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the following dissertation:**

**Treatment Patterns Of Antiepileptic Drugs And Economic Outcomes In Patients With  
Potential Refractory Epilepsy In The Texas Medicaid Program**

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## **Dedication**

To mom, dad, and my late grandparents for always believing in me.

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# **Treatment Patterns Of Antiepileptic Drugs And Economic Outcomes In Patients With Potential Refractory Epilepsy In The Texas Medicaid Program**

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The University of Texas at Austin, 2015

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The purpose of the study was to characterize and compare demographic and clinical characteristics, treatment patterns (i.e., medication adherence, persistence, addition, and switching), and healthcare utilization and cost (i.e., all-cause and epilepsy-related) associated with refractory or non-refractory epilepsy. The study used Texas Medicaid claims data from 09/01/07-12/31/13. Prescription and medical service claims of eligible patients analyzed over a 30-month study period comprised of a 6-month pre-period (baseline) and a 24-month follow-up period (annual increments). Patients eligible for the study: 1) were between 18-62 years of age, 2) had a prescription claim for an antiepileptic drug (AED) during the identification period (03/01/08-12/31/11) with no baseline use of an AED and no prophylactic use of an AED at follow-up, and 3) had evidence of epilepsy diagnosis during the study period. Additionally, patients had to be continuously enrolled in Texas Medicaid with no dual eligibility for Medicare and Medicaid. The index date for both the cohorts was the date of the first AED claim. Dependent variables included: treatment patterns, healthcare utilization and cost. The primary independent variable was group (i.e., refractory vs. non-refractory epilepsy). Based on clinical expert opinion and the literature,

patients were categorized as “refractory” (i.e., three or more AEDs, excluding diazepam, in the identification period) and “non-refractory” (i.e., less than three AEDs in the identification period). The covariates included age, gender, race/ethnicity, type of epilepsy, type of index AED, baseline CCI, number of psychiatric comorbidities and presence of non-psychiatric comorbidities at follow-up, baseline pill burden, presence of baseline all-cause inpatient visits, baseline number of all-cause outpatient visits, and baseline all-cause total cost. Using a retrospective matched-cohort design, patients in the refractory cohort were matched 1:1 to patients in the non-refractory cohort using propensity scoring. The matched cohorts were compared for treatment patterns and healthcare utilization and costs using multivariate conditional regression models and non-parametric methods.

Of the 10,599 eligible patients, 2,789 (26.3%) patients in the refractory cohort were matched 1:1 to patients in the non-refractory cohort for a total of 5,596 patients. Mean ( $\pm$  SD) age of the patients in the matched cohort was 38.0 ( $\pm$  13.1) years, and the cohort was comprised of a higher proportion of females (56.0%), Caucasians (41.9%), patients with other convulsions (77.2%), and those with claims for sodium channel blockers (35.4%). A higher proportion of patients with refractory epilepsy were initiated on combination AEDs (26.5% vs. 10.7%), followed by GABA analogues (12.0% vs. 10.2%), and calcium channel action agents (7.7% vs. 3.4%) compared to patients with non-refractory epilepsy. During the second year of follow-up, patients with refractory epilepsy had a higher mean ( $\pm$  SD) (2.1 [ $\pm$  1.5] vs. 1.8 [ $\pm$  1.4]) number of psychiatric comorbidities, and a higher proportion (51.3% vs. 41.4%) of patients had one or more non-psychiatric comorbidities compared to patients with non-refractory epilepsy. Regarding treatment patterns, compared to patients with non-refractory epilepsy, patients with refractory epilepsy were 3.6 times (OR=3.553; 95% CI=3.060-4.125;  $p$ <0.0001) more likely to adhere to AEDs and had a 34.7%

(HR=0.653; 95% CI=0.608-0.702;  $p<0.0001$ ) lower hazard rate of discontinuation of AEDs during the second-year of follow-up, after controlling for covariates. Among those patients on two or more AEDs, patients with refractory epilepsy were 3.7 times (OR=3.723; 95% CI=2.902-4.776;  $p<0.0001$ ) more likely to add an alternative AED and 3.6 times (OR=3.591; 95% CI=3.010-4.284;  $p<0.0001$ ) more likely to switch to an alternative AED during the first-year of follow-up, after controlling for covariates. Regarding healthcare utilization and costs during the second year of follow-up, compared to patients with non-refractory epilepsy, patients with refractory epilepsy had a significantly higher number of all-cause outpatient visits ( $p<0.0001$ ) and pharmacy claims ( $p<0.0001$ ), higher epilepsy-related inpatient hospital and emergency department (ED) visits ( $p<0.0001$ ), outpatient visits ( $p<0.0001$ ), and pharmacy ( $p<0.0001$ ) claims, after controlling for covariates. Consequently, these patients incurred higher costs for all-cause outpatient visits ( $p=0.0190$ ) and pharmacy claims ( $p<0.0001$ ), and higher costs for epilepsy-related inpatient hospital and ED visits ( $p<0.0001$ ), outpatient visits ( $p<0.0001$ ), and pharmacy ( $p<0.0001$ ) claims, after controlling for covariates. Although a majority of the estimates were higher than the second year of follow-up, a similar trend in results was observed during the first-year of follow-up.

In conclusion, findings from this study provide evidence for the dynamic patterns of AED use in clinical practice and provide current estimates of the resource utilization and costs associated with Texas Medicaid patients with refractory epilepsy. Management of epilepsy extends beyond the control of seizures and encompasses improvement in overall burden of the disease. As the costs in the second year were lower than in the first year, timely identification and early treatment optimization may help prevent long-term clinical and economic consequences associated with refractory epilepsy.

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## List of Abbreviations

US	United States
AED	Antiepileptic Drug
ILAE	International League Against Epilepsy
DRE	Drug-Resistant Epilepsy
MOA	Mechanism Of Action
IBE	International Bureau for Epilepsy
CDC	Center of Disease Control and Prevention
NHIS	National Health Interview Survey
WHO	World Health Organization
VNS	Vagus Nerve Stimulation
QD	Quaque Die (once a day)
BID	Bis In Die (twice a day)
TID	Ter In Die (three times a day)
Nav1.1–Nav1.7	Voltage-gated sodium channel isoforms
GABA	Gamma-Aminobutyric Acid
GAT-1	Gamma-aminobutyric acid transporter
NMDA	N-methyl-D-Aspartate
Kv7	Voltage-dependent potassium channels subfamily
NCP	Neurocybernetic Prosthesis
EEG	Electroencephalography
MRI	Magnetic Resonance Imaging

NIS	National Inpatient Sample
MEPS	Medical Expenditure Panel Survey
ED	Emergency Department
SUDEP	Sudden Unexplained Death In Epilepsy
HRQOL	Health-Related Quality Of Life
SD	Standard Deviation
DRG	Diagnosis-Related Groups
INHIS	Italian National Health Service
HVFA	Health Care Financing Administration
AAN	American Academy of Neurology
AES	American Epilepsy Society
OXC	Oxcarbazepine
FDA	Food and Drug Administration
SC	Sodium Channel blockers
G	Gamma-aminobutyric acid analogs
SV2	Synaptic Vesicle protein 2A binding
M	Multiple mechanisms
MMAS	Morisky Medication Adherence Scale
MPR	Medication Possession Ratio
BDI-II	Beck Depression Inventory-II
NDDI-E	Neurologic Disorders Depression Inventory-Epilepsy
PHQ-GAD 7	Patient Health Questionnaire-Generalized Anxiety Disorder7
IRB	Institutional Review Board

CCI	Charlson Comorbidity Index
GCN	Generic Code Number
NDC	National Drug Code
AHFS	American Hospital Formulary Service
PDC	Proportion of Days Covered
ICD-9-CM	The International Classification of Diseases, 9th Revision, Clinical Modification
CPT	Current Procedural Terminology
HCPCS	Healthcare Common Procedure Coding System
GEE	Generalized Estimating Equation
ZIP	Zero-Inflated Poisson regression
GLM	Generalized Linear Models
PASS	Power Analysis & Sample Size

## **Chapter 1 Introduction**

### **1.1 Background**

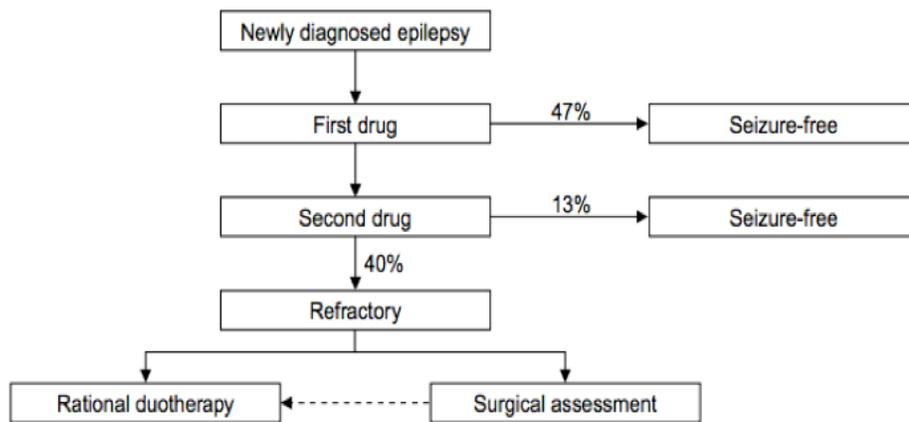
Epilepsy is the fourth most common neurological condition after migraine, stroke, and Alzheimer's disease with a prevalence of 2.2 million cases and an annual incidence of 150,000 new cases per year in the United States (U.S.).<sup>1,2</sup> The age-adjusted prevalence of epilepsy ranges from 5 to 7.1 cases per 1,000 persons, while the age-adjusted incidence of epilepsy ranges from 16 to 51 cases to 100,000 person-years. Also, the prevalence of epilepsy is higher in males than in females, while the age-adjusted prevalence is higher for African-Americans (8.2 cases per 1,000 persons) as compared to Caucasians (5.4 cases per 1,000 persons).<sup>3</sup>

In 1995, the average annual direct cost for epilepsy prevalent cases was \$1,072 per case, while the per member per year direct cost for the treatment of epilepsy in 2009 was estimated at \$8,206.<sup>4,5</sup> Potential drivers for the high and increasing burden of epilepsy include costs associated with injury, hospitalization, and adverse effects on a patient's mental health, which include anxiety, depression, and other cognitive impairment. The indirect costs drivers include epilepsy-related absenteeism, disability, and impaired quality of life.

Epilepsy treatment consists of vagal nerve stimulation, surgery, and pharmacotherapy. Due to the limited effectiveness of the first two options, pharmacotherapy is the foremost epilepsy treatment paradigm.<sup>6</sup> A 1984 Scottish prospective study of 525 newly-diagnosed epilepsy patients, aged 9 to 93 years, reported that about half (47%) of the patients became seizure-free while receiving their first antiepileptic drug (AED), and 13% became seizure-free with the first alternative monotherapy.<sup>7</sup> Thus, about 60% of the patients with newly-diagnosed epilepsy may

have seizure remission with less than three trials of AED regimens, while the remaining 40% of patients are considered refractory or drug-resistant and are candidates for additional AED trials or epilepsy surgery (Figure 1.1).<sup>8</sup> Further, about 1% of refractory patients may become seizure-free with a second alternative monotherapy, and 3% may become seizure-free with two AEDs.<sup>7</sup>

**Figure 1.1: Strategies for Managing Newly Diagnosed Epilepsy**



Source: Brodie et al. (2001)<sup>8</sup>

The International League Against Epilepsy (ILAE) commission defines drug-resistant epilepsy (DRE) (often used inter-changeably with “uncontrolled,” “medically refractory/intractable,” or “pharmacoresistant”) as “failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.”<sup>9</sup> Replicating the ILAE definition in population studies, the prevalence of refractory epilepsy in the U.S. population ranges from 1.7% to 29%.<sup>10-14</sup> Estimates of DRE are heavily based on patient self-reported data from literature and expert panels. Very few studies have evaluated the utilization of AEDs using administrative claims databases while assessing medically refractory epilepsy.<sup>10-14</sup> The epilepsy-related and non-epilepsy related medical

cost of care for establishment of epilepsy control in patients with refractory epilepsy is significant. The cost drivers include frequent hospitalizations and emergency department (ED) visits, longer hospital lengths of stay, and more neurologist, diagnostic imaging and other outpatient visits. Moreover, patients with refractory epilepsy are at an increased risk of fractures, head injuries, status epilepticus, motor-vehicle accident-related injuries, and sudden death.<sup>13</sup> The risk of sudden death among patients with refractory epilepsy is about 1.1 to 5.9 per 1,000 person-years with a cumulative probability of death of 8.7% at 6 years as compared to patients without refractory epilepsy.<sup>15-17</sup>

Previous studies by Manjunath et al. (2012), Chen et al. (2013), and Cramer et al. (2014) used commercial claims to quantify the economic burden of refractory epilepsy in adults.<sup>11,13,18,19</sup> Manjunath et al. assessed the burden among the Medicaid populations in Florida, Iowa, Kansas, Missouri, and New Jersey, and reported high health care utilization and costs for the patients with refractory epilepsy.<sup>13</sup> With more than half of Medicaid recipients living in poverty and having physical or cognitive limitations, refractory epilepsy is particularly debilitating for these patients.<sup>13</sup>

In patients with refractory epilepsy, when monotherapy fails, a small percentage of patients (14%) become seizure-free by switching to an alternative monotherapy.<sup>8,20</sup> Also, previous studies have hypothesized that small differences in between-product bioavailability from switching between brand-name and generic versions of AEDs, even within the narrow bounds of allowable variation that determine bioequivalence, can lead to adverse clinical outcomes. Studies have reported recurrence of seizures, high switchback rates from generic to brand name AEDs, and subsequent high health resource utilization due to antiepileptic drug substitutions.<sup>21-23</sup> As a result, an AED is often added to the initial regimen.<sup>24</sup>

Choosing an alternative AED from the many AEDs available is often a problem for the practicing physician. The drug selection may differ due to such things as formulary restrictions and an individual's reaction to medications. However, determining the optimal combination of AEDs is an area that is not yet well defined. Previous studies have illustrated the clinical efficacy of adding an AED over placebo or no treatment in patients with epilepsy; however, direct comparison between individual trials has not been possible due to baseline differences in the population. The concept of "rational polytherapy" has gained increased attention in epilepsy. Rational polytherapy indicates that AED combinations with different mechanisms of action (MOAs) are more effective than AED combinations with similar MOAs.<sup>20,25,26,27</sup> In light of the limited evidence to support the optimal combination of AEDs, refractory epilepsy treatment patterns in real world clinical practice need to be evaluated.

Data from a national survey indicate that 18% of the individuals with epilepsy were covered by Medicaid in the U.S. in 1994.<sup>28</sup> There is concern that patients on Medicaid may not be adherent to their regimen, which is associated with serious outcomes. A quarter of patients with epilepsy covered by Medicaid during the period from January 1997 to June 2006, in Florida, Iowa, and New Jersey were non-adherent to their AED regimen.<sup>29</sup> The lifetime prevalence of epilepsy in the state of Texas was reported to be 1.7% in 2005.<sup>30</sup> About 16% of Texans are enrolled in the Medicaid program.<sup>31</sup> Given the limited resources of the enrollees, the clinical burden of refractory epilepsy on the patients and the economic burden on the state need to be quantified. Also, previous studies have assessed epilepsy-related healthcare utilization before the U.S. Food and Drug Administration (FDA) approval of third-generation AEDs (e.g., rufinamide, retigabine/ezogabine, clobazam, lacosamide, and eslicarbazepine acetate were approved after 2008).<sup>10,24,29,32</sup> In the absence of real world evidence on the outcomes of patients with refractory epilepsy taking these

medications, it is imperative to evaluate the treatment patterns and associated economic outcomes in recent times.

## **1.2 Study Aim**

To better understand refractory epilepsy in Medicaid patients, this study uses Texas Medicaid medical and prescription claims data to characterize and compare the demographic and clinical characteristics, treatment patterns (consisting of medication adherence and persistence, and adding or switching to alternative therapy), and healthcare utilization and costs associated with patients who have refractory or non-refractory epilepsy.

## **1.3 Study Relevance**

Findings from this study about treatment patterns, resource utilization, and healthcare costs using real world data can be useful in filling a missing gap in the currently published literature. Evidence on patterns of AED use in clinical practice may contribute to the understanding of seizure control, and may thereby reduce subsequent epileptic events and costs. Likewise, the results of the analyses can help identify unmet needs in the epileptic population by improving seizure control, promoting better medication use behavior, and reducing economic burden. The results can also serve as input parameters in economic models for treatment interventions targeting this population.

## **Chapter 2 Literature Review**

### **Chapter Overview**

This chapter is divided into two sub-sections: epilepsy and refractory epilepsy. The first sub-section describes the epidemiology, management, economic, and humanistic burden of epilepsy. The second sub-section includes a detailed discussion on the definition, prevalence, and economic burden of refractory epilepsy. This chapter concludes with a discussion of AED treatment patterns and the impact of comorbid conditions on refractory epilepsy. Finally, it discusses Texas Medicaid, summarizes the literature, and lists the objectives and hypotheses of the study.

### **2.1 Epilepsy**

#### **2.1.1 Definition, Classification and Etiology of Epilepsy**

There is an ongoing debate regarding the classification of epilepsy as a disease or a syndrome.<sup>33,34</sup> The Commission of the ILAE describes an epileptic syndrome as “an epileptic disorder characterized by a cluster of signs and symptoms customarily occurring together; which include the type of seizure, etiology, anatomy, precipitating factors, age of onset, severity, chronicity, diurnal, and circadian cycling, and sometimes prognosis.” Thus, epileptic syndrome involves more than just the seizure type. In contrast, epilepsy disease is described as “a pathological condition with a single, specific, well-defined etiology.” This disease-syndrome distinction depends on the context of use.<sup>34</sup> For simplicity and consistency, the ILAE and the International Bureau for Epilepsy (IBE) define epilepsy as “a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neuro-biologic, cognitive, psychological, and social consequences of this condition.” Epilepsy requires the occurrence of at

least one epileptic seizure, described as “a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.”<sup>35,36</sup>

Based on the mode of seizure onset, seizures are mainly classified as generalized and focal seizures. Generalized seizures originate at a point and rapidly distribute in bilateral networks of the brain, which include the cortical and subcortical structures. The clinical manifestation of these seizures may vary from mild alterations in consciousness to convulsions. Generalized epileptic seizures are further categorized as: tonic-clonic seizures, absence seizures, myoclonic seizures, clonic seizures, tonic seizures, and atonic seizures. Tonic-clonic seizures, also known as grand mal seizures, are characterized by loss of consciousness and stiffening of the body followed by contraction of the muscles; absence seizures, also known as petit mal seizures, include brief lapses in awareness; myoclonic seizures involve sudden muscular contractions; clonic seizures consist of alternating successions of contractions and relaxations of a muscle; tonic seizures are depicted by an onset of increased muscle tone; and atonic seizures are characterized by a sudden loss of muscle tone. In contrast to generalized seizures, focal seizures originate within networks limited to a single hemisphere. These seizures may manifest with or without impairment of consciousness or awareness depending on the disruption in brain activity. Seizures can also be categorized as belonging to the unknown type.<sup>35,37</sup> Table 2.1 summarizes the classification of seizures as adopted by the ILAE.<sup>35</sup>

**Table 2.1: Classification of Seizures**

Generalized seizures
Tonic–clonic (in any combination)
Absence
Typical
Atypical
Absence with special features
Myoclonic absence
Eyelid myoclonia
Myoclonic
Myoclonic
Myoclonic atonic
Myoclonic tonic
Clonic
Tonic
Atonic
Focal seizures
Unknown
Epileptic spasm

Seizure that cannot be clearly diagnosed into one of the preceding categories is considered unclassified until further information allows their accurate diagnosis. This is not considered a classification category.

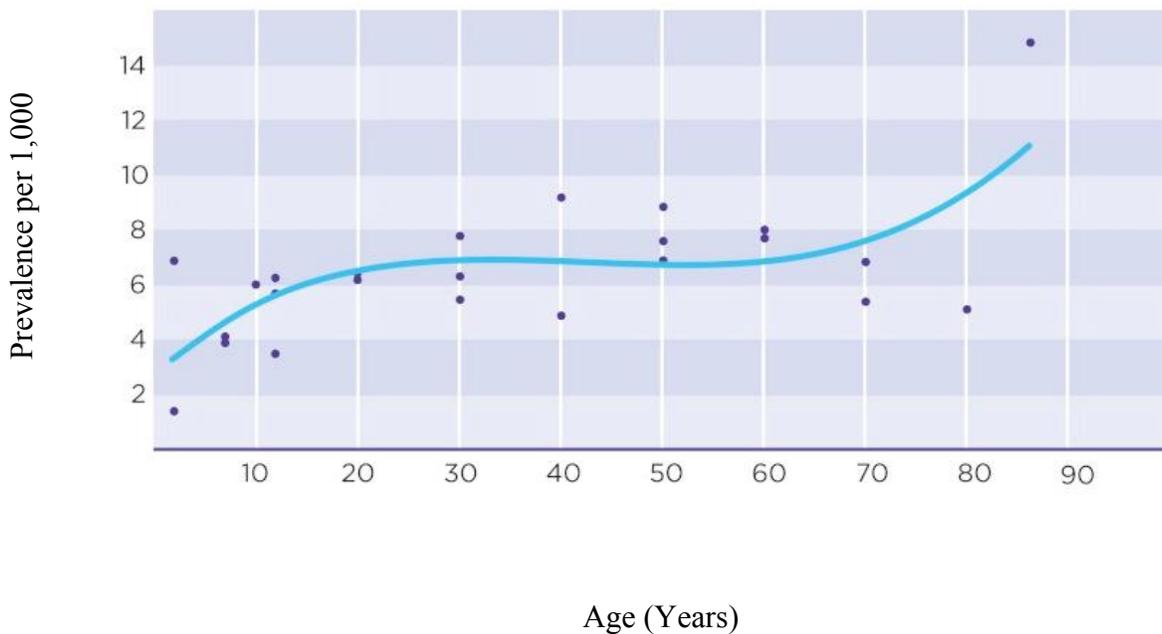
Source: Berg et al. (2010)<sup>35</sup>

The underlying cause of epilepsy may be genetic, structural, or unknown. Epilepsy may be a symptom of a known genetic deficit or an environmental external factor that may contribute to the expression of the disease. Structural or metabolic conditions such as stroke, trauma, infection, or tuberous sclerosis may increase the risk of developing epilepsy. The etiology of epilepsy may also be unknown due to an unrecognized disorder or a core genetic deficit.<sup>35</sup>

### 2.1.2 Epidemiology of Epilepsy

Epilepsy affects about 1% of adults in the U.S.<sup>38</sup> National estimates of the prevalence of epilepsy are scarce. The earliest report by the Centers of Disease Control and Prevention (CDC) found the overall prevalence of epilepsy to be 4.7 cases per 1,000 persons during 1986 – 1990.<sup>39</sup> Recent estimates from a composite of studies conducted in the U.S. (1978 – 2005) suggest that the incidence of epilepsy is bimodal, with peak incidence rates in young children and older adults, while the number of people with epilepsy at any point in their lifetime increase as age increases.<sup>37</sup> Figure 2.1 depicts the prevalence of epilepsy by age (1978-2005).

**Figure 2.1: Prevalence of Epilepsy by Age in the U.S. (1978-2005)**



Source: England et al. (2012)<sup>37</sup>

Children and adolescents have seizures due to genetic or unknown causes, while severe head injury, stroke, and tumor are frequently considered as triggers of seizures in adults. Unlike adults, symptoms in children often resolve as age increases. Compared to adults, children respond

differently to medications and have different side effects. As a result, they typically need more frequent dose adjustments. Moreover, as brain development is rapid in the initial years of life, children require regular monitoring to assess the impact of seizures and treatment on cognition and learning abilities that reflect ongoing maturational changes. Also, the frequency of seizures experienced by children is much higher than those experienced by adults. As a result, the neuropsychological compromise seen in children is much more widespread than in adults.<sup>40</sup> This heterogeneity makes it a challenge to study epilepsy in children, and most studies using administrative claims data have focused on understanding the etiology and burden of epilepsy in adults.

If a patient is being treated for epilepsy, and the most recent seizure occurred within two and five years, the patient is characterized as having active epilepsy.<sup>41</sup> Data from the National Health Interview Survey (NHIS) indicated that about 1.9% of adults with annual family income levels less than or equal to \$34,999 had active epilepsy in 2010.<sup>38</sup> In the Ohio Medicaid program, the prevalence of active epilepsy was 13.2 cases per 1,000 persons, and the incidence was 362 cases per 100,000 person-years from 1992 – 2006.<sup>42</sup> According to a report by the ILAE, IBE, and the World Health Organization (WHO), the low-income population in the U.S. carries a disproportionate amount of epilepsy burden, and deserves attention for its health care needs and supportive services.<sup>43</sup>

Patients with epilepsy are at a higher risk of mortality than the general population. The causes of death in patients with epilepsy include internal causes, such as cardiovascular and cerebrovascular diseases, neoplasms, and pneumonia, and external causes, such as suicide, drowning, accidents, and injury. Data pooled from studies across multiple countries show that

patients with epilepsy have a 1.6-11.4 times greater mortality rate than patients without epilepsy.<sup>44</sup> Also, the rate of sudden unexplained death in epilepsy (SUDEP) is reported to be nearly 24 times higher than the general population expected death rate, with a standardized mortality ratio of 23.7% and overall incidence of 0.35 cases per 1,000 person-years.<sup>15-17</sup> SUDEP is defined as sudden, unexpected, non-traumatic, and non-drowning death in patients with epilepsy. In the U.S., about 2,000 deaths occur each year due to SUDEP. The years of potential life lost to SUDEP is 73,000 per year, which outweighs the values for multiple sclerosis, Alzheimer's disease, and Parkinson's disease.<sup>44</sup> The rates of SUDEP and epilepsy-related mortality are estimated to be higher in adults than in children.<sup>45</sup>

### **2.1.3 Treatment of Epilepsy**

The therapies commonly used to prevent seizures include pharmacotherapy, diet changes, and brain surgery. Vagus Nerve Stimulation (VNS) is another option, when other treatments are not effective.

#### **2.1.3.1 Pharmacotherapy**

Medications used to treat seizures can be grouped by two classifications; generation and mechanism of action (MOA).

##### **2.1.3.1.1 Generations of Antiepileptic Drugs**

Pharmacotherapy consisting of AEDs available before 1980 are classified as "first-generation," those available after 1993 are classified as "second-generation," and those available after 2007 are classified as "third generation".<sup>46,47</sup> The newer AEDs are generally recognized to

have better safety and tolerability profiles.<sup>48,49</sup> AEDs classified as first, second, and third generation are listed in Table 2.2, while Table 2.3 displays the most common AED regimens used in adults listed by year of introduction.<sup>48,50</sup>

**Table 2.2: List of Antiepileptic Drugs**

<b>Generation</b>	<b>Generic Name</b>	<b>Brand Name</b>
First Generation	Phenobarbital	Luminal®
	Phenytoin	Dilantin®, Phenytek®
	Primidone	Mysoline®
	Ethosuximide	Zarontin®
	Ethotoin	Peganone®
	Carbamazepine	Carbatrol®, Epitol®, Equetro®, Tegretol®
	Valproate/valproic acid	Depakote®, Depakene®, Stavzor®
	Clonazepam	Klonopin®
Second Generation	Oxcarbazepine	Oxtellar®, Trileptal®
	Zonisamide	Zonegran®
	Lamotrigine	Lamictal®
	Felbamate	Felbatol®
	Gabapentin	Gabarone®, Gralise®, Neurontin®
	Fosphenytoin	Cerebyx®
	Diazepam	Diastat®
	Topiramate	Topamax®, Topiragen®, Trokendi®
	Tiagabine	Gabitril®
	Levetiracetam	Keppra®
	Pregabalin	Lyrica®
	Third Generation	Lacosamide
Rufinamide		Banzel®
Vigabatrin		Sabril®
Clobazam		Onfi®
Retigabine/ezogabine		Potiga®
Eslicarbazepine acetate		Aptiom®

**Table 2.3: Dosages and Major Safety Issues of Antiepileptic Drugs in Adults**

<b>AED (Year of introduction)</b>	<b>Suggested titration</b>	<b>Suggested range of average target dose (total mg/day; frequency of dosing)</b>	<b>Safety Issues</b>
Phenobarbital (1912)	50 mg every 7 days	50–200 mg; qd, bid	Idiosyncratic rash; rarely toxic epidermal necrolysis; hepatotoxicity; osteomalacia; Dupuytren's contracture
Phenytoin (1938)	50–100 mg every 3–5 days; beyond 200 mg in 25–30 mg steps	200–300 mg; bid, tid	Idiosyncratic rash; rarely pseudolymphoma; peripheral neuropathy; Stevens-Johnson syndrome; Dupuytren's contracture; hepatotoxicity; osteomalacia
Primidone (1952)	62.5–250 mg every 7 days	500–750 mg; tid	Idiosyncratic rash; rarely agranulocytosis; thrombocytopenia; lupus-like syndrome
Ethosuximide (1953)	250 mg daily every 4-7 days	500 mg; qd	Rarely idiosyncratic rash; Stevens-Johnson syndrome; aplastic anaemia
Ethotoin (1957)	1 g or less in 4-6 divided doses daily	2-3 g daily	Blood problems; liver problems; swollen glands; lupus; serious rash
Carbamazepine (1963)	200 mg every 3 days	600–1200 mg; bid or tid	Idiosyncratic reactions; rarely Stevens-Johnson syndrome; aplastic anaemia; hepatotoxicity

**Table 2.3: Dosages and Major Safety Issues of Antiepileptic Drugs in Adults (Continued)**

AED (Year of introduction)	Suggested titration	Suggested range of average target dose (total mg/day; frequency of dosing)	Safety Issues
Valproate (1968)	500 mg every 3–7 days	600–1500 mg; bid slow release, tid	Teratogenicity; rarely acute pancreatitis; hepatotoxicity; thrombocytopenia; encephalopathy; polycystic ovarian syndrome
Clonazepam (1975)	Increments of 0.5-1 mg every 3 days	20 mg; tid	Drowsiness; ataxia; behavioral changes
Oxcarbazepine (1990)	150 mg every 3–7 days	800–1800 mg; bid, tid	Idiosyncratic rash; hyponatraemia
Zonisamide (1990)	25 mg	300 mg; bid	Rash; rarely blood dyscrasias
Lamotrigine (1991)	Monotherapy: 25 mg for 2 weeks, 50 mg for the next 2 weeks, then increases of 50–100 mg/week. Add-on in the presence of Valproic acid: 25 mg every other day for 2 weeks, 25 mg/day for the next 2 weeks, then increases of 25–50 mg/week. Add-on in the presence of enzyme- inducing AEDs: 50 mg for 2 weeks, 100 mg for the next 2 weeks, then increases of 50–100 mg/week.	100–400 mg; qd, bid	Idiosyncratic rashes; rarely Stevens-Johnson syndrome; Toxic epidermal necrolysis; liver failure; aplastic anaemia; multiorgan failure

**Table 2.3: Dosages and Major Safety Issues of Antiepileptic Drugs in Adults (Continued)**

<b>AED (Year of introduction)</b>	<b>Suggested titration</b>	<b>Suggested range of average target dose (total mg/day; frequency of dosing)</b>	<b>Safety Issues</b>
Felbamate (1993)	300 mg every 7 days	2400–3600 mg; bid, tid	Hepatic failure; aplastic anaemia
Gabapentin (1993)	300 mg every 1-3 days	900–2400 mg; bid, tid	Paradoxical increase in seizures
Fosphenytoin (1996)	Expressed as phenytoin sodium equivalents. 1.5 mg of fosphenytoin sodium is equivalent to 1 mg phenytoin sodium. Loading dose of 15-20 mg PE/kg administered at 100-150 mg PE/min	4–6 mg PE/kg/day in divided doses	Pruritus; dizziness, somnolence, ataxia
Diazepam (1997)	Rectal get dose of 0.2 mg/kg of body weight to treat no more than five episodes per month and no more than one episode every 5 days.	A second dose, when required, may be given 4-12 hours after the first dose.	Sedation; agitation; chest pain; rash
Topiramate (1995)	25 mg for 1–2 weeks; beyond 100 mg, 25–50 mg per week	100–400 mg; bid	Weight loss; kidney stones; impaired cognition
Tiagabine (1996)	6 mg every 5–7 days	36–60 mg; tid	Increased seizures; non-convulsive status
Levetiracetam (1999)	500 mg every 1–3 days	1000–3000 mg; bid	Behavioural problems

**Table 2.3: Dosages and Major Safety Issues of Antiepileptic Drugs in Adults (Continued)**

<b>AED (Year of introduction)</b>	<b>Suggested titration</b>	<b>Suggested range of average target dose (total mg/day; frequency of dosing)</b>	<b>Safety Issues</b>
Pregabalin (2004)	75–150 mg every 3–7 days	150–600 mg; bid	Weight gain; rarely increased seizures
Lacosamide (2007)	Monotherapy: 100 mg twice daily increased at weekly intervals to 150-200 mg twice daily. Adjunctive therapy: 50 mg twice daily increased at weekly intervals to 100-200 mg twice daily.	200-400 mg; qd	Dizziness; nausea; vomiting
Rufinamide (2008)	400-800 mg per day administered in two equally divided doses increased by 400-800 mg every other day until a maximum daily dose of 3200 mg in two equally divided doses.	3200 mg; qd	Dizziness; nausea; diplopia; ataxia
Vigabatrin (2009)	500 mg every 7 days	500–3000 mg; bid	Visual field defects; increased seizures
Clobazam (2011)	10 mg per day	10–20 mg; bid	Rarely idiosyncratic rash
Retigabine /Ezogabine (2011)	150 mg per day	600-1200 mg; qd	Dizziness; somnolence; headache; fatigue

**Table 2.3: Dosages and Major Safety Issues of Antiepileptic Drugs in Adults (Continued)**

AED (Year of introduction)	Suggested titration	Suggested range of average target dose (total mg/day; frequency of dosing)	Safety Issues
Perampanel (2012)	2 mg once daily	4-12 mg; qd	Dizziness; somnolence; fatigue; irritability; falls; nausea; weight gain; vertigo; ataxia; headache; vomiting; contusion; abdominal pain; anxiety
Eslicarbazepine acetate (2013)	400 mg once daily increased to 800 mg once daily after one week.	800-1200 mg; qd	Dizziness; headache; diplopia

AED = Antiepileptic drug

qd = quaque die (once a day); bid = bis in die (twice a day); tid = ter in die (three times a day)

Source: Schmidt, 2009; Druga-FDA; Brodie et al. (2011); Duncan et al. (2006); Lason et al. (2006); Rho et al. (1994); Bazil et al. (2003); Uthman, (2000); Morris et al. (2013); Landy et al. (1993)<sup>48,50-58</sup>

### 2.1.3.1.2 Mechanism of Action of Antiepileptic Drugs

Table 2.4 lists the MOA of AEDs based on the foremost targets at therapeutic concentration.<sup>51</sup> Figure 2.2 depicts the main targets of AEDs.<sup>52</sup> The most common targets among AEDs are sodium channels. The voltage-dependent sodium channels generate both normal action potentials and seizures. Antagonists of sodium channels prolong the time of the channel inactivation during epileptic discharges. Inactivation leads to conformational changes from an open channel to a non-conducting state. Carbamazepine, derivatives of carbamazepine (i.e., eslicarbazepine acetate, oxcarbazepine), phenytoin, fosphenytoin, ethotoin, lamotrigine, and rufinamide bind to the fast-inactivated state of the voltage-gated sodium channel through isoforms such as Nav1.1–Nav1.4, Nav1.6, and Nav1.7. In contrast, lacosamide binds to the slow-inactivated state of the voltage-gated sodium channels through isoforms Nav1.5, Nav1.8, and Nav1.9, which reduces the channel conductance.<sup>51,53</sup>

Benzodiazepines, barbiturates, vigabatrin, and tiagabine target the synaptic Gamma-aminobutyric acid (GABA) transmission. Diazepam, clonazepam, clobazam, phenobarbital, and primidone work as GABA<sub>A</sub> receptor agonists. Activation of GABA<sub>A</sub> receptor generates fast inhibitory postsynaptic potentials, which inhibit seizures. GAT-1, a GABA transporter, participates in GABA uptake and is the target for the efficient antiepileptic drug tiagabine. Vigabatrin is an irreversible GABA transaminase inhibitor. Inhibition of GABA transaminase, an enzyme that catabolizes GABA, increases the GABA level in brain tissue and leads to an elevated seizure threshold.<sup>51,53</sup>

Gabapentin, pregabalin, and ethosuximide act on the voltage-gated calcium channels. The

foremost mechanism of action of gabapentin, pregabalin, and ethosuximide is blockage of calcium channels; gabapentin and pregabalin block the high-voltage-activated calcium channel of the P/Q-type, and ethosuximide blocks the low-voltage-activated calcium channel of the T-type. This prevents synchronized depolarization of neurons, resulting in seizure control.<sup>51,53</sup> Valproic acid/sodium valproate, felbamate, topiramate, and zonisamide have multiple MOAs. The mechanism of valproic acid is not fully known. It may act through a combination of mechanisms involving sodium flux, potassium channel inhibition, and modulation of GABA levels. Felbamate has dual actions in inhibiting N-methyl-D-Aspartate (NMDA) and potentiating (GABA) brain mechanisms.<sup>54</sup> Topiramate prolongs inactivation of sodium channels, acts as a GABA<sub>A</sub> agonist, and a non-NMDA glutamate receptor antagonist. Perampanel is an antagonist of the glutamate receptor. Zonisamide blocks sodium channels and T-type calcium channels, binds to the GABA receptor, and facilitates dopaminergic neurotransmission.<sup>51,55</sup>

Levetiracetam binds to stereoselective sites on synaptic vesicles in the central nervous system, inhibits N-type calcium channels, and reverses inhibition of GABA and glycine-gated currents. Retigabine/ezogabine acts as a potassium channel agonist. Specifically, retigabine binds to a hydrophobic amino acid pocket and stabilizes the neuronal Kv7 channels in an open conformation preventing epileptic discharges. Kv7, a subfamily of the voltage-dependent potassium channels, regulates the response of neurons to excitation and forms a potent inhibitory mechanism in the brain.<sup>51,53</sup>

**Table 2.4: Mechanism of Action of Antiepileptic Drugs based on the Foremost Targets at Therapeutic Concentration**

<b>Antiepileptic drug<sup>a</sup></b>	<b>Target</b>	<b>Mechanism</b>
Carbamazepine <sup>1</sup> , Eslicarbazepine Acetate <sup>2</sup> , Oxcarbazepine <sup>2</sup> , Phenytoin <sup>1</sup> , Fosphenytoin <sup>2</sup> , Ethotoin <sup>1</sup> , Lamotrigine <sup>2</sup> , Rufinamide <sup>3</sup>	Sodium channel actions	Blockade by stabilizing fast-inactivated state
Lacosamide <sup>3</sup>		Blockade by stabilizing slow-inactivated state
Diazepam <sup>2</sup> , Clonazepam <sup>1</sup> , Clobazam <sup>3</sup> , Phenobarbital <sup>1</sup> , Primidone <sup>1</sup>	GABA-related actions	Activation of GABA <sub>A</sub> receptor
Tiagabine <sup>2</sup>		Blockade of GABA transporter-1
Vigabatrin <sup>3</sup>		Inhibition of GABA transaminase
Gabapentin <sup>2</sup> , Pregabalin <sup>2</sup>	Calcium channel actions	Blockade of high voltage-activated channel (P/Q-type)
Ethosuximide <sup>1</sup>		Blockade of low voltage-activated channel (T-type)
Sodium Valproate/Valproic Acid <sup>1</sup> , Felbamate <sup>2</sup> , Topiramate <sup>2</sup> , Perampanel <sup>3</sup> , Zonisamide <sup>2</sup>	Multiple actions	Various actions on multiple targets
Levetiracetam <sup>2</sup>	SV2A actions	Modulation of SV2A
Retigabine/Ezogabine <sup>3</sup>	Potassium channel activity	Opens Kv7 potassium channels

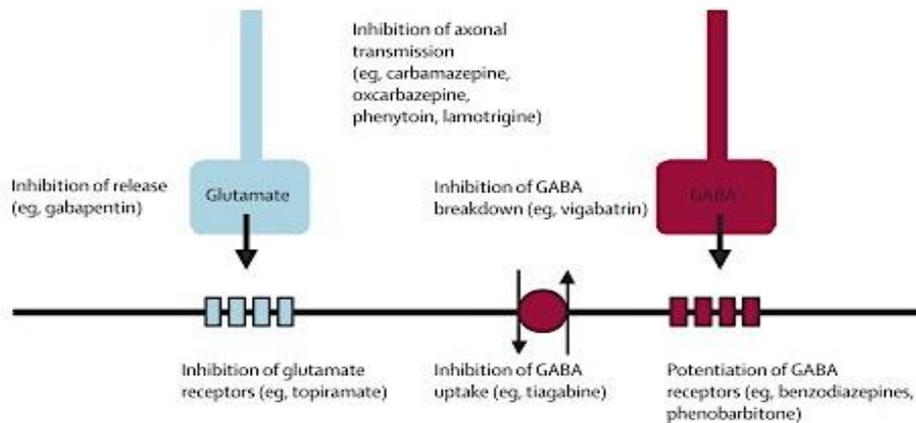
GABA = Gamma-aminobutyric acid

SV2A = Synaptic vesicle protein 2A

<sup>a</sup>Generation (see Table 2.2) 1 = First generation; 2 = Second generation; 3 = Third generation

Source: Margolis et al. (2014); Engel, 1996<sup>27,59</sup>

**Figure 2.2: Main Targets of Antiepileptic Drugs**



GABA = Gamma-aminobutyric acid  
Source: Duncan et al. (2006)<sup>52</sup>

### 2.1.3.2 Vagus Nerve Stimulation

VNS was first approved for use in 1997 as an adjunctive therapy in reducing seizure frequency in adults and adolescents (>12 years) with partial onset seizures not controlled by AEDs. VNS may also be used in treating generalized epilepsy.<sup>56,57</sup>

The neurocybernetic prosthesis (NCP) system of the VNS is an implantable pulse-generator surgically implanted into the upper left chest with the lead tunneled under the skin and wound around the left vagus nerve in the neck area. The VNS causes enhancement of inhibition by interrupting the events proceeding and leading to a seizure, thus preventing a seizure.<sup>56</sup> Generally, implantation of a VNS device requires less than two hours and patients are discharged within 24 hours. The follow-up visits among patients with VNS are similar to the regular visits among patients on AEDs.<sup>58</sup>

### 2.1.3.3 Surgery

In patients who fail to achieve seizure remission with the use of AEDs, surgery may be used as a remediable option.<sup>59</sup> The surgical intervention is determined by diagnostic tests that involve the use of electroencephalography (EEG), magnetic resonance imaging (MRI), positron-emission tomography, single-photon-emission computed tomography, and neuropsychological testing.<sup>60</sup> In the past, video EEG monitoring was performed on an inpatient basis with several days of continuous monitoring required to record a sufficient number of seizures, resulting in an expensive pre-surgical evaluation.<sup>61</sup> In recent times, outpatient EEG recording with home-monitoring systems, and the use of MRI and other modern diagnostic techniques, have made pre-surgical evaluation less expensive. Few surgical procedures commonly performed to treat epilepsy include Anterior temporal lobectomy, amygdalohippocampectomy, neocortical resection, lesionectomy, multiple subpial transections, hemispherectomy and large multilobar resections, and corpus callosotomy.<sup>59</sup> An estimated 70% and 25% of appropriately selected candidates may be seizure-free with temporal and frontal resection, respectively.<sup>62</sup>

Despite the advances, surgery is often underutilized in patients with epilepsy in the U.S.<sup>63</sup> Data from the Nationwide Inpatient Sample (NIS) hospital discharge database (1990 - 2008) showed that the hospitalizations for lobectomy significantly ( $p < 0.01$ ) reduced from 6.9% during 1990 – 1994 to 4.3% during 2004 – 2008. Also, patients with Medicaid had notably lower rates of surgery than patients with private insurance.<sup>63</sup>

#### **2.1.4 Economic and Humanistic Burden of Epilepsy**

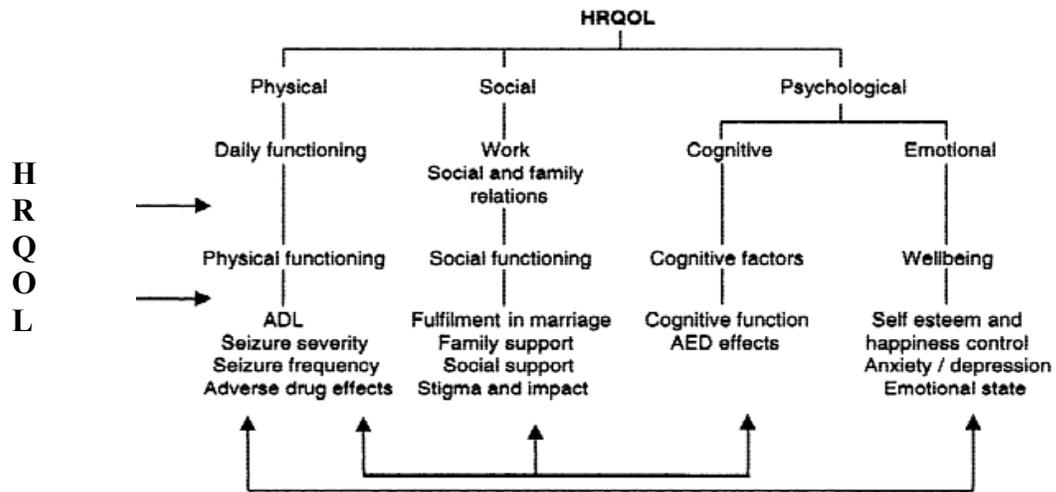
The impact of epilepsy is multi-faceted, affecting the economic, clinical, and humanistic outcomes of patients. In the case of economic burden, patients with epilepsy have higher healthcare utilization and costs than patients without epilepsy.<sup>4,5,64-66</sup> In 1995, the average direct cost for epilepsy prevalent cases in the U.S. derived using population claims data was \$6,429 per case over a 6-year period, and the annual direct cost of the 2.3 million extrapolated prevalent cases was \$1.7 billion. Indirect costs consisting of morbidity- and mortality-related costs accounted for 85% (\$10.8 billion) of the total healthcare costs.<sup>4</sup> Data pooled from the 1996 – 2004 Medical Expenditure Panel Survey (MEPS) estimated the excess total medical expenditures for those with epilepsy at \$4,523 (2004 dollars), with a mean unadjusted total expenditure estimated at \$9,181 (95% CI=\$7,889 to \$10,473) and the annual economic impact of epilepsy of the 2.1 million cases at \$9.6 billion (95% CI=\$6.7 billion to \$12.4 billion) composed of medical expenditures and informal care.<sup>66</sup> Among privately insured U.S. patients between 1999 through 2005, the direct annual cost for patients with epilepsy was \$10,258 (2005 dollars) per patient with epilepsy-related costs of \$2,057. Also, the annual indirect cost for employees with epilepsy was \$3,192 (2005 dollars).<sup>64</sup> Kurth et al. (2010) assessed the health care resource utilization of patients using the Thomas-Reuters insurance database from 2005-2007, and found that patients with active epilepsy averaged 10 physician visits per year, 24 diagnostic tests or procedures per year, more than 30 drug dispensings per year, and more than one ED visit per year.<sup>65</sup> In 2009, the estimated direct health plan paid cost (\$, per member per year) in the U.S. for treatment of epilepsy was \$8,206.<sup>5</sup>

Thus, there is heterogeneity in the estimates reported by previous studies. In summary, in 1995, the annual total direct cost of patients with epilepsy was estimated at \$1,072 per-patient and

the annual indirect cost comprising of morbidity- and mortality-related cost was estimated at \$328,481 per-patient (i.e., morbidity-related cost of \$10,057 and mortality related-cost of \$318,424).<sup>4</sup> In 2005, the annual total direct cost was estimated at \$10,258 per-patient and the annual indirect cost comprising of informal care days provided by family members was estimated at \$3,192 per-patient.<sup>4,64</sup> Further, the 1995 annual total direct cost of the 2.3 million cases with epilepsy was estimated at \$1.7 billion, while the 2004 annual total direct cost of the 2.1 million cases with epilepsy was estimated at \$9.5 billion.<sup>4,66</sup> The direct cost estimates reported in 1995 are conservative as the projections reflect the treatment patterns available through the mid-1990s. Newer therapies, such as VNS and the second- and third-generation AEDs available in recent years, were not included. The epilepsy-related cost was estimated at \$9,181 per-patient, in 2004, in a general population using survey data, while in 2005, it was estimated at \$2,057 per-patient, in a privately insured population using claims data.<sup>64,66</sup> Thus, direct comparison of these estimates are not possible due to differences in the patient population, type of costs included in the study, and methods used to quantify the burden.

According to the WHO, disability due to epilepsy accounts for approximately 1% of the global burden of disease.<sup>67</sup> The negative effects of epilepsy extend beyond the duration of individual seizures.<sup>68</sup> Potential drivers for the high burden of epilepsy include injury, hospitalization, mortality, and adverse effects on a patient's mental health, including anxiety, depression, and other cognitive impairment. The substantial indirect costs associated with epilepsy include medically-related absenteeism, disability, and affected quality of life. Epilepsy may affect the physical, social, neuropsychological, and psychological functioning of patients, and, thus, impact daily functioning, social and family relations, cognitive factors, self-esteem, and happiness (Figure 2.3).<sup>69</sup>

**Figure 2.3: Factors Affecting the Health-Related Quality of Life (HRQOL) for Patients with Epilepsy**



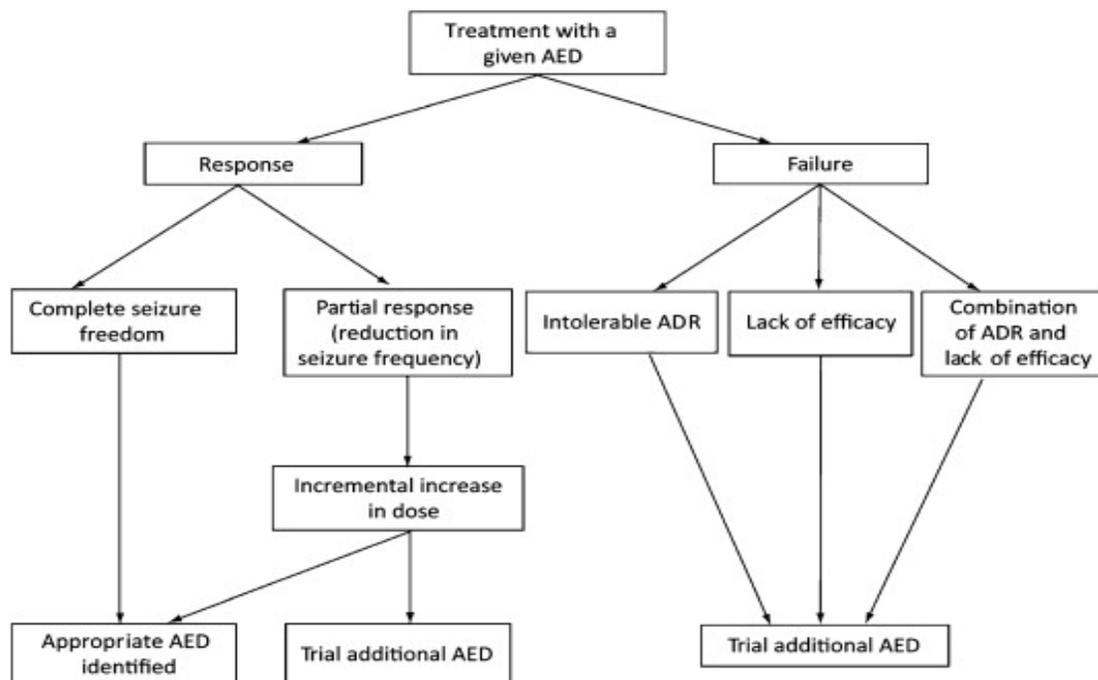
Source: Baker, 2001<sup>69</sup>

## 2.2 Refractory Epilepsy

### 2.2.1 Definition and Classification of Refractory Epilepsy

Despite advances in epilepsy pharmacotherapy, about one-third of patients are drug-resistant or refractory. These patients often receive polytherapy and additional AED trials are needed to identify optimal therapy. Figure 2.4 outlines the treatment outcomes of patients.

