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Trends in utilization of smoking cessation agents before and after the passage of FDA boxed warning in the United States

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Abstract

Background—In 2009, the FDA required a black box warning (BBW) on bupropion and varenicline, the two commonly prescribed smoking cessation agents due to reports of adverse neuropsychiatric events. We investigated if there was a decline in use of bupropion and varenicline after the BBW by comparing the percent using these medications before and after BBW.

Methods—We conducted a retrospective observational study using data from the Medical Expenditure Panel Survey from 2007 to 2014. The study sample consisted of adult smokers, who were advised by their physicians to quit smoking. We divided the time period into “pre-warning”, “post-warning: immediate”, and “post-warning: late.” Unadjusted analysis using chi-square tests and adjusted analyses using logistic regressions were conducted to evaluate the change in bupropion and varenicline use before and after the BBW. Secondary analyses using piecewise regression were also conducted.

Results—On an average, 49.04% of smokers were advised by their physicians to quit smoking. We observed a statistically significant decline in varenicline use from 22.1% in year 2007 to 9.23% in 2014 (p value < 0.001). In the logistic (Adjusted Odds Ratio = 0.36, 95% CI = 0.22–0.58) and piecewise regressions (Odds Ratio = 0.64, 95% CI = 0.41–0.99) smokers who were advised to quit smoking by their physicians were less likely to use varenicline in the immediate post-BBW period as compared to pre-BBW period. While the use of varenicline continued to be significantly low in the late post-BBW period (AOR = 0.45, 95% CI = 0.31–0.64) as compared to

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Contributions: Drishti Shah and Anuj Shah were responsible for developing the initial concept, study design and data analysis section of the study. Drishti Shah was responsible for data interpretation and writing the manuscript under Dr. Sambamoorthi's and Dr. Tan's supervision. Dr. Sambamoorthi mentored Drishti and worked closely with her to develop the methodology, interpreting the study findings and drafting the manuscript. Anuj Shah and Dr. Tan provided useful feedback on conceptualizing the study, identifying appropriate methodologies and also helped in editing the final manuscript. All authors approved of the final manuscript before submission.

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the pre-BBW period, the trend in use as seen in piecewise regression remained stable (OR = 0.90, 95% CI = 0.75–1.06). We did not observe significant differences in bupropion use between the pre- and post-BBW periods.

Conclusion—The passage of the FDA boxed warning was associated with a significant decline in the use of varenicline, but not in the use of bupropion.

Keywords

Smoking cessation agents; Varenicline; Bupropion; Trends; Boxed warning; Neuropsychiatric adverse events

1. Introduction

Tobacco use remains a significant threat to public health due to its strong association with morbidity and mortality with an estimated 480,000 premature deaths per year in the United States (US) (US Department of Health Human Services, 2014). Smoking cessation can significantly reduce the health risks that would have been incurred by smokers (Rigotti, 2013). The US Surgeon General has characterized smoking cessation as “the single most important step that smokers can take to enhance the length and quality of their lives” (CDC, 2003). While there has been a steady decline in the percentage of adults who smoke from 20.9% in 2005–17.8% in 2013 (CDC, 2013), the rate of successful smoking cessation or quit attempts remains low (Nides, 2008).

Of all the current smoking cessation strategies – counseling, behavioral, and pharmacotherapy; pharmacotherapy with smoking cessation agents has been found to be more effective (Okuyemi et al., 2000). For example, smokers using pharmacotherapy are twice as likely to quit smoking as compared to those using behavioral therapies (Hughes et al., 2004). First-line pharmacotherapy includes nicotine replacement therapy (NRTs), sustained release bupropion (Zyban®), approved by the Food and Drug Administration (FDA) in 1997 and varenicline (Chantix®), approved by the FDA in 2006 (Herman and Sofuoglu, 2010). Bupropion and varenicline have been reported to be more effective than placebo and NRTs, when used as either single agents or with NRTs in combination (Anthenelli et al., 2016; Cahill et al., 2013; Jorenby et al., 1999). Further, a vast majority of studies have shown that varenicline is associated with higher rate of continuous abstinence from smoking, causes fewer withdrawal symptoms, and has the highest rate of success compared to NRTs or bupropion (Anthenelli et al., 2016; Aubin et al., 2008; Ebbert et al., 2010; Kotz et al., 2014; Kralikova et al., 2013; Wu et al., 2006).

