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Epidemiology of Post-traumatic Epilepsy and Its Risk Factors: An Analysis of U.S. Health Insurance Claims Data, 2006-2012

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Abstract

Epidemiology of Post-traumatic Epilepsy and Its Risk Factors: An Analysis of U.S. Health Insurance Claims Data, 2006-2012

By Xinyao G de Grauw

BACKGROUND: About 1.7 million people experience a medically attended traumatic brain injury (TBI) each year in the United States. The occurrence of early seizures (wthin seven days after head injury) is a recognized complication. Chronic post-traumatic epilepsy (PTE) is a disabling life-long outcome of TBI. The purpose of this study is to examine the incidence of PTE and early seizure; the probability of developing PTE within 9 years after TBI, the risk factors associated with PTE, and the prevalence and duration of anti-epileptic drugs (AEDs) use among individuals with PTE.

METHODS: Using the MarketScan Commercial Claims and Encounters and Medicare Supplemental (CC&M) data set, we examined new TBI patients between 2006 and 2012. We examined the incidence of early seizure and the cumulative incidence of PTE among TBI patients. We examined the probability of developing PTE within nine years among TBI patients with risk factors (age, gender, TBI severity, early seizure, and AED use). We conducted univariate and multivariable survival analysis to obtain estimates of crude and adjusted hazard ratios (cHRs, aHRs) of PTE and 95% confidence intervals by constructing Cox proportional hazard model among TBI cases. We estimated the prevalence and durations of AE use among TBI patients.

RESULTS: The annual incidence of early seizure stayed at 0.5%. A total of 8,704 individuals with TBI experienced early seizures. The cumulative incidence of PTE increased with the severity. Most patients with TBI (92.4%) were not prescribed any AED. Of those who received AEDs, about 97% stopped their use within 90 days. Gender was not associated with PTE. The risk of PTE significantly increased with age and TBI severity, and decreased with the duration of AED use ($p<0.05$). The risk of PTE for individuals with early seizures was 18-times higher than those without early seizures (cHR=18.1; 95% CI: 17.3, 18.9). The probability of developing PTE among individuals with early seizures on clonazepam or gabapentin was significantly lower than that for those without AED. Among age 15-45 year olds, aHR for clonazepam was o.48 and for gabapentin was 0.29 ($p<0.05$). Among age 45 and older, aHR for clonazepam was 0.33 and for gabapentin was 0.26 ($p<0.05$). The probability of developing PTE was significantly lower among those without early seizure on acetazolamide compared to those who did not use AED (aHR: 0.45, $p<0.05$).

CONCLUSIONS: We found that nearly 1% of individuals with TBI developed PTE over one year and more than 10% developed PTE over three years. Most of the individuals did not receive AED after TBI. Most of individuals who received a prescription stopped their AED use within 90 days. Clonazepam and gabapentin appeared

to prevent PTE in the individuals with early seizures. There was no evidence suggesting AEDs helped to prevent PTE in the individuals without early seizure, with possible exception of acetazolamide. With the possible exception of clonazepam, gabapentin and acetazolamide, this analysis provides no evidence that prophylactic AED use is effective in decreasing the risk of PTE. However, further studies may be needed to test the efficacy of acetazolamide in preventing PTE.

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TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION

Background of the Problem:

The United States Centers for Disease Control and Prevention (CDC) defines traumatic brain injury (TBI) as "an occurrence of injury to the head (arising from blunt or penetrating trauma or from acceleration/deceleration forces) that is associated with any of these symptoms attributable to the injury: decreased level of consciousness, amnesia, other neurologic or neuropsychological abnormalities, skull fracture, diagnosed intracranial lesions, or death" [1].

About 1.7 million people visited emergency departments because of TBI each year in the US[2], with additionally 200,000 treated in hospital outpatient departments or physicians' offices [3]. According to the National Hospital Discharge Survey, overall the incidence of TBI is between 180 and 250 per 100,000 population per year in US [4]. When stratified by age, children aged less than 5 years have the highest incidence of TBI treated in hospital emergency departments [4, 5]. The median estimate of annual incidence for children and youths is 691 TBI per 100,000 population [5].

In epidemiologic studies, the severity of TBI is usually categorized as mild, moderate, or severe [6]. Severity classifications may be based on:

- depth of coma when first medically evaluated, e.g., the Glasgow coma scale (GCS) [7],
- duration of loss of consciousness (LOC), or posttraumatic amnesia (PTA), and
- presence, nature, and extent of traumatic craniocerebral lesions [6].

The International Classification of Diseases, 9th Revision, Clinical Modification codes TBI severity information regarding: (a) duration of LOC (none, <1 hour, ≥1 hour but <24 hours, and ≥24 hours), and (b) the presence and nature of traumatic craniocerebral lesions (e.g., skull fracture, intracranial hemorrhage or hematoma, and cerebral lacerations, contusions, or edema). The encoded information allows conversion to three or more categories of severity suitable for epidemiologic analyses.

The conceptual definition of epilepsy by the International League Against Epilepsy in 2005 is "a disorder characterized by an enduring pre-disposition to generate epileptic seizures and by neurobiological, cognitive, psychological and social consequences of this condition. The definition requires the occurrence of at least one epileptic seizure" [8]. An epileptic seizure is defined as " a transient occurrence of signs and /or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" [8]. The usual operational definition identifies epilepsy after two or more unprovoked seizures occurring at least 24 hours apart [9].

The latency of seizure occurrence is commonly categorized according to three intervals. Immediate seizures occur less than 24 hours after TBI, and early seizures occur less than one week after TBI, arising from the acute pathophysiologic changes in cerebral function immediately following TBI or in the acute period after TBI, respectively [10]. Late seizures occur more than a week after TBI, and if recurrent, constitute the diagnosis of PTE [11]. About 90% of seizures happening within the first four weeks after TBI will happen in the first week [10].

The occurrence of early seizures is a recognized complication of TBI, and PTE is one of the major long-term outcomes of TBI [10]. The reported probability of developing

epilepsy after TBI varies considerably [11-13]. In a study identifying 5984 episodes of TBI in Olmsted County, Minnesota from 1935 to 1984, the probability of PTE ranges 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 [12]. Other estimates of the incidence of epilepsy after TBI among civilian populations range from 2.1% to 16.3% for early seizures and 1.9% to 25.3% for PTE [11]. The cumulative incidence of epilepsy after severe penetrating TBI among military veterans is as high as 53% [13]. There has been no study of PTE representing the entire population of the US.

Risk factors of PTE include chronic alcoholism, age of 65 years or older, penetrating injuries, intracranial hemorrhage, severity of injury, posttraumatic amnesia or loss of consciousness for more than one day, focal neurologic deficits, depressed skull fractures, cerebral contusions, and retained bone and metal fragments [12, 14].

An important goal in the acute and long-term management of TBI is the prevention of PTE. Several randomized clinic trials have shown the effectiveness of anti-epileptic drugs (AEDs) in the management of early seizures after TBI [15]. Prophylactic anti-epileptics are effective in reducing early seizures after the head injury [16, 17]. 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 [15, 18].

Goal of the study:

The goal of our study was to describe the epidemiologic characteristics of PTE in a representative sample of US population, the incidence of early seizures and PTE, and the association between AED use and PTE. We used data from the Truven Health

Analytics Inc. MarketScan Commercial Claims and Encounters and Medicare Supplemental database (CC&M) from across the United States (2006-2012) to examine our study questions.

Research Questions:

- What is the incidence of early seizures and PTE after TBI?
- What is the prevalence and duration of AED use?
- What is probability of developing epilepsy within 9 years after TBI?
- If AED use can prevent PTE after TBI?

Importance of the study:

To date the incidence of PTE and early seizures, the prevalence and duration of AED use and the association between PTE and the risk factors have not been addressed in published epidemiological studies. Although the use of AEDs in individuals with PTE is standard, the important question of effectiveness of using AEDs prophylactically after TBI to prevent the development of PTE is unanswered. There is a need to better understand the extent of early use of AEDs following TBI and the effect of their early use on the occurrence of PTE in general populations. We expect our study to contribute to the understanding of the incidence of PTE and the prevalence of AED use, and of the differences in the probability of developing epilepsy after TBI in relation to the risk factors including age, gender, TBI severity and AED use. Findings from this study will help to better understand the epidemiologic characteristics of PTE in a more broadly representative and statistically robust sample of the spectrum of epilepsy than

community-based studies or clinic-based studies and the efficacy, if any, of AEDs in epilepsy prevention. Our goal is to help improve TBI management to prevent epilepsy.

CHAPTER 2: LITERATURE REVIEW

Introduction:

This literature review will focus on: 1) the occurrence of TBI in the United States; 2) the incidence and probability of early seizure and PTE after TBI in the United States; 3) known risk factors of PTE; 4) prevention of PTE by using AEDs among TBI.

Occurrence of TBI:

TBI is considered a " silent epidemic" because of a general lack of awareness of its magnitude in society [19]. The blue book of traumatic brain injury from CDC published in 2010 reports that an estimated 1.7 million people sustain a TBI annually, among which 52,000 die, 275,000 are hospitalized and 1,365 million (nearly 80%) are treated and released from an emergency department [2]. A third of injury-related death in the United States is TBI-related [2]. The most likely ages to sustain a TBI include 0-4 years, 15-19 years and 65+ years [2]. Every year, nearly 473,000 children aged 0-14 years visit emergency departments because of TBI [2]. The highest rates of TBI-related hospitalization and death are among people age 75 years and older [2]. TBI rates are higher in males than in females in all age groups [2]. The highest rates for TBI-related emergency department visits, hospitalization, and death combined are among 0-4 years old boys [2]. The leading cause of TBI is falls, which mostly happen among children 0-4 years and adults 75 years and older [2]. Nearly 522,000 TBI-related emergency department visits and 62,000 hospitalizations are caused by falls [2]. The leading cause of TBI-related death is motor vehicle traffic injury, with highest rates among 20-24 year olds [2]. The proportion of TBI-related emergency department visits and hospitalizations

increased between 2002 and 2006 (14.4%, 19.5%, respectively) [2]. Fall-related TBI seen in emergency departments increased 62% among 14 year olds and younger, and 46% among 65 year olds and older between 2002 and 2006 [2].

A study using the Nationwide Emergency Department Sample (NEDS) database shows that between 2006 and 2010, emergency department visits for TBI increased by 29.1% [20]. By 2010, there were an estimated 2,544,087 emergency department visits for TBI [20]. TBI rates increased most in children younger than 3 years and adults older than 60 years [20]. Another study using the Nationwide Inpatient Sample (NIS) shows the leading cause of adolescent TBI was motor vehicle occupant accidents [21].

Incidence and probability of early seizure and PTE after TBI:

The estimated incidence of early seizures after TBI is between 2.6% and 16.3% depending on study populations (veterans, rehabilitation centers, or hospitalized) [22]. Early seizures predispose to developing PTE, and are thought of as an epiphenomenon and result of an acute injury [22]. The pathophysiologic mechanisms leading to early seizures are not clearly understood, and multiple factors are thought to play a role, including interruption of the blood-brain barrier, presence of hemorrhage, and injury-related neuronal excitotoxicity [22].

The overall incidence of PTE in hospitalized populations, comprising a range of TBI severity mainly from closed head injuries, is about 3-5% [12, 23]. Veterans with penetrating head injury suffer the highest incidence of PTE, ranging from a 5-year cumulative incidence of 28% to a 15-year cumulative incidence of 53% [13, 24-26]. In the series of non-missile combat injuries, that incidence reaches 12-24% [23]. More than

90% of PTE happened within the first 10 years after TBI in a study of Vietnam veterans[13]. A study of Afghanistan and Iraq veterans shows the prevalence of PTE is 6.1 per 1,000, with the odds to develop PTE of 18.8 compared to the veterans without TBI [27].

