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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).

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Disclosures

All authors have nothing to disclose in regards to this study.

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.

**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.

### Keywords

Traumatic brain injury; Epilepsy; Anti-epilepsy drug; Early seizure

## 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. 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 documented or < 1 h; severity level I), to very severe (having indicator of intracranial lesion and loss of consciousness ≥24 h; severity level V). The ICD-9-CM codes to identify the TBI severity are listed in Appendices A and B.

Analysis variables included age category, sex, severity of TBI, early seizure, PTE, prescribed AEDs, duration of AED prescription before diagnosed as PTE in days. We also included the pre-existing neurologic diseases as independent epilepsy risk factors (central nervous system [CNS] infection, stroke or other cerebrovascular disease [CVD], primary and secondary

brain tumors, senile dementias, childhood static encephalopathy [CSE], cerebral degenerative diseases, other CNS lesions and disorders,

We categorized 28 AEDs included in this study into 13 groups. We counted prescribed AED anytime from the date of TBI to the diagnosis of PTE or end of follow-up. Because the numbers of the patients on those AEDs were less than 1000, we combined ethosuximide, ethotoin, felbamate, fosphenytoin sodium, lacosamide, mephobarbital, methsuximide, phenobarbital, primidone, tiagabine hydrochloride, trimethadione, vigabatrin, clobazam, and zonisamide into one group (other AEDs). The multiple AEDs included the patients on more than one AED.

### 2.3. Statistical analysis

**2.3.1. TBI and control groups—**The cumulative incidence of PTE or epilepsy was calculated at nine years following index date based on life tables, adjusting for participants who did not complete nine years follow up (Armitage et al., 2008; Penman and Johnson, 2008). The test for equality of cumulative incidence between TBI and non-TBI controls described by Gray (1988) was used.

**2.3.2. TBI only—**PTE cases were summarized by count (frequency and percentage) and the prevalence of prescribed AED was compared using Chi-square test among different categories of age, gender, early seizure, severity of TBI and duration of AED use. Cumulative incidences of PTE were calculated as described above.

We examined the probability of developing PTE with risk factors (age, gender, TBI severity, early seizure) and the probability of PTE prevention by prescribed AED using survival analysis. TBI patients were followed up to 9 years until diagnosed with epilepsy or censored due to lost follow-up, unenrollment, death, or the end of the study. A Cox proportional hazard model (PROC PHREG) was constructed to obtain estimates of crude hazard ratio (cHR), adjusted hazard ratio (aHR) and 95% confidence interval for age, gender, TBI severity, and AED prescription. The backward selection was used to screen the first-order interaction terms, and the following variables were forced into the final model: age group, sex, early seizure, region, health plan type, severity of TBI, AED, stroke and other cerebrovascular disease, primary and secondary brain tumors, CSE, dementias and cerebral degenerative diseases, CNS infection, other CNS lesions and disorders, death, and length of AED use. The proportional hazards assumption was verified using Shoenfeld residuals.

All tests of hypotheses were two-sided and used $\alpha = 0.05$ level of significance. SAS version 9.4 (SAS Institute Inc., Cary, NC) was used in all data analyses. The study was approved by the Institutional Review Board of Emory University.

## 3. Results

From 2006 to 2012, we identified 2,345,758 total TBI patients (1,851,368 patients from commercial and Medicare databases and 494,390 patients from Medicaid databases, Fig. 1) among whom there were 77,014 (3.3%) pre-existing epilepsy patients and 263,149 (11.2%) patients who were taking AEDs prior to TBI. We excluded those patients with preexisting

epilepsy or prior AED use from the TBI cases that we analyzed. The study population included 2,059,870 TBI patients and 2,198,173 non-TBI matched controls (Fig. 1).

### 3.1. TBI and control groups

The cumulative incidence of epilepsy among TBI patients is significantly higher than that among control groups ($p < 0.0001$) (Fig. 2). Among TBI patients, the cumulative incidence was 0.98% (95% CI: 0.96, 1.00) at one year, increasing to 4.01% (95% CI: 3.54, 4.52) at nine years. Among non-TBI patients, the cumulative incidence increased from 0.19% (95% CI: 0.18, 0.20) at one year to 1.79% (95% CI: 1.65, 1.94) at nine years.

### 3.2. TBI group only

Among all 2,059,870 TBI patients (with no prior indicators of epilepsy), a total of 11,150 (0.5%) experienced early seizures, and a total of 31, 521 (1.5%) developed PTE. Among these PTE patients, 3678 (11.7%) had early seizures (Table 2). In contrast, among all 2,028,349 TBI patients who did not develop PTE, 7472 (0.4%) had early seizures (Table 2).

The risk of developing PTE among older age groups compared with the youngest age group yielded aHRs ranging from 1.1 to 2.6, higher with advancing age, controlling for all the other variables in the final model (Table 2). The risk of developing PTE for individuals with early seizures was 37 times higher than that for individuals without early seizure (aHR = 36.8, 95% CI: 29.9–45.3) (Table 2). The risk of PTE for individuals with severe TBI (level V) was 13.7 times higher than that for individuals with mild TBI (level I) (aHR = 13.7, 95% CI: 8.0–23.5) (Table 2).

AED's in general, did not prevent PTE. Notably, the risk of developing PTE among patients using acetazolamide (aHR = 0.6, 95% CI: 0.4, 0.9) was significantly lower than that for patients without any AED use (Table 2). Patients using the other 10 specified AEDs appeared to have higher risk of PTE compared to those with no AED use ($p < 0.0001$) (Table 2).

Table 3 shows the cumulative incidences of PTE from one to nine years. Consistent with corresponding hazard ratios, the cumulative incidences increased significantly with advancing age, early seizures and severe TBI (Table 3, Figs. 3,4 and 5).

Table 4 shows the variation in AED use—from time of injury and prior to PTE diagnosis or end of follow-up—by age, severity of TBI, and early seizure occurrence. Overall, 93% did not use AED. Findings varied by age: 99.3% of 0–4 year-olds did not use AEDs, decreasing to 86.4% among 65–74 year-olds. Among patients without early seizures, 93.2% did not use AED, compared to 47.2% among patients with early seizures. And 93.7% of those with mild TBI did not use AED compared to 80.7% among patients with severe TBI.

