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Medication Use Patterns of Antiepileptics and Epileptic Events

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Medication Use Patterns of Antiepileptics and Epileptic Events

by

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Dedication

To my amazing mother and my loving husband

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Medication Use Patterns of Antiepileptics and Epileptic Events

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The purpose of this study was to identify clinical and demographic predictors of seizure recurrence in medically-treated patients with epilepsy. Innovus Invision™ Data Mart insurance claims from January 1, 2007 to September 30, 2010 were retrospectively analyzed. Patients aged 18-64 years with a primary or secondary diagnosis of epilepsy and ≥1 prescription claim for an antiepileptic drug (AED) pre-index were included. The primary outcome was incidence of seizures defined as an occurrence of an emergency room visit, ambulance service use or hospitalization with a primary or secondary diagnosis of epilepsy during the 1-year follow-up period. Predictor variables included antiepileptic drug (AED) adherence (Proportion of Days Covered ≥ 80 %), general comorbidity (Charlson's Comorbidity Index ≥ 1), any mental health comorbidity,

evidence of a prior seizure, type of epilepsy diagnosis (intractable versus non-intractable), presence of AED-interacting medications and any bioequivalent AED switch. The covariates included age, gender and geographic region of residence. The overall incidence of post-index seizures in the 1-year follow-up period for all four monotherapy cohorts combined was 5.3 % (n=166/3140), but was higher for the Keppra®/levetiracetam cohort (7.9%; n=88/1114) compared to the other cohorts [Lamictal®/lamotrigine (3.9%; n=45/1143), Trileptal®/oxcarbazepine (4.0%; n=18/456) and Topamax®/topiramate (3.5%; n=15/427)]. The combined cohort analysis demonstrated that pre-index seizures (odds ratio [OR] = 4.28; 95% CI, 2.81-6.53), any mental health comorbidity ([OR] = 3.41; 95% CI, 2.10-5.54), Charlson comorbidity Index ≥1 ([OR] = 2.88; 95% CI, 1.96-4.24) and monotherapy with Keppra®/levetiracetam ([OR] = 1.54; 95% CI, 1.03-2.31) were significant predictors of seizure recurrence. Among covariates, only geographic region was a significant predictor, with patients residing in the Northeast U.S. having higher odds of post-index seizure ([OR] = 1.92; 95% CI, 1.19-3.10), while controlling for clinical, medication and demographic characteristics. A bioequivalent AED switch, type of epilepsy diagnosis, AED adherence and the presence of interacting medications were not significant predictors of seizure recurrence in the combined cohort ($p>0.05$). Results indicate that epilepsy patients with comorbid conditions (both mental and somatic diseases), as well as patients who may have initially been unstable (with previous seizure occurrences) were more likely to experience seizures during the follow-up period.

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CHAPTER ONE

Introduction

In the United States, 2.5 million people are affected with epilepsy and 200,000 new cases are diagnosed annually.[1] The total medical and lost productivity costs associated with the condition are estimated at $15.5 billion.[2] Achievement of seizure-free status is one of the main goals of treatment in patients with epilepsy. The management of psychosocial aspects of the disease, such as normal activity limitations, mental health and emotional/social support, is also paramount.[3] Factors that have been identified in the clinical literature that affect achievement of seizure-free status include age of epilepsy onset, seizure type, electroencephalogram epileptiform activity, medication therapy adherence, physician specialist managing the patient (general neurologist versus epileptologist), mental health retardation, as well as, with the continuing introduction of generic antiepileptic drugs, bioequivalent switches between antiepileptic medications.[4-11] Risk factors such as bioequivalent antiepileptic drug switches are inconclusive with regards to their impact on seizure recurrence.[8-10,12-14]

Information is limited with regard to predictors of seizure recurrence in patients with epilepsy when examining large patient populations with broad patient demographic, disease, medication and healthcare utilization characteristics.[7,8,12,13] Several studies that

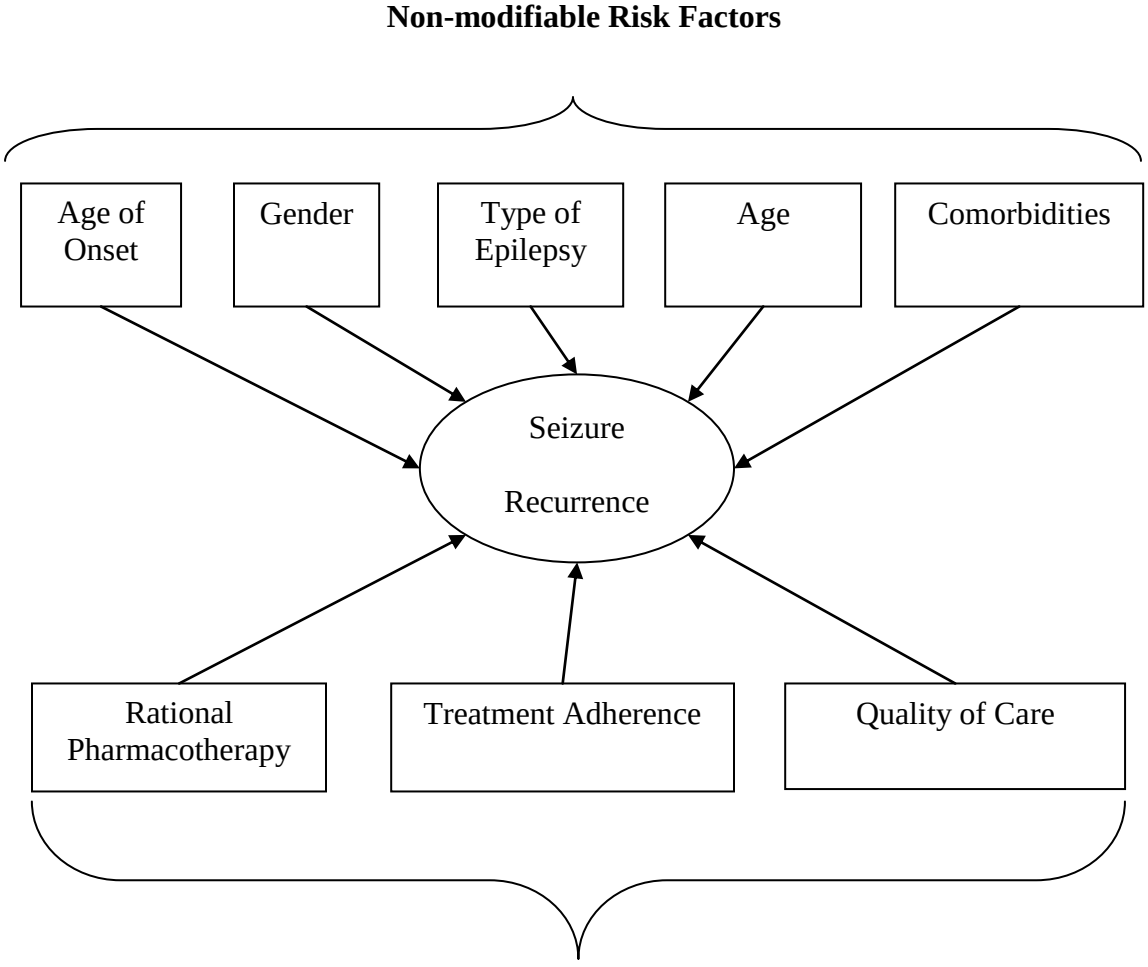
assessed predictors of seizures in patients with epilepsy were primarily conducted using chart reviews and focused on patients with subtypes of epilepsy (e.g., treatment refractory epilepsy, epilepsy after surgery).[11,15,16] Larger studies focused primarily on one specific factor (i.e., adherence, bioequivalent switch) deemed responsible for seizure remission or lack thereof.[7,9,10] There is a need to examine multiple predictors of seizure recurrence using large patient populations with epilepsy in order to help practicing clinicians identify patients at higher risk of seizures and deliver targeted interventions in a timely manner. The proposed study models seizure events along multiple risk factors known to contribute to lack of seizure control including demographic, disease, comorbidity and medication utilization variables.

Conceptual Framework

The conceptual framework for this study (presented in Figure 1) was based on a premise that patients' risk of having a recurrent seizure may be affected by a multitude of modifiable and non-modifiable risk factors.[17-21] Some of the factors are better researched and understood, while others are inconclusive or still under investigation (i.e., bioequivalent antiepileptic drug substitutions).[8-10,12,13,22,23] The non-modifiable risk factors include gender,[19,24] age,[25] age of disease onset,[20] epilepsy type[17] and comorbidites.[21] The modifiable risk factors include rational antiepileptic pharmacotherapy (i.e., aiming towards monotherapy maintenance treatment, avoiding enzyme-inducing antiepileptic drugs (AEDs) in patients over 60, and monitoring of drug interactions),[22,26] treatment adherence,[7] and quality of care.[22,23,27] Quality of care is an umbrella term that can include care provided by an epileptologist versus a general neurologist or primary care physician, care coordination between epileptologists and other clinicians through monitoring of interacting medications prescribing and place of care (patients cared for at specialized epilepsy centers may be less prone to seizure recurrence through provision of more comprehensive seizure management services).[23,28,29] This study provides insights into the complex picture of modifiable and non-modifiable risk factors and their association with seizure recurrence in a geographically-diverse, U.S. epilepsy patient population. Knowledge of the independent risk factors, especially those of a modifiable nature, may help guide policy makers and

clinicians in creating care models that minimize seizure recurrence and increase patients' quality of life.

Figure 1 Conceptual Framework



Literature Review

This section covers background information related to epilepsy including classification, epidemiology, diagnosis, clinical manifestations, treatment modalities and treatment outcomes, as well as the economic burden of the condition. In addition, it examines the literature regarding the factors known to contribute to poor outcomes (i.e., lack of seizure control) including non-adherence, bioequivalent AED switches and comorbidities.

