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The risk of varenicline-induced seizure among those who have attempted to quit smoking using pharmacotherapy☆

Divyan A. Chopra [a], Anuj B. Shah [a], Aisha H. Vadhariya [b], Jacob T. Painter [a,*]

[a] Division of Pharmaceutical Evaluation and Policy, University of Arkansas for Medical Sciences, Little Rock, AR, USA
[b] Department of Pharmaceutical Health Outcomes and Policy, University of Houston College of Pharmacy, Houston, TX, USA

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ABSTRACT

Objective: Varenicline is an effective smoking cessation agent; however, its use is limited because of black box warnings issued by regulatory agencies in the U.S. and Australia. The U.S. Food and Drug Administration updated the label for varenicline in 2015 to warn about the risk of varenicline-induced seizures. The objective of this study was to examine the risk of seizure associated with varenicline use.
Methods: A nested case–control study was performed using IMS LifeLink PharMetrics Plus administrative claims data (2009–2015). The outcome was presumptive seizures. All smokers making an attempt to quit smoking and having no recent seizure events were included in the nest. Cases and controls were matched (1:4) on age (±5 years), sex, index date (±30 days), event date, and duration of enrollment. An exposure period of 90 days preceding the event date was used. Chi-square tests were used to compare the characteristics of cases and controls. Conditional logistic regression was conducted to determine if an association between presumptive seizures and varenicline use exists.
Results: Our final sample was comprised of 1342 cases and 5368 controls. The adjusted analysis showed that odds of a seizure for patients with a varenicline prescription were 1.09 (confidence interval [CI] = 0.88–1.36) times those of patients with no varenicline exposure.
Conclusions: This study did not find a significant association between varenicline and increased risk of presumptive seizures. These findings raise questions regarding the necessity for a warning label for increased risk of seizures associated with varenicline.

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1. Introduction

Smoking is a leading cause of preventable mortality and morbidity in the U.S. [1] and is responsible for about 6 million deaths globally each year [2]. Even though smoking has declined over the past 30 years, it is still prevalent in the US resulting in $300 billion in annual costs [3] [4]. Tobacco use can lead to many disorders such as cancer, cardiovascular disease, and lung disease [5]. Promoting smoking cessation among current smokers may reduce morbidity and mortality associated with it. The Patient Protection and Affordable Care Act of 2010 (ACA), considers smoking cessation as a 'preventive service,' mandating tobacco-use counseling and evidence-based tobacco-cessation interventions by new health plans at no cost for insurance beneficiaries [6].

Prevention, diagnosis, and treatment of tobacco dependence are essential components of primary care [7]. Because of the addictive nature of smoking, developing effective interventions aimed at gradual reduction and tapering of tobacco use could be more effective in helping smokers quit [8]. A Clinical Practice Guideline from the US Public Health Service encourages the prescribing of Food and Drug Administration (FDA)-approved medications for smoking cessation by clinicians to patients who can tolerate it [9]. Varenicline (Chantix® in the USA, also known as Champix® in the EU and other countries) is a smoking cessation agent approved by the FDA in 2006 [10]. A survey of 31 countries in 2007 found that 19% of the countries' guidelines recommend varenicline for smoking cessation [11].

Varenicline exerts its effects by acting as a partial agonist at the α4β2 nicotinic acetylcholine receptor [12]. Stimulation of the receptor by varenicline partly mimics effects of nicotine but reduces cravings and withdrawal symptoms [13]. Varenicline is the most effective smoking cessation agent currently marketed [14]; studies comparing smoking cessation rates have shown varenicline to be more effective than other smoking cessation agents such as bupropion [15,16]. Varenicline was dispensed to almost 1.2 million patients in 2013 [17].

Despite the great potential to improve smoking cessation rates, varenicline has been associated with worrying adverse events. After the introduction of varenicline into the market in the form of Chantix,

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* Corresponding author at: Pharmaceutical Evaluation and Policy, University of Arkansas for Medical Sciences College of Pharmacy, 4301 W. Markham, Slot 522-4, Little Rock, AR 72205, USA.
E-mail address: JTPainter@uams.edu (J.T. Painter).