A single AED was prescribed for 5.5% TBI patients. TBI patients who at some point developed PTE, most commonly used levetiracetam (6.5%), and TBI patients who did not develop PTE most commonly used gabapentin (1.9%). TBI patients with early seizures most commonly used AED's levetiracetam (16.8%), and those without early seizures most commonly used gabapentin (1.9%). The percentage of AED use increased with age and TBI

severity. Those 0–4 years old most commonly used divalproex sodium (0.1%), levetiracetam (0.1%), and oxcarbazepine (0.1%). Those 5–14 years old most commonly used topiramate (0.7%), Divalproex sodium (0.4%), and gabapentin (0.3%); and those age 15 years and older most commonly used Clonazepam (1%–2%) and gabapentin (1%–5.3%). Among the patients with mild TBI, clonazepam and gabapentin were most commonly used, while among the patients with moderate and severe TBI, Levetiracetam and gabapentin were most commonly used. Among those patients who used AEDs, Levetiracetam (28.9%) and phenytoin (23.8%) were most commonly used in the first 7 days. Clonazepam and gabapentin were most commonly used after 7 days.

## 4. Discussion

Overall, the 9-year cumulative incidence of epilepsy among TBI patients in our study was more than two-fold that among non-TBI controls. This is consistent with other population-based studies demonstrating an increased risk of PTE across the spectrum of TBI severity, although the effect is lower in magnitude than in those studies. (Annegers et al., 1998; Ferguson et al., 2010) This is because our study population includes milder TBIs seen in emergency departments or outpatient clinics, whereas some other studies only included more serious injuries admitted to hospital. We may also note that the one-year incidence of epilepsy (0.19%) in our control population was also substantially higher than annual incidence rates commonly cited for general populations. This may be explainable in part by the age distribution of our controls, given that these are matched to a TBI population. TBI populations, including ours, over-represents children under 15 (and especially children under 5) years of age, where incidence rates of TBI are much higher, as are incidence rates of epilepsy.

The incidence of early seizures after TBI was 0.5% in our study, lower than the incidence reported in other studies, which have established early seizures as a known risk factor for PTE. (Szaflarski et al., 2014) The reason is that our study population is a somewhat different from some other studies. Estimates from other studies have ranged from 2.1% (in a population-based Olmsted County, Minnesota study) to 16.3% (in a TBI rehabilitation center) (Englander et al., 2003; Annegers et al., 1998, 1980; Asikainen et al., 1999). The differences may be attributed to variations in definitions, study designs, and study populations, some of which (e.g., TBI rehabilitation centers) have more severely injured subjects. We included all visits to EDs, which means that more mild cases were allowed. Our study is the first to report early seizure occurrence in a broad spectrum of privately insured, Medicaid and Medicare TBI patients in the U.S. population.

We found the cumulative incidence of epilepsy over nine years approached 50% among TBI patients with early seizures, and the risk of epilepsy among TBI patients with early seizures was 37 times higher than that for those without early seizures. The apparent risk of epilepsy among patients with severe TBI was nearly 14 times higher than that for those with mild TBI. This appears consistent with other population-based studies of U.S. localities, although the actual incidence of PTE in relation to these factors was quite different (Annegers et al., 1998; Ferguson et al., 2010). The study by Annegers (Annegers et al., 1998) found a much lower incidence of PTE in the early seizure group. It is not clear how to explain that

difference, but the definition of PTE may have been different. The Ferguson study (Ferguson et al., 2010) only looked at inpatients and found similar tendencies, but at a higher incidence, which would be expected, since those subjects may have been more severe TBI patients. Both studies had a fairly small number of PTE patients.

Recent guidelines for the management of severe TBI from the Brain Trauma Foundation and the American Association of Neurological Surgeons suggest patients with severe TBI may be placed on an AED soon after trauma to prevent early seizures (Carney et al., 2016). Our findings indicate that in practice, 47% of patients with early seizures and 80% of patients with severe TBI had no recorded AED use prior to the diagnosis of PTE. However, it is possible that some received AEDs only while hospitalized, which is not recorded in the database. An older survey of 127 neurosurgery clinics on antiepileptic prophylaxis in patients with TBI indicates a variety of attitudes towards prophylaxis for seizures: in 12% of the responding institutions, antiepileptic prophylaxis is given to every patient, in 36%, no prophylaxis is carried out, and in 52% some patients receive prophylaxis while others do not (Dauch et al., 1996). Penetrating injuries, intracranial hemorrhages and electroencephalographic abnormalities were the most frequent reasons for the prophylaxis.

The prophylactic use of any standard AED we examined appeared to confer no reduction in risk of PTE. Indeed that risk appeared elevated for nearly all drugs, a result we suspect may be attributable to un-detected cases of preexisting epilepsy in our study population, as well as confounding risk factors such as type of injury and nuances of severity that we were unable to take account of. Our findings are consistent with other studies that have examined the potential efficacy of specific AEDs—phenytoin, carbamazepine, valproate, and levetiracetam—finding no benefit, as described in a recent systematic review (Thompson et al., 2015).

One possible exception of interest was acetazolamide, which we found was associated with a decreased risk of PTE. This suggestive finding, of course, needs replication through more rigorous studies. Most likely it was not used as an anti-epileptic drug, but as a treatment of brain edema following TBI (Sturdivant et al., 2016). If verified, possible explanations may involve acetazolamide's unique action among AEDs as a selective inhibitor of carbonic anhydrase. Acetazolamide increases local cerebral blood flow (Bickler et al., 1988), an effect confirmed in an animal model of brain injury, which finds a normalization of the ratio between local cerebral metabolic rate for glucose and local cerebral blood flow and a consequent reduction in axonal injury (Harris et al., 2012). Apart from these effects, in animal models of epilepsy, acetazolamide also generally decreases the interval of occurrence of ictal and interictal discharges (Hamidi and Avoli, 2015).

Our definitions of TBI and epilepsy, using coded administrative data, are consistent with recent international recommendations. The large number of TBI cases and PTE cases is statistically robust, providing credible estimates of the incidence of early seizures, PTE, and the association between AEDs and PTE. The sample draws subjects across the spectrum of epilepsy from multiple sectors throughout the insured population of the United States, thereby being more broadly representative than either local community-based studies or

clinic-based studies. And our 11 years of data can provide a longitudinal view of the development of PTE following TBI and prophylaxis.

There are, however, several limitations to our analysis. The dataset we used in this study is claim-based and susceptible to miscoding and missing information. ICD-9-CM-based coding can result in misclassifications of the occurrence of both TBI and epilepsy. The accuracy of ICD-9-CM coding for our indicators of TBI severity have not been validated. AED use may be misclassified in some patients. As noted above, AED received during hospitalization are not recorded in the database. Also, claimed-based data represent prescriptions filled only; it cannot be determine whether patients adhered to medication used the AEDs as prescribed.

Misclassification of some preexisting epilepsy cases as new PTE cases may occur also. Because the minimum 2-year baseline is not always long enough to detect prevalent epilepsy cases (International League Against Epilepsy et al., 1993; Thurman et al., 2011), we may have included pre-existing epilepsy patients who have infrequent or mild seizures for which they rarely obtain medical care or do not take medication, or who receive care in part from other sources not covered by insurance plans included in our data set.