In about 6% of people with epilepsy in general populations, the condition is attributed to previous TBI [22, 28]. The five-year cumulative probability of developing epilepsy was 0.7% following mild TBI, 1.2 % with moderate TBI, and 10% with severe TBI [12]. Annegers reported that the 30-year cumulative incidence was 2.1% with mild TBI, 4.2% with moderate TBI and 16.7% with severe TBI [12]. Compared to the uninjured population, the risk of PTE was increased 1.5 times after mild TBI, 2.9 times after moderate TBI and 17.0 times after severe TBI [12].

Known risk factors of PTE:

TBI is one of the identified acquired causes of epilepsy. Added risk factors of PTE include chronic alcoholism, age of 65 years or older, penetrating injuries, intracranial hemorrhage, severity of injury, posttraumatic amnesia or loss of consciousness for more than one day, focal neurologic deficits, depressed skull fractures, cerebral contusions, and retained bone and metal fragments [12, 14].

TBI is a multi-faceted disorder reflected in several potentially epileptogenic alterations in the brain. These include mechanical neuronal and vascular damage, parenchymal and subarachnoid hemorrhage, subsequent toxicity caused by iron-rich hemoglobin breakdown products, and energy disruption resulting in secondary injuries, including excitotoxicity, gliosis, and neuroinflammation [29]. It initiates cascades of molecular and cellular changes, resulting in several comorbidities, including

epileptogenesis (the process by which a normal brain becomes epileptic, i.e., a process whereby CNS tissue acquires the capability to generate the abnormal and spontaneous electrical activity that underlies seizures) [30, 31] and eventually PTE [32]. Brain injury, intracerebral hematoma formation, and hemorrhagic cerebral infarction cause extravasation of the intravascular contents, red blood cell (RBC) hemolysis, hemosiderin deposition within the neuropil and an increased incidence of epilepsy [33]. David Cantu *et al*. using controlled cortical impact in a rat model of TBI, found that specific cortical neuronal microcircuits may initiate and facilitate the spread of epileptiform activity following TBI [34]. They suggest increased glutamatergic signaling due to loss of GABAergic control may provide a mechanism by which TBI can give a rise to PTE [34]. PTE is the one of the most intractable consequences of TBI [24]. TBI may account for 10-20% of symptomatic epilepsy [32]. CT scan findings and neurosurgical procedures performed were the most useful findings in defining if individuals at high risk for PTE [14].

Prevention of PTE by using AEDs after TBI

Prophylaxis against early seizures is a part of standard therapy in the acute phase of moderate or severe TBIs, which are associated with acute increase in intra-cranial pressure [22, 35]. Based on the guidelines from the Brain Trauma Foundation and the American Academic of Neurology, patients with moderate or severe TBI are typically placed on an AED right after the initial trauma, most commonly phenytoin (PHT), recently also levetiracetam (LEV), in order to prevent early seizures [22]. If seizures are not present in the first 7 days after TBI, the AED is usually weaned, with an expectation that seizures in most instances will not occur in the future[22]. Information on the

efficacy of using AEDs in the first 7 days after TBI in preventing the later development of PTE is sparse.

Reports are conflicting in regards of the efficacy of using AEDs in patients with TBI to prevent the development of PTE. PHT has been most frequently tested for an AED effect [36]. The first study was done in the 1940s [37], which reported that among head-injured World War II veterans, 4% of those who received 200 mg of PHT daily and 38% of those who served as untreated controls developed PTE after the first four years of the study [38]. In 1979, a retrospective study showed that among 62 patients with severe TBI, 10% of the 50 treated with PHT and 50% of the 12 without PHT developed PTE, with a maximum follow-up period of six years[38]. But in 1983, randomized double-blind placebo-controlled studies showed that the early administration of PHT did not lessen the occurrence of early seizures [39], nor late seizures [40] after TBI. Another randomized double-blind placebo-controlled study with the largest sample size (408 patients) showed that there was a substantial effect of PHT on early seizures and lack of a positive effect on late seizures [17]. Then Temkin *et al.* reported a similar conclusion after a meta-analysis of all the trials [41]. Willmore *et al.* found that PHT treatment did not affect lipid peroxidation in rat with brain injury. They suggested treatment to prevent peroxidation may be more effective for epilepsy prophylaxis than using PHT, if PTE developed because of red blood cell extravasation, hemolysis, parenchymal deposition of heme compounds, and initiation of lipid peroxidation [33].

In a 1983 study of 139 patients with severe TBI, the investigators started prophylaxis immediately after the accident and continued it for one and half to two years [42]. The results showed that carbamazepine (CBZ) reduced early seizures but did not

affect the incidence of PTE even if seizures started during the treatment period [43]. A randomized, double-blind, single-center, parallel-group clinic trial on 379 patients with TBI was conducted in three groups: PHT for 1 week, or valproic acid (VPA) for 1 month, or VPA for 6-months. All the cases were followed up to 2 years [18]. The results showed VPA did not offer any benefit for prevention of early or late seizures [18]. There was a trend toward a higher mortality rate among VPA-treated patients [18]. Formisano *et al.* found that there is no significant difference of development of PTE between TBI patients with and without prophylactic treatment [35].

However, there are theoretical grounds for the use of AEDs to prevent PTE [22]. Possibilities of effective AEDs include lamotrigine and topiramate, which exert activity against AMPA receptors [22, 44]. Topiramate in the setting of therapeutic hypothermia shows neuroprotection [45]. In animal models, talampanel and parampanel, AMPA antagonists, and lacosamide show antiepileptogenic effect, and talampanel shows neuroprotective activity [46, 47]. Another AMPA-receptor antagonist with similar action to parampanel, NS 1209 can decrease hyperexcitability by targeting glutamate activity at post-synaptic AMPA receptors and it also shows neuro-protection and effectiveness in epilepsy [44].

Conclusion

This literature review shows insufficient epidemiological description of early seizures and PTE occurrence in general populations. Reports are conflicting in regards of the efficacy of using AEDs in patients with TBI to prevent the development of PTE. The highest quality evidence (from human randomized clinic trials) fails to demonstrate any benefit of AEDs studied so far (PHT, CBZ and VPA).

CHAPTER 3: METHODS

Data Source:

We conducted a retrospective study using data from Truven Health Analytics Inc. MarketScan Commercial Claims and Encounters and Medicare Supplemental database (CC&M) from across the United States. 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. 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 (types of private plans), 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, and Emory Institutional Review Board exemption was obtained.

Study population

We included individuals enrolled in the CC&M Databases between January 2004 and December 2014. Data in 2005 and 2006 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. The study population included patients enrolled

between January 2006 and December 2012. Eligibility for inclusion in this study was limited to: (a) patients aged ≥2 years who were continuously 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.[6]

Consistent with recommendations of Helmers, *et al.*[48], 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.

We identified 1,851,368 total TBI patients among whom there were 41,357 (2.23%) pre-existing epilepsy patients and an additional 176,374 (9.53%) patients without epilepsy diagnoses 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.

Outcome – PTE:

The outcome of primary interest was from 7 days after the onset date of TBI to the occurrence of epilepsy. Cases of PTE were identified among the TBI cases who met the case definition of epilepsy beginning 7 days after TBI. Occurrences of early seizures within 7 days were considered acute provoked seizures and not indicators of epilepsy.

Use of AEDs following TBI:

We categorized 28 AEDs included in this study into 13 groups. Because the numbers of the patients on those AEDs were less than 500, we combined ethosuximide, ethotoin, felbamate, fosphenytoin sodium, lacosamide, mephobarbital, methsuximide, phenobarbital, primidone, tiagabine hydrochloride, trimethadione, vigabatrin, clobazam, and zonisamide into one group. The multiple drugs included the patients on more than one AED.

Co-variables:

We examined following co-variables in our analysis:

- demographic variables: age in years (0-4, 5-14, 15-24, 25-44, 45-64, 65-74, 75+), and gender (male, female);
- TBI severity: categorized into five groups we adapted using published principles [6]: loss of consciousness duration and intracranial lesion documentation, ranging from very mild TBI (severity =1), to very severe TBI (severity =5) The ICD-9-CM codes to identify the TBI severity are listed in **Table 1, Appendix A and B**;
- duration of AED prescription before diagnosed as PTE in days (0-7 days, 8-30 days, 31-90 days, 91-180 days, 181-365 days, and 365+ days);

- previous neurologic diseases as independent epilepsy risk factors: stroke, cerebral palsy, intellectual disability, brain tumor, central neuron system infection, cardiovascular disease, and alcohol, substance abuse (yes, no) (**Appendix C)**.

Statistical Analysis

Aim 1: We calculated the proportion of early seizures and cumulative incidence of PTE during the first three years following TBI. Frequencies and percentages were tabulated. The cumulative incidence of PTE was calculated based on life tables to adjusted for participants who did not complete three years follow up[49, 50].

Aim 2: we calculated the prevalence of AED among different age, gender, PTE, early seizures, severity of TBI duration of AED using Chi-square test.

Aim 3: We examined the probability of developing PTE with risk factors (age, gender, TBI severity, early seizure) using survival analysis.

Aim 4: We examined the probability of PTE prevention by AEDs use 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. Since there were interactions between early seizure and AED prescription, early seizure and TBI severity, a Cox proportional hazard model (PROC PHREG) was constructed to first obtain estimates of cHR and 95% confidence interval of PTE for early seizures. Then a Cox proportional hazard model stratified by acute seizure was constructed to obtain estimates of cHR, aHR and 95% confidence intervals for age, gender, TBI severity, AED

prescription and the duration of AED prescription. The proportional hazards assumption was verified using Shoenfeld residuals.

The Kaplan Meier method (PROC LIFETEST) was used to draw unadjusted survival curves among TBI patients stratified by early seizures. Logrank tests were carried out to determine whether, in unadjusted analyses, there were statistically significantly differences between the two survival curves.

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 Institutional Review Board of Emory University.

CHAPTER 4: RESULTS

Among all 1,608,539 TBI patients, a total of 8,704 (0.54%, CI: 0.53%, 0.55%) TBI patients experienced early seizures. The proportion of early seizure was about 5% every year, with few change from 2006 to 2012 **(Table 2).** Among all 22,046 patients who developed PTE, 2,728 (12.37%, CI: 11.37%, 12.82%) had early seizures. In contrast, among all 1,580,517 patients who did not develop PTE, 5,796 (0.37%, CI: 0.36%, 0.38%) had early seizures. The cumulative incidence of PTE increased from 0.59% (severity level =1) and 9.26% (severity level=5) at one year, to 0.81% (severity level =1) and 13.13% (severity level=5) at two years, and to 0.95% (severity level=1) to 14.03% (severity level=5) at three years of follow-up **(Table 3).**

Most (92.4%) TBI patients were not prescribed any AED after discharge from hospital **(Table 4).** A small proportion were prescribed a single AED (6.17%) or multiple AEDs (1.45%) **(Table 4).** Clonazepam (CLZ), gabapentin (GABA), lacosamide (LAM), pregabalin (PRE), and topiramate (TOP) were used more often in females than in males **(Table 4).** Divalproex sodium (VPA), levetiracetam (LEV), oxcarbazepine (OXC), PHT were used more often in males than in females **(Table 4).** Among TBI patients with early seizures, the most commonly used AED was LEV (1536 TBI patients), followed by PHT (602 TBI patients) **(Table 5).** Among individuals without early seizures, the most commonly used AED was GABA (33,527 patients), followed by CLZ (14,947) and TOP (9,320) **(Table 5)**.