Epilepsy: Classification, Diagnosis, Natural History, Epidemiology

The International League Against Epilepsy (ILAE) defines epilepsy as "a disorder characterized by an enduring predisposition to generate epileptic seizures and by neurobiologic, cognitive, psychological and social consequences of this condition."[30] The definition requires the occurrence of at least one epileptic seizure.[30] An epileptic seizure is "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain."[30] Active epilepsy is ascertained if a patient is being treated for the condition and the most recent seizure occurred within two to five years.[31] At times the range is narrowed to one year due to difficulties associated with recall over a longer period.[31] Although conditions such as febrile seizures, neonatal seizures, solitary unprovoked seizures and provoked seizures may be associated with recurrent seizures, they are not considered 'epilepsy.'[32] In order to diagnose epilepsy, the

American Academy of Neurology and the American Epilepsy Society recommend electronencephalography (EEG), computed tomographic (CT) scanning and magnetic resonance imaging (MRI) of the head, in addition to a panel of blood tests.[6] EEG abnormalities are found in about 50 percent of patients with a first seizure, and additional video EEG monitoring becomes important in order to distinguish the diagnosis of epilepsy from other non-epileptic events.[5,6] About 25 percent of patients with a first unprovoked seizure and an absence of an apparent risk factor (epileptiform activity on EEG) face the risk of recurrence within the following two years.[33]

The most recent classification of epilepsies updated by the ILAE divides seizures into two main groups: generalized (bilateral) and focal (limited to one hemisphere).[34] Table 1 summarizes the ILAE's classification. For the purposes of epidemiological studies, the ILAE suggests a simplified classification that is presented in Table 2.

Table 1 Classification of Seizures

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

Adapted from: Table 1 in Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. 2010 Apr;51(4):676-85.

Table 2 Simplified Clinical Classification of Seizure Type

	Generalized	Focal	Undetermined
Predominantly motor			
Convulsive	Generalized convulsive[a]	Focal onset with secondary generalization[b]	Convulsive undetermined[c]
Other motor	Generalized other motor[d]	Focal motor[e]	Other motor undetermined[f]
Predominantly nonmotor			
Impaired responsiveness[g]	Generalized absense[h]	Discognitive focal seizures (formerly complex partial)[i]	Impaired responsiveness undetermined[j]
Other nonmotor	NA	Sensory, psychic, and other, including autonomic[k]	NA
Unknown	Generalized seizure unspecified	Focal seizure unspecified	Seizure unspecified

[a] Seizure onset is manifested by generalized tonic and/or clonic (convulsive) motor activity and unconsciousness. Focal features may occur.
[b] Seizure onset has focal manifestations that evolve to generalized convulsive activity.
[c] Focal or generalized nature of seizure onset is undetermined, but seizures manifest generalized convulsive activity.
[d] Include myoclonic seizures, eyelid myoclonus, epileptic spasms, atonic seizures, other, and unspecified generalized motor seizures with or without impairment of consciousness.
[e] Seizure has focal manifestations (including myoclonic, inhibitory, Jacksonian march, focal asymmetric tonic, hemiclonic, hyperkinetic, and other focal motor seizures) that do not evolve to generalized convulsive activity.
[f] Unspecified motor seizures; includes neonatal and other seizures.
[g] Staring spells, unresponsiveness, or other alteration of consciousness.
[h] Includes typical and atypical absence seizures.
[i] Focal seizures associated with impairment of consciousness (formerly termed "complex partial") without secondary generalization (Commission in Classification and Terminology of the International Leagues Against Epilepsy, 1989).
[j] Seizure manifested by transient decreased responsiveness or "staring," undetermined if absence or dyscognitive in type.
[k] Includes auras without alteration of consciousness or secondary generalization (including somatosensory and experiential seizures), autonomic and other nonmotor seizures.

Adapted from: Table 1 in Thurman DJ, Beghi E, Begley CE, Berg AT, Buchhalter JR, Ding D, et al. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia. 2011 Sep;52 Suppl 7:2-26.

The current estimated prevalence of epilepsy is about 65 million worldwide.[35] In the United States, approximately 2.5 million people are affected, with 200,000 new cases diagnosed annually.[1] The incidence of epilepsy is 48 per 100,000 population.[25] Higher incidence rates are observed in subpopulations of people, for example, those older than 60 and children/adolescents.[25] The incidence rates reported in children and adolescents is 57 per 100,000 per year.[25] The prevalence among all age groups is about 700 per 100,000 population.[25]

Seizure activity may affect different areas and anatomical structures of the brain and it is clinically manifested through sensorial (auras), motor, consciousness, and autonomic features.[36] Focal or partial seizures are the most common seizures in children and account for about 60 percent of all childhood epilepsies.[37] The main characteristics of these seizures are aura as well as abrupt changes in the behavior. A small region in one hemisphere is affected in a simple partial seizure and the patient is typically alert.[38] Meanwhile, patients with a complex partial seizure (where the affected region is wider) may experience altered consciousness. Partial seizures are manifested with slowed and purposeless movements, motor automatisms such as eye blinking, lip smacking, grimacing, groaning, chewing, unbuttoning and buttoning clothing.[38] Generalized seizures are less common in childhood epilepsy.[37] The generalized seizures are characterized by lack of focus of onset, with large cortex areas or subcortical structures affected. Clinically, these seizures may be hypomotor (absence seizures) or hypermotor (myoclonic, tonic, tonic-clonic), as well as atonic (loss of postural tone). [38]

The typical age of onset for absence seizures is 3 to 12 years old.[39] Seizures may arise in broad brain regions and are manifested clinically through brief arrests with impaired consciousness that may occur several times a day.[38] Children usually would continue a simple motor activity (walking, looking at something) but may not be able to respond quickly to another task. Although absence seizures are considered a most benign type of epilepsy, they still may present psychosocial challenges if witnessed by friends/family or interfere with learning, and also may be a potential hazard if a child continues walking without awareness of his/ her environment.[38]

Tonic-clonic and tonic seizures are manifested clinically with an unusual cry, raspy breathing, cyanosis and incontinence. Anatomically, the seizure activity involves both hemispheres, although initially it can arise focally and then spread. Myoclonic and atonic seizures may have a variety of clinical manifestations including motor events in the neck, trunk and extremities at times leading to abrupt loss of posture. Just like absence seizures, myoclonic and atonic seizures may occur several times a day and may involve trauma associated with a fall as well as impaired consciousness.[38]

Epilepsy may be a self-limited condition that can be resolved over a few years under influence of multiple factors such as: gene product expression, molecular maturation of channels, anatomic developmental changes and altered exposure to environmental triggers.[38] These factors complicate understanding the natural history of the disease. Several studies in children showed changes in epilepsy type or location of the

spike focus in EEG upon follow-up of two to eight years. [37,40] The seizure threshold may be determined by the age of the child, with some children "growing into" and some "outgrowing" the epilepsy due to morphologic and chemical changes in networks.[41] Schmidt and Sillanpaa summarized the evidence-based literature on the natural history of epilepsies and concluded that between 20 and 44 percent of patients who are untreated or undertreated for their condition still achieve remission.[42] As for newly treated patients with epilepsy, the authors argued whether there have been any merits of modern pharmacotherapy by comparing the 64 percent remission rate for one year in patients treated with modern AEDs with that of 70 percent for one year in patients treated with bromide in 1881.[42] However, the authors did acknowledge that two of the three newly diagnosed and treated patients achieved long term remission.[42]

Among patients with refractory epilepsy, about 10 percent may achieve so-called late remission after a period of about nine years.[43] The risk of relapse in pharmaco-resistant patients who achieve remission for one year was shown to be about 71 percent.[44] About 30 percent of patients with refractory epilepsy may have an intermittent pattern of relapse and remission.[45]

Economic Burden of Epilepsy

The costs that are important in calculations of direct economic impact of epilepsy include those for AEDs, hospital and physician visits, diagnostic procedures, treatment of injuries and adverse effects of AEDs.[46] While calculating direct costs, the ILAE suggests including only costs associated with epilepsy, but cautions on the technical difficulty of separating epilepsy costs from those incurred for the treatment of epilepsy-related comorbidities.[47] Indirect (i.e., productivity) costs typically include employment losses and early retirement.[46,48] A recent economic study evaluating the cost burden of epilepsy from a third-party payer perspective in the U.S. found that patients with a diagnosis of epilepsy incurred 2.5 times more direct and indirect costs when compared with patients without the diagnosis ($US 10,258 vs $US 3,862, $p<0.0001$ and $US 3,192 vs $US 1,242, $p<0.0001$, respectively).[49] Strzelczyk et al. reviewed cost-of-illness studies in epilepsy across multiple countries and found that indirect costs as a percentage of total annual costs varied between 12 percent and 85 percent depending on the methodology of the study.[50] For example, the lowest estimate (12%) was from a study conducted in Italy,[51] where productivity loss was calculated through the time spent in the hospital and for ambulatory visits, while the highest estimate (85%) was from a study conducted in the US[52] where lost earnings, working hours and home productivity costs were included. Regarding the breakdown of direct costs by type, Strzelczyk et al.[50] showed that in some studies, the costs of medical treatment with antiepileptic drugs were higher than costs associated with hospitalizations, [48,53,54] whereas, in newly-diagnosed patients, hospitalizations accounted for 47 to 66 percent of annual direct costs.[53,55] Strzelczyk et al. also reviewed the cost of epilepsy as a proportion of national healthcare expenditures and found that it varied between 0.12 and 1.12 percent.[50] Analysis of nationally representative

data of U.S. nonfederal hospital discharges of patients with epilepsy (by Vivas et al.) showed that, in the period between 1993 and 2008, the inflation adjusted mean hospital charges per admission for patients with epilepsy increased from $10,050 in 1993 to $16,046 in 2008.[56] Zachry et al. quantified the dollar impact of the loss of seizure control which required emergency room (ER) care in initially stable patients and found that both epilepsy-related and non-epilepsy-related post-ER costs were significantly higher than pre-ER costs ($15,274 and $7087 versus $12,745 and $2,013, respectively).[57] The authors concluded that return to seizure control after an acute event is associated with significant increases in the costs of care.[57] Besides overall financial burden of epilepsy on healthcare systems, economic burden associated with inpatient care is substantial and maintenance of seizure-free status may allow avoiding costly hospital stays as well as costs associated with reestablishment of seizure control.[49,56,57]