**Figure 2.4: Response with Antiepileptic Drug**



Source: Laxer et al. (2014)<sup>44</sup>

Early working definitions used to operationalize DRE (i.e., refractory epilepsy) among pediatrics and adults, evaluated seizure remission by assessing tolerability of drugs, and followed patients for 12-18 months (Table 2.5).<sup>7,70-72</sup> Note that all three of the studies focused on pediatric patients and only one included adults. All the three diagnostic criteria had favorable observer agreement and were credible over long-term follow-up. In other words, as the length of follow-up increased, the outcome (i.e., refractoriness) became more apparent.<sup>73</sup>

**Table 2.5: Definitions of Drug-Resistant Epilepsy**

<b>Author</b>	<b>Patient population</b>	<b>Definition</b>
Camfield and Camfield, 1996 <sup>70</sup>	Pediatrics	Patients with an average of two or more seizures in each 2-month period during the last year of observation, despite treatment with at least three AEDs as monotherapy or polytherapy
Kwan and Brodie, 2000 <sup>7</sup>	Pediatrics and adults	Patients who had seizures without a seizure free status (i.e., lack of seizures of any type for a minimum of 1 year while receiving the same dose of AED or while not taking any medication) were considered to be refractory
Berg, 2006 <sup>71,72</sup>	Pediatrics	Failure of two medications for seizure control or failure of one for seizure control and two others for intolerable side effects, and at least one seizure per month on average over an 18-month period. A child could have up to but no more than a 3-month seizure-free period

Source: Tellez-Zenteno et al. (2014)<sup>74</sup>

Recognizing the need to standardize DRE definitions and shorten the length of follow-up to diagnose refractoriness, the ILAE Commission on therapeutic strategies provided a two-hierarchical level framework to define DRE in 2010.<sup>9</sup> Level 1 is comprised of a broad categorization of outcomes to each therapeutic intervention (whether pharmacologic or non-pharmacologic) and includes a minimum dataset needed for determining the outcomes. The categories of outcomes include “seizure-free,” “treatment failure,” and “undetermined,” which are further subdivided into three groups based on outcomes with respect to adverse effects (A: no occurrence; B: occurrence; and C: undetermined occurrence of adverse events) (Table 2.6). Capturing this information often aids clinicians in determining interventions.

**Table 2.6: Scheme for Categorizing Outcome(s) of a Drug Intervention for Epilepsy**

<b>Seizure control</b>	<b>Occurrence of adverse effects</b>	<b>Outcome category</b>
1. Seizure-free	A. No B. Yes C. Undetermined	1A 1B 1C
2. Treatment failure	A. No B. Yes C. Undetermined	2A 2B 2C
3. Undetermined	A. No B. Yes C. Undetermined	3A 3B 3C

Source: Kwan et al. (2010)<sup>9</sup>

The minimum dataset required to determine whether the trial of an intervention is informative in an individual patient, as stated by the ILAE, includes:

- Nature of the intervention (e.g., type of drug)
- Mode of application (e.g., formulation, dose, dosing interval, and patient compliance)
- Duration of exposure
- Occurrence of seizures and adverse effects during the trial period
- Whether there was any effort to optimize dose
- Reason(s) for discontinuation (if applicable)
  - Unsatisfactory seizure control
  - Adverse effects
  - Long-term seizure freedom
  - Psychosocial reasons, for example, planning for pregnancy
  - Administrative reasons, for example, lost to follow up
  - Financial issues, for example, cannot afford treatment
  - Patient/caretaker preference
  - Other reasons

Level 2 provides a core definition of DRE, which is defined as “failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.” This classification of DRE is valid for a given point in time and does not imply that a patient would never become seizure-free on further titrations of AEDs. After careful deliberation of the available evidence from prospective and retrospective studies, the ILAE commission adopted the failure of two AED schedules in the

definition to represent a testable hypothesis and to prevent delay in the evaluation. In addition, consideration is also given to frequency of seizures and duration of follow-up.

Using the scheme of level 1 (Table 2.6), drug resistance is defined as having a Category 2 outcome for trials of at least two AEDs (monotherapy or in combination) without a Category 1 outcome on the drug(s) currently taken. A patient may have a Category 1 outcome if seizure-free for a minimum of three times the longest pretreatment inter-seizure interval or for 12 months, whichever is longer.<sup>9</sup>

The ILAE definition has been established as a valid and reliable measure to define refractory epilepsy in comparison to clinically significant constructs. Comparison of the ILAE definition with previously established definitions by Berg, Kwan and Brodie and Campfield and Campfield showed the highest interobserver ( $\kappa = 0.77$  vs.  $\kappa = 0.56$  vs.  $\kappa = 0.58$  vs.  $\kappa = 0.69$ ) and intraobserver ( $\kappa = 0.82$  vs.  $\kappa = 0.81$  vs.  $\kappa = 0.82$  vs.  $\kappa = 0.72$ ) reliability. Also, the Phi correlation between the ILAE definition and the definitions by Berg ( $\Phi = 0.75$ ), Campfield and Campfield ( $\Phi = 0.81$ ) and Kwan and Brodie ( $\Phi = 0.93$ ) were high. This corroborates that the ILAE definition provides accurate diagnosis of refractory epilepsy.<sup>74</sup>

## 2.2.2 Prevalence Estimates of Refractory Epilepsy

Applying the ILAE definition to clinical practice, the prevalence of refractory epilepsy ranges from 1.7% to 33% (Table 2.7).<sup>10-13,74,75</sup> The estimates of the prevalence of refractory epilepsy have not been consistent due to differences in population selection, terminology, and characterization of epilepsy.

Two studies conducted in Spain and Canada used the ILAE definition to classify refractory epilepsy. In 2012, a prospective study in Spain among 508 children less than 14 years of age treated for epilepsy reported the prevalence of refractory epilepsy as 10% (95% CI=7,13), 19% (95% CI=15,23) and 23% (95% CI=19,27) at two, six, and ten years after diagnosis, respectively.<sup>75</sup> Similarly, a 2014 retrospective chart review in an adult Canadian epilepsy center at Saskatchewan followed 250 patients with severe epilepsy (i.e., refractory epilepsy) with a mean ( $\pm$  standard deviation (SD)) duration of epilepsy of 22.6 ( $\pm$ 14.0) years. The study estimated the point prevalence of refractory epilepsy at 33%.<sup>74</sup>

Three studies conducted in the U.S. used working definitions of refractory epilepsy to operationalize refractoriness. These retrospective studies used population-based administrative claims data to characterize the patients. Manjunath et al. (2012) used a restrictive definition to develop a selection algorithm to replicate the levels of the ILAE definition using public and private insurance claims data. In addition to the ILAE criteria, this study also included restrictions regarding time for changes (i.e., 30 days) and requiring an ED visit or hospitalization. The study used Medicaid claims (1997 – 2009) for five states (Florida, Iowa, Kansas, Missouri, New Jersey), and private insurance claims data (1999 – 2008) from the Ingenix employer database. The study identified patients with refractory epilepsy as those with at least two consecutive changes in AED

therapy (switch to a different compound or addition of an adjunctive compound) occurring at least 30 days apart, followed by at least one epilepsy-related ED visit or hospitalization during the next 365 days. An interval of at least 30 days between each AED therapy was used as a proxy to ensure that the AED changes occurred due to inadequate treatment and not due to tolerability issues. Any change in AED therapy occurring within 30 days was assumed to occur due to tolerability issues. The inclusion criterion requiring an epilepsy-related ED visit or hospitalization following an AED change restricted the study to patients with severe seizures (i.e., requiring ED visit or hospitalization). Thus patients who may have had drug changes but managed on an outpatient basis (i.e., not requiring ED visit or hospitalization) were not included, thus refractory epilepsy prevalence was likely underestimated. The study found the prevalence of refractory epilepsy to be 3.2% in the 110,312 eligible Medicaid sample, and 1.7% in the 36,529 eligible employer population.<sup>13</sup> The study's more restrictive sample identification criteria may explain the relatively low prevalence estimates.

Chen et al. (2013) evaluated the prevalence of refractory epilepsy in patients with partial epilepsy observed in the U.S. Thomson Medstat MarketScan commercial insurance database from 2004 - 2008. Refractoriness was defined based on having three lifetime AEDs observed in the dataset. Patients were included in the refractory group on receiving the third AED. Since the onset of seizures could not be determined from the data, the study used a less restrictive definition that did not require patients to have an ED visit or hospitalization following the third AED therapy. Using this definition, the study reported the prevalence of refractory epilepsy to be 11% among the 79,149 eligible patients with partial epilepsy on commercial insurance in the U.S.<sup>10</sup> Using the same U.S. Thomson Reuters MarketScan commercial database, Cramer et al. used a modified definition of ILAE to define refractory epilepsy. Using the restrictive definition, patients who

added AEDs to an existing regimen during the year of observation, were classified as refractory. Addition of AED(s) was defined as at least three months of baseline therapy, followed by at least three months with both baseline and additional AED(s). The study did not include patients who switched AED therapy, as a switch was more likely to represent intolerance to an AED. In contrast, adding an AED was suggestive of poor control of seizures and need of greater intensity of treatment. Though the definition of refractory epilepsy is restrictive, the study reported a prevalence of 15.2% among the 10,107 eligible patients with epilepsy on commercial insurance in 2008, which is higher than the prevalence reported by Manjunath et al. in 2008.<sup>11</sup> Also, using the same definition of refractory epilepsy (i.e., patients who added AEDs to an existing regimen during the year of observation), the authors reported a prevalence of 19.4% among children less than 12 years of age with partial epilepsy.<sup>19</sup> The prevalence of refractory epilepsy among children is higher as changes in brain typically lead to more drug therapy changes.

**Table 2.7: Prevalence of Refractory Epilepsy**

<b>Author</b>	<b>Patient population</b>	<b>Definition</b>	<b>Prevalence estimates</b>
Ramos-Lizana et al. (2012) <sup>75</sup>	Children <14 years of age (n=508) with newly diagnosed epilepsy observed at a tertiary referral center in Spain	Failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapy or in combination) to achieve seizure freedom <sup>a</sup>	10%, 19%, and 23% of the patients treated for epilepsy at two, six and ten years after diagnosis, respectively
Manjunath et al. (2012) <sup>13</sup>	Adults ≥18 years of age with epilepsy on Medicaid (n=110,312) and private insurance (n=36,529) in the U.S.	Patients with at least two consecutive changes in AED therapy (switch to a different compound or addition of an adjunctive compound) occurring at least 30 days apart, followed by at least one epilepsy-related emergency department visit or hospitalization during the next 365 days	3.2% of the Medicaid, and 1.7% of the employer population with epilepsy identified in a data collection period of 12 and 8 years, respectively
Chen et al. (2013) <sup>10</sup>	Adults <65 years of age with partial epilepsy on commercial insurance (n=79,149) in the U.S.	Patients with three lifetime AEDs	11% of the patients with partial epilepsy identified in a data collection period of 4 years
Cramer et al. (2014) <sup>11</sup>	Adults ≥18 years of age with partial epilepsy on commercial insurance (n=10,107) in the U.S.	Patients adding additional AED(s) with at least three months of baseline therapy, followed by at least three months with both baseline and additional AED(s)	15.2% of the patients with epilepsy identified in a data collection period of 4 years
Cramer et al. (2014) <sup>19</sup>	Children <12 years of age with partial epilepsy on commercial insurance (n=2,172) in the U.S.	Patients adding additional AED(s) with at least three months of baseline therapy, followed by at least three months with both baseline and additional AED(s)	19.4% of the patients with epilepsy identified in a data collection period of 4 years
Tellez-Zenteno et al. (2014) <sup>74</sup>	Adults diagnosed with epilepsy (n=250) at a Canadian epilepsy center	Failure of adequate trials of two tolerated, appropriately chosen and used AED schedules to achieve sustained seizure freedom <sup>a</sup>	33% of the patients diagnosed with epilepsy with a mean epilepsy duration of 22.6 (±14.0) years

<sup>a</sup>ILAE = International League Against Epilepsy; AED = Antiepileptic drug

Source: Ramos-Lizana et al. (2012); Manjunath et al. (2012); Chen et al. (2013); Cramer et al. (2014); Cramer et al. (2014); Tellez-Zenteno et al. (2014)<sup>10-13,81,82</sup>

### **2.2.3 Risk Factors of Refractory Epilepsy**

There is varying risk of refractory epilepsy by age group. Findings from epidemiological studies suggest an increase in the prevalence of epilepsy with increasing age.<sup>37</sup> Disease burden, polytherapy, susceptibility to drug-drug interactions and intolerable side effects, and age-related physiological changes may increase the risk of pharmacoresistance in older patients.<sup>76</sup> Age is an independent risk factor for the onset of epilepsy. Studies have shown patients who develop epilepsy at a later age are less likely to become refractory than younger patients.<sup>77,78</sup> Likewise, patients developing epilepsy at an early age may become refractory at a later age, after a period of remission.<sup>79</sup>

According to published studies, there are gender differences in the risk of epilepsy with males reported to have a higher overall risk of developing epilepsy than females.<sup>3</sup> This difference has been reported to vary by epilepsy type. Males are more prone to develop partial or focal epilepsy due to the higher prevalence of lesions in men. On the other hand, females are more likely to develop generalized epilepsy due to structural and functional changes in the cerebral networks.<sup>80</sup> With regards to race, African Americans have been reported to have a higher risk of epilepsy as compared to whites or any other race. Also, a study reported lower likelihood of epileptic surgery and poor epilepsy control among African Americans in comparison to Caucasians.<sup>81</sup>

Regarding epilepsy type, most research has reported that localization-related seizures or partial seizures are more common than generalized seizures in patients with refractory epilepsy. About 60% - 70% of patients with refractory seizures suffer from partial epilepsy. Studies have shown a higher probability of achieving remission in patients with generalized seizures as compared to patients with partial seizures. Patients with partial seizures who have already failed their first treatment schedule fare worse and have poorer outcomes than patients with generalized

seizures.<sup>82,83</sup> In addition, patients with multiple seizures also have worse outcomes in adults with epilepsy in comparison to those without multiple seizures.<sup>84</sup>

## 2.2.4 Economic Burden of Refractory Epilepsy

Previous literature has evaluated the healthcare resource utilization and costs of patients with stable epilepsy, with a few studies estimating the overall and epilepsy-related healthcare resource utilization and costs of patients with refractory epilepsy. These studies found significant epilepsy-related and non-epilepsy related direct medical cost of care for reestablishment of epilepsy control in patients with refractory epilepsy.<sup>85</sup> However, direct comparison of the cost estimates reported by the studies is challenging due to the heterogeneity in the studies. Table 2.8 provides a summary of the direct cost estimates of refractory epilepsy. Most of the estimates of the economic burden of refractory epilepsy are based on patient self-reported data from literature and expert panels.<sup>14,86-89</sup> The studies conducted outside the U.S. used national reimbursement rates over varying time periods to compute the healthcare utilization and costs of patients.<sup>86-89</sup> In the U.S., the first study on refractory patients by Murray et al. (1996) modeled the prevalence rates and estimated the healthcare costs using the 1994 Red Book Prices, the 1994 Health Care Financing Administration (HCFA) Medicare program physician and laboratory standard rates based on the consensus of a physician panel.<sup>14</sup> Three other studies conducted in U.S. settings used commercial claims to assess the treatment patterns of patients in clinical practice.<sup>10,11,13</sup> The cost estimates of the studies differed due to the varying definitions and data sources used to characterize refractory epilepsy. The subsequent paragraphs discuss the non-U.S. and U.S. studies in detail.

Among non-U.S. studies, three prospective and one retrospective study evaluated the costs of treating patients with refractory epilepsy.<sup>86-89</sup> A 2002 Italian study by Tetto et al. evaluated and compared the cost of 525 children and adults with epilepsy differing in disease severity from the Italian National Health Service (INHS) perspective. The study derived the costs of AEDs by multiplying the mean unit cost per mg for each product by the total number of milligrams for each

drug consumed over a one-year follow-up period, while the costs of hospital admissions were extrapolated from the corresponding diagnosis-related groups (DRG). Refractory epilepsy, which was defined as physician-reported relapsing seizures within 1-2 years of diagnosis that could not be improved by further treatment changes or surgery, was reported in 20.4% of the patients. The study found the costs of outpatient, hospital services as well as treatment costs to be significantly different for refractory epileptic adults and children as compared their non-refractory counterparts. The average total annual cost for a patient with refractory epilepsy in 2002 was estimated at €2,198 (U.S.\$2,054), consisting of costs associated with outpatient visits (€165) (U.S.\$154), drug treatments (€1,398) (U.S.\$1,306), and hospital admissions (€636) (U.S.\$594) (Note: no standard deviations were provided).<sup>89</sup>

Another non-U.S. prospective study by Boon et al. (2002) at a Belgian hospital quantified the epilepsy-related direct medical costs incurred by 84 patients with refractory seizures. The costs of AEDs were based on the official reimbursement rates published in the 1999 Medication Compendium of the Belgian Health Authority. Similarly, the costs of clinical visits, hospital admissions, and laboratory tests were calculated using fixed reimbursement rates. The study sample consisted of pre-surgical candidates (5-71 years) with a mean duration of epilepsy of 21 years, of which 29% of the patients were assigned AED polytherapy using expert opinion of a multi-disciplinary team involving noninvasive tests and neurophysiological examinations. The study found the mean annual epilepsy-related direct medical costs to be U.S.\$2,421 (range = \$387 - \$7,409) per person after an average follow-up of 25 months (range = 12 - 48 months). The average cost of hospital admissions was U.S.\$870 (range = 0\$ - \$6,310), cost of clinic visits was U.S.\$93 (range = \$22 - \$132), cost of AEDs was U.S.\$1,218 (range = \$110 - \$2,285), and cost of laboratory tests was U.S.\$241 (range = \$110 - \$441).<sup>86</sup> When compared to the previous study, the average annual direct costs were comparable (\$2,054 vs. \$2,421, respectively).<sup>86,89</sup>

Hamer et al. (2006) evaluated the all-cause direct and indirect costs of refractory epilepsy in a German epilepsy center over a three-month period. Direct costs included direct medical costs of providing inpatient, outpatient, ancillary treatment, and diagnostic procedure services; direct non-medical costs of providing assistive or protective equipment; and dental care for side effects of AED, which were obtained from the official German price list of drugs and the charges listed in the official doctor's fee scale. Indirect costs due to a patient's early retirement and productivity losses were calculated using the human capital method. The study sample consisted of a "convenience sample" of 101 adults, with disease duration of 18.1 ( $\pm 15.3$ ) years, recruited from the outpatient clinic of a tertiary epilepsy center consisting of patients who were not newly diagnosed and were not presenting with their first seizure. The study estimated the mean ( $\pm$ SD) total costs of refractory epilepsy in Germany (2003 €) at €2,610 ( $\pm 4,200$ ) (U.S.\$3,183 ( $\pm 5,122$ )) per patient. Direct costs contributed 39% (€1,010 ( $\pm 1,600$ ) (U.S.\$1,232 ( $\pm 1,951$ ))) to the total costs, while the remaining indirect costs (€1,610 ( $\pm 3,460$ ) (U.S.\$1,963 ( $\pm 4,220$ ))) were mainly attributed to losses due to early retirement (€780 ( $\pm 2,690$ ) (U.S.\$951 ( $\pm 3,280$ ))).<sup>87</sup> When compared to the previous studies, the three-month average direct cost (\$1,232) extrapolated to annual costs (\$4,928) was higher owing to the inclusion of patients more advanced in their disease trajectory (i.e., with a mean disease duration of 18.1 ( $\pm 15.3$ ) years).<sup>86,87,89</sup>

Sancho et al. (2008) conducted a cost of illness study to estimate the previous 12-month healthcare and non-healthcare resource use of 762 adult outpatients with refractory epilepsy in Spain. Direct health costs including hospital stays, medical visits, tests, and pharmacological and non-pharmacological treatments were obtained from the official Pharmacist Colleges General Council catalogue and from the Soikos Institute and multiplying by the number of resources used. Direct non-healthcare costs consisting of transportation and other out of pocket expenses were computed by asking the patient to recall the expenses over a three-month period and then

extrapolating it to one-year costs. Indirect cost consisting of productivity losses was calculated using the human capital method. Refractory epilepsy was defined as failure of at least three drugs, in monotherapy or combination therapy, to provide seizure control, with overall treatment duration of at least one year, and at least one seizure during the previous three months. The prevalence of refractory epilepsy among patients attending general clinics was 18.5% and 36.0% among patients in specialized clinics. The total annual mean cost per-patient was estimated at €6,838 ( $\pm 8,100$ ) (U.S.\$9,910 ( $\pm 11,745$ )). Direct healthcare, non-healthcare and indirect costs accounted for 72.8% (€4,977 ( $\pm 6,490$ ) (U.S.\$7,217 ( $\pm 9,411$ ))), 3.7% (€255 ( $\pm 1,275$ ) (U.S.\$370 ( $\pm 1,849$ ))) and 23.6% (€1,618 ( $\pm 4,527$ ) (U.S.\$2,346 ( $\pm 6,564$ ))) of the total cost. When compared to previous studies, the mean annual direct costs (U.S.\$7,217 ( $\pm 9,411$ )) were higher due to methodological differences in extrapolating costs, and higher health expense consumption per capita in Spain, which differs from other countries.<sup>88</sup>

Among U.S. studies, a 1996 study by Murray et al. was the first study to report the economic burden of refractory epilepsy among adults in the U.S. Direct costs included diagnostic procedures, laboratory tests charges, hospital physician service charges, surgery charges, AED-associated costs, costs of AED-associated adverse reactions, and costs associated with breakthrough seizures, which were determined from the 1994 Red Book Prices, the 1994 HCFA Medicare program physician and laboratory standard rates and expert panels. The indirect costs consisting of decreased productivity or loss of income for the patient, and decreased or lost earnings to the caretaker were calculated based on literature and a physician panel. The study defined refractory epilepsy based on model parameters estimated using literature and by a panel of three physicians with expertise in the field of epilepsy, chosen by a review of published literature involving authors of manuscripts discussing refractory epilepsy or quality of life issues. The study modeled the prevalence of refractory epilepsy to be 45% of the patients with partial seizures and

5% of the patients with generalized seizures in the incidence cohort (consisting of 84,755 new adult epilepsy cases) as well as in the prevalence cohort (consisting of 1,155,746 cases of adult epilepsy). The estimated total health care cost for prevalent cases was \$11,745 per patient per year (1994 dollars), and \$12,962 per patient per year (1994 dollars) for incident cases. Direct costs were found to be \$2,817 per patient per year for prevalent cases and \$4,116 per patient per year for incident cases. The high costs of treating incident cases was attributed to the additional medical resource use in diagnosis and management of the patients. The indirect costs were estimated at \$8,929 per patient per year for prevalent cases, and \$8,846 per patient per year for incident cases.<sup>14</sup>

Manjunath et al. quantified the economic burden of patients with refractory epilepsy in the U.S. and compared it to patients whose epilepsy was well controlled. The economic burden consisted of all-cause and epilepsy-related direct healthcare resource utilization and costs among privately insured patients (1999 – 2008) identified from the Ingenix employer database and patients on Medicaid (1997 – 2009) for five states (Florida, Iowa, Kansas, Missouri, New Jersey), and indirect costs consisting of work days lost due to short- and long-term disability and sick leaves for the private insurance patients. The healthcare resource utilization included hospitalizations, length of hospital stays, ED visits, outpatient visits, neurologist visits, other services, and AED and non-AED prescriptions. The study defined uncontrolled epilepsy (i.e., refractory epilepsy) as patients with at least two consecutive changes in AED therapy (switch to a different compound or addition of an adjunctive compound) occurring at least 30 days apart, followed by at least one epilepsy-related ED visit or hospitalization during the next 365 days (Table 2.9). The study found the prevalence of uncontrolled epilepsy to be 3.2% in the 110,312 eligible Medicaid patients, and 1.7% in the 36,529 eligible employer population in the U.S. Patients with uncontrolled epilepsy on private insurance had \$14,582 (95% CI = \$12,019 to \$17,097) (2009 dollar) higher average annual direct costs, while those patients on Medicaid had \$12,258 (95% CI = \$10,482 to \$14,083)

(2009 dollars) higher average annual direct costs as compared to patients with well-controlled epilepsy. The major drivers of the high healthcare resource utilization among both private insured employees and those on Medicaid included prescriptions of AEDs and non-AEDs, hospitalizations, outpatient visits, and neurologist visits. Also, patients with uncontrolled epilepsy had longer hospital stays and two times the number of fractures and injuries than patients with well-controlled epilepsy. In the case of productivity losses, privately insured employees with uncontrolled epilepsy had 2.5 times higher workday losses, with associated indirect costs of \$2,857 (2009 dollars).<sup>13</sup>

Chen et al. assessed the economic burden of direct healthcare utilization and costs for refractory epileptic patients with partial onset seizures observed in the U.S. Thomson Medstat MarketScan Commercial Insurance database from 2004 - 2008. The direct healthcare utilization and costs included all-cause and epilepsy-related inpatient admissions, ED visits, outpatient visits, diagnostic tests, and AED and non-AED prescriptions for each calendar year converted to 2008 dollars. Refractory epilepsy was defined based on having three lifetime AEDs. The study reported the prevalence of refractory epilepsy to be 11% among the 79,149 eligible patients in the U.S. The study found the average annual all-cause total (\$33,613 vs. \$19,085), inpatient (\$11,780 vs. \$6,076), outpatient (\$13,431 vs. \$8,637), and pharmacy costs (\$8,402 vs. \$4,372) to be significantly higher for refractory patients as compared to non-refractory patients. In the case of epilepsy-related costs, the average annual total (\$10,804 vs. \$4,032), inpatient (\$4,621 vs. \$1,384), outpatient (\$904 vs. \$391), and pharmacy costs (\$5,280 vs. \$2,256) were significantly higher for refractory patients as compared to non-refractory patients.<sup>10</sup>

A 2014 study by Cramer et al. compared the economic burden of patients with refractory epilepsy to patients with stable epilepsy using data from the U.S. Thomson Reuters MarketScan

Commercial database for a period from 2007 - 2009. The economic burden (2009 dollar) was comprised of all-cause and epilepsy-related inpatient hospitalizations, days of stay among patients with inpatient hospitalizations, ED visits, physician office visits, and AED and non-AED prescriptions. The study defined uncontrolled epilepsy (i.e., refractory epilepsy) as patients who added AEDs to an existing regimen during the year of observation. Addition of AED(s) was defined as at least three months of baseline therapy, followed by at least three months with both baseline and additional AED(s). The study reported a prevalence of 15.2% among the 10,107 eligible patients in 2008. Patients with uncontrolled epilepsy were more likely to be hospitalized for any diagnosis (18.3% vs. 9.8%) and for epilepsy-related diagnoses (15.7% vs. 7%), had higher mean of all-cause (12 vs. 9) and epilepsy-related physician office visits (3.6 vs. 2.2), and were more likely to have a brain imaging (34.4% and 18.5%) as compared to patients with stable epilepsy. Also, patients with uncontrolled epilepsy had higher all-cause (\$23,238 ( $\pm$ 42,894) vs. \$13,839 ( $\pm$ 31,355)) and epilepsy-related (\$12,399 ( $\pm$ 25,773) vs. \$5,511 ( $\pm$ 11,730)) total costs per patient-per year (PPY) as compared to patients with stable epilepsy. Of the total all-cause costs, \$15,842 ( $\pm$ \$40,999) vs. \$9,214 ( $\pm$ \$2,457) PPY were for medical services and \$7,247 ( $\pm$ \$6,411) vs. \$4,349 ( $\pm$ \$5,085) PPY were for AEDs in patients with uncontrolled epilepsy as compared to patients with well-controlled epilepsy, respectively. Of the total epilepsy-related costs, \$7,257 ( $\pm$ \$25,202) vs. \$2,751 ( $\pm$ \$11,029) PPY were for medical services and \$5,142 ( $\pm$ \$4,110) vs. \$2,760 ( $\pm$ \$3,361) PPY were for AEDs in patients with uncontrolled epilepsy as compared to patients with well-uncontrolled epilepsy, respectively.<sup>11</sup>

In conclusion, among privately insured employees in the U.S., the average all-cause annual direct costs of refractory patients ranged from \$23,238 ( $\pm$ \$42,894) to \$24,853 ( $\pm$ \$81,299) in 2009, and \$33,613 (Note: no standard deviations provided) in 2008, while the average all-cause annual direct costs of non-refractory patients ranged from \$9,005 ( $\pm$ \$28,038) to \$13,839 ( $\pm$ \$31,355) in

2009 and \$19,085 (Note: no standard deviations provided) in 2008.<sup>10,11,13</sup> When comparing refractory and non-refractory patients among Medicaid patients from Florida, Iowa, Kansas, Missouri and New Jersey, the average all-cause annual direct costs (2009 dollars) were \$38,708 ( $\pm$ \$114,904) vs. \$29,635 ( $\pm$ \$105,644), respectively.<sup>13</sup> Thus, the economic burden associated with refractory epilepsy is substantial (Table 2.8) and empirical study is needed to provide current estimates of the healthcare utilization and costs associated with Texas Medicaid patients who have refractory epilepsy.

**Table 2.8: Direct Cost Estimates of Refractory Epilepsy**

Author (year)	Study population	Refractory Prevalence/Definition	Direct cost categories	Direct healthcare cost
<b>Non-U.S.</b>				
Tetto et al. (2002)	525 children and adults with epilepsy differing in disease severity in Italy	20.4% of patients with relapsing seizures within 1-2 years of diagnosis, reported by the treating physician, that could not be improved by further treatment changes or surgery	Annual cost (2002 dollars) <i>Total</i> Hospital services Outpatient visits AED Treatment	(Mean) €2,198 (U.S.\$2,054) €636 (U.S.\$594) €165 (U.S.\$154) €1,398 (U.S.\$1,306)
Boon et al. (2002)	84 pre-surgical candidates (5-71 years) with a mean duration of epilepsy of 21 years in Belgium	29% of patients with a mean duration of epilepsy of 21 years, assigned AED polytherapy using expert opinion of a multi-disciplinary team involving noninvasive tests and neurophysiological examinations	Epilepsy-related annual cost (2002 dollars) <i>Total</i> Hospitalizations Clinic visits AEDs Laboratory tests	(Mean) \$2,421 (range = \$387 - \$7,409) \$870 (range = 0\$ - \$6,310) \$93 (range = \$22 - \$132) \$1,218 (range = \$110 - \$2,285) \$241 (range = \$110 - \$441)
Hamer et al. (2006)	101 adults (convenience sample) recruited from the outpatient clinic of a tertiary epilepsy center in Germany	100% of patients with disease duration of 18.1 ( $\pm 15.3$ ) years, who were not newly diagnosed and were not presenting with their first seizure	Three month cost (2003 dollars) <i>Total</i> Inpatient visits Outpatient visits Diagnostic procedure services Rehabilitation Physical therapy Special equipment	(Mean ( $\pm$ SD)) €1,010 ( $\pm 1,600$ ) (\$1,232 ( $\pm 1,952$ )) €280 ( $\pm 1,150$ ) (\$342 ( $\pm 1,403$ )) €10 ( $\pm 50$ ) (\$12 ( $\pm 61$ )) €20 ( $\pm 50$ ) (\$24 ( $\pm 61$ )) €90 ( $\pm 890$ ) (\$110 ( $\pm 1,086$ )) €10 ( $\pm 40$ ) (\$12 ( $\pm 49$ )) €3 ( $\pm 10$ ) (\$4 ( $\pm 12$ ))

**Table 2.8: Direct Cost Estimates of Refractory Epilepsy (Continued)**

Author (year)	Study population	Refractory Prevalence/Definition	Direct cost categories	Direct healthcare cost
Sancho et al. (2008)	762 adults outpatients in Spain	18.5% of patients in general clinics and 36.0% in specialized clinics with failure of at least three drugs, in monotherapy or combination therapy, to provide seizure control, with overall treatment duration of at least one year, and at least one seizure during the previous three months	Annual cost (2005 dollars) <i>Total</i> Hospitalizations Medical visits Treatments Tests	(Mean (±SD)) €4,977 (±6,490) (\$7,217 (±9,411)) €1,400 (±6,034) (\$2,030 (±8,749)) €317 (±325) (\$460 (±471)) €2,924 (±2,277) (\$4,240 (±3,302)) €341 (±592) (\$494 (±858))
<b>U.S.</b>				
Murray et al. (1996)	84,755 new adult epilepsy cases and the prevalence cohort consisting of 1,155,746 cases of adult epilepsy	45% of patients with partial seizures and 5% of the patients with generalized seizures based on model parameters estimated using literature and by a panel of three physicians with expertise in the field of epilepsy, chosen by a review of published literature involving authors of manuscripts discussing refractory epilepsy or quality of life issues	Annual cost (1994 dollars)  Prevalent cases <i>Total</i> Incident cases Total	(Mean) (standard deviation not reported) Prevalent cases \$2,817 Incident cases \$4,116

**Table 2.8: Direct Cost Estimates of Refractory Epilepsy (Continued)**

Author (year)	Study population	Refractory Prevalence/Definition	Direct cost categories	Direct healthcare cost
Manjunath et al. (2012)	Adults $\geq 18$ years of age with epilepsy among 110,312 eligible Medicaid and among 36,529 eligible private insurance in the U.S.	3.2% in the Medicaid patients, and 1.7% in the employer population defined as at least two consecutive changes in AED therapy (switch to a different compound or addition of an adjunctive compound) occurring at least 30 days apart, followed by at least one epilepsy-related ED visit or hospitalization during the next 365 days	Annual cost (2009 dollars) Medicaid; employer population All-cause <i>Total</i> Hospitalizations ED visits Outpatient services Neurologist visits Other healthcare services Epilepsy-related <i>Total</i> Hospitalizations ED visits Outpatient services Neurologist visits Other healthcare services AEDs Non-AEDs	(Mean ( $\pm$ SD)) Medicaid; employer population All-cause $\$38,708 \pm \$114,904$ ; $\$24,853 \pm \$81,299$ $\$6,902 \pm \$31,181$ ; $\$11,308 \pm \$62,399$ $\$400 \pm \$1,496$ ; $\$586 \pm \$4,392$ $\$2,416 \pm \$11,759$ ; $\$5,757 \pm \$24,888$ $\$86 \pm \$850$ ; $556 \pm \$4,306$ $\$22,022 \pm \$106,033$ ; $\$1,008 \pm \$5,428$ Epilepsy-related <i>Not reported</i> $\$4,102 \pm \$19,775$ ; $\$6,700 \pm \$48,095$ $\$109 \pm \$610$ ; $\$152 \pm \$972$ $\$467 \pm \$2,218$ ; $\$703 \pm \$3,072$ $\$60 \pm \$712$ ; $\$235 \pm \$1,797$ $\$1,502 \pm \$14,424$ ; $\$103 \pm \$752$ $\$1,352 \pm \$4,580$ ; $\$1,697 \pm \$3,979$ $\$5,615 \pm \$15,730$ ; $\$4,497 \pm \$11,374$
Chen et al. (2013)	79,149 eligible adults <65 years of age with partial epilepsy on commercial insurance in the U.S.	11% of the patients based on having three lifetime AEDs	Annual cost (2008 dollars) All-cause <i>Total</i> Inpatient Outpatient Pharmacy Epilepsy-related <i>Total</i> Inpatient Outpatient Pharmacy	(Mean) All-cause $\$33,613$ $\$11,780$ $\$13,431$ $\$8,402$ Epilepsy-related <i>Total</i> $\$10,804$ $\$4,621$ $\$904$ $\$5,280$

**Table 2.8: Direct Cost Estimates of Refractory Epilepsy (Continued)**

Author (year)	Study population	Refractory Prevalence/Definition	Direct cost categories	Direct healthcare cost
Cramer et al. (2014)	10,107 adults $\geq 18$ years of age with partial epilepsy on commercial insurance in the U.S.	15.2% of the patients who added AED(s) with at least three months of baseline therapy, followed by at least three months with both baseline and additional AED(s)	Annual cost (2009 dollars) All-cause <i>Total</i> Medical services Pharmacy Epilepsy-related <i>Total</i> Medical services Pharmacy	(Mean ( $\pm$ SD)) All-cause \$23,238 ( $\pm 42,894$ ) \$15,842 ( $\pm 40,999$ ) \$7,247 ( $\pm 6,411$ ) Epilepsy-related \$12,399 ( $\pm 25,773$ ) \$7,257 ( $\pm 25,202$ ) \$5,142 ( $\pm 4,110$ )

AED = Antiepileptic drug

SD = Standard deviation

Source: Tetto et al. (2002); Boon et al. (2002); Hamer et al. (2006); Sancho et al. (2008); Murray et al. (1996); Manjunath et al. (2012); Chen et al. (2013); Cramer et al. (2014)<sup>10,11,13,14,93-96</sup>

## 2.2.5 Pharmacotherapy in Refractory Epilepsy

The treatment of refractory epilepsy varies with the type of epilepsy. Based on guidelines of the American Academy of Neurology (AAN) and the American Epilepsy Society (AES), there is sufficient evidence of efficacy and safety to use topiramate and oxcarbazepine as monotherapy in patients with refractory partial epilepsy. Gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide are recommended for use as adjunctive treatment in patients with refractory partial epilepsy. In contrast, topiramate is the only drug that may be used for the treatment of generalized tonic-clonic seizures in adults (Table 2.9).<sup>90,91</sup>

**Table 2.9: Use of Antiepileptic drugs in the Management of Refractory Partial and Generalized Epilepsy**

AED	As adjunctive therapy in partial epilepsy	As monotherapy in partial epilepsy	In generalized epilepsy
Gabapentin	Appropriate to use (Level A)	Insufficient evidence (Level U)	Insufficient evidence (Level U)
Lamotrigine	Appropriate to use (Level A)	Can be used (Level B, downgraded due to dropouts)	Insufficient evidence (Level U)
Topiramate	Appropriate to use (Level A)	Can be used (Level A)	May be used (Level A)
Tiagabine	Appropriate to use (Level A)	Insufficient evidence (Level U)	Insufficient evidence (Level U)
Oxcarbazepine	Appropriate to use (Level A)	Can be used (Level A)	Insufficient evidence (Level U)
Levetiracetam	Appropriate to use (Level A)	Insufficient evidence (Level U)	Insufficient evidence (Level U)
Zonisamide	Appropriate to use (Level A)	Insufficient evidence (Level U)	Insufficient evidence (Level U)

AED = Antiepileptic drug

Level of recommendation given by the American Academy of Neurology (AAN):

Level A = Established as effective, ineffective or harmful or as useful/predictive or not useful/predictive;

Level B = Probably effective, ineffective or harmful or useful/ predictive or not useful/predictive;

Level U = Data inadequate or conflicting; treatment, test, or predictor unproven.

Source: Giussani et al. (2013); Faught et al. (2012)<sup>97,98</sup>

### 2.2.5.1 Treatment Patterns in Refractory Epilepsy

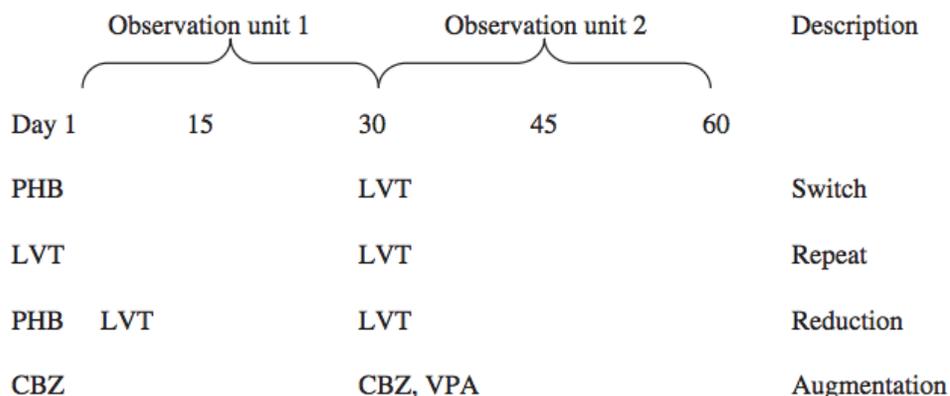
There is a dearth of well-controlled trials evaluating the utilization of AEDs in patients with refractory epilepsy. The only randomized prospective study by Alexandre et al. (2010), the study of outcome of pharmacoresistance in epilepsy (SOPHIE), evaluated the AED utilization patterns of 933 adults and 191 children with refractory epilepsy in 11 tertiary centers in Italy.<sup>92</sup> The study reported that 79% of patients were taking polytherapy regimens, of which 54% received a combination of two AEDs, 35% received three AEDs, 9% received four AEDs, and 2% received five AEDs. Seventy-four percent of patients were prescribed at least one first-generation AED, while 81% were prescribed at least one second-generation AED. Levetiracetam was the most commonly prescribed AED (35%) followed by carbamazepine (34%), lamotrigine (30%), oxcarbazepine (23%), valproic acid (21%), topiramate (19%), phenobarbital (17%), clobazam (14%), and phenytoin (9%).<sup>93</sup>

A study by Priscila de Freitas-Lima et al. (2013) evaluated the drug utilization patterns among 112 adults with refractory epilepsy attending a tertiary referral center in Brazil. The authors reported that 7.1% of patients were on monotherapy, 60.7% were on polytherapy with two AEDs, and 32.1% were on polytherapy with three or more AEDs. Carbamazepine was the most common AED in monotherapy. Of the patients on polytherapy, all but one patient had at least one first-generation AED, while at least one second-generation AED was prescribed to 70.5% of the patients.<sup>94</sup>

Previous retrospective studies assessing the use of AED polytherapy in insurance claims datasets in the U.S. have reported about 80% of patients are on monotherapy as compared to polytherapy at baseline in patients with refractory epilepsy.<sup>10,11,13</sup> Cunnington et al. (2011) followed patients with newly diagnosed epilepsy to identify the predictors of frequent AED

regimen change, early in the course of illness. The study employed a retrospective cohort design using the U.S. Invision Data Mart Multiplan Database 2004 - 2008 to evaluate the treatment patterns consisting of a switch (change in the AED(s)), repeat (remaining on the same AED(s)), augmentation (increase in the number of AEDs prescribed), reduction (decrease in the number of AEDs with retention of at least one AED), termination (no additional AED within 180 days of previous AED use), and initiation (initiation of AED following termination). (Note: The study did not define overlapping periods in the treatment patterns). Patients with a gap of 31 to 180 days between AED refills were ignored and prescription claims on either side of the treatment gap were reviewed to classify as a switch, repeat, augmentation, or reduction (**Figure 2.5**). Eleven percent patients received polytherapy with an overlap of an adjunctive AED in the first 14 days epilepsy diagnosis, which was suggestive of severe epilepsy. Phenytoin was commonly used as monotherapy (33%), while the combination of phenytoin and levetiracetam was the most common polytherapy regimen (25.8%). The most common type of regimen change after the diagnosis was switch, followed by reduction, and then augmentation (**Table 2.10**). With the exception of initiating a new AED following termination, about 18% - 27% of patients' changed AED regimen at least once in the first year post-diagnosis. The risk of a regimen change significantly reduced as time since epilepsy diagnosis increased and decreased with a previous regimen change. Specifically, 57.6% of patients showed changes in AED regimen (mean=1.3) in the first year, which was followed by 45.1% of patients who showed changes in AED regimen in the second year (mean=1.1) post diagnosis, possibly due to the use of rescue medications in the initial year followed by the prescription of a more stable long-term regimen. Use of polytherapy immediately after diagnosis had a higher risk of regimen change in comparison to monotherapy use.<sup>32</sup>

**Figure 2.5: Examples of Antiepileptic Drug Regimen Change**



PHB = phenobarbital  
 LVT = levetiracetam  
 CBZ = carbamazepine  
 VPA = valproate  
 Days of supply is 30 days  
 Source: Cunnington et al. (2011)<sup>32</sup>

**Table 2.10: Frequency of Regimen Change in Patients with Newly Diagnosed Epilepsy**

Type of regimen change	Summary statistic in one year after diagnosis*
Switch (Change in the AED(s))	Mean number of changes per person = 0.41 % Patients with $\geq 1$ regimen change = 27.3
Augmentation (Increase in the number of AEDs prescribed)	Mean number of changes per person = 0.32 % Patients with $\geq 1$ regimen change = 20.3
Reduction (Decrease in the number of AEDs with retention of at least one AED)	Mean number of changes per person = 0.36 % Patients with $\geq 1$ regimen change = 24.8
Termination (No additional AED within 180 days of previous AED use)	Mean number of changes per person = 0.18 % Patients with $\geq 1$ regimen change = 17.8

\*No standard deviation reported  
 Source: Cunnington et al. (2011)<sup>32</sup>

The study by Chen et al. was the only study to conduct an in depth evaluation of the treatment patterns of AED(s) among refractory patients with partial epilepsy in the U.S. using real world claims commercial claims data from 2004 - 2008. The study characterized the treatment pattern of patients before they reached refractory status, that is, following the use of the first AED by patients. Refractory epilepsy was subsequently defined based on having three lifetime AEDs. The most commonly prescribed AEDs in patients on monotherapy were phenytoin (15.2%) and levetiracetam (15.2%), followed by carbamazepine (12.2%), oxcarbazepine (11.3%), and lamotrigine (11.0%). Of the patients on polytherapy with two AEDs, levetiracetam was most frequently used along with phenytoin (6.4%), lamotrigine (6.0%), carbamazepine (5.3%), topiramate (4.7%), and oxcarbazepine (4.5%). The study further assessed the patterns of adding or switching to another AED among the patients. Addition was defined as the addition of another AED to the initial AED with at least a 30-day overlap in medication supply between the dispensing of these two AEDs, while a switch in therapy was defined as the discontinuation of the initial AED and start of another AED with less than a 30-day overlap in medication supply between the dispensing of the two AEDs. Among patients on monotherapy, 57.4% added another AED, while 42.6% switched to another AED subsequently. Of the patients on combination therapy, 41.6% added a third AED, 42.6% discontinued one of the AEDs in combination therapy. Levetiracetam was the most common add-on or switch-to AED.<sup>10</sup>

Monotherapy is usually the preferred treatment in patients with epilepsy as it is associated with; better compliance, fewer drug interactions, lower complexity in patients treated for other comorbid conditions, less adverse drug reactions, and lower health care costs. However, in the case of refractory epilepsy, seizure control usually needs drug trials consisting of switching or adding an alternative monotherapy to the existing AED regimen.<sup>9</sup>

There is no evidence suggesting the clinical benefit of adding an adjunctive AED as compared to switching to an alternative monotherapy in patients with refractory epilepsy. A prospective randomized controlled study among patients with refractory partial epilepsy did not find differences in seizure remission and adverse events between patients switched to an alternative monotherapy and those patients who added an adjunctive AED to the pre-existing treatment. The patients had failed previous monotherapy once before being randomized to the two treatment strategies. Also, there was no difference in the probability of remaining on the allocated treatment between the two study groups.<sup>95</sup>

In the case of cost savings, a 2005 study by Lee et al. compared the economic burden of switching and adding an adjunctive AED in patients with partial epilepsy, refractory to initial monotherapy. The study used the PharMetrics patient-centric database, to compare the healthcare utilization and costs of providing hospital admissions, ED visits, outpatient visits, office-based visits, and prescriptions in the six-month pre-period consisting of monotherapy and a 12-month post-period consisting of switching and adding an adjunctive AED. The six-month pre-index costs were doubled to annualize the costs. Monotherapy was defined as patients having a prescription for a single AED consisting of carbamazepine, phenytoin or valproic acid for at least six months. Adjunctive drugs in the add-on cohort consisted of carbamazepine, clorazepate dipotassium, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, phenobarbital, phenytoin, primidone, tiagabine hydrochloride, topiramate, valproic acid, and zonisamide, while the switch-to cohort consisted of patients whose non-oxcarbazepine (OXC) AED monotherapy was changed to OXC monotherapy. The switching group had an annual per-patient cost savings of \$1,165 ( $p < 0.05$ ) over the group that received an additional AED. Pharmacy cost differences were the primary cost drivers for the cost savings in the switch-to cohort. Also, the add-on cohort was 50%

more likely (Odds ratio (OR)=1.52, 95% CI=1.07-2.15,  $p<0.05$ ) than the switch-to cohort to have an emergency department visit.<sup>96</sup>

With the use of first-generation AEDs, adding an AED to an existing regimen was associated with side effects in patients. However, with the advent of newer drugs, adding a second- and a third-generation AED is reported to improve outcomes in comparison to switching to another AED. A study using the Truven Health MarketScan Commercial Claims and Encounter Database (2007 - 2009) found cost savings in potentially DRE patients with partial onset seizures who changed from monotherapy to adjunctive therapy. The study assessed the 12-month all-cause and epilepsy-related healthcare utilization and costs comprising of hospitalizations, ED visits, outpatient visits, and AED and non-AED prescriptions following the change to adjunctive therapy. Use of adjunctive therapy was defined as those who received monotherapy and were changed to adjunctive therapy with an overlap of greater than 60 days with the initial AED. The average per-month all-cause hospitalizations (5.3% vs. 3.0%,  $p<0.0001$ ) and ED visits (8.2% vs. 4.8%,  $p<0.0001$ ) and epilepsy-related hospitalizations (4.0% vs. 1.7%,  $p<0.0001$ ) and ED visits (4.5% vs. 2.2%,  $p<0.0001$ ) significantly reduced after the patients changed to adjunctive therapy from initial monotherapy. Likewise, the adjusted all-cause total costs significantly reduced from \$4,205 per-month to \$2,994 per-month ( $p<0.0001$ ). In case of the epilepsy-related costs, there was a slight non-significant increase in pharmacy costs from U.S.\$189 to \$194 per-month ( $p=0.2082$ ), while the adjusted epilepsy-related total costs significantly reduced from \$1,601 per-month to \$909 per-month ( $p<0.0001$ ), after patients transitioned to adjunctive therapy.<sup>24</sup>

The newer AEDs have different MOAs and better side effect profiles as compared to the first generation AEDs. Most of these drugs have been approved by the Food and Drug Administration (FDA) for use as adjunctive therapy, and are often used in patients with refractory

epilepsy.<sup>20</sup> There is increasing evidence that combining drugs with different MOAs may be more effective and result in fewer adverse-effects due to their ability to act on multiple drug targets as opposed to combining drugs with the same MOA.<sup>20,25,97</sup> However, there is a dearth of randomized controlled trials and real-world evidence analyzing this approach.