Among all the TBI individuals without AED prescription, 89% of those were with mild TBI, and 0.2% were with severe TBI **(Table 4).** The most often used AED was GABA among patients with mild TBI, and LEV among patients with severe TBI **(Table**

4). Five percent (5%) individuals with severe TBI were on multiple AEDs, and only 1% individuals with mild TBI on multiple AEDs **(Table 4).**

Seventy percent (70%) of TBI individuals with early seizures, 90% of TBI individuals with severe TBI and 89% of TBI individuals with PTE stopped using AED after 90 days of TBI **(Table 6).** 15% of TBI individuals with early seizures, 3% of TBI individuals with severe TBI, 3.5% of TBI individuals with PTE were on AED more than one year **(Table 6).**

The risk of PTE for individuals with early seizures was 18 times higher compared to those without early seizures (cHR=18.1, 95%CI: 17.3, 18.9). The unadjusted Kaplan Meier survival curves stratified by early seizure occurrence show that TBI patients with early seizures were associated with subsequent diagnosis of epilepsy. There were significant differences among the survival curves for TBI patients with early seizure and for TBI patients without early seizure ($p<0.0001$) (**Figure 1**).

Among TBI patients with early seizures, there was no significant difference in hazard ratios of epilepsy between males and females **(Table 7).** Comparing PTE incidence among all older age groups with the youngest age group, yielded similar aHRs about 1.3, controlling for gender, severity of TBI, AED prescription, insurance plan type and comorbidity risk factors **(Table 7).** The hazard of epilepsy for severe TBI (level 5) was 50% (95% CI: 19%, 110%) higher than that for mild TBI (level 1) **(Table 7).** The hazard of epilepsy decreased significantly when the duration of AED use was longer than one year. The hazard of epilepsy for using AED more than a year was 82% lower than for no AED use (95% CI: 10%, 40%)**(Table 7)**.

Among TBI patients without early seizures, there was also no significant difference in hazard ratio of epilepsy between males and females **(Table 7).** The hazard of PTE increased with age. The hazard of epilepsy among individuals 65 years and older was 150% (95% CI: 130%, 270%) higher than that among individuals younger than 15 years **(Table 7).** The hazard of epilepsy increased significantly with increasing TBI severity ($p<0.0001$) **(Table 7).** Patients with severe TBI (level 5) had a hazard of epilepsy 7.5 times higher than patients with mild TBI (level 1) (95% CI: 6.7, 8.5) **(Table 7)**. The hazard of epilepsy decreased significantly when the duration of AED use was longer than one year. The hazard of epilepsy for using AED more than a year was 55% lower than for no AED use (95% CI: 21%, 74%)**(Table 7)**

Among TBI patients with early seizures, in all the age groups the hazards of PTE for using LEV were significantly higher than those not using AED **(Table 8A)** ($p<0.05$). Among individuals old than 45 years, the hazards of epilepsy for using CLZ or GABA appeared lower than those not using any AED (aHR[GABA]=0.3, 95% CI: 0.1, 0.5) **(Table 8A)**.

Among individuals without early seizures, in all age groups the hazards of PTE for individuals using AEDs, except ACZ, were significantly higher than for patients not using AEDs **(Table 8B)**. The highest aHR of epilepsy was in individuals using LEV: 20.2 (95% CI: 15.5, 26.5) for those aged 15 years younger, 11.4 (95% CI: 9.9, 13.2) for those aged 15-45 years, and 8.8 (95% CI: 8.2, 9.5) for those aged 45 years or older **(Table 8B)**. The risk of epilepsy among individuals older than 45 years using ACZ appeared lower than those without using AED (aHR=0.5, 95% CI: 0.3, 0.8) **(Table 8B).**

CHAPTER 5: DISCUSSION

The incidence of early seizures after TBI was 0.5% each year of the study, which is different from other studies. Previous studies have shown a higher incidence of early seizures ranging from 2.1% (Olmsted County, Minnesota, population-based) to 16.3% (TBI rehab center) [12, 14, 51, 52]. The differences are probably caused by variations in study designs, and study populations, e.g., TBI rehab centers have a more severely injured population. The study in Minnesota identified early seizures in the first week after TBI, or within a month if injuries had a protracted course [12]. The study in a TBI rehab center [52] did not describe how to define early seizures, and also the study population comprising predominantly severe or complicated TBIs. This study is the first and only report on early seizures (in one week) after TBI representing the privately insured population in U.S.

The cumulative incidence of PTE over three years ranged from 0.93% for mild TBI to 11.2% for severe TBI. Ferguson *et al.* reported the cumulative incidences of PTE during three years after discharge among a population-based sample of older adolescents and adults hospitalized with TBI in South Carolina were 4.4% for mild TBI, 7.6% for moderate TBI and 13.6% for severe TBI [53]. Annegers *et al.* reported that the incidence ratio of PTE among a population-based sample of all ages for inpatient, outpatient and emergency room visits with TBI in Olmsted County, Minnesota were 1.5 for mild TBI, 2.9 for moderate TBI and 17.0 for severe TBI [12, 53]. Cumulative incidences of PTE in our study were calculated without any stratification by age.

Based on the guidelines for the management of severe TBI fourth edition from the Brain Trauma Foundation and the American Association of Neurological Surgeons,

patients with severe TBI may be placed on an AED right after the initial trauma, in order to prevent early seizures [54]. It is surprising to see in this study that half of individuals with early seizures, 87% individuals with moderate TBI and 79% of individuals with severe TBI had no recorded AEDs use prior to the diagnosis of PTE. This may be because the risk of developing PTE was considered low from a clinical point of view. Also some may have received AEDs only while hospitalized, which is not recorded in the database. A survey of 127 neurosurgery clinics on antiepileptic prophylaxis in patient 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 [55]. Penetrating injuries, intracranial hemorrhages and electroencephalographic abnormalities were the most frequent reasons for the prophylaxis [55]. A study of 124 patients with TBI admitted for rehabilitation shows that 60% of high risk patients and 30% of the patients who did not belong to the high risk categories received prophylaxis [56].

The most interesting findings of this study are that compared to individuals who did not receive AED, those with early seizures who received CLZ or GABA and those without early seizure who received ACZ appeared less likely to develop epilepsy after TBI. The rest of AEDs showed no effect or appeared more likely to develop PTE, especially LEV, CBZ, OXC and PHT. Also, individuals who were on AED more than one year were less likely to develop PTE.

There are studies showing that PHT treatment groups had a higher rate of PTE than the placebo groups, with risk ratios greater than 1 [17, 18, 39, 57]. Temkin *et al.*

found that 21.5% of the PHT group and 15.7% of the placebo group developed PTE between day 8 and the end of year 2 [17]. Temkin *et al.* also reported that VPA shows no benefit over short-term PHT for prevention of early seizures and neither treatment prevents PTE; the rates of PTE did not differ among treatment groups followed up to 6 months [18]. A study of CBZ shows high rates of PTE in both treated and control groups [42].

LEV, which is non-enzyme-inducing, is a second generation AED currently approved by the FDA [58], with a different mechanism from that of classic AEDs and unrelated to known mechanisms of neurotransmission [59]. It diminishes the effects of negative allosteric modulators on the two main inhibitory ionotropic receptor systems: y-aminobutyric acid and glycine-gated currents [59]. Compared to PHT, LEV does not offer better benefit for early seizure prevention [60] or PTE prevention after TBI [61, 62]. LEV monotherapy in the first seven days following severe TBI is associated with an increased seizure tendency and increased epileptiform activity on electroencephalograms compared with PHT [61], which may explain that individuals on LEV were 10 time more likely to develop PTE than individuals on PHT or without AED showing in this study.

A recent review of 10 randomized clinical trials consisting of 2,326 participants found low-quality evidence that early treatment with PHT or CBZ compared with placebo or standard care reduced the risk of early seizures. There was no evidence to support a reduction in the risk of PTE. There was insufficient evidence to make any conclusions regarding the effectiveness or safety comparing PHT with LEV or VPA [63].

Studies in human and animals have shown that axonal injury is responsible for much of the morbidity and mortality associated with TBI. Diffuse axonal injury is one of

the most important types of brain damage that can occur as a result of closed head injury [64]. There are two stages in the development of axonal injury: one is shearing of axons and sealing of fragmented axonal membranes within 60 minutes, the other one is consequent axonal swelling and disconnection occurring at a minimum of 2 hour after injury [65].

The extent and timing of post-traumatic cerebral hemodynamic disturbances has significant impact on the monitoring and treatment of patients with TBI [66]. Cerebral blood flow (CBF) in the first few hours after TBI is often low, followed by a hyperemic phase that peaks at 24 hours [66, 67]. The increase of the ratio between local cerebral metabolic rate for glucose (LCMRglc) and local CBF, including local CBF reduction in white matter regions, has been strongly associated with the development of axonal injury[68].

ACZ is a selective inhibitor of carbonic anhydrase that can increase local CBF via local tissue acidosis[69]. Although it is not known why individuals on ACZ appeared less likely to develop epilepsy than those without AEDs, some possible reasons are suggested in the literature. For instance, CBZ and oxcarbazepine interact with adenosine receptors in the brain[70]. Adenosine has recently been identified as a possible anti-epileptogenic neurotransmitter[71]. Harris *et al.* found in rats that ACZ increased local CBF globally after brain injury, and did not affect brain LCMRglc, which therefore normalized the ratio between local metabolic rate for LCMRglc and local CBF[68]. It thus reduced early cerebrovascular dysfunction which has a beneficial effect of preventing ongoing axonal injury[68]. Hamidi *et al.* reported in a Sprague-Dawley rat experiment that blocking carbonic anhydrase activity by using ACZ disrupted the pattern

of epileptiform activity, and markedly reduced the duration of the ictal discharges[72]. Also ACZ decreased the interval of occurrence of ictal and interictal discharges, decreased the occurrence of ripples and fast ripples thought the duration of ictal discharges[72]. Thus, ACZ may offer benefit both in preventing axonal injury and reducing seizures.

Strengths:

Our definition of TBI and epilepsy was rigorous and consistent with recent international recommendations. The large number of TBI cases and PTE cases is statistically robust which we have shown provides a credible estimate of the incidence of early seizures, PTE and the association between AEDs and PTE, drawing from multiple sectors across the U.S. population. This study helps us to better understand the epidemiologic characteristics of PTE in a more broadly representative sample of the spectrum of epilepsy than community-based studies or clinic-based studies, and provides the largest numbers of any study in the United States. Our 10 years of data can provide a longitudinal view of the development of PTE following TBI and prophylaxis.

Limitations:

There are several limitations to our analysis. The dataset we used in this study is claim-based; thus miscoding, missing information, underreporting and misreporting of epilepsy may occur.

When we identified TBI patients, 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 [9, 73], 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. Since the annual total number of enrolled patients is different from 2006 to 2012 and the dataset contributed by over 150 large employers may have changed over the years, we did not perform a trend test.

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, these codes do not distinguish new-onset from long-established cases[9].

The claims data that we analyzed 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. Also a large proportion of children with epilepsy are insured through Medicaid[48]. Medicaid and uninsured groups were not included. All these factors may substantially reduce confidence in any extrapolation to findings for the U.S. population as a whole.

Public Health Implications and Conclusions:

The annual incidence of PTE is about 1% We identified age, early seizures and TBI severity as risk factors of PTE. The risk of developing PTE increases with advancing

age, early seizures or severe TBI, while this risk decreases among individuals with early seizures using AEDs longer than half of a year. Among TBI patients with early seizures, in individuals older than 45 years, using CLZ and GABA appears to decrease the risk of PTE. Among those without early seizures, using ACZ appears to decrease that risk.

By complementing more expensive traditional community-based epidemiologic studies, this study helps identify important health concerns and potential improvements in care of TBI for PTE prevention, to better inform best practices in prophylaxis of PTE, and to better understand what factors could contribute to the development of PTE. Such understanding will help address the needs of all stakeholders and inform policy decisions concerning TBI and PTE. These data have identified an apparent decreased risk of PTE with early ACZ use. Further studies are needed to test the epilepsy prevention efficacy of ACZ for PTE 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.