Epilepsy: Treatment

Several treatment modalities exist for epilepsy management, such as vagal nerve stimulation, surgery and pharmacotherapy. However, due to restricted patient subgroups eligible for the first two modalities, as well as their limited effectiveness, pharmacotherapy is the usual initial epilepsy treatment paradigm.[11] The Cleveland Clinic reports that 64 percent of patients seen in its Epilepsy Center from 2007 to 2010 were treated solely with medications.[58]

Pharmacologically, anticonvulsants work by reducing seizure frequency through suppression of neuron excitability via multiple molecular targets in the synapse, including voltage-gated sodium channels, glutamate and GABAa (gamma-aminobutyric type A) receptors.[59] In addition, anticonvulsants may act through modulating synaptic vesicle protein 2A (SV2A).[59] Anticonvulsants are classified into broad-spectrum and narrow-spectrum classes, with the former being effective in a variety of epilepsy diagnoses. The broad-spectrum drugs include valproate, lamotrigine, topiramate, levetiracetam and zonisomide. The narrow-spectrum drugs include carbamazepine, phenytoin, gabapentin, tiagabine, oxcarbazepine and pregabalin. The narrow-spectrum drugs are used in patients with focal epilepsy with partial and secondarily generalized seizures.[60] The narrow-spectrum drugs may be less effective in idiopathic generalized epilepsy syndromes, such as juvenile myoclonic epilepsy and childhood absence epilepsy, and may even lead to seizure exacerbations.[61] Among the newest AEDs, lacosamide (Vimpat®) was approved by the FDA in 2008 (and introduced to the U.S. market in 2009) as an add-on agent for treatment of partial seizures.[62] Another new AED agent, rufinamide (Banzel®), was

approved by the FDA in 2008 as an add-on in the treatment of Lennox-Gastaut Syndrome (LGS) (a rare severe type of epilepsy affecting about 1 to 4 percent of all patients with epilepsy-type disorders).[63]

Consensus with starting therapy after the first unprovoked seizure has not been achieved. A comparison of randomized groups, where treatment was started at once and those where treatment was started upon a recurrence, showed that 76 percent of patients in the immediate and 77 percent of patients in the deferred treatment groups achieved seizure-free status at five years follow-up.[64] However, treatment is justified in most cases when the diagnosis of epilepsy has been confirmed.

An antiepileptic drug is considered effective if it achieves a 50 percent or greater reduction in seizure frequency.[59] About half of patients become seizure-free with their initial medication.[65] For those adding a second medication, two-thirds experience freedom from seizures.[66] Approximately 30 percent of patients may never reach remission with pharmacotherapy.[66,67] Nevertheless, a nationwide survey of patients with refractory epilepsy found that over 70 percent of patients continue to rely on medications for seizure managment.[68]

The selection of pharmacotherapy is based on patient characteristics including age, gender and comorbidities, as well as AED characteristics including effectiveness, safety, tolerability, pharmacokinetic properties, formulations and costs.[69] When patients were asked what was important in their antiepileptic pharmacotherapy in a national survey, seizure control, fewer side effects, convenient dosing regimen and cost were rated in descending order of importance.[70]

Table 3 provides a list of antiepileptic drugs used as monotherapy, with respective doses and titration schedules. Monotherapy is considered the most beneficial medical treatment modality.[71,72] A study of quality indicators in epilepsy care by Pugh et al. in epilepsy patients from a tertiary medical center in New England (n=311) reported the mean number of AEDs prescribed was 1.42 (SD=0.9; Median=1) with over 50 percent of patients being treated with monotherapy.[73] A recent study in the U.K. examined the trends of antiepileptic prescribing between 1999 and 2008 in patients with epilepsy and found that over 70 percent of person-years were treated with monotherapy.[74] The authors also found that use of newer antiepileptics (i.e., lamotrigine and levetiracetam) has steadily increased in all age groups over the study period.[74]

No consensus has been achieved regarding when to stop antiepileptic pharmacotherapy.[75,76] Studies reported a 12 to 66 percent incidence of seizure recurrence upon medication withdrawal after a 2-year seizure-free period.[77] Factors that discourage discontinuation of treatment include: adolescent or adult age (versus children); presence of another clinical condition; abnormal EEG (in children); and epilepsy syndrome with a high likelihood for relapse (any symptomatic epilepsy including juvenile myoclonic epilepsy).[77] Factors that favor withdrawal include: high susceptibility to adverse events of treatment (women of childbearing age); normal EEG (in children); and idiopathic epilepsy.[77,78]

Table 3 Antiepileptic Drugs Used as Monotherapy in Epilepsy

Drug	Starting Daily Dose and Titration	Typical Initial Target Dose (mg/day)
Carbamazepine (Tegretol®, Carbatrol®, Tegretol XR®)	200 mg; increase daily dose by 200 mg every 3 days	400-600
Gabapentin (Neurontin®)	300-600 mg; increase daily dose by 300-600 mg each week [a]	900
Lamotrigine (Lamictal®, Lamictal XR®)	25mg; Initial pharmacotherapy: 25mg/day for 2 wk, followed by increases in the daily dose of 25-50 mg each week	100-200
Levetiracetam (Keppra®, Keppra I ®)	250-500 mg; increase daily dose by 250-500 mg each wk [a,b]	1000-2000
Oxcarbazepine (Trileptal®)	300-600 mg; increase daily dose by 300-600 mg each wk	900-1200
Phenytoin (Dilantin®, Phenytek®)	If initiated without titration, 3-5 mg/kg; may be initiated with a loading dose [a,b]	200-300
Phenobarbital (generic only)	30 mg; increase daily dose by 30 mg every 2 wk	60-120
Pregabalin (Lyrica®)	75-150 mg; increase daily dose by 75-150 mg each wk [a]	Not established
Tiagabine (Gabitril®)	4 mg; increase daily dose by 4 mg each wk	16-36
Topiramate (Topamax®)	25-50 mg; increase daily dose by 25-50 mg each wk	100-200
Valproate, valproic acid (Depakine®, Depacon®), divalproex sodium (Depakote®, Depakote ER®)	250-500 mg, or 10-15 mg/kg orally once a day; increase daily dose by 250-500 mg each wk	750-2000
Zonisamide (Zonegran®)	50 mg, increase daily dose by 50 mg each wk	100-200
a This drug can be initiated at a therapeutic dose b This drug can be administered intravenously		

Partially adapted from: Table 2 in French JA, Pedley TA. Clinical practice. Initial management of epilepsy. N Engl J Med. 2008 Jul 10;359(2):166-76.

Treatment Outcomes and Quality of Care in Epilepsy

Successful epilepsy management includes the reduction in seizure frequency and severity, leading to complete seizure cessation.[79] In clinical trials, outcomes are measured by calculating: the percent of patients who achieved at least a 50 percent seizure reduction; the percent of patients who are seizure-free; and/or the time to the first seizure recurrence.[79] Rating scales are also used to measure outcomes in epilepsy both in clinical trials and clinical practice.[58,79] Examples of these scales include: the Veterans Administration (VA) Seizure Frequency Scale; the Liverpool Seizure Severity Scale; and the National Hospital Severity Scale (NHS3).[79] The Cleveland Clinic in its Epilepsy Center Outcomes Report also includes indicators such as reduction in patients' depression and anxiety symptoms as well as reduction in seizure-related hospitalizations and ER visits.[58]

Pugh et al. proposed a set of indicators to be used in the assessment of quality of care provided to patients with epilepsy.[22] The indicators were selected based on extensive literature reviews, patient focus groups and an expert panel. The final set included 22 primary and secondary quality indicators (QIs) for which consensus was achieved in that they are appropriate, feasible or necessary. The indicators take the form of if-then statements. For example: "IF a patient is diagnosed with a seizure disorder/epilepsy and started on therapy, THEN the patient should be treated with monotherapy;" "IF the

patient reports unacceptable side-effects from AED monotherapy, THEN an alternative AED should be started (with carefully planned crossover);" "IF the patient is on AEDs for two or more years, THEN providers should assess bone health."[22] The indicators were classified into four categories: evaluation of first seizure (3 QIs), initial treatment of epilepsy (7 QIs), follow-up/ chronic epilepsy care (9 QIs), epilepsy care unique to women (3 QIs). In addition, patient-identified quality indicators (5 QIs) included items about providers referring patients to local support groups and social services, educating patients about the condition and communicating about various aspects of treatment and its side effects.[22] When Pugh et al. applied the developed indicators to assess actual quality of care provided to patients with epilepsy in a tertiary care center, they found that only about 50 percent of recommendations within the QI framework were performed.[73] The lowest concordance with suggested recommendations was in care unique to women. In addition, the authors found that patients receiving shared care (provided by a primary care physician and a neurologist) had higher concordance with QIs than patients cared solely by either one of the providers.[73]

Quality of Life in Epilepsy

Use of medications as well as successful management of chronic conditions are accompanied by a multitude of factors beyond correct diagnosis and appropriate treatment, i.e., patients' attitudes about their disease, beliefs about medications, quality of physician-patient relationships, and perceptions of stigma associated with the disease.[80-83] Achieving physiologic homeostasis with medications and other interventions in chronic diseases may not always translate into equivalent 'homeostasis' in the psychosocial realm of the disease, i.e. patients' ability to incorporate disease management techniques into their lifestyles, relationships with the loved ones, as well as achievement of acceptable overall and health-related quality of life.[84]

Because of the transient nature of seizures, periods between seizures comprise more than 99 percent of the lives of most epilepsy patients.[85] Gillam et al. conducted a study to examine concerns that patients with moderate to severe epilepsy report most frequently.[86] Among those concerns, driving, independence and employment, rather than seizures and treatment, were named by patients as most important.[86] Meanwhile, Fisher et al. examined perceptions of patients with epilepsy regarding their seizures and found that the most common two concerns patients stated were uncertainty and fear of having a seizure.[87] A nationwide survey of patients with refractory epilepsy conducted by Wheless found that between 50 and 64 percent of patients believed that their condition was not accepted by society.[68] The European Quality of Life study reported that over 50 percent of patients with epilepsy experience stigma - with a significantly higher level of stigma

reported by patients with frequent seizures.[88] Another study of patients with epilepsy in Korea found that 31 percent of survey participants reported being stigmatized because of their condition, with 21 percent of patients in remission for at least two years still reporting stigmatization.[89] Type of seizure was also associated with the level of stigma, with tonic-clonic seizures being reported as the most stigmatized.[90]

