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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 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.

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,

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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 doperidol 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