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Table 1. Traumatic Brain Injury severity definition

Traumatic Brain Injury	Definition
Severity =1	(Intracranial lesion undocumented) AND (LOC unspecified OR
Severity =2	(Intracranial lesion undocumented AND (LOC >= 1 hour)
Severity =3	(Intracranial lesion documented) AND (LOC unspecified or LOC
Severity =4	(Intracranial lesion documented) AND (LOC 1 to <24 hours)
Severity =5	(Intracranial lesion documented) AND (LOC >= 24 hours)

Table 2. Descriptive characteristic of Traumatic Brain Injury patients, 2006-2012

Total	**2006 n=17,832,783**	**2007 n=30,849,228**	**2008 n=36,932,820**	**2009 n=43,009,675**	**2010 n=48,796,212**	**2011 n=56,673,919**	**2012 n=57,193,893**
	TBI (79,175) col% (0.44%)	**TBI (145,596) col% (0.47%)**	**TBI (175,353) col% (0.47%)**	**TBI (260,977) col% (0.61%)**	**TBI (292,862) col% (0.60%)**	**TBI (323,727) col% (0.57%)**	**TBI (330,849) col% (0.56%)**
Age Group (yr)							
0-4	10,651 (13.5)	20,616 (14.2)	25,951 (14.8)	40,514 (15.5)	40,977 (14.0)	41,684 (12.9)	42,467 (12.8)
5-14	14,622 (18.5)	28,289 (19.4)	34,163 (19.5)	53,177 (20.4)	60,610 (20.7)	67,306 (20.8)	75,034 (22.7)
15-24	13,303 (16.8)	26,383 (18.1)	30,854 (17.6)	44,201 (16.9)	51,494 (17.6)	61,700 (19.1)	67,685 (20.5)
25-44	10,170 (12.8)	21,353 (14.7)	26,250 (15.0)	37,961 (14.5)	40,317 (13.8)	40,267 (12.4)	41,874 (12.7)
45-64	13,338 (16.8)	26,860 (18.4)	33,184 (18.9)	47,037 (18.0)	51,451 (17.6)	52,571 (16.2)	52,609 (15.9)
65-74	4,664 (5.9)	6,076 (4.2)	6,680 (3.8)	11,137 (4.3)	14,199 (4.8)	17,436 (5.4)	15,503 (4.7)
75+	12,427 (15.7)	16,019 (11.0)	18,271 (10.4)	26,950 (10.3)	33,814 (11.5)	42,763 (13.2)	35,677 (10.8)
Gender							
Male	42,006 (53.1)	78,671 (54.0)	94,041 (53.6)	135,609 (52.0)	154,258 (52.7)	169,078 (52.2)	174,927 (52.9)
Female	37,169 (46.9)	66,925 (46.0)	81,312 (46.4)	125,368 (48.0)	138,604 (47.3)	154,649 (47.8)	155,922 (47.1)
Early seizures							
Yes	410 (0.5)	915 (0.6)	969 (0.6)	1,416 (0.5)	1,678 (0.6)	1,715 (0.5)	1,601 (0.5)
No	78,765 (99.5)	144,681 (99.4)	174,384 (99.4)	259,561 (99.5)	291,184 (99.4)	322,012 (99.5)	329,248 (99.5)
CSE							
Yes	166 (0.2)	268 (0.2)	418 (0.2)	696 (0.3)	699 (0.2)	834 (0.3)	1,007 (0.3)
No	79,009 (99.8)	145,328 (99.8)	174,935 (99.8)	260,281 (99.7)	292,163 (99.8)	322,893 (99.7)	329,842 (99.7)
Infection							
Yes	132 (0.2)	226 (0.2)	321 (0.2)	513 (0.2)	574 (0.2)	821 (0.3)	863 (0.3)
No	79,043 (99.8)	145,370 (99.8)	175,032 (99.8)	260,464 (99.8)	292,288 (99.8)	322,906 (99.7)	329,986 (99.7)
Malignant							

Tumor							
Yes	107 (0.1)	215 (0.1)	243 (0.1)	330 (0.1)	361 (0.1)	448 (0.1)	472 (0.1)
	79,068	145,381	175,110	260,647	292,501	323,279	330,377
No	(99.9)	(99.9)	(99.9)	(99.9)	(99.9)	(99.9)	(99.9)
Other Tumor							
Yes	243 (0.3)	464 (0.3)	565 (0.3)	803 (0.3)	844 (0.3)	1,142 (0.4)	1,187 (0.4)
	78,932	145,132	174,788	260,174	292,018	322,585	329,662
No	(99.7)	(99.7)	(99.7)	(99.7)	(99.7)	(99.6)	(99.6)
Senile Dementias							
Yes	1,234 (1.6)	1,722 (1.2)	2,055 (1.2)	3,016 (1.2)	3,595 (1.2)	5,079 (1.6)	4,409 (1.3)
	77,941	143,874	173,298	257,961	289,267	318,648	326,440
No	(98.4)	(98.8)	(98.8)	(98.8)	(98.8)	(98.4)	(98.7)
Stroke or CVD							
Yes	4,413 (5.6)	6,558 (4.5)	8,128 (4.6)	11,312 (4.3)	13,005 (4.4)	17,643 (5.4)	17,788 (5.4)
	74,762	139,038	167,225	249,665	279,857	306,084	313,061
No	(94.4)	(95.5)	(95.4)	(95.7)	(95.6)	(94.6)	(94.6)
Other CSE							
Yes	18 (0.0)	29 (0.0)	51 (0.0)	71 (0.0)	77 (0.0)	88 (0.0)	118 (0.0)
	79,157	145,567	175,302	260,906	292,785	323,639	330,731
No	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)
CNS Degeneration							
Yes	2,416 (3.1)	3,683 (2.5)	4,779 (2.7)	7,246 (2.8)	8,392 (2.9)	11,250 (3.5)	11,910 (3.6)
	76,759	141,913	170,574	253,731	284,470	312,477	318,939
No	(96.9)	(97.5)	(97.3)	(97.2)	(97.1)	(96.5)	(96.4)
Other CNS Malignancy							
Yes	60 (0.1)	107 (0.1)	92 (0.1)	176 (0.1)	174 (0.1)	205 (0.1)	212 (0.1)
	79,115	145,489	175,261	260,801	292,688	323,522	330,637
No	(99.9)	(99.9)	(99.9)	(99.9)	(99.9)	(99.9)	(99.9)
MISC.							
Yes	4,067 (5.1)	6,346 (4.4)	8,023 (4.6)	12,322 (4.7)	14,552 (5.0)	19,887 (6.1)	20,054 (6.1)
	75,108	139,250	167,330	248,655	278,310	303,840	310,795
No	(94.9)	(95.6)	(95.4)	(95.3)	(95.0)	(93.9)	(93.9)
Other CVD							
Yes	4,216 (5.3)	6,230 (4.3)	7,731 (4.4)	11,183 (4.3)	12,814 (4.4)	17,692 (5.5)	18,521 (5.6)
	74,959	139,366	167,622	249,794	280,048	306,035	312,328
No	(94.7)	(95.7)	(95.6)	(95.7)	(95.6)	(94.5)	(94.4)

Data Source: MarketScan Commercial Claims and Encounters and Medicare Supplemental database, 2006-2012

CSE: Childhood Static Encephalopathy
CNS: Central Neuron System
PTE: Posttraumatic Epilepsy
CVD: Cerebrovascular Disease
MISC: Miscellaneous

Table 3. Cumulative incidence of Post-traumatic Epilepsy over one, two, and three years.

Severity of TBI	Over 1 year	Over 2 years	Over 3 years
	CumInc % (95% CI)	CumInc % (95% CI)	CumInc % (95% CI)
Level 1	0.59 (0.58%, 0.61)	0.81 (0.80, 0.83)	0.95 (0.93, 0.96)

Level 2	1.17 (0.86, 1.61)	1.66 (1.27, 2.17)	1.90 (1.48, 2.43)
Level 3	2.42 (2.35, 2.49)	3.01 (2.94, 3.10)	3.30 (3.21, 3.38)
Level 4	4.47 (3.60, 5.54)	5.91 (4.88, 7.16)	6.30 (5.22, 7.58)
Level 5	9.26 (8.27, 10.35)	13.13 (11.84, 14.53)	14.03 (12.69, 15.49)

TBI: traumatic brain injury
CumInc: cumulative incidence
PTE: post-traumatic epilepsy
CI: confidence interval

Table 4. Descriptive characteristics of Traumatic Brain Injury patients by AED use

AED	**No AED**	**ACZ**	**CBZ**	**CLZ**	**VPA**	**GABA**	**LAM**	**LEV**	**OXC**	**PHT**	**PRE**	**TOP**	**OD**	**MD**
n	**1,493,286**	**2,228**	**954**	**15,050**	**6,026**	**33,662**	**3,913**	**7,653**	**1,177**	**3,950**	**6,318**	**9,468**	**837**	**23,348**
(col %)	**(92.38)**	**(0.14)**	**(0.06)**	**(0.94)**	**(0.37)**	**(2.09)**	**(0.24)**	**(0.48)**	**(0.07)**	**(0.25)**	**(0.39)**	**(0.59)**	**(0.05)**	**(1.45)**
Age Groups*														
	222,067	26	14	48	53	75	41	160	70	58	1	77	44	126
0-4 yrs	(14.9)	(1.2)	(1.5)	(0.3)	(0.9)	(0.2)	(1.0)	(2.1)	(5.9)	(1.5)	(0.0)	(0.8)	(2.9)	(0.5)
	324,555	249	88	900	694	1,080	845	414	371	214	88	1,968	87	1,648
5-14 yrs	(21.7)	(11.2)	(9.2)	(6.0)	(11.5)	(3.2)	(21.6)	(5.4)	(31.5)	(5.4)	(1.4)	(20.8)	(5.8)	(7.1)
	278,029	325	169	3,266	1,069	2,784	1,350	890	293	563	354	2,572	174	3,782
15-24 yrs	(18.6)	(14.6)	(17.7)	(21.7)	(17.7)	(8.3)	(34.5)	(11.6)	(24.9)	(14.3)	(5.6)	(27.2)	(11.6)	(16.2)
	195,010	316	175	4,055	617	5,863	743	972	161	617	1,163	2,721	167	5,612
25-44 yrs	(13.1)	(14.2)	(18.3)	(26.9)	(10.2)	(17.4)	(19.0)	(12.7)	(13.7)	(15.6)	(18.4)	(28.7)	(11.1)	(24.0)
	243,192	626	271	4,014	689	11,829	685	2,345	136	1,241	2,701	1,817	311	7,193
45-64 yrs	(16.3)	(28.1)	(28.4)	(26.7)	(11.4)	(35.1)	(17.5)	(30.6)	(11.6)	(31.4)	(42.8)	(19.2)	(20.7)	(30.8)
	64,728	279	72	935	430	4,382	105	983	44	474	799	175	209	2,080
65-74 yrs	(4.3)	(12.5)	(7.5)	(6.2)	(7.1)	(13.0)	(2.7)	(12.8)	(3.7)	(12.0)	(12.6)	(1.8)	(13.9)	(8.9)
	165,705	407	165	1,832	2,474	7,649	144	1,889	102	783	1,212	138	514	2,907
75+ yrs	(11.1)	(18.3)	(17.3)	(12.2)	(41.1)	(22.7)	(3.7)	(24.7)	(8.7)	(19.8)	(19.2)	(1.5)	(34.1)	(12.5)
Gender*														
	799,394	1,081	484	6,093	3,399	13,761	1,696	4,475	668	2,592	2,513	2,422	689	9,323
Male	(53.5)	(48.5)	(50.7)	(40.5)	(56.4)	(40.9)	(43.3)	(58.5)	(56.8)	(65.6)	(39.8)	(25.6)	(45.8)	(39.9)
	693,892	1,147	470	8,957	2,627	19,901	2,217	3,178	509	1,358	3,805	7,046	817	14,025
Female	(46.5)	(51.5)	(49.3)	(59.5)	(43.6)	(59.1)	(56.7)	(41.5)	(43.2)	(34.4)	(60.2)	(74.4)	(54.2)	(60.1)
Early seizures*														
	4,112	6	70	103	161	138	144	1,536	110	602	33	141	67	1,481
Yes	(0.3)	(0.3)	(7.3)	(0.7)	(2.7)	(0.4)	(3.7)	(20.1)	(9.3)	(15.2)	(0.5)	(1.5)	(4.4)	(6.3)
	1,489,174	2,222	884	14,947	5,865	33,524	3,769	6,117	1,067	3,348	6,285	9,327	1,439	21,867
No	(99.7)	(99.7)	(92.7)	(99.3)	(97.3)	(99.6)	(96.3)	(79.9)	(90.7)	(84.8)	(99.5)	(98.5)	(95.6)	(93.7)
PTE*														
	15,654	20	108	344	378	663	186	1,701	106	752	175	331	142	1,486
Yes	(1.0)	(0.9)	(11.3)	(2.3)	(6.3)	(2.0)	(4.8)	(22.2)	(9.0)	(19.0)	(2.8)	(3.5)	(9.4)	(6.4)
	1,477,632	2,208	846	14,706	5,648	32,999	3,727	5,952	1,071	3,198	6,143	9,137	1,364	21,862
No	(99.0)	(99.1)	(88.7)	(97.7)	(93.7)	(98.0)	(95.2)	(77.8)	(91.0)	(81.0)	(97.2)	(96.5)	(90.6)	(93.6)
Severity of TBI*														
	1,331,966	1,921	754	13,154	4,863	28,740	3,420	2,614	1,000	941	5,254	8,341	1,186	18,406
Level 1	(89.2)	(86.2)	(79.0)	(87.4)	(80.7)	(85.4)	(87.4)	(34.2)	(85.0)	(23.8)	(83.2)	(88.1)	(78.8)	(78.8)
	2,952	2	5	43	17	81	9	18	4	4	21	18	4	63
Level 2	(0.2)	(0.1)	(0.5)	(0.3)	(0.3)	(0.2)	(0.2)	(0.2)	(0.3)	(0.1)	(0.3)	(0.2)	(0.3)	(0.3)
	154,648	297	180	1,804	1,094	4,689	464	4,793	168	2,874	1,012	1,079	289	4,642
Level 3	(10.4)	(13.3)	(18.9)	(12.0)	(18.2)	(13.9)	(11.9)	(62.6)	(14.3)	(72.8)	(16.0)	(11.4)	(19.2)	(19.9)
	1,378	1	6	19	18	58	10	84	2	60	8	12	10	79
Level 4	(0.1)	(0.0)	(0.6)	(0.1)	(0.3)	(0.2)	(0.3)	(1.1)	(0.2)	(1.5)	(0.1)	(0.1)	(0.7)	(0.3)
	2,342	7	9	30	34	94	10	144	3	71	23	18	17	158
Level 5	(0.2)	(0.3)	(0.9)	(0.2)	(0.6)	(0.3)	(0.3)	(1.9)	(0.3)	(1.8)	(0.4)	(0.2)	(1.1)	(0.7)