This study uses linked inpatients and outpatient data that describe all medical encounters for all individuals in a population. When individuals have multiple medical encounters described by epilepsy or seizure codes, the likelihood of identifying true cases of epilepsy is high; however, the codes *per se* do not distinguish new-onset from long-established cases (Thurman et al., 2011).

The claims data that we analyzed do not represent persons lacking health insurance (a status more frequent among younger adults) and may not fully represent the insured population of the United States. The commercial and Medicare supplemental datasets are contributed by over 150 large employers and about 20 health plans. The population submitting Medicare Supplemental claims may differ from the Medicare population without supplemental private insurance, which was not included in our study.

All these factors may substantially reduce confidence in any extrapolation to findings for the U.S. population as a whole.

Finally, information identifying race was not provided in Medicare and Commercial Claims data, although incomplete information was contained in Medicaid data. We combined Medicaid, Medicare and Commercial claims data together, and thus could not use race as a variable.

We identified advancing age, early seizures, and increased severity TBI as risk factors of PTE. In caring for and following patients with these factors, counseling and increased vigilance to provide early treatment of emerging PTE may be indicated.

Further studies are needed to test the epilepsy prevention efficacy of acetazolamide prophylaxis, as are studies of prognostic indicators, including biomarkers, to identify which patients will develop epilepsy and which might benefit from preventive treatment. Finally,

more research needs to be done on the effectiveness of AEDs in the first seven days or more after TBI.

## 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 |

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Thurman DJ, et al., 2011 Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia 52 (s7), 2–26. [PubMed: 21899536]

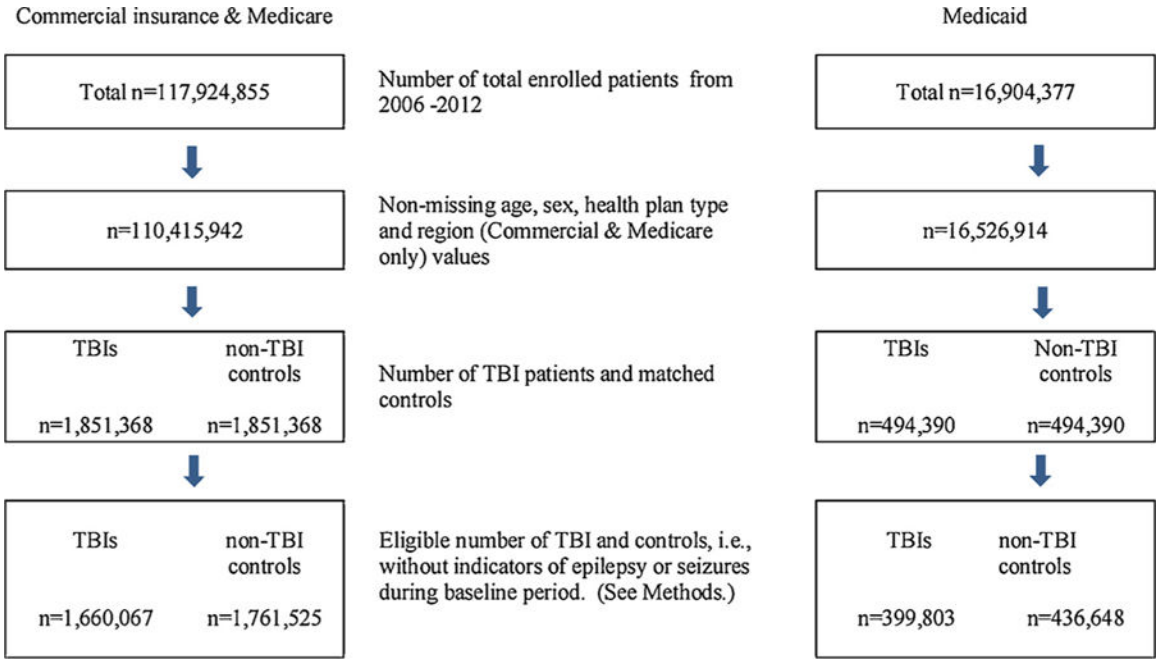


**Fig. 1.**

Sample selection of patients with traumatic brain injury (TBI) and matched non-TBI controls in MarketScan.2004–2014.

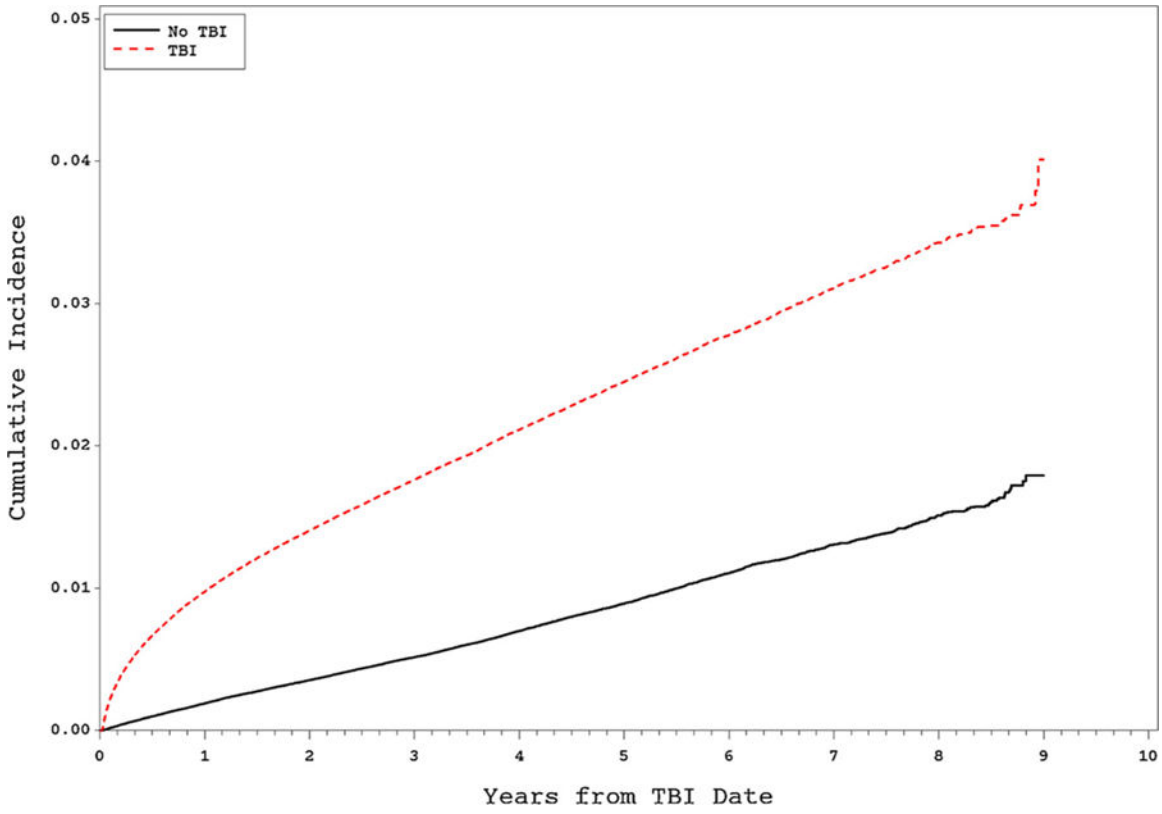


**Fig. 2.**

Cumulative Incidence of Epilepsy among TBI and One-by-one Matched Non-TBI Group, 2006–2014 (TBI: N = 2,059,870).