The national survey by Wheless found that patients with refractory epilepsy reported that they felt they were a burden to the people around them, and about 50 percent expressed the desire to be more active socially and civically.[68] When asked to name something that would improve their quality of life, patients listed the following: reduction in seizures and fatigue, improvement of medication effectiveness, and increased participation in social and community functions.[68] When asked to name the worst thing about having epilepsy, patients in a U.S. study by Fisher et al. listed the following: lifestyle limitations (28.2%), social stigma (23.8%), having to take medications (18.7%) and cognitive problems (7.7%).[87] It is important to consider that depending on the type of epilepsy (intractable versus non-intractable), quality of life of epilepsy patients may be affected differently. [68,91,92] Patients with well-controlled seizures report a quality of life that is similar to that of general population.[92] A review by Taylor et al. summarized predictors of health-related quality of life in patients with epilepsy.[93] The authors showed that multiple studies consistently point to a negative association between depression/anxiety and health-related quality of life in both AED-treated and pharmacoresistant patients.[93] Studies by Johnson et al.[94] and Suurmeijer et al.[95] showed

that 30 to 35 percent of variance in health-related quality of life in patients with epilepsy was explained by psychological factors, while only up to 20 percent was explained by seizure frequency and severity. The studies discussed previously point out the different domains that patients with epilepsy identify as important for their well-being - with social functioning and seizure control appearing most frequently. In summary, it is paramount to consider the psychosocial impact of epilepsy in addition to the impact of seizure frequency and severity on patients' quality of life and well-being.

Role of Adherence in Epilepsy Treatment Outcomes

Overall, adherence to antiepileptic medications (similar to adherence to other chronic disease medications) is suboptimal.[96] Patients with epilepsy who are non-adherent may experience an increased rate of seizures leading to trauma, job losses and increased mortality.[7] Davis et al. conducted a study using a large managed care database (PharMetrics Integrated Outcomes Database with 75 commercial health plans included) and found that 39 percent of patients with epilepsy were non-adherent to their therapy.[97] Ettinger et al. found that 41 percent of the elderly patients (>=65 years) with epilepsy were not taking their AEDs as prescribed.[98] Adherence in both studies was measured using the Medication Possession Ratio (MPR). The Medication Possession Ratio is one of the most commonly used measures of adherence to chronic medications using retrospective databases and is calculated using the following formula.[99]

$$MPR = \frac{\text{sum of the days supplied in the observation period}}{\text{days in the observation period}} \text{ x } 100\%$$

It is reported as a ratio or as a percent. The typical cutoff point for considering a patient as being adherent with chronic medications is 0.8, or 80 percent. However, this cutoff is somewhat arbitrary and different studies may use different cutoff points (varying between 50 and 93 percent in some studies).[100] Cramer criticized the use of 80 percent as the cutoff reported in one of the studies examining non-adherence to AEDs and suggested that a 60 percent cutoff be used to distinguish adherent and non-adherent epilepsy patients.[98,101] The rationale is that seizure exacerbations happen at the point when patients take less than 60 percent of their prescribed AED regimen according to the author's own research and her interpretations of findings of other investigators.[101,102] Nevertheless, most AED adherence studies rely on the 80 percent cutoff.[97,98,103] This cutoff is also widely used in adherence studies for other chronic conditions.[96,104-106]

In the Davis et al. study, annual rates of non-adherence to specific AEDs varied from about 32 percent for levetiracetam to about 44 percent for topiramate.[97] Non-adherent patients had a higher likelihood of hospitalization (OR=1.110, p=0.0013), ER visit (OR=1.479, p<0.0001), as well as higher inpatient costs ($1799, p=0.001) and ER costs ($260, p=0.001).[97] Table 4 summarizes the findings of non-adherence patterns by AED from two claims database studies, by Davis et al. and Ettinger et al.

Faught et al. examined the impact of non-adherence to AEDs among a Medicaid population and found that non-adherent patients had a 39 percent higher incidence rate for hospitalizations, a 76 percent higher incidence rate for inpatient days, and a 19 percent higher incidence rate for ER visits than adherent patients (all measured via Incidence Rate Ratio (IRR)).[103] In monetary terms, the effects of non-adherence translated into $4,320 (95% CI: $4,077-$4,564) adjusted incremental costs for inpatient care and $320 (95% CI: $273-$334) adjusted incremental costs for ER visits.[103]

Table 4 Patterns of Non-adherence to Antiepileptic Drugs

Generic Name	Davis et al. (2008)[1] N=10,892		Ettinger et al. (2009)[2] N=1,278	
	Rate of non-adherence, %	Mean MPR	Rate of non-adherence, %	Mean MPR
Topiramate	44.3	0.76	nr*	0.76
Levetiracetam	32.1	0.82	nr	0.87
Valproate sodium	41.9	0.77	nr	0.83
Lamotrigine	32.3	0.83	nr	0.83
Phenytoin	31.9	0.82	nr	0.83
Gabapentin	52.7	0.70	nr	0.71
Oxcarbazepine	37.6	0.80	nr	0.80
Zonisamide	41.9	0.77	nr	0.86
Tiagabine	45.4	0.77	nr	nr
Carbamazepine	37.3	0.80	nr	0.78
Phenobarbital	39.4	0.79	nr	0.63
Overall	39.3	0.78	41.0	0.76

Sources: [1]Davis KL, Candrilli SD, Edin HM. Prevalence and cost of nonadherence with antiepileptic drugs in an adult managed care population. Epilepsia. 2008 Mar;49(3):446-54; [2] Ettinger AB, Manjunath R, Candrilli SD, Davis KL. Prevalence and cost of nonadherence to antiepileptic drugs in elderly patients with epilepsy. Epilepsy Behav. 2009 Feb;14(2):324-9.
*nr=not reported

Ettinger et al. examined non-adherence to AEDs and associated costs among a population of patients who were 65 years or older.[98] The study found that 41 percent of study patients had adherence lower than 0.8 (as measured by MPR) and 25 percent of patients had adherence lower than 0.6.[98] Mean MPR for all antiepileptic agents was found to be 0.76, with the highest MPR for levitiracetam (0.87), zonisamide (0.86) and lamotrigine (0.83).[98] Results of a multivariate regression showed that patients who were non-adherent to their AEDs (MPR<0.8) had 0.19 additional hospital admissions

(p=0.0071), 2.3 additional inpatients days (p=0.0003), 0.225 additional ER admissions (p=0.0002) and $2674 total incremental costs (p=0.0059).[98]

In summary, according to the findings from Davis et al. and Ettinger et al., 39 to 41 percent of non-Medicaid commercial insurance patients with epilepsy were non-adherent to their AED therapy. The non-adherent patients had significantly higher resource utilization and costs compared to adherent patients while controlling for differences between the two groups.[7,97,98] Adherence appears to play a role in seizure exacerbations requiring medical services use in medically treated patients with epilepsy.

Drug-drug Interactions in Antiepileptic Pharmacotherapy

Antiepileptic medications as a drug class are responsible for the largest number of drug-drug interactions.[107] However, those are more prevalent among older first generation antiepileptics (carbamazepine, phenytoin, phenobarbital and valproate). Newer AEDs have a much lower rate of interacting properties, with lamotrigine and topiramate being the most interactive newer antiepeileptics and levetiracetam being the least interactive AED.[107,108] Drug-drug interactions may be pharmacokinetic or pharmacodynamic in nature.[109] Pharmacokinetic drug interactions can occur through a variety of mechanisms and include enzyme inhibition or induction, changes in protein binding, metabolism or excretion.[110] The simplified clinical classification of drug interactions includes three levels.[110] Level 1 interactions are to be avoided because those may result in serious clinical consequences. Level 2 interactions may require dosage

adjustment because combinations may be difficult to avoid. Level 3 interactions typically do not lead to a change in serum concentrations and, hence, do not require dosage adjustment. Older antiepileptic drugs, such as carbamazepine and phenytoin, are strong enzyme-inducers - with carbamazepine also being an autoinducer because it increases its own metabolism. The clinical relevance of the interaction may be especially prominent when an AED-enzyme inducer is taken with another AED. For example, when co-administered with an inducer, lamotrigine's half-life may be shortened from 30 to 15 hours[111] and the clearance of levetiracetam may increase up to 37 percent.[112,113] On the other hand, valproic acid is a strong enzyme inhibitor, and may increase concentrations of other AEDs to toxic levels. When co-administered with valproic acid, lamotrigine's concentration may increase up to 211 percent [114] and rufinamide's up to 70 percent.[115] In addition to drug-drug interactions between AEDs, drugs from other therapeutic classes may interact with antiepileptics. For example, co-administration of lamotrigine with oral contraceptives may significantly reduce serum concentration of the former (from 28 to 12 μmol/L) and result in reduced seizure control (a level 1 interaction).[116] Interaction of valproic aid with oral contraceptives is less pronounced (22% to 45% increase in clearance of total valproic acid) and constitutes a level 2 interaction.[117]

Pharmacodynamic drug interactions may cause a change in pharmacological effect at the site of drug action without a change in drug concentrations.[109] Typically these interactions can be predicted based on the knowledge of the drugs' mechanisms of action and can be classified as additive, synergistic, and antagonistic.[109] For example, carbamazepine and oxcarbazepine have similar mechanisms of action and co-administration may lead to an additive effect causing neurotoxicity.[118] At the same time,

pharmacodynamic drug interactions may be beneficial during co-administration of drugs with different mechanisms of action. For example, co-administration of lamotrigine with valproic acid, though difficult pharmacokinetically due to inhibition of lamotrigine metabolism, may be remarkably effective in the control of refractory complex partial seizures, absence seizures and other seizure types.[119,120] Because many AED drug interactions may impact the clinical outcome (seizure control), consideration should be given to assess potential interactions and make appropriate adjustments.