Some commonly reported side effects of bupropion and varenicline include nausea, headache and insomnia (Gonzales et al., 2006). However, there was a concern that these medications may be associated with neuropsychiatric symptoms such as depressed mood, hostility, and suicidal thoughts. (Kuehn, 2009; Moore et al., 2009; Moore et al., 2011) Following these case reports, in February 2008, the FDA issued an alert to warn the prescribing physicians and consumers of the possible adverse events associated with these medications (US FDA, 2013). Although the neuropsychiatric side effects of bupropion and varenicline were rare, in 2009, the FDA issued its strongest safety warning mandating that

these two smoking cessation agents carry a boxed warning, commonly referred to as a “black box warning” (BBW) (US FDA, 2009). The FDA warning received widespread media coverage in television networks and major newspapers (Kim et al., 2016).

Existing literature suggests that FDA mandated BBW can have a considerable impact on the prescribing behavior of physicians and use by consumers. For example, a study conducted after the passage of FDA BBW on antidepressants reported that the prescriptions of Selective Serotonin Reuptake Inhibitors (SSRIs) declined significantly and was associated with substantial reduction in antidepressant treatment in young adults suffering from depression (Libby et al., 2007). The BBW issued for doxepin in 2001 resulted in a number of critical articles asserting that these warnings have led to patients being less willing to accept beneficial pharmaceutical treatments (Habib and Gan, 2003; van Zwieten et al., 2004). While some FDA issued BBWs may have immediate, strong impacts, others may have delayed or very little impact on healthcare utilization and health outcomes.

Further, as pharmacotherapy with non-nicotine containing smoking cessation agents has been found to be more effective than counseling and other behavioral therapies (Hughes et al., 2004; Okuyemi et al., 2000), it is important to examine the impact of FDA BBW on utilization rates of bupropion and varenicline. The introduction of varenicline was associated with an increase in the number of quit attempts by smokers (Kasza et al., 2015). Therefore, the FDA BBW may have a negative effect on the prescription and use of these smoking cessation agents leading to reduction in the number of successful quit attempts. Comparison of bupropion and varenicline use before and after FDA BBW may direct future research in this area to help policy makers evaluate the influence of their decisions on real-world outcomes.

To date, only one study has attempted to examine the change in varenicline use as compared to use of bupropion and NRTs after the introduction of varenicline (Kasza et al., 2015). Another study reported that direct-to-consumer advertising (DTCA) had a significant impact on varenicline use from 2006 to 2009 (Kim et al., 2016). These studies evaluated the trends after the introduction of varenicline in 2006. A study by Jarlenski et al., examined the trends in use of smoking cessation medications from 2007 to 2012 among elderly and disabled Medicare beneficiaries (Jarlenski et al., 2016). However there is a gap in literature with respect to studies evaluating the trends in the utilization of the two medications before and after the passage of BBW using a nationally representative sample of the US population. Therefore, the primary objective of our study was to analyze the trends in use of bupropion and varenicline from 2007 to 2014 (before and after the passage of the FDA BBW) among smokers who were advised by their physicians to quit smoking.

2. Methods

2.1. Conceptual framework

We used the “concept of diffusion of innovation,” developed by Rogers and Shoemaker to guide the selection of variables for the current study (Rogers and Shoemaker, 1971). As per the model, the general decision making process after the innovation of a product or passage of a new policy is guided by the social, economic and educational environment that allows

individuals to readily adopt recommendations related to the use of smoking cessation agents (Black, 1983; Rogers and Shoemaker, 1971). Socio-economic factors (education, income, poverty level, employment status, health insurance coverage) and demographic characteristics (patient age, race, ethnicity, and marital status) may affect individuals' knowledge regarding the FDA BBW on smoking cessation agents (bupropion and varenicline). Furthermore, the presence of chronic conditions may also affect a clinician's as well as the patient's decision to use smoking cessation agents (Zhu et al., 1999).