Duration of AED*														
0 days	1,493,286 (100.0)	6 (0.3)	8 (0.8)	34 (0.2)	30 (0.5)	79 (0.2)	12 (0.3)	15 (0.2)	2 (0.2)	10 (0.3)	15 (0.2)	28 (0.3)	6 (0.4)	19 (0.1)
0-7 days	0 (0.0)	779 (35.0)	38 (4.0)	662 (4.4)	101 (1.7)	488 (1.4)	29 (0.7)	1,566 (20.5)	23 (2.0)	1,300 (32.9)	176 (2.8)	57 (0.6)	99 (6.6)	19 (0.1)
8-30 days	0 (0.0)	1,018 (45.7)	393 (41.2)	6,029 (40.1)	1,664 (27.6)	12,994 (38.6)	882 (22.5)	2,327 (30.4)	352 (29.9)	1,255 (31.8)	2,467 (39.0)	3,581 (37.8)	469 (31.1)	260 (1.1)
31-90 days	0 (0.0)	215 (9.6)	196 (20.5)	3,322 (22.1)	1,359 (22.6)	7,871 (23.4)	782 (20.0)	1,544 (20.2)	288 (24.5)	701 (17.7)	1,376 (21.8)	2,408 (25.4)	325 (21.6)	4,863 (20.8)
91-180 days	0 (0.0)	88 (3.9)	108 (11.3)	1,791 (11.9)	964 (16.0)	4,213 (12.5)	601 (15.4)	848 (11.1)	160 (13.6)	301 (7.6)	779 (12.3)	1,267 (13.4)	189 (12.5)	4,332 (18.6)
181-365 days	0 (0.0)	63 (2.8)	95 (10.0)	1,537 (10.2)	924 (15.3)	3,610 (10.7)	666 (17.0)	662 (8.7)	152 (12.9)	195 (4.9)	705 (11.2)	1,130 (11.9)	182 (12.1)	4,920 (21.1)
>365 days	0 (0.0)	59 (2.6)	116 (12.2)	1,675 (11.1)	984 (16.3)	4,407 (13.1)	941 (24.0)	691 (9.0)	200 (17.0)	188 (4.8)	800 (12.7)	997 (10.5)	236 (15.7)	8,935 (38.3)
CSE*														
Yes	4,180 (0.3)	4 (0.2)	6 (0.6)	24 (0.2)	16 (0.3)	55 (0.2)	9 (0.2)	20 (0.3)	8 (0.7)	8 (0.2)	14 (0.2)	18 (0.2)	3 (0.2)	57 (0.2)
No	1,489,106 (99.7)	2,224 (99.8)	948 (99.4)	15,026 (99.8)	6,010 (99.7)	33,607 (99.8)	3,904 (99.8)	7,633 (99.7)	1,169 (99.3)	3,942 (99.8)	6,304 (99.8)	9,450 (99.8)	1,503 (99.8)	23,291 (99.8)
Infection*														
Yes	3,047 (0.2)	6 (0.3)	0 (0.0)	41 (0.3)	23 (0.4)	124 (0.4)	6 (0.2)	34 (0.4)	2 (0.2)	18 (0.5)	26 (0.4)	23 (0.2)	6 (0.4)	94 (0.4)
No	1,490,239 (99.8)	2,222 (99.7)	954 (100.0)	15,009 (99.7)	6,003 (99.6)	33,538 (99.6)	3,907 (99.8)	7,619 (99.6)	1,175 (99.8)	3,932 (99.5)	6,292 (99.6)	9,445 (99.8)	1,500 (99.6)	23,254 (99.6)
Tumor8														
Yes	5,999 (0.4)	23 (1.0)	9 (0.9)	82 (0.5)	47 (0.8)	289 (0.9)	15 (0.4)	196 (2.6)	4 (0.3)	60 (1.5)	52 (0.8)	42 (0.4)	10 (0.7)	270 (1.2)
No	1,487,287 (99.6)	2,205 (99.0)	945 (99.1)	14,968 (99.5)	5,979 (99.2)	33,373 (99.1)	3,898 (99.6)	7,457 (97.4)	1,173 (99.7)	3,890 (98.5)	6,266 (99.2)	9,426 (99.6)	1,496 (99.3)	23,078 (98.8)
Senile Dementias*														
Yes	18,933 (1.3)	22 (1.0)	21 (2.2)	243 (1.6)	766 (12.7)	366 (1.1)	31 (0.8)	162 (2.1)	13 (1.1)	69 (1.7)	46 (0.7)	18 (0.2)	64 (4.2)	356 (1.5)
No	1,474,353 (98.7)	2,206 (99.0)	933 (97.8)	14,807 (98.4)	5,260 (87.3)	33,296 (98.9)	3,882 (99.2)	7,491 (97.9)	1,164 (98.9)	3,881 (98.3)	6,272 (99.3)	9,450 (99.8)	1,442 (95.8)	22,992 (98.5)
Stroke or CVD*														
Yes	67,930 (4.5)	196 (8.8)	85 (8.9)	954 (6.3)	916 (15.2)	3,696 (11.0)	106 (2.7)	1,330 (17.4)	48 (4.1)	524 (13.3)	687 (10.9)	218 (2.3)	219 (14.5)	1,938 (8.3)
No	1,425,356 (95.5)	2,032 (91.2)	869 (91.1)	14,096 (93.7)	5,110 (84.8)	29,966 (89.0)	3,807 (97.3)	6,323 (82.6)	1,129 (95.9)	3,426 (86.7)	5,631 (89.1)	9,250 (97.7)	1,287 (85.5)	21,410 (91.7)
Other CNS Degeneration*														
Yes	43,374 (2.9)	92 (4.1)	43 (4.5)	860 (5.7)	651 (10.8)	1,874 (5.6)	117 (3.0)	424 (5.5)	22 (1.9)	172 (4.4)	339 (5.4)	191 (2.0)	216 (14.3)	1,301 (5.6)
No	1,449,912 (97.1)	2,136 (95.9)	911 (95.5)	14,190 (94.3)	5,375 (89.2)	31,788 (94.4)	3,796 (97.0)	7,229 (94.5)	1,155 (98.1)	3,778 (95.6)	5,979 (94.6)	9,277 (98.0)	1,290 (85.7)	22,047 (94.4)
MISC*														
Yes	75,380 (5.0)	134 (6.0)	88 (9.2)	1,048 (7.0)	1,585 (26.3)	2,504 (7.4)	207 (5.3)	910 (11.9)	90 (7.6)	314 (7.9)	431 (6.8)	416 (4.4)	223 (14.8)	1,921 (8.2)
No	1,417,906 (95.0)	2,094 (94.0)	866 (90.8)	14,002 (93.0)	4,441 (73.7)	31,158 (92.6)	3,706 (94.7)	6,743 (88.1)	1,087 (92.4)	3,636 (92.1)	5,887 (93.2)	9,052 (95.6)	1,283 (85.2)	21,427 (91.8)
Other CVD*														
Yes	68,506 (4.6)	172 (7.7)	70 (7.3)	955 (6.3)	939 (15.6)	3,372 (10.0)	163 (4.2)	916 (12.0)	62 (5.3)	365 (9.2)	575 (9.1)	356 (3.8)	159 (10.6)	1,777 (7.6)
No	1,424,780 (95.4)	2,056 (92.3)	884 (92.7)	14,095 (93.7)	5,087 (84.4)	30,290 (90.0)	3,750 (95.8)	6,737 (88.0)	1,115 (94.7)	3,585 (90.8)	5,743 (90.9)	9,112 (96.2)	1,347 (89.4)	21,571 (92.4)

Data Source: MarketScan Commercial Claims and Encounters and Medicare Supplemental database, 2006-2014

ACZ: Acetazolamide
AED: Antiepileptic Drug
CBZ: Carbamazepine
CLZ: Clonazepam
CSE: Childhood Static Encephalopathy
VPA: Divalproex Sodium
GABA: Gabapentin
LAM: Lamotrigine
LEV: Levetiracetam
MISC: Miscellaneous
OXC: Oxcarbazepine
OD: Other Drugs

PHT: Phenytoin
TBI: Traumatic Brain Injury
MD: Multiple Drugs
PRE: Pregabalin
TOP: Topiramate
* Chi-Square test, P value <0.0001

Table 5. Descriptive characteristics of Traumatic Brain Injury patient by Post-traumatic Epilepsy