Margolis et al. (2014) studied the clinical and economic outcomes of adding an AED with a same MOA as compared to adding an AED with a different MOA in patients with partial-onset seizures. The study described the addition of an AED as an overlap of the days of supply of the AEDs for at least 90 days following initiation of the second AED. Patients were selected from the Truven Health MarketScan Commercial Claims and Encounters Database. Persistence was defined as the number of days from the addition of the AED to the end of available data when there was no claim for one of the AEDs prior to the last days of supply allowing for a gap of 30 days or half the days of supply from the previous prescription claim. Healthcare use consisted of inpatient admissions, ED visits and physician office visits. The AED classes based on their primary MOA consisted of sodium channel blockers (SC), gamma-aminobutyric acid analogs (G), synaptic vesicle protein 2A binding (SV2), and multiple mechanisms (M). The SC class included carbamazepine, ethosuximide, fosphenytoin, lacosamide, lamotrigine, oxcarbazepine, and phenytoin, while the G class included clonazepam, diazepam, gabapentin, phenobarbital, pregabalin, primidone, tiagabine, and vigabatrin. SV2 class included levetiracetam, while the M class included divalproex sodium, felbamate, topiramate, valproate sodium, valproic acid, and zonisamide. Patients on same-MOA (G+G and SC+SC) combinations had shortest persistence (344 ( $\pm$ 345 days) and 513 ( $\pm$ 530 days)) as compared to patients on different-MOA combinations. Also, the results showed that patients on different-MOA combinations had a lower hazard of discontinuation compared to patients on same-MOA combinations. Also, the health care utilization differed by the cohorts. SC combinations of different MOAs had a lower risk of emergency department visits

(OR=0.85, 95% CI=0.74-0.98,  $p<0.05$ ) compared to patients with SC combinations of same MOAs. In addition, G combinations of different MOAs had a lower risk of inpatient admissions (OR=0.72, 95% CI=0.54-0.95,  $p<0.05$ ) compared to patients with SC combinations with the same MOAs.<sup>27</sup> This was the only study that compared the utilization of patients on different MOA combinations. However, the study assessed patients with partial onset seizures alone. There is still a need to study the patterns of AED use and associated outcomes in patients with refractory epilepsy, given that these patients need frequent drug titrations.

## 2.2.6 Adherence to Antiepileptic Drug Therapy

Medication non-adherence is an important concern in epilepsy.<sup>98</sup> Early studies using self-reported patient estimates of adherence have reported that about half of the patients were adherent to AED therapy.<sup>99,100</sup> The Morisky Medication Adherence Scale (MMAS) has been widely used to measure adherence of patients during an office visit. This patient-reported scale consisted of four questions with a score of 4 representing high adherence, and a score of 1 representing low adherence.<sup>101</sup> Studies using claims data have reported that the rate of AED non-adherence ranges between 26% and 50% using a threshold of less than 0.8 to describe non-adherence in patients with epilepsy.<sup>29,102-106</sup> It has been reported that poor adherence with AEDs leads to seizure recurrence and an increase in health care utilization and costs. Specifically, studies have reported higher ED costs (+\$143 to +\$260), inpatient costs (+\$872 to +\$1,799), and total health care costs (+\$1,466 to +\$2,674) in patients' non-adherent to their AED regimen in comparison to patients' adherent to AED regimen.<sup>102-104</sup> The majority of the studies have assessed medication adherence in patients on monotherapy regimens, while no known studies have assessed adherence to AEDs among refractory patients. Due to lower pill burden and less regimen complexity, monotherapy patients may have better adherence rates than patients requiring two or more daily doses.<sup>102</sup>

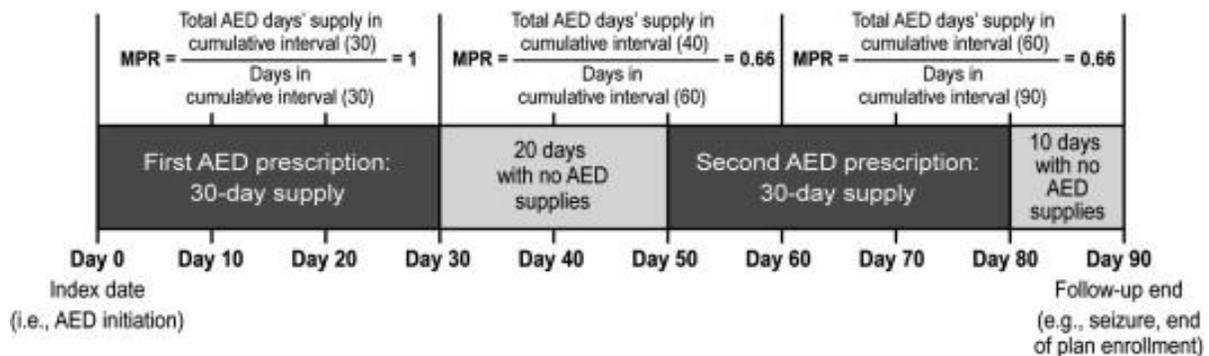
In the U.S. Medicaid population, the RANSOM (Research on Antiepileptic Non-adherence and Serious Outcomes in Medicaid) study is the only study that used prescription claims to evaluate the adherence of adults with epilepsy to AED regimen. The study assessed healthcare utilization and costs among adults using state Medicaid claims data from Florida, Iowa, and New Jersey from 1997 through 2006. The study assessed adherence of patients on any of the 12 AEDs (carbamazepine, ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate, valproic acid, and

zonisamide) using an open-cohort design. As all patients may not have required continuous AED throughout the observation, the study allowed a gap in AED use of 180 days or more as untreated periods and assessed adherence for each 90-day quarter. Adherence for each treated quarter was calculated using the medication possession ratio (MPR) method with numerator consisting of the number of days in a quarter with supplies for at least one AED and denominator consisting of the number of days in a quarter. The study reported that 26% of the patients were non-adherent (MPR less than 80%) to AEDs, and AED non-adherence was associated with a higher incidence of hospitalizations, inpatient days, and ED visits.<sup>29</sup>

Among privately insured adults in the U.S., four retrospective studies used prescription claims to evaluate adherence of patients with epilepsy to AED regimens using MPR. Briesacher et al. (2008) used the MarketScan research database from 2001 - 2004 to measure adherence using MPR in patients newly diagnosed with epilepsy. MPR included the days of supply of dispensed drug during the follow-up year as the numerator and the number of days in the year as the denominator. The study eliminated patients with overlaps in the dispensed days for different generic drugs and summed those overlaps for same generic drugs. Overlaps for different dispensed drugs were eliminated as leftover supplies from previous refills were assumed to be discarded to begin the new drug. In contrast, overlaps for same dispensed drugs were not eliminated as patients were assumed to continue taking the drug from previous refills as part of the same regimen. In addition, patients with MPRs higher than 100% were truncated for 27% of the patients. The study found 60.8% of the patients had an MPR of 80% or more.<sup>105</sup> Davis et al. (2008) used the PharMetrics Integrated Outcomes Database from 2000 - 2005 to identify AED adherence among adult patients aged 21 years or older in the U.S. MPR used to measure adherence was defined as the days of supply for all AED prescriptions divided by the number of days between AED initiation and the expiration of the days of supply of the last observed AED refill. The study found a mean

MPR of 0.78 and 61% of the patients adherent (MPR of 80% or more) to AED prescriptions.<sup>103</sup> Manjunath et al. (2009) used the PharMetrics Patient Centric Database from 2000 - 2005 to measure adherence to AEDs in a large cohort of adult patients diagnosed with epilepsy. The study operationalized MPR as a time-dependent variable and calculated the cumulative adherence from the time a patient initiated an AED to the end of each month, which was computed until the end of the follow-up period (Figure 2.6). The numerator of the MPR consisted of days of supply of AED to total days within each cumulative interval following AED initiation. The study reported 50% of the patients had an MPR of 80% or more.<sup>106</sup>

**Figure 2.6: Time Dependent Calculation of Adherence**



Source: Manjunath et al. (2009)<sup>106</sup>

Cramer et al. (2015) conducted a cross-sectional study of claims from the OptumInsight™ database for the year 2011 and evaluated the adherence to AED in adults diagnosed with epilepsy on a monotherapy regimen only. MPR was defined as the total days of therapy available in the study period divided by 365 days. The study reported a mean MPR of 0.899 (±0.13) in long-acting AED users and an MPR of 0.903 (±0.13) in short-acting AED users. Long-acting AEDs included phenytoin extended release, carbamazepine extended release, topiramate, divalproex extended release, divalproex delayed release, phenobarbital, levetiracetam extended release, and

zonisamide, while short-acting AEDs included levetiracetam, lamotrigine, carbamazepine, and oxcarbazepine.<sup>102</sup>

The adherence estimates mainly depend on the patient population, the medication regimen, and the method used to measure adherence (Table 2.11). A reason cited in literature for inadequate seizure control in patients with epilepsy is suboptimal adherence to AEDs.<sup>107</sup> In patients commonly on polytherapy, adherence may be affected by the tolerance to multiple AEDs and the development of side effects.<sup>108</sup> A study measuring the serum drug concentrations in hospitalized patients with refractory focal epilepsy reported poor adherence to AEDs.<sup>109</sup> In medically refractory patients, adherence to AEDs in clinical practice has not been specifically studied, however, its study is important as seizure relapses can be minimized with optimal treatment adherence. Thus, no known studies have assessed the adherence patterns of medically refractory patients, which needs to be explored further.

**Table 2.11: Adherence to Antiepileptic drugs in the U.S.**

<b>Author (year)</b>	<b>Study population</b>	<b>Adherence definition</b>	<b>Adherence estimate</b>
<b>Patients on Medicaid</b>			
Faught et al. (2009)	Adults (N=33,658) on Medicaid from Florida, Iowa, and New Jersey (1997-2006)	MPR included the number of days in a quarter (each 90 days) with supplies for at least one AED number of days in a quarter as the denominator.	74% of the patients had an MPR of 80% or more
<b>Patients on Commercial insurance</b>			
Briesacher et al. (2008)	Patients (N=4,984) newly diagnosed with epilepsy identified using MarketScan research database (2001-2004)	MPR included the days of supply of dispensed drug during the follow-up year as the numerator and the number of days in the year as the denominator.	60.8% of the patients had an MPR of 80% or more
Davis et al. (2008)	Adults (N=10,892) aged 21 years or older using PharMetrics Integrated Outcomes Database (2000-2005)	MPR used to measure adherence was defined as the days of supply for all AED prescriptions divided by the number of days between AED initiation and the expiration of the days of supply of the last observed AED refill.	61% of the patients had an MPR of 80% or more; Mean MPR of 0.78
Manjunath et al. (2009)	Adults (N=18,073) diagnosed with epilepsy using PharMetrics Patient Centric Database (2000-2005)	MPR consisted of days of supply of AED to total days within each cumulative interval following AED initiation.	50% of the patients had an MPR of 80% or more
Cramer et al. (2015)	Adults (N=8,180) with epilepsy on a monotherapy regimen using OptumInsight™ 2011	MPR was defined as the total days of therapy available in the study period divided by 365 days.	Mean MPR of 0.899 (±0.13) in long-acting AED users; Mean MPR of 0.903 (±0.13) in short-acting AED users

Source: Faught et al. (2009); Briesacher et al. (2008); Davis et al. (2008); Manjunath et al. (2009); Cramer et al. (2015)<sup>29,102,103,105,106</sup>

### 2.2.7 Comorbidities in Refractory Epilepsy

Seidenberg et al. (2009) summarized data from six large studies from different countries and reported that 26.8% to 84% of patients with epilepsy had at least one comorbid condition.<sup>110</sup> Psychiatric disorders such as major depression, anxiety disorder, and psychosis have been commonly cited in literature.<sup>111</sup> Depression is one of the most common comorbidities with a prevalence of about 60% in patients with drug-resistant focal epilepsy.<sup>112</sup> Comorbidities in patients with seizure disorders impose a significant burden on patients, and their families, and affect the quality of life of patients. Also, these comorbidities have an impact on the tolerance of AEDs.<sup>113</sup> AEDs such as zonisamide may lead to psychiatric adverse events such as psychosis and mania.<sup>114</sup> Also, AEDs such as barbiturates, phenytoin, carbamazepine, and topiramate may have detrimental effects on cognition functioning, motor speed, and attention, further complicating the management of epilepsy.<sup>115</sup>

Comorbid conditions raise the cost of medical care, through increased pharmacy, outpatient office visits, and inpatient hospitalization.<sup>111</sup> A study by Lee et al. (2005) assessed the effect of comorbidities on medical care use and costs among patients with partial seizure disorder refractory to initial monotherapy regimen using administrative claims data from PharMetrics (2000 - 2002). The study found higher odds of hospitalizations (OR=3.7, 95% CI=1.7-7.9) and higher mean treatment costs ( $p < 0.0001$ ) in patients with at least one comorbidity (\$26,579 ( $\pm$ \$15,407)) as compared to patients without any comorbidity (\$10,471 ( $\pm$ \$30,089)). Comorbid depression had the highest impact on the odds of hospitalization (OR=3.5, 95% CI=2.13–5.8) and 83.1% greater treatment costs as compared to patients without depression.<sup>116</sup>

In addition, comorbid psychiatric conditions may lead to differences in epilepsy management in refractory epilepsy patients. Epileptologists are more likely to refer patients to

inpatient settings for diagnostic evaluations of psychogenic non-epileptic events, thereby increasing the healthcare costs.<sup>117</sup> A 2014 study by Hamilton et al. retrospectively followed 83 patients with drug-resistant focal epilepsy for two years and assessed anxiety and/or depressive symptoms using 3 self-reported surveys; the Beck Depression Inventory-II (BDI-II), the Neurologic Disorders Depression Inventory-Epilepsy (NDDI-E), and the Patient Health Questionnaire-Generalized Anxiety Disorder 7 (PHQ-GAD 7). The study illustrated that the patients with anxiety and depressive symptoms had higher missed outpatient visits (median 0.84 vs. median 0.48,  $p=0.02$ ) and were more likely to undergo an inpatient admissions (56% vs. 24%,  $p=0.02$ ) as compared to patients without those symptoms.<sup>118</sup>

In addition, non-psychiatric comorbidities such as Alzheimer's disease, brain tumor, meningitis, migraine, multiple sclerosis, and stroke are common in patients with uncontrolled epilepsy.<sup>10,13</sup> Cramer et al. reported higher all-cause costs in patients with uncontrolled epilepsy as compared to patients with well-controlled epilepsy, suggesting that comorbid conditions may contribute to additional healthcare utilization and costs in those patients. Patients with uncontrolled epilepsy had a higher mean Charlson comorbidity index ( $0.7 (\pm 1.5)$  vs.  $0.5 (\pm 1.3)$ ,  $p < 0.001$ ), with a significantly higher percentage of patients with head injury (1.3% vs. 0.7%,  $p < 0.05$ ), brain tumor (6.2% vs. 3.5%,  $p < 0.001$ ), cerebrovascular disease or stroke (12.7% vs. 6.3%,  $p < 0.001$ ), depression and other mood disorders (10.9% vs. 6.3%,  $p < 0.001$ ) as compared to patients with stable epilepsy.<sup>11</sup> Thus, managing medically refractory epilepsy involves improvement in overall burden of the disease.

## 2.3 Texas Medicaid

Texas Medicaid was instituted by the state and approved by the U.S. Department of Health and Human Services Commission (HHSC) under Section 1902 of the Social Security Act. The Texas Medicaid program provides health insurance coverage for low-income families, individuals with chronic disabilities, blind persons, low-income pregnant women, elderly people or seniors, non-disabled children, and caretakers of dependent children. Medicaid enrollment in the state of Texas for clients under 21 was 2,780,581 million and for clients 21 and older was 833,943 in December 2013.<sup>119</sup>

Currently, most Medicaid services in Texas are delivered through managed care, with a large shift from the traditional Medicaid program to managed care in 2012. HHSC contracts with managed care organizations licensed by the Texas Department of Insurance and pays them a monthly amount to coordinate health services for the Medicaid members enrolled in their plans. The health plans contract directly with doctors and other health care providers to create provider networks for their members. There are four Medicaid programs in Texas: traditional Medicaid, STAR, STAR+PLUS, and STAR Health. The traditional Medicaid program has a fee-for-service (FFS) payment structure. The STAR program is Medicaid for children, newborns, and pregnant women, while STAR+PLUS is a Medicaid program for people who have disabilities or are 65 years or older. Finally, STAR Health is Medicaid for children covered through the Texas Department of Family and Protective Services.<sup>120</sup>

## 2.4 Summary of Literature Review

Epilepsy is a chronic disorder characterized by repeated seizures that affects about 2.2 million cases in the U.S. and 50 million cases worldwide.<sup>2</sup> Seizures are broadly categorized as generalized and partial seizures. Pharmacotherapy with AEDs is the foremost treatment paradigm in epilepsy. Monotherapy with an AED is usually effective in 60% of the patients with epilepsy, while the remaining patients, considered refractory, are candidates for additional treatment options such as AED titrations, VNS, and surgery.<sup>8</sup> The ILAE commission defines refractory epilepsy as “failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.”<sup>34</sup> Pseudoresistance due to incorrect diagnosis, inappropriate AED choice, dosage or administration regimen, and poor medication adherence needs to be ruled out before considering a patient as refractory.<sup>44</sup> Applying the variations of ILAE definition, retrospective studies conducted in the U.S. using population-based administrative claims data have reported the prevalence of refractory epilepsy to be 1.7% to 15.2%.<sup>10,11,13</sup> This wide range in the prevalence estimates of refractory epilepsy may be due to differences in population selection, and characterization of epilepsy.

Patients with refractory epilepsy account for most of the burden associated with epilepsy due to higher number of comorbidities, increased hospitalization, ED and outpatient visits, social stigmatization, reduced quality of life, and a decreased life expectancy. Most of the estimates of the economic burden of refractory epilepsy are based on patient self-reported data from literature and expert panels. Of the few retrospective studies assessing the economic burden of refractory epilepsy in the U.S., the average all-cause annual direct cost (2009 dollar) was estimated at \$23,238 ( $\pm$ 42,894) to \$24,853 ( $\pm$ 81,299) for privately insured employees and commercially insured patients.<sup>10,11</sup> The only study on Medicaid enrollees from the states of Florida, Iowa, Kansas,

Missouri and New Jersey estimated the average all-cause annual direct cost (2009 dollar) at \$38,708 ( $\pm$ \$114,904).<sup>13</sup> The state Medicaid programs differ substantially from private insurance plans in terms of the demographic characteristics of the populations served, services covered, and payment arrangements. The Medicaid program in the state of Texas has the highest proportion of Hispanics (63%) among non-elderly enrollees as compared to any other state.<sup>121</sup> In the state of Texas, the lifetime prevalence of epilepsy was estimated at 1.7%. About 16% of Texans are enrolled in the Medicaid program. In 2013, patient encounters for AEDs ranked second amongst the patient encounters for medications prescribed for neurological disorders, with 850,916 encounters which accounted for \$48,307,471 in reimbursed AED claims.<sup>122</sup> Given the high utilization of AEDs, an empirical study is needed to provide current estimates of the healthcare utilization and costs associated with Texas Medicaid patients who have refractory epilepsy.

In patients with newly diagnosed epilepsy, monotherapy is usually the preferred treatment approach. However, in the case of refractory epilepsy, seizure control usually needs drug trials consisting of switching or adding an alternative monotherapy to the existing AED regimen.<sup>8,20</sup> There is insufficient evidence suggesting the clinical and economic benefit of adding an adjunctive AED as compared to switching to an alternative monotherapy in patients with refractory epilepsy. Previous studies assessed the AED utilization in clinical practice before the approval of newer AEDs in the U.S.<sup>10,24,29,32</sup> As a result, there is a need to study the recent patterns of AED use and associated outcomes in patients with refractory epilepsy. Also, previous studies characterizing the adherence to AEDs are restricted to patients with epilepsy.<sup>29,102,103,105,106</sup> No known study assessed the persistence behavior in patients with refractory epilepsy. Given the higher pill burden and regimen complexity in patients with refractory epilepsy, the role of adherence and persistence in refractory epilepsy needs to be explored. In the case of comorbidities, about three-fourths of the patients with refractory epilepsy have one or more comorbid conditions, which poses a significant

clinical burden and complicates the management of epilepsy.<sup>110</sup> Moreover, comorbid conditions raise the cost of medical care, through increased pharmacy, outpatient office visits, and inpatient hospitalization, which gives the need to evaluate the impact of comorbidities in refractory epilepsy.<sup>111</sup>

## 2.5 Objectives and Hypotheses

This study has 3 objectives concerning the (1) demographic and clinical characteristics, (2) treatment patterns, and (3) healthcare utilization and costs of patients with and without refractory epilepsy. The objectives are listed below along with their related hypotheses.

### 2.5.1 Objective 1: Demographic and Clinical Characteristics

1. To compare the demographic and clinical characteristics of patients with refractory and non-refractory epilepsy.

**H<sub>01A</sub>**: There is no significant difference in the mean age of patients between the refractory and non-refractory groups.

**H<sub>01B</sub>**: The proportion of gender categories does not differ between the refractory and non-refractory groups.

**H<sub>01C</sub>**: The proportion of race/ethnicity categories does not differ between the refractory and non-refractory groups.

**H<sub>01D</sub>**: The proportion of epilepsy type categories does not differ between the refractory and non-refractory groups.

**H<sub>01E</sub>**: There is no significant difference in the comorbidity burden of patients between the refractory and non-refractory groups.

**H<sub>01F</sub>**: There is no significant difference in the proportion of different types of index AED used between the refractory and non-refractory groups.

**H<sub>01G</sub>:** There is no significant difference in the pill burden of patients between the refractory and non-refractory groups.

### **2.5.2 Objective 2: Treatment Patterns**

To compare the treatment patterns of patients with refractory and non-refractory epilepsy while controlling for age, gender, race/ethnicity, type of epilepsy, type of index AED, baseline CCI, number of psychiatric and presence of non-psychiatric comorbidities at follow-up, baseline pill burden, baseline all-cause inpatient visits, baseline number of all-cause outpatient visits, baseline all-cause total cost.

**H<sub>2A</sub>:** Patients with refractory epilepsy are less likely to be adherent to AEDs as compared to patients with non-refractory epilepsy, while controlling for covariates.

**H<sub>2B</sub>:** Patients with refractory epilepsy are less likely to be persistent (i.e., duration of medication use) to AEDs as compared to patients with non-refractory epilepsy, while controlling for covariates.

**H<sub>2C</sub>:** Patients with refractory epilepsy are more likely to add an alternative AED as compared to patients with non-refractory epilepsy.

**H<sub>2D</sub>:** Patients with refractory epilepsy are more likely to switch to an alternative AED as compared to patients with non-refractory epilepsy.

### 2.5.3 Objective 3: Healthcare Utilization and Costs

To compare the all-cause and epilepsy-related healthcare utilization and costs between refractory and non-refractory patients while controlling for age, gender, race/ethnicity, type of epilepsy, type of index AED, baseline CCI, number of psychiatric and presence of non-psychiatric comorbidities at follow-up, baseline pill burden, baseline all-cause inpatient visits, baseline number of all-cause outpatient visits, baseline all-cause total cost.

#### Healthcare Utilization

**H<sub>3A-C</sub>**: Patients with refractory epilepsy have a higher number of all-cause medical visits consisting of inpatient hospitalizations (H<sub>3A</sub>), ED visits (H<sub>3B</sub>), and outpatient visits (H<sub>3C</sub>) at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.

**H<sub>3D-F</sub>**: Patients with refractory epilepsy have a higher number of epilepsy-related medical visits consisting of inpatient hospitalizations (H<sub>3D</sub>), ED visits (H<sub>3E</sub>), and outpatient visits (H<sub>3F</sub>) at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.

**H<sub>3G</sub>**: Patients with refractory epilepsy have longer lengths of stay for all-cause hospitalization as compared to patients with non-refractory epilepsy, while controlling for covariates.

**H<sub>3H</sub>**: Patients with refractory epilepsy have longer lengths of stay for epilepsy-related hospitalization as compared to patients with non-refractory epilepsy, while controlling for covariates.

**H<sub>3I-J</sub>**: Patients with refractory epilepsy have a higher number of all-cause pharmacy claims (**H<sub>3I</sub>**) and epilepsy-related pharmacy claims (**H<sub>3J</sub>**) as compared to patients with non-refractory epilepsy, while controlling for covariates.

#### Healthcare Cost

**H<sub>3K-M</sub>**: Patients with refractory epilepsy have a higher all-cause medical costs consisting of inpatient hospitalizations (**H<sub>3K</sub>**), ED visits (**H<sub>3L</sub>**), and outpatient visits (**H<sub>3M</sub>**) at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.

**H<sub>3N-P</sub>**: Patients with refractory epilepsy have a higher epilepsy-related medical costs consisting of inpatient hospitalizations (**H<sub>3N</sub>**), ED visits (**H<sub>3O</sub>**), and outpatient visits (**H<sub>3P</sub>**) at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.

**H<sub>3Q-R</sub>**: Patients with refractory epilepsy have a higher cost of all-cause pharmacy claims (**H<sub>3Q</sub>**) and epilepsy-related pharmacy claims (**H<sub>3R</sub>**) as compared to patients with non-refractory epilepsy, while controlling for covariates.

## **Chapter 3 Methodology**

### **Chapter Overview**

This chapter provides a description of the methodology used to evaluate the treatment patterns and healthcare utilization and costs between patients with refractory and non-refractory epilepsy. The chapter includes a description of the data source, study population, sample selection criteria, study design, study variables, statistical analyses, sample size calculations, and potential limitations for the study.

### **3.1 Institutional Review Board Approval**

The study proposal was reviewed by the Institutional Review Board (IRB) of The University of Texas at Austin and by Texas Medicaid. A waiver of informed consent was requested as the study used de-identified patient claims and, as a result, did not meet the definition of research involving human subjects.

### **3.2 Data Source**

The proposed study used Texas Medicaid claims data from September 01, 2007 through December 31, 2013. The services provided by the Texas Medicaid program include office-based outpatient services, inpatient and outpatient hospital services, long-term care services, lab services, and pharmacy services.<sup>120</sup>

### **3.3 Study Population**

All patients enrolled in Texas Medicaid between September 01, 2007 and December 31, 2013 (Figure 3.1) who met the sample selection criteria, as discussed in the next section, were included in the study.

#### **3.3.1 Study Inclusion Criteria**

Patients were included in the study if they: 1) had at least one AED prescription claim in the identification period (March 01, 2008 through December 31, 2011); 2) had at least one inpatient claim and/or at least two outpatient claims associated with an epilepsy diagnosis (ICD-9-CM code: 345.xx) or other convulsions (ICD-9-CM code: 780.39) in any diagnosis field within 6 months of the first AED use; 3) had two epilepsy-related outpatient claims at least 30 days apart to ensure that the claims were not to rule out the condition; 4) were 18-62 years of age at the index date; 5) were continuously enrolled in Texas Medicaid from 6 months prior to the first AED use through 24 months after the first AED use.

#### **3.3.2 Study Exclusion Criteria**

Patients were excluded from the study if they: 1) had an AED claim in the 6-month period prior to their first AED use during the identification period; 2) had less than three months of any AED use, excluding diazepam, without a gap of more than 60 days in the post-identification period to ensure that the AEDs were not dispensed for prophylactic use; 3) had evidence of pregnancy in the study period; and 4) were dual eligible for Medicare and Medicaid during the study period.

### 3.4 Study Design

The study employed a retrospective cohort design using individual patient claims from Texas Medicaid medical and prescription databases. The study outcomes were compared across two mutually exclusive cohorts: 1) patients on three or more AEDs, excluding diazepam, in the 12-month identification period were defined as the refractory cohort; and 2) all other patients who met the study selection criteria were defined as the non-refractory cohort (i.e., they had less than 3 AEDs in the 12-month identification period). Below is an explanation regarding the basis for which the above cohorts were defined.

To better characterize these patients and to increase the validity of refractory AED use in this study, medication profiles from the study sample were reviewed and discussed with a clinician expert (Appendix IA). Based on these discussions, a determination regarding the classification of refractory and non-refractory patients was made. Since diazepam is not used chronically, it was not considered in the definition of refractory epilepsy (see point 1 above). The stepwise selection algorithm defining the refractory cohort considers the sequential nature of refractory epilepsy and is consistent with the ILAE definition.<sup>9</sup> The ILAE commission defines refractory epilepsy as “failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.<sup>9</sup> This definition has been previously used by Chen et al. to characterize refractory epilepsy.<sup>10</sup> Manjunath et al., who used a Medicaid retrospective database, employed a criterion that each AED therapy had to have an interval of 30 days. This was a proxy for AED intolerance or inefficacy.<sup>13</sup> However, this criterion was not employed in this study based on consultations with the clinical expert and review of patient profiles (Appendix IA). Technically, use of retrospective databases precludes clinical determination of refractory AED use, and more specifically whether AED changes were

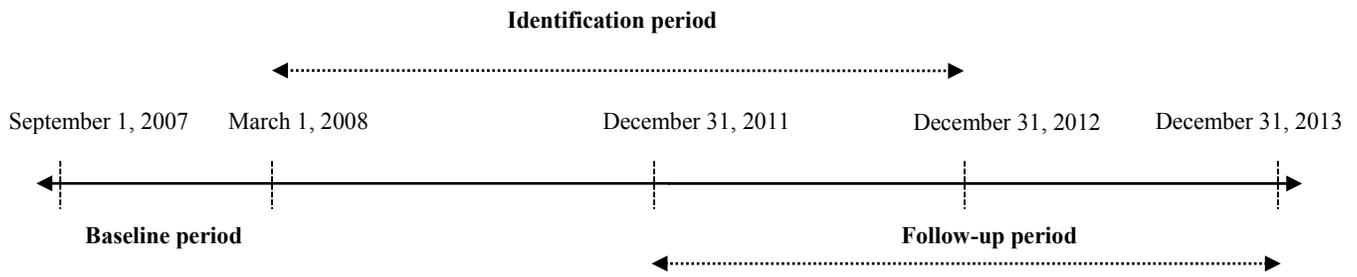
made due to inefficacy and intolerance. Thus, this study employed clinical expert opinion, which led to the definition of refractory patients as those with at least three AEDs in the 12-month follow-up period.

For objectives 1, 2, and 3, demographic and clinical characteristics, treatment patterns (adherence and persistence), and all-cause and epilepsy-related healthcare utilization and costs were compared between the two cohorts, that is, refractory vs. non-refractory epilepsy cohorts for the first and second year. In addition, treatment patterns consisting of addition and switch were compared between the two cohorts for the first year only. To minimize sample selection bias that may occur due to differences between the refractory and non-refractory groups, propensity score matching was used and will be discussed in the statistical analysis section.

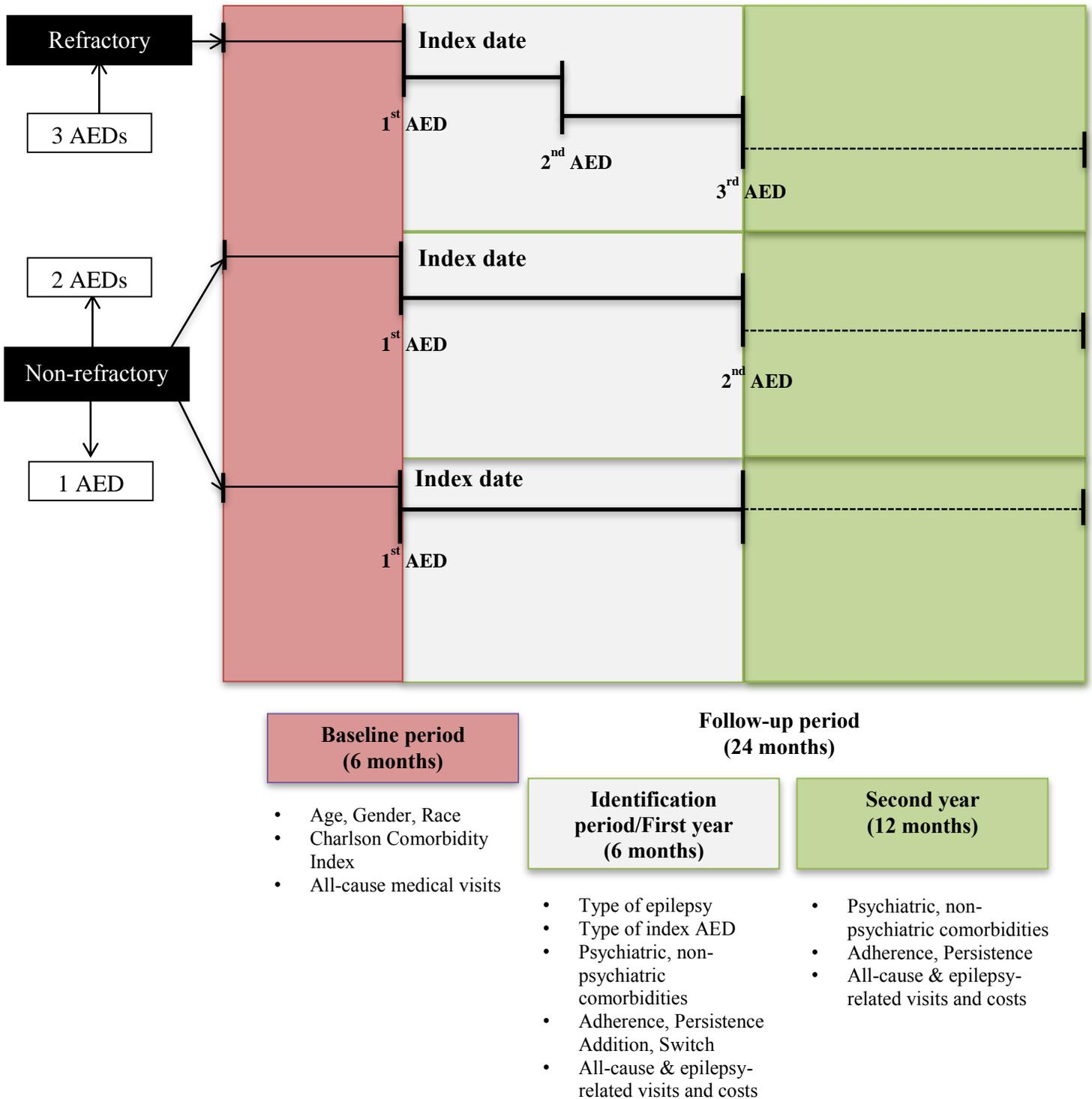
#### **3.4.1 Refractory vs. Non-refractory Epilepsy Cohorts**

The identification period began the date of the first AED claim, while the baseline period (i.e., no AED use) was defined as the 6-month period prior to the beginning of the identification period (i.e., prior to the first AED claim). The index date was the date of the first AED claim. The identification period for both cohorts was the 12-month period used to characterize refractory and non-refractory cohorts. The follow-up period for both the cohorts was the 24-month period after the index date. Figure 3.1 illustrates the data collection period and Figure 3.2 illustrates the study design for objective 1-3.

**Figure 3.1: Data Collection Period**



**Figure 3.2: Study Design Framework**



### **3.5 Study Variables**

The following section describes the dependent and independent variables, and the covariates for each objective. The cohorts have been explained in section 3.4.1.

#### **3.5.1 Demographic and Clinical Characteristics**

For objective 1, the demographic and clinical characteristics of the study population will be described and compared among the refractory and non-refractory cohorts (Table 3.1). The demographic characteristics consisted of age at index date, gender, race; and the clinical characteristics consisted of type of epilepsy, type of index AED use, Charlson Comorbidity Index (CCI), and pill burden. CCI and pill burden were measured during the baseline period.

The main independent variable for objectives 1-3 was the cohort consisting of refractory and non-refractory epilepsy (Table 3.1). Regarding covariates (Table 3.1), the demographic characteristics included age, gender and race, and the clinical characteristics included type of epilepsy (Table 3.1), type of index AED (Table 3.2), comorbidity burden, and pill burden (Table 3.3).

The Deyo adaptation of the Charlson Comorbidity Index (CCI) was used to assess the baseline comorbidity burden (Table 3.3).<sup>123</sup> Though the CCI was initially developed to predict in-hospital mortality, it has been adapted and is widely used to measure comorbidity burden in administrative and claims databases.<sup>19</sup> The number of psychiatric and non-psychiatric comorbidities was also evaluated to measure the comorbidity burden in the follow-up period. Psychiatric and non-psychiatric comorbidities identified in the first year were used as covariates for evaluating the effect on adherence, persistence, addition, switch, and healthcare utilization and costs assessed during the first year follow-up period for objectives 2 and 3. In contrast, chronic

psychiatric and non-psychiatric comorbidities identified in the first and second year follow-up periods and acute non-psychiatric comorbidities identified in the second year follow-up period were used as covariates for evaluating the effect on adherence, persistence, and healthcare utilization and costs assessed in the second year period for objectives 2 and 3.

**Table 3.1: Summary of Operational Definition of Independent Variables and Covariates**

<b>Variables</b>	<b>Operational Definitions</b>
Cohort	0=Non-refractory 1=Refractory
<b>Demographics</b>	
Age	Age of the respondent at the index date
Gender	0=Female 1=Male
Race	1=Caucasian 2=Hispanic 3=African American 4=Other/Unknown
<b>Clinical Characteristics</b>	
Type of epilepsy	1=Generalized (ICD-9-CM Code=345.00-345.31) 2=Partial (ICD-9-CM Code=345.4x, 345.5x, 345.7x) 3=Other convulsions (ICD-9-CM Code=780.39) 4=Multiple types
Type of index AED (See Table 3.2)	1=Sodium channel blockers 2=GABA analogues 3=Calcium channel actions 4=Multiple actions 5=Synaptic vesicle protein 2A binding 6= Potassium channel activity 7=Combination
Charlson Comorbidity Index (See Table 3.3)	Deyo adaptation of the Charlson Comorbidity index
Non-psychiatric comorbidities (First and second <sup>a</sup> follow-up years) (See Appendix IB)	Number of non-psychiatric comorbidities: Alzheimer’s disease, Brain tumor, Head injury, Meningitis, Migraine, Stroke, Multiple Sclerosis,  <sup>a</sup> Fracture, Dislocation, Sprains and strains, Open wounds, Burns
Psychiatric comorbidities (First and second follow-up years) (See Appendix IB)	Number of psychiatric comorbidities: Anxiety disorders, Bipolar disorder, Depression, Psychosis, Personality disorder, Mental retardation
Pill burden	Number of AED and non-AED prescriptions

ICD-9-CM=The International Classification of Diseases, 9th Revision, Clinical Modification

**Table 3.2: Categorization for Type of Antiepileptic Drugs**

<b>Mechanism of Action</b>	<b>Antiepileptic Drugs</b>
Sodium channel blocker	Acetazolamide, carbamazepine, eslicarbazepine acetate, oxcarbazepine, phenytoin, fosphenytoin, ethotoin, lamotrigine, rufinamide, lacosamide
GABA-related actions	Diazepam, clonazepam, clobazam, phenobarbital, primidone, tiagabine, vigabatrin
Calcium channel actions	Gabapentin, pregabalin, ethosuximide
Multiple actions	Sodium valproate/valproic acid, felbamate, topiramate, perampanel, zonisamide
SV2A actions	Levetiracetam
Potassium channel activity	Retigabine/ezogabine

Source: Margolis et al. (2014); Brodie et al. (2011)<sup>27,59</sup>

**Table 3.3: Deyo Adaptation of the Charlson Comorbidity Index**

<b>Comorbid Conditions</b>	<b>Weights</b>	<b>Deyo et al. codes</b>
Myocardial infarction	1	410.xx, 412
Congestive heart failure	1	428.x
Peripheral vascular disease	1	441.x, 443.9, 785.4, V43.4, 38.48
Cerebrovascular disease	1	430-437.x, 438
Dementia	1	290.x
Chronic pulmonary disease	1	490-496, 500-505, 506.4
Connective tissue disease	1	710.0-710.1, 710.4, 714.0-714.2, 714.81, 725
Ulcer disease	1	531.4x-531.7x, 532.4x-532.7x, 533.4x-533.7x, 534.4x-534.7x, 531.0x-531.3x, 532.0x-532.3x, 533.0x-533.3x, 534.0x-534.3x, 531.9, 532.9, 533.9, 534.9
Mild liver disease	1	571.2, 571.4, 571.5, 571.6
Diabetes	1	250.0x-250.3x, 250.7x
Diabetes with end organ damage	2	250.4x-250.6x
Hemiplegia	2	342.x, 344.1
Moderate or severe renal disease	2	582.x, 583.0-583.7, 585, 586, 588.x
Any tumor	2	140.x-172.x
Leukemia	2	174.x-195.x
Lymphoma	2	200.xx-208.xx
Moderate or severe liver disease	3	572.2-582.8, 456.0-456.2x
Metastatic solid tumor	6	196.x-199.x
AIDS	6	042.x-044.x

Source: Deyo et al. (1992)<sup>123</sup>

### **3.5.2 Treatment Patterns**

For objective 2, AED treatment patterns consisting of adherence, persistence, addition, and switching were compared among the refractory and non-refractory cohorts (Table 3.5). For the treatment pattern variables of addition and switching, only those patients on two or more AEDs in the identification period were included. Treatment patterns included AED utilization measured from the Texas Medicaid pharmacy claims database. The pharmacy claims database includes: label name, GCN (Generic Code Number), NDC (National Drug Code), AHFS (American Hospital Formulary Service) code, dispense dates, quantity supplied, days of supply, and amount paid. The AHFS codes for AEDs based on the AHFS Drug Information Directory are listed in Table 3.4.<sup>124</sup>

**Table 3.4: AHFS codes for Antiepileptic Drugs**

<b>AHFS code</b>	<b>Class</b>	<b>Generic name</b>
281204	Anticonvulsant, Barbiturates	Phenobarbital, Phenobarbital Sodium Primidone
281208	Anticonvulsant, Benzodiazepines	Clobazam Clonazepam Diazepam
281212	Anticonvulsant, Hydantoins	Ethotoin Fosphenytoin Sodium Phenytoin, Phenytoin Sodium
281220	Anticonvulsant,	Ethosuximide
281292	Anticonvulsant, Miscellaneous	Carbamazepine Eslicarbazepine Ezogabine, Retigabine Felbamate Gabapentin Lacosamide Lamotrigine Levetiracetam Oxcarbazepine Perampanel Pregabalin Rufinamide Tiagabine Hydrochloride Topiramate Valproate Sodium, Valproic Acid, Divalproex Sodium Vigabatrin Zonisamide
524012	Antiglaucoma agent, Carbonic Anhydrase Inhibitor	Acetazolamide

Source: STAT, 2015<sup>124</sup>

Label names (generic and brand name) and GCNs were used to identify specific AEDs. Based on literature, the AEDs listed in Table 3.2 are identified for the treatment of epilepsy and were included in the study.<sup>10,11,27</sup>

### 3.5.2.1 Medication Adherence and Persistence

Medication adherence and persistence was assessed in both the first and second year follow-up periods after the index date. Adherence to AEDs was measured using the proportion of days covered (PDC) method, which is the number of days of possession of at least one AED divided by the total number of days in the follow-up period.

For the purpose of this study, the following formula was used for calculating PDC<sup>29</sup>:

$$\text{PDC} = \frac{\text{Number of days with a prescription for at least one AED}}{\text{Number of days in follow-up period (365 days)}}$$

A PDC of  $\geq 0.80$  was defined as adherent, while a PDC of  $< 0.80$  was defined as non-adherent. This threshold has been used in previous studies measuring AED adherence.<sup>29,103</sup> A sensitivity analysis was conducted using 70% and 90% as cut-offs for adherence. Even if patients were on multiple therapies, PDC was measured based on a monotherapy assumption (i.e., did the patients have at least one AED in their possession during the follow-up period).

Medication persistence was computed to determine the duration of medication use and was compared between the refractory and non-refractory cohorts. Medication persistence was defined as the number of days of continuous AED therapy without a gap of more than 60 days in the follow-up period of 365 days. This approach has been previously used in assessing AED treatment patterns.<sup>27</sup> A pre-specified gap of 60 days allows for delays in the refill of a prescription. Since there is no standard gap for the calculation of persistence in epilepsy, a sensitivity analysis using

30 and 90 days was conducted. Table 3.5 provides a summary of operational definitions of treatment pattern variables.

### **3.5.2.2 Addition and Switching of Antiepileptic Drugs**

Medication addition and switching was assessed in the first follow-up period after the index date. Since a proportion of patients in the non-refractory cohort were on one AED only in the one-year identification period, their addition and switch patterns could not be assessed. As a result, only those patients on dual therapy or more (i.e., on two or more AEDs in the identification period) were included in the study for assessing the addition and switch patterns. These patients were matched 1:1 with the patients in the refractory group. Section 3.6 explains the propensity score matching procedure used in the study.

After discussion with a clinical expert, definitions for addition and switching were developed. Addition and switching was assessed based on generic drug names. Addition of an AED was defined as the addition of an alternative AED to the first or second AED with an overlap of at least 30 consecutive days. Switching was defined as the discontinuation of the first or second AED for at least 60 consecutive days and the start of an alternative AED within 30 days of discontinuing the initial AED.<sup>13,32</sup> Addition and switch patterns based on AED mechanism of action were also described.

**Table 3.5: Summary of Operational Definitions of Treatment Pattern Variables**

Variables	Operational Definitions
<b>Treatment patterns</b>	
Addition	Addition of at least one alternative AED 0=No addition 1=Addition
Switch	Switch to an alternative AED 0=No switch 1=Switch
Adherence	Measured using the PDC method 0=Non-adherent (PDC < 0.8) 1=Adherent (PDC ≥ 0.80)
Persistence	Number of days of continuous therapy without a gap of more than 60 days

PDC = Proportion of Days Covered

### 3.5.3 Healthcare Utilization and Costs

Healthcare utilization and costs were assessed using the Texas Medicaid medical and prescription claims databases (Table 3.6). The medical claims database includes information on outpatient visits and inpatient visits, primary and secondary diagnoses, date of service, admission and discharge dates, type of provider, and amount paid. For objective 3, the annual epilepsy-related and all-cause healthcare utilization and costs in the first and second years in the follow-up period after the index date were computed and compared between the refractory and non-refractory cohorts.

#### 3.5.3.1 Epilepsy-related and All-cause Healthcare Utilization

Epilepsy-related healthcare utilization was defined as the number of medical service claims associated with an epilepsy diagnosis (ICD-9-CM codes: 345.xx or 780.39) in the primary and/or secondary diagnosis fields.<sup>11,24</sup> All-cause healthcare utilization included all medical service claims. Medical services included inpatient hospitalizations, ED visits, and outpatient visits. All-cause pharmacy utilization consisted of the number of AEDs and non-AEDs.

### **3.5.3.2 Epilepsy-related and All-cause Healthcare Costs**

The total epilepsy-related (i.e., diagnosis-related) healthcare costs included cost of epilepsy-related medical visits consisting of inpatient hospitalizations, ED visits, and outpatient visits and cost of AED prescriptions. The total all-cause healthcare costs included cost of all-cause medical visits consisting of inpatient hospitalizations, ED visits, and outpatient visits and cost of AED and non-AED prescriptions.

**Table 3.6: Summary of Operational Definitions of Healthcare Utilization and Cost**

**Variables**

<b>Variables</b>	<b>Operational Definitions</b>
<b>Epilepsy-Related Healthcare Resource Utilization</b>	
Number of epilepsy-related inpatient hospitalizations	Number of inpatient visits with an epilepsy diagnosis
Number of epilepsy-related ED visits	Number of ED visits with an epilepsy diagnosis
Number of epilepsy-related outpatient visits	Number of outpatient visits with an epilepsy diagnosis
Number of epilepsy-related pharmacy claims	Number of AEDs
<b>All-Cause Healthcare Resource Utilization</b>	
Number of all-cause inpatient hospitalizations	Number of inpatient hospitalizations with and without an epilepsy diagnosis
Number of all-cause ED visits	Number of ED visits with and without an epilepsy diagnosis
Number of all-cause outpatient visits	Number of outpatient visits with and without an epilepsy diagnosis
Number of all-cause pharmacy claims	Number of AEDs and non-AEDs
<b>Epilepsy-Related Healthcare Costs</b>	
Epilepsy-related inpatient hospitalization cost	Cost of inpatient hospitalizations with an epilepsy diagnosis
Epilepsy-related ED visit cost	Cost of ED visits with an epilepsy diagnosis
Epilepsy-related outpatient visit cost	Cost of outpatient visits with an epilepsy diagnosis
Epilepsy-related pharmacy costs	Sum of the costs of AED prescriptions
Epilepsy-related total costs	Sum of the epilepsy-related medical costs, and AED prescription costs
<b>All-Cause Healthcare Costs</b>	
All-cause inpatient hospitalization cost	Cost of inpatient hospitalizations with and without an epilepsy diagnosis
All-cause ED visit cost	Cost of ED visits with and without an epilepsy diagnosis
All-cause outpatient visit cost	Cost of outpatient visits with and without an epilepsy diagnosis
All-cause pharmacy costs	Sum of the costs of AED and non-AED prescriptions
All-cause total costs	Sum of the all-cause medical visit costs, and AED and non-AED prescription costs
<b>Baseline Healthcare Utilization and Costs</b>	
Baseline All-cause inpatient visits	Number of inpatient visits with and without an epilepsy diagnosis
Baseline All-cause outpatient visits	Number of outpatient visits with and without an epilepsy diagnosis
Baseline All-cause total health care costs	Sum of the all-cause medical visit costs and non-AED prescription costs

### **3.6 Statistical Analyses**

All statistical analyses were two-tailed, performed using SAS for Windows, Version 9.3 (SAS Institute, Cary, NC) with a priori significance of  $p < 0.05$ . Frequencies, histograms, and normality tests were computed to check data distribution and abnormalities. Propensity scores were calculated using a logistic regression with a nearest neighbor match using a caliper set at 0.05. A classification of refractory epilepsy (1=Yes, 0=No) was the binary dependent variable, and baseline covariates consisting of age, gender, race/ethnicity, type of epilepsy, baseline comorbidity burden measured using CCI, baseline pill burden, and baseline all-cause total costs were the predictors of selection in the refractory or non-refractory epilepsy group.

Before matching, statistical comparison of baseline characteristics between the unmatched cohorts were conducted using Chi-square for categorical variables and Student's t-test for continuous variables. After matching, to determine if a balance was achieved among the matched groups, statistical comparisons of baseline characteristics between the matched cohorts were conducted using McNemar's tests for categorical variables and two-sided paired Student's t-tests for continuous variables. In the case of baseline healthcare costs, due to the skewed nature of cost data, unadjusted comparisons between the matched cohorts were conducted using the Wilcoxon signed-rank test.

### **3.6.1 Objective 1: Demographic and Clinical Characteristics**

For objective 1, differences in baseline demographic and clinical characteristics comprising of gender, race, type of epilepsy, and type of index AED, were computed using the Pearson Chi-square tests for categorical variables, while differences in age, comorbidity burden measured using the Deyo adaptation of CCI, and pill burden were computed using Student's t-tests and Wilcoxon test for continuous variables across the unmatched refractory and non-refractory cohorts. After matching, comparisons of baseline characteristics between the matched cohorts were conducted using McNemar's tests for categorical variables and two-sided paired Student's t-tests and Wilcoxon signed-rank test for continuous variables.