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postmarketing surveillance and FDA Adverse Event Reporting System (FAERS) reports have warned of worsening of depression, agitation, and suicidal thoughts or actions [18] resulting in a black box warning on the product label regarding the occurrence of neuropsychiatric events [19]. This was followed by another FDA warning in 2011 regarding an increase in the risk of certain cardiovascular events [20]. Recently, based on a review of a large clinical trial to determine neuropsychiatric safety and efficacy of pharmacologic options for smokers with and without neuropsychiatric events, the FDA decided to remove the black box warning from varenicline and bupropion [21,22].

In 2015, the FDA reported 64 cases of seizures in patients using varenicline through FAERS [10,23]. Greater than 50% of the cases were in patients with no previous history of seizure, with the risk being highest during the first month of use [24]. Aligning with these reports, a previous study of seizure in rats showed increased occurrence after administration of high doses of varenicline [25]. As per our knowledge, no study evaluating the risk of seizures associated with varenicline has been conducted using a large claims database. The present study was conducted using a nested case–control study design using claims data that provides more rigor than previously published case reports or examination of FAERS data.

2. Methods

2.1. Data and study design

The sample was derived from the IMS LifeLink PharMetrics Plus database [26]. These data are representative of the commercially insured U.S. population. Data are collected at the patient-level and comprise enrollment data, pharmacy claims, and medical claims. A nested case–control study was carried out using data from January 2006 to July 2015.

2.2. Nest definition

All patients who attempted to quit smoking identified as those with a pharmacy claim for one or more pharmacological smoking deterrent agents (varenicline, bupropion, or nicotine replacement) were included in the study nest. Claims for smoking deterrent agents were identified using generic product identifier (GPI) codes (Table 1). The start date of the first prescription of a smoking deterrent agent was defined as the index date.

2.3. Cases

A presumptive seizure was identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for convulsions, epilepsy, progressive myoclonus, electroencephalogram (EEG) monitoring, or localization of seizures (Table 1) [27]. For the selection of cases, within our nest, any patient with a presumptive seizure after their index date was defined as a case. The first episode of presumptive seizure after the index date was determined to be the event date. Patients who were less than 18 years of age, had an inpatient or outpatient record of presumptive seizures, or noncontinuous medical and pharmacy benefits 12 months prior to their event date were excluded.

2.4. Controls

Cases were matched to eligible controls based on the following variables: age (year of birth (±5 years)), gender, region, duration of continuous benefits, and index date (±30 days). For each control, an event date was imputed based on the event date of the case, and prior continuous pharmacy and medical benefits were calculated based on the imputed event date. Matching was carried out based on the duration of prior continuous pharmacy and medical benefits to ensure that cases and controls have an equal opportunity to be exposed and have a similar record length for identifying potential confounders. For the selection of controls, each patient with a diagnosis of presumptive seizures was matched with 4 controls with no diagnosis of presumptive seizures without replacement (1:4 matching).

Table 1
Summary of codes used for identifying study characteristics.

Code	Description	Type
Presumptive seizures		
780.3	Convulsions [27,41]	ICD-9-CM
345.0–345.9	Epilepsy [42]	ICD-9-CM
333.2	Progressive myoclonus [43]	ICD-9-CM
95,950, 95,951	8-channel electroencephalogram (EEG) for identification and lateralization of cerebral seizures [27,44]	CPT
95,953, 95,954	16-channel EEG monitoring for localization of seizure [27,44]	CPT
95,956	EEG recording and interpretation by channel [45]	CPT
95,961, 95,962	Functional cortical mapping by stimulation to provoke seizures [46]	CPT
89.13–89.15	Neurologic examination, EEG, other nonoperative neurologic function tests [27,45]	ICD-9-CM PRC
89.19	Video and radio telemetered EEG monitoring [27,45]	ICD-9-CM PRC
Covariates		
	Acquired CNS	
320–349 (exclude 343, 345)	CNS pathology (including meningitis, encephalitis, cerebritis)	ICD-9-CM
437	Cerebrovascular disease	ICD-9-CM
800–804, 850–854, 870–879	Cerebral trauma	ICD-9-CM
	Acquired systematic	
571	Hepatic disorders	ICD-9-CM
250–252, 270–279	Metabolic disturbances	ICD-9-CM
580–589	Renal disorders	ICD-9-CM
	Acquired substance	
291, 303	Alcohol	ICD-9-CM
5,900,000,000	Antipsychotics/antimanic agents	GPI
5,800,000,000	Antidepressants	GPI
960–989	Poisoning	ICD-9-CM
Exposures		
6,210,008,020	Varenicline [47]	GPI
6,210,000,210	Bupropion [47]	GPI
6,210,001,000, 6,210,000,500	Nicotine Replacement Therapy [47]	GPI
7,200,000,000	Antiepileptic drugs [47]	GPI