	Traumatic brain injury with early seizures				Traumatic brain injury without early seizure			
	PTE (N=2,728) n (%)	**Non-PTE (N=5,976) n (%)**	**Total (N=8,704) n (%)**	**Overall P-value***	**PTE (19,318) n (%)**	**Non PTE (1,632,045) n (%)**	**Total (1,651,363) n (%)**	**Overall P-value***
Sex				0.3948				<.0001
Male	1,498 (54.9)	3,223 (53.9)	4,721 (54.2)		9,563 (49.5)	868,792 (53.2)	878,355 (53.2)	
Female	1,230 (45.1)	2,753 (46.1)	3,983 (45.8)		9,755 (50.5)	763,253 (46.8)	773,008 (46.8)	
Severity of TBI				<.0001				<.0001
Level 1	1,731 (63.5)	4,063 (68.0)	5,794 (66.6)		13,638 (70.6)	1,450,801 (88.9)	1,464,439 (88.7)	
Level 2	11 (0.4)	23 (0.4)	34 (0.4)		60 (0.3)	3,232 (0.2)	3,292 (0.2)	
Level 3	924 (33.9)	1,800 (30.1)	2,724 (31.3)		5,226 (27.1)	173,513 (10.6)	178,739 (10.8)	
Level 4	13 (0.5)	36 (0.6)	49 (0.6)		95 (0.5)	1,623 (0.1)	1,718 (0.1)	
Level 5	49 (1.8)	54 (0.9)	103 (1.2)		299 (1.5)	2,876 (0.2)	3,175 (0.2)	
Age (yr)				0.2838				<.0001
0-4	152 (5.6)	375 (6.3)	527 (6.1)		1,271 (6.6)	227,171 (13.9)	228,442 (13.8)	
5-14	317 (11.6)	628 (10.5)	945 (10.9)		2,182 (11.3)	344,838 (21.1)	347,020 (21.0)	
15-24	425 (15.6)	1,020 (17.1)	1,445 (16.6)		2,762 (14.3)	308,003 (18.9)	310,765 (18.8)	
25-44	559 (20.5)	1,229 (20.6)	1,788 (20.5)		2,767 (14.3)	222,288 (13.6)	225,055 (13.6)	
45-64	769 (28.2)	1,674 (28.0)	2,443 (28.1)		4,349 (22.5)	275,672 (16.9)	280,021 (17.0)	
65-74	201 (7.4)	404 (6.8)	605 (7.0)		2,029 (10.5)	73,061 (4.5)	75,090 (4.5)	
75+	305 (11.2)	646 (10.8)	951 (10.9)		3,958 (20.5)	181,012 (11.1)	184,970 (11.2)	
Duration of AED				<.0001				<.0001
0 days	1,392 (51.0)	2,733 (45.7)	4,125 (47.4)		14,282 (73.9)	1,526,671 (93.5)	1,540,953 (93.3)	
1-7 days	138 (5.1)	81 (1.4)	219 (2.5)		473 (2.4)	4,645 (0.3)	5,118 (0.3)	
8-30 days	373 (13.7)	472 (7.9)	845 (9.7)		1,315 (6.8)	31,531 (1.9)	32,846 (2.0)	
31-90 days	339 (12.4)	529 (8.9)	868 (10.0)		1,211 (6.3)	23,171 (1.4)	24,382 (1.5)	
91-180 days	168 (6.2)	471 (7.9)	639 (7.3)		764 (4.0)	14,238 (0.9)	15,002 (0.9)	
181-365 days	146 (5.4)	551 (9.2)	697 (8.0)		673 (3.5)	13,471 (0.8)	14,144 (0.9)	
>365 days	172 (6.3)	1,139 (19.1)	1,311 (15.1)		600 (3.1)	18,318 (1.1)	18,918 (1.1)	
AED				<.0001				<.0001
NONE	1,385 (50.8)	2,727 (45.6)	4,112 (47.2)		14,269 (73.9)	1,526,423 (93.5)	1,540,692 (93.3)	
ACZ	2 (0.1)	4 (0.1)	6 (0.1)		18 (0.1)	2,204 (0.1)	2,222 (0.1)	
CBZ	30 (1.1)	40 (0.7)	70 (0.8)		326 (1.7)	14,621 (0.9)	14,947 (0.9)	
CLZ	18 (0.7)	85 (1.4)	103 (1.2)		330 (1.7)	5,537 (0.3)	5,867 (0.4)	
VPA	48 (1.8)	113 (1.9)	161 (1.8)		647 (3.3)	32,880 (2.0)	33,527 (2.0)	
GABA	16 (0.6)	122 (2.0)	138 (1.6)		150 (0.8)	3,619 (0.2)	3,769 (0.2)	

LAM	36 (1.3)	108 (1.8)	144 (1.7)	1,149 (5.9)	4,968 (0.3)	6,117 (0.4)
LEV	552 (20.2)	984 (16.5)	1,536 (17.6)	66 (0.3)	1,001 (0.1)	1,067 (0.1)
OXC	40 (1.5)	70 (1.2)	110 (1.3)	520 (2.7)	2,830 (0.2)	3,350 (0.2)
PHT	232 (8.5)	370 (6.2)	602 (6.9)	170 (0.9)	6,115 (0.4)	6,285 (0.4)
PRE	5 (0.2)	28 (0.5)	33 (0.4)	305 (1.6)	9,024 (0.6)	9,329 (0.6)
TOP	26 (1.0)	115 (1.9)	141 (1.6)	78 (0.4)	807 (0.0)	885 (0.1)
OD	21 (0.8)	46 (0.8)	67 (0.8)	121 (0.6)	1,318 (0.1)	1,439 (0.1)
MD	317 (11.6)	1,164 (19.5)	1,481 (17.0)	1,169 (6.1)	20,698 (1.3)	21,867 (1.3)

Data Source: MarketScan Commercial Claims and Encounters and Medicare Supplemental database, 2006-2014
ACZ: Acetazolamide
AED: Antiepileptic Drug
CBZ: Carbamazepine
CLZ: Clonazepam
CSE: Childhood Static Encephalopathy
GABA: Gabapentin
LAM: Lamotrigine
LEV: Levetiracetam
OD: Other Drugs
OXC: Oxcarbazepine
MD: Multiple Drugs
PHT: Phenytoin
PRE: Pregabalin
PTE: Post-traumatic Epilepsy
TBI: Traumatic Brain Injury
TOP: Topiramate
VPA: Divalproex Sodium
* Chi-Square test

Table 6. Selected characteristics of Traumatic Brain Injury patients by the durations of Anti-epileptic Drug use

	0 days (N=1,493,550) n (row %)	**1-7 days (N=5,337) n (row %)**	**8-30 days (N=33,691) n (row %)**	**31-90 days (N=25,250) n (row %)**	**91-180 days (N=15,641) n (row %)**	**181-365 days (N=14,841) n (row %)**	**>365 days (N=20,229) n (row %)**	**Total**
Early seizure								
Yes	4,125 (47.4)	219 (2.5)	845 (9.7)	868 (10.0)	639 (7.3)	697 (8.0)	1,311 (15.1)	8,704
No	1,489,425 (93.1)	5,118 (0.3)	32,846 (2.1)	24,382 (1.5)	15,002 (1.0)	14,144 (0.9)	18,918 (1.2)	1,599,835
PTE								
Yes	15,674 (71.1)	611 (2.8)	1,688 (7.7)	1,550 (7.0)	932 (4.2)	819 (3.7)	772 (3.5)	22,046
No	1,477,876 (93.2)	4,726 (0.3)	32,003 (2.0)	23,700 (1.5)	14,709 (0.9)	14,022 (0.9)	19,457 (1.2)	1,586,493
Severity of TBI								
Level 1	1,332,165 (93.6)	2,668 (0.2)	27,118 (1.9)	20,051 (1.4)	12,393 (0.9)	11,908 (0.8)	16,257 (1.1)	1,422,560
Level 2	2,953 (91.1)	5 (0.2)	77 (2.4)	80 (2.5)	40 (1.2)	33 (1.0)	53 (1.6)	3,241
Level 3	154,709 (86.9)	2,591 (1.5)	6,257 (3.5)	4,883 (2.7)	3,055 (1.7)	2,768 (1.6)	3,770 (2.1)	178,033
Level 4	1,378 (79.0)	44 (2.5)	94 (5.4)	88 (5.0)	51 (2.9)	36 (2.1)	54 (3.1)	1,745
Level 5	2,345 (79.2)	29 (1.0)	145 (4.9)	148 (5.0)	102 (3.4)	96 (3.2)	95 (3.2)	2,960

Data Source: MarketScan Commercial Claims and Encounters and Medicare Supplemental database, 2006-2014
TBI: Traumatic Brain Injury
PTE: Posttraumatic Epilepsy

Table 7. Association between PTE and age, sex, severity of TBI and duration of AED prescription among TBI patients

	TBI with early seizures				TBI without early seizure			
	cHR (95% CI)	**P-value**	**aHR (95% CI)**	**Adjusted P-value**	**cHR (95% CI)**	**P-value**	**aHR (95% CI)**	**Adjusted P-value**
Sex								
Male	1.065 (0.988-1.149)	0.1010	1.002 (0.928-1.082)	0.9599	0.902 (0.876-0.927)	<.0001	1.020 (0.991-1.049)	0.1868
Female	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Severity of TBI								
Level 1	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
Level 2	1.084 (0.599-1.962)	0.7886	0.970 (0.535-1.760)	0.9202	1.959 (1.520-2.524)	<.0001	1.648 (1.279-2.124)	0.0001
Level 3	1.146 (1.058-1.241)	0.0008	1.087 (0.999-1.183)	0.0520	3.061 (2.965-3.160)	<.0001	2.039 (1.970-2.111)	<.0001
Level 4	0.855 (0.495-1.475)	0.5724	0.898 (0.519-1.554)	0.7012	6.128 (5.008-7.498)	<.0001	3.365 (2.747-4.121)	<.0001
Level 5	1.565 (1.178-2,079)	0.0020	1.585 (1.192-2.109)	0.0015	13.410 (11.959-15.04)	<.0001	7.548 (6.720-8.477)	<.0001
Age								
0-4 yrs	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
5-14 yrs	1.249 (1.029-1.515)	0.0245	1.314 (1.082-1.596)	0.0058	1.151 (1.074-1.233)	<.0001	1.083 (1.011-1.161)	0.0235
15-24 yrs	1.128 (0.937-1.358)	0.2026	1.185 (0.983-1.429)	0.0748	1.838 (1.720-1.965)	<.0001	1.572 (1.471-1.681)	<.0001
25-44 yrs	1.172 (0.980-1.402)	0.0825	1.323 (1.103-1.586)	0.0025	2.391 (2.237-2.555)	<.0001	1.900 (1.776-2.032)	<.0001
45-64 yrs	1.169 (0.982-1.391)	0.0793	1.370 (1.148-1.634)	0.0005	2.887 (2.712-3.073)	<.0001	2.002 (1.878-2.134)	<.0001
65-74 yrs	1.191 (0.964-1.470)	0.1047	1.406 (1.126-1.756)	0.0027	4.644 (4.330-4.981)	<.0001	2.502 (2.320-2.699)	<.0001
75+ yrs	1.179 (0.971-1.433)	0.0965	1.311 (1.057-1.627)	0.0136	4.145 (3.891-4.415)	<.0001	2.065 (1.921-2.220)	<.0001
Duration of AED								
0 days	1.0 (reference)		1.0 (reference)		1.0 (reference)		1.0 (reference)	
1-7 days	2.824 (2.371- 3.364)	<.0001	2.392 (1.107-5.170)	0.0265	9.003 (8.215-9.867)	<.0001	0.959 (0.552-1.667)	0.8821
8-30 days	1.469 (1.310-1.647)	<.0001	1.285 (0.602-2.742)	0.5168	3.415 (3.228-3.614)	<.0001	0.896 (0.519-1.548)	0.6942
31-90 days	1.127 (1.001-1.269)	0.0480	0.892 (0.418-1.903)	0.7672	4.222 (3.981-4.477)	<.0001	0.979 (0.567-1.692)	0.9403
91-180 days	0.657 (0.560-0.771)	<.0001	0.512 (0.238-1.101)	0.0865	4.260 (3.960-4.581)	<.0001	0.928 (0.536-1.607)	0.7896
181-365 days	0.502 (0.423-0.595)	<.0001	0.370 (0.172-0.798)	0.0112	3.855 (3.568-4.165)	<.0001	0.846 (0.488-1.465)	0.5495
>365 days	0.244 (0.208-0.286)	<.0001	0.181 (0.084-0.391)	<.0001	2.196 (2.023-2.383)	<.0001	0.454 (0.262-0.788)	0.0050