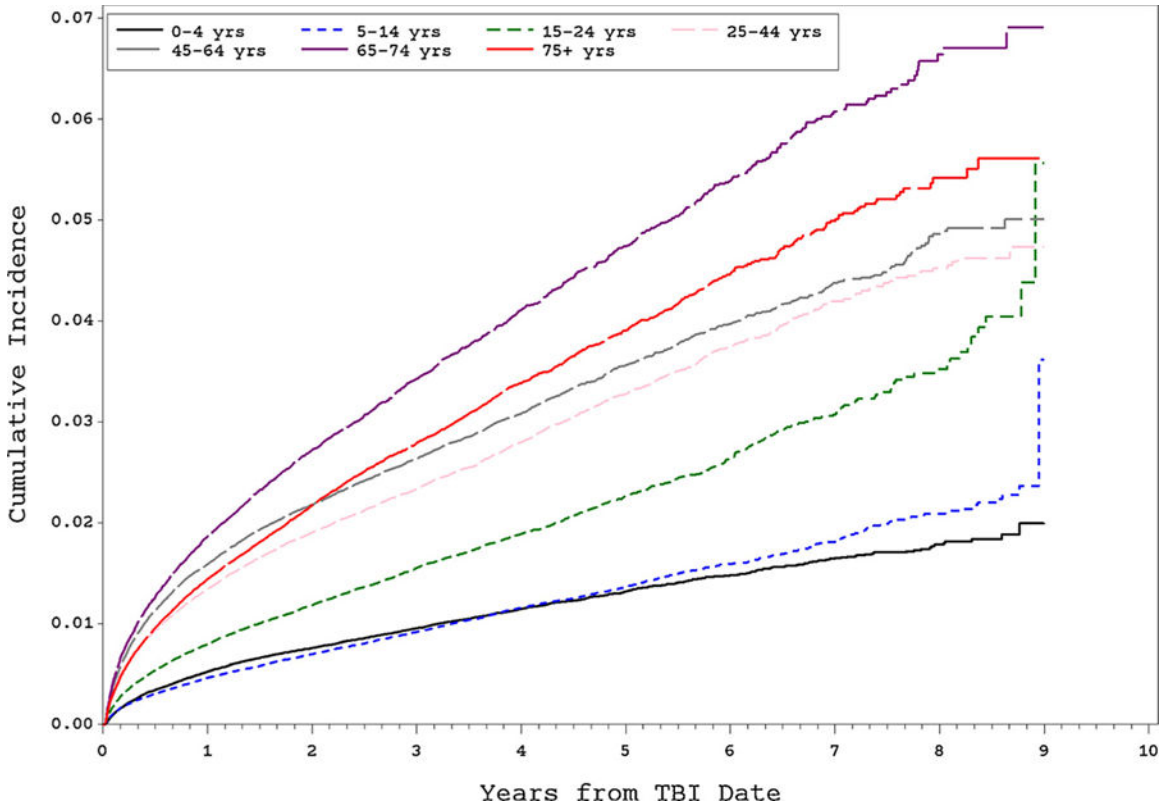


**Fig. 3.**

Cumulative Incidence of Epilepsy by Age Group among TBI Patients, 2006–2014 (TBI: N = 2,059,870).

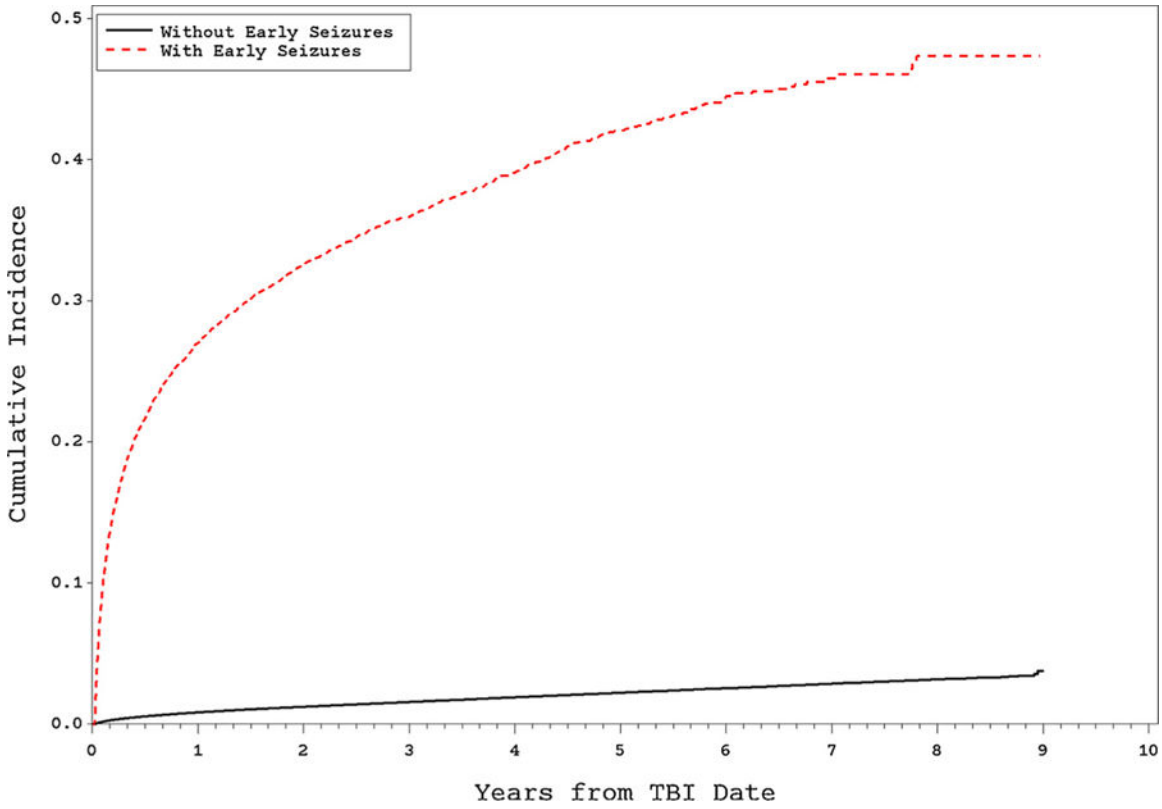


**Fig. 4.**

Cumulative Incidence of Epilepsy by Early Seizures among TBI Patients, 2006–2014 (TBI: N = 2,059,870).