### **3.6.2 Objective 2: Treatment Patterns**

For objective 2, adjusted comparisons of medication adherence, and addition and switching with the refractory and non-refractory cohorts were computed using Conditional Logistic Regression, while the differences in medication persistence among the cohorts were evaluated using the Cox Proportional Hazards Regression model. The control variables included age, gender, race/ethnicity, type of epilepsy, type of initial AED, baseline CCI, number of psychiatric and non-psychiatric comorbidities at follow-up, baseline pill burden, baseline number of all-cause inpatient visits, baseline number of all-cause outpatient visits, and baseline number of all-cause costs.

### 3.6.2.1 Logistic Regression Analysis

A multiple logistic regression analysis was used to account for a nominal variable and two or more independent variables. For objective 2, the nominal variable was treatment patterns (i.e., addition, switch, adherence), and the independent variables were the cohort covariates, to study the effect of the independent variables on the probability of having a specified treatment pattern. A conditional logistic regression analysis was employed to account for the matched nature of the sample.

The assumptions for a logistic regression model are<sup>125</sup>:

- 1) The observations are independent.
- 2) The natural log of the odds ratio and the measurement variables have a linear relationship or a data transformation is needed.
- 3) The dependent variable is a dichotomous variable.

The structure of a logistic regression model is:

$$\text{Logit}[\theta(x)] = \log[\theta(x)/1 - \theta(x)] = \beta_0 + \beta_{1x_1} + \beta_{2x_2} + \dots + \beta_{nx_n}$$

Where,

$\theta(x)$ : probability of success;

$1 - \theta(x)$ : probability of failure;

$\beta_0$ : constant of equation;

$\beta_{1-n}$ : regression coefficients;

$X_{1-n}$ : independent or predictor variable.

### 3.6.2.2 Cox Proportional Hazards Regression

Cox proportional hazards regression with a strata statement was used to account for the matched nature of the sample. A Cox model provides an estimate of the treatment effect on survival or a time dependent measure (i.e., persistence), after adjusting for other covariates. The model from a Cox proportional hazards regression analysis yields an equation for the hazard as a function of several predictor variables.<sup>126</sup>

The structure of a Cox proportional hazards regression model is<sup>127</sup>:

$$\log_e \left\{ \frac{h_1(t)}{h_0(t)} \right\} = \beta_1 X_{i1} + \beta_2 X_{i2} + \dots + \beta_k X_{ik}$$

Where,

$h_i(t)$ : the hazard at time t;

$h_0(t)$ : the baseline hazard;

$X$ : an independent variable in the model;

$\beta$ : the regression coefficient for the corresponding independent variable.

### **3.6.3 Objective 3: Healthcare Utilization and Costs**

For objective 3, the number of visits for epilepsy-related and all-cause healthcare utilization and the annual epilepsy-related and all-cause healthcare costs were computed and compared among the refractory and non-refractory cohorts. Poisson regression models were used to compute healthcare utilization in objective 3. Regarding healthcare costs, a Generalized Linear Model (GLM) was used to account for the matched nature of the sample. The covariates in the models included age, gender, race/ethnicity, type of epilepsy, type of index AED, baseline CCI, baseline pill burden, baseline number of all-cause inpatient visits, baseline number of all-cause outpatient visits, baseline all-cause costs, and number of psychiatric and non-psychiatric comorbidities at follow-up.

### 3.6.3.1 Poisson Regression

Poisson regression is used to model count data. Zero-inflated Poisson (ZIP) regression models were used with data that was comprised of excess of zeros. A ZIP model has two parts, a Poisson count model and a logit model for predicting excess zeros. In ZIP, the excess zeros are generated by a separate process from the count values and can be modeled independently.<sup>128</sup>

The simplest Poisson regression equation can be written as:

$$\log(\mu) = \beta_0 + \beta_1 E + \log(N)$$

Where,

$\mu = \lambda N$ : number of events per person-time at risk;

$E$ : independent variable;

$\exp(\beta_1)$ : rate ratio;

$\beta_0$ : constant of equation;

$\beta_1$ : regression coefficient.

### 3.6.3.2 Generalized Linear Models

A multiple regression model typically takes the following form:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \dots + \beta_k X_k + e$$

Where,

$Y$  variable: a vector of observations;

$X$  variables: linearly associated covariates;

$\beta$ : regression coefficients;

$e$ : error variability that cannot be accounted for by the predictors.

## Generalized Linear Models

Generalized linear models (GLM) relate the responses of the dependent variable and predictor variables by providing a framework comprising of traditional linear model theory to nonlinear data.<sup>129</sup>

GLMs take on the following standard model form:

$$Y = g(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \dots + \beta_k X_k + e)$$

Where,

$Y$  variable: a vector of observations;

$X$  variables: linearly associated covariates;

$\beta$ : regression coefficients;

$e$ : error variability that cannot be accounted for by the predictors;

$g(\dots)$ : a monotonic function which acts on  $E(y)$  relating the means of the responses to the linear predictors.

Weighting the observations inversely according to the variance functions then completes the estimation of the nonlinear regression equation. This weighting procedure is equivalent to maximum likelihood estimation (MLE), of which the Newton-Raphson and Fisher-Scoring methods are among the most efficient and widely used, to determine the values of the  $\beta$  coefficients.

The inverse function of  $g(\dots)$ , is called the link function. For the general linear model, the dependent variable values follow the normal distribution where the link function is a simple identity function (the linear combination of values for the non-transformed predictor variables). Other commonly used link functions chosen depending on the assumed distribution of the  $y$

variable include logistic regression with a proportional response variable, binomial distribution and logit link function, Poisson regression in log linear model with a counting response variable, Poisson distribution and log link function, and gamma model with log link that include a positive and continuous response variable, gamma distribution and a log link function.<sup>130,131</sup>

### 3.7 Sample Size Calculations

This section describes the sample size calculations for all statistical analyses. For objective 1, sample size calculations were not conducted as it involves descriptive statistics.

#### 3.7.1 Logistic Regression Analysis

Sample size estimates for the model were based on the G-power software. By varying the sample parameters required for sample size calculations, the largest sample size of 1,283 was chosen for the logistic regression (Table 3.7).<sup>132</sup>

**Table 3.7: Estimates of Sample Size for Logistic Regression Analysis**

Odds Ratio	1.5	2.0	2.5	3.0
Pr(Y=1 X=1)Ho <sup>a</sup>	0.03	0.03	0.03	0.03
R-squared <sup>b</sup>	0.1	0.1	0.1	0.1
<b>Total Sample Size</b>	<b>988</b>	<b>324</b>	<b>182</b>	<b>126</b>
Odds Ratio	1.5	2.0	2.5	3.0
Pr(Y=1 X=1)Ho <sup>a</sup>	0.03	0.03	0.03	0.03
R-squared <sup>b</sup>	0.2	0.2	0.2	0.2
<b>Total Sample Size</b>	<b>1,123</b>	<b>364</b>	<b>204</b>	<b>141</b>
Odds Ratio	1.5	2.0	2.5	3.0
Pr(Y=1 X=1)Ho <sup>a</sup>	0.03	0.03	0.03	0.03
R-squared <sup>b</sup>	0.3	0.3	0.3	0.3
<b>Total Sample Size</b>	<b>1,283</b>	<b>416</b>	<b>233</b>	<b>161</b>

Y = dependent variable; X = independent variables (IV); test family = Z tests number of tails = 2,  $\alpha = 0.05$  (two tailed),  $\beta = 0.20$  (power = 80%), a binomial distribution was assumed for the IV of interest (X1)

a Denotes the probability of an event under Ho (lowest possible value which translates to highest possible sample size after evaluating the values reported across studies in the literature). b The value achieved when X1 is regressed on the other IVs or covariates in the regression

### 3.7.2 Cox Proportional Hazards Regression Analysis

The estimates of sample size required for the Cox proportional hazards regression analysis were obtained using the PASS (Power Analysis & Sample Size) software. By varying the sample parameters required for sample size calculations, the largest sample size of 1,662 was chosen for the Cox proportional hazards regression (Table 3.8).<sup>133</sup>

**Table 3.8: Estimates of Sample Size for Cox Proportional Hazards Regression Analysis**

B (log Hazard ratio) <sup>a</sup>	1.5	1.5	1.5
P(Overall Event Rate) <sup>b</sup>	0.3	0.5	0.7
R-squared <sup>c</sup>	0.1	0.1	0.1
<b>Total Sample Size</b>	<b>1,292</b>	<b>776</b>	<b>554</b>
B (log Hazard ratio) <sup>a</sup>	1.5	1.5	1.5
P(Overall Event Rate) <sup>b</sup>	0.3	0.5	0.7
R-squared <sup>c</sup>	0.3	0.3	0.3
<b>Total Sample Size</b>	<b>1,662</b>	<b>997</b>	<b>712</b>
B (log Hazard ratio) <sup>a</sup>	3.0	3.0	3.0
P (Overall Event Rate) <sup>b</sup>	0.3	0.5	0.7
R-squared <sup>c</sup>	0.1	0.1	0.1
<b>Total Sample Size</b>	<b>323</b>	<b>194</b>	<b>139</b>
B (log Hazard ratio) <sup>a</sup>	3.0	3.0	3.0
P(Overall Event Rate) <sup>b</sup>	0.3	0.5	0.7
R-squared <sup>c</sup>	0.3	0.3	0.3
<b>Total Sample Size</b>	<b>416</b>	<b>250</b>	<b>178</b>
B (log Hazard ratio) <sup>a</sup>	4.5	4.5	4.5
P(Overall Event Rate) <sup>b</sup>	0.3	0.5	0.7
R-squared <sup>c</sup>	0.1	0.1	0.1
<b>Total Sample Size</b>	<b>144</b>	<b>87</b>	<b>62</b>
B (log Hazard ratio) <sup>a</sup>	4.5	4.5	4.5
P (Overall Event Rate) <sup>b</sup>	0.3	0.5	0.7
R-squared <sup>c</sup>	0.3	0.3	0.3
<b>Total Sample Size</b>	<b>185</b>	<b>111</b>	<b>80</b>

Y = dependent variable; X = independent variables (IV);  $\alpha = 0.05$  (two tailed),  $\beta = 0.20$  (power = 80%), standard deviation = 0.1

<sup>a</sup> Known as the regression coefficient defined as the predicted change in log(base e) hazards at one unit change in X1 when the other covariates are held constant

<sup>b</sup> Denotes the proportion of subjects in which the event of interest occurs during the duration of the study (Based on values reported in the literature, the modeled event was medication discontinuation over a 12-month follow-up period)

<sup>c</sup>The value achieved when X1 is regressed on the other IVs or covariates in the regression

### 3.7.3 Multiple Regression Analysis

The sample size for the GLM model was estimated using the multiple regression test in the G-power software.<sup>132</sup> The sample size estimate was calculated using a fixed effect linear multiple regression model with  $R^2$  deviation from zero,  $\alpha$  of 0.05, and a power of 0.80. Based on the number of predictor variables ( $n = 12$ ) and an effect size of 0.02, a sample size of 1,304 patients was required to test objectives 3 and 4. Thus, for all statistical analyses, a minimum sample size of 1,662 was required for the study.

**Table 3.9: Summary of Objectives, Hypotheses, Study Variables, and Statistical Tests**

Objectives and Hypotheses	Dependent Variable	Measurement Levels	Independent Variables	Measurement Levels	Statistical Analyses
<b>Objective 1:</b> To compare the demographic and clinical characteristics of patients with refractory and non-refractory epilepsy					
<b>H<sub>01A</sub>:</b> There is no significant difference in the mean age of patients between the refractory and non-refractory groups.	Age	Continuous	Refractory or non-refractory	Categorical	Paired Student's t-test <sup>a</sup>
<b>H<sub>01B</sub>:</b> The proportion of gender categories does not differ between the refractory and non-refractory groups.	Gender	Categorical	Refractory or non-refractory	Categorical	McNemar's tests <sup>a</sup>
<b>H<sub>01C</sub>:</b> The proportion of race/ethnicity categories does not differ between the refractory and non-refractory groups.	Race	Categorical	Refractory or non-refractory	Categorical	McNemar's tests <sup>a</sup>
<b>H<sub>01D</sub>:</b> The proportion of epilepsy type categories does not differ between the refractory and non-refractory groups.	Type of epilepsy	Categorical	Refractory or non-refractory	Categorical	McNemar's tests <sup>a</sup>
<b>H<sub>01E</sub>:</b> There is no significant difference in the comorbidity burden of patients between the refractory and non-refractory groups.	Comorbidity burden	Continuous	Refractory or non-refractory	Categorical	Paired Student's t-test <sup>a</sup>
<b>H<sub>01F</sub>:</b> There is no significant difference in the proportion of different types of index AED used between the refractory and non-refractory groups.	Type of index AED	Categorical	Refractory or non-refractory	Categorical	McNemar's tests <sup>a</sup>
<b>H<sub>01G</sub>:</b> There is no significant difference in the pill burden of patients between the refractory and non-refractory groups.	Pill burden	Continuous	Refractory or non-refractory	Categorical	Wilcoxon signed rank test <sup>a</sup>

<sup>a</sup>Statistical analyses will be done on matched sample

**Table 3.9: Summary of Objectives, Hypotheses, Study Variables, and Statistical Tests (Continued)**

Objectives and Hypotheses	Dependent Variable	Measurement Levels	Independent Variables	Measurement Levels	Statistical Analyses
<b>Objective 2:</b> To compare the treatment patterns of patients with refractory and non-refractory epilepsy					
<b>H<sub>2A</sub>:</b> Patients with refractory epilepsy are less likely to be adherent to AEDs as compared to patients with non-refractory epilepsy, while controlling for covariates.	Adherence	Categorical	Cohort covariates	Continuous /Categorical	Conditional Logistic Regression
<b>H<sub>2B</sub>:</b> Patients with refractory epilepsy have lesser duration of medication use prior to discontinuation as compared to patients with non-refractory epilepsy, while controlling for covariates.	Persistence (Survival time)	Continuous	Cohort covariates	Continuous /Categorical	Cox Proportional Hazards Regression
<b>H<sub>2C</sub>:</b> Patients with refractory epilepsy are more likely to add an adjunctive AED as compared to patients with non-refractory epilepsy.	Addition	Categorical	Cohort covariates	Continuous /Categorical	Conditional Logistic Regression
<b>H<sub>2D</sub>:</b> Patients with refractory epilepsy are more likely to switch to an alternative AED as compared to patients with non-refractory epilepsy.	Switching	Categorical	Cohort covariates	Continuous /Categorical	Conditional Logistic Regression

**Table 3.9: Summary of Objectives, Hypotheses, Study Variables, and Statistical Tests (Continued)**

Objectives and Hypotheses	Dependent Variable	Measurement Levels	Independent Variables	Measurement Levels	Statistical Analyses
<b>Objective 3:</b> To compare the all-cause and epilepsy-related healthcare utilization and costs between refractory and non-refractory patients					
<b>H3A-C:</b> Patients with refractory epilepsy have a higher number of all-cause medical visits consisting of inpatient hospitalizations (H3A), ED visits (H3B), and outpatient visits (H3C) at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.	Number of all-cause medical visits	Count	Cohort covariates	Continuous /Categorical	Poisson Regression
<b>H3D-F:</b> Patients with refractory epilepsy have a higher number of epilepsy-related medical visits consisting of inpatient hospitalizations (H3D), ED visits (H3E), and outpatient visits (H3F) at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.	Number of epilepsy-related medical visits	Count	Cohort covariates	Continuous /Categorical	Poisson Regression
<b>H3G:</b> Patients with refractory epilepsy have longer length of stays for all-cause hospitalization as compared to patients with non-refractory epilepsy, while controlling for covariates.	All-cause length of hospitalization stay	Count	Cohort covariates	Continuous /Categorical	Poisson Regression
<b>H3H:</b> Patients with refractory epilepsy have longer length of stays for epilepsy-related hospitalization as compared to patients with non-refractory epilepsy, while controlling for covariates.	Epilepsy-related length of hospitalization stay	Count	Cohort covariates	Continuous /Categorical	Poisson Regression

**Table 3.9: Summary of Objectives, Hypotheses, Study Variables, and Statistical Tests (Continued)**

<b>Objectives and Hypotheses</b>	<b>Dependent Variable</b>	<b>Measurement Levels</b>	<b>Independent Variables</b>	<b>Measurement Levels</b>	<b>Statistical Analyses</b>
<b>H<sub>3I-J</sub></b> : Patients with refractory epilepsy have a higher number of all-cause pharmacy claims (H <sub>3I</sub> ) and epilepsy-related pharmacy claims (H <sub>3J</sub> ) as compared to patients with non-refractory epilepsy, while controlling for covariates.	Pill burden	Count	Cohort covariates	Continuous /Categorical	Poisson Regression
<b>H<sub>3K-M</sub></b> : Patients with refractory epilepsy have a higher all-cause medical costs consisting of inpatient hospitalizations (H <sub>3K</sub> ), ED visits (H <sub>3L</sub> ), and outpatient visits (H <sub>3M</sub> ) at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.	All-cause medical costs	Continuous	Cohort covariates	Continuous /Categorical	Generalized Linear Model
<b>H<sub>3N-P</sub></b> : Patients with refractory epilepsy have a higher epilepsy-related medical costs consisting of inpatient hospitalizations (H <sub>3N</sub> ), ED visits (H <sub>3O</sub> ), and outpatient visits (H <sub>3P</sub> ) at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.	Epilepsy-related medical costs	Continuous	Cohort covariates	Continuous /Categorical	Generalized Linear Model
<b>H<sub>3Q-R</sub></b> : Patients with refractory epilepsy have a higher cost of all-cause pharmacy claims (H <sub>3Q</sub> ) and epilepsy-related pharmacy claims (H <sub>3R</sub> ) as compared to patients with non-refractory epilepsy, while controlling for covariates.	Prescription costs	Continuous	Cohort covariates	Continuous /Categorical	Generalized Linear Model

\*Cohort covariates include: age, gender, race/ethnicity, type of epilepsy, type of AED, baseline CCI, number of psychiatric and presence of non-psychiatric comorbidities at follow-up, baseline pill burden, presence of baseline all-cause inpatient visits, baseline all-cause outpatient visits, and baseline all-cause costs

## **Chapter 4 Results**

### **Chapter Overview**

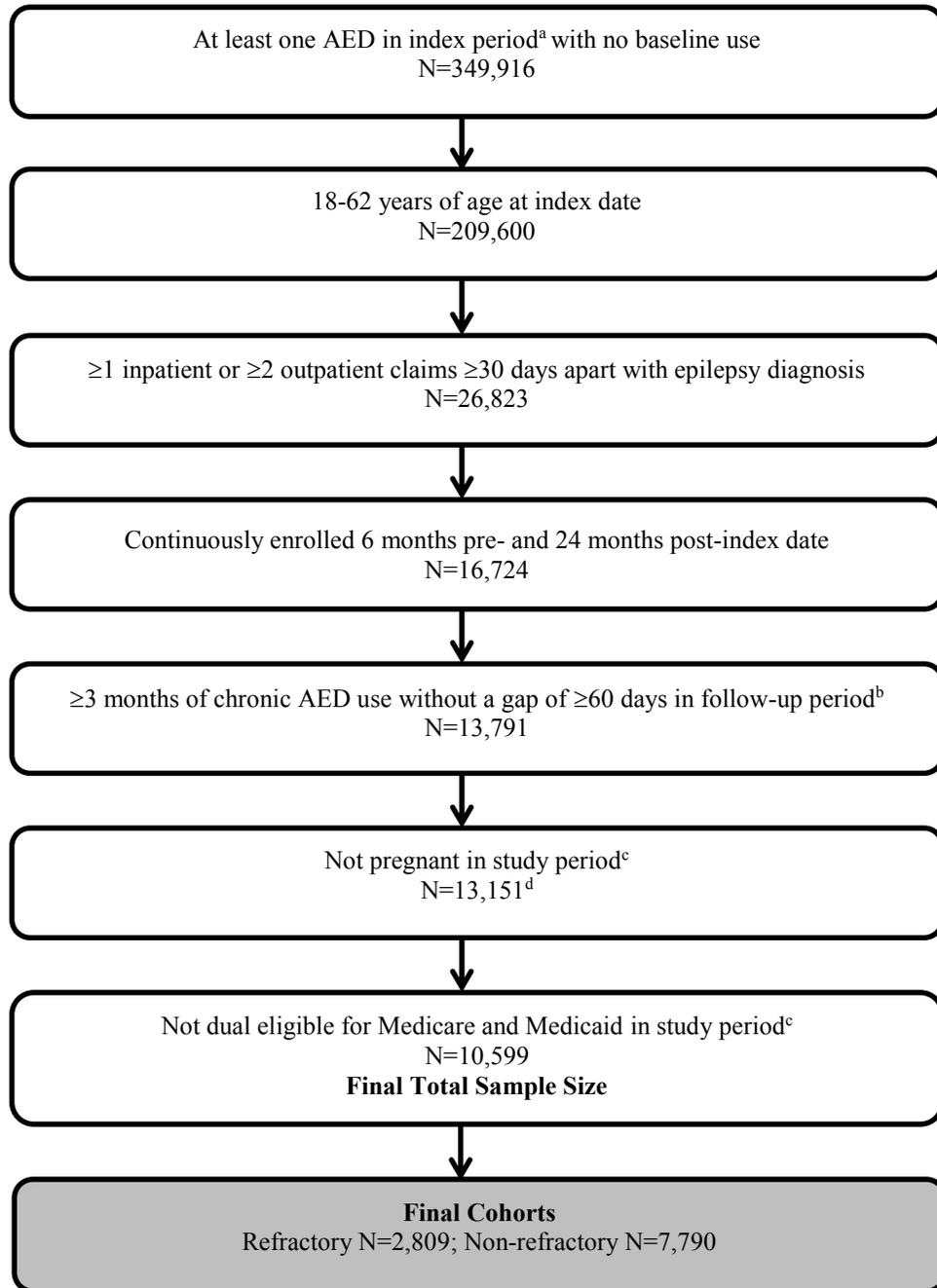
This chapter provides a detailed description of the study results. First, the sample attrition table is presented, followed by the characteristics of the study sample. Next, the results of the study are presented in the order of the study objectives and hypotheses.

### **4.1 Sample Selection**

For the present study, each patient in Texas Medicaid was followed for 2.5 years. The identification period began on the date of first AED claim, while the baseline period (i.e., no AED use) was defined as the 6-month period prior to the beginning of the identification period (i.e., prior to the AED claim). The index date was the date of the first AED claim. The 12-month identification period was used to characterize refractory and non-refractory cohorts. Patients were followed for a 24-month period after the index date.

All patients in Texas Medicaid between September 01, 2007 and December 31, 2013 who met the sample selection criteria were included in the study (Figure 4.1). The Texas Medicaid population was comprised of 349,916 patients who had at least one AED prescription in the index period (i.e., between March 01, 2008 and December 31, 2011). After applying the remaining study inclusion and exclusion criteria, a sample size of 10,599 patients was obtained. Of these, 2,809 patients were identified as refractory and 7,790 patients were identified as non-refractory.

**Figure 4.1: Study Selection Flowchart in Texas Medicaid**



<sup>a</sup>March 01, 2008 – December 31, 2011

<sup>b</sup>2 years from index date

<sup>c</sup>6-month pre- and 2-years post-index date

<sup>d</sup>13 patients on diazepam only in the identification period were excluded

AED=Antiepileptic drug

## **4.2 Descriptive Statistics of the Entire Study Sample**

Patient characteristics consisting of demographics, clinical characteristics, and healthcare utilization and costs for the entire study sample are presented in Table 4.1.

### **4.2.1 Demographic Characteristics**

The patients (n=10,599) had a mean ( $\pm$  SD) age of 38.7 ( $\pm$  13.2) years. A slightly higher proportion of patients were females (51.6%) as compared to males (48.4%). Also, the highest proportion of patients were Caucasians (40.2%), followed by Hispanics (31.7%), African American (20.3%), and others or unknown race (7.8%).

### **4.2.2 Clinical Characteristics**

The mean ( $\pm$  SD) number of AEDs in the identification period (i.e., within 12 months of index date) was (2.0 ( $\pm$  1.0)). The highest proportion of patients was on one AED (38.5%), followed by patients on two AEDs (35.0%), and patients on three or more AEDs (26.5%). Also, a majority of the patients was on monotherapy (82.7%) on the index date (i.e., date of the first AED use). A majority of the patients had an epilepsy diagnosis classified as other convulsions (79.8%). The highest proportion of patients had claims for sodium channel blockers (40.5%) on the index date, followed by those with claims for AEDs with multiple actions (20.0%), AED combinations (14.5%), and GABA analogues (10.9%). Patients had a mean of 1.0 ( $\pm$  1.1) psychiatric comorbidity at baseline (i.e., within 6 months pre-index), 1.4 ( $\pm$  1.3) in the first year of follow-up, and 1.8 ( $\pm$  1.4) in the second year of follow-up. Of the psychiatric comorbidities, the highest proportion of patients had personality disorder in both the first (36.1%) and second (46.1%) year of follow-up, followed by depression in both the first (26.2%) and the second (34.3%) year of follow-up.

Regarding non-psychiatric comorbidities, the mean ( $\pm$  SD) number at baseline was 0.4 ( $\pm$  0.7), 0.6 ( $\pm$  0.8) in the first year of follow-up, and 0.6 ( $\pm$  0.9) in the second year of follow-up. Of the non-psychiatric comorbidities, the highest proportion of patients had stroke in the first (11.0%) and second (14.8%) year of follow-up, followed by sprain in the first year (10.1%) of follow-up and migraine in the second year (10.2%) of follow-up. The mean ( $\pm$  SD) CCI score in the baseline period was 0.8 ( $\pm$  1.4). 64.0% of patients had a CCI score of 0. In the baseline period, the mean ( $\pm$  SD) pill burden of patients was 7.8 ( $\pm$  6.5). 23.9% of patients had a pill burden of greater than or equal to 11 pills.

#### **4.2.3 Healthcare Utilization and Costs**

In the baseline period, the mean ( $\pm$  SD) prescription cost per patient was \$3,286 ( $\pm$  \$4,503). Although, the majority of patients did not have an all-cause inpatient visit (80.9%), the patients had a mean ( $\pm$  SD) all-cause inpatient visit cost of \$2,006 ( $\pm$  \$9,020). 25.8% of patients had 18 or more all-cause outpatient visits and had a mean ( $\pm$  SD) all-cause outpatient visit cost of \$3,984 ( $\pm$  \$8,445). Also, the mean all-cause total cost of patients was \$9,276 ( $\pm$  \$15,000).

**Table 4.1: Baseline Characteristics of Study Sample (N=10,599)**

Characteristics	All	
	n=10,599	
	N	%
<b>Demographic Characteristics</b>		
<b>Age at index date<sup>†</sup></b>		
Mean ± SD, year	38.7 ± 13.2	
<b>Gender</b>		
Male	5,131	48.4
Female	5,468	51.6
<b>Race/Ethnicity</b>		
Caucasian	4,262	40.2
African American	2,152	20.3
Hispanic	3,357	31.7
Other/Unknown <sup>a</sup>	828	7.8
<b>Clinical Characteristics</b>		
<b>Number of antiepileptic drugs in the identification period<sup>§</sup></b>		
Mean ± SD	2.0 ± 1.0	
One Antiepileptic drug	4,081	38.5
Two Antiepileptic drugs	3,709	35.0
Three or more Antiepileptic drugs	2,809	26.5
<b>Type of therapy at index date<sup>b</sup></b>		
Monotherapy	8,769	82.7
Dual therapy	1,429	13.5
Triple therapy or more	236	2.2
<b>Type of epilepsy at first visit</b>		
Generalized	1,003	9.4
Partial	750	7.1
Other convulsions	8,453	79.8
Multiple types <sup>c</sup>	393	3.7
<b>Type of index Antiepileptic drug</b>		
Sodium channel blockers	4,297	40.5
Gamma-aminobutyric acid (GABA) analogues	1,157	10.9
Calcium channel blockers	492	4.6
Multiple actions	2,115	20.0
Synaptic vesicle protein 2A binding	1,004	9.5
Potassium channel agonist	0	0.0
Combination <sup>d</sup>	1534	14.5

**Table 4.1: Baseline Characteristics of Study Sample (N=10,599) (Continued)**

Characteristics	All	
	n=10,599	
	N	%
<b>Clinical Characteristics</b>		
<b>Baseline psychiatric comorbidities</b>		
Mean $\pm$ SD	1.0 $\pm$ 1.1	
0	4,464	42.1
1	3,210	30.3
>1	2,925	27.6
<b>Follow-up psychiatric comorbidities (First year)</b>		
Mean $\pm$ SD	1.4 $\pm$ 1.3	
0	3,263	30.8
1	3,212	30.3
>1	4,124	38.9
<b>Type of psychiatric comorbidities (First year)<sup>e</sup></b>		
Depression	2,775	26.2
Anxiety	2,034	19.2
Bipolar disorder	911	8.6
Psychosis	2,253	21.3
Personality disorder	3,827	36.1
Mental retardation	2,592	24.5
<b>Follow-up psychiatric comorbidities (Second year)</b>		
Mean $\pm$ SD	1.8 $\pm$ 1.4	
0	2,260	21.3
1	2,931	27.7
>1	2,649	25.0
<b>Type of psychiatric comorbidities (Second year)<sup>e</sup></b>		
Depression	3,638	34.3
Anxiety	2,805	26.5
Bipolar disorder	1,265	11.9
Psychosis	2,817	26.6
Personality disorder	4,884	46.1
Mental retardation	3,201	30.2
<b>Baseline non-psychiatric comorbidities<sup>f</sup></b>		
Mean $\pm$ SD	0.4 $\pm$ 0.7	
0	7,683	72.5
1	2,242	21.2

**Table 4.1: Baseline Characteristics of Study Sample (N=10,599) (Continued)**

Characteristics	All	
	n=10,599	
	N	%
<b>Clinical Characteristics</b>		
<b>Baseline non-psychiatric comorbidities<sup>f</sup></b>		
>1	634	6.0
<b>Follow-up non-psychiatric comorbidities (First year)</b>		
Mean ± SD	0.6 ± 0.8	
0	6,437	60.7
1	2,836	26.8
>1	1,326	12.5
<b>Type of non-psychiatric comorbidities (First year)<sup>e</sup></b>		
Fracture	809	7.6
Dislocation	193	1.8
Sprain	1,067	10.1
Open wounds	1,007	9.5
Burns	39	0.4
Alzheimer's disease	364	3.4
Brain tumor	156	1.5
Head injury	205	1.9
Meningitis	51	0.5
Migraine	763	7.2
Stroke	1,163	11.0
Multiple sclerosis	83	0.8
<b>Follow-up non-psychiatric comorbidities (Second year)</b>		
Mean ± SD	0.6 ± 0.9	
0	5,988	56.5
1	3,000	28.3
>1	1,611	15.2
<b>Type of non-psychiatric comorbidities (Second year)<sup>e</sup></b>		
Fracture	725	6.8
Dislocation	169	1.6
Sprain	981	9.3
Open wounds	966	9.1
Burns	57	0.5
Alzheimer's disease	523	4.9
Brain tumor	216	2.0

**Table 4.1: Baseline Characteristics of Study Sample (N=10,599) (Continued)**

Characteristics	All	
	n=10,599	
	N	%
<b>Type of non-psychiatric comorbidities (Second year)<sup>e</sup></b>		
Head injury	325	3.1
Meningitis	97	0.9
Migraine	1,077	10.2
Stroke	1,573	14.8
Multiple sclerosis	122	1.2
<b>Baseline Charlson Comorbidity Index</b>		
Mean ± SD	0.8 ± 1.4	
0	6,784	64.0
1	1,979	18.7
>1	1,836	17.3
<b>Baseline pill burden</b>		
Mean ± SD	7.8 ± 6.5	
0	628	5.9
1	497	4.7
2-4	2,555	24.1
5-7	2,594	24.5
8-10	1,792	16.9
≥11	2,533	23.9
<b>Healthcare Utilization and Costs</b>		
<b>Baseline prescription cost</b>		
Mean ± SD, \$	3,286 ± 4,503	
<b>Baseline all-cause inpatient visit</b>		
Mean ± SD	0.3 ± 0.7	
0	8,574	80.9
1	1,443	13.6
>1	582	5.5
<b>Baseline all-cause inpatient cost</b>		
Mean ± SD, \$	2,006 ± 9,020	
<b>Baseline all-cause outpatient visit</b>		
Mean ± SD	14.2 ± 14.9	
0	132	1.2
1	432	4.1
2-5	2,326	22.0

**Table 4.1: Baseline Characteristics of Study Sample (N=10,599) (Continued)**

Characteristics	All	
	n=10,599	
	N	%
<b>Healthcare Utilization and Costs</b>		
<b>Baseline all-cause outpatient visit</b>		
6-9	2,176	20.5
10-13	1,658	15.6
14-17	1,140	10.8
≥18	2,735	25.8
<b>Baseline all-cause outpatient cost</b>		
Mean ± SD, \$	3,984 ± 8,445	
<b>Baseline all-cause total healthcare cost</b>		
Mean ± SD, \$	9,276 ± 15,000	

<sup>¶</sup>Date of first AED use; <sup>§</sup>12 months of index date

<sup>a</sup>Other race was comprised of patients belonging to American Indian and Asian race

<sup>b</sup>Totals may not add up to 100.0% as patients on diazepam (1.6%) only in identification period are not included

<sup>c</sup>Patients with more than one type of epilepsy seizures at first visit

<sup>d</sup>Patients with more than one AED of a different type on index date

<sup>e</sup>Totals may not add up to 100.0% as patients may have had more than one comorbidity

<sup>f</sup>Totals do not add up to 100.0% due to rounding error

### **4.3 Descriptive Statistics of Patient cohorts (Unmatched)**

Of the entire study sample comprising of 10,599 patients, 26.5% of the patients had three or more AEDs in the identification period and were identified as refractory, while the remaining 73.5% of the patients, with one or two AEDs in the identification period, were identified as non-refractory. Patient characteristics consisting of demographics, clinical characteristics, and baseline healthcare utilization and costs stratified by refractory and non-refractory status, before matching, are presented in Table 4.2. Overall, there were statistically significant differences ( $p < 0.05$ ) in all the characteristics, except for baseline CCI and multiple types of epilepsy, among the refractory and non-refractory cohorts.

#### **4.3.1 Demographic Characteristics**

Table 4.2 shows that the mean ( $\pm$  SD) age of the patients in the refractory group (38.0 [ $\pm$  12.7]) was significantly lower ( $p = 0.0015$ ) than the mean ( $\pm$  SD) age of the patients in the non-refractory group (38.9 [ $\pm$  13.4]). A significantly lower ( $p < 0.0001$ ) proportion of patients in the refractory group (44.6%) compared to patients in the non-refractory group (49.8%) were male. Regarding race/ethnicity, a significantly higher proportion of patients in the refractory group were Caucasian (42.8% vs. 39.3%;  $p = 0.011$ ) and Hispanic (34.4% vs. 30.7%;  $p = 0.0003$ ) compared to patients in the non-refractory group. In contrast, a significantly lower proportion of patients in the refractory group were African American (15.9% vs. 21.9%;  $p < 0.0001$ ) and other/unknown race/ethnicity (6.9% vs. 8.1%;  $p < 0.0001$ ) compared to patients in the non-refractory group.

### 4.3.2 Clinical Characteristics

A significantly higher proportion of patients in the refractory group had epilepsy of the generalized (10.7% vs. 9.0%;  $p=0.0082$ ) and partial type (8.6% vs. 6.5%;  $p=0.0003$ ) compared to patients in the non-refractory group. In contrast, a significantly lower proportion of patients in the refractory group had other convulsions (77.0% vs. 80.7%;  $p=0.0003$ ) compared to patients in the non-refractory group. Regarding index AED type, a significantly higher proportion of the patients were on GABA analogues (12.1% vs. 10.5%;  $p=0.0153$ ), calcium channel actions (7.7% vs. 3.5%;  $p<0.0001$ ), and on combination AEDs (26.5% vs. 10.1%;  $p<0.0001$ ) compared to patients in the non-refractory group. In contrast, a significantly lower proportion of patients in the refractory group were on sodium channel blockers (27.6% vs. 45.2%;  $p<0.0001$ ), AEDs with multiple actions (18.3% vs. 20.6%;  $p=0.0104$ ), and on synaptic vesicle protein 2A binding agents (7.8% vs. 10.1%;  $p=0.0004$ ) compared to patients in the non-refractory group. In the case of comorbidity burden, there was no significant difference in the CCI measured in the baseline period between patients in the refractory and non-refractory groups. Patients in the refractory group (1.6 [ $\pm$  1.4]) had significantly ( $p<0.0001$ ) higher mean ( $\pm$  SD) number of psychiatric comorbidities in the first year follow-up period compared to patients in the non-refractory group (1.4 [ $\pm$  1.3]). Also, a significantly higher ( $p<0.0001$ ) proportion of patients in the refractory group (47.1%) had at least one non-psychiatric comorbidity compared to patients in the non-refractory group (36.4%). Similarly, patients in the refractory group (2.1 [ $\pm$  1.5]) had significantly ( $p<0.0001$ ) higher mean ( $\pm$  SD) number of psychiatric comorbidities in the second year follow-up period compared to patients in the non-refractory group (1.6 [ $\pm$  1.4]). Also, a significantly higher ( $p<0.0001$ ) proportion of patients in the refractory group (51.2%) had at least one non-psychiatric comorbidity compared to patients in the non-refractory group (40.7%). The median pill burden of the patients

in the refractory group (8 pills) was significantly higher ( $p<0.0001$ ) than the median pill burden of the patients in the non-refractory group (6 pills).

### **4.3.3 Healthcare Utilization and Costs**

In the baseline period, a significantly higher ( $p<0.0001$ ) proportion of patients in the refractory group (21.6%) had at least one all-cause inpatient visit compared to patients in the non-refractory group (18.2%). Patients in the refractory group (12 visits) had significantly higher ( $p=0.0330$ ) median all-cause outpatient visits compared to patients in the non-refractory group (10 visits). Also, patients in the refractory group (\$7,808) had significantly higher ( $p<0.0001$ ) median all-cause total healthcare cost compared to patients in the non-refractory group (\$4,651).

**Table 4.2: Comparison of Patient Characteristics by Refractory/Non-Refractory Status (Unmatched) (N=10,599)**

Characteristics	All		Refractory		Non-refractory		p-value
	n=10,599		n=2,809		n=7,790		
	N	%	N	%	N	%	
<b>Demographics</b>							
<b>Age at index date<sup>a</sup></b>							
Mean ± SD, year	38.7 ± 13.2		38.0 ± 12.7		38.9 ± 13.4		<b>0.0015</b>
<b>Gender<sup>b</sup></b>							
Male	5,131	48.4	1,252	44.6	3,879	49.8	<b>&lt;0.0001</b>
Female	5,468	51.6	1,557	55.4	3,911	50.2	
<b>Race/Ethnicity<sup>b</sup></b>							
Caucasian	4,262	40.2	1,202	42.8	3,060	39.3	<b>0.0011</b>
African American	2,152	20.3	446	15.9	1,706	21.9	<b>&lt;0.0001</b>
Hispanic	3,357	31.7	966	34.4	2,391	30.7	<b>0.0003</b>
Other/Unknown	828	7.8	195	6.9	633	8.1	<b>&lt;0.0001</b>
<b>Clinical Characteristics</b>							
<b>Type of epilepsy at first visit<sup>b</sup></b>							
Generalized	1,003	9.5	301	10.7	702	9.0	<b>0.0082</b>
Partial	750	7.1	241	8.6	509	6.5	<b>0.0003</b>
Other convulsions	8,453	79.8	2,164	77.0	6,289	80.7	<b>&lt;0.0001</b>
Multiple types	393	3.7	103	3.7	290	3.7	0.8930
<b>Type of index Antiepileptic drug<sup>b</sup></b>							
Sodium channel blockers	4,297	40.5	774	27.6	3,523	45.2	<b>&lt;0.0001</b>
GABA analogues	1,157	10.9	341	12.1	816	10.5	<b>0.0153</b>
Calcium channel actions	492	4.6	217	7.7	275	3.5	<b>&lt;0.0001</b>
Multiple actions	2,115	20.0	514	18.3	1,601	20.6	<b>0.0104</b>
Synaptic vesicle protein 2A binding	1,004	9.5	219	7.8	785	10.1	<b>0.0004</b>
Combination	1534	14.5	744	26.5	790	10.1	<b>&lt;0.0001</b>
<b>Baseline Charlson Comorbidity Index<sup>a,b</sup></b>							
Mean ± SD	0.8 ± 1.4		0.8 ± 1.4		0.7 ± 1.4		0.5050
0	6,784	64.0	1,775	63.2	5,009	64.3	0.2931
1	1,979	18.7	534	19.0	1,445	18.5	0.5910
>1	1,836	17.3	500	17.8	1,336	17.2	0.4353
<b>Number of psychiatric comorbidities (First year)<sup>a,d</sup></b>							
Mean ± SD	1.4 ± 1.3		1.6 ± 1.4		1.4 ± 1.3		<b>&lt;0.0001</b>

**Table 4.2: Comparison of Patient Characteristics by Refractory/Non-Refractory Status (Unmatched) (N=10,599) (Continued)**

Characteristics	All		Refractory		Non-refractory		p-value
	n=10,599		n=2,809		n=7,790		
	N	%	N	%	N	%	
<b>Clinical Characteristics</b>							
<b>Non-psychiatric comorbidities (First year)<sup>b,d</sup></b>							
Yes	4,162	39.3	1,324	47.1	2,838	36.4	<b>&lt;0.0001</b>
No	6,437	60.7	1,485	52.9	4,952	63.6	
<b>Number of psychiatric comorbidities (Second year)<sup>a,d</sup></b>							
Mean ± SD	1.8 ± 1.4		2.1 ± 1.5		1.6 ± 1.4		<b>&lt;0.0001</b>
<b>Non-psychiatric comorbidities (Second year)<sup>b,d</sup></b>							
Yes	4,611	43.5	1,437	51.2	3,174	40.7	<b>&lt;0.0001</b>
No	5,988	56.5	1,372	48.8	4,616	59.3	
<b>Baseline pill burden<sup>c</sup></b>							
Median (Mean ± SD)	6 (7.8 ± 6.5)		8 (9.6 ± 7.5)		6 (7.2 ± 6.0)		<b>&lt;0.0001</b>
<b>Baseline Healthcare Utilization and Cost</b>							
<b>Baseline all-cause inpatient visit<sup>b</sup></b>							
Yes	2,025	19.1	607	21.6	1418	18.2	<b>&lt;0.0001</b>
No	8,574	80.9	2202	78.4	6372	81.8	
<b>Baseline all-cause outpatient visit<sup>c</sup></b>							
Median (Mean ± SD)	10 (14.2 ± 14.9)		12 (15.8 ± 15.3)		10 (13.7 ± 14.7)		<b>0.0330</b>
<b>Baseline all-cause total healthcare cost<sup>c</sup></b>							
Median, \$ (Mean ± SD), \$	5,485 (9,276 ± 15,000)		7,808 (11,778 ± 17,101)		4,651 (8,373 ± 14,058)		<b>&lt;0.0001</b>

<sup>a</sup>T-test

<sup>b</sup>Chi-square test

<sup>c</sup>Wilcoxon test

<sup>d</sup>Measured in the follow-up period

Significant at p<0.05 (in bold)

## **4.4 Characteristics of Patient cohorts (Matched)**

### **4.4.1 Use of Propensity Score Matching**

For the present study, as refractory and non-refractory groups differed on the baseline characteristics (Table 4.2), 1:1 propensity score matching was performed to minimize the sample selection bias that may occur due to residual differences between the groups. Propensity scores were estimated using a logistic regression with a nearest neighbor matching approach using a caliper set at 0.05. A classification of refractory epilepsy (1=Yes, 0=No) was specified as the binary dependent variable in the model. Groups were matched on baseline covariates consisting of age, gender, race/ethnicity, type of epilepsy, comorbidity burden measured using CCI, pill burden, and all-cause total cost.

To check if group balance was achieved among the matched groups, statistical comparisons of baseline characteristics between the matched pairs were conducted using McNemar's tests for categorical variables and two-sided paired Student's t-tests for continuous variables. In the case of baseline healthcare utilization and cost, due to the skewed nature of the data, unadjusted comparisons between the matched cohorts were conducted using the Wilcoxon signed-rank test.

Table 4.3 presents the patient characteristics consisting of demographics, clinical characteristics, healthcare utilization and costs stratified by refractory and non-refractory status, after matching. Overall, the propensity score matching balanced the covariates of age, gender, Caucasian and other/unknown race/ethnicity, partial, other and multiple types of epilepsy, baseline CCI, and baseline pill burden across the two groups. However, there were significant differences in African American and Hispanic race/ethnicity, generalized type of epilepsy, and baseline all-cause total healthcare cost across the two groups for the variables used in the propensity score

matching process. For the other covariates included in the study, there were significant differences in type of index antiepileptic drug, and number of psychiatric comorbidities and presence of one or more non-psychiatric comorbidities at first and second year of follow-up. Nearly 47.2% of the study sample was lost during the propensity score matching process. The matched study sample was comprised of 5,596 patients: 2,798 patients in the refractory group and 2,798 patients in the non-refractory group.

#### **4.4.2 Objective 1: Demographic and Clinical Characteristics**

1. To compare the demographic and clinical characteristics of patients with refractory and non-refractory epilepsy.

##### **Age**

**H<sub>01A</sub>:** There is no significant difference in the mean age of patients between the refractory and non-refractory groups.

The mean ( $\pm$  SD) age of patients in the refractory group was 38.0 ( $\pm$  12.7) years and in the non-refractory group was 37.9 ( $\pm$  13.6) years. Paired T-test test showed that the mean age of patients did not differ significantly among the groups.

**H<sub>01A</sub>: Failed to reject**

##### **Gender**

**H<sub>01B</sub>:** The proportion of gender categories does not differ between the refractory and non-refractory groups.

For patients in the refractory group, the proportion of males was 44.7% and females was 55.3%, while for patients in the non-refractory group; the proportion of males was 43.4% and 56.6%. McNemar's test revealed that the gender categories did not differ significantly among the groups.

**H<sub>01B</sub>: Failed to reject**

## **Race/Ethnicity**

**H<sub>01C</sub>:** The proportion of race/ethnicity categories does not differ between the refractory and non-refractory groups.

For patients in the refractory group, the proportion of Caucasians was 42.9%, African Americans was 15.9%, Hispanics was 34.3%, and other/unknown race was 6.9%, while for patients in the non-refractory group; the proportion of Caucasians was 40.9%, African Americans was 20.9%, Hispanics was 30.5%, and other/unknown race was 7.8%. McNemar's test revealed that the proportion of African Americans ( $p < 0.0001$ ) and Hispanics ( $p = 0.0020$ ) differed significantly ( $p < 0.0001$ ) among the groups. However, the proportion of Caucasians and other/unknown race did not differ significantly among the groups.

**H<sub>01C</sub>: Rejected**

## **Type of epilepsy**

**H<sub>01D</sub>:** The proportion of epilepsy type categories does not differ between the refractory and non-refractory groups.

For patients in the refractory group, the proportion of patients with generalized epilepsy was 10.7%, partial epilepsy was 8.6%, other convulsions was 77.1%, and multiple epilepsy types was 3.6%, while for patients in the non-refractory group; the proportion of patients generalized epilepsy was 12.5%, partial epilepsy was 7.2%, other convulsions was 77.3%, and multiple epilepsy types was 3.0%. McNemar's test revealed that the proportion of patients with generalized

epilepsy differed significantly ( $p=0.0288$ ) among the groups. However, the proportion of patients with partial, other and multiple types of epilepsy did not differ significantly among the groups.

**H<sub>01D</sub>: Rejected**

### **Comorbidity burden**

**H<sub>01E</sub>:** There is no significant difference in the comorbidity burden of patients between the refractory and non-refractory groups.

The mean ( $\pm$  SD) comorbidity burden of patients in the refractory group and non-refractory group was 0.8 ( $\pm$  1.4). Paired T-test test showed that the mean comorbidity burden of patients did not differ significantly among the groups.

**H<sub>01E</sub>: Failed to reject**

### **Type of index AED**

**H<sub>01F</sub>:** The proportion of the AED type categories does not differ between the refractory and non-refractory groups.

For patients in the refractory group, the proportion of patients on sodium channel blockers was 27.6%, on GABA analogues was 12.0%, on calcium channel action agents was 7.7%, on multiple action agents was 18.3%, on synaptic vesicle protein 2A binding agents was 7.8%, and on AED combinations was 26.5%, while for patients in the non-refractory group; the proportion of patients on sodium channel blockers was 43.2%, on GABA analogues was 10.2%, on calcium channel action agents was 3.4%, on multiple action agents was 22.7%, on synaptic vesicle protein

2A binding agents was 9.8%, and on AED combinations was 26.5%. McNemar's test revealed that the proportion of patients on sodium channel blockers ( $p < 0.0001$ ), GABA analogues ( $p = 0.0325$ ), calcium channel action agents ( $p < 0.0001$ ), multiple action agents ( $p < 0.0001$ ), synaptic vesicle protein 2A binding agents ( $p = 0.0082$ ), and AED combinations ( $p < 0.0001$ ) differed significantly among the groups.

**H<sub>01F</sub>: Rejected**

### **Pill burden**

**H<sub>01G</sub>:** There is no significant difference in the pill burden of patients between the refractory and non-refractory groups.

The median pill burden of patients in the refractory group and non-refractory group was 8 pills. Wilcoxon signed-rank test showed that the median pill burden of patients did not differ significantly among the groups.

**H<sub>01G</sub>: Failed to reject**

Although not part of the study objectives, there were significant differences in the number of psychiatric comorbidities and the presence of one or more non-psychiatric comorbidities at first and second year of follow-up, and baseline all-cause total healthcare cost across the two groups. Paired t-test showed that patients in the refractory group (1.6 [ $\pm$  1.4]; 1.3 [ $\pm$  1.3]) had significantly higher mean ( $\pm$  SD) number of psychiatric comorbidities compared to patients in the non-refractory group (2.1 [ $\pm$  1.5]; 1.8 [ $\pm$  1.4]) at first ( $p < 0.0001$ ) and second ( $p < 0.0001$ ) year of follow-up, respectively. Also, McNemar's test revealed that a significantly higher proportion of patients

in the refractory group (47.2%; 51.2%) had one or more non-psychiatric comorbidities compared to patients in the non-refractory group (38.0%; 41.4%) at first ( $p < 0.0001$ ) and second ( $p < 0.0001$ ) year of follow-up, respectively. Regarding baseline all-cause total healthcare cost, Wilcoxon signed-rank test showed that patients in the refractory group (\$7,778) had significantly higher ( $p < 0.0001$ ) median all-cause total healthcare cost compared to patients in the non-refractory group (\$6,216). In addition, McNemar's test revealed that the proportion of patients with at least one baseline all-cause inpatient visit did not differ significantly among the groups. Also, Wilcoxon signed-rank test showed that the median baseline all-cause outpatient visits of patients did not differ significantly among the groups.