Role of Bioequivalent Switches in Epilepsy Treatment Outcomes

Bioequivalence is defined as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administrated at the same molar dose under similar conditions in an appropriately designed study."[121] The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Act) gave a boost to the growth of generic drugs.[122] The Hatch-Waxman Act significantly simplified a generic manufacturer's path to product approval. As long as a generic version of drug X is bioequivalent (i.e., A-rated) to its brand name counterpart, it is listed in the Federal Drug Administration (FDA) publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (Orange book). A-rated generic drug products may be dispensed interchangeably with a brand product or a product of another generic manufacturer that is A-rated as well. The availability of generic medications brings increased patient access and lower prices resulting in cost savings to both patients and payers.[123]

A retrospective analysis from the Division of Bioequivalence of the FDA Office of Generic Drugs evaluated bioequivalence measures from 2,070 single-dose bioequivalence studies of drugs from multiple medication classes approved between 1996 and 2007.[124] The authors found that the average difference between generic and innovator products in the rate of absorption and extent of absorption was 4.35 and 3.56 percent,

respectively.[124] In addition, 98 percent of the studies showed less than a 10 percent difference in the extent of absorption in the generic product versus the brand drug product.[124] These observed differences between innovator and test products may seem small and grant confidence in the comparable quality of generic drugs. However, there still remains controversy within the medical community and among patients regarding the equivalence of generic drug products in certain therapeutic classes (e.g., antiepileptic drugs, immunosuppressive products, warfarin, drugs with a narrow therapeutic index, drugs with variable absorption patterns and drugs with nonlinear pharmacokinetics).[125-127] Krauss et al. conducted a study evaluating drug exposure (AUC_{0-t}) and peak concentration (Cmax) of multiple generic antiepileptic drugs and comparing those with reference (i.e., innovator) products.[128] The authors found that AUC_{0-t} and Cmax differed by <15 percent and <17 percent in 99 percent and 89 percent of bioequivalence studies, respectively. However, when they ran simulations with 595 pairs of AED generic formulation switches, they found that in 17 percent of the pairs the AUC_{0-t} differed >15 percent, while Cmax differed by > 15 percent in 39 percent of the examined pairs. Although total drug delivery was similar between generic-to-generic formulations switches, the peak concentration differences were more prevalent among those switches. Krauss et al. also found that differences in bioavailability between formulations were more pronounced in AEDs with low solubility and bioavailability. This study showed that there might be a larger variability between brands and generics in the case of antiepileptic drugs that found in general bioequivalence studies of brands and generics without therapeutic class breakdown.

To date, several studies have assessed the association between bioequivalent antiepileptic medication switches and patients' seizure control using insurance claims databases.[8-10,12-14] A summary of these studies' characteristics, including patient populations, study designs and main findings is presented in Table 5. All identified studies (6) selected presence of the diagnosis of epilepsy with the ICD-9 code of 345.xx (excluding 345.6x (infantile spasms)) as the main inclusion criterion. Gagne et al. also included ICD-9 code 780.3x (convulsions), while Erickson et al. included codes 780.3 and 780.39 (non-febrile convulsions) and Devine at al. included code 798.3x (convulsions).[12-14] Rascati et al., Zachry et al. and Hansen et al. included patients 12-64 years of age. Devine et al. included patients 18-64 years old. Erickson et al. and Gagne et al. did not specify the age range of included patients and only reported mean (SD) age of cases of 61.2 (16.9) and 35.2 (23.8) years, respectively.

Three studies used a case-control design with the cases defined as patients who experienced acute epilepsy exacerbations with an ambulance service, an ER visit or an inpatient hospitalization with an epilepsy diagnosis code and the exposure variable defined as the occurrence of an A-rated medication switch.[8-10] Rascati et al. and Hansen et al. built their methodologies on Zachry et al.'s study, but used different datasets. One study used a nested-case control design, albeit with similar definitions of cases and exposure as the previous three studies.[13] Yet another study by Erickson et al. used a retrospective cohort study design and compared patients who experienced an antiepileptic medication switch with those who maintained their initial medication.[12] The outcome variables included rate of AED discontinuation, addition of another AED as well as all-cause (not epilepsy-related only) ER visits and hospitalizations.[12] Finally, Gagne et al.

used a case-crossover design with the exposure variable of refill of an AED defined as a refill of the same medication or a bioequivalent version of the antiepileptic medication.[14] Case-control studies stipulated absence of ambulance service use, ER visit or hospitalization six months prior to the index date as patients' inclusion criterion. In all the studies, patients were required to have continuous insurance eligibility six months prior to the index date and at least one year post-index. The majority of studies included only patients who were adherent to their treatment regimens (had at least 145 days of supply of medication in the 180-day pre-index period).[8-10,12]

When conducting matched analyses of cases and controls in case-control studies, patients were matched based on type of epilepsy diagnosis and age (within 5 years range).[8-10,13] In terms of covariates, their number varied in each study and included the following: comorbidity (measured by a comorbidity index score),[13] total number of antiepileptic medications dispensed,[8,13] as well as number of interacting medications.[13]

Studies by Rascati et al., Zachry et al and Hansen et al. found that patients who experienced an AED bioequivalent substitution were 57 to 81 percent more likely to experience a seizure-related event (i.e. ER visit, ambulance service use or hospitalization).[8-10] The study by Erickson et al. did not find a difference in ER-visits and hospitalizations in the AED switched versus continuing cohorts of patients which was similar to results from the Devine et al. nested case-control study.[12,13] Gagne et al. found that refilling the same AED was by itself associated with increased risk of ER visit or hospitalization (OR=2.31, CI: 1.56-3.44), whereas switching to a bioequivalent AED was not associated with increased risk of seizure events when the odds ratio was adjusted for refill-attributed risk (OR=1.19, CI: 0.35-3.99).[14] Taking into account the variability in

the number of potential confounders that were controlled in the studies examined, the effect of the bioequivalent antiepileptic switch on seizure events remains uncertain.

Table 5 Summary of AED Bioequivalent Switch Studies

Study/Data Source/Timeframe[1]	Patient Population	Design, index date definition and statistical analysis	Findings
Zachry et al. Epilepsia. 2009 Mar;50(3):493-500. Ingenix Lab Rx (managed Medicare, Medicaid and employed commercially insured patients) 1/1/2006-12/31/2006 N=1,664 (416 cases and 1,248 controls)	1. 12-64 y.o. 2 .Diagnosis 345.xx (excl. 345.6x) 3. Continuous insurance eligibility 4. No ER visit, ambulance service or hospitalization with above diagnosis 6 months prior to the index date 5. 145 days of supply of AED in 6 months prior to the index date	1. Case-control 2. Index date for cases: inpatient admission, ER visit or ambulance service between 7/1/2006-12/31/2006; Index date for controls: ambulatory visit with epilepsy diagnosis; 3. Exposure: presence of the switch between A-rated AEDs 4. Discordant pairs analysis	OR=1.81 (95% CI 1.25 to 2.63) with cases having 81% greater odds of an A-rated switch

Table 5 Summary of AED Bioequivalent Switch Studies (Continued)

Study/Data Source/Timeframe	Patient Population	Design, index date definition and statistical analysis	Findings
Rascati et al, Pharmacotherapy. 2009 Jul;29(7):769-74. PharMetrics (data from 75 managed care organization) 10/1/2005-12/31/2006 N=3,964 (991 cases and 2,973 controls)	1. 12-64 y.o. 2. Diagnosis 345.xx (excl. 345.6x) 3. Continuous insurance eligibility 4. No ER visit, ambulance service or hospitalization with above diagnosis 6 months prior to the index date 5. 145 days of supply of AED in 6 months prior to the index date	1. Case-control 2. Index date for cases: inpatient admission, ER visit or ambulance service between 10/1/2005-12/31/2006; Index date for controls: patients diagnosed with epilepsy in a clinician's office within the same time period; 3. Exposure: presence of the switch between A-rated AEDs 4. Discordant pairs analysis	OR=1.84 (95% CI 1.44 to 2.36) with cases having 84% greater odds of an A-rated switch

Table 5 Summary of AED Bioequivalent Switch Studies (Continued)

Study/Data Source/Timeframe[1]	Patient Population	Design, Index Date Definition and Statistical Analysis	Findings
Hansen et al. Epilepsy Behav. 2009 Aug;15(4):481-5 Thompson Healthcare MarketScan 1/1/2006-12/31/2006 N=3,028 (757 cases and 2,271 controls)	1. 12-64 y.o. 2. Diagnosis 345.xx (excl. 345.6x) 3.Continuous insurance eligibility 4. No ER room visit, ambulance service or hospitalization with above diagnosis 6 months prior to the index date 5.145 days of supply of AED in 6 months prior to the index date	1. Case-control 2. Index date for cases: inpatient admission, ER visit or ambulance service between 6/1-12/12/2006; Index date for controls: ambulatory visit with epilepsy diagnosis; 3. Exposure: presence of the switch between A-rated AEDs 4. Discordant pairs analysis	OR=1.84 (95% CI 1.44 to 2.36) with cases having 84% greater odds of an A-rated switch OR=1.78 (95% CI 1.35 to 2.36) with cases having 78% greater odds of an A-rated switch; OR=1.57 (95% CI 1.17 to 2.10) when adjusted for gender and total number of AEDs filled; Time from last switch to the index date was 13.1 days shorter for cases (95% CI=1.2-25); Cases tended to have switches between generic formulations (59.5%), while controls tended to have more brand-to-generic switches (43.5%)

Table 5 Summary of AED Bioequivalent Switch Studies (Continued)

Study/Data Source/Timeframe[1]	Patient Population	Design, Index Date Definition and Statistical Analysis	Findings
Gagne et al. Clin Pharmacol Ther. 2010 Sep;88(3):347-53. Healthcare database from British Columbia, Canada 1997-2005 N=1,762	1.Diagnosis 345.xx (excl. 345.6x) or 780.3x (convulsions) 2. At least one diagnosis of epilepsy or seizure recorded in the outpatient file 365 days prior to the index date.	1. Case-crossover 2. Index date for cases: occurrence of the diagnosis of interest in the inpatient file 3. Exposure risk windows and induction periods for refilling/switching were defined as follows 1-day induction period and a 21-day exposure window (i.e., case period) 4. Discordant pairs analysis	OR=2.31 (95% CI 1.56 to 3.44) for seizure-related event associated with refill; OR=2.75 (95% CI 0.88 to 8.64) for seizure-related event associated with the switch. OR=1.19 (95% CI 0.35 to 3.99) for seizure-related event associated with the switch adjusting for refill.

