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# Epidemiology of traumatic brain injury-associated epilepsy and early use of anti-epilepsy drugs: An analysis of insurance claims data, 2004–2014☆

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ABSTRACT

*Background:* About 2.8 million TBI-related emergency department visits, hospitalizations and deaths occurred in 2013 in the United States. Post-traumatic epilepsy (PTE) can be a disabling, life-long outcome of TBI.
*Objectives:* The purpose of this study is to address the probability of developing PTE within 9 years after TBI, the risk factors associated with PTE, the prevalence of anti-epileptic drug (AEDs) use, and the effectiveness of using AEDs prophylactically after TBI to prevent the development of PTE.
*Methods:* Using MarketScan® databases covering commercial, Medicare Supplemental, and multi-state Medicaid enrollees from 2004 to 2014, we examined the incidence of early seizures (within seven days after TBI) and cumulative incidence of PTE, the hazard ratios (HR) of PTE by age, gender, TBI severity, early seizure and AED use (carbamazepine, clonazepam, divalproex sodium, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, pregabalin, topiramate, acetazolamide). We used backward selection to build the final Cox proportional hazard model and conducted multivariable survival analysis to obtain estimates of crude and adjusted HR (cHRs, aHRs) of PTE and 95% confidence intervals (CI).
*Results:* The incidence of early seizure among TBI patients in our study was 0.5%. The cumulative incidence of PTE increased from 1.0% in one year to 4.0% in nine years. Most patients with TBI (93%) were not prescribed any AED. Gender was not associated with PTE. The risk of PTE was higher for individuals with older age, early seizures, and more severe TBI. Only individuals using prophylactic acetazolamide had significantly lower risk of PTE (aHR = 0.6, CI 0.4-0.9) compared to those not using any AED.
*Conclusion:* The probability of developing PTE increased within the study period. The risk of developing PTE significantly increased with age, early seizure and TBI severity. Most of the individuals did not receive AED after TBI. There was no evidence suggesting AEDs helped to prevent PTE with the possible exception of acetazolamide. However, further studies may be needed to test the efficacy of acetazolamide in preventing PTE.

## 1. Introduction

A recent report from the Centers for Disease Control and Prevention (CDC) estimates 2.8 million traumatic brain injury (TBI) deaths, hospitalizations and emergency department visits occurred in the United States in 2013. That number includes 56,000 deaths, 282,000 hospitalizations, and 2.5 million emergency department (ED) visits related to TBI. The latter increased more than 50% between 2007 and 2013 (Taylor et al., 2017).

Among the potential consequences of TBI are seizures and epilepsy.

*Abbreviations:* TBI, traumatic brain injury; PTE, post-traumatic epilepsy; AED, anti-epilepsy drug; CDC, the Centers for Disease Control and Prevention; ED, emergency department; PHT, phenytoin; CBZ, carbamazepine; VPA, valproate; CCMC, the MarketScan Commercial Claims and Medicare; CPT, Current Procedural Terminology; NDC, National Drug Codes; CNS, central neuron system; CVD, cerebrovascular disease; CSE, childhood static encephalopathy; cHR, crude hazard ratio; aHR, adjusted hazard ratio

☆ The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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The latency of seizure occurrence after TBI is commonly categorized according to three intervals. Immediate seizures occur less than 24 h after TBI. Early seizures occur less than one week after TBI, attributed to acute, but not necessarily irreversible, pathophysiologic changes in cerebral function (Englander et al., 2003). Late seizures occur more than a week after TBI, and if recurrent, constitute the diagnosis of post traumatic epilepsy (PTE) (Lowenstein, 2009). TBI can result in several potentially epileptogenic alterations, including neuronal, axonal, and vascular damage, as well as parenchymal and subarachnoid hemorrhage. TBI initiates cascades of molecular and cellular changes including excitotoxicity, gliosis, and neuroinflammation, as well as later toxicity caused by iron-rich hemoglobin breakdown products. (Glushakov et al., 2016; McNamara et al., 2006; Pitkänen et al., 2016, 2014)

The overall incidence of PTE in hospitalized populations, comprising a range of TBI severity mainly from closed head injuries, is about 3–5% (Chen et al., 2009; Annegers et al., 1998). In a study identifying 5984 episodes of TBI in Olmsted County, Minnesota from 1935 to 1984, the probability of PTE ranged from 0.7% to 10.0% in five years follow-up and 2.1% to 16.7% in 30 years follow-up, correlating with the severity of TBI (Annegers et al., 1998). Penetrating head injuries as seen in military veterans show the highest incidence of PTE, with estimates ranging from a 5-year cumulative incidence of 28% to a 15-year cumulative incidence of 53% (Salazar et al., 1985; Salazar and Grafman, 2014; Raymont et al., 2010; Caveness et al., 1979). There has been no study of PTE representing the entire population of the US.

Identified risk factors of PTE include chronic alcoholism, age of 65 years or older, penetrating injuries, traumatic intracranial hemorrhage, severity of injury, posttraumatic amnesia or loss of consciousness for more than one day, trauma-related focal neurologic deficits, depressed skull fractures, cerebral contusions, and retained bone and metal fragments (Englander et al., 2003; Annegers et al., 1998).