2.2. Study design

We conducted a retrospective, observational study with pre-post design using 2007–2014 data from the nationally representative Medical Expenditure Panel Survey (MEPS).

2.3. Data source

MEPS is a nationally representative survey of non—institutionalized US civilian population and is sponsored by the Agency for Healthcare Research and Quality (AHRQ). It is administered every year and has a rotating panel design where the US population is interviewed five times over a period of thirty months. MEPS is designed to provide national estimates of healthcare use, demographic characteristics, expenditures, sources of payment, prescription drugs and health conditions (Cohen et al., 1996). We selected the years 2007 through 2014 because varenicline was approved in 2006, and the FDA BBW was issued in 2009.

2.4. Study sample

The analytical sample consisted of adults above 18 years of age who identified themselves to be current smokers, were alive during the observation year and were advised by their physicians to quit smoking. Those who have answered “yes” to the question “do you currently smoke?” were identified as current smokers. Since MEPS does not ask the participants a direct question to assess if they attempted to quit smoking, a proxy variable was used. Those who answered “yes” to the question, “In the last 12 months, did a doctor advise you to quit smoking?” were considered to be the most likely to make a quit attempt.

2.5. Measures

2.5.1. Dependent variable—The dependent variable was the prescription of either bupropion or varenicline in each year (2007 through 2014) among the study sample. The medication names and national drug codes are linked in MEPS to a Multum-lexicon classification scheme which classifies prescription drugs into various therapeutic classes. In the current study, prescription of bupropion and varenicline was identified from the prescribed medicines files of MEPS using the multum therapeutic sub-classification variable for smoking cessation agents (TCIS1 = 320). Further, the medication name (RXNAME variable) was used to identify the specific smoking cessation agents.

2.5.2. Key independent variable: pre- warning and post-warning periods—The time period between 2007 and 2014 was divided into three segments: (1) the pre-warning period (years 2007 and 2008); (2) the immediate post- warning period (years 2010 and

2011); and (3) the late post-warning period (years 2012, 2013, and 2014). We considered 2009 as the phase-in period, to allow for the diffusion of the warnings and to allow sufficient time for patients and clinicians to learn about the BBW, gain knowledge about the neuropsychiatric adverse effects, and make decisions to use or not to use these agents. Two post-warning periods were used to evaluate the immediate and late prescription rates of smoking cessation agents after the intervention of the FDA BBW.

2.5.3. Other independent variables—Demographic characteristics (patient age, race, ethnicity, and marital status), socio-economic factors (education, income, poverty level, employment status, and health insurance coverage) and number of chronic conditions were used as other independent variables. These variables were selected based on the diffusion of innovation conceptual model (Rogers and Shoemaker, 1971) and factors reported in previous studies that were deemed likely to influence the smoking status of an individual (Lee and Kahende, 2007).

2.6. Statistical analyses

Unadjusted significant group differences in each of the explanatory variables over time were tested with chi-square statistics. Separate multivariable logistic regression models were built for bupropion and varenicline to evaluate the differences in the use of each drug in the pre-warning and post-warning periods (immediate and late) after adjusting for the other explanatory variables. Secondary analyses were conducted using piecewise (segmented) regression (Wagner et al., 2002) to estimate changes in our outcome measure between the pre-warning years (2007 and 2008) and the post-warning years: immediate (2010 and 2011) and late (2012–2014). This enabled us to assess if the change in use of the smoking cessation agents in each segment (pre-warning and post-warning periods) were significant. In a piecewise (segmented) regression model, the independent variable (time) is partitioned into intervals and a separate line is fit to each interval. This enabled us to statistically estimate the differences in the intercept and slope coefficients before and after the FDA BBW. Additional sensitivity analyses were conducted by excluding smokers with depression who were prescribed bupropion, as bupropion could also be used as an antidepressant. All data analyses accounted for the complex survey design of MEPS and were conducted using SAS 9.4 (SAS Institute, Cary, NC) with an a priori significance level of 0.05.