Table 5 Summary of AED Bioequivalent Switch Studies (Continued)

Study/Data Source/Timeframe[1]	Patient Population	Design, Index Date Definition and Statistical Analysis	Findings
Devine et al. Curr Med Res Opin. 2010 Feb;26(2):455-63. Thomson Reuters MarketScan Research 1/1/2005-12/31/2007 N=11,796 (2,949 cases and 8,847 controls)	1. 18-64 y.o. 2. Diagnosis 798.3x, 345.0x-345.5x; 345.7x-345.9x 3.Continuous insurance eligibility 4. No ER or inpatient visit with above diagnosis in the period 7/1/2005-12/31/2005	1. Nested Case-control; 2. Index date for cases: first acute epilepsy exacerbation claim; 3. Exposure: presence of the switch between A-rated AEDs (brand to generic, generic to generic, generic A to generic B)during 90 days before the index date 4. Discordant pairs analysis	OR=1.51 (95% CI 1.29 to 1.76) unadjusted; OR=1.08 (95% CI 0.91 to 1.29) adjusted for confounders: age, comorbidity, total number of AEDs, total number of interacting medications, total number of new AEDs in the 90 days prior to the index date, change in epilepsy diagnosis in the 180 days prior to the index date

Table 5 Summary of AED Bioequivalent Switch Studies (Continued)

Study/Data Source/Timeframe[1]	Patient Population	Design, Index Date Definition and Statistical Analysis	Findings
Erickson et al. Epilepsia. 2011 Jul;52(7):1365-71 Medicare and commercial claims database Identification periods for patient cohorts: 1/1/2002-9/30/2008 (phenytoin cohort); n=745 in each cohort 7/29/2008-9/30/2008 (divalproex cohorts); n=399 in each cohort 7/23/2008-9/30/2008 (lamotrigine cohorts); n=995 in each cohort	1. 18-64 y.o. 2. Diagnosis 345.xx or 780.3x or 780.39 as main or secondary 3. At least one ER visit or hospitalization in the 365 days preceding the index date 4. >=144 days of supply of AED in 6 months prior to the index date	1. Retrospective cohort study 2.Switch and non-switch cohorts 3. Primary Outcome Measures: a) incidence rate ratios (IRR) of discontinuation of index AED; change in dose of index AED or addition of another AED; b) event rate ratio (ERR) of the composite all cause ED visit or hospitalization	IRR for lamotrigine cohort between switchers and non-switchers : 1.00 (95% CI 0.84 to 1.19); IRR for divalproex cohort between switchers and non-switchers : 1.02 (95% CI 0.88 to 1.42); IRR for phenytoin cohort between switchers and non-switchers : 1.85 (95% CI 1.50 to 2.29); ERRs between switchers and non-switchers for all cohorts were non-significantly different

[1]For case control studies: case= index claim for ER-visit, ambulance ride or hospitalization with a primary or secondary diagnosis of epilepsy; exposure= claim for a generic AED prior to index claim

Comorbidities in Epilepsy

Comorbidities in patients with epilepsy impact mortality as well as patients' quality of life.[129,130] An epidemiological study of comorbidity in patients with epilepsy in the UK found that 41 percent of patients had a psychiatric diagnosis - including 18 percent having depression, 15 percent anxiety and 9 percent psychoses.[131] A Canadian study of adult patients with epilepsy found the prevalence of mental health conditions to be about 23.5 percent.[132] Conditions such as organic and nonorganic psychoses, schizophrenia and alcohol dependence had a four to six times higher prevalence in patients with epilepsy than in the general population without the condition.[131] On the other hand, a study of patients with epilepsy and intellectual disability in UK found that prevalence of mental health disorders (such as schizophrenia spectrum disorders, personality and anxiety disorders and depression) was lower in patients with epilepsy than in patients without epilepsy.[133] The authors of the UK study considered that possible explanations of the findings might be two-fold: psychotropic and mood-stabilizing effects of antiepileptic drugs or, alternatively, reluctance of clinicians to give additional diagnoses to patients with intellectual disabilities and epilepsy.[133] Pugh et al. examined the prevalence of psychiatric comorbidities in veterans with epilepsy and found that 48% of veterans with epilepsy had at least one psychiatric comorbidity.[134] The authors found that patients with comorbid psychiatric conditions had higher rates of emergency and primary care utilization than patients with epilepsy only.[134]

Somatic comorbidity varied by patients' age and gender cohorts, with younger patients having three times more occurrences of congenital abnormalities and a two times higher risk of blood disorders - with the risk in both groups being higher for male patients.[131] A study of cause-specific mortality rates in patients with epilepsy in Sweden found the general standardized mortality ratio (SMR) was 3.6, which was a significantly higher mortality risk than that of the general population.[135] The excess risk rate was attributable to different comorbid conditions including: neoplasms (SMR=2.6), cardiovascular diseases (SMR=3.1), injuries and poisoning (SMR= 5.6)

Psychiatric, cognitive and behavioral disorders are common in patients with epilepsy, with some research findings suggesting that those disorders by themselves increase the risk of epilepsy onset.[136,137] A study of children with recent onset epilepsy showed that children diagnosed with idiopathic epilepsy within one year or less had higher lifetime-to-date rate of depressive disorders (22.6% vs 4% in healthy controls), anxiety disorders (35.8% vs 22% in healthy controls) and attention deficit disorders (24.6% vs 10% in healthy controls). [138]

Regarding alcohol dependence, a few studies have investigated the prevalence of this comorbidity in patients with epilepsy.[139,140] Alcohol consumption itself may be a risk factor for epilepsy through head trauma leading patients with alcohol dependence to posttraumatic epilepsy.[139] In addition, alcohol-dependent patients after prolonged drinking may experience several seizures six to 48 hours after cessation of alcohol consumption.[141] A review by Chan identified a 12 to 36 percent prevalence of alcoholism in patients with seizures, although some studies included in the review did not distinguish between seizures due to epilepsy versus seizures due to alcohol withdrawal.[140]

Unpublished data from Sweden showed that the prevalence of alcoholism in male patients with epilepsy was 40.5 percent, while in female patients it was 6.9 percent. [142]

A recent U.S. national study examined the prevalence of comorbidities in children (0 to 17 years) with epilepsy and found that 50 percent had developmental delays and 56 percent had learning disabilities.[143] In addition, children with a current seizure disorder were more likely than those never diagnosed with the condition to have depression (8% vs 2%), anxiety (17% vs 3%), attention-deficit/hyperactivity disorder (23% vs 6%) and autism spectrum disorders (16% vs 1%).[143] From the epidemiological studies examined, it is apparent that patients with epilepsy may have multiple comorbidities, with some comorbidities (e.g., alcoholism) at times playing a causal role in seizure onset.

Sudden Unexpected Death in Epilepsy

Sudden unexpected death in epilepsy (SUDEP) is defined as "sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death of patients with epilepsy with or without evidence of seizure, excluding documented status epilepticus, and in whom post-mortem examination does not reveal a structural or toxicological cause of death." [144] The incidence estimates of SUDEP in patients with epilepsy vary depending on the patient population being studied.[144] Tomson et al. summarized the incidence estimates of SUDEP across 26 studies of different populations with epilepsy and showed a range of 0.09-0.35 per 1000 person-years in unselected cohorts of patients with epilepsy to 9.3 per 1000 person-years in a cohort of patients with epilepsy seeking surgery.[144] A recent study by Hesdorffer et al. examined risk factors for SUDEP by pooling four case-control studies conducted in the U.S., Sweden, Scotland and England.[145] The authors included studies that examined patients with more than one seizure in the past five years with death that occurred suddenly and unexpectedly (no apparent illness responsible) and the cause being unexplained after autopsy.[145] The authors used logistic regression to adjust for study, patient age, gender and duration of epilepsy and found that increased frequency of generalized tonic-clonic seizures, polytherapy, young age at onset, male gender, symptomatic etiology and lamotrigine therapy were significant risk factors for SUDEP.[145] Male patients were at a 1.4-fold higher risk for SUDEP, while patients with epilepsy of idiopathic/cryptogenic etiology or idiopathic generalized epilepsy had a reduced risk for SUDEP.[145] The authors suggested that improved management of generalized tonic-clonic seizures would be more important in preventing SUDEP than reduction in number of AEDs prescribed. Another study of 24 patients with SUDEP in Canada found that age between 20 and 29 years and lack of compliance to antiepileptic

pharmacotherapy (post-mortem confirmed subtherapeutic concentrations in the blood) were seen most commonly among this small cohort examined.[146] SUDEP is a major concern for patients with epilepsy and awareness and mitigation of modifiable risk factors (e.g., improvement of patient compliance, achievement of monotherapy regimen) of SUDEP may prevent or reduce mortality among epilepsy patient population.