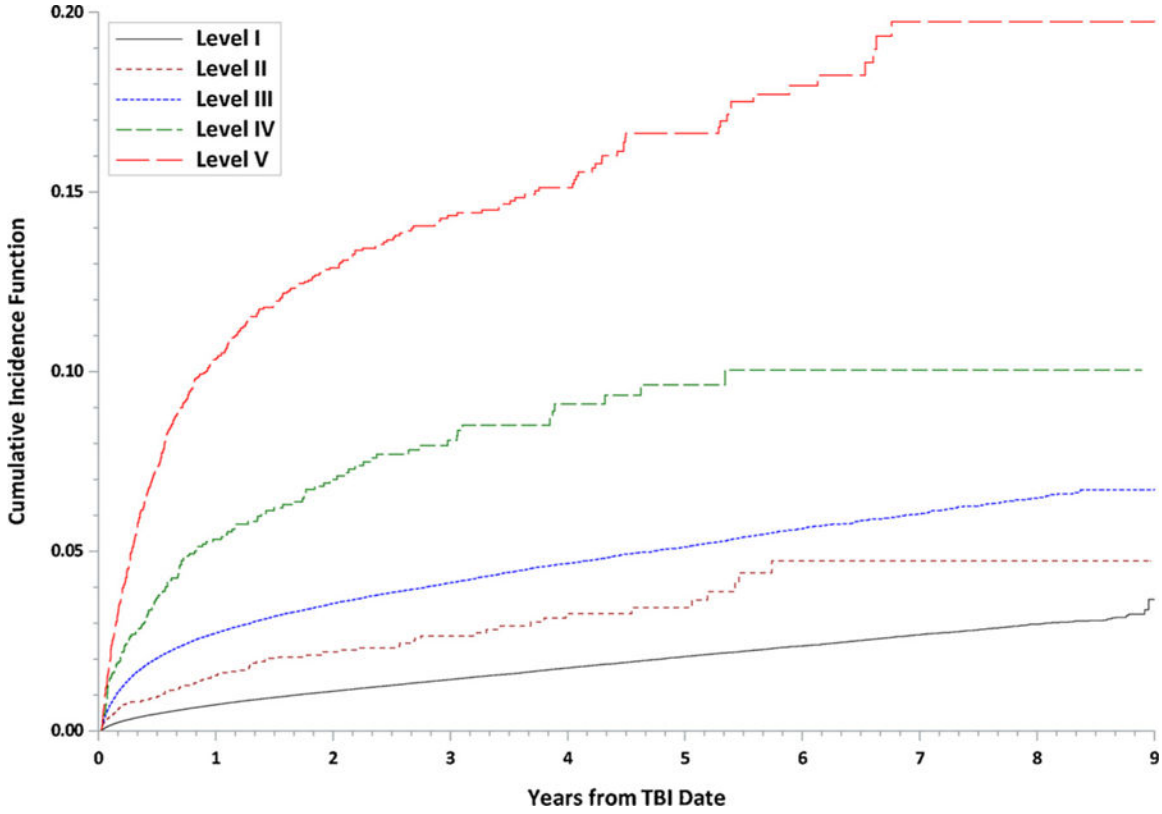


**Fig. 5.**

Cumulative Incidence of Epilepsy by TBI Severity among TBI Patients, 2006–2014 (TBI: N = 2,059,870).

**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.

*Epilepsy Res*. Author manuscript; available in PMC 2019 October 01.

**Table 2**

Association between PTE and age, sex, severity of TBI, and AED among TBI patients.

| | No Epilepsy (N = 2,028,349) n (%) | Epilepsy (N = 31,521) n (%) | Total (N = 2,059,870) n (%) | Crude Hazard Ratio (95% CI) | P-value | Adjusted Hazard Ratio * (95% CI) | Adjusted P-value |
|---|---|---|---|---|---|---|---|
| **Age Groups** | | | | | | | |
| 0–4 yrs | 341,884 (16.9) | 3098 (9.8) | 344,982 (16.7) | 1.0 (reference) | | 1.0 (reference) | |
| 5–14 yrs | 468,453 (23.1) | 4113 (13.0) | 472,566 (22.9) | 1.00 (0.96–1.05) | 0.9641 | 1.08 (0.91–1.28) | 0.3743 |
| 15–24 yrs | 368,448 (18.2) | 4446 (14.1) | 372,894 (18.1) | 1.67 (1.60–1.75) | < .0001 | 1.49 (1.26–1.75) | < .0001 |
| 25–44 yrs | 251,973 (12.4) | 5034 (16.0) | 257,007 (12.5) | 2.53 (2.42–2.65) | < .0001 | 1.66 (1.40–1.97) | < .0001 |
| 45–64 yrs | 304,139 (15.0) | 7126 (22.6) | 311,265 (15.1) | 2.83 (2.72–2.96) | < .0001 | 1.81 (1.54–2.11) | < .0001 |
| 65–74 yrs | 85,071 (4.2) | 2808 (8.9) | 87,879 (4.3) | 3.71 (3.53–3.90) | < .0001 | 2.55 (2.13–3.06) | < .0001 |
| 75+ yrs | 208,381 (10.3) | 4896 (15.5) | 213,277 (10.4) | 3.03 (2.89–3.17) | < .0001 | 2.48 (2.11–2.92) | < .0001 |
| **Sex** | | | | | | | |
| Male | 1081,548 (53.3) | 15,948 (50.6) | 1,097,496 (53.3) | 0.93 (0.91–0.95) | < .0001 | 1.01 (0.91–1.11) | 0.8587 |
| Female | 946,801 (46.7) | 15,573 (49.4) | 962,374 (46.7) | 1.0 (reference) | | 1.0 (reference) | |
| **Early Seizures** | | | | | | | |
| No | 2,020,877 (99.6) | 27,843 (88.3) | 2,048,720 (99.5) | 1.0 (reference) | | 1.0 (reference) | |
| Yes | 7472 (0.4) | 3678 (11.7) | 11,150 (0.5) | 30.35 (29.33–31.41) | < .0001 | 36.77 (29.87–45.26) | < .0001 |
| **Severity of TBI** | | | | | | | |
| Level I | 1,804,850 (89.0) | 22,697 (72.0) | 1,827,547 (88.7) | 1.0 (reference) | | 1.0 (reference) | |
| Level II | 3707 (0.2) | 86 (0.3) | 3793 (0.2) | 1.91 (1.55–2.36) | < .0001 | 4.91 (1.64–14.72) | 0.0046 |
| Level III | 214,414 (10.6) | 8139 (25.8) | 222,553 (10.8) | 2.91 (2.83–2.98) | < .0001 | 1.70 (1.50–1.94) | < .0001 |
| Level IV | 1902 (0.1) | 136 (0.4) | 2038 (0.1) | 5.72 (4.83–6.77) | < .0001 | 6.62 (2.75–15.96) | < .0001 |
| Level V | 3476 (0.2) | 463 (1.5) | 3939 (0.2) | 12.61 (11.50–13.82) | < .0001 | 13.68 (7.97–23.48) | < .0001 |
| **Anti-Epilepsy Drug** | | | | | | | |
| No Drug Taken | 1,893,125 (93.3) | 22,480 (71.3) | 1,915,605 (93.0) | 1.0 (reference) | | 1.0 (reference) | |
| Carbamazepine | 1197 (0.1) | 172 (0.5) | 1369 (0.1) | 9.04 (7.78–10.50) | < .0001 | 5.15 (4.42–5.99) | < .0001 |
| Clonazepam | 18,480 (0.9) | 650 (2.1) | 19,130 (0.9) | 2.27 (2.10–2.45) | < .0001 | 1.80 (1.67–1.95) | < .0001 |
| Divalproex Sodium | 9001 (0.4) | 693 (2.2) | 9694 (0.5) | 5.06 (4.69–5.46) | < .0001 | 3.58 (3.31–3.87) | < .0001 |
| Gabapentin | 38,756 (1.9) | 978 (3.1) | 39,734 (1.9) | 1.62 (1.52–1.73) | < .0001 | 1.27 (1.19–1.36) | < .0001 |
| Lamotrigine | 5062 (0.2) | 258 (0.8) | 5320 (0.3) | 3.23 (2.86–3.65) | < .0001 | 3.29 (2.91–3.73) | < .0001 |
| Levetiracetam | 6607 (0.3) | 2034 (6.5) | 8641 (0.4) | 22.43 (21.43–23.47) | < .0001 | 5.95 (5.65–6.28) | < .0001 |