3. Results

The characteristics of our study sample by each year are summarized in Table 1. The weighted percentages of adult smokers advised by their physicians to quit smoking increased from 43.2% in year 2007–51.2% in 2014. The percentage of adults advised to quit smoking differed by the age group across the study years (2007–2014) with a decrease among adults in the age group 18–29 years and an increase among those aged 65 and older. The study population differed based on marital status, employment status, and number of chronic conditions across each year. No statistically significant differences were observed by gender, education level and insurance coverage in the study population across each year.

Fig. 1 displays the trend in the use of bupropion and varenicline among adult smokers advised to quit smoking after the passage of the FDA BBW. We observed a constant decline

in proportion of varenicline users with the greatest change in the post-warning period from 16% in year 2009–4.8% in year 2011. We noticed an increase in the percentage of varenicline users from 5.7% in year 2012–9.23% in year 2014. We observed a decline in the use of bupropion from 13.3% in 2007–10.1% in 2008 and an increase from 11.3% in the year 2009–13.2% in 2014. There were no statistically significant changes in the percentage of bupropion users over the 8 year observation period (p value = 0.654).

3.1. Multivariable logistic regression on bupropion and varenicline use

Adjusted odds ratios (AOR) and 95% confidence intervals (CI) from multivariable logistic regressions on bupropion and varenicline use are presented in Table 2. After adjusting for other explanatory variables, adults who had been advised by their healthcare providers to quit smoking were less likely to use varenicline in both, the immediate (AOR = 0.36, 95% CI = 0.22–0.58; $p < 0.0001$) and the late (AOR = 0.45, 95% CI = 0.31–0.64; $p < 0.0001$) post-warning periods as compared to those in the pre-warning period. However no such decline was observed in bupropion use between the pre-warning and post-warning immediate and late period (AOR = 1.02, 95% CI = 0.73–1.43; $p = 0.912$ and AOR = 1.03, 95% CI = 0.74–1.44; $p = 0.852$ respectively).

Other characteristics that were significantly associated with bupropion use were: gender, race, education level, employment status, and number of chronic conditions. Females and individuals with multiple chronic conditions were more likely than their counterparts to be prescribed bupropion. On the other hand blacks and those who had high school education had lower likelihood of using bupropion as compared to whites and those individuals who had greater than high school education respectively. Blacks were also less likely to use varenicline as compared to whites. Those with private insurance and public insurance were significantly more likely to use varenicline as compared to their uninsured counterparts (Table 2).

3.2. Secondary analyses results

Results from piecewise (segmented) regressions (Table 3) revealed that adult smokers who were advised to quit were 64% less likely to use varenicline in the immediate post-warning years (OR = 0.64, 95% CI = 0.41–0.99). No significant differences were observed in the trend of varenicline use in the pre-warning years (2007 and 2008) (OR = 0.76, 95% CI = 0.52–1.09) and the late post-warning years (2012–2014) (OR = 0.90, 95% CI = 0.75–1.06) suggesting a stable trend in the late post-warning period. Additionally, we did not observe a statistically significant difference in bupropion use in the pre-warning years, 2007 and 2008 (OR = 0.84, 95% CI = 0.62–1.13) as well as the immediate (2010 and 2011) and late post-warning years (2012–2014) (OR = 1.22, 95% CI = 0.93–1.60 and OR = 1.09, 95% CI = 0.96–1.24 respectively).

3.3. Sensitivity analyses

We excluded smokers with depression, who were prescribed bupropion in our sensitivity analyses because bupropion can also be used to treat depression. Depression was identified using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes. Results from multivariable logistic regression were consistent with the

primary analyses. As in primary analyses, there were not statistically significant differences in the bupropion use during immediate post-warning period (AOR = 1.47, 95% CI = 0.78–2.75) and the late post-warning period (AOR = 1.49, 95% CI = 0.78–2.84) as compared to the pre-warning period. Further, piecewise regression analyses indicated no statistically significant differences in bupropion use in the pre-warning and the immediate and late post-warning periods (Supplementary Material, Tables 1 and 2).

4. Discussion

This is the first study to specifically evaluate the trend in use of smoking cessation agents (bupropion and varenicline) after the passage of BBW using a nationally representative data on adult smokers who had been advised by physicians to quit smoking. The key findings of the study are that the passage of the FDA BBW is associated with significant reduction in the use of varenicline in the US and no such decline was observed for bupropion use which was also subjected to the FDA BBW. These findings were robust to different specification of the models.