Regional Variation in Epilepsy Care

Geographic differences in treatment patterns exist and are documented for a variety of disease states.[147-150] Koubeissi et al. examined in-hospital mortality and predictors of the need for blood transfusion in pediatric patients with refractory epilepsy undergoing hemispherectomy and found that geographic region was a significant predictor of mortality and complications (patients in the Midwest and South were about 5 times more likely to be in need of transfusion).[151] Several retrospective claims database studies that examined the association between bioequivalent antiepileptic medication switch and occurrence of ER visits and/or hospitalizations controlled for geographic region in their statistical analyses.[8-10,13]

Insurance Claims Databases and Outcomes Research

Insurance claims databases, although initially created solely for administrative and reimbursement purposes, are now a substantial resource for conducting research in health outcomes, pharmacoepidemiology and medication safety, as well as health economics.[152-154] Commercial vendors aggregate medical and pharmacy claims data from multiple commercial insurance health plans and provide the data to pharmaceutical companies, consulting agencies and research organizations. Some of the popular commercial database vendors in the U.S. include Optum Insight (formerly Ingenix), Wolters Kluwer, Thomson Reuters (MarketScan database) and IMS Health (PharMetrics Integrated Database). The benefits of relying on the claims databases as the data source for outcomes research include affordable cost and timeliness. With the expansion of electronic medical records documenting medical history and diagnostic test results, database studies may answer more complex research questions with increased validity.[154] Although randomized controlled trials and prospective observational cohort studies may provide a higher level of evidence in answering research questions, both are expensive to conduct, take more time and, in certain circumstances, may not be feasible. For instance, if a randomized trial is to be launched to compare outcomes in patients taking a brand antiepileptic versus a generic one, the study would require multiple arms in addition to the main two arms due to a multitude of generic manufacturers present in the marketplace. However, database studies may have several limitations including potential misclassifications due to coding errors, use of proxies to ascertain occurrence of certain

events (e.g., seizure-related primary diagnosis in the inpatient or ER claim as a proxy of seizure event) and threats to internal validity, whereby it is only possible to establish association and not causation between the variables of interest. Meanwhile, the proper database study design and methodology may highlight the direction of the relationships between variables, which in turn may lead to further more rigorous investigations supported by initial database generated evidence.

Study Rationale, Objectives and Hypotheses

To date, few studies are available that examined predictors of breakthrough seizures in medically-treated patients with epilepsy using large patient populations with the condition. [7-10] Many studies focus on a single factor (adherence, bioequivalent switch) while assessing its effect on seizure control.[7,10] There has been a need for a large population-based study to assess simultaneously multiple factors that may affect seizure control in medically-treated patients with epilepsy. The proposed study attempted to fill the existing gap and assess simultaneously multiple factors, modifiable and non-modifiable, known to contribute to acute seizure events in medically treated patients with epilepsy. The study objectives were:

1. To determine healthcare utilization patterns of medically treated patients with epilepsy by calculating:

   i) Number of ER visits, ambulance services and hospitalizations with a primary or secondary diagnosis of epilepsy in a distinct cohort of patients with epilepsy treated with AED monotherapy.
   ii) Medication adherence.
   iii) Frequency of patients' concomitant use of AED-interacting medications.
   iv) Seizure types most prevalent among medically treated patients in each of the monotherapy cohorts.
   v) Comorbidity status of medically treated patients.
   vi) Mental health comorbidity status of medically treated patients.

vii) Frequency of bioequivalent AED switches in medically treated patients.

Descriptive statistics (means, frequencies, percent) were used to achieve this study objective.

2. To develop a prediction model of acute seizure events resulting in ER visits, ambulance services or hospitalizations based on the factors identified in the literature, including: AED adherence, bioequivalent AED medication switch, presence of AED-interacting medications, type of epilepsy diagnosis, prior seizures and presence of mental comorbidities, while controlling for covariates such as age, gender and geographic region.

Study hypotheses together with measurement levels for dependent and independent variables and statistical tests used are presented in Table 6.

Table 6 Study Hypotheses, Study Measures and Statistical Tests

Description	DV[1]	Measurement	IV[2]	Measurement	Statistical Test
H1: AED nonadherence is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.	Post-index seizure	Nominal	Adherence	Continuous Nominal	Pearson Chi-Square; logistic regression
H2: A bioequivalent medication switch is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.	Post-index seizure	Nominal	Bioequivalent Switch	Nominal	Pearson Chi-Square; logistic regression
H3: Presence of AED-interacting medications is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.	Post-index seizure	Nominal	Interacting Medications	Nominal	Pearson Chi-Square; logistic regression
H4: Type of epilepsy diagnosis is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.	Post-index seizure	Nominal	Type of epilepsy diagnosis	Nominal	Pearson Chi-Square; logistic regression
H5: A prior acute seizure event is a significant predictor of seizure recurrence in medically-treated patients with epilepsy.	Post-index seizure	Nominal	Pre-index seizure event status	Nominal	Pearson Chi-Square; logistic regression
H6: A mental health diagnosis is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.	Post-index seizure	Nominal	Mental Health Diagnosis	Nominal	Pearson Chi-Square; logistic regression

Table 6 Study Hypotheses, Study Measures and Statistical Tests (Continued)

Description	DV[1]	Measurement	IV[2]	Measurement	Statistical Test
H7: Presence of comorbidity is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy	Post-index seizure	Nominal	Comorbidity	Nominal	Pearson Chi-Square; logistic regression
H8: Higher age is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy	Post-index seizure	Nominal	Age	Continuous Nominal	Pearson Chi-Square; logistic regression
H9: Female gender is a significant predictor of breakthrough seizures in medically treated patients with epilepsy.	Post-index seizure	Nominal	Gender	Nominal	Pearson Chi-Square; logistic regression
H10: U.S. Region is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy	Post-index seizure	Nominal	U.S. Geographic Region	Nominal	Pearson Chi-Square; logistic regression
H11: Type of AED monotherapy is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy (tested in the combined cohort only)	Post-index seizure	Nominal	Type of AED agent	Nominal	Pearson Chi-Square; logistic regression

[1] DV=Dependent Variable; [2]IV=Independent Variable.

CHAPTER TWO

Methodology

Objectives of the proposed study were addressed using eligibility, prescription and medical claims data obtained through a data agreement with Quality Metric,[155] an intermediary that provided access to the Innovus Invision™ Data Mart dataset. The Innovus Invision™ database is offered to clients of i3 Innovus for the purposes of outcomes and healthcare services research.[156] The study's protocol received Institutional Review Board (IRB) approval from The University of Texas at Austin IRB Board. This chapter describes the variables that were included in this study, their operational definitions, study design and statistical analyses.

Data Source

Prescription and medical claims for this study were extracted from the de-identified Innovus Invision™ Data Mart database that represents an employed, commercially-insured population and their dependents. The database represents a geographically diverse population across the U.S. of approximately 15 million covered lives. These patients received health care through a variety of health plans (e.g., preferred provider organizations (PPOs), point-of-service (POS) plans, exclusive provider

organizations (EPOs), indemnity plans and health maintenance organizations (HMOs). Patient enrollment, demographic (e.g., date of birth, gender) and plan type information was extracted from the member file, while individual patient-level inpatient and outpatient medical and outpatient pharmacy claims were extracted from the medical and pharmacy files, respectively. Database access for the purposes of this dissertation study was granted through a third-party agreement between The University of Texas at Austin and QualityMetric, the database owner. The data used for this study included records for the period between January 1, 2007 and September 30, 2010. These were the most recent data available. One of the study hypotheses tested the association between bioequivalent AED switch and subsequent seizure events, and the study time frame included the periods following generic launches of several AEDs: oxcarbazepine (October 2007), lamotrigine (July 2008), levetiracetam (November 2008), and topiramate (April 2009). As a result, it was possible to assess bioequivalent switches (from brand to generic AED) as possible predictors, potentially affecting hospitalizations, ER visits and ambulance service use.

ER Visits and Hospitalizations as Proxies of Seizures

Although no studies were identified that validated ICD-9 codes for epilepsy in ER and hospital discharge records in the U.S., a study in Canada examined the validity of ICD-9 coding on a random sample of charts of ER visits or hospitalizations of patients with an epilepsy diagnosis.[157] The positive and negative predictive values for ER records and discharge records were 99 percent and 97 percent, and 98 percent and 99 percent, respectively.[157] Using epilepsy codes (345.XX) while excluding 780.3 (convulsions) is suggested to be more specific in identifying cohorts of patients with true epilepsy.[157] Several studies in the U.S. and Canada relied on ICD-9 codes as proxies for seizure diagnosis and seizure ascertainment.[8-10,13,14]

Regarding assessment of only seizure/epilepsy-specific inpatient service use, some researchers argued that seizures may lead to hospitalizations with other diagnosis codes (e.g., traumas that may have been triggered by a seizure).[12] In one retrospective cohort study (Erickson et al.), the authors used all-cause ER visits and hospitalizations rather than selecting patients with only seizure-specific diagnosis codes when using those as proxies for seizure activity.[12] However, it may be possible that in the case of all-cause events, instances such as routinely scheduled surgeries or other seizure-unrelated hospitalizations may be mistakenly classified as seizure-related. The vast majority of other studies focused on a seizure-specific diagnosis as a reason for an ER visit or hospitalization. [8-10,13,14] This study also focused on ER visits, ambulance service use and hospitalizations that occurred with an epilepsy-specific primary or secondary diagnosis

(ICD-9: 345.XX), assuming that either the first or second code would ascertain the occurrence of an event possibly triggered by a seizure (e.g., injury or trauma).

Study Design and Statistical Analysis

To address objectives of this study, a historical cohort design was used.[158] Studies conducted to date primarily used a case-control design and focused on the bioequivalent switch as the exposure variable, with some studies showing increased risk upon the switch[8-10] and one showing lack thereof.[13] One retrospective cohort study also focused solely on the impact of the switch on seizure occurrence and the findings showed no impact of the switch on ER visits or hospitalizations.[12] This study used a retrospective cohort design and aimed to identify predictors of seizures among patients medically treated for epilepsy. Potential predictors were assessed based on a literature review that examined associations between mortality, morbidity and resource utilization in epilepsy patients and the following factors were identified: prior hospitalizations, bioequivalent antiepileptic medication switches, AED adherence, comorbid mental health conditions, other medical comorbidities, and epilepsy types (i.e., partial versus generalized, intractable versus non-intractable). Covariates such age, gender, and U.S. geographic region were also included in the current study.