| | No Epilepsy (N = 2,028,349) n (%) | Epilepsy (N = 31,521) n (%) | Total (N = 2,059,870) n (%) | Crude Hazard Ratio (95% CI) | P-value | Adjusted Hazard Ratio* (95% CI) | Adjusted P-value |
|---|---|---|---|---|---|---|---|
| Oxcarbazepine | 2128 (0.1) | 165 (0.5) | 2293 (0.1) | 4.62 (3.97–5.39) | < .0001 | 3.84 (3.29–4.49) | < .0001 |
| Phenytoin | 3554 (0.2) | 931 (3.0) | 4485 (0.2) | 18.95 (17.74–20.22) | < .0001 | 5.13 (4.78–5.50) | < .0001 |
| Pregabalin | 6657 (0.3) | 219 (0.7) | 6876 (0.3) | 2.17 (1.99–2.48) | < .0001 | 1.69 (1.48–1.94) | < .0001 |
| Topiramate | 11,906 (0.6) | 516 (1.6) | 12,422 (0.6) | 2.75 (2.52–3.00) | < .0001 | 2.74 (2.51–3.00) | < .0001 |
| Acetazolamide | 2340 (0.1) | 28 (0.1) | 2368 (0.1) | 0.77 (0.53–1.12) | 0.1688 | 0.64 (0.44–0.93) | 0.0176 |
| Other Drugs | 1327 (0.1) | 185 (0.6) | 1512 (0.1) | 8.81 (7.62–10.18) | < .0001 | 4.52 (3.90–5.24) | < .0001 |
| Multiple Drugs | 28,209 (1.4) | 2212 (7.0) | 30,421 (1.5) | 4.48 (4.29–4.69) | < .0001 | 3.56 (3.38–3.76) | < .0001 |

Data Source: MarketScan Commercial Claims and Encounters and Medicare Supplemental database, 2006–2014. TBI: Traumatic Brain Injury. PTE: Posttraumatic Epilepsy AED: anti-epileptic drug.

*The variables in the final Cox model included: age group, sex, early seizure, region, health plan type, severity of TBI, AED, stroke and other cerebrovascular disease, primary and secondary brain tumors, CSE, dementias and cerebral degenerative diseases, CNS infection, other CNS lesions and disorders, death, length of AED use and all significant first-order interaction terms. This table only shows the results of the selected variables from the final model.

**Table 3**

Cumulative incidences of PTE among TBI patients.

| | 1-year (%, 95% CI) (N = 550,343) | 3-year (%, 95%CI) (N = 778,101) | 5-year (%, 95%CI) (N = 456,984) | 7-year (%, 95%CI) (N = 202,315) | 8-year (%, 95%CI) (N = 46,814) | 9-year (%, 95%CI) (N = 25,313) |
|---|---|---|---|---|---|---|
| **Age Groups** | | | | | | |
| 0–4 yrs | 0.52 (0.50, 0.55) | 0.95 (0.92, 0.99) | 1.32 (1.27, 1.37) | 1.65 (1.57, 1.73) | 1.78 (1.68, 1.89) | 1.99 (1.74, 2.27) |
| 5–14 yrs | 0.46 (0.44, 0.48) | 0.92 (0.89, 0.95) | 1.36 (1.32, 1.41) | 1.81 (1.73, 1.89) | 2.09 (1.98, 2.21) | 3.61 (1.70, 6.69) |
| 15–24 yrs | 0.79 (0.76, 0.82) | 1.55 (1.50, 1.60) | 2.27 (2.18, 2.36) | 3.07 (2.91, 3.25) | 3.52 (3.27, 3.79) | 5.57 (3.45,8.38) |
| 25–44 yrs | 1.34 (1.30, 1.39) | 2.33 (2.26, 2.40) | 3.27 (3.16, 3.38) | 4.20 (4.02, 4.38) | 4.52 (4.29, 4.76) | 4.74 (4.40, 5.08) |
| 45–64 yrs | 1.59 (1.54, 1.63) | 2.64 (2.57, 2.70) | 3.56 (3.46, 3.66) | 4.38 (4.22, 4.54) | 4.86 (4.62, 5.11) | 5.00 (4.71, 5.32) |
| 65–74 yrs | 1.86 (1.77, 1.96) | 3.43 (3.29, 3.57) | 4.74 (4.54, 4.94) | 6.07 (5.76, 6.40) | 6.64 (6.21, 7.08) | 6.91 (6.32, 7.52) |
| 75+ yrs | 1.44 (1.39, 1.50) | 2.79 (2.71, 2.88) | 3.91 (3.77, 4.04) | 4.99 (4.76, 5.23) | 5.42 (5.09, 5.76) | 5.61 (5.20, 6.04) |
| **Early Seizure** | | | | | | |
| Yes | 27.02 (26.17, 27.88) | 35.94 (34.92, 36.95) | 42.03 (40.76, 43.30) | 45.77 (44.04, 47.48) | 47.33 (45.05, 49.59) | — |
| No | 0.82 (0.81, 0.84) | 1.56 (1.54, 1.58) | 2.22 (2.19, 2.25) | 2.86 (2.81, 2.91) | 3.17 (3.10, 3.24) | 3.76 (3.29, 4.28) |
| **Severity of TBI** | | | | | | |
| Level I | 0.73 (0.72, 0.75) | 1.43 (1.41, 1.45) | 2.07 (2.04, 2.10) | 2.67 (2.62, 2.73) | 2.98 (2.90, 3.06) | 3.66 (3.07, 4.33) |
| Level II | 1.54 (1.16, 2.01) | 2.65 (2.08, 3.32) | 3.43 (2.65, 4.36) | 4.73 (3.45–6.31) | — | — |
| Level III | 2.72 (2.65, 2.80) | 4.12 (4.03, 4.22) | 5.12 (5.00, 5.25) | 6.04 (5.87, 6.22) | 6.48 (6.25, 6.71) | 6.71 (6.43, 7.00) |
| Level IV | 5.33 (4.35, 6.44) | 8.08 (6.75, 9.56) | 9.363 (7.96, 11.49) | 10.04 (8.22, 12.08) | — | — |
| Level V | 10.36 (9.35, 11.43) | 14.34 (13.06, 15.68) | 16.63 (15.08, 18.25) | 19.73 (17.42, 22.16) | — | — |