Both multivariable logistic regression and piecewise regression analyses revealed that there was a decline in the use of varenicline and not in the use of bupropion during both, the immediate and late post-warning periods. Our study findings are consistent with two studies that also reported a decline in use of varenicline after BBW (Jarlenski et al., 2016; Kasza et al., 2015). It has to be noted that the use of varenicline did not decline significantly during the years 2012–2014 despite the FDA announcement of increased risk of cardiovascular adverse events associated with varenicline (US Food Drug Administration, 2011).

Although there is mixed evidence on the adverse neuropsychiatric effects of both smoking cessation agents, we observed a decline in the use of varenicline and not bupropion. Our study did not directly explore the effect of patient preferences and physician prescribing practices behind the absence of a declining trend in bupropion use or the presence of a declining trend in varenicline use. However, we can speculate that the “newness” of the medication in the market, greater media coverage and the epidemiological phenomenon of weber effect may have contributed to the decline in varenicline use. For example, bupropion has been in the market since 1997, much longer than varenicline, which was introduced only in 2006. Furthermore, after the FDA approval of varenicline, its use dramatically increased (Aubin et al., 2008) because it was a newer and more efficacious smoking cessation agent and would have therefore received more media coverage compared to bupropion (Ebbert et al., 2010).

Varenicline use could also have been affected by the Weber effect (Weber et al., 1984). The Weber effect is an epidemiologic phenomenon which suggests that there is a rise in the number of reported adverse drug events until approximately the middle to the end of second year after the drug's approval (Brodovicz et al., 2001; Weber, 1984). Therefore, when the FDA BBW was issued, varenicline may have been hit harder than bupropion. However, further research to assess the reasons for the variation in use of these two medications after the passage of BBW is needed to address this question.

It has to be noted that after the FDA BBW, several studies reported varenicline to be safe (Gibbons and Mann, 2013; Lorenz et al., 2010; Tonstad et al., 2010) and it has been found that nicotine withdrawal is associated with psychiatric disorders independent of the smoking cessation treatment (Bolton and Robinson, 2010; Mendelsohn, 2012). Further, a vast majority of meta-analysis, systematic reviews and real-world retrospective studies that were conducted independent of Pfizer (the manufacturer of varenicline) found no significant association between the use of varenicline and psychiatric disorders (Anthenelli et al., 2013; Gibbons and Mann, 2013; Gunnell et al., 2009). Therefore, the post-marketing reports leading to the FDA BBW may have been confounded by other reasons such as tobacco-withdrawal symptoms or preexisting psychiatric illnesses (Lorenz et al., 2010). Additionally, individuals with pre-existing serious mental disorders have reported that Varenicline was well tolerated, with no evidence of exacerbation of neuropsychiatric symptoms (Anthenelli et al., 2013; Chengappa et al., 2014; Evins et al., 2014; Williams et al., 2012). The data underlying the FDA boxed warning was based on reports with no placebo reference group. It is plausible that smokers with pre-existing psychiatric disorders have higher frequency of neuropsychiatric adverse events, but as pointed by Anthenelli et al., the adverse events among varenicline users were as high as those assigned to the placebo group (Anthenelli et al., 2016). This conclusion was drawn from a recent multicenter, multinational, double-blind randomized controlled, Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) (Anthenelli et al., 2016). It is interesting to note that despite the evidence against adverse neuropsychiatric symptoms, the use of varenicline declined. We speculate that such decline may be due to wide-spread media coverage and the publicity surrounding the FDA communications.

FDA warnings have the potential for unintended negative health consequences (Dusetzina et al., 2012). Recent evidence from a double-blind randomized controlled EAGLES trial and an expert opinion on use of varenicline as a smoking cessation agent concluded that varenicline is safe, most efficacious monotherapy for smoking cessation in smokers with and without psychiatric disorders, and has two times long-term cessation rates as compared to other smoking cessation agents (Anthenelli et al., 2016; Williams et al., 2011). The evidence suggesting that the risk of neuropsychiatric adverse events associated with bu-propion and varenicline are lower than previously suspected led the FDA to lift the BBW on the two smoking cessation agents in December 2016 (US Food and Drug Administration, 2016). Findings from the present study and the surmounting evidence suggesting safety of varenicline warrants future studies to rigorously evaluate its relationship with occurrence of neuropsychiatric adverse. Considering that the use of smoking cessation medications remain low, especially after the passage of the boxed warning, future studies can assess if the use of these two smoking cessation agents further increases as a result of the removal of the boxed warning by the FDA.