2.5. Exposure

Exposure was defined as having at least one pharmacy claim for varenicline within 90 days prior to the event date.

2.6. Covariates

Potential confounders were identified using medical and pharmacy claims in the one year preceding the event date (Table 1) [28]. Confounders were further classified as central nervous system (CNS), systemic, or substance-related. Central nervous system factors included cerebral trauma, cerebrovascular disorders, and CNS pathological disorders. Systemic factors comprised of hepatic disorders, metabolic disorders, and renal disorders. Concomitant drug exposures, alcohol use disorders, and poisoning, which were included in the substance-related risk factors, were identified on the basis of their potential for causing or reducing the seizure threshold.

2.7. Analysis

Analyses were carried out using SAS v9.3 (SAS Institute Inc., Cary, NC). Frequency and percentages were used for categorical variables.

Chi-square tests were employed to test for significant differences between cases and controls with respect to baseline covariates. Conditional logistic regression was used to test for an association between exposure to varenicline and the occurrence of a presumptive seizure. The risk of presumptive seizure with varenicline use was measured as unadjusted and adjusted odds ratios (ORs). We tested alternative specifications of our exposure period to assess the robustness of our findings. Sensitivity analyses were carried out, by altering the time to exposure of cases and controls to the drugs from 3 months to 1 month. This study was determined as a nonhuman subject research; Institutional Review Board (IRB) Protocol No: 205981.

3. Results

A total of 142,986 patients formed our nest of those who used pharmacotherapy for smoking cessation (Fig. 1). Out of 142,986 patients, 2485 had a presumptive seizure event after their first claim of a smoking cessation agent. After excluding patients not having continuous pharmacy and medical benefits and less than 18 years of age, 1780 patients remained. After matching with potential controls and excluding patients with previous seizure event, we were left with 1461 cases and 51,072 potential controls. In the final step, 1:4 matching was carried out, and 1342 cases and 5368 controls formed the final sample.

Table 2
Characteristics of cases and controls.

Description	Cases N (%) (1342)	Control N (%) (5368)	Odds ratio (OR)	95% CI
Acquired CNS				
CNS pathology	496 (36.96)	615 (11.46)	3.16	2.70–3.70
Cerebrovascular disease	52 (3.87)	21 (0.39)	5.77	3.32–10.06
Cerebral trauma	53 (3.95)	59 (1.10)	2.38	1.54–3.70
Acquired systematic				
Hepatic disorders	32 (2.38)	47 (0.88)	1.00	0.56–1.76
Metabolic disturbances	666 (49.63)	1947 (36.27)	1.22	1.06–1.40
Renal disorders	96 (7.15)	62 (1.15)	3.34	2.29–4.88
Acquired substance				
Alcohol	88 (6.56)	84 (1.56)	2.50	2.30–4.88
Antipsychotics/antimanic agents	221 (16.47)	205 (3.82)	2.52	2.00–3.18
Antidepressants	681 (50.75)	1652 (30.7)	1.63	1.41–1.88
Poisoning	51 (3.80)	52 (0.97)	1.74	1.08–2.80

Adjusted analysis showed that cases were more likely to have comorbidities compared with matched controls (Table 2). The presence of CNS effects was significantly associated with the risk of development