An important goal in the acute and long-term management of TBI is the prevention of PTE. Several randomized clinical trials have shown the effectiveness of anti-epileptic drugs (AEDs) in the management of early seizures after TBI (Kirmani et al., 2016), including prophylactic anti-epileptics (Schierhout and Roberts, 2012; Temkin et al., 1990). Longer, limited-term prophylactic use of three older AEDs: phenytoin (PHT), carbamazepine (CBZ), and valproate (VPA) have been evaluated in clinical trials, but have shown no benefit in the prevention of late seizures or epilepsy (Kirmani et al., 2016; Temkin et al., 1999).

This study addresses the incidence of PTE and its risk factors—including TBI severity and early seizures—among persons with medically attended TBI who are enrolled in a large database broadly representing the U.S. insured population. We also explore the possible effectiveness of prophylactic AED use after TBI to prevent the development of PTE, as this has not been evaluated for many AEDs.

## 2. Methods

### 2.1. Data source

We conducted a retrospective study using combined data from Truven Health Analytics, Inc.: the MarketScan Commercial Claims and Medicare (CCMC) database and the Multi-state Medicaid database (Medicaid). These databases contained de-identified information including inpatient, outpatient, pharmacy claims and insurance coverage data from more than 100 million persons, including commercially insured individuals, individuals aged 65 years and older with supplemental Medicare coverage, and individuals with Medicaid coverage. The inpatient and outpatient datasets include International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes, Current Procedural Terminology (CPT) Fourth Edition codes, dates and place of service, provider type. The pharmacy claims dataset includes National Drug Codes (NDC), dispensing date, quantity, days supplies, and payments made for each claim. The enrollment file provides information on age, gender, health insurance plan type, U.S. Census region and monthly enrollment status. Inpatient, outpatient, pharmacy claims and enrollment file are linkable by an encrypted patient identification number. The databases are compliant with Health Insurance Portability and Accountability Act.

### 2.2. Study population

We included persons enrolled between January 2004 and December 2014. Individuals with missing age, sex, region (if CCMC), and health plan type were excluded. Data in 2004 and 2005 were used as the two-year baseline for patients enrolled in 2006. Data in 2013 and 2014 were used for minimum two-year follow-up for patients enrolled in 2012.

Eligibility for inclusion in this study was limited to: (a) patients aged ≥2 years who were enrolled for a minimum baseline period of 2 years without diagnostic codes indicating epilepsy or seizures and without prescriptions for AEDs; and (b) children aged < 2 years whose records included no diagnostic codes for epilepsy, seizures, and AED prescriptions since birth.

Our operational definition of a case of TBI was based on ICD-9-CM codes used to identify TBI: 800.0–801.9, 803.0–804.9, 850.0–854.1, 950.1–950.3, 959.01 and 995.55 (Baker and Li, 2012). Patients were eligible for inclusion if these codes were assigned in hospital, emergency department, or outpatient care site. Dates of TBI were assigned as the initial date of service of the medical encounter including these codes.

Consistent with recommendations of Helmers et al. (2015), a case of epilepsy was identified if it met any of the following conditions:

- an occurrence of ≥2 ICD-9-CM codes 345.xx among separate medical encounters (separate dates in any care venue)
- an occurrence of 1 ICD-9-CM code 345.xx AND ≥ 1 ICD-9-CM code 780.3x among separate medical encounters
- an occurrence of 1 ICD-9-CM code 345.xx AND code(s) for AED prescription, or
- an occurrence of ≥2 ICD-9-CM codes 780.3x among separate medical encounters AND code(s) for AED prescription.

Cases of PTE were identified among the TBI cases who met the case definition of epilepsy beginning 7 days or more after TBI. Occurrences of early seizures within 7 days were considered acute provoked seizures and not indicators of epilepsy.

Non-TBI controls were selected, matched one-to-one by enrollment year, gender, age, region and insurance plan type with TBI cases. As controls did not have TBI dates, controls were assigned index dates equal to onset dates of the matched TBI cases. Controls aged ≥2 years were enrolled for a minimum baseline period of 2 years without diagnostic codes indicating epilepsy or seizures and without prescriptions for AEDs. Controls aged < 2 years required an absence of diagnostic codes for epilepsy, seizures, and AED prescriptions since birth.

We adopted published principles (Baker and Li, 2012) to assign TBI severity based on duration of loss of consciousness and documentation of traumatic intracranial lesion(s) (Table 1), ranging from mild (lacking indicator of intracranial lesion and loss of consciousness either not

**Table 1**
Traumatic brain injury severity levels.

| Level | Definition |
|---|---|
| I | (Intracranial lesion undocumented) AND (LOC* unspecified OR LOC < 1 h) |
| II | (Intracranial lesion undocumented AND (LOC > = 1 h) |
| III | (Intracranial lesion documented) AND (LOC unspecified or LOC < 1 h) |
| IV | (Intracranial lesion documented) AND (LOC 1 to < 24 h) |
| V | (Intracranial lesion documented) AND (LOC > = 24 h) |

* LOC – loss of consciousness.