Another noteworthy observation was the increase in proportion of adult smokers, who had been advised by their healthcare providers to quit smoking from 2007 to 2014. However, this increase was not accompanied by a corresponding increase in the use of varenicline and bupropion, the most efficacious smoking cessation therapies (Herman and Sofuoglu, 2010; Hughes et al., 2004). Additionally, a study by Kasza et al. (2015) reported that the trend in use of any form of NRTs in the US almost remained the same during the years 2004–2011

(pre- and post-varenicline introduction). Taken together, these findings suggest a need for future studies to explore trends in the use of other smoking cessation therapies before and after the passage of FDA BBW.

The findings from this study need to be interpreted in the light of its strengths and limitations. The strengths include nationally representative findings, availability of prescription information, adjustment with a comprehensive set of variables and sensitivity analyses to confirm the robustness of findings. The study had some limitations. As we used a cross-sectional study design, we cannot establish causal effect between the passage of FDA BBW and use of smoking cessation agents. Our study is also susceptible to history bias as there may be events in the study time period that may influence utilization such as marketing campaigns, variations in effects of media coverage and drug promotion efforts on the two drugs. Since MEPS does not directly query whether a smoker attempted to quit smoking, the study findings are based on smokers who had been advised by their physicians to quit smoking. Therefore, we did not have information on whether the smokers who were advised to quit actually engaged in quit attempts. Furthermore, it was difficult to assess the reason for prescription of bupropion; it may have been used for depression rather than as a smoking cessation agent. Although, we found that after exclusion of individuals with depression, the findings remained the same. Additionally, all the measures used in the study are self-reported and may be subjected to recall and social desirability bias. We were unable to directly control for the differences in media coverage and direct to physician marketing strategies for the two drugs, which could play a significant role on physician prescription choice (Gönül et al., 2001). Lastly, we could not assess whether the decrease in varenicline prescription was accompanied by a simultaneous increase in the use of NRTs as MEPS does not provide information on over-the-counter medications.

5. Conclusion

The key findings of the study are that the passage of the FDA BBW may have significantly reduced the use of varenicline in the US and no such decline was observed for bupropion use. Future studies need to explore, whether the decline in varenicline use is accompanied by an increase in the rate of unsuccessful quit attempts. Our findings suggest need for further investigation into the causal link between bupropion and varenicline use and adverse neuropsychiatric effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Weighted Percent of bupropion and varenicline use between 2007 and 2014 among adults, who were advised to quit smoking.

FDA issues alert: In February 2008, the FDA issued an alert to warn the prescribing physicians and consumers of the possible adverse events associated with bupropion and varenicline.

Passage of BBW: In July 2009, the FDA issued a black box warning (BBW) for bupropion and varenicline.

The proportions in the above figure represent row percentages.

Bupropion use: p value = 0.654; Varenicline use: p value < 0.001.

Table 1

Characteristics of the Study Sample by Year of Observation: Adults, who had been advised by their physicians to quit smoking; Medical Expenditure Panel Survey, 2007–2014.

