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Mental health status of varenicline and bupropion users during a quit attempt compared to current smokers, other quitters, and non-smokers☆

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ABSTRACT

Background: Varenicline and bupropion are commonly prescribed non-nicotine containing smoking cessation agents. Post-marketing reports suggest an increased incidence of psychiatric disturbances associated with varenicline and bupropion. However, pre-existing psychiatric disorders may confound the association between these smoking cessation agents and psychiatric disturbances. We compared the mental health status of individuals using varenicline or bupropion to that of people quitting without medication, current smokers, and non-smokers while controlling for pre-existing conditions.
Methods: A cross-sectional design was used. Data were from 2006–2011 Medical Expenditure Panel Survey. Mental health status was assessed using the mental component summary (MCS) from the 12-item Short Form survey (SF-12v2), 2-item Patient Health Questionnaire (PHQ-2), and Kessler 6 Scale (K6). Differences in MCS score were compared using linear regression. Logistic regressions were used to compare positive screenings for depression using PHQ-2 and for psychological distress using K6.
Results: Of 578 use episodes, 453 (78.38%) were bupropion and 125 (21.62%) were varenicline. After adjusting for potential confounders, mental health status of varenicline users was not different from current smokers or people who quit smoking without medication, but worse than non-smokers; bupropion was strongly associated with lower mental health status relative to all groups across all three measures.
Conclusion: Varenicline was not associated with worse mental health compared to smokers or those who quit without medication, after adjusting for pre-existing psychiatric disorders. Bupropion was associated with worse mental health status than smokers, former smokers who quit without medication, and nonsmokers, even after adjusting for pre-existing psychiatric disorders.

1. Introduction

Tobacco use is a major public health concern and is considered to be the leading cause of preventable deaths in the United States (USDHHS, 2014). In 2012, the prevalence of cigarette smoking in the United States was estimated to be 18.1% (42.1 million) leading to approximately 480,000 deaths annually, including 41,000 deaths related to exposure to second-hand smoke (Agaku et al., 2014). The economic burden of smoking in the United States is estimated to be $289 billion a year, $133 billion from direct medical costs and $156 billion as indirect costs from lost productivity (Ward et al., 2014).

Smoking cessation agents (SCAs) currently approved by the United States Food and Drug Administration (FDA) include nicotine replacement therapy (NRT) products (nicotine gum, lozenges, patch, inhalers, and sprays) and two non-nicotine products—bupropion (Zyban®) and varenicline (Chantix®; Herman and Sofuoglu, 2010) There is mixed evidence on the effectiveness of various forms of NRTs on smoking cessation. While a systematic review by Woolacott et al. showed that NRTs are two-fold more effective in increasing smoking cessation rate compared to placebos, another large cross-sectional survey showed that NRTs do not significantly improve smoking cessation rates in the long-term (Woolacott et al., 2002; Pierce and Gilpin, 2002). The major alternatives to NRTs are bupropion and varenicline, both of which have been shown to be more effective than placebos and NRTs when

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used as single agents or in combination with NRTs (Jorenby et al., 1999; Cahill et al., 2013; Smith et al., 2003).

In 2009, the FDA issued a black-box warning for bupropion and varenicline regarding the risk of psychiatric events such as depressed mood, suicidal tendency, and hostility (US FDA, 2013). This decision was based on post-marketing reports, which may have been confounded by underlying nicotine dependence, tobacco-withdrawal, or other psychiatric illnesses (Lorenz et al., 2010). For instance, previous studies show that the suicide rate in smokers is approximately double that of non-smokers and stopping smoking is associated with an increased risk of depression and suicide attempts (Miller et al., 2000). Nicotine withdrawal is also associated with psychiatric disorders independent of smoking cessation treatment (Bolton and Robinson, 2010; Mendelsohn, 2012; Leventhal et al., 2013). As a result, it is still unclear whether bupropion and varenicline use leads to increased risk of psychiatric events. A review of randomized clinical trials and an observational study revealed no evidence for varenicline to be associated with new or worsening of psychiatric disturbances (Gibbons and Mann, 2013; Gunnell et al., 2009). Another systematic review assessing risk of suicidal outcomes among the subjects with psychiatric disorders found no association between varenicline use and suicidal outcomes (Hughes, 2015). A Cochrane review found little evidence of increased risk of psychiatric adverse events associated with bupropion use, except one study using the FDA's Adverse Event Reporting System (AERS) database, which found elevated risk associated with both varenicline and bupropion use; however, it is still unclear whether this link is causal (Hughes et al., 2014).