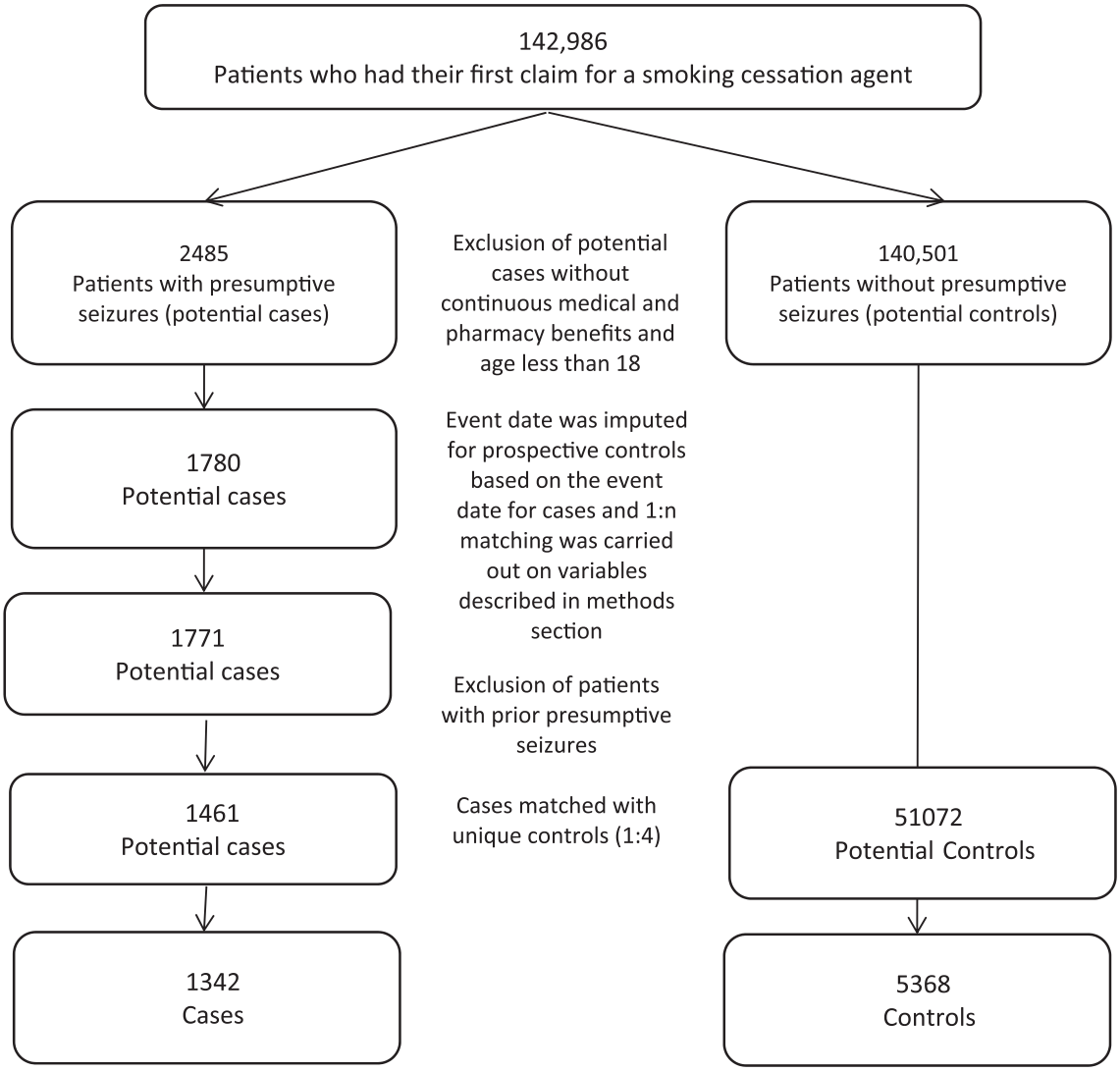

Fig. 1. Flowchart representing the attrition of the study population.