Data Source: MarketScan Commercial Claims and Encounters and Medicare Supplemental database, 2006-2012
AED: Antiepileptic Drug TBI: Traumatic Brain Injury
PTE: Posttraumatic Epilepsy cHR: Crude Hazard Ratio
aHR: Adjusted Hazard Ratio

Table 8A. Association between PTE and AED prescription among TBI patients with early seizures

	0<= age <15 yr		15<= age <45 yr		Age >=45 yr	
	cHR (95% CI)	**aHR (95% CI)**	**cHR (95% CI)**	**aHR (95% CI)**	**cHR (95% CI)**	**aHR (95% CI)**
NONE	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
ACZ	---	---	1.00 (0.14-7.14)	0.93 (0.13-6.79)	1.33 (0.19-9.49)	1.39 (0.19-9.93)
CBZ	1.06 (0.44-2.55)	1.78 (0.72-4.40)	0.96 (0.53-1.75)	1.69 (0.92-3.09)	1.52 (0.90-2.59)	2.39 (1.40-4.08)*
CLZ	0.92 (0.23-3.71)	1.13 (0.28-4.57)	0.43 (0.23-0.77)*	0.48 (0.27-0.88)*	0.27 (0.11-0.65)*	0.33 (0.14-0.81)*
VPA	0.53 (0.26-1.08)	1.16 (0.57-2.37)	0.66 (0.40-1.06)	1.08 (0.66-1.76)	0.96 (0.64-1.47)	1.40 (0.92-2.14)
GABA	0.68 (0.22-2.11)	1.03 (0.32-3.26)	0.24 (0.10-0.57)*	0.29 (0.12-0.70)*	0.20 (0.10-0.39)*	0.26 (0.13-0.52)*
LAM	0.88 (0.42-1.87)	3.44 (1.57-7.56)*	0.54 (0.35-0.85)	1.04 (0.66-1.64)	0.54 (0.28-1.04)	1.03 (0.53-1.99)
LEV	1.06 (0.82-1.38)	2.16 (1.61-2.89)*	1.04 (0.87-1.23)	1.61 (1.34-1.94)*	0.95 (0.83-1.09)	1.50 (1.28-1.75)*
OXC	1.06 (0.68-1.67)	2.67 (1.64-4.34)*	0.93 (0.50-1.74)	1.50 (0.80-2.83)	1.15 (0.62-2.15)	1.51 (0.80-2.84)
PHT	1.09 (0.66-1.81)	1.36 (0.81-2.30)	1.09 (0.85-1.39)	1.30 (1.01-1.67)*	1.11 (0.92-1.33)	1.59 (1.31-1.93)*
PRE	---	---	0.14 (0.02-0.98)*	0.19 (0.03-1.34)	0.41 (0.15-1.10)	0.55 (0.20-1.47)
TOP	0.29 (0.09-0.91)*	0.50 (0.16-1.56)	0.46 (0.28-0.74)*	0.66 (0.41-1.08)	0.45 (0.20-0.99)*	0.68 (0.30-1.52)
OD	1.29 (0.72-2.29)	2.13 (1.18-3.86)*	0.72 (0.32-1.61)	0.99 (0.44-2.23)	0.32 (0.10-1.00)	0.40 (0.13-1.23)
MD	0.28 (0.18-0.44)*	1.38 (0.82-2.32)	0.41 (0.34-0.50)*	1.03 (0.81-1.30)	0.55 (0.46-0.64)*	1.25 (1.03-1.51)*

Data Source: MarketScan Commercial Claims and Encounters and Medicare Supplemental database, 2006-2014
ACZ: Acetazolamide AED: Antiepileptic Drug
CBZ: Carbamazepine CLZ: Clonazepam
CSE: Childhood Static Encephalopathy GABA: Gabapentin
LAM: Lamotrigine LEV: Levetiracetam
OD: Other Drugs OXC: Oxcarbazepine
MD: Multiple Drugs PHT: Phenytoin
PRE: Pregabalin PTE: Post-traumatic Epilepsy
TBI: Traumatic Brain Injury TOP: Topiramate
VPA: Divalproex Sodium cHR: Crude Hazard Ratio
aHR: Adjusted Hazard Ratio * $p<0.05$

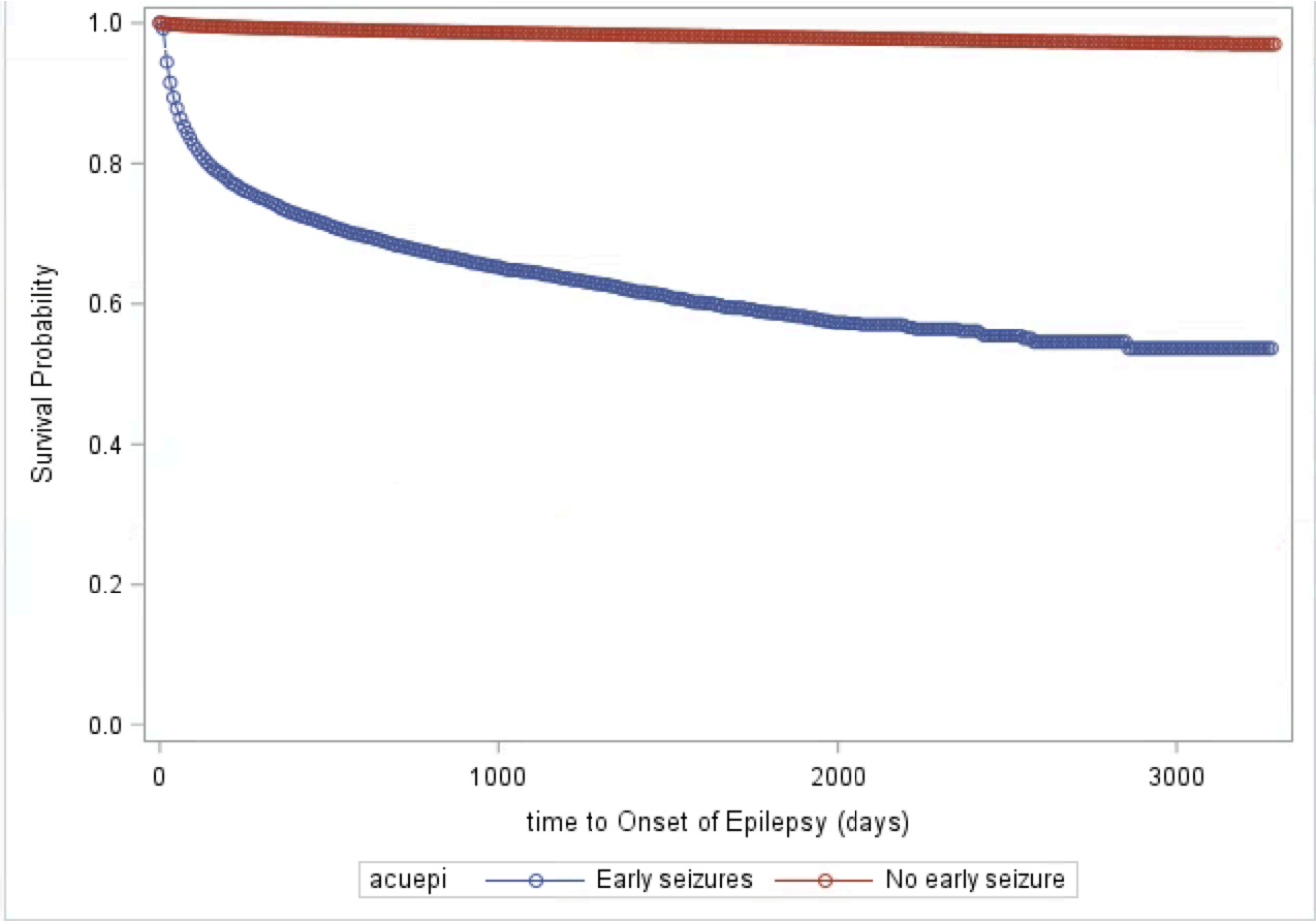
Table 8B. Association between PTE and AED prescription among TBI patients without early seizures

	0<=Age<15 yr		15<=Age<45 yr		Age>=45 yr	
	cHR (95% CI)	**aHR (95% CI)**	**cHR (95% CI)**	**aHR (95% CI)**	**cHR (95% CI)**	**aHR (95% CI)**
NONE	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
ACZ	1.37 (0.44-4.24)	1.33 (0.43-4.13)	0.42 (0.13-1.29)	0.38 (0.12-1.19)	0.43 (0.25-0.76)*	0.45 (0.25-0.79)*
CBZ	4.27 (3.05-5.99)*	4.27 (3.03-6.00)*	1.80 (1.53-2.13)*	1.98 (1.67-2.34)*	1.10 (0.93-1.29)	1.27 (1.07-1.49)*
CLZ	7.22 (5.27-9.91)*	8.02 (5.80-11.08)*	6.28 (5.14-7.66)*	6.15 (5.03-7.53)*	3.10 (2.69-3.58)*	2.75 (2.37-3.18)*
VPA	3.58 (2.53-5.08)*	3.40 (2.39-4.83)*	1.92 (1.65-2.23)*	1.95 (1.67-2.26)*	0.87 (0.79-0.96)*	1.03 (0.93-1.14)
GABA	3.92 (2.68-5.73)*	4.85 (3.28-7.17)*	3.43 (2.72-4.31)*	4.23 (3.35-5.35)*	2.84 (2.14-3.76)*	3.72 (2.80-4.94)*
LAM	29.54 (22.78-38.30)*	20.25 (15.46-26.53)*	22.69 (19.88-25.89)*	11.43 (9.92-13.16)*	13.15 (12.25-14.11)*	8.82 (8.17-9.52)*
LEV	7.81 (5.22-11.67)*	8.75 (5.80-13.19)*	4.60 (2.96-7.14)*	5.08 (3.27-7.89)*	4.60 (3.03-6.99)*	4.88 (3.21-7.42)*
OXC	10.57 (6.25-17.88)*	7.25 (4.26-12.35)*	15.24 (12.68-18.32)*	7.67 (6.35-9.28)*	11.21 (10.12-12.41)*	7.17 (6.45-7.98)*
PHT	2.76 (0.69-11.02)	2.35 (0.59-9.42)	3.03 (2.29-4.02)*	2.92 (2.20-3.88)*	1.24 (1.03-1.49)*	1.43 (1.19-1.72)*
PRE	4.23 (3.31-5.41)*	4.46 (3.46-5.74)*	2.87 (2.46-3.36)*	3.16 (2.69-3.71)*	1.82 (1.45-2.28)*	2.31 (1.84-2.89)*
TOP	9.41 (4.23-20.97)*	10.43 (4.67-23.29)*	9.14 (6.34-13.17)*	8.79 (6.09-12.68)*	4.77 (3.53-6.43)*	4.85 (3.59-6.55)*
OD	22.62 (14.04-36.44)*	15.33 (9.31-25.23)*	9.23 (6.48-13.14)*	8.23 (5.78-11.73)*	3.76 (2.99-4.74)*	3.97 (3.14-5.00)*
MD	6.87 (5.60-8.44)*	8.70 (6.77-11.18)*	4.43 (4.03-4.88)*	5.51 (4.90-6.20)*	2.42 (2.23-2.63)*	3.18 (2.88-3.50)*