Weighted, % Characteristics	Pre-warming Period		BBW	Post-warming period: Immediate		Post-warming period: Late			
	2007 N=1663 43.2 Wt. %	2008 N=1819 47.2 Wt. %		2009 N=2008 49.3 Wt. %	2010 N=1776 49.8 Wt. %	2011 N =1962 52.1 Wt. %	2012 N = 2069 51.0 Wt. %	2013 N = 1841 48.7 Wt. %	2014 N = 1617 51.2 Wt. %
Sex									
Female	49.6	50.4	51.4	49.8	51.4	50.5	50.8	52.4	
Men	50.4	49.6	48.6	50.2	48.6	49.5	49.2	47.6	
Race/Ethnicity									
White	74.4	77.9	78.3	74.3	75.2	76.0	72.1	74.0	
Black	12.3	11.2	11.0	12.8	12.1	12.3	14.5	13.1	
Latino	7.2	6.3	6.3	7.8	7.5	7.4	8.1	7.2	
Other	6.1	4.5	4.4	5.2	5.3	4.4	5.3	5.7	
Age in Years									
18–29	18.8	17.9	17.8	16.2	14.1	16.9	14.9	15.1	
30–64	71.7	72.1	72.2	71.8	72.1	70.0	70.6	70.6	
65	9.5	10.1	10.1	12.0	13.8	13.1	14.6	14.3	
Marital status									
Married	47.0	48.0	48.0	43.8	41.6	42.2	43.2	42.9	
Widow	6.2	5.4	5.6	5.9	5.3	5.7	5.4	6.7	
Separated/Divorced	21.8	22.7	23.1	23.5	26.2	25.3	25.8	25.4	
Never married	25.0	23.9	23.3	26.8	26.8	26.8	25.6	26.0	
Education level ^ϕ									
< High school	23.2	23.9	22.8	21.2	20.7	20.2	18.3	17.4	
High school	38.3	36.0	37.9	36.8	36.2	37.7	35.8	37.2	
> High school	37.9	39.2	38.8	41.5	42.7	42.1	45.3	42.1	
Employment status									
Employed	68.4	66.2	60.0	58.3	58.8	59.4	57.6	55.9	
Not employed	31.6	33.8	40.0	41.7	41.2	40.6	42.4	44.1	
Insurance									

Weighted.% Characteristics	Pre-warming Period		BBW	Post-warming period: Immediate		Post-warming period: Late			
	2007 N=1663 43.2 Wt.%	2008 N=1819 47.2 Wt.%		2009 N=2008 49.3 Wt.%	2010 N=1776 49.8 Wt.%	2011 N =1962 52.1 Wt.%	2012 N = 2069 51.0 Wt.%	2013 N = 1841 48.7 Wt.%	2014 N = 1617 51.2 Wt.%
Private	63.7	63.1	62.6	59.8	59.8	59.9	58.6	55.1	54.2
Public	21.3	22.6	22.9	24.7	24.7	25.6	28.3	31.3	36.0
Uninsured	15.0	14.3	14.5	15.5	15.5	14.4	13.1	13.7	9.8
Poverty level ^a									
Poor/near poor	36.1	36.4	38.7	39.9	39.9	40.3	44.2	46.6	49.6
Middle Income	30.8	33.0	31.0	32.9	32.9	31.4	28.7	28.3	25.0
High Income	33.1	30.5	30.3	27.2	27.2	28.3	27.1	25.1	25.4
Chronic conditions number ^b									
0–1	62.8	54.4	54.7	53.2	53.2	53.1	52.9	46.6	49.0
2–4	33.5	39.0	38.0	38.4	38.4	38.3	39.0	42.4	42.0
5	3.7	6.5	7.3	8.4	8.4	8.6	8.0	11.0	9.0
Smoking Cessation Agents									
Bupropion	3.7	2.5	2.8	3.3	3.3	3.4	3.3	3.1	3.9
Varenicline	3.1	2.6	2.0	1.5	1.5	0.6	0.7	1.2	1.5

Note: Based on adults who were alive in each calendar year and who were advised to quit smoking by their physicians. The percentages in the above table represent column percentages. Weighted% refers to the percentage of adult smokers who were advised to quit smoking by their physician.

^φThe percentage of this variable does not sum up to 100% due to missing values.

^aPoverty level: poor/near poor (<200% of federal poverty line i.e., FPL), middle income (200% FPL < 400%) and high income (400% of FPL).

^bChronic conditions consisted of anxiety, asthma, arthritis, cancer, chronic obstructive pulmonary disease, depression, gastro esophageal reflux, hypertension, heart disease, osteoporosis, and thyroid disorders.

Adjusted Odds Ratio and 95% Confidence Intervals from Multivariable Logistic Regression on the Use of Bupropion and Varenicline before and after the FDA BBW; Medical Expenditure Panel Survey, 2007–2014.