of presumptive seizures. Among the CNS effects, CNS pathology (OR = 3.16, confidence interval [CI] = 2.70–3.70), cerebrovascular disease (OR = 5.77, CI = 3.32–10.06), and cerebral trauma (OR = 2.38, CI = 1.54–3.70) had a significantly higher likelihood among cases than controls. Among systemic effects, metabolic disorders (OR = 1.22, CI = 1.06–1.40) and renal disorders (OR = 3.34, CI = 2.29–4.88) were prominent risk factors for the development of presumptive seizures. Within the substance use category, cases showed a significantly higher likelihood of alcohol use (OR = 2.50, CI = 2.30–4.88), antipsychotic use (OR = 2.52, CI = 2.00–3.18), antidepressant use (OR = 1.63, CI = 1.41–1.88), and poisoning (1.74, CI = 1.08–2.80) compared with controls.

The risk of presumptive seizures with varenicline use was measured as crude and adjusted ORs. Crude (OR = 0.98, CI = 0.80–1.20) as well as adjusted estimates (OR = 1.09, CI = 0.88–1.36) depict no evidence of significant increase in risk of presumptive seizures with varenicline exposure. Sensitivity analyses did not alter the results to a large extent. Changing the exposure period from 3 months to 1 month did not qualitatively change the estimates (OR = 1.07, CI = 0.80–1.42 vs OR = 1.09, CI = 0.88–1.36).

4. Discussion

The FDA updated the labeling of varenicline in 2015, to include the risk of seizures based on the adverse events reported to the FAERS [23]. It was found that more than 50% of the 64 cases reported to FAERS occurred in those with no prior history of seizures [23]. There has also been a previous mention regarding the risk of seizures with varenicline in a case report [10]. The Australian Adverse Drug Reactions Bulletin, which is similar to FAERS, has also obtained reports of cases of seizures linked to the use of varenicline [29]. As noted by Cahill et al. and Gibbons et al., these data sources are accustomed to confounding by indication, repeated counting from multiple sources, and the inability to represent a generalizable population [30,31]. Increased media reports and intermittent warnings could also pave ways for greater adverse event reporting for varenicline.

There is no evidence of results from controlled studies examining the link between varenicline and seizures. To our knowledge, this is the first study that quantifies the risk of presumptive seizures with the use of varenicline among the general population, when controlled for seizure risk factors such as CNS conditions, systemic illness conditions, and substance use disorders. This study adds to the existing literature obtained from FAERS and case reports, and is a subsequent step in the detection of any probable association between varenicline use and risk of seizures among the general population.

This study has limitations as well. Patients who had a previous seizure diagnosis were excluded in an attempt to identify as only first-time seizure cases after a prescription for a smoking cessation agent was received. This approach could underestimate the incidence of presumptive seizures among our smoking population. Moreover, the diagnosis of a nonchronic seizure event or a spontaneous event could easily be missed or misdiagnosed, when using administrative claims.

Despite these limitations, our study has important clinical and regulatory implications. The findings provide information for regulatory agencies to decide whether the label needs to be revised with respect to seizures related to varenicline. The health consequences of smoking are well-known, and so are the benefits of quitting. Smokers lose three years of life expectancy for every year of smoking [32]. Varenicline is recommended as first-line therapy for smoking cessation [33] and is the most efficacious smoking cessation aid [34]. The introduction of black box warnings has shown a decrease in varenicline prescriptions [35]. The cardiovascular safety warning issued by the FDA based on FAERS reports led to a decrease in the prescription and use of varenicline independent of patient characteristics [32,36]. However, observational studies and meta-analyses carried out in consideration of the FDA neuropsychiatric and cardiovascular adverse event warnings have failed to identify any significant differences between varenicline and other smoking cessation agents with regard to adverse event rates related to disorders such as depression, self-harm, suicide, hospitalizations related to neuropsychiatric events, and cardiovascular events such as cerebral infarction, heart failure, ischemic heart disease, and cardiac arrhythmia [31–33,37–39]. These findings have been corroborated by a clinical trial, and the black box warnings regarding depression and suicidality have been removed from the labeling of Chantix [40].

This underlines the need for strong observational studies to be able to explore further the safety profile of drugs, and especially those that are highly prescribed and used in the market.

Declaration of Competing Interest

None.

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