**Table 4.3: Comparison of Patient Characteristics by Refractory/Non-Refractory Status (Matched) (N=10,599)**

Characteristics	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
<b>Demographics</b>							
<b>Age at index date<sup>a,e</sup></b>							
Mean ± SD, year	38.0 ± 13.1		38.0 ± 12.7		37.9 ± 13.6		0.7184
<b>Gender<sup>b,e</sup></b>							
Male	2,464	44.0	1,251	44.7	1,213	43.4	0.3055
Female	3,132	56.0	1,547	55.3	1,585	56.6	
<b>Race/Ethnicity<sup>b,e</sup></b>							
Caucasian	2,343	41.9	1,199	42.9	1,144	40.9	0.1391
African American	1,030	18.4	446	15.9	584	20.9	<0.0001
Hispanic	1,813	32.4	960	34.3	853	30.5	0.0020
Other/Unknown	410	7.3	193	6.9	217	7.8	0.2183
<b>Clinical Characteristics</b>							
<b>Type of epilepsy at first visit<sup>b,e</sup></b>							
Generalized	650	11.6	299	10.7	351	12.5	0.0288
Partial	442	7.9	241	8.6	201	7.2	0.0504
Other convulsions	4,319	77.2	2,156	77.1	2,163	77.3	0.8237
Multiple types	185	3.3	102	3.6	83	3.0	0.1486
<b>Type of index Antiepileptic drug<sup>b</sup></b>							
Sodium channel blockers	1,983	35.4	773	27.6	1,210	43.2	<0.0001
GABA analogues	623	11.1	337	12.0	286	10.2	0.0325
Calcium channel actions	310	5.5	216	7.7	94	3.4	<0.0001
Multiple actions	1,149	20.5	513	18.3	636	22.7	<0.0001
Synaptic vesicle protein 2A binding	490	8.8	217	7.8	273	9.8	0.0082
Combination	1,041	18.6	742	26.5	299	10.7	<0.0001
<b>Baseline Charlson Comorbidity Index<sup>a,b</sup></b>							
Mean ± SD <sup>e</sup>	0.8 ± 1.4		0.8 ± 1.4		0.8 ± 1.4		0.8124
0	3,515	62.8	1,773	63.4	1,742	62.3	0.3698
1	1,085	19.4	531	19.0	554	19.8	0.4288
>1	996	17.8	494	17.7	502	17.9	0.7220
<b>Number of psychiatric comorbidities (First year)<sup>a,d</sup></b>							
Mean ± SD	1.5 ± 1.3		1.6 ± 1.4		1.3 ± 1.3		<0.0001

**Table 4.3: Comparison of Patient Characteristics by Refractory/Non-refractory Status (Matched) (Continued) (N=10,599)**

Characteristics	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
<b>Clinical Characteristics</b>							
<b>Non-psychiatric comorbidities (First year)<sup>b,d</sup></b>							
Yes	2,382	42.6	1,320	47.2	1,062	38.0	<b>&lt;0.0001</b>
No	3,214	57.4	1,478	52.8	1,736	62.0	
<b>Number of psychiatric comorbidities (Second year)<sup>a,d</sup></b>							
Mean ± SD	1.9 ± 1.4		2.1 ± 1.5		1.8 ± 1.4		<b>&lt;0.0001</b>
<b>Non-psychiatric comorbidities (Second year)<sup>b,d</sup></b>							
Yes	2,592	46.3	1,434	51.3	1,158	41.4	<b>&lt;0.0001</b>
No	3,004	53.7	1,364	48.7	1,640	58.6	
<b>Baseline pill burden<sup>c,e</sup></b>							
Median (Mean ± SD)	8 (9.5 ± 7.3)		8 (9.5 ± 7.3)		8 (9.4 ± 7.3)		0.8133
<b>Baseline Healthcare Utilization and Cost</b>							
<b>Baseline all-cause inpatient visit<sup>b</sup></b>							
Yes	1,202	21.5	600	21.4	602	21.5	0.9469
No	4,394	78.5	2,198	78.6	2,196	78.5	
<b>Baseline all-cause outpatient visit<sup>c</sup></b>							
Median (Mean ± SD)	12 (16.1 ± 15.9)		11.5 (15.7 ± 15.1)		12 (16.5 ± 16.7)		0.2534
<b>Baseline all-cause total healthcare cost<sup>c,e,f</sup></b>							
Median (Mean ± SD)	7,064 (11,308 ± 17,509)		7,778 (11,308 ± 17,509)		6,216 (11,164 ± 19,442)		<b>&lt;0.0001</b>

<sup>a</sup>Paired T-test

<sup>b</sup>McNemar's test

<sup>c</sup>Wilcoxon signed-rank test

<sup>d</sup>Measured in the follow-up period

<sup>e</sup>Used as predictors of selection in refractory or non-refractory group with caliper set at 0.05(matching)

<sup>f</sup>Adjusted to 2013 US dollars

Significant at p<0.05 (in bold)

#### 4.4.3 Objective 2: Treatment Patterns

To compare the treatment patterns of patients with refractory and non-refractory epilepsy while controlling for age, gender, race/ethnicity, type of epilepsy, type of index AED, baseline CCI, number of psychiatric and presence of non-psychiatric comorbidities at follow-up, baseline pill burden, presence of baseline all-cause inpatient visits, baseline number of all-cause outpatient visits, and baseline all-cause total cost.

##### 4.4.3.1 Medication Adherence

**H<sub>2A</sub>:** Patients with refractory epilepsy are less likely to be adherent to AEDs as compared to patients with non-refractory epilepsy, while controlling for covariates.

Medication adherence was assessed in the first and second year follow-up period after the index date. Adherence to AEDs was measured using the proportion of days covered (PDC) method.

For the purpose of this study, the following formula was used for calculating PDC:

$$\text{PDC} = \frac{\text{Number of days with a prescription for at least one AED}}{\text{Number of days in follow-up period (365 days)}}$$

Medication adherence was measured using both descriptive statistics and regression models. Patients with a PDC value of greater than or equal to 80% were considered adherent and a PDC value of less than 80% were considered non-adherent. A sensitivity analysis on 70% and 90% cut-off was conducted. Paired T-test was used to assess differences in adherence as a continuous measure. McNemar's test was used to assess differences in the proportions of patients

who were adherent (categorical). Conditional logistic regression was used to compare and determine differences in medication adherence patterns of patients with refractory and non-refractory epilepsy while controlling for age, gender, race/ethnicity, type of epilepsy, type of index AED, baseline CCI, number of psychiatric and presence of non-psychiatric comorbidities at follow-up, baseline pill burden, presence of baseline all-cause inpatient visits, baseline number of all-cause outpatient visits, and baseline all-cause total cost.

#### 4.4.3.1.1 Medication Adherence (Unadjusted Analyses using Paired T-Test and McNemar's test)

Table 4.4 presents medication adherence patterns stratified by refractory and non-refractory status. Mean ( $\pm$  SD) adherence of patients in the second year of follow-up was 82.8% ( $\pm$  23.4%). The mean ( $\pm$  SD) adherence of the patients in the refractory group (88.6 [ $\pm$  19.1]) was significantly higher ( $p < 0.0001$ ) than the mean ( $\pm$  SD) adherence of the patients in the non-refractory group (77.0% [ $\pm$  25.8%]). A significantly higher ( $p < 0.0001$ ) proportion of patients in the refractory group (85.7%) compared to patients in the non-refractory group (62.8%) were adherent ( $PDC \geq 80\%$ ) in the second year of follow-up. Although overall medication adherence was higher, a similar trend was observed in the first year of follow-up (Appendix II).

**Table 4.4: Comparison of Medication Adherence in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)**

Medication Adherence	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
<b>PDC</b>							
Mean $\pm$ SD, %	82.8 $\pm$ 23.4		88.6 $\pm$ 19.1		77.0 $\pm$ 25.8		<b>&lt;0.0001<sup>a</sup></b>
Adherent ( $PDC \geq 80\%$ )	4,156	74.3	2,399	85.7	1,757	62.8	<b>&lt;0.0001<sup>b</sup></b>
Non-Adherent ( $PDC < 80\%$ )	1,440	25.7	399	14.3	1,041	37.2	

PDC=Proportion of days covered

<sup>a</sup>Paired T-test

<sup>b</sup>McNemar's test

Significant at  $p < 0.05$  (in bold)

#### 4.4.3.1.2 Medication Adherence (Adjusted Analysis using Conditional Logistic Regression)

Table 4.5 presents the results of the conditional logistic regression model comparing the likelihood of being adherent in the second-year of follow-up by refractory and non-refractory groups while controlling for covariates. The results of the overall model fit testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected ( $p < 0.05$ ). Results showed that compared to patients in the non-refractory group, patients in the refractory group were 3.6 times (OR=3.553; 95% CI=3.060-4.125;  $p < 0.0001$ ) more likely to adhere to AEDs, after controlling for covariates. Regarding covariates, African Americans had 28.5% (OR=0.715; 95% CI=0.547-0.935;  $p = 0.0142$ ) lower likelihood than Caucasians to adhere to AEDs, after controlling for covariates. Patients with a CCI score of 1 had 28.2% (OR=0.718; 95% CI=0.528-0.977;  $p = 0.0348$ ) lower likelihood than patients with a CCI score of 0 to adhere to AEDs, after controlling for covariates. Patients with one or more inpatient visits in the baseline period had 24.2% (OR=0.758; 95% CI=0.575-0.998;  $p = 0.0486$ ) lower likelihood than patients with no inpatient visits in the baseline period to adhere to AEDs, after controlling for covariates. Results were robust in the sensitivity analyses conducted using 70% and 90% cut-off for adherence (Appendix II). Similarly, results of the conditional logistic regression model comparing the likelihood of being adherent in the first year of follow-up by refractory and non-refractory groups showed that compared to patients in the non-refractory group, patients in the refractory group had significantly higher ( $p < 0.05$ ) likelihood of adhering to AEDs, after controlling for covariates (Appendix II).

**Table 4.5: Conditional Logistic Regression Analysis Comparing the Likelihood of being Adherent in the Second Year of Follow-Up among Refractory/Non-Refractory Patients (N=5,596)**

	<b>Odds Ratio</b>	<b>95% CI</b>	<b>Wald X<sup>2</sup></b>	<b>p-value</b>
Refractory <sup>a</sup>	3.553	3.06-4.125	277.01	<b>&lt;0.0001</b>
Age at index	0.998	0.982-1.015	0.05	0.8277
Male <sup>a</sup>	1.347	0.965-1.88	3.06	0.0804
African American race <sup>a</sup>	0.715	0.547-0.935	6.02	<b>0.0142</b>
Other race <sup>a</sup>	0.865	0.684-1.095	1.46	0.2282
Partial type of epilepsy at first visit <sup>a</sup>	1.382	0.805-2.373	1.38	0.2404
Other type of epilepsy at first visit <sup>a</sup>	0.973	0.554-1.71	0.01	0.9244
Multiple actions of index AED <sup>a</sup>	1.235	0.996-1.532	3.69	0.0548
Baseline CCI of 1 <sup>a</sup>	0.718	0.528-0.977	4.46	<b>0.0348</b>
Baseline CCI greater than 1 <sup>a</sup>	0.699	0.424-1.15	1.99	0.1584
Number of psychiatric comorbidities at follow-up	0.940	0.872-1.014	2.57	0.1095
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.940	0.756-1.169	0.31	0.5792
Baseline pill burden	1.024	0.929-1.128	0.23	0.6321
Baseline all-cause inpatient visits <sup>a</sup>	0.758	0.575-0.998	3.89	<b>0.0486</b>
Number of baseline all-cause outpatient visits	1.000	0.992-1.009	0.01	0.9562
Baseline total all-cause healthcare cost	1.000	1.000-1.000	0.21	0.6511

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Model Fit: likelihood ratio=424.1450; df=16; p<0.0001

Significant at p<0.05 (in bold)

**H<sub>2A</sub>:** Patients with refractory epilepsy are less likely to be adherent to AEDs as compared to patients with non-refractory epilepsy, while controlling for covariates.

**Rejected**

#### 4.4.3.2 Medication Persistence

**H<sub>2B</sub>:** Patients with refractory epilepsy are less likely to be persistent (i.e., duration of medication use) to AEDs as compared to patients with non-refractory epilepsy, while controlling for covariates.

Medication persistence (duration of medication use prior to discontinuation) was assessed in the first and second year follow-up period after the index date. Medication persistence was defined as the number of days of continuous AED therapy without a gap of more than 60 days in the follow-up period of 365 days. A pre-specified gap of 60 days allowed for delays in the refill of a prescription. Since there was no standard gap for the calculation of persistence in epilepsy, a sensitivity analysis on 30 and 90 days was conducted.

Medication persistence was measured using both descriptive statistics and regression models. A paired T-test was used to assess differences in persistence as a continuous measure. Cox proportional hazards regression was used to compare and determine differences in the duration of medication use prior to discontinuation (persistence) of patients with refractory and non-refractory epilepsy while controlling for age, gender, race/ethnicity, type of epilepsy, type of index AED, baseline CCI, number of psychiatric and presence of non-psychiatric comorbidities at follow-up, baseline pill burden, presence of baseline all-cause inpatient visits, baseline number of all-cause outpatient visits, and baseline all-cause total cost.

#### 4.4.3.2.1 Medication Persistence (Unadjusted Analysis using Paired T-Test)

Table 4.6 presents medication persistence patterns stratified by refractory and non-refractory status. Mean ( $\pm$  SD) persistence of patients in the second year of follow-up was 311.5 ( $\pm$  102.5). The mean ( $\pm$  SD) persistence of the patients in the refractory group (328.0 [ $\pm$  87.3]) was significantly higher ( $p < 0.0001$ ) than the mean ( $\pm$  SD) persistence of the patients in the non-refractory group (294.9 [ $\pm$  113.4]). Although overall medication persistence was higher, a similar trend was observed in the first year of follow-up (Appendix III).

**Table 4.6: Comparison of Medication Persistence in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)**

Medication Persistence	All	Refractory	Non-refractory	p-value
	n=5,596	n=2,798	n=2,798	
<b>Persistence (60 day gap)</b>				
Mean $\pm$ SD	311.5 $\pm$ 102.5	328.0 $\pm$ 87.3	294.9 $\pm$ 113.4	<b>&lt;0.0001<sup>a</sup></b>

<sup>a</sup>Paired T-test

Significant at  $p < 0.05$  (in bold)

#### **4.4.3.2.2 Medication Persistence (Adjusted Analysis using Cox Proportional Hazard Regression)**

Table 4.7 presents the results of the Cox proportional hazard regression model comparing the discontinuation (persistence) in the second-year of follow-up by refractory and non-refractory groups while controlling for covariates. The results of the overall model fit testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected ( $p < 0.05$ ). Results showed that compared to patients in the non-refractory group, patients in the refractory group had 34.7% (HR=0.653; 95% CI=0.608-0.702;  $p < 0.0001$ ) lower hazard rate, after controlling for covariates. Regarding covariates, males had 31.7% (HR=0.805; 95% CI=0.687-0.944;  $p = 0.0076$ ) lower hazard rate than females, after controlling for covariates. Patients with a CCI of 1 in the baseline period had 16.9% (HR=1.169; 95% CI=1.008-1.356;  $p = 0.0394$ ) higher hazard rate than patients with CCI of 0 in the baseline period, after controlling for covariates. Patients with one or more inpatient visits in the baseline period had 17.0% (HR=1.170; 95% CI=1.022-1.338;  $p = 0.0227$ ) higher hazard rate than patients with no inpatient visit in the baseline period, after controlling for covariates. Results were robust in the sensitivity analyses conducted using 30 and 90-day gap period (Appendix III). Similarly, results of the cox proportional hazard regression model comparing the discontinuation (persistence) in the first year of follow-up by refractory and non-refractory groups showed that compared to patients in the non-refractory group, patients in the refractory group had significantly lower ( $p < 0.05$ ) hazard rate, after controlling for covariates (Appendix III).

**Table 4.7: Cox Proportional Hazard Regression Analysis Comparing the Likelihood of Discontinuation (Persistence 60 Day Gap) in the Second Year of Follow-Up among Refractory/Non-Refractory Patients (N=5,596)**

	<b>Hazards Ratio</b>	<b>95% CI</b>	<b>Wald X<sup>2</sup></b>	<b>p-value</b>
Refractory <sup>a</sup>	0.653	0.608 - 0.702	135.04	<b>&lt;0.0001</b>
Age at index	0.994	0.986 - 1.002	2.07	0.1500
Male <sup>a</sup>	0.805	0.687 - 0.944	7.13	<b>0.0076</b>
African American race <sup>a</sup>	1.077	0.938 - 1.237	1.12	0.2910
Other race <sup>a</sup>	0.985	0.881 - 1.101	0.07	0.7894
Partial type of epilepsy at first visit <sup>a</sup>	0.88	0.689 - 1.125	1.04	0.3080
Other type of epilepsy at first visit <sup>a</sup>	0.822	0.625 - 1.082	1.96	0.1618
Multiple actions of index AED <sup>a</sup>	0.941	0.849 - 1.042	1.36	0.2439
Baseline CCI of 1 <sup>a</sup>	1.169	1.008 - 1.356	4.24	<b>0.0394</b>
Baseline CCI greater than 1 <sup>a</sup>	1.021	0.799 - 1.305	0.03	0.8677
Number of psychiatric comorbidities at follow-up	1.027	0.991 - 1.065	2.14	0.1435
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.973	0.874 - 1.083	0.25	0.6188
Baseline pill burden	1.028	0.982 - 1.077	1.38	0.2399
Baseline all-cause inpatient visits <sup>a</sup>	1.170	1.022 - 1.338	5.19	<b>0.0227</b>
Number of baseline all-cause outpatient visits	0.999	0.995 - 1.003	0.18	0.6698
Baseline total all-cause healthcare cost	1.000	1.000 – 1.000	0.97	0.3243

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

*Model Fit: likelihood ratio=187.7891; df=16; p<0.0001*

Significant at p<0.05 (in bold)

**H<sub>2B</sub>:** Patients with refractory epilepsy are less likely to be persistent to AEDs as compared to patients with non-refractory epilepsy, while controlling for covariates.

**Rejected**

#### **4.4.3.3 Medication Addition and Switching (Sample Selection)**

Medication addition and switch patterns were assessed in the first year follow-up period after the index date. For the purpose of this analysis, only those patients on dual therapy (i.e., on two AEDs only in the identification period) of the 7,790 patients in the non-refractory group were included. This left a sample of 3,709 patients in the non-refractory group. This was necessary because it was not possible for patients on monotherapy (i.e., on one AED only in the identification period) to addition or switch to an alternative AED. These 3,709 patients were matched 1:1 with the 2,809 patients in the refractory group. Propensity scores were estimated using a logistic regression with a nearest neighbor matching approach using a caliper set at 0.05. A classification of refractory epilepsy (1=Yes, 0=No) was specified as the binary dependent variable in the model. Groups were matched on baseline covariates consisting of age, gender, race/ethnicity, type of epilepsy, comorbidity burden measured using CCI, pill burden, and all-cause total cost.

Overall, the propensity score matching balanced the covariates of age, gender, Caucasian, Hispanic and other race/ethnicity, type of epilepsy, GABA analogues, AEDs with multiple actions and synaptic vesicle 2A protein binding agents, baseline CCI, and baseline pill burden across the two groups (Appendix IV). 16.9% of the study sample was lost during the propensity score matching process. The matched study sample was comprised of 5,414 patients consisting of 2,707 patients in the refractory group and 2,707 patients in the non-refractory group.

#### **4.4.3.3.1 Medication Addition**

**H<sub>2c</sub>:** Patients with refractory epilepsy are more likely to add an alternative AED as compared to patients with non-refractory epilepsy.

Addition of an AED was defined as the addition of an alternative AED to the first or second AED with an overlap of at least 30 consecutive days. Medication addition was measured using both descriptive statistics and regression models. McNemar's test was used to assess differences in the proportions of patients who added an AED (categorical) by refractory/non-refractory status. Conditional logistic regression was used to compare and determine differences in the medication addition patterns of patients with refractory and non-refractory epilepsy while controlling for age, gender, race/ethnicity, type of epilepsy, type of index AED, baseline CCI, number of psychiatric and presence of non-psychiatric comorbidities at follow-up, baseline pill burden, presence of all-cause inpatient visits, baseline number of all-cause outpatient visits, and baseline all-cause total cost.

#### 4.4.3.3.1.1 Medication Addition (Unadjusted Analysis using McNemar’s test)

Table 4.8 presents medication addition patterns stratified by refractory and non-refractory status. A significantly higher ( $p < 0.0001$ ) proportion of patients in the refractory group (95.1%) compared to patients in the non-refractory group (85.2%) added an alternative AED in the first year of follow-up.

Table 4.9 presents the descriptive statistics of medication addition patterns of refractory and non-refractory patients stratified by the MOA of alternative AED. Of all the patients adding an AED, a higher proportion of patients added an alternative AED of a different MOA (76.4%) as compared to patients adding an alternative AED of a same MOA (23.6%). A significantly lower ( $p < 0.0001$ ) proportion of patients in the refractory group (67.1%) compared to patients in the non-refractory group (86.8%) added an alternative AED of a different MOA in the first year of follow-up.

**Table 4.8: Comparison of Medication Addition in the First Year of Follow-Up by Refractory/Non-Refractory Status (N=5,414)**

Medication Addition	All		Refractory		Non-refractory		p-value
	n=5,414		n=2,707		n=2,707		
	N	%	N	%	N	%	
Yes	4,880	90.1	2,573	95.1	2,307	85.2	<b>&lt;0.0001<sup>a</sup></b>
No	534	9.9	134	4.9	400	14.8	

<sup>a</sup>McNemar’s test

Significant at  $p < 0.05$  (in bold)

**Table 4.9: Comparison of Medication Addition in the First Year of Follow-Up Stratified by Mechanism of Action of Alternative AED and Refractory/Non-Refractory Status (N=5,414)**

Medication Addition	All		Refractory		Non-refractory		p-value
	n=5,414		n=2,707		n=2,707		
	N	%	N	%	N	%	
Same MOA <sup>a</sup>	1,151	23.6	846	32.9	305	13.2	<b>&lt;0.0001<sup>c</sup></b>
Different MOA <sup>b</sup>	3,729	76.4	1,727	67.1	2,002	86.8	
Total	4,880	100.0	2,573	100.0	2,307	100.0	

MOA=Mechanism of Action

<sup>a</sup>Adding an alternative AED of same MOA

<sup>b</sup>Adding an alternative AED of different MOA

<sup>c</sup>McNemar's test

Significant at p<0.05 (in bold)

#### **4.4.3.3.1.2 Medication Addition (Adjusted Analysis using Conditional Logistic Regression)**

Table 4.10 presents the results of the conditional logistic regression model comparing the likelihood of addition in the first-year of follow-up by refractory and non-refractory groups while controlling for covariates. The results of the overall model fit testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected ( $p < 0.05$ ). Results showed that compared to patients in the non-refractory group, patients in the refractory group were 3.7 times (OR=3.723; 95% CI=2.902-4.776;  $p < 0.0001$ ) more likely to add an alternative AED, after controlling for covariates. Regarding covariates, patients on AEDs with multiple actions were 2.2 times (OR=2.150; 95% CI=1.510-3.063;  $p < 0.0001$ ) more likely than patients on AEDs with single actions to add an alternative AED, after controlling for covariates. Patients with a CCI score greater than 1 had 45.4% (OR=0.546; 95% CI=0.303-0.981;  $p = 0.0431$ ) lower likelihood than patients with a CCI score of 0 to add an alternative AED, after controlling for covariates. With every unit increase in the number of psychiatric comorbidities, the likelihood of adding an alternative AED decreased by 20.2% (OR=0.798; 95% CI=0.698-0.912;  $p = 0.0010$ ), after controlling for covariates. Patients with one or more non-psychiatric comorbidities in the first-year follow-up period had 32.2% (OR=0.678; 95% CI=0.481-0.956;  $p = 0.0268$ ) lower likelihood than patients with no non-psychiatric comorbidity in the first-year follow-up period to add an alternative AED, after controlling for covariates.

**Table 4.10: Conditional Logistic Regression Analysis Comparing the Likelihood of Addition in the First Year of Follow-Up among Refractory/Non-Refractory Patients (N=5,414)**

	<b>Odds Ratio</b>	<b>95% CI</b>	<b>Wald X<sup>2</sup></b>	<b>p-value</b>
Refractory <sup>a</sup>	3.723	2.902-4.776	106.96	<b>&lt;0.0001</b>
Age at index	1.027	0.976-1.081	1.06	0.3028
Male <sup>a</sup>	1.541	0.956-2.483	3.15	0.0759
African American race <sup>a</sup>	0.957	0.61-1.502	0.04	0.8482
Other race <sup>a</sup>	0.944	0.651-1.368	0.09	0.7606
Partial type of epilepsy at first visit <sup>a</sup>	2.541	0.875-7.376	2.94	0.0865
Other type of epilepsy at first visit <sup>a</sup>	1.316	0.394-4.397	0.20	0.6553
Multiple actions of index AED <sup>a</sup>	2.150	1.510-3.063	18.00	<b>&lt;0.0001</b>
Baseline CCI of 1 <sup>a</sup>	0.643	0.412-1.003	3.78	0.0517
Baseline CCI greater than 1 <sup>a</sup>	0.546	0.303-0.981	4.09	<b>0.0431</b>
Number of psychiatric comorbidities at follow-up	0.798	0.698-0.912	10.89	<b>0.0010</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.678	0.481-0.956	4.909	<b>0.0268</b>
Baseline pill burden	0.961	0.755-1.225	0.109	0.7490
Baseline all-cause inpatient visits <sup>a</sup>	0.891	0.568-1.398	0.259	0.6157
Number of baseline all-cause outpatient visits	1.005	0.991-1.019	0.549	0.4624
Baseline total all-cause healthcare cost	1.000	1.000-1.000	0.47	0.4943

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Model Fit: likelihood ratio=225.4370; df=16; p<0.0001

Significant at p<0.05 (in bold)

**H<sub>2c</sub>**: Patients with refractory epilepsy are more likely to add an alternative AED as compared to patients with non-refractory epilepsy.

**Failed to reject**

#### 4.4.3.3.2 Medication Switch

**H<sub>2D</sub>:** Patients with refractory epilepsy are more likely to switch to an alternative AED as compared to patients with non-refractory epilepsy.

Switching was defined as the discontinuation of the first or second AED for at least 60 consecutive days and the start of an alternative AED within (before/after) 30 days of discontinuing the initial AED. Medication switch was measured using both descriptive statistics and regression models. McNemar's test was used to assess differences in the proportions of patients who switched to an alternative AED (categorical) by the refractory/non-refractory status. Conditional logistic regression was used to compare and determine differences in the medication switch of patients with refractory and non-refractory epilepsy while controlling for age, gender, race/ethnicity, type of epilepsy, type of index AED, baseline CCI, and number of psychiatric and presence of non-psychiatric comorbidities at follow-up, baseline pill burden, presence of baseline all-cause inpatient visits, baseline number of all-cause outpatient visits, and baseline all-cause total cost.

#### 4.4.3.3.2.1 Medication Switch (Unadjusted Analysis using McNemar’s test)

Table 4.11 presents medication switch patterns stratified by refractory and non-refractory status. A significantly higher ( $p < 0.0001$ ) proportion of patients in the refractory group (28.7%) compared to patients in the non-refractory group (10.6%) switched to an alternative AED in the first year of follow-up.

Table 4.12 presents the descriptive statistics of switch patterns of refractory and non-refractory patients stratified by the MOA of alternative AED. Of all the patients switching to an alternative AED, a higher proportion of patients switched to an alternative AED of a different MOA (79.1%) as compared to patients switching to an alternative AED of a same MOA (20.9%). A significantly lower ( $p < 0.0001$ ) proportion of patients in the refractory group (77.9%) compared to patients in the non-refractory group (82.5%) switched to an alternative AED of a different MOA in the first year of follow-up.

**Table 4.11: Comparison of Medication Switch in the First Year of Follow-Up by Refractory/Non-Refractory Status (N=5,414)**

Medication Switch	All		Refractory		Non-refractory		p-value
	n=5,414		n=2,707		n=2,707		
	N	%	N	%	N	%	
Yes	1,063	19.6	777	28.7	286	10.6	<b>&lt;0.0001<sup>a</sup></b>
No	4,351	80.4	1,940	71.3	2,421	89.4	

<sup>a</sup>McNemar’s test

Significant at  $p < 0.05$  (in bold)

**Table 4.12: Comparison of Medication Switch in the First Year of Follow-Up Stratified by Mechanism of Action of Alternative AED and Refractory/Non-Refractory Status (N=5,414)**

Medication Switch	All		Refractory		Non-refractory		p-value
	n=5,414		n=2,707		n=2,707		
	N	%	N	%	N	%	
Same MOA <sup>a</sup>	222	20.9	172	22.1	50	17.5	<b>&lt;0.0001<sup>c</sup></b>
Different MOA <sup>b</sup>	841	79.1	605	77.9	236	82.5	
Total	1,063	100.0	777	100.0	286	100.0	

MOA=Mechanism of Action

<sup>a</sup>Switch to an alternative AED of same MOA

<sup>b</sup>Switch to an alternative AED of different MOA

<sup>c</sup>McNemar's test

Significant at p<0.05 (in bold)

#### 4.4.3.3.2.2 Medication Switch (Adjusted Analysis using Conditional Logistic Regression)

Table 4.13 presents the results of the conditional logistic regression model comparing the likelihood of switch in the first-year of follow-up by refractory and non-refractory groups while controlling for covariates. The results of the overall model fit testing the null hypothesis that all parameter estimates are equal to zero indicated that the null hypothesis was rejected ( $p < 0.05$ ). Results showed that compared to patients in the non-refractory group, patients in the refractory group were 3.6 times (OR=3.591; 95% CI=3.010-4.284;  $p < 0.0001$ ) more likely to switch to an alternative AED, after controlling for covariates. Regarding covariates, with every year increase in age, the likelihood of switching to an alternative AED was 5.8% lower (OR=0.942; 95% CI=0.902-0.984;  $p = 0.0073$ ), after controlling for covariates. Males had 48.0% (OR=0.520; 95% CI=0.352-0.770;  $p = 0.0011$ ) lower likelihood than females to switch to an alternative AED, after controlling for covariates. Patients with partial epilepsy had 66.5% (OR=0.335; 95% CI=0.168-0.670;  $p = 0.0020$ ) lower likelihood than patients with generalized epilepsy to switch to an alternative AED, after controlling for covariates. Patients with other types of epilepsy had 73.1% (OR=0.269; 95% CI=0.105-0.692;  $p = 0.0065$ ) lower likelihood than patients with generalized epilepsy to switch to an alternative AED, after controlling for covariates. Patients on AEDs with multiple actions had 41.9% (OR=0.581; 95% CI=0.453-0.745;  $p < 0.0001$ ) lower likelihood than patients on AEDs with single actions to switch to an alternative AED, after controlling for covariates. Patients with a CCI score of 1 were 1.5 times (OR=1.458; 95% CI=1.032-2.058;  $p = 0.0323$ ) more likely than patients with a CCI score of 0 to switch to an alternative AED, after controlling for covariates. With every unit increase in the number of psychiatric comorbidities, the likelihood of switching to an alternative AED increased by 1.2 times (OR=1.219; 95% CI=1.108-1.341;  $p < 0.0001$ ), after controlling for covariates. With every unit increase in the pill burden in

the baseline period, the likelihood of switching to an alternative AED increased by 1.3 times (OR=1.270; 95% CI=1.033-1.562; p=0.0232), after controlling for covariates.

**Table 4.13: Comparison of Medication Switch in the First Year of Follow-Up Stratified by Mechanism of Action of Alternative AED and Refractory/Non-Refractory Status (N=5,414)**

	<b>Odds Ratio</b>	<b>95% CI</b>	<b>Wald X<sup>2</sup></b>	<b>p-value</b>
Refractory <sup>a</sup>	3.591	3.010-4.284	201.71	<b>&lt;0.0001</b>
Age at index	0.942	0.902-0.984	7.20	<b>0.0073</b>
Male <sup>a</sup>	0.520	0.352-0.770	10.67	<b>0.0011</b>
African American race <sup>a</sup>	1.036	0.738-1.455	0.04	0.8372
Other race <sup>a</sup>	1.054	0.816-1.362	0.16	0.6872
Partial type of epilepsy at first visit <sup>a</sup>	0.335	0.168-0.670	9.56	<b>0.0020</b>
Other type of epilepsy at first visit <sup>a</sup>	0.269	0.105-0.692	7.42	<b>0.0065</b>
Multiple actions of index AED <sup>a</sup>	0.581	0.453-0.745	18.24	<b>&lt;0.0001</b>
Baseline CCI of 1 <sup>a</sup>	1.458	1.032-2.058	4.58	<b>0.0323</b>
Baseline CCI greater than 1 <sup>a</sup>	1.215	0.769-1.921	0.70	0.4038
Number of psychiatric comorbidities at follow-up	1.219	1.108-1.341	16.56	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.927	0.719-1.195	0.34	0.5584
Baseline pill burden	1.270	1.033-1.562	5.15	<b>0.0232</b>
Baseline all-cause inpatient visits <sup>a</sup>	1.272	0.882-1.836	1.66	0.1976
Number of baseline all-cause outpatient visits	1.007	0.996-1.017	1.58	0.2083
Baseline total all-cause healthcare cost	1.000	1.000-1.000	4.92	0.0266

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Model Fit: likelihood ratio=424.1450; df=16; p<0.0001

Significant at p<0.05 (in bold)

**H<sub>2D</sub>**: Patients with refractory epilepsy are more likely to switch to an alternative AED as compared to patients with non-refractory epilepsy.

**Failed to Reject**

#### **4.4.4 Objective 3: Healthcare Utilization and Costs**

To compare all-cause and epilepsy-related healthcare utilization and costs between refractory and non-refractory patients while controlling for age, gender, race/ethnicity, type of epilepsy, type of index AED, baseline CCI, number of psychiatric and presence of non-psychiatric comorbidities at follow-up, baseline pill burden, presence of baseline all-cause inpatient visits, baseline number of all-cause outpatient visits, and baseline all-cause total cost.

##### **4.4.4.1 Healthcare Utilization**

**H<sub>3A-C</sub>**: Patients with refractory epilepsy have a higher number of all-cause medical visits consisting of inpatient hospitalizations (H<sub>3A</sub>), ED visits (H<sub>3B</sub>), and outpatient visits (H<sub>3C</sub>) at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.

**H<sub>3D-F</sub>**: Patients with refractory epilepsy have a higher number of epilepsy-related medical visits consisting of inpatient hospitalizations (H<sub>3D</sub>), ED visits (H<sub>3E</sub>), and outpatient visits (H<sub>3F</sub>) at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.

**H<sub>3G</sub>**: Patients with refractory epilepsy have longer lengths of stay for all-cause hospitalization as compared to patients with non-refractory epilepsy, while controlling for covariates.

**H<sub>3H</sub>**: Patients with refractory epilepsy have longer lengths of stay for epilepsy-related hospitalization as compared to patients with non-refractory epilepsy, while controlling for covariates.

**H<sub>3I-J</sub>**: Patients with refractory epilepsy have a higher number of all-cause pharmacy claims (**H<sub>3I</sub>**) and epilepsy-related pharmacy claims (**H<sub>3J</sub>**) as compared to patients with non-refractory epilepsy, while controlling for covariates.

All-cause and epilepsy-related healthcare utilization of the patients was assessed in the first and second year of follow-up after the index date. All-cause healthcare utilization consisted of the number of medical service and pharmacy claims. Epilepsy-related healthcare utilization was defined as the number of medical service claims associated with an epilepsy diagnosis (ICD-9-CM codes: 345.xx or 780.39) in the primary and/or secondary diagnoses field and pharmacy claims. Medical services included inpatient hospitalizations, ED visits, and outpatient visits. All-cause pharmacy claims consisted of the number of AEDs and non-AEDs. Epilepsy-related pharmacy claims consisted of the number of AEDs. Healthcare utilization was measured using McNemar's test, Wilcoxon signed-rank test, and regression models. Zero-inflated Poisson regression or Poisson regression was used to compare and determine differences in healthcare utilization of patients with refractory and non-refractory epilepsy while controlling for covariates. Cox proportional hazards regression was used to compare and determine differences in lengths of hospitalization stay of patients with refractory and non-refractory epilepsy while controlling for covariates. The covariates included in the models were age, gender, race/ethnicity, type of epilepsy, type of index AED, baseline CCI, number of psychiatric comorbidities and presence of non-psychiatric comorbidities at follow-up, baseline pill burden, presence of baseline all-cause inpatient visits, baseline number of all-cause outpatient visits, and baseline all-cause total cost.

#### **4.4.4.1.1 All-Cause Inpatient Hospitalization and ED Visits**

Of the 5,596 patients, 26.2% of the patients had at least one all-cause inpatient hospitalization, and 58.1% of the patients had at least one all-cause ED visit. For the present study, all-cause inpatient hospitalization and ED visits were combined to compare and determine differences in the patients with refractory and non-refractory epilepsy while controlling for covariates.

##### **4.4.4.1.1.1 All-Cause Inpatient Hospitalization and ED Visits (Unadjusted Analyses using Wilcoxon Signed-Rank Test and McNemar's Test)**

Table 4.14 presents the all-cause inpatient hospitalization and ED visits stratified by refractory and non-refractory status. Patients in the refractory group (3.0 [ $\pm$  5.1]) had significantly higher ( $p < 0.0001$ ) mean ( $\pm$  SD) all-cause inpatient hospitalization and ED visits compared to patients in the non-refractory group (2.3 [ $\pm$  4.5]). Also, a significantly higher ( $p < 0.0001$ ) proportion of patients in the refractory group (65.7%) had at least one all-cause inpatient hospitalization and ED visit compared to patients in the non-refractory group (56.1%). Although slightly higher numbers and proportions than second year of follow-up, a similar trend in the number of all-cause inpatient hospitalization and ED visits was observed in the first year of follow-up (Appendix VA).

**Table 4.14: Comparison of All-Cause Inpatient Hospitalization and ED Visits in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)**

	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
<b>All-Cause Inpatient Hospitalization and ED Visits</b>							
Median (Mean ± SD)	1 (2.7 ± 4.8)		1 (3.0 ± 5.1)		1 (2.3 ± 4.5)		<b>&lt;0.0001<sup>a</sup></b>
Yes	3,410	60.9	1,839	65.7	1,571	56.1	<b>&lt;0.0001<sup>b</sup></b>
No	2,186	39.1	959	34.3	1,227	43.9	

<sup>a</sup>Wilcoxon signed-rank test

<sup>b</sup>McNemar's test

Significant at p<0.05 (in bold)

#### **4.4.4.1.1.2 All-Cause Inpatient Hospitalization and ED Visits (Adjusted Analysis using Zero-Inflated Poisson Regression)**

Table 4.15 presents the results of the zero-inflated Poisson (ZIP) regression model comparing the all-cause inpatient hospitalization and ED visits in the second-year of follow-up by refractory and non-refractory groups while controlling for covariates. The results of the overall model fit testing the full model without a model with predictors' states that the model, as a whole, is statistically significant ( $p < 0.05$ ). Also, results of the Vuong test comparing ZIP model with standard Poisson regression indicated that the ZIP model was better ( $p < 0.05$ ). Note: The ZIP model first tests zero vs. non-zero (dichotomous) and then it tests all values  $> 0$ . Results of the dichotomous ZIP model indicated, patients in the refractory group had 38.0% [ $\exp(-0.4774)$ ] lower odds ( $p < 0.0001$ ) of being in a "certain zero" group as compared to patients in the non-refractory group (results not shown). Also, of all the patients with  $> 0$  all-cause inpatient hospitalization and ED visits, there was no significant difference in the expected number of the visits between patients in the refractory and non-refractory groups, after controlling for covariates. Regarding covariates, increasing age, male gender, index AED with multiple actions, and increasing pill burden were associated with a significantly lower ( $p < 0.05$ ) number of all-cause inpatient hospitalization and ED visits. In contrast, African American race, other types of epilepsy, baseline CCI of 1 and greater than 1, increasing number of psychiatric comorbidities, one or more non-psychiatric comorbidities, one or more baseline inpatient visits, and increasing number of baseline outpatient visits were associated with a significantly higher ( $p < 0.05$ ) number of all-cause inpatient hospitalization and ED visits.

**Table 4.15: Zero-Inflated Poisson Regression Comparing the All-Cause Inpatient Hospitalization and ED Visits in the Second Year of Follow-Up among Refractory/Non-Refractory Patients (N=5,596)**

	Estimate	95% CI	Wald X <sup>2</sup>	p-value
Refractory <sup>a</sup>	0.0233	-0.0118 - 0.0585	1.69	0.1936
Age at index	-0.0031	-0.0046 - -0.0016	16.67	< <b>0.0001</b>
Male <sup>a</sup>	-0.0569	-0.0924 - -0.0213	9.83	<b>0.0017</b>
African American race <sup>a</sup>	0.1495	0.1043 - 0.1946	42.1	< <b>0.0001</b>
Other race <sup>a</sup>	-0.0281	-0.0668 - 0.0106	2.02	0.1553
Partial type of epilepsy at first visit <sup>a</sup>	-0.0888	-0.1867 - 0.0092	3.15	0.0757
Other type of epilepsy at first visit <sup>a</sup>	0.1302	0.0684 - 0.192	17.05	< <b>0.0001</b>
Multiple actions of index AED <sup>a</sup>	-0.1118	-0.1474 - -0.0762	37.97	< <b>0.0001</b>
Baseline CCI of 1 <sup>a</sup>	0.2022	0.1585 - 0.2459	82.43	< <b>0.0001</b>
Baseline CCI greater than 1 <sup>a</sup>	0.2014	0.1545 - 0.2483	70.82	< <b>0.0001</b>
Number of psychiatric comorbidities at follow-up	0.2871	0.2754 - 0.2988	2306.27	< <b>0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.4629	0.4228 - 0.5030	511.15	< <b>0.0001</b>
Baseline pill burden	-0.0024	-0.0046 - -0.0001	4.33	<b>0.0375</b>
Baseline all-cause inpatient visits <sup>a</sup>	0.2077	0.1678 - 0.2475	104.41	< <b>0.0001</b>
Number of baseline all-cause outpatient visits	0.0060	0.0049 - 0.0072	98.07	< <b>0.0001</b>
Baseline total all-cause healthcare cost	0.0000	-0.0000 - 0.0000	1.52	0.2179

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Model Fit: likelihood ratio chi-squared=4562.18; df=16; p<0.0001;

Vuong test of ZIP vs. standard poisson: z=15.15; p<0.0001

Significant at p<0.05 (in bold)

**H<sub>3A-B</sub>**: Patients with refractory epilepsy have a higher number of all-cause medical visits consisting of inpatient hospitalizations and ED visits at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.

**Failed to reject for zero vs. non-zero (dichotomous); Rejected for all values > 0**

#### **4.4.4.1.2 All-Cause Outpatient Visits**

Wilcoxon signed-rank test, McNemar's test, and zero-inflated Poisson regression models were used to compare and determine differences in the all-cause outpatient visits among patients with refractory and non-refractory epilepsy while controlling for covariates.

##### **4.4.4.1.2.1 All-Cause Outpatient Visits (Unadjusted Analyses using Wilcoxon Signed-Rank Test and McNemar's Test)**

Table 4.16 presents the all-cause outpatient visits stratified by refractory and non-refractory status. Patients in the refractory group ( $40.4 \pm [37.1]$ ) had significantly higher ( $p < 0.0001$ ) mean ( $\pm$  SD) all-cause outpatient visits compared to patients in the non-refractory group ( $37.0 \pm [36.9]$ ). However, there was no significant difference in the proportion of patients with at least one all-cause outpatient visit among patients in the refractory and non-refractory groups. A similar trend in the number of all-cause outpatient visits was observed in the first year of follow-up (Appendix VB).

**Table 4.16: Comparison of All-Cause Outpatient Visits in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)**

	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
<b>All-Cause Outpatient Visits</b>							
Median (Mean ± SD)	28 (38.7 ± 37.0)		30 (40.4 ± 37.1)		26 (37.0 ± 36.9)		<b>&lt;0.0001<sup>a</sup></b>
Yes	5,575	99.6	2,788	99.6	2,787	99.6	0.8273 <sup>b</sup>
No	21	0.4	10	0.4	11	0.4	

<sup>a</sup>Wilcoxon signed-rank test

<sup>b</sup>McNemar's test

Significant at p<0.05 (in bold)

#### **4.4.4.1.2.2 All-Cause Outpatient Visits (Adjusted Analysis using Zero-inflated Poisson Regression)**

Table 4.17 presents the results of the zero-inflated Poisson regression model comparing the all-cause outpatient visits in the second-year of follow-up by refractory and non-refractory groups while controlling for covariates. The results of the overall model fit testing the full model without a model with predictors' states that the model, as a whole, is statistically significant ( $p < 0.05$ ). Also, results of the Vuong test comparing ZIP model with standard Poisson regression indicates that the ZIP model is better ( $p < 0.05$ ). Results of the dichotomous ZIP model indicated, there was no significant difference in the odds of being in a "certain zero" group between patients in the refractory and non-refractory groups (results not shown). Also, of all the patients with  $> 0$  all-cause outpatient visits, the expected number of the visits among patients in the refractory group were 1.1 times [ $\exp(0.0548)$ ] significantly higher (95% CI=1.047-1.066;  $p < 0.0001$ ) than the expected number of the visits among patients in the non-refractory group, after controlling for covariates. Regarding covariates, male gender and index AED with multiple actions were associated with a significantly lower ( $p < 0.05$ ) number of all-cause outpatient visits. In contrast, increasing age, African American and other race, other type of epilepsy, CCI of 1 and greater than 1, increasing number of psychiatric comorbidities, one or more non-psychiatric comorbidities, increasing baseline pill burden, increasing number of baseline outpatient visits, and increasing baseline total cost were associated with a significantly higher ( $p < 0.05$ ) number of all-cause outpatient visits.

**Table 4.17: Zero-Inflated Poisson Regression Comparing the All-Cause Outpatient Visits in the Second Year of Follow-Up among Refractory/Non-Refractory Patients (N=5,596)**

	Estimate	95% CI	Wald X <sup>2</sup>	p-value
Refractory <sup>a</sup>	0.0548	0.0462 - 0.0635	155.87	<b>&lt;0.0001</b>
Age at index	0.0033	0.003 - 0.0037	325.14	<b>&lt;0.0001</b>
Male <sup>a</sup>	-0.0524	-0.0612 - -0.0436	136.25	<b>&lt;0.0001</b>
African American race <sup>a</sup>	0.1096	0.0978 - 0.1213	333.38	<b>&lt;0.0001</b>
Other race <sup>a</sup>	0.1165	0.1070 - 0.1260	578.88	<b>&lt;0.0001</b>
Partial type of epilepsy at first visit <sup>a</sup>	-0.0120	-0.0334 - 0.0095	1.19	0.2745
Other type of epilepsy at first visit <sup>a</sup>	0.0893	0.0750 - 0.1035	151	<b>&lt;0.0001</b>
Multiple actions of index AED <sup>a</sup>	-0.0537	-0.0625 - -0.0448	140.96	<b>&lt;0.0001</b>
Baseline CCI of 1 <sup>a</sup>	0.1766	0.1655 - 0.1877	969.14	<b>&lt;0.0001</b>
Baseline CCI greater than 1 <sup>a</sup>	0.1704	0.1583 - 0.1825	763.16	<b>&lt;0.0001</b>
Number of psychiatric comorbidities at follow-up	0.1158	0.1128 - 0.1188	5748.45	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.2211	0.2118 - 0.2303	2191.82	<b>&lt;0.0001</b>
Baseline pill burden	0.0086	0.008 - 0.0091	859.52	<b>&lt;0.0001</b>
Baseline all-cause inpatient visits <sup>a</sup>	-0.0007	-0.0113 - 0.0098	0.02	0.8924
Number of baseline all-cause outpatient visits	0.0160	0.0158 - 0.0163	20016.5	<b>&lt;0.0001</b>
Baseline total all-cause healthcare cost	0.0000	-0.0000 - 0.0000	475.44	<b>&lt;0.0001</b>

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Model Fit: likelihood ratio chi-squared= 62812.22; df=16; p<0.0001;

Vuong test of ZIP vs. standard poisson: z=3.38; p=0.0004

Significant at p<0.05 (in bold)

**H<sub>3c</sub>**: Patients with refractory epilepsy have a higher number of all-cause medical visits consisting of outpatient visits at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.

**Rejected for zero vs. non-zero (dichotomous); Failed to reject for all values > 0**

#### **4.4.4.1.3 Epilepsy-Related Inpatient Hospitalization and ED Visits**

Of the 5,596 patients, 15.7% of the patients had at least one epilepsy-related inpatient hospitalization, and 24.6% of the patients had at least one epilepsy-related ED visit in the second year of follow-up. For the present study, epilepsy-related inpatient hospitalization and ED visits were combined to compare and determine differences in the patients with refractory and non-refractory epilepsy while controlling for covariates.

##### **4.4.4.1.3.1 Epilepsy-Related Inpatient Hospitalization and ED Visits (Unadjusted Analyses using Wilcoxon Signed-Rank Test and McNemar's Test)**

Table 4.18 presents the epilepsy-related inpatient hospitalization and ED visits stratified by refractory and non-refractory status. Patients in the refractory group (1.0 [ $\pm$  2.2]) had significantly higher ( $p < 0.0001$ ) mean ( $\pm$  SD) epilepsy-related inpatient hospitalization and ED visits compared to patients in the non-refractory group (0.5 [ $\pm$  1.2]). Also, a significantly higher ( $p < 0.0001$ ) proportion of patients in the refractory group (39.3%) had at least one epilepsy-related inpatient hospitalization and ED visit compared to patients in the non-refractory group (26.5%). Although higher numbers and proportions than second year of follow-up, a similar trend in the number of epilepsy-related inpatient hospitalization and ED visits was observed in the first year of follow-up (Appendix VC).

**Table 4.18: Comparison of Epilepsy-Related Inpatient Hospitalization and ED Visits in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)**

	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
<b>Epilepsy-Related Inpatient Hospitalization and ED Visits</b>							
Median (Mean ± SD)	0 (0.8 ± 1.8)		0 (1.0 ± 2.2)		0 (0.5 ± 1.2)		<b>&lt;0.0001<sup>a</sup></b>
Yes	1,840	32.9	1,099	39.3	741	26.5	<b>&lt;0.0001<sup>b</sup></b>
No	3,756	67.1	1,699	60.7	2,057	73.5	

<sup>a</sup>Wilcoxon signed-rank test

<sup>b</sup>McNemar's test

Significant at p<0.05 (in bold)

#### **4.4.4.1.3.2 Epilepsy-Related Inpatient Hospitalization and ED Visits (Adjusted Analysis using Zero-inflated Poisson Regression)**

Table 4.19 presents the results of the zero-inflated Poisson regression model comparing the epilepsy-related inpatient hospitalization and ED visits in the second-year of follow-up by refractory and non-refractory groups while controlling for covariates. The results of the overall model fit testing the full model without a model with predictors' states that the model, as a whole, is statistically significant ( $p < 0.05$ ). Also, results of the Vuong test comparing ZIP model with standard Poisson regression indicates that the ZIP model is better ( $p < 0.05$ ). Results of the dichotomous ZIP model indicated, patients in the refractory group had 30.2% [ $\exp(-0.3598)$ ] lower odds ( $p < 0.0001$ ) of being in a "certain zero" group as compared to patients in the non-refractory group (results not shown). Also, of all the patients with  $> 0$  epilepsy-related inpatient hospitalization and ED visits, the expected number of the visits among patients in the refractory group were 1.4 times [ $\exp(0.3568)$ ] significantly higher (95% CI=1.316-1.551;  $p < 0.0001$ ) than the expected number of the visits among patients in the non-refractory group, after controlling for covariates. Regarding covariates, increasing age, CCI of 1, and baseline increasing pill burden were associated with a significantly lower ( $p < 0.05$ ) number of epilepsy-related inpatient hospitalization and ED visits. In contrast, African American race, increasing number of psychiatric comorbidities, one or more non-psychiatric comorbidities, and one or more baseline inpatient visits were associated with a significantly higher ( $p < 0.05$ ) number of epilepsy-related inpatient hospitalization and ED visits.

