Following the removal of the FDA warning, VAMedSafe communicated the revised FDA warning to providers through a drug safety newsletter and provided updated prescribing recommendations on their internal website.[25]

Far fewer studies have assessed the removal of boxed warnings.[13,26] A 2019 study of rosiglitazone[26]—a medication to treat type 2 diabetes—evaluated prescribing of the medication before and after the subsequent removal of a black box warning originally placed for increased risk of myocardial infarction. Following removal of the boxed warning, use of rosiglitazone remained less than 1% despite evidence against the initial safety concerns.

Multiple factors may have influenced the lack of return of prescribing of varenicline to pre-warning levels by December 2019. Providers and patients may not know about the removal of the drug safety warning, given higher levels of communication typically at the initiation of drug safety warnings rather than after a reversal of drug safety warnings.[26] Additionally, both providers and patients may have chosen not to resume treatment with varenicline based on the availability of perceived less risky alterative medications (eg, NRT, bupropion). Despite the publication of studies suggesting that varenicline may be more effective than other pharmacologic treatment options in assisting smoking cessation,[7] both providers and patients may avoid considering varenicline use given the initial boxed warnings. Such prescribing changes have implications for utilization of effective treatment options and highlight the importance of ongoing communication regarding evolving drug safety warnings—especially after information regarding the safety of a medication changes. Finally, increasing varenicline drug costs may have further led to reductions in prescribing, as reports indicated that the cost of varenicline more than doubled from 2013 to 2018.[27]

This study has several limitations. First, this analysis of prescription fills does not capture actual medication use. However, we sought to evaluate changes in prescribing behavior after the drug safety warnings rather than medication use per se. Second, our analyses may have

overestimated the study denominator if current smokers quit smoking during the month of outcome evaluation. Third, our sample included a high proportion of men, and our study results may not generalize to other clinical populations and health care systems. Fourth, we cannot determine the exact reason why treatment with varenicline declined (eg, directly due to the drug safety warning or given patient preference). Lastly, our study period ended on December 31, 2019, and it remains unclear if use of varenicline has continued to increase over subsequent years.

This study demonstrated that incident varenicline use declined significantly among veterans with and without mental health disorders following the 2008 FDA warning regarding neuropsychiatric side effects associated with use of this medication. Communication strategies through the VAMedSafe within the VA PBM may have helped contribute to the substantial reductions in varenicline use observed after the FDA warning—suggesting that responsiveness could be potentially lower in health systems without such communication strategies. A concomitant increase in NRT use suggests that providers substituted treatments for smoking cessation. Moreover, reductions in new use of varenicline indicate that providers may avoid using varenicline after the FDA warnings, even following the subsequent removal of the boxed warning. Although new use started to slightly increase after the removal of the boxed warning, rates of use remained significantly lower than prewarning levels. Lack of clarity about whether patients with underlying mental health disorders remained at increased risk of side effects, provider substitution of other perceived less risky smoking cessation treatment such as NRT, and lack of provider and patient knowledge regarding the removal of the boxed warning may have led to limited prescribing after the removal of the boxed warning. Lack of education surrounding the removal of boxed warnings and ongoing fear regarding the concerns highlighted by the initial warning may prevent useful treatments from returning to pre-warning levels of use and may reduce access to beneficial medications. Consequently, continued communication and education efforts following the removal of the varenicline boxed warning—as well as other boxed warnings—to increase use of effective therapies could prove beneficial.

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Additional information: We performed analyses using data from the Veterans Affairs Corporate Data Warehouse domains that are available only within a secure research environment behind the US Department of Veterans Affairs firewall. The restrictions are in place to maintain veteran privacy and confidentiality.

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