Data Source: MarketScan Commercial Claims and Encounters and Medicare Supplemental database, 2006–2014. TBI: Traumatic Brain Injury. —: cumulative incidences are not available.

**Table 4**

Descriptive characteristics of Traumatic Brain Injury patients by selected AED* use from time of injury to time of epilepsy diagnosis or end of follow-up.

| | No AED (1,915,605) (93.00%) n (%) | CBZ (1369) (0.07%) n (%) | CLZ (19,130) (0.93%) n (%) | VPA (9694) (0.47%) n (%) | GABA (39,734) (1.93%) n (%) | LAM (5320) (0.26%) n (%) | LEV (8641) (0.42%) n (%) | OXC (2293) (0.11%) n (%) | PHT (4485) (0.22%) n (%) | PRE (6876) (0.33%) n (%) | TOP (12,422) (0.60%) n (%) | ACZ (2368) (0.11%) n (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age Groups** | | | | | | | | | | | | |
| 0–4 yrs | 342,581 (99.3) | 49 (0.0) | 99 (0.0) | 341 (0.1) | 176 (0.1) | 128 (0.0) | 388 (0.1) | 307 (0.1) | 102 (0.0) | 3 (0.0) | 242 (0.1) | 35 (0.0) |
| 5–14 yrs | 458,101 (96.9) | 205 (0.0) | 1157 (0.2) | 1913 (0.4) | 1458 (0.3) | 1401 (0.3) | 608 (0.1) | 973 (0.2) | 277 (0.1) | 102 (0.0) | 3171 (0.7) | 282 (0.1) |
| 15–24 yrs | 349,482 (93.7) | 278 (0.1) | 4040 (1.1) | 1860 (0.5) | 3624 (1.0) | 1797 (0.5) | 1079 (0.3) | 494 (0.1) | 684 (0.2) | 404 (0.1) | 3451 (0.9) | 349 (0.1) |
| 25–44 yrs | 226,437 (88.1) | 270 (0.1) | 5233 (2.0) | 1091 (0.4) | 7735 (3.0) | 961 (0.4) | 1071 (0.4) | 200 (0.1) | 711 (0.3) | 1342 (0.5) | 3239 (1.3) | 347 (0.1) |
| 45–64 yrs | 271,282 (87.2) | 319 (0.1) | 5015 (1.6) | 1057 (0.3) | 14,031 (4.5) | 770 (0.2) | 2535 (0.8) | 159 (0.1) | 1402 (0.5) | 2951 (0.9) | 1982 (0.6) | 655 (0.2) |
| 65–74 yrs | 75,955 (86.4) | 79 (0.1) | 1252 (1.4) | 563 (0.6) | 4681 (5.3) | 112 (0.1) | 1014 (1.2) | 47 (0.1) | 497 (0.6) | 828 (0.9) | 191 (0.2) | 285 (0.3) |
| 75+ yrs | 191,767 (89.9) | 169 (0.1) | 2334 (1.1) | 2869 (1.3) | 8029 (3.8) | 151 (0.1) | 1946 (0.9) | 113 (0.1) | 812 (0.4) | 1246 (0.6) | 146 (0.1) | 415 (0.2) |
| **Sex** | | | | | | | | | | | | |
| Male | 1,035,543 (94.4) | 732 (0.1) | 7512 (0.7) | 5786 (0.5) | 16,239 (1.5) | 2274 (0.2) | 5046 (0.5) | 1401 (0.1) | 2916 (0.3) | 2716 (0.2) | 3446 (0.3) | 1139 (0.1) |
| Female | 880,062 (91.4) | 637 (0.1) | 11,618 (1.2) | 3908 (0.4) | 23,495 (2.4) | 3046 (0.3) | 3595 (0.4) | 892 (0.1) | 1569 (0.2) | 4160 (0.4) | 8976 (0.9) | 1229 (0.1) |
| **Early Seizures** | | | | | | | | | | | | |
| No | 1,910,343 (93.2) | 1277 (0.1) | 18,978 (0.9) | 9442 (0.5) | 39,549 (1.9) | 5160 (0.3) | 6771 (0.3) | 2141 (0.1) | 3723 (0.2) | 6838 (0.3) | 12,245 (0.6) | 2360 (0.1) |
| Yes | 5262 (47.2) | 92 (0.8) | 152 (1.4) | 252 (2.3) | 185 (1.7) | 160 (1.4) | 1870 (16.8) | 152 (1.4) | 762 (6.8) | 38 (0.3) | 177 (1.6) | 8 (0.1) |
| **PTE** | | | | | | | | | | | | |
| No | 1,893,125 (93.3) | 1197 (0.1) | 18,480 (0.9) | 9001 (0.4) | 38,756 (1.9) | 5062 (0.2) | 6607 (0.3) | 2128 (0.1) | 3554 (0.2) | 6657 (0.3) | 11,906 (0.6) | 2340 (0.1) |
| Yes | 22,480 (71.3) | 172 (0.5) | 650 (2.1) | 693 (2.2) | 978 (3.1) | 258 (0.8) | 2034 (6.5) | 165 (0.5) | 931 (3.0) | 219 (0.7) | 516 (1.6) | 28 (0.1) |
| **Severity of TBI** | | | | | | | | | | | | |
| Level I | 1,712,605 (93.7) | 1081 (0.1) | 16,716 (0.9) | 7962 (0.4) | 34,022 (1.9) | 4658 (0.3) | 3064 (0.2) | 1972 (0.1) | 1130 (0.1) | 5738 (0.3) | 11,002 (0.6) | 2042 (0.1) |
| Level II | 3444 (90.8) | 5 (0.1) | 54 (1.4) | 21 (0.6) | 96 (2.5) | 10 (0.3) | 19 (0.5) | 4 (0.1) | 4 (0.1) | 24 (0.6) | 23 (0.6) | 2 (0.1) |
| Level III | 194,758 (87.5) | 260 (0.1) | 2295 (1.0) | 1624 (0.7) | 5437 (2.4) | 630 (0.3) | 5304 (2.4) | 306 (0.1) | 3200 (1.4) | 1080 (0.5) | 1361 (0.6) | 316 (0.1) |
| Level IV | 1621 (79.5) | 6 (0.3) | 23 (1.1) | 25 (1.2) | 67 (3.3) | 11 (0.5) | 90 (4.4) | 2 (0.1) | 69 (3.4) | 9 (0.4) | 14 (0.7) | 1 (0.0) |
| Level V | 3177 (80.7) | 17 (0.4) | 42 (1.1) | 62 (1.6) | 112 (2.8) | 11 (0.3) | 164 (4.2) | 9 (0.2) | 82 (2.1) | 25 (0.6) | 22 (0.6) | 7 (0.2) |
| **AED days** | | | | | | | | | | | | |
| 0 days | 1,915,605 (100.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 1–7 days | 0 (0.0) | 54 (0.9) | 820 (13.3) | 167 (2.7) | 563 (9.1) | 37 (0.6) | 1781 (28.9) | 28 (0.5) | 1467 (23.8) | 198 (3.2) | 103 (1.7) | 804 (13.0) |