Table 2

	Varenicline Use			Bupropion Use		
	AOR	95% CI	sig	AOR	95% CI	sig
Black Box Warning (ref: Pre-warning)						
Post-warning: immediate	0.36	[0.22,0.58]	***	1.02	[0.73,1.43]	
Post-warning: late	0.45	[0.31,0.64]	***	1.03	[0.74,1.44]	
Age in years (ref: 65)						
18–29	0.71	[0.28,1.79]		0.92	[0.44,1.92]	
30–65	1.33	[0.69,2.56]		1.40	[0.86,2.29]	
Sex (ref: Male)						
Female	0.84	[0.57,1.22]		1.65	[1.21,2.23]	**
Race/Ethnicity (ref: White)						
Black	0.32	[0.16,0.65]	**	0.59	[0.42,0.83]	**
Latino	0.54	[0.28,1.05]		0.75	[0.42,1.33]	
Others	0.81	[0.38,1.72]		0.67	[0.36,1.27]	
Health Insurance (ref: Uninsured)						
Private	3.34	[1.49,7.52]	**	1.42	[0.81,2.49]	
Public	2.61	[1.07,6.36]	*	1.59	[0.92,2.75]	
Education level (ref: more than HS)						
Less than HS	0.66	[0.39,1.11]		0.74	[0.52,1.04]	
High School	0.79	[0.55,1.15]		0.64	[0.45,0.91]	*
Marital Status (ref: married)						
Widowed	0.99	[0.47,2.08]		1.18	[0.66,2.09]	
Divorced	0.84	[0.56,1.25]		0.95	[0.67,1.33]	
Never married	0.99	[0.57,1.70]		0.78	[0.52,1.15]	
Poverty level ² (ref: High income)						
Poor/near poor	0.69	[0.43,1.09]		1.07	[0.74,1.55]	
Middle Income	0.97	[0.64,1.47]		1.00	[0.72,1.38]	
Employment status (ref: Unemployed)						

	Varenicline Use				Bupropion Use			
	AOR	95% CI	sig		AOR	95% CI	sig	
Employed	0.98	[0.67,1.42]			1.38	[1.02,1.86]	*	
Chronic conditions number ^b (ref:0-1)								
2-4	1.36	[0.95,1.96]			4.03	[2.89,5.63]	***	
5	2.11	[1.00,4.46]			8.19	[5.59,11.9]	***	

Note: Based on adults who were alive in each calendar year and who were advised to quit smoking by their physicians. Asterisks represent significant group differences.

The reference group for the dependent variable in the logistic regression for model 1 was “did not use varenicline” and model 2 was “did use bupropion”.

AOR: Adjusted odds ratio; CI: Confidence Interval; Sig: significance.

^aPoverty level: poor/hear poor (< 200% of federal poverty line i.e. FPL), middle income (200% FPL < 400%) and high income (400% of FPL).

^bChronic conditions consisted of anxiety, asthma, arthritis, cancer, chronic obstructive pulmonary disease, depression, gastro esophageal reflux, hypertension, heart disease, and thyroid disorders.

* 0.01 < p < 0.05.

** 0.001 < p < 0.01.

*** p < 0.001.

Odds Ratio and 95% Confidence Intervals from Piecewise Regression to Assess the Trend in Use of Bupropion and Varenicline before and after the FDA
BBW; Medical Expenditure Panel Survey, 2007–2014.

Table 3

	Varenicline Use			Bupropion Use		
	OR	95% CI	sig	OR	95% CI	Sig
Pre-warning (Year 2007–2008)	0.76	[0.52,1.09]		0.84	[0.62,1.13]	
Post- warning: immediate (Year 2010 – 2011)	0.64	[0.41,0.99]	*	1.22	[0.93,1.60]	
Post-warning: late (Year 2012–2014)	0.90	[0.75,1.06]		1.09	[0.96,1.24]	

Note: Based on adults who were alive in each calendar year and who were advised to quit smoking by their physicians. Asterisks represent significant difference.

OR: Odds ratio; CI: Confidence Interval; Sig: significance;

* : 0.01 < p < 0.05.