Data Source: MarketScan Commercial Claims and Encounters and Medicare Supplemental database, 2006-2014

ACZ: Acetazolamide
AED: Antiepileptic Drug
CBZ: Carbamazepine
CLZ: Clonazepam
CSE: Childhood Static Encephalopathy
GABA: Gabapentin
LAM: Lamotrigine
LEV: Levetiracetam
OD: Other Drugs
OXC: Oxcarbazepine
MD: Multiple Drugs
PHT: Phenytoin
PRE: Pregabalin
PTE: Post-traumatic Epilepsy
TBI: Traumatic Brain Injury
TOP: Topiramate
VPA: Divalproex Sodium
cHR: Crude Hazard Ratio
aHR: Adjusted Hazard Ratio
* $p<0.05$

Figure 1. Unadjusted Kaplan Meier survival curves stratified by early seizure among TBI individuals (Logrank test, p<0.0001)



APPENDIX A:
ICD-9-CM Classification Criteria of Intracranial Injury Documentation

	1st 3 digits	4th digit	5th digit
	If 800, 801, 803, or 804	0 or 5	(any value or missing)
0 = Not documented	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 (LOCD)

LOCD	1st 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 hour	If 800, 801, 803, or 804	(any value)	1 or 2
	If 850	0 or 1	N/A
	If 851 - 854	(any value)	1 or 2
2 = 1-24 hours	If 800, 801, 803, or 804	(any value)	3
	If 850	2	N/A
	If 851 - 854	(any value)	3
3 = >24 hours	If 800, 801, 803, or 804	(any value)	4
	If 850	3 or 4	N/A
	If 851 - 854	(any value)	4
4 = >24 hours, persisting	If 800, 801, 803, or 804	(any value)	5
	If 850	3 or 4	N/A
	If 851 - 854	(any value)	5

APPENDIX C

ICD 9 codes for epilepsy risk factors

ICD	Condition	Disease Category
318	Other specified mental retardation (excl. mild)	CSE
343	Infantile cerebral palsy	CSE
767.0	Perinatal Subdural and cerebral hemorrhage	CSE
768	Intrauterine hypoxia and birth asphyxia	CSE

771.0	Congenital rubella	CSE
771.1	Congenital cytomegalovirus infection	CSE
772.1	Perinatal Intraventricular hemorrhage	CSE
772.2	Perinatal Subarachnoid hemorrhage	CSE
779.7	Periventricular leukomalacia	CSE
V40.0	Problems with learning	CSE
006.5	Amebic brain abcess	Infection
013.0	Tuberculous meningitis	Infection
013.1	Tuberculoma of meninges	Infection
013.2	Tuberculoma of brain	Infection
013.3	Tuberculous abscess of brain	Infection
013.6	Tuberculous encephalitis or myelitis	Infection
013.8	Other specified tuberculosis of central NS	Infection
013.9	Unspecified tuberculosis of central NS	Infection
018	Miliary tuberculosis	Infection
036	Meningococcal infection	Infection
052.0	Postvaricella encephalitis	Infection
053.0	Herpes zoster with meningitis	Infection
054.3	Herpetic meningoencephalitis	Infection
054.72	Herpes simplex meningitis	Infection
055.0	Postmeasles encephalitis	Infection
056.0	Rubella with neurological complications	Infection
062	Mosquito-borne viral encephalitis	Infection
063	Tick-borne viral encephalitis	Infection
064	Viral encephalitis transmitted by other and unspecified arthropods	Infection
066	Other arthropod-borne viral diseases	Infection
072.1	Mumps meningitis	Infection
072.2	Mumps encephalitis	Infection
086.3	Gambian trypanosomiasis	Infection
086.4	Rhodesian trypanosomiasis	Infection
086.5	African trypanosomiasis, unspecified	Infection
086.9	Trypanosomiasis, unspecified	Infection
090	Congenital syphilis	Infection
094	Neurosyphilis	Infection
098.82	Gonococcal meningitis	Infection
112.83	Candidal meningitis	Infection
114.2	Coccidioidal meningitis	Infection
115.01	Histoplasma capsulatum meningitis	Infection
115.11	Infection by Histoplasma duboisii meningitis	Infection
115.91	Histoplasmosis, unspecified meningitis	Infection
123.1	Cysticercosis	Infection
130	Meningoencephalitis due to toxoplasmosis	Infection
137.1	Late effects of central nervous system tuberculosis	Infection
139.0	Late effects of viral encephalitis	Infection
320	Bacterial meningitis	Infection
323	Encephalitis, myelitis, and encephalomyelitis	Infection

324.0	Intracranial abscess	Infection
326	Late effects of intracranial abscess or pyogenic infection	Infection
191	Malignant neoplasm of brain	Malignant tumor
192.0	Malignant neoplasm of Cranial nerves	Malignant tumor
192.1	Malignant neoplasm of Cerebral meninges	Malignant tumor
194.3	Malignant neoplasm of Pituitary gland and craniopharyngeal duct	Malignant tumor
194.4	Malignant neoplasm of Pineal gland	Malignant tumor
V10.85	Personal history of malignant neoplasm of brain	Malignant tumor
192.9	Malignant neoplasm of Nervous system, part unspecified	Malignant tumor
198.3	Secondary malignant neoplasm of Brain and spinal cord	Malignant tumor
198.4	Secondary malignant neoplasm of Other parts of NS	Malignant tumor
225.0	Benign neoplasm of Brain	Other tumor
225.1	Benign neoplasm of Cranial nerves	Other tumor
225.2	Benign neoplasm of Cerebral meninges	Other tumor
228.02	Hemangioma of intracranial structures	Other tumor
237.7	Neurofibromatosis	Other tumor
V12.41	Personal history of benign neoplasm of the brain	Other tumor
225.9	Benign neoplasm of Nervous system, part unspecified	Other tumor
237	Neoplasm of uncertain behavior of Pituitary gland and craniopharyngeal duct	Other tumor
237.1	Neoplasm of uncertain behavior of Pineal gland	Other tumor
237.5	Neoplasm of uncertain behavior of Brain and spinal cord	Other tumor
237.6	Neoplasm of uncertain behavior of Meninges	Other tumor
237.9	Neoplasm of uncertain behavior of Other and unspecified parts of NS	Other tumor
331.0	Alzheimers disease	Senile dementias
331.2	Senile degeneration of brain	Senile dementias
325	Phlebitis and thrombophlebitis of intracranial venous sinuses	Stroke or CVD
430	Subarachnoid hemorrhage	Stroke or CVD
431	Intracerebral hemorrhage	Stroke or CVD
432	Other and unspecified intracranial hemorrhage	Stroke or CVD
433.0	Basilar artery occlusion and stenosis	Stroke or CVD
433.1	Carotid artery occlusion and stenosis	Stroke or CVD
433.2	Vertebral artery occlusion and stenosis	Stroke or CVD
433.3	Multiple and bilateral occlusion and stenosis of precerebral arteries	Stroke or CVD
433.8	Other specified precerebral artery occlusion and stenosis	Stroke or CVD
433.9	Unspecified precerebral artery occlusion and stenosis	Stroke or CVD
434.0	Cerebral thrombosis	Stroke or CVD
434.1	Cerebral embolism	Stroke or CVD
434.9	Cerebral artery occlusion, unspecified	Stroke or CVD
437.4	Cerebral arteritis	Stroke or CVD
437.6	Nonpyogenic thrombosis of intracranial venous sinus	Stroke or CVD
438	Late effects of cerebrovascular disease	Stroke or CVD
997.02	Iatrogenic cerebrovascular infarction or hemorrhage	Stroke or CVD
319	Unspecified mental retardation	Other CSE
773.4	Kernicterus due to isoimmunization	Other CSE
774.7	Kernicterus not due to isoimmunization	Other CSE

330	Cerebral degenerations usually manifest in childhood	Other CNS degneration
331.1	Picks disease	Other CNS degneration
331.7	Cerebral degeneration in diseases classified elsewhere	Other CNS degneration
331.8	Other cerebral degeneration	Other CNS degneration
331.9	Cerebral degeneration, unspecified	Other CNS degneration
332	Parkinson's disease	Other CNS degneration
333	Other extrapyramidal disease and abnormal movement disorders	Other CNS degneration
334	Spinocerebellar disease	Other CNS degneration
335	Anterior horn cell disease	Other CNS degneration
008.04	Enterohemorrhagic E. coli	Other CNS degneration
042	Human immunodeficiency virus disease	Other CNS degneration
045	Acute poliomyelitis	Other CNS degneration
046	Slow virus infection of central NS	Other CNS degneration
047	Meningitis due to enterovirus	Other CNS degneration
048	Other enterovirus diseases of central NS	Other CNS degneration
049	Other non-arthropod-borne viral diseases of central NS	Other CNS degneration
078.5	Cytomegaloviral disease	Other CNS degneration
084.9	Other pernicious complications of malaria	Other CNS degneration
088	Other arthropod-borne diseases	Other CNS degneration
100.81	Leptospiral meningitis (aseptic)	Other CNS degneration
117.3	Aspergillosis	Other CNS degneration
117.5	Cryptococcosis	Other CNS degneration
122.3	Echinococcus granulosus infection, other	Other CNS degneration
122.6	Echinococcus multilocularis infection, other	Other CNS degneration
122.9	Echinococcosis, other and unspecified	Other CNS degneration
130.9	Toxoplasmosis, unspecified	Other CNS degneration
136.2	Specific infections by free-living amebae	Other CNS degneration
321	Meningitis due to other organisms	Other CNS degneration
322	Meningitis of unspecified cause	Other CNS degneration
324.9	Intracranial or intraspinal abscess of unspecified site	Other CNS degneration
270	Disorders of amino-acid transport and metabolism	Misc.
290	Senile and presenile organic psychotic conditions	Misc.
294	Other organic psychotic conditions (chronic)	Misc.
310	Specific nonpsychotic mental disorders due to organic brain damage	Misc.
331.3	Communicating hydrocephalus	Misc.
331.4	Obstructive hydrocephalus	Misc.
340	Multiple sclerosis	Misc.
342	Hemiplegia and hemiparesis	Misc.
344.8	Other specified paralytic syndromes	Misc.
344.9	Paralysis, unspecified	Misc.
348	Other conditions of brain	Misc.
349	Other and unspecified disorders of the NS	Misc.
740	Anencephalus and similar anomalies	MIsc.
742	Other congenital anomalies of NS	MIsc.
780.01	Coma	MIsc.
780.03	Persistent vegetative state	MIsc.

781.8	Neurologic neglect syndrone	MIsc.
784.3	Aphasia	MIsc.
993.3	Caisson disease	Misc.
994.1	Drowning and nonfatal submersion	Misc.
994.7	Asphyxiation and strangulation	Misc.
997.01	Central nervous system complication of medical or surgical care	Misc.
V45.2	Presence of cerebrospinal fluid drainage device	Misc.
435	Transient cerebral ischemia	Other CVD
436	Acute, but ill-defined, cerebrovascular disease	Other CVD
437.0	Cerebral atherosclerosis	Other CVD
437.1	Other generalized ischemic cerebrovascular disease	Other CVD
437.2	Hypertensive encephalopathy	Other CVD
437.3	Cerebral aneurysm, nonruptured	Other CVD
437.5	Moyamoya disease	Other CVD
437.7	Transient global amnesia	Other CVD
437.8	Other cerebrovascular disease	Other CVD
437.9	Unspecified cerebrovascular disease	Other CVD
446.5	Giant cell arteritis	Other CVD
446.6	Thrombotic microangiopathy	Other CVD
448.0	Hereditary hemorrhagic telangiectasia	Other CVD
900.00	Injury to Carotid artery, unspecified	Other CVD
900.01	Injury to Common carotid artery	Other CVD
900.03	Injury to Internal carotid artery	Other CVD

CSE: Childhood static encephalopathy
NS: nervous system CNS: central nervous system