**Table 4.19: Zero-Inflated Poisson Regression Comparing the Epilepsy-Related Inpatient Hospitalization and ED Visits in the Second Year of Follow-Up among Refractory/Non-Refractory Patients (N=5,596)**

	Estimate	95% CI	Wald X <sup>2</sup>	p-value
Refractory <sup>a</sup>	0.3568	0.2745 - 0.4391	72.26	<b>&lt;0.0001</b>
Age at index	-0.0094	-0.0124 - -0.0065	38.3	<b>&lt;0.0001</b>
Male <sup>a</sup>	-0.0394	-0.1097 - 0.0308	1.21	0.2712
African American race <sup>a</sup>	0.2051	0.1127 - 0.2974	18.93	<b>&lt;0.0001</b>
Other race <sup>a</sup>	0.0638	-0.0132 - 0.1407	2.64	0.1043
Partial type of epilepsy at first visit <sup>a</sup>	-0.0073	-0.1762 - 0.1615	0.01	0.9320
Other type of epilepsy at first visit <sup>a</sup>	-0.0691	-0.1865 - 0.0483	1.33	0.2487
Multiple actions of index AED <sup>a</sup>	0.0085	-0.0614 - 0.0784	0.06	0.8110
Baseline CCI of 1 <sup>a</sup>	-0.1259	-0.2163 - -0.0356	7.47	<b>0.0063</b>
Baseline CCI greater than 1 <sup>a</sup>	0.0043	-0.0935 - 0.1021	0.01	0.9314
Number of psychiatric comorbidities at follow-up	0.2500	0.2265 - 0.2735	435.3	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.4791	0.3999 - 0.5582	140.74	<b>&lt;0.0001</b>
Baseline pill burden	-0.0073	-0.0126 - -0.0021	7.51	<b>0.0061</b>
Baseline all-cause inpatient visits <sup>a</sup>	0.2965	0.2133 - 0.3796	48.85	<b>&lt;0.0001</b>
Number of baseline all-cause outpatient visits	0.0015	-0.0012 - 0.0042	1.22	0.2690
Baseline total all-cause healthcare cost	-0.0000	-0.0000 - 0.0000	1.33	0.2487

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Model Fit: likelihood ratio chi-squared=885.18; df=16; p<0.0001;

Vuong test of ZIP vs. standard Poisson: z=12.48; p<0.0001

Significant at p<0.05 (in bold)

**H<sub>3D-E</sub>**: Patients with refractory epilepsy have a higher number of epilepsy-related medical visits consisting of inpatient hospitalization and ED visits at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.

**Failed to reject**

#### **4.4.4.1.4 Epilepsy-Related Outpatient Visits**

Wilcoxon signed-rank test, McNemar's test, and zero-inflated Poisson regression models were used to compare and determine differences in the epilepsy-related outpatient visits among patients with refractory and non-refractory epilepsy while controlling for covariates.

##### **4.4.4.1.4.1 Epilepsy-Related Outpatient Visits (Unadjusted Analyses using Wilcoxon Signed-Rank Test and McNemar's Test)**

Table 4.20 presents the epilepsy-related outpatient visits stratified by refractory and non-refractory status. Patients in the refractory group ( $8.1 \pm [11.6]$ ) had significantly higher ( $p < 0.0001$ ) mean ( $\pm$  SD) epilepsy-related outpatient visits compared to patients in the non-refractory group ( $5.7 \pm [9.3]$ ). Also, a significantly higher ( $p < 0.0001$ ) proportion of patients in the refractory group (99.6%) had at least one epilepsy-related outpatient visit compared to patients in the non-refractory group (85.3%). Although higher numbers than second year of follow-up, a similar trend in the number of epilepsy-related outpatient visits was observed in the first year of follow-up (Appendix VD).

**Table 4.20: Comparison of Epilepsy-Related Outpatient Visits in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)**

	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
<b>Epilepsy-Related Outpatient Visits</b>							
Median (Mean ± SD)	4 (6.9 ± 10.6)		5 (8.1 ± 11.6)		4 (5.7 ± 9.3)		<b>&lt;0.0001<sup>a</sup></b>
Yes	4,935	88.2	2,788	99.6	2,388	85.3	<b>&lt;0.0001<sup>b</sup></b>
No	661	11.8	251	9.0	410	14.7	

<sup>a</sup>Wilcoxon signed-rank test

<sup>b</sup>McNemar's test

Significant at p<0.05 (in bold)

#### **4.4.4.1.4.2 Epilepsy-Related Outpatient Visits (Adjusted Analysis using Zero-inflated Poisson Regression)**

Table 4.21 presents the results of the zero-inflated Poisson regression model comparing the epilepsy-related outpatient visits in the second-year of follow-up by refractory and non-refractory groups while controlling for covariates. The results of the overall model fit testing the full model without a model with predictors' states that the model, as a whole, is statistically significant ( $p < 0.05$ ). Also, results of the Vuong test comparing ZIP model with standard Poisson regression indicated that the ZIP model is better ( $p < 0.05$ ). Results of the dichotomous ZIP model indicated, patients in the refractory group had 41.9% [ $\exp(-0.5426)$ ] lower odds ( $p < 0.0001$ ) of being in a "certain zero" group as compared to patients in the non-refractory group (results not shown). Also, of all the patients with  $> 0$  epilepsy-related outpatient visits, the expected number of the visits among patients in the refractory group were 1.3 times [ $\exp(0.2594)$ ] significantly higher (95% CI=1.270-1.323;  $p < 0.0001$ ) than the expected number of the visits among patients in the non-refractory group, after controlling for covariates. Regarding covariates, increasing age, index AED with multiple actions, and increasing baseline pill burden were associated with a significantly lower ( $p < 0.05$ ) number of epilepsy-related outpatient visits. In contrast, male gender, African American and other race, CCI of 1, increasing number of psychiatric comorbidities, one or more non-psychiatric comorbidities, and increasing baseline outpatient visits were associated with a significantly higher ( $p < 0.05$ ) number of epilepsy-related outpatient visits.

**Table 4.21: Zero-Inflated Poisson Regression Comparing the Epilepsy-Related Outpatient Visits in the Second Year of Follow-Up among Refractory/Non-Refractory Patients (N=5,596)**

	Estimate	95% CI	Wald X <sup>2</sup>	p-value
Refractory <sup>a</sup>	0.2594	0.2387 - 0.2800	606.12	< <b>0.0001</b>
Age at index	-0.0050	-0.0058 - -0.0041	128.85	< <b>0.0001</b>
Male <sup>a</sup>	0.0717	0.0512 - 0.0922	46.94	< <b>0.0001</b>
African American race <sup>a</sup>	0.0777	0.0492 - 0.1063	28.49	< <b>0.0001</b>
Other race <sup>a</sup>	0.1186	0.0963 - 0.141	108.3	< <b>0.0001</b>
Partial type of epilepsy at first visit <sup>a</sup>	0.0183	-0.027 - 0.0636	0.63	0.4277
Other type of epilepsy at first visit <sup>a</sup>	-0.0248	-0.0564 - 0.0067	2.39	0.1224
Multiple actions of index AED <sup>a</sup>	-0.0775	-0.0983 - -0.0567	53.34	< <b>0.0001</b>
Baseline CCI of 1 <sup>a</sup>	0.0749	0.0478 - 0.1019	29.48	< <b>0.0001</b>
Baseline CCI greater than 1 <sup>a</sup>	0.0131	-0.0172 - 0.0435	0.72	0.3967
Number of psychiatric comorbidities at follow-up	0.0749	0.0677 - 0.0821	413.23	< <b>0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.1970	0.1754 - 0.2186	319.86	< <b>0.0001</b>
Baseline pill burden	-0.0019	-0.0034 - -0.0003	5.54	<b>0.0186</b>
Baseline all-cause inpatient visits <sup>a</sup>	0.0155	-0.0114 - 0.0425	1.28	0.2587
Number of baseline all-cause outpatient visits	0.0075	0.0069 - 0.0081	536.46	< <b>0.0001</b>
Baseline total all-cause healthcare cost	0.0000	-0.0000 - 0.0000	2.63	0.1050

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Model Fit: likelihood ratio chi-squared=3076.98; df=16; p<0.0001;

Vuong test of ZIP vs. standard Poisson: z=18.11; p<0.0001

Significant at p<0.05 (in bold)

**H<sub>3F</sub>**: Patients with refractory epilepsy have a higher number of epilepsy-related medical visits consisting of outpatient visits at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.

**Failed to reject**

#### **4.4.4.1.5 All-Cause Length of Hospitalization Stay**

Of the 5,596 patients, only 26.2% of the patients had at least one all-cause inpatient hospitalization. As majority of the patients did not have an all-cause inpatient hospitalization, the length of hospitalization stay was not evaluated.

**H<sub>3G</sub>:** Patients with refractory epilepsy have longer lengths of stay for all-cause hospitalization as compared to patients with non-refractory epilepsy, while controlling for covariates.

**Not evaluated**

#### **4.4.4.1.6 Epilepsy-Related Length of Hospitalization Stay**

Of the 5,596 patients, only 15.7% of the patients had at least one epilepsy-related inpatient hospitalization. As majority of the patients did not have an epilepsy-related inpatient hospitalization, the length of hospitalization stay was not evaluated.

**H<sub>3H</sub>:** Patients with refractory epilepsy have longer lengths of stay for epilepsy-related hospitalization as compared to patients with non-refractory epilepsy, while controlling for covariates.

**Not evaluated**

#### **4.4.4.1.7 All-Cause Pharmacy Claims**

Of the 5,596 patients, 99.6% of the patients had at least one all-cause pharmacy claim (i.e., AED and non-AED prescriptions) in the second year of follow-up. Results of the Vuong test comparing ZIP model with standard Poisson regression was not significant, which indicated that a standard Poisson regression model was better.

##### **4.4.4.1.7.1 All-Cause Pharmacy Claims (Unadjusted Analyses using Wilcoxon Signed-Rank Test and McNemar's Test)**

Table 4.22 presents the all-cause pharmacy claims stratified by refractory and non-refractory status. Patients in the refractory group (9.9 [ $\pm$  6.8]) had significantly higher ( $p < 0.0001$ ) mean ( $\pm$  SD) all-cause pharmacy claims compared to patients in the non-refractory group (8.6 [ $\pm$  6.3]). However, there was no significant difference in the proportion of patients with at least one all-cause pharmacy claim among patients in the refractory and non-refractory groups. Although higher numbers and proportions than second year of follow-up, a similar trend in the number of all-cause pharmacy claims was observed in the first year of follow-up (Appendix VE).

**Table 4.22: Comparison of All-Cause Pharmacy Claims in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)**

	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
<b>All-Cause Pharmacy Claims</b>							
Median (Mean ± SD)	8 (9.3 ± 6.6)		8 (9.9 ± 6.8)		7 (8.6 ± 6.3)		<b>&lt;0.0001<sup>a</sup></b>
Yes	5,576	99.6	2,790	99.7	2,786	99.6	0.3711 <sup>b</sup>
No	20	0.4	8	0.3	12	0.4	

<sup>a</sup>Wilcoxon signed-rank test

<sup>b</sup>McNemar's test

Significant at p<0.05 (in bold)

#### **4.4.4.1.7.2 All-Cause Pharmacy Claims (Adjusted Analysis using Poisson Regression)**

Table 4.23 presents the results of the Poisson regression model comparing the all-cause pharmacy claims in the second-year of follow-up by refractory and non-refractory groups while controlling for covariates. The results of the overall model fit testing the full model without a model with predictors' states that the model, as a whole, is statistically significant ( $p < 0.05$ ). Results of the Poisson model indicated that the expected number of all-cause pharmacy claims among patients in the refractory group were 1.1 times [ $\exp(0.0895)$ ] significantly higher (95% CI=1.075-1.113;  $p < 0.0001$ ) than the expected number of all-cause pharmacy claims among patients in the non-refractory group, after controlling for covariates. Regarding covariates, male gender, African American and other race, index AED with multiple actions, and one or more inpatient visits were associated with a significantly lower ( $p < 0.05$ ) number of all-cause pharmacy claims. In contrast, CCI of 1 and greater than 1, increasing number of psychiatric comorbidities, one or more non-psychiatric comorbidities, increasing baseline pill burden, increasing baseline outpatient visits, and increasing baseline all-cause total cost were associated with a significantly higher ( $p < 0.05$ ) number of all-cause pharmacy claims.

**Table 4.23: Poisson Regression Comparing the All-Cause Pharmacy Claims in the Second Year of Follow-Up among Refractory/Non-Refractory Patients (N=5,596)**

	Estimate	95% CI	Wald X <sup>2</sup>	p-value
Refractory <sup>a</sup>	0.0895	0.0720 - 0.1071	99.73	<b>&lt;0.0001</b>
Age at index	0.0035	0.0028 - 0.0042	86.1	<b>&lt;0.0001</b>
Male <sup>a</sup>	-0.0979	-0.1161 - -0.0797	111.27	<b>&lt;0.0001</b>
African American race <sup>a</sup>	-0.0473	-0.0718 - -0.0229	14.4	<b>0.0001</b>
Other race <sup>a</sup>	-0.0202	-0.0395 - -0.0009	4.23	<b>0.0398</b>
Partial type of epilepsy at first visit <sup>a</sup>	-0.0251	-0.0679 - 0.0176	1.33	0.2492
Other type of epilepsy at first visit <sup>a</sup>	0.0098	-0.0185 - 0.0381	0.46	0.4974
Multiple actions of index AED <sup>a</sup>	-0.0238	-0.0418 - -0.0059	6.77	<b>0.0093</b>
Baseline CCI of 1 <sup>a</sup>	0.1046	0.0819 - 0.1273	81.76	<b>&lt;0.0001</b>
Baseline CCI greater than 1 <sup>a</sup>	0.0462	0.0207 - 0.0716	12.64	<b>0.0004</b>
Number of psychiatric comorbidities at follow-up	0.0731	0.067 - 0.0793	543.03	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.1644	0.1456 - 0.1833	292.43	<b>&lt;0.0001</b>
Baseline pill burden	0.0370	0.0359 - 0.0382	4136.93	<b>&lt;0.0001</b>
Baseline all-cause inpatient visits <sup>a</sup>	-0.0243	-0.0465 - -0.0022	4.62	<b>0.0315</b>
Number of baseline all-cause outpatient visits	0.0009	0.0003 - 0.0016	7.41	<b>0.0065</b>
Baseline total all-cause healthcare cost	0.0000	-0.0000 - 0.0000	10.81	<b>0.0010</b>

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Model Fit: likelihood ratio chi-squared=10684.29; df=16; p<0.0001

Significant at p<0.05 (in bold)

**H31:** Patients with refractory epilepsy have a higher number of all-cause pharmacy claims as compared to patients with non-refractory epilepsy, while controlling for covariates.

**Failed to reject**

#### **4.4.4.1.8 Epilepsy-Related Pharmacy Claims**

Of the 5,596 patients, 97.9% of the patients had at least one epilepsy-related pharmacy claim (i.e., AED prescriptions) in the second year of follow-up. Results of the Vuong test comparing ZIP model with standard Poisson regression was not significant, which indicated that a standard Poisson regression model was better.

##### **4.4.4.1.8.1 Epilepsy-Related Pharmacy Claims (Unadjusted Analyses using Wilcoxon Signed-Rank Test and McNemar's Test)**

Table 4.24 presents the epilepsy-related pharmacy claims stratified by refractory and non-refractory status. Patients in the refractory group (3.1 [ $\pm$  1.5]) had significantly higher ( $p < 0.0001$ ) mean ( $\pm$  SD) epilepsy-related pharmacy claims compared to patients in the non-refractory group (1.8 [ $\pm$  1.1]). Also, a significantly higher ( $p < 0.0001$ ) proportion of patients in the refractory group (98.9%) had at least one epilepsy-related pharmacy claim compared to patients in the non-refractory group (97.0%). Although slightly higher numbers and proportions than second year of follow-up, a similar trend in the number of epilepsy-related pharmacy claims was observed in the first year of follow-up (Appendix VF).

**Table 4.24: Comparison of Epilepsy-Related Pharmacy Claims in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)**

	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
<b>Epilepsy-Related Pharmacy Claims</b>							
Median (Mean ± SD)	2 (2.4 ± 1.5)		3 (3.1 ± 1.5)		2 (1.8 ± 1.1)		<b>&lt;0.0001<sup>a</sup></b>
Yes	5,481	97.9	2,768	98.9	2,713	97.0	<b>&lt;0.0001<sup>b</sup></b>
No	115	2.1	30	1.1	85	3.0	

<sup>a</sup>Wilcoxon signed-rank test

<sup>b</sup>McNemar's test

Significant at p<0.05 (in bold)

#### **4.4.4.1.8.2 Epilepsy-Related Pharmacy Claims (Adjusted Analysis using Poisson Regression)**

Table 4.25 presents the results of the Poisson regression model comparing the epilepsy-related pharmacy claims in the second-year of follow-up by refractory and non-refractory groups while controlling for covariates. The results of the overall model fit testing the full model without a model with predictors' states that the model, as a whole, is statistically significant ( $p < 0.05$ ). Results of the Poisson model indicated that the expected number of epilepsy-related pharmacy claims among patients in the refractory group were 1.7 times [ $\exp(0.5179)$ ] significantly higher (95% CI=1.620-1.739;  $p < 0.0001$ ) than the expected number of epilepsy-related pharmacy claims among patients in the non-refractory group, after controlling for covariates. Regarding covariates, increasing age was associated with a significantly lower ( $p < 0.05$ ) number of epilepsy-related pharmacy claims. In contrast, increasing number of psychiatric comorbidities, one or more non-psychiatric comorbidities at follow-up, and increasing baseline pill burden were associated with a significantly higher ( $p < 0.05$ ) number of epilepsy-related pharmacy claims.

**Table 4.25: Comparison of Epilepsy-Related Pharmacy Claims in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)**

	Estimate	95% CI	Wald X <sup>2</sup>	p-value
Refractory <sup>a</sup>	0.5179	0.4824 - 0.5533	820.69	<b>&lt;0.0001</b>
Age at index	-0.0019	-0.0034 - -0.0005	6.82	<b>0.0090</b>
Male <sup>a</sup>	0.0072	-0.0274 - 0.0418	0.17	0.6839
African American race <sup>a</sup>	-0.0462	-0.0946 - 0.0021	3.52	0.0608
Other race <sup>a</sup>	-0.0210	-0.0583 - 0.0163	1.21	0.2704
Partial type of epilepsy at first visit <sup>a</sup>	0.0357	-0.0408 - 0.1122	0.84	0.3602
Other type of epilepsy at first visit <sup>a</sup>	-0.0273	-0.0807 - 0.0261	1.01	0.3157
Multiple actions of index AED <sup>a</sup>	0.0023	-0.0323 - 0.037	0.02	0.8944
Baseline CCI of 1 <sup>a</sup>	-0.0453	-0.0921 - 0.0014	3.61	0.0575
Baseline CCI greater than 1 <sup>a</sup>	-0.0316	-0.0833 - 0.0200	1.44	0.2298
Number of psychiatric comorbidities at follow-up	0.0410	0.0289 - 0.0531	44.00	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.0476	0.0113 - 0.0838	6.62	<b>0.0101</b>
Baseline pill burden	0.0086	0.006 - 0.0112	41.57	<b>&lt;0.0001</b>
Baseline all-cause inpatient visits <sup>a</sup>	0.0023	-0.0436 - 0.0481	0.01	0.9226
Number of baseline all-cause outpatient visits	0.0001	-0.0012 - 0.0014	0.03	0.8642
Baseline total all-cause healthcare cost	0.0000	-0.0000 - 0.0000	0.46	0.4961

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Model Fit: likelihood ratio chi-squared=1109.55; df=16; p<0.0001;

Significant at p<0.05 (in bold)

**H3J:** Patients with refractory epilepsy have a higher number of epilepsy-related pharmacy claims as compared to patients with non-refractory epilepsy, while controlling for covariates.

**Failed to reject**

#### 4.4.4.2 Healthcare Cost

**H<sub>3K-M</sub>**: Patients with refractory epilepsy have a higher all-cause medical costs consisting of inpatient hospitalizations (H<sub>3K</sub>), ED visits (H<sub>3L</sub>), and outpatient visits (H<sub>3M</sub>) at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.

**H<sub>3N-P</sub>**: Patients with refractory epilepsy have a higher epilepsy-related medical costs consisting of inpatient hospitalizations (H<sub>3N</sub>), ED visits (H<sub>3O</sub>), and outpatient visits (H<sub>3P</sub>) at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.

**H<sub>3Q-R</sub>**: Patients with refractory epilepsy have a higher cost of all-cause pharmacy claims (H<sub>3Q</sub>) and epilepsy-related pharmacy claims (H<sub>3R</sub>) as compared to patients with non-refractory epilepsy, while controlling for covariates.

All-cause and epilepsy-related healthcare cost of the patients was assessed in the first and second year of follow-up after the index date. All-cause healthcare cost consisted of the cost of medical service and pharmacy claims of the patients. Epilepsy-related healthcare cost included medical service claims associated with an epilepsy diagnosis (ICD-9-CM codes: 345.xx or 780.39) in the primary and/or secondary diagnoses field and pharmacy claims. Cost of medical services included inpatient hospitalizations, ED visits, and outpatient visits. All-cause pharmacy cost consisted of the cost of AED and non-AED claims. Epilepsy-related pharmacy cost consisted only of the cost of AED claims. Healthcare cost was measured using Wilcoxon signed-rank test and regression models. Generalized linear model was used to compare and determine differences in healthcare cost of patients with refractory and non-refractory epilepsy while controlling for

covariates. Modified Park test was used to define distribution and the functional form. The covariates included in the models were age, gender, race/ethnicity, type of epilepsy, type of index AED, baseline CCI, number of psychiatric and non-psychiatric comorbidities at follow-up, baseline pill burden, baseline all-cause inpatient visits, baseline number of all-cause outpatient visits, and baseline all-cause total cost. Overall, in the second-year of follow-up, patients in the refractory group (\$23,136 [ $\pm$  \$25,827]) had significantly higher ( $p < 0.0001$ ) mean ( $\pm$  SD) unadjusted cost of all-cause medical and pharmacy claims compared to patients in the non-refractory group (\$19,813 [ $\pm$  \$25,907]). Similarly, patients in the refractory group (\$7,811 [ $\pm$  \$10,084]) had significantly higher ( $p < 0.0001$ ) mean ( $\pm$  SD) unadjusted cost of epilepsy-related medical and pharmacy claims compared to patients in the non-refractory group (\$3,893 [ $\pm$  \$7,047]).

#### 4.4.4.2.1 All-Cause Inpatient Hospitalization and ED Visit Cost

Of the 5,596 patients, the median cost of all-cause inpatient hospitalization was \$0 in the second year of follow-up. For the present study, cost of all-cause inpatient hospitalization and ED visits were combined to compare and determine differences in patients with refractory and non-refractory epilepsy while controlling for covariates.

##### 4.4.4.2.1.1 All-Cause Inpatient Hospitalization and ED Visit Cost (Unadjusted Analysis using Wilcoxon Signed-Rank Test)

Table 4.26 presents the cost of all-cause inpatient hospitalization and ED visits stratified by refractory and non-refractory status. Patients in the refractory group (\$3,147 [ $\pm$  \$8,343]) had significantly higher ( $p < 0.0001$ ) mean ( $\pm$  SD) cost of all-cause inpatient hospitalization and ED visits compared to patients in the non-refractory group (\$2,647 [ $\pm$  \$7,941]). Although the mean ( $\pm$  SD) and median costs were higher than second year of follow-up, a similar trend in the cost of all-cause inpatient hospitalization and ED visits was observed in the first year of follow-up (Appendix VIA).

**Table 4.26: Comparison of Cost of All-Cause Inpatient Hospitalization and ED Visits in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)**

	All n=5,596	Refractory n=2,798	Non-refractory n=2,798	p-value
<b>All-Cause Inpatient Hospitalization and ED Visit Cost</b>				
Median (Mean $\pm$ SD)	\$0 (\$2,897 $\pm$ \$8,147)	\$0 (\$3,147 $\pm$ \$8,343)	\$0 (\$2,647 $\pm$ \$7,941)	<b>&lt;0.0001<sup>a</sup></b>

<sup>a</sup>Wilcoxon signed-rank test  
Significant at  $p < 0.05$  (in bold)

#### **4.4.4.2.1.2 All-Cause Inpatient Hospitalization and ED Visit Cost (Adjusted Analysis using Generalized Linear Model)**

Table 4.27 presents the results of the generalized linear model with gamma distribution and log-link function comparing the cost of all-cause inpatient hospitalization and ED visits in the second-year of follow-up by refractory and non-refractory groups while controlling for covariates. Results of the model indicated, there was no significant difference in the cost of all-cause inpatient hospitalization and ED visits of patients in the refractory and non-refractory groups, after controlling for covariates. Regarding covariates, baseline CCI of greater than 1, increasing number of psychiatric comorbidities, one or more non-psychiatric comorbidities at follow-up, increasing baseline pill burden, one or more baseline inpatient visits, and increasing baseline total cost were associated with a significantly higher ( $p < 0.05$ ) cost of all-cause inpatient hospitalization and ED visits. In the first-year of follow-up, the cost of all-cause inpatient hospitalization and ED visits of patients in the refractory group was significantly higher ( $p < 0.05$ ) than the cost of all-cause inpatient hospitalization and ED visits of patients in the non-refractory group, after controlling for covariates (Appendix VIA).

**Table 4.27: Generalized Linear Model Comparing the Cost of All-Cause Inpatient Hospitalization and ED Visits in the Second Year of Follow-Up among Refractory/Non-Refractory Patients (N=5,596)**

	Estimate	95% CI	z	p-value
Refractory <sup>a</sup>	0.0621	-0.1051 – 0.2293	0.73	0.4660
Age at index	0.0027	-0.0041 – 0.0094	0.77	0.4390
Male <sup>a</sup>	0.1044	-0.0651 – 0.2740	1.21	0.2270
African American race <sup>a</sup>	0.2476	0.0157 – 0.4796	2.09	0.0360
Other race <sup>a</sup>	0.1009	-0.0831 – 0.2850	1.07	0.2820
Partial type of epilepsy at first visit <sup>a</sup>	0.1744	-0.2070 – 0.5557	0.9	0.3700
Other type of epilepsy at first visit <sup>a</sup>	-0.0204	-0.2788 – 0.2379	-0.15	0.8770
Multiple actions of index AED <sup>a</sup>	-0.0739	-0.2452 – 0.0974	-0.85	0.3980
Baseline CCI of 1 <sup>a</sup>	0.2571	0.0348 – 0.4793	2.27	0.0230
Baseline CCI greater than 1 <sup>a</sup>	0.3190	0.0732 – 0.5648	2.54	<b>0.0110</b>
Number of psychiatric comorbidities at follow-up	0.3014	0.2441 – 0.3587	10.32	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.8278	0.6588 – 0.9970	9.6	<b>&lt;0.0001</b>
Baseline pill burden	0.0195	0.0059 – 0.0331	2.81	<b>0.0050</b>
Baseline all-cause inpatient visits <sup>a</sup>	0.5467	0.3257 – 0.7678	4.85	<b>&lt;0.0001</b>
Number of baseline all-cause outpatient visits	0.0025	-0.0042 – 0.0092	0.74	0.4610
Baseline total all-cause healthcare cost	0.0000	0.0000 – 0.0000	3.14	<b>0.0020</b>

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Significant at p<0.05 (in bold)

**H<sub>3K-L</sub>**: Patients with refractory epilepsy have a higher all-cause medical costs consisting of inpatient hospitalizations and ED visits at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.

**Rejected**

#### 4.4.4.2.2 All-Cause Outpatient Visit Cost

Wilcoxon signed-rank test and Generalized linear model was used to compare and determine differences in all-cause outpatient visit costs of patients with refractory and non-refractory epilepsy while controlling for covariates.

##### 4.4.4.2.2.1 All-Cause Outpatient Visit Cost (Unadjusted Analysis using Wilcoxon Signed-Rank Test)

Table 4.28 presents the cost of all-cause outpatient visits stratified by refractory and non-refractory status. Patients in the refractory group (\$9,891 [ $\pm$  \$18,044]) had significantly higher ( $p < 0.0001$ ) mean ( $\pm$  SD) cost of all-cause outpatient visits compared to patients in the non-refractory group (\$9,459 [ $\pm$  \$18,559]). A similar trend in the cost of all-cause outpatient visits was observed in the first year of follow-up (Appendix VIB).

**Table 4.28: Comparison of Cost of All-Cause Outpatient Visits in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)**

	All n=5,596	Refractory n=2,798	Non-refractory n=2,798	p-value
<b>All-Cause Outpatient Visit Cost</b>				
Median (Mean $\pm$ SD)	\$4,201 (\$9,675 $\pm$ \$18,303)	\$4,711 (\$9,891 $\pm$ \$18,044)	\$3,644 (\$9,459 $\pm$ \$18,559)	<b>&lt;0.0001<sup>a</sup></b>

<sup>a</sup>Wilcoxon signed-rank test  
Significant at  $p < 0.05$  (in bold)

#### **4.4.4.2.2.2 All-Cause Outpatient Visit Cost (Adjusted Analysis using Generalized Linear Model)**

Table 4.29 presents the results of the generalized linear model with gamma distribution and log-link function comparing the cost of all-cause outpatient visits in the second-year of follow-up by refractory and non-refractory groups while controlling for covariates. Results of the model indicated that the cost of all-cause outpatient visits of patients in the refractory group was 1.1 times [ $\exp(0.0906)$ ] significantly higher (95% CI=1.015-1.181;  $p=0.0190$ ) than the cost of all-cause outpatient visits of patients in the non-refractory group, after controlling for covariates. Regarding covariates, African American and other race, baseline CCI of 1 and greater than 1, increasing number of psychiatric comorbidities, one or more non-psychiatric comorbidities at follow-up, increasing baseline outpatient visits, and increasing baseline total cost were associated with a significantly higher ( $p<0.05$ ) cost of all-cause outpatient visits. In contrast, index AED with multiple actions was associated with a significantly lower ( $p<0.05$ ) cost of all-cause outpatient visits. Similarly, in the first-year of follow-up the cost of all-cause outpatient visits of patients in the refractory group was significantly higher ( $p<0.05$ ) than the cost of all-cause outpatient visits of patients in the non-refractory group, after controlling for covariates (Appendix VIB).

**Table 4.29: Generalized Linear Model Comparing the Cost of All-Cause Outpatient in the Second Year of Follow-Up among Refractory/Non-Refractory Patients (N=5,596)**

	Estimate	95% CI	z	p-value
Refractory <sup>a</sup>	0.0906	0.0150 – 0.1662	2.35	<b>0.0190</b>
Age at index	-0.0007	-0.0034 – 0.0023	-0.47	0.6350
Male <sup>a</sup>	-0.0480	-0.1237 – 0.0278	-1.24	0.2150
African American race <sup>a</sup>	0.1833	0.0798 – 0.2869	3.47	<b>0.0010</b>
Other race <sup>a</sup>	0.0877	0.0059 – 0.1695	2.1	<b>0.0360</b>
Partial type of epilepsy at first visit <sup>a</sup>	-0.0689	-0.2386 – 0.1008	-0.8	0.4260
Other type of epilepsy at first visit <sup>a</sup>	0.0335	-0.0825 – 0.1494	0.57	0.5710
Multiple actions of index AED <sup>a</sup>	-0.1143	-0.1914 – -0.0373	-2.91	<b>0.0040</b>
Baseline CCI of 1 <sup>a</sup>	0.2248	0.1237 – 0.3259	4.36	<b>&lt;0.0001</b>
Baseline CCI greater than 1 <sup>a</sup>	0.2214	0.1115 – 0.3314	3.95	<b>&lt;0.0001</b>
Number of psychiatric comorbidities at follow-up	0.0867	0.0602 – 0.1132	6.42	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.2854	0.2071 – 0.3637	7.14	<b>&lt;0.0001</b>
Baseline pill burden	-0.0013	-0.0073 – 0.0047	-0.41	0.6830
Baseline all-cause inpatient visits <sup>a</sup>	-0.0367	-0.1372 – 0.0638	-0.72	0.4740
Number of baseline all-cause outpatient visits	0.0226	0.0187 – 0.0266	11.27	<b>&lt;0.0001</b>
Baseline total all-cause healthcare cost	0.0000	0.0000 – 0.0000	9.72	<b>&lt;0.0001</b>

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Significant at p<0.05 (in bold)

**H<sub>3M</sub>**: Patients with refractory epilepsy have a higher all-cause medical costs consisting of outpatient visits (**H<sub>3M</sub>**) at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.

**Failed to reject**

#### 4.4.4.2.3 Epilepsy-Related Inpatient Hospitalization and ED Visit Cost

Of the 5,596 patients, the median cost of epilepsy-related inpatient hospitalization and epilepsy-related ED visit was \$0 in the second year of follow-up. For the present study, cost of epilepsy-related inpatient hospitalization and ED visits were combined to compare and determine differences in patients with refractory and non-refractory epilepsy while controlling for covariates.

##### 4.4.4.2.3.1 Epilepsy-Related Inpatient Hospitalization and ED Visit Cost (Unadjusted Analysis using Wilcoxon Signed-Rank Test)

Table 4.30 presents the cost of epilepsy-related inpatient hospitalization and ED visits stratified by refractory and non-refractory status. Patients in the refractory group (\$1,443 [ $\pm$  \$4,558]) had significantly higher ( $p < 0.0001$ ) mean ( $\pm$  SD) cost of epilepsy-related inpatient hospitalization and ED visits compared to patients in the non-refractory group (\$872 [ $\pm$  \$4,069]). Although the mean ( $\pm$  SD) costs were higher than second year of follow-up, a similar trend in the cost of epilepsy-related inpatient hospitalization and ED visits was observed in the first year of follow-up (Appendix VIC).

**Table 4.30: Comparison of Cost of Epilepsy-Related Inpatient Hospitalization and ED Visits in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)**

	All n=5,596	Refractory n=2,798	Non-refractory n=2,798	p-value
<b>Epilepsy-Related Inpatient Hospitalization and ED Visit Cost</b>				
Median (Mean $\pm$ SD)	\$0 (\$1,158 $\pm$ \$4,329)	\$0 (\$1,443 $\pm$ \$4,558)	\$0 (\$872 $\pm$ \$4,069)	<b>&lt;0.0001<sup>a</sup></b>

<sup>a</sup>Wilcoxon signed-rank test; Significant at  $p < 0.05$  (in bold)

#### **4.4.4.2.3.2 Epilepsy-Related Inpatient Hospitalization and ED Visit Cost (Adjusted Analysis using Generalized Linear Model)**

Table 4.31 presents the results of the generalized linear model with gamma distribution and log-link function comparing the cost of epilepsy-related inpatient hospitalization and ED visits in the second-year of follow-up by refractory and non-refractory groups while controlling for covariates. Results of the model indicated that the cost of epilepsy-related inpatient hospitalization and ED visits of patients in the refractory group was 1.5 times [ $\exp(0.3991)$ ] significantly higher (95% CI=1.215-1.828;  $p<0.0001$ ) than the cost of epilepsy-related inpatient hospitalization and ED visits of patients in the non-refractory group, after controlling for covariates. Regarding covariates, other race, increasing number of psychiatric comorbidities, one or more non-psychiatric comorbidities at follow-up, and one or more baseline inpatient visit were associated with a significantly higher ( $p<0.05$ ) cost of epilepsy-related inpatient hospitalization and ED visits. Similarly, in the first-year of follow-up the cost of epilepsy-related inpatient hospitalization and ED visits of patients in the refractory group was significantly higher ( $p<0.05$ ) than the cost of epilepsy-related inpatient hospitalization and ED visits of patients in the non-refractory group, after controlling for covariates (Appendix VIC).

**Table 4.31: Generalized Linear Model Comparing the Cost of Epilepsy-Related Inpatient Hospitalization and ED Visits in the Second Year of Follow-Up among Refractory/Non-Refractory Patients (N=5,596)**

	Estimate	95% CI	z	p-value
Refractory <sup>a</sup>	0.3991	0.1949 – 0.6032	3.83	<b>&lt;0.0001</b>
Age at index	-0.0022	-0.0106 – 0.0063	-0.50	0.6160
Male <sup>a</sup>	-0.0259	-0.2371 – 0.1853	-0.24	0.8100
African American race <sup>a</sup>	0.2500	-0.0332 – 0.5332	1.73	0.0840
Other race <sup>a</sup>	0.3195	0.0934 – 0.5457	2.77	<b>0.0060</b>
Partial type of epilepsy at first visit <sup>a</sup>	0.3617	-0.1033 – 0.8268	1.52	0.1270
Other type of epilepsy at first visit <sup>a</sup>	-0.2747	-0.5960 – 0.04662	-1.68	0.0940
Multiple actions of index AED <sup>a</sup>	0.0178	-0.1943 – 0.2300	0.16	0.8690
Baseline CCI of 1 <sup>a</sup>	0.2273	-0.0462 – 0.5009	1.63	0.1030
Baseline CCI greater than 1 <sup>a</sup>	0.1821	-0.1140 – 0.4782	1.21	0.2280
Number of psychiatric comorbidities at follow-up	0.3041	0.2320 – 0.3762	8.26	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.6966	0.4895 – 0.9037	6.59	<b>&lt;0.0001</b>
Baseline pill burden	-0.0047	-0.0212 – 0.0118	-0.56	0.5790
Baseline all-cause inpatient visits <sup>a</sup>	0.7588	0.4809 – 1.0368	5.35	<b>&lt;0.0001</b>
Number of baseline all-cause outpatient visits	-0.0039	-0.0123 – 0.0046	-0.90	0.3680
Baseline total all-cause healthcare cost	0.0000	-0.0000 – 0.0000	0.79	0.4270

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Significant at p<0.05 (in bold)

**H<sub>3N-O</sub>:** Patients with refractory epilepsy have a higher all-cause medical costs consisting of epilepsy-related inpatient hospitalizations and ED visits at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.

**Failed to reject**

#### 4.4.4.2.4 Epilepsy-Related Outpatient Visit Cost

Wilcoxon signed-rank test and Generalized linear model was used to compare and determine differences in epilepsy-related outpatient visit costs of patients with refractory and non-refractory epilepsy while controlling for covariates.

##### 4.4.4.2.4.1 Epilepsy-Related Outpatient Visit Cost (Unadjusted Analysis using Wilcoxon Signed-Rank Test)

Table 4.32 presents the cost of epilepsy-related outpatient visits stratified by refractory and non-refractory status. Patients in the refractory group (\$1,767 [ $\pm$  \$5,111]) had significantly higher ( $p < 0.0001$ ) mean ( $\pm$  SD) cost of epilepsy-related outpatient visits compared to patients in the non-refractory group (\$1,195 [ $\pm$  \$4,415]). Although the mean ( $\pm$  SD) and median costs were higher than second year of follow-up, a similar trend in the cost of epilepsy-related outpatient visits was observed in the first year of follow-up (Appendix VID).

**Table 4.32: Comparison of Cost of Epilepsy-Related Outpatient Visits in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)**

	All n=5,596	Refractory n=2,798	Non-refractory n=2,798	p-value
<b>Epilepsy-Related Outpatient Visit Cost</b>				
Median (Mean $\pm$ SD)	\$436 (\$1,481 $\pm$ \$4,784)	\$612 (\$1,767 $\pm$ \$5,111)	\$313 (\$1,195 $\pm$ \$4,415)	<b>&lt;0.0001<sup>a</sup></b>

<sup>a</sup>Wilcoxon signed-rank test  
Significant at  $p < 0.05$  (in bold)

#### **4.4.4.2.4.2 Epilepsy-Related Outpatient Visit Cost (Adjusted Analysis using Generalized Linear Model)**

Table 4.33 presents the results of the generalized linear model with gamma distribution and log-link function comparing the cost of epilepsy-related outpatient visits in the second-year of follow-up by refractory and non-refractory groups while controlling for covariates. Results of the model indicated that the cost of epilepsy-related outpatient visits of patients in the refractory group was 1.5 times [ $\exp(0.4010)$ ] significantly higher (95% CI=1.312-1.699;  $p<0.0001$ ) than the cost of epilepsy-related outpatient visits of patients in the non-refractory group, after controlling for covariates. Regarding covariates, African American race, increasing number of psychiatric comorbidities, one or more non-psychiatric comorbidities at follow-up, increasing baseline outpatient visits, and increasing baseline total cost were associated with a significantly higher ( $p<0.05$ ) cost of epilepsy-related outpatient visits. In contrast, increasing age and increasing pill burden were associated with a significantly lower ( $p<0.05$ ) cost of epilepsy-related outpatient visits. Similarly, in the first-year of follow-up the cost of epilepsy-related outpatient visits of patients in the refractory group was significantly higher ( $p<0.05$ ) than the cost of epilepsy-related outpatient visits of patients in the non-refractory group, after controlling for covariates (Appendix VID).

**Table 4.33: Comparison of Cost of Epilepsy-Related Outpatient Visits in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)**

	Estimate	95% CI	z	p-value
Refractory <sup>a</sup>	0.4010	0.2717 – 0.5303	6.08	<b>&lt;0.0001</b>
Age at index	-0.0091	-0.0144 - -0.0038	-3.36	<b>0.0010</b>
Male <sup>a</sup>	-0.0172	-0.1464 – 0.1120	-0.26	0.7940
African American race <sup>a</sup>	0.1932	0.01556 – 0.3708	2.13	<b>0.0330</b>
Other race <sup>a</sup>	0.0354	-0.1051 – 0.17585	0.49	0.6220
Partial type of epilepsy at first visit <sup>a</sup>	-0.0836	-0.3750 – 0.2078	-0.56	0.5740
Other type of epilepsy at first visit <sup>a</sup>	-0.1386	-0.3365 – 0.05937	-1.37	0.1700
Multiple actions of index AED <sup>a</sup>	-0.1107	-0.2423 – 0.0210	-1.65	0.1000
Baseline CCI of 1 <sup>a</sup>	0.0528	-0.1228 – 0.2283	0.59	0.5560
Baseline CCI greater than 1 <sup>a</sup>	-0.1269	-0.3171 – 0.0634	-1.31	0.1910
Number of psychiatric comorbidities at follow-up	0.1098	0.0652 – 0.1543	4.83	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.3424	0.2111 – 0.4738	5.11	<b>&lt;0.0001</b>
Baseline pill burden	-0.0196	-0.0301 - -0.0091	-3.65	<b>&lt;0.0001</b>
Baseline all-cause inpatient visits <sup>a</sup>	-0.1432	-0.3129 – 0.0266	-1.65	0.0980
Number of baseline all-cause outpatient visits	0.0146	0.0082 – 0.0209	4.5	<b>&lt;0.0001</b>
Baseline total all-cause healthcare cost	0.0000	0.0000 – 0.0000	5.47	<b>&lt;0.0001</b>

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Significant at p<0.05 (in bold)

**H<sub>3P</sub>**: Patients with refractory epilepsy have a higher epilepsy-related medical costs consisting of outpatient visits (**H<sub>3P</sub>**) at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.

**Failed to reject**

#### 4.4.4.2.5 All-Cause Pharmacy Cost

Wilcoxon signed-rank test and Generalized linear model was used to compare and determine differences in all-cause pharmacy costs of patients with refractory and non-refractory epilepsy while controlling for covariates.

##### 4.4.4.2.5.1 All-Cause Pharmacy Cost (Unadjusted Analysis using Wilcoxon Signed-Rank Test)

Table 4.34 presents the cost of all-cause pharmacy stratified by refractory and non-refractory status. Patients in the refractory group (\$9,764 [ $\pm$  \$8,989]) had significantly higher ( $p < 0.0001$ ) mean ( $\pm$  SD) cost of all-cause pharmacy claims compared to patients in the non-refractory group (7,466 [ $\pm$  \$11,082]). Although the mean ( $\pm$  SD) and median costs were higher than second year of follow-up, a similar trend in the cost of all-cause pharmacy claims was observed in the first year of follow-up (Appendix VIE).

**Table 4.34: Comparison of Cost of All-Cause Pharmacy Claims in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)**

	All n=5,596	Refractory n=2,798	Non-refractory n=2,798	p-value
<b>All-Cause Pharmacy Cost</b>				
Median (Mean $\pm$ SD)	\$6,213 (\$8,615 $\pm$ \$10,154)	\$7,410 (\$9,764 $\pm$ \$8,989)	\$4,807 (\$7,466 $\pm$ \$11,082)	<b>&lt;0.0001<sup>a</sup></b>

<sup>a</sup>Wilcoxon signed-rank test  
Significant at  $p < 0.05$  (in bold)

#### **4.4.4.2.5.2 All-Cause Pharmacy Cost (Adjusted Analysis using Generalized Linear Model)**

Table 4.35 presents the results of the generalized linear model with gamma distribution and log-link function comparing the cost of all-cause pharmacy claims in the second-year of follow-up by refractory and non-refractory groups while controlling for covariates. Results of the model indicated that the cost of all-cause pharmacy claims of patients in the refractory group was 1.3 times [ $\exp(0.2958)$ ] significantly higher (95% CI=1.280-1.411;  $p<0.0001$ ) than the cost of all-cause pharmacy claims of patients in the non-refractory group, after controlling for covariates. Regarding covariates, male gender, partial type of epilepsy, index AED with multiple actions, baseline CCI of greater than 1, increasing number of psychiatric comorbidities, increasing baseline pill burden, and increasing baseline total cost were associated with a significantly higher ( $p<0.05$ ) cost of all-cause pharmacy claims. In contrast, increasing age, African Americana and other race, one or more baseline inpatient visits, and increasing baseline outpatient visits were associated with a significantly lower ( $p<0.05$ ) cost of all-cause pharmacy claims. Similarly, in the first-year of follow-up the cost of all-cause pharmacy claims of patients in the refractory group was significantly higher ( $p<0.05$ ) than the cost of all-cause pharmacy claims of patients in the non-refractory group, after controlling for covariates (Appendix VIE).

**Table 4.35: Comparison of Cost of All-Cause Pharmacy Claims in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)**

	<b>Estimate</b>	<b>95% CI</b>	<b>z</b>	<b>p-value</b>
Refractory <sup>a</sup>	0.2958	0.2471 – 0.3445	11.91	<b>&lt;0.0001</b>
Age at index	-0.0028	-0.0048 - -0.0007	-2.65	<b>0.0080</b>
Male <sup>a</sup>	0.0811	0.0317 – 0.1305	3.22	<b>0.0010</b>
African American race <sup>a</sup>	-0.1350	-0.2027 - -0.0674	-3.91	<b>&lt;0.0001</b>
Other race <sup>a</sup>	-0.1276	-0.1810 - -0.0741	-4.68	<b>&lt;0.0001</b>
Partial type of epilepsy at first visit <sup>a</sup>	0.1286	0.0177 – 0.2394	2.27	<b>0.0230</b>
Other type of epilepsy at first visit <sup>a</sup>	-0.0362	-0.1122 – 0.0398	-0.93	0.3500
Multiple actions of index AED <sup>a</sup>	0.1189	0.0690 – 0.1688	4.67	<b>&lt;0.0001</b>
Baseline CCI of 1 <sup>a</sup>	0.0107	-0.0561 – 0.0775	0.31	0.7530
Baseline CCI greater than 1 <sup>a</sup>	0.1090	0.0354 – 0.1826	2.90	<b>0.0040</b>
Number of psychiatric comorbidities at follow-up	0.1003	0.0828 – 0.1179	11.20	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	-0.0119	-0.0634 – 0.0397	-0.45	0.6510
Baseline pill burden	0.0449	0.0407 – 0.0490	21.00	<b>&lt;0.0001</b>
Baseline all-cause inpatient visits <sup>a</sup>	-0.1939	-0.2597 - -0.1281	-5.78	<b>&lt;0.0001</b>
Number of baseline all-cause outpatient visits	-0.0055	-0.0073 - -0.0036	-5.84	<b>&lt;0.0001</b>
Baseline total all-cause healthcare cost	0.0000	0.0000 – 0.0000	13.87	<b>&lt;0.0001</b>

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Significant at p<0.05 (in bold)

**H3Q:** Patients with refractory epilepsy have a higher cost of all-cause pharmacy claims at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.

**Failed to reject**

#### 4.4.4.2.6 Epilepsy-Related Pharmacy Cost

Wilcoxon signed-rank test and Generalized linear model was used to compare and determine differences in epilepsy-related pharmacy costs of patients with refractory and non-refractory epilepsy while controlling for covariates.

##### 4.4.4.2.6.1 Epilepsy-Related Pharmacy Cost (Unadjusted Analysis using Wilcoxon Signed-Rank Test)

Table 4.36 presents the cost of epilepsy-related pharmacy claims stratified by refractory and non-refractory status. Patients in the refractory group (\$4,478 [ $\pm$  \$5,971]) had significantly higher ( $p < 0.0001$ ) mean ( $\pm$  SD) cost of epilepsy-related pharmacy claims compared to patients in the non-refractory group (\$1,767 [ $\pm$  \$2,835]). Although the mean ( $\pm$  SD) and median costs were higher than second year of follow-up, a similar trend in the cost of epilepsy-related pharmacy claims was observed in the first year of follow-up (Appendix VIF).

**Table 4.36: Comparison of Cost of Epilepsy-Related Pharmacy Claims in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)**

	All n=5,596	Refractory n=2,798	Non-refractory n=2,798	p-value
<b>Epilepsy-Related Pharmacy Cost</b>				
Median (Mean $\pm$ SD)	\$1,532 (\$3,122 $\pm$ \$4,866)	\$2,775 (\$4,478 $\pm$ \$5,971)	\$803 (\$1,767 $\pm$ \$2,835)	<b>&lt;0.0001<sup>a</sup></b>

<sup>a</sup>Wilcoxon signed-rank test  
Significant at  $p < 0.05$  (in bold)

#### **4.4.4.2.6.2 Epilepsy-Related Pharmacy Cost (Adjusted Analysis using Generalized Linear Model)**

Table 4.37 presents the results of the generalized linear model with gamma distribution and log-link function comparing the cost of epilepsy-related pharmacy claims in the second-year of follow-up by refractory and non-refractory groups while controlling for covariates. Results of the model indicated that the cost of epilepsy-related pharmacy claims of patients in the refractory group was 2.5 times [ $\exp(0.9038)$ ] significantly higher (95% CI=2.308-2.641;  $p<0.0001$ ) than the cost of epilepsy-related pharmacy claims of patients in the non-refractory group, after controlling for covariates. Regarding covariates, partial type of epilepsy, index AED with multiple actions, increasing pill burden, and increasing baseline total cost were associated with a significantly higher ( $p<0.05$ ) cost of epilepsy-related pharmacy visits. In contrast, increasing age, African Americans and other race, other type of epilepsy, baseline CCI of 1 and greater than 1, increasing number of psychiatric comorbidities, one or more baseline inpatient visits, and increasing baseline outpatient visits were associated with a significantly lower ( $p<0.05$ ) cost of epilepsy-related pharmacy claims. Similarly, in the first-year of follow-up the cost of epilepsy-related pharmacy claims of patients in the refractory group was significantly higher ( $p<0.05$ ) than the cost of epilepsy-related pharmacy claims of patients in the non-refractory group, after controlling for covariates (Appendix VIF).