Previous studies that have examined the risk of psychiatric disturbances associated with bupropion and varenicline often used ICD-9 codes to define these events (Meyer et al., 2013; McClure et al., 2010). However, mental health problems and psychiatric events are often under diagnosed and underreported (Rahman et al., 2014), leading to potential underestimation of mental health disturbances. A number of measures using self-administered questionnaires such as the mental health component summary (MCS) of the 12-item Short-Form survey (SF-12v2), the two-item Patient Health Questionnaire (PHQ-2) and the six-item Kessler Scale (K6) have been developed and validated to assess mental health status and psychological distress (Gandek et al., 1998; Kroenke et al., 2003; Montazeri et al., 2011; Veldhuizen et al., 2007). The objective of our study was to assess if the use of bupropion and varenicline is associated with a difference in self-perceived mental health status measured using these instruments. This study sought to compare the mental health status of subjects who used bupropion or varenicline during a quit attempt relative to non-smokers, current smokers, and individuals who have quit smoking over the study period without using bupropion or varenicline.

2. Methods

2.1. Data source

Data were from the Medical Expenditure Panel Survey (MEPS) collected during 2006–2011. MEPS is nationally representative of the non-institutionalized civilian US population. Details on the survey design, methodology and collection of data have been described elsewhere (Hill et al., 2014). We used the full year consolidated data files for information on demographic characteristics, health status, employment, insurance coverage, smoking status, and responses to mental health status questionnaires. The type of smoking cessation agent used was determined using the prescribed medicines files and presence of pre-existing psychiatric disorders was determined using the medical condition files.

2.2. Study subjects

Adults with new episodes of bupropion and varenicline use were identified using the "Prescribed Medicines" files. MEPS uses an over-lapping panel design and data are collected in five rounds across two calendar years. Measurements using the three instruments (SF-12v2, PHQ-2, K6) were taken only in rounds 2 and 4. Therefore, we defined new episodes of bupropion and varenicline use as use of either drug in round 2 or 4 without any use in round 1 or 3, respectively. With this approach, it is possible for an individual to contribute two episodes in our sample. We conducted a post-hoc sensitivity analysis restricting to only the first episode of use. Since bupropion could also be used as an antidepressant, we used both the drug class, "smoking cessation agents", and medication names to identify the specific smoking cessation agents. For this study, NRT use was not considered because most NRT products are available over-the-counter (OTC) and MEPS does not have information on OTC medications.

Users of bupropion and varenicline were compared to three, mutually exclusive groups: (1) current smokers, (2) smokers who quit without bupropion or varenicline, and (3) non-smokers. Current smokers were those who reported being a cigarette smoker in rounds 2 and 4 (comparison group 1). Smokers who quit without any agents were those who reported being a current smoker in round 2 and not a smoker in round 4 without reporting bupropion or varenicline use in any rounds (comparison group 2). Non-smokers were those who reported no cigarette use in both round 2 and 4 (comparison group 3). For all three comparison groups, round 4 mental health measures were used.

To be included in the study, individuals must be 18 years or older and have participated in the survey for all five rounds. Subjects who used both bupropion and varenicline ($n = 5$) in round 2 or round 4 were excluded because reliable estimates could not be obtained. We also excluded subjects who had missing information for all of the mental health measures.

2.3. Outcome variables

The outcome of interest was mental health status and was measured using MCS, PHQ-2 and K6. The MCS score ranges from 0 to 100 and is a self-reported measure of mental health status. A lower MCS indicates worse mental health status and a two-unit change in the total score is considered to be a clinically meaningful difference (Hope et al., 2010). The K6 is validated screening tool for non-specific, self-perceived psychological distress in the past 30 days with a score ranging from 0 to 24. The PHQ-2 is a validated screening tool for depression with a summary score ranging from 0 to 6 (Kroenke et al., 2003). A K6 score $\geq$13 or a PHQ-2 score $\geq$3 were considered positive screening (Kessler et al., 2003; Lowe et al., 2005).

2.4. Covariates

2.4.1. Pre-existing psychiatric disorders. Subjects who reported any psychiatric disorders in the previous round (i.e., in round 1 for round 2 users and round 3 for round 4 users and comparison groups) were considered to have pre-existing psychiatric disorders. Psychiatric disorders were identified based on 3-digit ICD-9 codes or Clinical Classification codes (CCC): drug-induced (292.xx) and transient (293.xx) mental disorders, schizophrenia (295.xx), episodic and mood disorders (296.xx), delusional disorders (297.xx), nonorganic psychoses (298.xx), anxiety disorder (300.xx), personality disorders (301.xx), post-traumatic stress disorder (309.xx), depressive disorder (311.xx), suicide attempt (CCC 662) (Meyer et al., 2013). Previous and concurrent psychotropic