| | No AED (1,915,605) (93.00%) n (%) | CBZ (1369) (0.07%) n (%) | CLZ (19,130) (0.93%) n (%) | VPA (9694) (0.47%) n (%) | GABA (39,734) (1.93%) n (%) | LAM (5320) (0.26%) n (%) | LEV (8641) (0.42%) n (%) | OXC (2293) (0.11%) n (%) | PHT (4485) (0.22%) n (%) | PRE (6876) (0.33%) n (%) | TOP (12,422) (0.60%) n (%) | ACZ (2368) (0.11%) n (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8–30 days | 0 (0.0) | 553 (1.4) | 7332 (17.9) | 2684 (6.6) | 15,051 (36.8) | 1278 (3.1) | 2649 (6.5) | 639 (1.6) | 1448 (3.5) | 2659 (6.5) | 4730 (11.6) | 1076 (2.6) |
| 31–90 days | 0 (0.0) | 305 (1.0) | 4233 (13.4) | 2276 (7.2) | 9339 (29.5) | 1140 (3.6) | 1729 (5.5) | 566 (1.8) | 794 (2.5) | 1514 (4.8) | 3234 (10.2) | 243 (0.8) |
| 91–180 days | 0 (0.0) | 160 (0.8) | 2381 (11.9) | 1492 (7.4) | 5114 (25.5) | 813 (4.1) | 968 (4.8) | 337 (1.7) | 340 (1.7) | 861 (4.3) | 1684 (8.4) | 100 (0.5) |
| 181–365 days | 0 (0.0) | 132 (0.7) | 2118 (11.1) | 1461 (7.6) | 4360 (22.8) | 888 (4.6) | 742 (3.9) | 302 (1.6) | 218 (1.1) | 785 (4.1) | 1418 (7.4) | 76 (0.4) |
| > 1 year | 0 (0.0) | 165 (0.6) | 2246 (8.5) | 1614 (6.1) | 5307 (20.1) | 1164 (4.4) | 772 (2.9) | 421 (1.6) | 218 (0.8) | 859 (3.3) | 1253 (4.8) | 69 (0.3) |

Data Source: MarketScan Commercial Claims and Encounters and Medicare Supplemental databases, 2006–2014. ACZ: Acetazolamide, AED: Antiepileptic Drug.

CBZ: Carbamazepine, TOP: Topiramate.

CLZ: Clonazepam, GABA: Gabapentin.

LAM: Lamotrigine, LEV: Levetiracetam.

PRE: Pregabalin, OXC: Oxcarbazepine.

TBI: Traumatic Brain Injury, PHT: Phenytoin.

VPA: Divalproex Sodium.

*Multiple AED and other AED use are not included in the table due to the space limit.

## Appendix A.

ICD-9-CM Classification Criteria of Intracranial Injury Documentation

| | 1 st 3 digits | 4th digit | 5th digit |
|---|---|---|---|
| **0 = Not documented** | If 800, 801, 803, or 804 | 0 or 5 | (any value or missing) |
| | If 850 | (any value) | (any value) |
| | If 959 | 0 | 1 |
| **1 = Documented** | If 800, 801, 803, or 804 | 1,2,3,4,6,7,8, or 9 | (any value or missing) |
| | If 851 – 854 | (any value or missing) | (any value or missing) |

## Appendix B.

ICD-9-CM Classification Criteria of Loss of Consciousness Duration (LOC)

| LOC | 1 st 3 digits | 4th digit | 5th digit |
|---|---|---|---|
| **0 = Unspecified** | If 800, 801, 803, or 804 | (any value or missing) | 0,6,9, or missing |
| | If 850 | 5, 9, or missing | N/A |
| | If 851–854 | (any value or missing) | 0,6,9, or missing |
| | If 959 | 0 | 1 |
| **1 = < 1 h** | If 800, 801, 803, or 804 | (any value) | 1 or 2 |
| | If 850 | 0 or 1 | N/A |
| **2 = 1–24 h** | If 851–854 | (any value) | 1 or 2 |
| | If 800, 801, 803, or 804 | (any value) | 3 |
| | If 850 | 2 | N/A |
| | If 851–854 | (any value) | 3 |
| **3 = > 24 h** | If 800, 801, 803, or 804 | (any value) | 4 |
| | If 850 | 3 or 4 | N/A |
| | If 851 – 854 | (any value) | 4 |
| **4 = > 24 h, persisting** | If 800, 801, 803, or 804 | (any value) | 5 |
| | If 850 | 3 or 4 | N/A |
| | If 851–854 | (any value) | 5 |