**Table 4.37: Comparison of Cost of Epilepsy-Related Pharmacy Claims in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)**

	Estimate	95% CI	z	p-value
Refractory <sup>a</sup>	0.9038	0.8364 – 0.9711	26.30	< <b>0.0001</b>
Age at index	-0.0194	-0.0222 - -0.0166	-13.42	< <b>0.0001</b>
Male <sup>a</sup>	0.0151	-0.0534 – 0.0836	0.43	0.6660
African American race <sup>a</sup>	-0.2212	-0.3144 - -0.1280	-4.65	< <b>0.0001</b>
Other race <sup>a</sup>	-0.0678	-0.1417 – 0.0061	-1.80	0.0720
Partial type of epilepsy at first visit <sup>a</sup>	0.2035	0.0504 – 0.3566	2.61	<b>0.0090</b>
Other type of epilepsy at first visit <sup>a</sup>	-0.1796	-0.2848 - -0.0745	-3.35	<b>0.0010</b>
Multiple actions of index AED <sup>a</sup>	0.2648	0.1963 – 0.3332	7.58	< <b>0.0001</b>
Baseline CCI of 1 <sup>a</sup>	-0.1999	-0.2929 - -0.1069	-4.21	< <b>0.0001</b>
Baseline CCI greater than 1 <sup>a</sup>	-0.2213	-0.3236 - -0.1189	-4.24	< <b>0.0001</b>
Number of psychiatric comorbidities at follow-up	-0.0929	-0.1174 - -0.0684	-7.44	< <b>0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	-0.0403	-0.1118 – 0.0312	-1.10	0.2700
Baseline pill burden	0.0147	0.0088 – 0.0207	4.85	< <b>0.0001</b>
Baseline all-cause inpatient visits <sup>a</sup>	-0.1871	-0.2784 - -0.0958	-4.02	< <b>0.0001</b>
Number of baseline all-cause outpatient visits	-0.0032	-0.0059 - -0.0005	-2.36	<b>0.0180</b>
Baseline total all-cause healthcare cost	0.0000	0.0000 – 0.0000	6.21	< <b>0.0001</b>

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Significant at p<0.05 (in bold)

**H<sub>3R</sub>**: Patients with refractory epilepsy have a higher cost of epilepsy-related pharmacy claims at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.

### Failed to reject

Table 4.38 presents a summary of the results for hypotheses testing for the present study.

**Table 4.38: Summary of Hypotheses Testing Results**

<b>Hypothesis</b>	<b>Hypothesis Statement</b>	<b>Result</b>
<b>Objective 1: To compare the demographic and clinical characteristics of patients with refractory and non-refractory epilepsy (Matched).</b>		
H <sub>01A</sub>	There is no significant difference in the mean age of patients between the refractory and non-refractory groups.	Failed to reject
H <sub>01B</sub>	The proportion of gender categories does not differ between the refractory and non-refractory groups.	Failed to reject
H <sub>01C</sub>	The proportion of race/ethnicity categories does not differ between the refractory and non-refractory groups.	Rejected
H <sub>01D</sub>	The proportion of epilepsy type categories does not differ between the refractory and non-refractory groups.	Rejected
H <sub>01E</sub>	There is no significant difference in the comorbidity burden of patients between the refractory and non-refractory groups.	Failed to reject
H <sub>01F</sub>	The proportion of the AED type categories does not differ between the refractory and non-refractory groups.	Rejected
H <sub>01G</sub>	There is no significant difference in the pill burden of patients between the refractory and non-refractory groups.	Failed to reject
<b>Objective 2: To compare the treatment patterns of patients with refractory and non-refractory epilepsy while controlling for covariates (Matched).</b>		
H <sub>2A</sub>	Patients with refractory epilepsy are less likely to be adherent to AEDs as compared to patients with non-refractory epilepsy, while controlling for covariates.	Rejected
H <sub>2B</sub>	Patients with refractory epilepsy are less likely to be persistent (i.e., duration of medication use) to AEDs as compared to patients with non-refractory epilepsy, while controlling for covariates.	Rejected
H <sub>2C</sub> (≥2 AEDs)	Patients with refractory epilepsy are more likely to add an alternative AED as compared to patients with non-refractory epilepsy.	Failed to reject
H <sub>2D</sub> (≥2 AEDs)	Patients with refractory epilepsy are more likely to switch to an alternative AED as compared to patients with non-refractory epilepsy.	Failed to reject

**Table 4.38: Summary of Hypotheses Testing Results (Continued)**

Hypothesis	Hypothesis Statement	Result
<b>Objective 3: To compare the all-cause and epilepsy-related healthcare utilization and costs between refractory and non-refractory patients while controlling for covariates (Matched).</b>		
H <sub>3A-B</sub>	Patients with refractory epilepsy have a higher number of all-cause medical visits consisting of inpatient hospitalizations and ED visits at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates. Note: Two-part ZIP model used	Failed to reject for zero vs. non-zero (dichotomous)
		Rejected for all values > 0
H <sub>3C</sub>	Patients with refractory epilepsy have a higher number of all-cause medical visits consisting of outpatient visits at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates. Note: Two-part ZIP model used	Rejected for zero vs. non-zero (dichotomous)
		Failed to reject for all values > 0
H <sub>3D-E</sub>	Patients with refractory epilepsy have a higher number of epilepsy-related medical visits consisting of inpatient hospitalization and ED visits at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.	Failed to reject
H <sub>3F</sub>	Patients with refractory epilepsy have a higher number of epilepsy-related medical visits consisting of outpatient visits at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.	Failed to reject
H <sub>3G</sub>	Patients with refractory epilepsy have longer lengths of stay for all-cause hospitalization as compared to patients with non-refractory epilepsy, while controlling for covariates.	Not evaluated
H <sub>3H</sub>	Patients with refractory epilepsy have longer lengths of stay for epilepsy-related hospitalization as compared to patients with non-refractory epilepsy, while controlling for covariates.	Not evaluated
H <sub>3I</sub>	Patients with refractory epilepsy have a higher number of all-cause pharmacy claims as compared to patients with non-refractory epilepsy, while controlling for covariates.	Failed to reject
H <sub>3J</sub>	Patients with refractory epilepsy have a higher number of epilepsy-related pharmacy claims as compared to patients with non-refractory epilepsy, while controlling for covariates.	Failed to reject
H <sub>3K-L</sub>	Patients with refractory epilepsy have a higher all-cause medical costs consisting of inpatient hospitalizations and ED visits at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.	Rejected

**Table 4.38: Summary of Hypotheses Testing Results (Continued)**

<b>Hypothesis</b>	<b>Hypothesis Statement</b>	<b>Result</b>
H <sub>3M</sub>	Patients with refractory epilepsy have a higher all-cause medical costs consisting of outpatient visits at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.	Failed to reject
H <sub>3N-O</sub>	Patients with refractory epilepsy have a higher all-cause medical costs consisting of epilepsy-related inpatient hospitalizations and ED visits at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.	Failed to reject
H <sub>3P</sub>	Patients with refractory epilepsy have a higher epilepsy-related medical costs consisting of outpatient visits at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.	Failed to reject
H <sub>3Q</sub>	Patients with refractory epilepsy have a higher cost of all-cause pharmacy claims at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.	Failed to reject
H <sub>3R</sub>	Patients with refractory epilepsy have a higher cost of epilepsy-related pharmacy claims at follow-up as compared to patients with non-refractory epilepsy, while controlling for covariates.	Failed to reject

## **Chapter 5 Discussion**

### **Chapter Overview**

This chapter includes a review of the study purpose followed by a discussion of the results by study objectives and possible explanations for study findings. This chapter concludes with study limitations and recommendations for future research.

### **5.1 Study Purpose**

The purpose of the study was to characterize the demographic and clinical characteristics, treatment patterns, and healthcare utilization and costs associated with patients with refractory epilepsy and compare these characteristics to patients with non-refractory epilepsy. Treatment patterns included medication adherence, persistence, addition and switch to an alternative AED. Healthcare utilization and costs included number of all-cause and epilepsy-related services and costs associated with medical visits and pharmacy claims. The study used Texas Medicaid claims data from September 01, 2007 through December 31, 2013. The results of the study are discussed in the subsequent section in accordance with the study objectives.

## 5.2 Study Characteristics

The mean ( $\pm$  SD) age of the epileptic patients in this study was 38.7 ( $\pm$  13.2), the proportion of females was 51.6%, and the proportion of Caucasians was 40.2%. The majority (79.8%) of patients had an epilepsy diagnosis classified as other convulsions (ICD-9-CM code: 780.39) at the first visit, and were initiated on (i.e., at index date) sodium channel blockers (40.5%). The highest proportion of patients were on one AED (38.5%), followed by patients on two AEDs (35.0%), and patients on three or more AEDs (26.5%) in the first year of follow-up (i.e., one-year identification period). Also, the majority of patients were on monotherapy (82.7%) on the index date (i.e., date of the first AED use). Personality disorder (46.1%) was the most common psychiatric comorbidity found in the patients in the second-year of follow-up, followed by depression (34.3%), mental retardation (30.2%), psychosis (26.6%), and anxiety (26.5%). The present study also found a higher prevalence of stroke (14.8%), followed by migraine (10.2%), sprain (9.3%), and open wounds (9.1%) at follow-up. At baseline, the patients had a mean ( $\pm$  SD) pill burden of 7.8 ( $\pm$ 13.7) pills and mean ( $\pm$  SD) number of all-cause outpatient visits of 14.2  $\pm$  (14.9) visits. Also, 19.1% of the patients had one or more all-cause inpatient visits at baseline in the study cohort. These characteristics are similar to previous studies on epilepsy conducted using Medicaid data.<sup>29,134</sup> These inherent characteristics are not surprising as Medicaid includes a significant proportion of patients with a physical or mental disability.<sup>13</sup> Psychiatric and non-psychiatric comorbidities have been commonly cited in literature among patients with epilepsy. These disorders further complicate the management of patients with epilepsy and reduce the quality of life of the patients.<sup>111,112,115,116</sup>

## 5.3 Study Objectives

### 5.3.1 Objective 1: Demographic and Clinical Characteristics

Objective 1 consisted of comparing the demographic and clinical characteristics of patients with refractory and non-refractory epilepsy. The present study identified 26.5% of the patients as refractory, which is within the range reported by previous prospective and retrospective studies (1.7% to 33.0%) using several working definitions to characterize refractoriness.<sup>10,11,13,19,74,75</sup> At baseline, the refractory and non-refractory patients differed in the demographic characteristics of age, gender, and race/ethnicity, in the clinical characteristics of epilepsy type, AED type, comorbidity, and pill burden, and in the all-cause healthcare utilization and cost parameters of inpatient visits, outpatient visits, and total healthcare costs. This necessitated the use of propensity score matching procedure to minimize bias at baseline. After matching, the refractory and non-refractory groups were balanced on the majority of covariates.

Patients with refractory epilepsy had a mean ( $\pm$  SD) age of 38.0 ( $\pm$  13.7) and were comprised of a higher proportion of females (55.3%), both of which are within the range of values reported by previous studies.<sup>10,11,13</sup> Previous studies using retrospective administrative databases to evaluate refractory epilepsy among adults in the U.S. reported the range of mean ( $\pm$  SD) age from 32.8 ( $\pm$  18.4) to 41.8 ( $\pm$  13.7) and the proportion of females between 50.7% and 60.5%.<sup>11,13,18</sup> Regarding race/ethnicity, the matched cohort in the present study consisted of 41.9% patients who were Caucasian, 32.4% who were Hispanic, and 18.4% who were African American. Faught et al. reported the prevalence of Caucasians to be 53.5% and African Americans to be 20.9% among patients with epilepsy enrolled in the Florida, New Jersey, and Iowa Medicaid programs.<sup>29</sup> The high proportion of Hispanics found in the present study was expected as Hispanics account for a

significant proportion (63%) of the non-elderly Texas Medicaid population.<sup>121</sup> In the present study, patients with refractory epilepsy had a lower proportion of African Americans (15.9% vs. 20.9%) and higher proportion of Hispanics (34.3% vs. 30.5%) compared to patients with non-refractory epilepsy. Under-reporting of the condition among African Americans may be a possible explanation for the slightly lower proportion of African Americans with refractory epilepsy.<sup>81,135</sup>

Regarding clinical characteristics, the matched cohort consisted of a high proportion of patients with other convulsions (77.2%) at first visit for both groups. A possible explanation may be that the first seizure (i.e., epilepsy diagnosis) observed in the study period was a single/isolated event that needed additional diagnostic work-up for the characterization of the seizure etiology.<sup>136</sup> Also, patients with refractory epilepsy consisted of a lower proportion of patients with generalized epilepsy (10.7% vs. 12.7%) compared to patients with non-refractory epilepsy. Earlier studies evaluating the impact of the type of seizure on patient outcomes have shown a high probability of achieving remission in patients with generalized epilepsy.<sup>82,83</sup> This may explain the lower proportion of generalized epilepsy among patients with refractory epilepsy in the current study. In terms of AED use, a higher proportion of patients with refractory epilepsy were initiated on more than one type of AED (i.e., combination AEDs; 26.5% vs. 10.7%), followed by GABA analogues (12.0% vs. 10.2%), and calcium channel action agents (7.7% vs. 3.4%) compared to patients with non-refractory epilepsy. The high proportion of combination AEDs was expected among patients with refractory epilepsy due to the uncontrolled nature of the condition. Also, GABA analogues such as benzodiazepines are usually given as first-line treatment for breakthrough seizures and for status epilepticus in patients with refractory epilepsy.<sup>137</sup> Conversely, in the present study a lower proportion of patients with refractory epilepsy were initiated on sodium channel blockers (27.6% vs. 43.2%), followed by multiple action agents (18.3% vs. 22.7%), and synaptic vesicle protein

2A binding agents (7.8% vs. 9.8%). First generation sodium channel blockers such as carbamazepine and phenytoin are among the earliest and most efficacious drugs used as monotherapy in patients with epilepsy and thus may be used more commonly in patients with a stable form of epilepsy (i.e., non-refractory epilepsy).<sup>138</sup> Also, phenytoin is typically not used as a monotherapy, but more often used as a rescue AED in combination therapy along with a chronic AED in patients with uncontrolled seizures, which may be a possible explanation for its lower use in patients with refractory epilepsy in the present study.<sup>32</sup>

The mean ( $\pm$  SD) CCI of the patients with refractory epilepsy in the present study was 0.8 ( $\pm$  1.4), which is consistent with the range of 0.7 ( $\pm$  1.5) to 1.1 ( $\pm$  1.8) reported by previous studies.<sup>10,11,13</sup> At follow-up, patients with refractory epilepsy had a higher mean ( $\pm$  SD) (2.1 [ $\pm$  1.5] vs. 1.8 [ $\pm$  1.4]) number of psychiatric comorbidities and a higher proportion (51.3% vs. 41.4%) of patients with one or more non-psychiatric comorbidity. Also, the median baseline all-cause total healthcare cost of the patients with refractory epilepsy was higher (\$7,778 vs. \$6,216) than patients with non-refractory epilepsy. These results are consistent with what was expected given the severe nature of refractory epilepsy and the resources used in the management of the condition.

### **5.3.2 Objective 2: Treatment Patterns**

Objective 2 was comprised a comparison of treatment patterns of patients with refractory and non-refractory epilepsy.

The present study used the PDC method to measure medication adherence to AED monotherapy. The matched cohort had a mean ( $\pm$  SD) adherence of 82.8% ( $\pm$  23.4%) and 74.3% of the patients were adherent to AEDs. Overall adherence found in the present study was

comparable to previous studies assessing adherence in patients with epilepsy. Previous studies of patients with epilepsy reported a mean ( $\pm$  SD) adherence of 78.0 (SD not reported) to 90.3 ( $\pm$  13.0) and 50% to 74% were adherent using a threshold of 0.8 or more to describe dichotomous adherence.<sup>29,102,103,105,106</sup> Another finding was that in the present study, mean ( $\pm$  SD) adherence of the patients with refractory epilepsy (88.6 [ $\pm$  19.1] vs. 77.0 [ $\pm$  25.8]) was higher than the patients with non-refractory epilepsy. Also, patients with refractory epilepsy were more likely to adhere to AEDs compared to patients with non-refractory epilepsy, after adjusting for covariates. This is contrary to what was expected as poor medication adherence has been purported to be a cause of refractoriness.<sup>107,109</sup> As a result, it was assumed that patients with refractory epilepsy would continue their non-adherent behavior. However, this turned out not to be the case. Thus, as the present study did not evaluate medication adherence prior to identification of refractoriness, these results highlight the medication adherence patterns after patients are identified as refractory. As refractory patients are, in general, sicker and may be more symptomatic compared to non-refractory patients, these patients may be less likely to omit taking medication(s). Nevertheless, among the refractory patients, the study used a liberal approach by evaluating adherence to AED monotherapy only. As a quarter (26.5%) of the refractory patients were initiated on polytherapy (i.e., on combination AEDs), adherence found in the study may have overestimated medication use behavior in those patients who were on multiple AEDs.

Among the non-refractory patients, about 40% of the patients were non-adherent to AED regimens. A clinical explanation for lower adherence among non-refractory patients could not be ascertained as suboptimal effectiveness, AED intolerance, psychological fear of AEDs, and frequency of seizures and remission periods could not be determined from the claims dataset. Perhaps, patients with non-refractory epilepsy had fewer or infrequent symptoms or seizures,

leading to a lack of perceived benefit of AED treatment and, as a result, the patients did not feel the need to adhere to their AED regimens. Nonetheless, the association between non-adherent behavior and increased risk of hospitalization and ED visits demonstrated by previous studies in patients with epilepsy suggest the need to improve the medication use behavior of these patients.<sup>102-104</sup> The study results also highlight that African Americans, patients with a high comorbidity burden (CCI), and patients who had one or more all-cause inpatient visits at baseline were less likely to adhere to AEDs. Disparities in access to healthcare among minorities such as African Americans have been previously depicted as an obstacle to medication adherence in patients with epilepsy.<sup>139</sup> Moreover, as the patients were of low socioeconomic status and may have lacked knowledge of the condition, there may be issues with health literacy. Clinicians need to be aware of these barriers and develop individualized patient plans to improve the adherence to AEDs in patients with epilepsy. In addition, high comorbidity burden and baseline all-cause inpatient visits may be indicative of disease severity and associated increase in drug therapies for treating comorbid conditions, thus increasing the regimen complexity, which may have negatively impacted the adherence to AEDs.

Similar to medication adherence, patients with refractory epilepsy (340.9 [ $\pm$  194.5]) had a higher mean ( $\pm$  SD) persistence compared to patients with non-refractory epilepsy (301.3 [ $\pm$  118.1]). Also, patients with refractory epilepsy were less likely to discontinue their AED regimens (i.e., more likely to persist to AEDs), after controlling for covariates. Perhaps, the symptomatic nature of refractoriness explaining the high medication adherence in patients with refractory epilepsy may also explain the high persistence observed in these patients. Likewise, the covariates of high comorbidity burden at baseline (CCI) and all-cause inpatient visit at baseline were found to be associated with a higher likelihood of discontinuation of the AED regimen (i.e., lower

persistence to AEDs). In addition, males had a lower likelihood of discontinuation (i.e., higher persistence to AEDs) compared to females. Chen et al. reported a lower prevalence of side effects attributable to AEDs in males compared to females, which may be a possible explanation for the lower discontinuation among males observed in the present study.<sup>140</sup>

Regarding addition of an alternative AED, the majority of patients with epilepsy (90.1%) on dual therapy or more added an alternative AED. Adding an alternative AED to the existing regimen may be suggestive of a lack of seizure control and a need of greater intensity of treatment in patients with epilepsy.<sup>11</sup> In contrast, a small proportion (19.6%) of the patients on dual therapy or more switched to an alternative AED and discontinued the existing regimen. Switching to an alternative AED may be suggestive of intolerance to the existing regimen leading to a change in the offending agent.<sup>11</sup> In clinical practice, maintaining monotherapy with the existing regimen or an alternative AED is the preferable treatment paradigm in patients with epilepsy due to better adherence; reduction in treatment complexity especially in patients receiving other non-AEDs; minimization of side-effects; and containment of treatment costs.<sup>97</sup> However, there may be high recurrence of seizures and associated high healthcare utilization due to AED switching as shown in previous studies. Thus, in clinical practice, if a patient is not responding to therapy, adding an AED is an alternative in patients with epilepsy, with the intent of tapering off the initial AED.<sup>21-24</sup> This may be a possible explanation for the high proportion of addition observed in the follow-up period of the present study. As, the process of tapering and switching to an alternative AED may take more than a year, it would be interesting to evaluate if a similar pattern of treatment exists with a longer follow-up period.

Another finding of the current study was that about three-fourths (76.4% and 79.1%, respectively) of the patients who changed their AED regimen (addition or switch) added an alternative AED and/or switched to an alternative AED of a different MOA than the existing regimen. Use of polytherapy consisting of AEDs with different MOAs may have greater benefits than the effects of individual drug when given alone, i.e., use of AEDs with different MOAs may have supra-additive therapeutic efficacy. This approach constitutes rational polytherapy in patients with epilepsy.<sup>20,25-27</sup> Yet, a lower proportion of patients with refractory epilepsy added and/or switched to an alternative AED of a different MOA compared to patients with non-refractory epilepsy. Though about one third (32.9%) of the refractory patients did not follow rational polytherapy, these patients may have tapered off their AED regimen at longer follow-up. In addition, perhaps, patients with refractory epilepsy may be less receptive to changes in chemical entity with a different MOA and less responsive or intolerant to a particular AED, thereby precluding use of AEDs based on the MOA. Nonetheless, the overall use of rational polytherapy by majority of patients with epilepsy (76.4% to 79.1%) in the present study is an indicator of good quality of care in patients enrolled in the Texas Medicaid program.

In the present study, compared to patients with non-refractory epilepsy (85.2%) a higher proportion of patients with refractory epilepsy (95.1%) added an alternative AED. Even after adjusting for covariates, patients with refractory epilepsy had a higher likelihood of adding an alternative AED compared to patients with non-refractory epilepsy. Though, patients on one AED were excluded, the inclusion of patients on three or more AEDs in the refractory group as opposed to patients with two AEDs in the non-refractory group, may have increased the likelihood of adding an alternative AED by patients with refractory epilepsy. Regarding covariates, not surprisingly, use of combination AEDs at index date was positively associated with addition of an alternative

AED. In contrast, patients who had higher comorbidity burden at baseline (measured using CCI) and at follow-up (psychiatric and non-psychiatric comorbidities) were less likely to add an alternative AED. As discussed previously, patients with higher comorbidity burden may have a high medication load associated with the comorbidity, which may make clinicians more prudent in adding medications. Medications used in the treatment of comorbid conditions may also exert anti-seizure effects (i.e., additive effect), thus complicating epilepsy management.<sup>141</sup> Likewise, AEDs may be associated with psychiatric adverse events such as psychosis and mania, and may be associated with detrimental effects on cognition functioning, motor speed, and attention, further complicating the management of epilepsy, especially among patients with psychiatric comorbidities.<sup>114,115</sup>

A similar trend was observed in the proportion of patients switching to an alternative AED; a higher proportion of patients with refractory epilepsy (28.7%) compared to patients with non-refractory epilepsy (10.6%) switched to an alternative AED. This relationship persisted even after adjusting for covariates. Patients with higher comorbidity burden at baseline (measured using CCI) and at follow-up (psychiatric and non-psychiatric comorbidities), and with a high pill burden at baseline were more likely to switch to an alternative AED. As discussed previously, managing medications may be complicated in patients with several comorbid conditions. As a result switching to an alternative AED, as opposed to adding an AED, may be an option to minimize pill burden and to prevent potential drug-drug interactions. Conversely, the covariates of increasing age, male gender, partial type of epilepsy, other convulsions, and AEDs with multiple actions were associated with a lower likelihood of switching in patients with epilepsy. Reasons for these associations are not very clear. However, associations between male gender and lower discontinuation (i.e., higher persistence) of AEDs found in the present study may explain the

association with lower switch rates and lower discontinuation of existing regimen in this group of patients. This result is consistent to a study by Cunnington et al. where patients with epilepsy reported a higher likelihood of regimen change among females compared to males.<sup>32</sup>

### **5.3.3 Objective 3: Healthcare Utilization and Cost**

Objective 3 compared healthcare utilization and cost between patients with refractory and non-refractory epilepsy. A higher proportion of patients with refractory epilepsy had at least one epilepsy-related inpatient hospitalization visit (19.5% vs. 11.8%) and at least one epilepsy-related ED visit (29.7% vs. 19.5%) compared to patients with non-refractory epilepsy. This finding was slightly higher than the proportions reported by Cramer et al. among privately insured patients. Cramer et al. reported the proportion of patients with refractory and non-refractory epilepsy with at least one epilepsy-related inpatient hospitalization visit to be 15.7% and 7.0%, respectively, and those with at least one epilepsy-related ED visit to be 21.2% and 12.0%, respectively.<sup>11</sup> A possible explanation may be due to the inherent differences in the patient populations. A higher proportion of patients in Medicaid may be more severe and have more physical or cognitive limitations, which may explain the higher number of visits in the present study.<sup>13</sup>

Furthermore, the combined mean ( $\pm$  SD) epilepsy-related inpatient hospitalization and ED visits of patients with refractory epilepsy (1.0 [ $\pm$  2.2] vs. 0.5 [ $\pm$  1.2]) was higher than that observed in patients with non-refractory epilepsy. Also, a higher proportion of patients with refractory epilepsy (39.3% vs. 26.5%) had at least one epilepsy-related inpatient hospitalization and ED visit compared to patients with non-refractory epilepsy, and this trend existed even after controlling for covariates. Also, African Americans, patients with higher comorbidity burden (psychiatric and non-psychiatric comorbidities) at follow-up, and with one or more all-cause inpatient visits at

baseline were associated with a higher number of epilepsy-related inpatient hospitalizations and ED visits. The negative association between African Americans and medication adherence and persistence found in the present study may explain the higher number of epilepsy-related inpatient hospitalizations and ED visits. Furthermore, other race, higher comorbidity burden, and baseline all-cause inpatient visits were associated with a higher cost of epilepsy-related inpatient hospitalizations and ED visits. Psychiatric and non-psychiatric comorbidities may be: a cause of seizures (e.g., stroke); a complication of having a seizure (e.g., fractures, sprains); or intensified by epilepsy (e.g., depression, anxiety). All of these may explain the positive association between comorbidity burden and epilepsy-related inpatient hospitalizations and ED visits and costs. Previous studies have reported that patients with comorbidities are more likely to have an inpatient admission and are more likely to be referred by epileptologists to inpatient settings for diagnostic evaluations of psychogenic non-epileptic events, thereby increasing the healthcare costs.<sup>117,118</sup> These results highlight the importance of better management of epilepsy and associated comorbidities, which may significantly decrease the utilization of healthcare resources by patients with epilepsy.

In the present study, mean ( $\pm$  SD) all-cause and epilepsy-related outpatient visits of patients with refractory epilepsy ( $40.4 \pm [37.1]$ ;  $8.1 \pm [11.6]$ ) was higher than visits among patients with non-refractory epilepsy ( $37.0 \pm [36.9]$ ;  $5.7 \pm [9.3]$ ) and was significantly higher even after controlling for covariates. Similar to inpatient hospitalization and ED visits, African American and other race/ethnicity, high comorbidity burden at baseline and follow-up, and increasing baseline all-cause outpatient visits were positively associated with increasing all-cause and epilepsy-related outpatient visits in patients with epilepsy. In addition, increasing baseline pill burden was positively associated with all-cause outpatient visits. Perhaps, high pill burden suggestive of higher

provider visits for comorbid conditions associated with epilepsy may have led to higher all-cause outpatient visits.

Regarding all-cause and epilepsy-related pharmacy claims (i.e., number of prescriptions), patients with refractory epilepsy (9.9 [ $\pm$  6.8]; 3.1 [ $\pm$  1.5]) had higher mean number of prescriptions compared to patients with non-refractory epilepsy (8.6 [ $\pm$  6.3]; 1.8 [ $\pm$  1.1]). Moreover, after adjusting for covariates, the all-cause and epilepsy-related pharmacy costs of patients with refractory epilepsy were 1.3 to 2.5 fold higher than the respective costs of patients with non-refractory epilepsy. Similar to medical visits and costs, the all-cause and epilepsy-related pharmacy claims were positively associated with increasing comorbidity burden at baseline and follow-up and increasing pill burden at baseline. Another notable finding is the negative association between other race/ethnicity and all-cause pharmacy visits and costs and epilepsy-related pharmacy costs in the present study.

Overall, in the present study (2013 dollars) the mean all-cause cost of medical visits and pharmacy claims for patients with refractory epilepsy was \$23,136 ( $\pm$  \$25,827) and for patients with non-refractory epilepsy was \$19,813 ( $\pm$  \$25,907). Also, the mean epilepsy-related cost of medical visits and pharmacy claims for patients with refractory epilepsy was \$7,811 ( $\pm$  \$10,084) and for patients with non-refractory epilepsy was \$3,893 ( $\pm$  \$7,047). These findings are similar to the cost estimates reported by Cramer et al. (2009 dollars) among privately insured patients. Cramer et al. estimated the mean all-cause cost of medical visits and pharmacy claims at \$23,238 ( $\pm$  42,894) for patients with refractory epilepsy and \$13,839 ( $\pm$  \$6,789) for patients with non-refractory epilepsy. Also, their study estimated the mean epilepsy-related cost of medical and pharmacy visits at \$12,399 ( $\pm$  \$25,773) for patients with refractory epilepsy and \$5,511 ( $\pm$  \$2647)

for patients with non-refractory epilepsy.<sup>11</sup> Similar estimates found in the present study (2013 dollars) suggest that the healthcare utilization and costs have remained unchanged after the introduction of newer AEDs in the U.S.

The cost estimates in the present study differ from the estimates reported by Manjunath et al. in a sample of Medicaid enrollees from the states of Florida, Iowa, Kansas, Missouri and New Jersey. The study estimated the mean all-cause cost of medical and pharmacy visits (2009 dollars) of refractory epilepsy at \$38,708 ( $\pm$ \$114,904) and of non-refractory epilepsy at \$29,635 ( $\pm$ \$105,644).<sup>13</sup> The state Medicaid program of Texas differs from the other states included by Manjunath et al. in the demographic characteristics of the populations served, services covered, and different structures of benefits and payments. The Medicaid program in the state of Texas has the highest proportion of Hispanics (63%).<sup>121</sup> Also, the study by Manjunath et al. used a restrictive identification criterion to define refractory epilepsy. The inclusion criterion required an epilepsy-related ED visit or hospitalization following two or more AED changes that restricted the study to patients with severe epilepsy.<sup>13</sup> This combination of the patient population served and the strict identification criteria may explain the higher cost estimates compared to the present study.

In summary, though all the individual cost categories were higher in patients with refractory epilepsy compared to patients with non-refractory epilepsy in the present study, the highest cost differences were found in epilepsy-related medical and pharmacy costs. Pharmacy costs of the patients with refractory epilepsy accounted for more than twice the costs of non-refractory patients, followed by differences in inpatient hospitalization and ED costs, and finally outpatient visit costs in comparison to patients with non-refractory epilepsy. Considerably higher cost of epilepsy-related prescriptions was anticipated, as patients with refractory epilepsy typically require multiple

AEDs to achieve satisfactory seizure control.<sup>10</sup> Also, use of urgent care for the treatment of breakthrough seizures and status epilepticus as well as surgical procedures may have increased the cost associated with hospitalization and ED visits.<sup>137</sup> Moreover, patients with refractory epilepsy may have had higher diagnostic work-up, which resulted in increased cost of outpatient visits. Another related finding was that epilepsy-related total costs were one-third of the all-cause total costs in patients with refractory epilepsy and 20% in patients with non-refractory epilepsy. This suggests the impact of comorbid conditions on the additional healthcare medical and pharmacy costs of patients with epilepsy. Thus, management of epilepsy extends beyond the control of seizures and encompasses improvement in overall burden of the disease.

## 5.4 Limitations

The present study has several limitations that must be noted when interpreting the results. First, confirmation of the onset of seizures could not be validated in the Texas Medicaid administrative and claims dataset, without access to laboratory or other diagnostic reports. The study used a combination of ICD-9-CM diagnoses codes and AED prescriptions to identify patients with epilepsy. This may have led to misclassification of the patients with epilepsy. A systematic review of studies assessing the validity of epilepsy algorithms in claims datasets reported that the best model to identify epilepsy cases was an algorithm that required an ICD-9-CM code in addition to a pharmacy fill for an AED. This model showed a positive predictive value of 83.9% and a sensitivity of 81.8%. Also, algorithms that had inpatient hospitalizations, had higher positive predictive values compared to those that relied only on outpatient visits.<sup>142</sup> Consequently, the present study used a more restrictive criterion for identifying outpatient visits that required patients to have two or more outpatient visits at least a month apart. This ensured that the outpatient visits were not to rule-out the diagnosis of epilepsy.<sup>11</sup> Moreover, the indication of each AED prescription could not be confirmed from the pharmacy claims. AEDs may have been used prophylactically for the treatment of neuropathic or chronic pain, fibromyalgia, bipolar disorder, migraine, stroke, trauma or brain tumor. However, based on clinical expert opinion, the present study required patients to have fills for AEDs for at least 90 days without a gap of more than 60 days to ensure use of AEDs in the treatment of epilepsy as opposed to their use in prophylaxis.

Second, as clinical determination of inefficacy or intolerance to AEDs to identify failure of AEDs could not be confirmed from medical charts, the definition of refractory epilepsy may

not be precise. The present study employed clinical expert opinion to identify patients with potential refractoriness. The study used an operational definition of the use of at least three AEDs in a one-year identification period. Using this definition, 26.5% of the patients with epilepsy were identified as refractory, which is within the range (1.7% to 33.0%) reported in the literature. Of the 26.5% of the patients with refractory epilepsy, 9% had partial seizures, which is similar to the prevalence of 11% for patients with refractory epilepsy reported by Chen et al. among commercially insured patients with partial epilepsy.<sup>10</sup> Although, Chen et al. used a similar operational definition to characterize refractoriness in patients with partial epilepsy, the study followed patients for a longer period of time (i.e., four years of data collection period), which may explain the slightly higher prevalence.

Third, the use of PDC to measure adherence, may not reflect actual adherence, as patients may not have taken the filled prescriptions. In addition, a hospitalization may have disrupted the continuity of prescription claims, underestimating the adherence and persistence patterns. Also, the study used a liberal approach by evaluating medication adherence to AED monotherapy only to account for the change in AED(s). This may have overestimated adherence and persistence patterns among the patients. Fourth, the study used a baseline period in which patients did not have an AED fill; however, this does not guarantee newly diagnosed epilepsy. Fifth, though propensity score matching was used to balance the refractory and non-refractory groups at baseline, there may be differences in matched cohorts due to unobservable clinical characteristics. Also, there were differences in race/ethnicity, type of epilepsy, and baseline all-cause total cost, even after matching. However, these differences were small and not practically significant. Sixth, the cost analyses were based on the costs to the Texas Medicaid program, which may not reflect the actual cost of services provided. Epilepsy may be associated with significant social and emotional

burden; however, indirect costs could not be evaluated using insurance claims. In addition, the study excluded about one quarter (24.1%) of patients who were dual eligible for Medicare and Medicaid. Thus, the cost estimates may not be representative of the entire Texas Medicaid population. Seventh, the external validity of the study results may be limited by the characteristics of the study population and the results may be generalizable to the Texas Medicaid non-dual eligible adult epilepsy population only. Lastly, as this study uses prescription and medical claims data, which have been collected for the purpose of payment and not for research. Therefore, any inaccuracies in coding the diagnoses or procedures could not be determined.

## **5.5 Conclusions, Recommendations for Future Research**

The main aim of the study was to characterize and compare the treatment patterns (consisting of medication adherence and persistence, and adding and switching to alternative therapy), and healthcare utilization and costs associated with patients who have refractory and non-refractory epilepsy. The results of the study suggest that patients with refractory epilepsy were significantly more likely to adhere and persist to AED regimen, and were significantly more likely to add and switch to an alternative AED than patients with non-refractory epilepsy. Also, patients with refractory epilepsy had a significantly higher number of all-cause outpatient visits and pharmacy claims, and epilepsy-related inpatient hospitalization and ED visits, outpatient visits, and pharmacy claims. Consequently, these patients incurred higher costs of all-cause outpatient visits and pharmacy claims, and higher costs of epilepsy-related inpatient hospitalization and ED visits, outpatient visits, and pharmacy claims. In addition, these analyses confirm that patients with refractory epilepsy have higher nonepilepsy-related service costs than patients with non-refractory epilepsy.

In conclusion, findings from this study provide evidence on the dynamic patterns of AED use in clinical practice. Medication profiles of African Americans, patients with a high pill burden as well as those with a high comorbidity burden need to be explored to improve medication use behavior and reduce healthcare utilization and costs of these patients. Also, the high adherence and persistence patterns and the overall use of rational polytherapy by a significant proportion of patients with epilepsy is an indicator of good quality of care in patients enrolled in the Texas Medicaid program. In addition, the present study provides current estimates of the resource utilization, and healthcare costs associated with Texas Medicaid patients with refractory epilepsy.

These results highlight the importance of better management of epilepsy and associated comorbidities, which may significantly decrease the utilization of healthcare resources by patients with epilepsy and as a result improve the overall burden of the disease. Patients failing three or more AEDs may trigger referral to comprehensive epilepsy centers for confirming accuracy of the etiology of epilepsy and determining potential refractoriness. This timely identification of patients with refractory epilepsy and early treatment optimization may help prevent long-term clinical and psychosocial consequences associated with the condition.

Future research needs to validate the claims-based refractory epilepsy identification algorithm in a different patient population. Also, the use of a hybrid study design that includes clinical information from medical charts in addition to claims-based records would help validate the definition used in the present study. Future studies also need to evaluate the medication use patterns and economic outcomes over a longer follow-up period and assess differences in patients with refractory and stable epilepsy.

## Appendices

### Appendix IA

Patient 1: This patient was identified as refractory as the patient is dispensed 3 chronic AEDs in the 1 year identification period.

Antiepileptic drug				Start date	Days of supply
<b>KEPPRA</b>	<b>500</b>	<b>MG</b>	<b>TABLET</b>	<b>17-Mar-08</b>	<b>30</b>
<b>NEURONTIN</b>	<b>600</b>	<b>MG</b>	<b>TABLET</b>	<b>17-Mar-08</b>	<b>30</b>
<b>PHENOBARBITAL</b>	<b>64.8</b>	<b>MG</b>	<b>TABLET</b>	<b>17-Mar-08</b>	<b>30</b>
KEPPRA	500	MG	TABLET	16-Apr-08	30
PHENOBARBITAL	32.4	MG	TABLET	16-Apr-08	30
KEPPRA	500	MG	TABLET	14-May-08	30
PHENOBARBITAL	32.4	MG	TABLET	14-May-08	30
KEPPRA	500	MG	TABLET	13-Jun-08	30
PHENOBARBITAL	32.4	MG	TABLET	13-Jun-08	30
NEURONTIN	600	MG	TABLET	27-Jun-08	30
KEPPRA	500	MG	TABLET	11-Jul-08	30
PHENOBARBITAL	32.4	MG	TABLET	11-Jul-08	30
NEURONTIN	600	MG	TABLET	12-Aug-08	30
KEPPRA	500	MG	TABLET	12-Aug-08	30
PHENOBARBITAL	32.4	MG	TABLET	12-Aug-08	30
NEURONTIN	600	MG	TABLET	12-Sep-08	30
KEPPRA	500	MG	TABLET	12-Sep-08	30
PHENOBARBITAL	32.4	MG	TABLET	12-Sep-08	30
KEPPRA	500	MG	TABLET	10-Oct-08	30
PHENOBARBITAL	32.4	MG	TABLET	10-Oct-08	30
KEPPRA	500	MG	TABLET	5-Nov-08	30
NEURONTIN	600	MG	TABLET	5-Nov-08	30
PHENOBARBITAL	32.4	MG	TABLET	5-Nov-08	30
KEPPRA	500	MG	TABLET	9-Dec-08	30
NEURONTIN	600	MG	TABLET	9-Dec-08	30
PHENOBARBITAL	32.4	MG	TABLET	9-Dec-08	30
KEPPRA	500	MG	TABLET	9-Jan-09	30
NEURONTIN	600	MG	TABLET	9-Jan-09	30
PHENOBARBITAL	32.4	MG	TABLET	9-Jan-09	30
KEPPRA	500	MG	TABLET	2-Feb-09	30
GABAPENTIN	600	MG	TABLET	2-Feb-09	30
PHENOBARBITAL	32.4	MG	TABLET	5-Feb-09	30
PHENOBARBITAL	32.4	MG	TABLET	5-Mar-09	30

Patient 2: This patient was identified as refractory as the patient is dispensed 3 chronic AEDs in the 1 year identification period.

Antiepileptic drug				Start date	Days of supply
DIAZEPAM	10	MG	TABLET	21-Feb-11	1
<b>PHENYTOIN SOD EXT</b>	<b>100</b>	<b>MG</b>	<b>CAP</b>	<b>25-Feb-11</b>	<b>30</b>
PHENYTOIN SOD EXT	100	MG	CAP	30-Mar-11	30
DIAZEPAM	10	MG	TABLET	25-Apr-11	4
PHENYTOIN SOD EXT	100	MG	CAP	8-May-11	30
<b>ZONISAMIDE</b>	<b>50</b>	<b>MG</b>	<b>CAPSULE</b>	<b>1-Jun-11</b>	<b>21</b>
ZONISAMIDE	100	MG	CAPSULE	18-Jun-11	35
ZONISAMIDE	100	MG	CAPSULE	14-Aug-11	30
<b>GABAPENTIN</b>	<b>400</b>	<b>MG</b>	<b>CAPSULE</b>	<b>2-Sep-11</b>	<b>90</b>
GABAPENTIN	300	MG	CAPSULE	3-Oct-11	30
GABAPENTIN	300	MG	CAPSULE	17-Nov-11	30
GABAPENTIN	300	MG	CAPSULE	16-Dec-11	30
GABAPENTIN	300	MG	CAPSULE	14-Jan-12	30
GABAPENTIN	300	MG	CAPSULE	6-Feb-12	30

Patient 3: This patient was identified as non-refractory as the patient is dispensed 2 chronic AEDs in the 1 year identification period.

Antiepileptic drug				Start date	Days of supply
<b>PHENYTOIN SOD EXT</b>	<b>100</b>	<b>MG</b>	<b>CAP</b>	<b>21-Oct-09</b>	<b>90</b>
DIAZEPAM	5	MG	TABLET	25-Nov-09	5
PHENYTOIN SOD EXT	100	MG	CAP	4-Jan-10	30
PHENYTOIN SOD EXT	100	MG	CAP	29-Jan-10	30
<b>LEVETIRACETAM</b>	<b>500</b>	<b>MG</b>	<b>TABLET</b>	<b>29-Jan-10</b>	<b>30</b>
PHENYTOIN SOD EXT	100	MG	CAP	25-Feb-10	30
LEVETIRACETAM	500	MG	TABLET	25-Feb-10	30
LEVETIRACETAM	500	MG	TABLET	20-Mar-10	15
LEVETIRACETAM	500	MG	TABLET	5-Apr-10	15
PHENYTOIN SOD EXT	100	MG	CAP	5-Apr-10	30
PHENYTOIN SOD EXT	100	MG	CAP	4-May-10	30
LEVETIRACETAM	500	MG	TABLET	7-May-10	30
LEVETIRACETAM	500	MG	TABLET	1-Jun-10	30
PHENYTOIN SOD EXT	100	MG	CAP	1-Jun-10	30
PHENYTOIN SOD EXT	100	MG	CAP	2-Jul-10	30
LEVETIRACETAM	500	MG	TABLET	12-Jul-10	30
PHENYTOIN SOD EXT	100	MG	CAP	28-Jul-10	30
LEVETIRACETAM	500	MG	TABLET	11-Aug-10	30
PHENYTOIN SOD EXT	100	MG	CAP	24-Aug-10	30
LEVETIRACETAM	500	MG	TABLET	9-Sep-10	30
PHENYTOIN SOD EXT	100	MG	CAP	17-Sep-10	30
LEVETIRACETAM	500	MG	TABLET	14-Oct-10	30
PHENYTOIN SOD EXT	100	MG	CAP	20-Oct-10	30

Patient 4: This patient was identified as refractory as the patient is dispensed 6 chronic AEDs in the 1 year identification period.

Antiepileptic drug				Start date	Days of supply
<b>KEPPRA</b>	<b>100</b>	<b>MG/ML</b>	<b>ORAL SOLN</b>	<b>5-Mar-08</b>	<b>100</b>
<b>OXCARBAZEPINE</b>	<b>600</b>	<b>MG</b>	<b>TABLET</b>	<b>27-Mar-08</b>	<b>30</b>
KEPPRA	100	MG/ML	ORAL SOLN	3-Apr-08	30
OXCARBAZEPINE	600	MG	TABLET	28-Apr-08	30
<b>PHENYTEK</b>	<b>300</b>	<b>MG</b>	<b>CAPSULE</b>	<b>30-Apr-08</b>	<b>30</b>
<b>DEPAKOTE ER</b>	<b>500</b>	<b>MG</b>	<b>TABLET</b>	<b>12-May-08</b>	<b>30</b>
KEPPRA	750	MG	TABLET	12-May-08	30
<b>CLONAZEPAM</b>	<b>1</b>	<b>MG</b>	<b>TABLET</b>	<b>26-May-08</b>	<b>30</b>
DEPAKOTE ER	500	MG	TABLET	2-Jun-08	30
CLONAZEPAM	1	MG	TABLET	27-Jun-08	30
DEPAKOTE ER	500	MG	TABLET	19-Jul-08	15
CLONAZEPAM	1	MG	TABLET	21-Jul-08	60
DEPAKOTE ER	500	MG	TABLET	20-Aug-08	30
CLONAZEPAM	1	MG	TABLET	4-Sep-08	30
DEPAKOTE ER	500	MG	TABLET	18-Sep-08	30
DEPAKOTE ER	500	MG	TABLET	20-Oct-08	30
<b>LAMICTAL</b>	<b>25</b>	<b>MG</b>	<b>TABLET</b>	<b>30-Oct-08</b>	<b>30</b>
DEPAKOTE ER	500	MG	TABLET	1-Dec-08	30
DEPAKOTE ER	500	MG	TABLET	28-Dec-08	30
DEPAKOTE ER	500	MG	TABLET	29-Jan-09	30
CLONAZEPAM	1	MG	TABLET	29-Jan-09	30

## Appendix IB

Comorbid Condition	ICD-9-CM Code
Anxiety disorders	292.8x, 293.8x, 300.0x, 300.2x, 308.0x, 309.2x
Bipolar disorder	296.0x, 296.1x, 296.4x-296.9x
Depression	296.2x, 296.3x, 298.0x, 300.4x, 309.0x, 309.1x, 311.xx, V79.0x
Psychosis	290.xx-299.xx (except 292.8x, 293.8x, 298.0x, and 296.xx)
Personality disorder	300.xx-316.xx (except 300.0x, 300.2x, 300.4x, 308.0x, 309.0x, 309.1x, 309.2x, and 311.x), V17.0x, V71.0x
Mental retardation	317.xx-319.xx
Alzheimer's disease	290.0x-290.3x, 294.10, 294.11, 331.0x, 331.82
Brain tumor	191.xx, 198.3x, 237.5x, 239.6x,
Head injury	854.x
Meningitis	047.xx, 094.2x, 320.xx-322.xx
Migraine	346.xx
Stroke	434.xx-436.xx
Multiple Sclerosis	340.xx
Fracture	800.xx-829.xx
Dislocation	830.xx-839.xx
Sprains and strains	840.xx-849.xx
Open wounds	870.xx-897.xx
Burns	940.xx-943.xx

ICD-9-CM=The International Classification of Diseases, 9th Revision, Clinical Modification

Source:<sup>13</sup>

## Appendix II

### Comparison of Medication Adherence (Sensitivity Analyses) in the Second Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)

Medication Adherence	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
<b>Adherence cut-off 70%</b>							
Adherent (PDC $\geq$ 70%)	4,578	81.8	2,518	90.0	2,060	73.6	<b>&lt;0.0001</b>
Non-Adherent (PDC<70%)	1,018	18.2	280	10.0	738	26.4	
<b>Adherence cut-off 90%</b>							
Adherent (PDC $\geq$ 90%)	3,426	61.2	2,125	76.0	1,301	46.5	<b>&lt;0.0001</b>
Non-Adherent (PDC<90%)	2,170	38.8	673	24.1	1,497	53.5	

PDC=Proportion of days covered

### Comparison of Medication Adherence in the First Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)

Medication Adherence	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
<b>PDC</b>							
Mean $\pm$ SD	91.6 $\pm$ 15.9		96.7 $\pm$ 10.4		86.5 $\pm$ 18.7		<b>&lt;0.0001</b>
Adherent (PDC $\geq$ 80%)	4,702	84.0	2,627	93.9	2,075	74.2	<b>&lt;0.0001</b>
Non-Adherent (PDC<80%)	894	16.0	171	6.1	723	25.8	

PDC=Proportion of days covered

**Conditional Logistic Regression Analysis (Sensitivity Analyses) Comparing the Likelihood of being Adherent (PDC $\geq$ 70) in the Second Year of Follow-Up among Refractory/Non-Refractory Patients (N=5,596)**

	<b>Odds Ratio</b>	<b>95% CI</b>	<b>Wald X<sup>2</sup></b>	<b>p-value</b>
Refractory <sup>a</sup>	3.378	2.846 - 4.010	193.73	<b>&lt;0.0001</b>
Age at index	1.010	0.993 - 1.028	1.38	0.2400
Male <sup>a</sup>	1.738	1.213 - 2.490	9.07	<b>0.0026</b>
African American race <sup>a</sup>	0.718	0.527 - 0.976	4.46	<b>0.0347</b>
Other race <sup>a</sup>	0.997	0.757 - 1.313	0.00	0.9832
Partial type of epilepsy at first visit <sup>a</sup>	1.670	0.884 - 3.157	2.49	0.1143
Other type of epilepsy at first visit <sup>a</sup>	1.537	0.819 - 2.885	1.79	0.1804
Multiple actions of index AED <sup>a</sup>	1.243	0.971 - 1.591	2.98	0.0843
Baseline CCI of 1 <sup>a</sup>	0.830	0.592 - 1.163	1.17	0.2790
Baseline CCI greater than 1 <sup>a</sup>	1.130	0.669 - 1.908	0.21	0.6474
Number of psychiatric comorbidities at follow-up	0.876	0.803 - 0.956	8.79	<b>0.0030</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.933	0.732 - 1.189	0.32	0.5743
Baseline pill burden	0.946	0.858 - 1.043	1.24	0.2661
Baseline all-cause inpatient visits <sup>a</sup>	0.853	0.622 - 1.168	0.99	0.3208
Number of baseline all-cause outpatient visits	0.998	0.988 - 1.007	0.22	0.6416
Baseline total all-cause healthcare cost	1.000	1.000 - 1.000	1.33	0.2493

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

*Model Fit: likelihood ratio=297.3227; df=16; p<0.0001*

Significant at p<0.05 (in bold)

**Conditional Logistic Regression Analysis (Sensitivity Analyses) Comparing the Likelihood of being Adherent (PDC $\geq$ 90) in the Second Year of Follow-Up among Refractory/Non-Refractory Patients (N=5,596)**

	<b>Odds Ratio</b>	<b>95% CI</b>	<b>Wald X<sup>2</sup></b>	<b>p-value</b>
Refractory <sup>a</sup>	3.649	3.192 - 4.172	359.77	<b>&lt;0.0001</b>
Age at index	0.993	0.978 - 1.009	0.78	0.3783
Male <sup>a</sup>	1.204	0.886 - 1.637	1.40	0.2361
African American race <sup>a</sup>	0.827	0.646 - 1.060	2.26	0.1332
Other race <sup>a</sup>	0.755	0.61 - 0.936	6.58	<b>0.0103</b>
Partial type of epilepsy at first visit <sup>a</sup>	1.686	1.050 - 2.706	4.68	<b>0.0305</b>
Other type of epilepsy at first visit <sup>a</sup>	1.150	0.679 - 1.949	0.27	0.6027
Multiple actions of index AED <sup>a</sup>	1.291	1.067 - 1.562	6.87	<b>0.0088</b>
Baseline CCI of 1 <sup>a</sup>	0.642	0.485 - 0.850	9.59	<b>0.0020</b>
Baseline CCI greater than 1 <sup>a</sup>	0.777	0.49 - 1.231	1.16	0.2819
Number of psychiatric comorbidities at follow-up	0.971	0.908 - 1.038	0.75	0.3876
Non-psychiatric comorbidities at follow-up <sup>a</sup>	1.008	0.826 - 1.23	0.01	0.9389
Baseline pill burden	1.029	0.938 - 1.127	0.36	0.5476
Baseline all-cause inpatient visits <sup>a</sup>	0.678	0.528 - 0.871	9.22	0.0024
Number of baseline all-cause outpatient visits	0.998	0.991 - 1.006	0.27	0.6048
Baseline total all-cause healthcare cost	1.000	1.000 - 1.000	0.92	0.3377

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

*Model Fit: likelihood ratio=559.4323; df=16; p<0.0001*

Significant at p<0.05 (in bold)

**Conditional Logistic Regression Analysis Comparing the Likelihood of being Adherent (PDC $\geq$ 80) in the First Year of Follow-Up among Refractory/Non-Refractory Patients (N=5,596)**

	<b>Odds Ratio</b>	<b>95% CI</b>	<b>Wald X<sup>2</sup></b>	<b>p-value</b>
Refractory <sup>a</sup>	6.513	5.126-8.276	235.02	<b>&lt;0.0001</b>
Age at index	1.030	1.007-1.053	6.44	<b>0.0112</b>
Male <sup>a</sup>	2.571	1.614-4.097	15.78	<b>&lt;0.0001</b>
African American race <sup>a</sup>	0.494	0.336-0.726	12.90	<b>0.0003</b>
Other race <sup>a</sup>	0.775	0.551-1.089	2.16	0.1416
Partial type of epilepsy at first visit <sup>a</sup>	3.162	1.404-7.12	7.72	<b>0.0054</b>
Other type of epilepsy at first visit <sup>a</sup>	2.008	0.919-4.387	3.05	0.0806
Multiple actions of index AED <sup>a</sup>	1.415	1.021-1.962	4.34	<b>0.0373</b>
Baseline CCI of 1 <sup>a</sup>	0.806	0.516-1.258	0.90	<b>0.3423</b>
Baseline CCI greater than 1 <sup>a</sup>	1.555	0.794-3.048	1.65	0.1983
Number of psychiatric comorbidities at follow-up	0.824	0.736-0.922	11.31	<b>0.0008</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.848	0.619-1.163	1.05	0.3060
Baseline pill burden	0.863	0.762-0.977	5.41	<b>0.0200</b>
Baseline all-cause inpatient visits <sup>a</sup>	0.567	0.377-0.851	7.49	<b>0.0062</b>
Number of baseline all-cause outpatient visits	1.002	0.99-1.015	0.14	0.7115
Baseline total all-cause healthcare cost	1.000	1.000-1.000	2.25	0.1339

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

*Model Fit: likelihood ratio=505.2191; df=16; p<0.0001*

Significant at p<0.05 (in bold)

### Appendix III

#### Comparison of Medication Persistence (Sensitivity Analyses) in the Second Year of Follow-Up by Refractory/ Non-Refractory Status (N=5,596)

Medication Persistence	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
<b>Persistence Gap of 30 days</b>							
Mean ± SD	283.7 ± 121.6		308.6 ± 105.9		258.8 ± 130.9		<b>&lt;0.0001</b>
<b>Persistence Gap of 90 days</b>							
Mean ± SD	322.7 ± 90.6		335.3 ± 77.2		310.0 ± 100.6		<b>&lt;0.0001</b>

#### Comparison of Medication Persistence in the First Year of Follow-Up by Refractory/ Non-Refractory Status (N=5,596)

Medication Persistence	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
<b>Persistence Gap of 60 days</b>							
Mean ± SD	337.1 ± 67.4		347.7 ± 53.7		326.5 ± 77.3		<b>&lt;0.0001</b>

**Cox Proportional Hazard Regression Analysis Comparing the Likelihood of Discontinuation (Persistence 30 Day Gap) in the Second Year of Follow-Up among Refractory/ Non-Refractory Patients (N=5,596)**

	<b>Hazards Ratio</b>	<b>95% CI</b>	<b>Wald X<sup>2</sup></b>	<b>p-value</b>
Refractory <sup>a</sup>	0.612	0.568 - 0.659	171.41	<b>&lt;0.0001</b>
Age at index	0.998	0.99 - 1.006	0.19	0.6598
Male <sup>a</sup>	0.855	0.727 - 1.005	3.60	0.0578
African American race <sup>a</sup>	1.083	0.940 - 1.246	1.22	0.2695
Other race <sup>a</sup>	1.037	0.925 - 1.162	0.38	0.5375
Partial type of epilepsy at first visit <sup>a</sup>	0.870	0.677 - 1.117	1.19	0.2746
Other type of epilepsy at first visit <sup>a</sup>	0.847	0.64 - 1.121	1.35	0.2452
Multiple actions of index AED <sup>a</sup>	0.928	0.836 - 1.031	1.94	0.1632
Baseline CCI of 1 <sup>a</sup>	1.232	1.059 - 1.434	7.28	<b>0.0070</b>
Baseline CCI greater than 1 <sup>a</sup>	1.032	0.804 - 1.325	0.06	0.8057
Number of psychiatric comorbidities at follow-up	1.022	0.985 - 1.06	1.30	0.2544
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.998	0.894 - 1.113	0.00	0.9670
Baseline pill burden	1.019	0.972 - 1.069	0.64	0.4252
Baseline all-cause inpatient visits <sup>a</sup>	1.146	0.999 - 1.315	3.79	0.0516
Number of baseline all-cause outpatient visits	0.999	0.995 - 1.003	0.20	0.6535
Baseline total all-cause healthcare cost	1.000	1.000 - 1.000	0.42	0.5188

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

*Model Fit: likelihood ratio=228.9262; df=16; p<0.0001*

Significant at p<0.05 (in bold)

**Cox Proportional Hazard Regression Analysis Comparing the Likelihood of Discontinuation (Persistence 90 Day Gap) in the Second Year of Follow-Up among Refractory/Non-Refractory Patients (N=5,596)**

	<b>Hazards Ratio</b>	<b>95% CI</b>	<b>Wald X<sup>2</sup></b>	<b>p-value</b>
Refractory <sup>a</sup>	0.675	0.629 - 0.725	117.25	<b>&lt;0.0001</b>
Age at index	0.995	0.987 - 1.003	1.44	0.2308
Male <sup>a</sup>	0.841	0.718 - 0.984	4.65	<b>0.0311</b>
African American race <sup>a</sup>	1.086	0.948 - 1.245	1.41	0.2350
Other race <sup>a</sup>	1.021	0.915 - 1.141	0.14	0.7066
Partial type of epilepsy at first visit <sup>a</sup>	0.855	0.671 - 1.089	1.61	0.2049
Other type of epilepsy at first visit <sup>a</sup>	0.821	0.626 - 1.078	2.02	0.1553
Multiple actions of index AED <sup>a</sup>	0.943	0.852 - 1.043	1.31	0.2526
Baseline CCI of 1 <sup>a</sup>	1.122	0.969 - 1.299	2.35	0.1253
Baseline CCI greater than 1 <sup>a</sup>	1.01	0.792 - 1.288	0.01	0.9372
Number of psychiatric comorbidities at follow-up	1.022	0.986 - 1.059	1.37	0.2421
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.979	0.88 - 1.088	0.16	0.6894
Baseline pill burden	1.027	0.981 - 1.076	1.29	0.2567
Baseline all-cause inpatient visits <sup>a</sup>	1.145	1.002 - 1.309	3.97	<b>0.0464</b>
Number of baseline all-cause outpatient visits	0.999	0.996 - 1.003	0.12	0.7335
Baseline total all-cause healthcare cost	1.000	1.000 - 1.000	0.81	0.3690

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Model Fit: likelihood ratio=158.7666; df=16; p<0.0001

Significant at p<0.05 (in bold)

**Cox Proportional Hazard Regression Analysis Comparing the Likelihood of Discontinuation (Persistence 60 Day Gap) in the First Year of Follow-Up among Refractory/Non-Refractory Patients (N=5,596)**

	<b>Hazards Ratio</b>	<b>95% CI</b>	<b>Wald X<sup>2</sup></b>	<b>p-value</b>
Refractory <sup>a</sup>	0.792	0.744 - 0.844	51.92	<b>&lt;0.0001</b>
Age at index	0.993	0.986 - 1.001	3.23	0.0724
Male <sup>a</sup>	0.827	0.717 - 0.953	6.87	<b>0.0088</b>
African American race <sup>a</sup>	1.170	1.035 - 1.323	6.29	<b>0.0122</b>
Other race <sup>a</sup>	1.057	0.958 - 1.167	1.22	0.2684
Partial type of epilepsy at first visit <sup>a</sup>	0.855	0.688 - 1.063	1.98	0.1595
Other type of epilepsy at first visit <sup>a</sup>	0.811	0.637 - 1.034	2.85	0.0913
Multiple actions of index AED <sup>a</sup>	0.953	0.871 - 1.043	1.08	0.2986
Baseline CCI of 1 <sup>a</sup>	1.052	0.922 - 1.200	0.70	0.4514
Baseline CCI greater than 1 <sup>a</sup>	0.901	0.725 - 1.120	0.88	0.3484
Number of psychiatric comorbidities at follow-up	1.015	0.980 - 1.051	0.71	0.4008
Non-psychiatric comorbidities at follow-up <sup>a</sup>	1.002	0.913 - 1.100	0.00	0.9639
Baseline pill burden	1.034	0.992 - 1.078	2.54	0.1111
Baseline all-cause inpatient visits <sup>a</sup>	1.075	0.953 - 1.213	1.39	0.2378
Number of baseline all-cause outpatient visits	0.999	0.996 - 1.003	0.15	0.7014
Baseline total all-cause healthcare cost	1.000	1.000 - 1.000	1.63	0.2013

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Model Fit: likelihood ratio=80.9658; df=16; p<0.0001

Significant at p<0.05 (in bold)

## Appendix IV

### Comparison of Patient Characteristics by Refractory/Non-Refractory Status (Excluding Patients on Monotherapy) (N=5,414)

Characteristics	All		Refractory		Non-refractory		p-value
	n=5,414		n=2,707		n=2,707		
	N	%	N	%	N	%	
<b>Demographics</b>							
<b>Age at index date<sup>a,e</sup></b>							
Mean ± SD, year	37.9 ± 12.9		37.9 ± 12.6		37.8 ± 13.2		0.7823
<b>Gender<sup>b,e</sup></b>							
Male	2,431	44.9	1,217	45.0	1,214	44.8	0.9342
Female	2,983	55.1	1,490	55.0	1,493	55.2	
<b>Race/Ethnicity<sup>b,e</sup></b>							
Caucasian	2,241	41.4	1,149	42.4	1,092	40.3	0.1185
African American	974	18.0	435	16.1	539	19.9	<b>0.0003</b>
Hispanic	1,819	33.6	936	34.6	883	32.6	0.1293
Other/Unknown	380	7.0	187	6.9	193	7.1	0.3200
<b>Clinical Characteristics</b>							
<b>Type of epilepsy at first visit<sup>b,e</sup></b>							
Generalized	589	10.9	284	10.5	305	11.3	0.3621
Partial	450	8.3	235	8.7	215	7.9	0.3221
Other convulsions	4,193	77.4	2,090	77.2	2,103	77.7	0.6704
Multiple types	182	3.4	98	3.6	84	3.1	0.2885
<b>Type of index Antiepileptic drug<sup>b</sup></b>							
Sodium channel blockers	1,724	31.8	758	28.0	966	35.7	<b>&lt;0.0001</b>
GABA analogues	617	11.4	320	11.8	297	11.0	0.3298
Calcium channel actions	322	5.9	199	7.4	123	4.5	<b>&lt;0.0001</b>
Multiple actions	1,026	19.0	491	18.1	535	19.8	0.1294
Synaptic vesicle protein 2A binding	450	8.3	211	7.8	239	8.8	0.1605
Combination	1,275	23.6	728	26.9	547	20.2	<b>&lt;0.0001</b>
<b>Baseline Charlson Comorbidity Index<sup>a,b</sup></b>							
Mean ± SD <sup>c</sup>	0.7 ± 1.4		0.7 ± 1.4		0.8 ± 1.4		0.7740
0	3,452	63.8	1,744	64.4	1,708	63.1	0.2897
1	1,009	18.6	500	18.5	509	18.8	0.7468
>1	953	17.6	463	17.1	490	18.1	0.7220

**Comparison of Patient Characteristics by Refractory/Non-Refractory Status (Excluding Patients on Monotherapy) (N=5,414) (Continued)**

Characteristics	All		Refractory		Non-refractory		p-value
	n=5,414		n=2,707		n=2,707		
	N	%	N	%	N	%	
<b>Number of psychiatric comorbidities (First year)<sup>a,d</sup></b>							
Mean ± SD	1.5 ± 1.3		1.6 ± 1.4		1.4 ± 1.3		<b>&lt;0.0001</b>
<b>Clinical Characteristics</b>							
<b>Non-psychiatric comorbidities (First year)<sup>b,d</sup></b>							
Yes	2,306	42.6	1,261	46.6	1,045	38.6	<b>&lt;0.0001</b>
No	3,108	57.4	1,446	53.4	1,662	61.4	
<b>Number of psychiatric comorbidities (Second year)<sup>a,d</sup></b>							
Mean ± SD	1.9 ± 1.4		2.0 ± 1.5		1.8 ± 1.4		<b>&lt;0.0001</b>
<b>Non-psychiatric comorbidities (Second year)<sup>b,d</sup></b>							
Yes	2,550	47.1	1,370	50.6	1,180	43.6	<b>&lt;0.0001</b>
No	2,864	52.9	1,337	49.4	1,527	56.4	
<b>Baseline pill burden<sup>c,e</sup></b>							
Median (Mean ± SD)	7 (9.0 ± 6.8)		7 (9.1 ± 6.9)		8 (9.0 ± 6.7)		0.5581
<b>Baseline Healthcare Utilization and Cost</b>							
<b>Baseline all-cause inpatient visit<sup>b</sup></b>							
Yes	1,092	20.2	551	20.4	541	20.0	0.7243
No	4,322	79.8	2,156	79.6	2,166	80.0	
<b>Baseline all-cause outpatient visit<sup>c</sup></b>							
Median (Mean ± SD)	11 (15.4 ± 15.2)		11 (15.1 ± 14.5)		11 (15.6 ± 15.8)		0.5835
<b>Baseline all-cause total healthcare cost<sup>c,e,f</sup></b>							
Median (Mean ± SD)	7,134 (10,703 ± 15,913)		7,557 (10,859 ± 14,656)		6,674 (10,547 ± 17,080)		<b>&lt;0.0001</b>

<sup>a</sup>Paired T-test

<sup>b</sup>McNemar's test

<sup>c</sup>Wilcoxon signed-rank test

<sup>d</sup>Measured in the follow-up period

<sup>e</sup>Used as predictors of selection in refractory or non-refractory group with caliper set at 0.05(matching)

<sup>f</sup>Adjusted to 2013 US dollars

Significant at p<0.05 (in bold)

## Appendix VA

### Comparison of All-Cause Inpatient Hospitalization and ED Visits in the First Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)

	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
Median (Mean ± SD)	1 (2.9 ± 5.3)		2 (3.5 ± 5.5)		1 (2.4 ± 5.0)		<b>&lt;0.0001<sup>a</sup></b>
Yes	3,550	63.4	1,950	69.7	1,600	57.2	<b>&lt;0.0001<sup>b</sup></b>
No	2,046	36.6	848	30.3	1,198	42.8	

<sup>a</sup>Wilcoxon signed-rank test

<sup>b</sup>McNemar's test

Significant at p<0.05 (in bold)

**Zero-Inflated Poisson Regression Comparing the All-Cause Inpatient Hospitalization and ED Visits in the First Year of Follow-Up among Refractory/ Non-Refractory Patients (N=5,596)**

	Estimate	95% CI	Wald X <sup>2</sup>	p-value
Refractory <sup>a</sup>	0.1262	0.0924 - 0.1599	53.59	<b>&lt;0.0001</b>
Age at index	-0.0014	-0.0028 - 0.0000	3.78	0.0519
Male <sup>a</sup>	-0.0983	-0.132 - -0.0645	32.62	<b>&lt;0.0001</b>
African American race <sup>a</sup>	0.2248	0.1826 - 0.2669	109.17	<b>&lt;0.0001</b>
Other race <sup>a</sup>	-0.0333	-0.0703 - 0.0038	3.10	0.0784
Partial type of epilepsy at first visit <sup>a</sup>	-0.2535	-0.3546 - -0.1524	24.16	<b>&lt;0.0001</b>
Other type of epilepsy at first visit <sup>a</sup>	0.1387	0.0784 - 0.1991	20.29	<b>&lt;0.0001</b>
Multiple actions of index AED <sup>a</sup>	-0.1034	-0.1375 - -0.0693	35.37	<b>&lt;0.0001</b>
Baseline CCI of 1 <sup>a</sup>	0.1183	0.0763 - 0.1604	30.42	<b>&lt;0.0001</b>
Baseline CCI greater than 1 <sup>a</sup>	0.2100	0.1655 - 0.2545	85.6	<b>&lt;0.0001</b>
Number of psychiatric comorbidities at follow-up	0.2807	0.2694 - 0.2921	2356.46	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.4600	0.4228 - 0.4972	588.28	<b>&lt;0.0001</b>
Baseline pill burden	0.0008	-0.0013 - 0.0029	0.60	0.4383
Baseline all-cause inpatient visits <sup>a</sup>	0.2340	0.1967 - 0.2714	150.79	<b>&lt;0.0001</b>
Number of baseline all-cause outpatient visits	0.0079	0.0068 - 0.0090	199.98	<b>&lt;0.0001</b>
Baseline total all-cause healthcare cost	0.0000	-0.0000 - 0.0000	15.40	<b>&lt;0.0001</b>

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Model Fit: likelihood ratio chi-squared=5573.18; df=16; p<0.0001;

Vuong test of ZIP vs. standard Poisson: z=12.70; p<0.0001;

Significant at p<0.05 (in bold)

## Appendix VB

### Comparison of All-Cause Outpatient Visits in the First Year of Follow-Up by Refractory/Non-Refractory Status (N=5,596)

	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
Median (Mean ± SD)	28 (39.1 ± 37.2)		31 (41.5 ± 37.5)		26 (36.6 ± 36.7)		<b>&lt;0.0001<sup>a</sup></b>
Yes	5,588	99.9	2,793	99.8	2,795	99.9	0.4795 <sup>b</sup>
No	8	0.1	5	0.2	3	0.1	

<sup>a</sup>Wilcoxon signed-rank test

<sup>b</sup>McNemar's test

Significant at p<0.05 (in bold)

**Zero-Inflated Poisson Regression Comparing the All-Cause Outpatient Visits in the First Year of Follow-Up among Refractory/ Non-Refractory Patients (N=5,596)**

	Estimate	95% CI	Wald X <sup>2</sup>	p-value
Refractory <sup>a</sup>	0.1107	0.1021 - 0.1193	639.06	<b>&lt;0.0001</b>
Age at index	0.0019	0.0015 - 0.0022	102.67	<b>&lt;0.0001</b>
Male <sup>a</sup>	-0.0549	-0.0636 - -0.0462	151.72	<b>&lt;0.0001</b>
African American race <sup>a</sup>	0.0782	0.0664 - 0.09	168.63	<b>&lt;0.0001</b>
Other race <sup>a</sup>	0.0871	0.0777 - 0.0965	330.31	<b>&lt;0.0001</b>
Partial type of epilepsy at first visit <sup>a</sup>	-0.0671	-0.0882 - -0.0459	38.64	<b>&lt;0.0001</b>
Other type of epilepsy at first visit <sup>a</sup>	0.0472	0.0333 - 0.0612	44.23	<b>&lt;0.0001</b>
Multiple actions of index AED <sup>a</sup>	-0.0574	-0.0662 - -0.0486	162.5	<b>&lt;0.0001</b>
Baseline CCI of 1 <sup>a</sup>	0.1631	0.152 - 0.1741	834.67	<b>&lt;0.0001</b>
Baseline CCI greater than 1 <sup>a</sup>	0.1708	0.1588 - 0.1828	776.28	<b>&lt;0.0001</b>
Number of psychiatric comorbidities at follow-up	0.1213	0.1181 - 0.1244	5731.1	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.1938	0.1847 - 0.2029	1746.22	<b>&lt;0.0001</b>
Baseline pill burden	0.0056	0.005 - 0.0062	372.42	<b>&lt;0.0001</b>
Baseline all-cause inpatient visits <sup>a</sup>	0.0090	-0.0015 - 0.0194	2.84	0.0921
Number of baseline all-cause outpatient visits	0.0203	0.0201 - 0.0205	42732.1	<b>&lt;0.0001</b>
Baseline total all-cause healthcare cost	0.0000	-0.0000 - 0.0000	334.33	<b>&lt;0.0001</b>

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Model Fit: likelihood ratio chi-squared= 81743.18; df=16; p<0.0001;

Vuong test of ZIP vs. standard Poisson: z=2.38; p=0.0086 ;

Significant at p<0.05 (in bold)

## Appendix VC

### Comparison of Epilepsy-Related Inpatient Hospitalization and ED Visits in the First Year of Follow-Up by Refractory/ Non-Refractory Status (N=5,596)

	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
Median (Mean ± SD)	0 (0.9 ± 2.1)		0 (1.3 ± 2.6)		0 (0.6 ± 1.3)		<b>&lt;0.0001<sup>a</sup></b>
Yes	2,226	39.8	1,360	48.6	866	31.0	<b>&lt;0.0001<sup>b</sup></b>
No	3,370	60.2	1,438	51.4	1,932	69.1	

<sup>a</sup>Wilcoxon signed-rank test

<sup>b</sup>McNemar's test

Significant at p<0.05 (in bold)

**Zero-Inflated Poisson Regression Comparing the Epilepsy-Related Inpatient Hospitalization and ED Visits in the First Year of Follow-Up among Refractory/ Non-Refractory Patients (N=5,596)**

	Estimate	95% CI	Wald X <sup>2</sup>	p-value
Refractory <sup>a</sup>	0.3688	0.2946 - 0.4431	94.73	<b>&lt;0.0001</b>
Age at index	-0.0060	-0.0086 - -0.0033	19.17	<b>&lt;0.0001</b>
Male <sup>a</sup>	0.0354	-0.0267 - 0.0975	1.25	0.2641
African American race <sup>a</sup>	0.2410	0.1597 - 0.3224	33.73	<b>&lt;0.0001</b>
Other race <sup>a</sup>	0.0873	0.0188 - 0.1558	6.24	<b>0.0125</b>
Partial type of epilepsy at first visit <sup>a</sup>	-0.1140	-0.2767 - 0.0487	1.89	0.1697
Other type of epilepsy at first visit <sup>a</sup>	0.0994	-0.0081 - 0.2069	3.28	<b>0.0700</b>
Multiple actions of index AED <sup>a</sup>	0.0333	-0.0291 - 0.0956	1.09	0.2954
Baseline CCI of 1 <sup>a</sup>	0.0331	-0.0474 - 0.1135	0.65	0.4204
Baseline CCI greater than 1 <sup>a</sup>	0.0218	-0.0680 - 0.1117	0.23	0.6336
Number of psychiatric comorbidities at follow-up	0.2357	0.2143 - 0.2572	465.37	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.4626	0.3945 - 0.5306	177.34	<b>&lt;0.0001</b>
Baseline pill burden	-0.0191	-0.0238 - -0.0144	63.34	<b>&lt;0.0001</b>
Baseline all-cause inpatient visits <sup>a</sup>	0.2879	0.2139 - 0.3619	58.11	<b>&lt;0.0001</b>
Number of baseline all-cause outpatient visits	0.0038	0.0014 - 0.0062	9.61	<b>0.0019</b>
Baseline total all-cause healthcare cost	0.0000	-0.0000 - 0.0000	0.29	0.5880

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Model Fit: likelihood ratio chi-squared=1096.18; df=16; p<0.0001;

Vuong test of ZIP vs. standard Poisson: z=10.51; p<0.0001;

Significant at p<0.05 (in bold)

## Appendix VD

### Comparison of Epilepsy-Related Outpatient Visits in the First Year of Follow-Up by Refractory/ Non-Refractory Status (N=5,596)

	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
Median (Mean ± SD)	5 (7.7 ± 11.6)		6 (9.1 ± 12.2)		4 (6.4 ± 10.8)		<b>&lt;0.0001<sup>a</sup></b>
Yes	5,352	95.6	2,713	97.0	2,639	94.3	<b>&lt;0.0001<sup>b</sup></b>
No	244	4.4	85	3.0	159	5.7	

<sup>a</sup>Wilcoxon signed-rank test

<sup>b</sup>McNemar's test

Significant at p<0.05 (in bold)

**Zero-Inflated Poisson Regression Comparing the Epilepsy-Related Outpatient Visits in the First Year of Follow-Up among Refractory/Non-Refractory Patients (N=5,596)**

	Estimate	95% CI	Wald X <sup>2</sup>	p-value
Refractory <sup>a</sup>	0.3187	0.2991 - 0.3383	1018.13	< <b>0.0001</b>
Age at index	-0.0063	-0.0072 - -0.0055	235.9	< <b>0.0001</b>
Male <sup>a</sup>	0.0388	0.0194 - 0.0582	15.36	< <b>0.0001</b>
African American race <sup>a</sup>	0.0220	-0.0054 - 0.0494	2.47	0.1157
Other race <sup>a</sup>	0.1187	0.0977 - 0.1397	122.66	< <b>0.0001</b>
Partial type of epilepsy at first visit <sup>a</sup>	-0.2425	-0.2881 - -0.197	108.95	< <b>0.0001</b>
Other type of epilepsy at first visit <sup>a</sup>	-0.0438	-0.0733 - -0.0144	8.51	<b>0.0035</b>
Multiple actions of index AED <sup>a</sup>	-0.0630	-0.0828 - -0.0433	39.22	< <b>0.0001</b>
Baseline CCI of 1 <sup>a</sup>	0.0989	0.0734 - 0.1243	58.1	< <b>0.0001</b>
Baseline CCI greater than 1 <sup>a</sup>	0.0245	-0.0042 - 0.0532	2.81	0.0939
Number of psychiatric comorbidities at follow-up	0.0623	0.0551 - 0.0696	283.65	< <b>0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.1684	0.1480 - 0.1888	261.52	< <b>0.0001</b>
Baseline pill burden	-0.0115	-0.0130 - -0.0100	229.75	< <b>0.0001</b>
Baseline all-cause inpatient visits <sup>a</sup>	0.0383	0.0131 - 0.0635	8.85	<b>0.0029</b>
Number of baseline all-cause outpatient visits	0.0134	0.0128 - 0.0139	2597.89	< <b>0.0001</b>
Baseline total all-cause healthcare cost	-0.0000	-0.0000 - 0.0000	0.000	0.9854

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Model Fit: likelihood ratio chi-squared=5744.05; df=16; p<0.0001;

Vuong test of ZIP vs. standard Poisson: z=9.68; p<0.0001;

Significant at p<0.05 (in bold)

## Appendix VE

### Comparison of All-Cause Pharmacy Visits in the First Year of Follow-Up by Refractory/ Non-Refractory Status (N=5,596)

	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
Median (Mean ± SD)	8 (9.7 ± 6.4)		9 (10.6 ± 6.7)		8 (8.8 ± 6.0)		<b>&lt;0.0001<sup>a</sup></b>
Yes	5,596	100.0	2,798	100.0	2,798	100.0	
No	0	0.0	0	0.0	0	0.0	

<sup>a</sup>Wilcoxon signed-rank test  
Significant at p<0.05 (in bold)

**Poisson Regression Comparing the All-Cause Pharmacy Claims in the First Year of Follow-Up among Refractory/ Non-Refractory Patients (N=5,596)**

	Estimate	95% CI	Wald X <sup>2</sup>	p-value
Refractory <sup>a</sup>	0.1470	0.1298 - 0.1642	280.38	< <b>0.0001</b>
Age at index	0.0027	0.002 - 0.0034	53.31	< <b>0.0001</b>
Male <sup>a</sup>	-0.0838	-0.1015 - -0.0661	86.09	< <b>0.0001</b>
African American race <sup>a</sup>	-0.0328	-0.0565 - -0.0091	7.36	<b>0.0067</b>
Other race <sup>a</sup>	-0.037	-0.0559 - -0.0182	14.83	<b>0.0001</b>
Partial type of epilepsy at first visit <sup>a</sup>	-0.0599	-0.1026 - -0.0172	7.56	<b>0.0060</b>
Other type of epilepsy at first visit <sup>a</sup>	0.0302	0.0023 - 0.0581	4.49	<b>0.0342</b>
Multiple actions of index AED <sup>a</sup>	-0.0728	-0.0905 - -0.0552	65.32	< <b>0.0001</b>
Baseline CCI of 1 <sup>a</sup>	0.1354	0.1132 - 0.1576	142.81	< <b>0.0001</b>
Baseline CCI greater than 1 <sup>a</sup>	0.1255	0.1009 - 0.1501	99.80	< <b>0.0001</b>
Number of psychiatric comorbidities at follow-up	0.0786	0.0722 - 0.085	579.39	< <b>0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.1407	0.1226 - 0.1589	231.20	< <b>0.0001</b>
Baseline pill burden	0.0353	0.0342 - 0.0364	3982.91	< <b>0.0001</b>
Baseline all-cause inpatient visits <sup>a</sup>	0.0162	-0.0052 - 0.0376	2.21	0.1368
Number of baseline all-cause outpatient visits	0.0012	0.0005 - 0.0018	12.79	<b>0.0003</b>
Baseline total all-cause healthcare cost	0.0000	0.0000 - 0.0000	17.34	< <b>0.0001</b>

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Model Fit: likelihood ratio chi-squared=11338.26; df=16; p<0.0001;

Significant at p<0.05 (in bold)

## Appendix VF

### Comparison of Epilepsy-Related Pharmacy Claims in the First Year of Follow-Up by Refractory/ Non-Refractory Status (N=5,596)

	All		Refractory		Non-refractory		p-value
	n=5,596		n=2,798		n=2,798		
	N	%	N	%	N	%	
Median (Mean ± SD)	2 (2.7 ± 1.5)		3 (3.6 ± 1.4)		2 (1.7 ± 0.9)		<b>&lt;0.0001<sup>a</sup></b>
Yes	5,596	100.0	2,798	100.0	2,798	100.0	
No	0	0.0	0	0.0	0	0.0	

<sup>a</sup>Wilcoxon signed-rank test  
Significant at p<0.05 (in bold)

**Poisson Regression Comparing the Epilepsy-Related Pharmacy Claims in the First Year of Follow-Up among Refractory/ Non-Refractory Patients (N=5,596)**

	Estimate	95% CI	Wald X <sup>2</sup>	p-value
Refractory <sup>a</sup>	0.7341	0.6993 - 0.7688	1714.56	<b>&lt;0.0001</b>
Age at index	-0.0024	-0.0037 - -0.001	11.32	<b>0.0008</b>
Male <sup>a</sup>	-0.0085	-0.0414 - 0.0245	0.25	0.6147
African American race <sup>a</sup>	-0.0272	-0.073 - 0.0186	1.35	0.2451
Other race <sup>a</sup>	-0.0222	-0.0577 - 0.0133	1.50	0.2200
Partial type of epilepsy at first visit <sup>a</sup>	-0.0138	-0.0883 - 0.0608	0.13	0.7171
Other type of epilepsy at first visit <sup>a</sup>	-0.0087	-0.0602 - 0.0427	0.11	0.7387
Multiple actions of index AED <sup>a</sup>	-0.1476	-0.181 - -0.1142	74.99	<b>&lt;0.0001</b>
Baseline CCI of 1 <sup>a</sup>	-0.0218	-0.0662 - 0.0225	0.93	0.3343
Baseline CCI greater than 1 <sup>a</sup>	-0.0004	-0.0491 - 0.0484	0.00	0.9879
Number of psychiatric comorbidities at follow-up	0.0522	0.0399 - 0.0645	69.32	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.0585	0.0241 - 0.0929	11.10	<b>0.0009</b>
Baseline pill burden	0.0058	0.0033 - 0.0083	21.05	<b>&lt;0.0001</b>
Baseline all-cause inpatient visits <sup>a</sup>	0.0470	0.0038 - 0.0902	4.55	<b>0.0329</b>
Number of baseline all-cause outpatient visits	0.0000	-0.0013 - 0.0012	0.01	0.9424
Baseline total all-cause healthcare cost	-0.0000	-0.0000 - 0.0000	0.00	0.9673

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Model Fit: likelihood ratio chi-squared=2182.72; df=16; p<0.0001 ;

Significant at p<0.05 (in bold)

## Appendix: VIA

### Comparison of Cost of All-Cause Inpatient Hospitalization and ED Visits in the First Year of Follow-Up by Refractory/ Non-Refractory Status (N=5,596)

	All n=5,596	Refractory n=2,798	Non-refractory n=2,798	p-value
Median (Mean ± SD)	\$118 (\$3,680 ± \$10,824)	\$239 (\$4,136 ± \$9,663)	\$65 (\$3,224 ± \$11,858)	<b>&lt;0.0001<sup>a</sup></b>

<sup>a</sup>Wilcoxon signed-rank test  
Significant at p<0.05 (in bold)

**Generalized Linear Model Comparing the Cost of All-Cause Inpatient Hospitalization and ED Visits in the First Year of Follow-Up among Refractory/ Non-Refractory Patients (N=5,596)**

	Estimate	95% CI	z	p-value
Refractory <sup>a</sup>	0.3756	0.2136 - 0.5375	4.55	<b>&lt;0.0001</b>
Age at index	-0.0012	-0.0075 - 0.0051	-0.36	0.7190
Male <sup>a</sup>	0.0320	-0.1288 - 0.1928	0.39	0.6960
African American race <sup>a</sup>	0.1836	-0.0382 - 0.4054	1.62	0.1050
Other race <sup>a</sup>	-0.0402	-0.2154 - 0.1350	-0.45	0.6530
Partial type of epilepsy at first visit <sup>a</sup>	0.1485	-0.2155 - 0.51253	0.80	0.4240
Other type of epilepsy at first visit <sup>a</sup>	0.2263	-0.0193 - 0.4719	1.81	0.0710
Multiple actions of index AED <sup>a</sup>	-0.1906	-0.3538 - -0.0274	-2.29	<b>0.0220</b>
Baseline CCI of 1 <sup>a</sup>	0.3051	0.0908 - 0.5194	2.79	<b>0.0050</b>
Baseline CCI greater than 1 <sup>a</sup>	0.4297	0.1948 - 0.6647	3.58	<b>&lt;0.0001</b>
Number of psychiatric comorbidities at follow-up	0.3421	0.2815 - 0.4028	11.06	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.5796	0.4136 - 0.7455	6.85	<b>&lt;0.0001</b>
Baseline pill burden	0.0115	-0.0009 - 0.0239	1.82	0.0680
Baseline all-cause inpatient visits <sup>a</sup>	0.6045	0.3939 - 0.8151	5.63	<b>&lt;0.0001</b>
Number of baseline all-cause outpatient visits	0.0019	-0.0050 - 0.0088	0.54	0.5900
Baseline total all-cause healthcare cost	0.0000	0.0000 - 0.0000	4.26	<b>&lt;0.0001</b>

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Significant at p<0.05 (in bold)

## Appendix: VIB

### Comparison of Cost of All-Cause Outpatient Visits in the First Year of Follow-Up by Refractory/ Non-Refractory Status (N=5,596)

	All n=5,596	Refractory n=2,798	Non-refractory n=2,798	p-value
Median (Mean ± SD)	\$4,260 (\$9,705 ± \$19,095)	\$4,925 (\$10,025 ± \$17,760)	\$3,682 (\$9,384 ± \$20,341)	<b>&lt;0.0001<sup>a</sup></b>

<sup>a</sup>Wilcoxon signed-rank test  
Significant at p<0.05 (in bold)

**Generalized Linear Model Comparing the Cost of All-Cause Outpatient Visits in the First Year of Follow-Up among Refractory/ Non-Refractory Patients (N=5,596)**

	<b>Estimate</b>	<b>95% CI</b>	<b>z</b>	<b>p-value</b>
Refractory <sup>a</sup>	0.1685	0.0962 - 0.2408	4.57	<b>&lt;0.0001</b>
Age at index	-0.0013	-0.0042 - 0.0016	-0.86	0.3900
Male <sup>a</sup>	-0.0642	-0.1368 - 0.0085	-1.73	0.0830
African American race <sup>a</sup>	0.1525	0.0534 - 0.2515	3.02	<b>&lt;0.0001</b>
Other race <sup>a</sup>	0.0716	-0.0066 - 0.1499	1.79	0.0730
Partial type of epilepsy at first visit <sup>a</sup>	-0.1005	-0.2626 - 0.0616	-1.22	0.2240
Other type of epilepsy at first visit <sup>a</sup>	0.1139	0.0028 - 0.2249	2.01	<b>0.0440</b>
Multiple actions of index AED <sup>a</sup>	-0.0926	-0.1662 - -0.0190	-2.47	<b>0.0140</b>
Baseline CCI of 1 <sup>a</sup>	0.2014	0.1046 - 0.2981	4.08	<b>&lt;0.0001</b>
Baseline CCI greater than 1 <sup>a</sup>	0.2237	0.1180 - 0.3293	4.15	<b>&lt;0.0001</b>
Number of psychiatric comorbidities at follow-up	0.0884	0.0606 - 0.1162	6.23	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.2544	0.1784 - 0.3305	6.56	<b>&lt;0.0001</b>
Baseline pill burden	-0.0064	-0.01201 - -0.0007	-2.21	<b>0.0270</b>
Baseline all-cause inpatient visits <sup>a</sup>	-0.0840	-0.1801 - 0.0122	-1.71	0.0870
Number of baseline all-cause outpatient visits	0.0274	0.0235 - 0.0313	13.7	<b>&lt;0.0001</b>
Baseline total all-cause healthcare cost	0.0000	0.0000 - 0.0000	11.38	<b>&lt;0.0001</b>

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Significant at p<0.05 (in bold)

## Appendix: VIC

### Comparison of Cost of Epilepsy-Related Inpatient Hospitalization and ED Visits in the First Year of Follow-Up by Refractory/ Non-Refractory Status (N=5,596)

	All n=5,596	Refractory n=2,798	Non-refractory n=2,798	p-value
Median (Mean ± SD)	\$0 (\$1,583 ± \$5,409)	\$0 (\$2,077 ± \$6,156)	\$0 (\$1,091 ± \$4,488)	<b>&lt;0.0001<sup>a</sup></b>

<sup>a</sup>Wilcoxon signed-rank test  
Significant at p<0.05 (in bold)

**Generalized Linear Model Comparing the Cost of Epilepsy-Related Inpatient Hospitalization and ED Visits in the First Year of Follow-Up among Refractory/ Non-Refractory Patients (N=5,596)**

	Estimate	95% CI	z	p-value
Refractory <sup>a</sup>	0.6104	0.4260 - 0.7947	6.49	<b>&lt;0.0001</b>
Age at index	0.0012	-0.0059 - 0.0084	0.33	0.7380
Male <sup>a</sup>	0.0874	-0.0966 - 0.2715	0.93	0.3520
African American race <sup>a</sup>	0.0068	-0.2420 - 0.2557	0.05	0.9570
Other race <sup>a</sup>	-0.0217	-0.2177 - 0.1744	-0.22	0.8290
Partial type of epilepsy at first visit <sup>a</sup>	0.1422	-0.2691 - 0.5534	0.68	0.4980
Other type of epilepsy at first visit <sup>a</sup>	0.1187	-0.1587 - 0.3961	0.84	0.4020
Multiple actions of index AED <sup>a</sup>	-0.1353	-0.3210 - 0.0505	-1.43	0.1540
Baseline CCI of 1 <sup>a</sup>	-0.0298	-0.2740 - 0.2143	-0.24	0.8110
Baseline CCI greater than 1 <sup>a</sup>	-0.0116	-0.2750 - 0.2518	-0.09	0.9310
Number of psychiatric comorbidities at follow-up	0.3255	0.2562 - 0.3948	9.21	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.5313	0.3439 - 0.71869	5.56	<b>&lt;0.0001</b>
Baseline pill burden	-0.0068	-0.02079 - 0.00729	-0.95	0.3430
Baseline all-cause inpatient visits <sup>a</sup>	0.7032	0.4662 - 0.9403	5.81	<b>&lt;0.0001</b>
Number of baseline all-cause outpatient visits	-0.0025	-0.0096 - 0.0047	-0.67	0.5020
Baseline total all-cause healthcare cost	0.0000	0.0000 - 0.0000	3.70	<b>&lt;0.0001</b>

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Significant at p<0.05 (in bold)

## Appendix: VID

### Comparison of Cost of Epilepsy-Related Outpatient Visits in the First Year of Follow-Up by Refractory/ Non-Refractory Status (N=5,596)

	All n=5,596	Refractory n=2,798	Non-refractory n=2,798	p-value
Median (Mean ± SD)	\$577 (\$1,741 ± \$6,418)	\$821 (\$1,980 ± \$5,716)	\$400 (\$1,503 ± \$7,044)	<b>&lt;0.0001<sup>a</sup></b>

<sup>a</sup>Wilcoxon signed-rank test  
Significant at p<0.05 (in bold)

**Generalized Linear Model Comparing the Cost of Epilepsy-Related Outpatient Visits in the First Year of Follow-Up among Refractory/ Non-Refractory Patients (N=5,596)**

	<b>Estimate</b>	<b>95% CI</b>	<b>z</b>	<b>p-value</b>
Refractory <sup>a</sup>	0.3900	0.2882 - 0.4918	7.51	<b>&lt;0.0001</b>
Age at index	-0.0107	-0.0149 - -0.0066	-5.05	<b>&lt;0.0001</b>
Male <sup>a</sup>	-0.0488	-0.1517 - 0.0542	-0.93	0.3530
African American race <sup>a</sup>	0.1634	0.0235 - 0.3032	2.29	<b>0.0220</b>
Other race <sup>a</sup>	0.0534	-0.0575 - 0.1643	0.94	0.3450
Partial type of epilepsy at first visit <sup>a</sup>	-0.1608	-0.3903 - 0.0688	-1.37	0.1700
Other type of epilepsy at first visit <sup>a</sup>	0.0650	-0.0915 - 0.2216	0.81	0.4150
Multiple actions of index AED <sup>a</sup>	-0.0716	-0.1753 - 0.03212	-1.35	0.1760
Baseline CCI of 1 <sup>a</sup>	0.1726	0.03604 - 0.3093	2.48	<b>0.0130</b>
Baseline CCI greater than 1 <sup>a</sup>	0.1239	-0.02481 - 0.2726	1.63	0.1020
Number of psychiatric comorbidities at follow-up	0.0878	0.0476 - 0.1279	4.29	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	0.3027	0.1961 - 0.4094	5.56	<b>&lt;0.0001</b>
Baseline pill burden	-0.0209	-0.0288 - -0.0130	-5.21	<b>&lt;0.0001</b>
Baseline all-cause inpatient visits <sup>a</sup>	-0.2088	-0.3403 - -0.0772	-3.11	<b>0.0020</b>
Number of baseline all-cause outpatient visits	0.0111	0.0064 - 0.0158	4.66	<b>&lt;0.0001</b>
Baseline total all-cause healthcare cost	0.0000	0.0000 - 0.0000	10.19	<b>&lt;0.0001</b>

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Significant at p<0.05 (in bold)

## Appendix: VIE

### Comparison of Cost of All-Cause Pharmacy Claims in the First Year of Follow-Up by Refractory/ Non-Refractory Status (N=5,596)

	All n=5,596	Refractory n=2,798	Non-refractory n=2,798	p-value
Median (Mean ± SD)	\$7,875 (\$10,190 ± \$12,267)	\$9,998 (\$11,857 ± \$9,058)	\$5,780 (\$8,525 ± \$14,607)	<b>&lt;0.0001<sup>a</sup></b>

<sup>a</sup>Wilcoxon signed-rank test  
Significant at p<0.05 (in bold)

**Generalized Linear Model Comparing the Cost of All-Cause Pharmacy Claims in the First Year of Follow-Up among Refractory/ Non-Refractory Patients (N=5,596)**

	<b>Estimate</b>	<b>95% CI</b>	<b>z</b>	<b>p-value</b>
Refractory <sup>a</sup>	0.3646	0.3205 - 0.4086	16.23	<b>&lt;0.0001</b>
Age at index	-0.0043	-0.0061 - -0.0024	-4.48	<b>&lt;0.0001</b>
Male <sup>a</sup>	0.0537	0.0090 - 0.0983	2.35	<b>0.0190</b>
African American race <sup>a</sup>	-0.1621	-0.2232 - -0.1011	-5.20	<b>&lt;0.0001</b>
Other race <sup>a</sup>	-0.0859	-0.1343 - -0.0375	-3.48	<b>0.0010</b>
Partial type of epilepsy at first visit <sup>a</sup>	0.0969	-0.0036 - 0.1974	1.89	0.0590
Other type of epilepsy at first visit <sup>a</sup>	-0.1309	-0.1997 - -0.0620	-3.73	<b>&lt;0.0001</b>
Multiple actions of index AED <sup>a</sup>	0.2149	0.1698 - 0.2600	9.34	<b>&lt;0.0001</b>
Baseline CCI of 1 <sup>a</sup>	-0.0448	-0.1054 - 0.0158	-1.45	0.1480
Baseline CCI greater than 1 <sup>a</sup>	0.0137	-0.0531 - 0.0804	0.40	0.6880
Number of psychiatric comorbidities at follow-up	0.0768	0.0593 - 0.0943	8.60	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	-0.0139	-0.0608 - 0.0330	-0.58	0.5610
Baseline pill burden	0.0430	0.0392 - 0.0469	22.08	<b>&lt;0.0001</b>
Baseline all-cause inpatient visits <sup>a</sup>	-0.2224	-0.2825 - -0.1624	-7.26	<b>&lt;0.0001</b>
Number of baseline all-cause outpatient visits	-0.0058	-0.0074 - -0.0041	-6.92	<b>&lt;0.0001</b>
Baseline total all-cause healthcare cost	0.0000	0.0000 - 0.0000	16.49	<b>&lt;0.0001</b>

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Significant at p<0.05 (in bold)

## Appendix: VIF

### Comparison of Cost of Epilepsy-Related Pharmacy Claims in the First Year of Follow-Up by Refractory/ Non-Refractory Status (N=5,596)

	All n=5,596	Refractory n=2,798	Non-refractory n=2,798	p-value
Median (Mean ± SD)	\$2,904 (\$4,783 ± \$5,634)	\$5,094 (\$6,810 ± \$6,499)	\$1,422 (\$2,756 ± \$3,610)	<b>&lt;0.0001<sup>a</sup></b>

<sup>a</sup>Wilcoxon signed-rank test  
Significant at p<0.05 (in bold)

**Generalized Linear Model Comparing the Cost of Epilepsy-Related Pharmacy Claims in the First Year of Follow-Up among Refractory/Non-Refractory Patients (N=5,596)**

	<b>Estimate</b>	<b>95% CI</b>	<b>z</b>	<b>p-value</b>
Refractory <sup>a</sup>	0.8967	0.8403 - 0.9531	31.17	<b>&lt;0.0001</b>
Age at index	-0.0157	-0.0181 - -0.0133	-12.96	<b>&lt;0.0001</b>
Male <sup>a</sup>	-0.0226	-0.0799 - 0.0345	-0.78	0.4380
African American race <sup>a</sup>	-0.2301	-0.3082 - -0.1520	-5.77	<b>&lt;0.0001</b>
Other race <sup>a</sup>	-0.0661	-0.1281 - -0.0040	-2.09	<b>0.0370</b>
Partial type of epilepsy at first visit <sup>a</sup>	0.1352	0.0068 - 0.2637	2.06	0.0390
Other type of epilepsy at first visit <sup>a</sup>	-0.2279	-0.31606 - -0.1398	-5.07	<b>&lt;0.0001</b>
Multiple actions of index AED <sup>a</sup>	0.3903	0.3330 - 0.4477	13.34	<b>&lt;0.0001</b>
Baseline CCI of 1 <sup>a</sup>	-0.1948	-0.2726 - -0.1171	-4.91	<b>&lt;0.0001</b>
Baseline CCI greater than 1 <sup>a</sup>	-0.2420	-0.3281 - -0.1559	-5.51	<b>&lt;0.0001</b>
Number of psychiatric comorbidities at follow-up	-0.0740	-0.0967 - -0.0512	-6.38	<b>&lt;0.0001</b>
Non-psychiatric comorbidities at follow-up <sup>a</sup>	-0.0501	-0.1101 - 0.0099	-1.64	0.1020
Baseline pill burden	0.0176	0.0126 - 0.0227	6.84	<b>&lt;0.0001</b>
Baseline all-cause inpatient visits <sup>a</sup>	-0.1992	-0.2763 - -0.1221	-5.06	<b>&lt;0.0001</b>
Number of baseline all-cause outpatient visits	-0.0031	-0.0053 - -0.0009	-2.73	<b>&lt;0.0001</b>
Baseline total all-cause healthcare cost	0.0000	0.0000 - 0.0000	7.14	<b>&lt;0.0001</b>

CI=Confidence Interval; AED=Antiepileptic drug; CCI=Charlson Comorbidity Index

<sup>a</sup>Reference categories: Non-refractory; Female; Caucasian; Generalized type of epilepsy; Single action of index AED; CCI=0; No non-psychiatric comorbidity; No baseline inpatient visit

Note: Some variable categories were collapsed due to small cell sizes.

Race/Ethnicity into three groups (Caucasian, African American and Other);

Type of epilepsy into three groups (Generalized, Partial and Other);

Type of index Antiepileptic drug into two groups (Single and Multiple actions).

Significant at p<0.05 (in bold)

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