Study Inclusion Criteria

To be included in the cohort, patients must have satisfied the following criteria:

1. Presence of primary or secondary diagnosis of epilepsy (ICD-9 code 345.XX);
2. Presence of at least one claim for an antiepileptic medication pre-index;
3. Patients aged 18 to 64 years at index;
4. Continuous insurance eligibility six months prior and 12 months following the index date; and
5. Presence of at least 60 days of antiepileptic medication (measured via proportion of days covered) during first 90 days of treatment post-index.

The index date for patient entry into the cohort was operationalized as presence of the first available outpatient claim with primary or secondary epilepsy diagnosis. Because the data were available for the period between January 1, 2007 and September 30, 2010, only patients with outpatient visits occurring between July 1, 2007 and September 30, 2009 were included in order to allow assessment of 180-day pre-index insurance eligibility and prior seizures, as well 365-days post-index follow-up.

Patients prescribed the following AEDs in a monotherapy regimen were studied:

1. Lamotrigine (Lamictal®)
2. Levetiracetam (Keppra®)
3. Topiramate (Topamax®)
4. Oxcarbazepine (Trileptal®)

The rationale for inclusion of these AEDs to assess predictors of seizures in medically-treated patients was two-fold. First, these AEDs recently lost patent protection and, thus, were open to generic competition. Table 7 presents a summary of generic launches for each respective AED.[159-163] Given the dates of data availability for the study, it was possible to capture the impact of bioequivalent switches of these AED medications on seizures. Second, these AEDs are considered newer and more frequently used than older products such as phenytoin and carbamazepine.[164] Finally, all AEDs except levetiracetam[108] are FDA-approved as monotherapy. However, levetiracetam was also included because several clinical and observational studies both in Europe and the U.S. have shown the efficacy and effectiveness of levetiracetam monotherapy and its successful use in patients with focal as well as generalized epilepsy disorders.[165-169]

Table 7 AED Generic Entrance

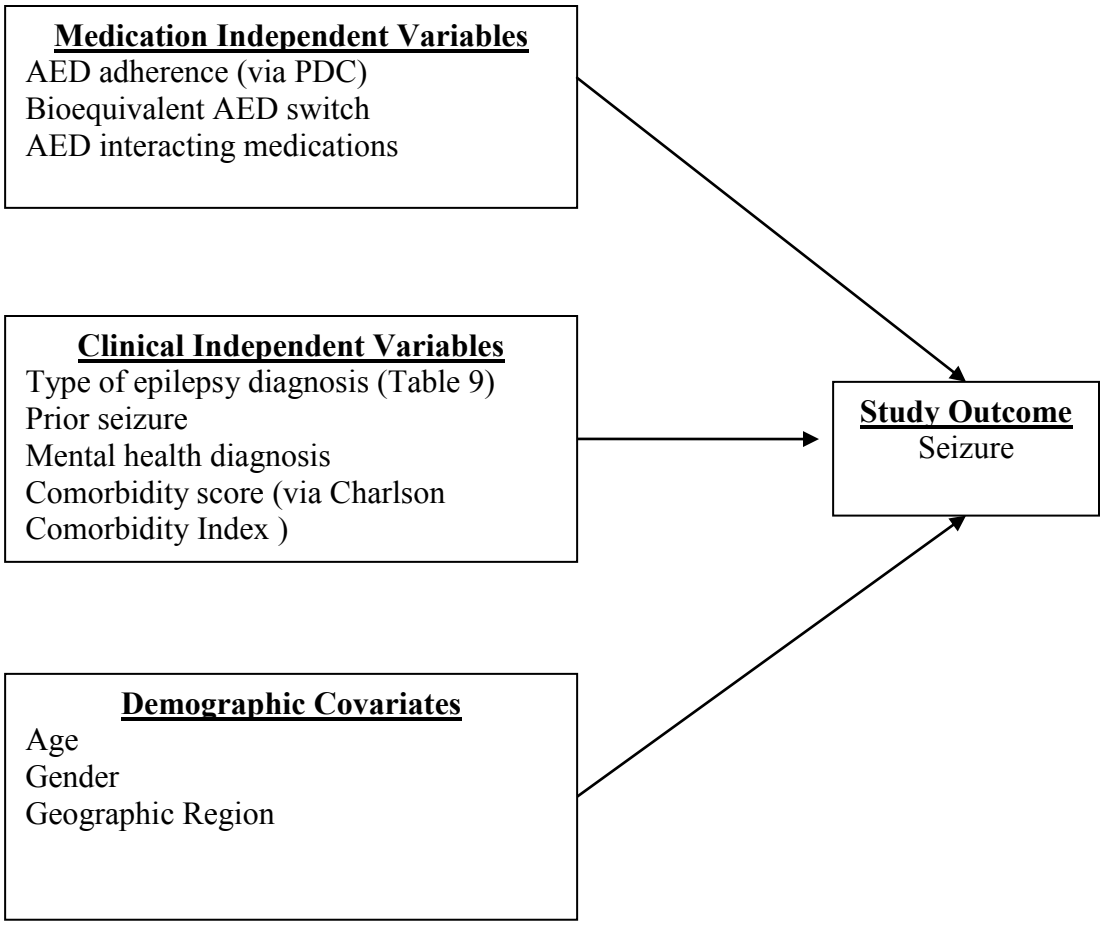
Brand Antiepileptic Drug	Generic Name	Generic Release
Trileptal®	Oxcarbazepine	October 2007
Lamictal®	Lamotrigine	July 2008
Keppra®	Levetiracetam	November 2008
Topamax®	Topiramate	April 2009

Although all of the AEDs included in the study may also be used in combination with each other as well as add-ons to other AEDs, this study only focused on patients who were treated by the above medications as monotherapy. Monotherapy is considered a preferred modality of pharmacotherapy aimed for long-term maintenance treatment.[71,72] Other advantages of monotherapy include lower possibility of drug-drug interactions, lower cost, better tolerability and better quality of life.[72,109,170,171] Examination of certain predictors (e.g., bioequivalent switches) in patients treated with AED monotherapy may be less confounded than in cases where patients were exposed to multiple antiepileptic medications with switches occurring for one of the AEDs, but not the others. In addition, assessment of the possible association between administration of concomitant drugs shown to affect pharmacokinetics or pharmacodynamics of AEDs (interacting medications) and seizure occurrence may be less confounded in patients who are prescribed only one antiepileptic agent.

Study Variables

Figure 2 provides a schematic of variables proposed to be examined in this study (i.e., the study model).

Figure 2 Study Model



STUDY DEPENDENT VARIABLE: OPERATIONAL DEFINITION

Seizure incidence post-index was the study's dependent variable. Seizure incidence was operationalized as occurrence of an ER visit, ambulance service use or hospitalization with the primary or secondary diagnosis of epilepsy (ICD-9 code 345.XX). The dependent variable was dichotomous with no post-index seizure (coded 0) versus at least one post-index seizure (coded 1).

MEDICATION INDEPENDENT VARIABLES: OPERATIONAL DEFINITIONS

ADHERENCE

Although previous studies of adherence to AEDs used medication possession ratio to calculate adherence and relied on an >=80 percent cutoff to define a patient as being adherent,[97,98,103] studies in other chronic diseases sometimes use another metric, proportion of days covered (PDC), with a similar cutoff to operationalize adherence.[172] The formula for calculating PDC is as follows:

$$PDC = \frac{\text{sum of the days when one or more drugs from the same therpeutic class are availbale}}{\text{days between first fill and end of the measument period}} 100\%$$

The use of PDC results is a more conservative estimate of adherence, when multiple medications from the same drug class are prescribed or when switching between

medication from the same drug class is common.[172,173] PDC has been endorsed by the Pharmacy Quality Alliance as a preferred adherence measure for health plans and pharmacy benefit management companies.[174] This study also used PDC to measure AED medication adherence. Adherence was measured both as a continuous and a dichotomous variable. The cutoff point to dichotomize adherence was set at 80 percent, but a sensitivity analysis with a 60 percent cutoff was also conducted.

BIOEQUIVALENT SWITCH

'Bioequivalent switch' was included as a predictor variable in the model due to the evidence in the literature showing that bioequivalent substitution between brand-generic, generic-generic or generic-brand antiepileptic medications may be associated with seizure exacerbations. The variable was coded as 0 and 1, with 0 indicating a patient who did not have a switch and continued filling an AED with the same National Drug Code (NDC), and 1 indicating a switch occurrence (e.g., switch from NDC 00078045705 [Trileptal® 300mg, Novartis] to NDC 68462013801 [Oxcarbazepine, 300 mg, Glenmark Generics]).

PRESENCE OF AED-INTERACTING MEDICATIONS

Concomitant administration of AEDs with medications from other drug classes may modify both the pharmacokintetics and pharmacodynamics of AEDs and, hence, may affect AED serum therapeutic concentrations or AED toxicity and, as consequence, may trigger occurrence of a seizure. Devine et al., in their case-control study of the association between bioequivalent AED switch and seizures, controlled for AED-interacting medications.[13] Devine and colleagues operationalized the interacting medication variable as absence or presence of one or more AED-interacting medications. Similarly to Devine et al., the interacting medications variable was dichotomized to indicate absence (coded 0) or presence (coded 1) of one or more interacting medications corresponding to each studied AED. Table 8 presents a summary of AED-interacting medications that were assessed.

Table 8 List of AED-interacting Medications

Antiepileptic Drug	Interacting Medications[a]
Lamotrigine	Estrogens Barbiturates Mefloquine Rifampicin Ritonavir Ketorolac (nasal and systemic) [b]
Topiramate	Ketorolac (nasal and systemic)[b] Mefloquine Thiazide diuretics
Levetiracetam	Ketorolac (nasal and systemic) [b] Mefloquine
Oxcarbazepine	Phenobarbital Thiazide diuretics [c]

[a]List was compiled using the package insert of each respective AED
[b]Ketorolac may diminish therapeutic effects of anticonvulsants (Risk C interaction requiring therapy monitoring)
[c] May enhance adverse/toxic effects of oxcarbazepine (i.e., hyponatremia)

CLINICAL INDEPENDENT VARIABLES: OPERATIONAL DEFINITIONS

TYPE OF EPILEPSY DIAGNOSIS

Studies have shown that depending on the type of epilepsy diagnosis, patients may be less or more likely to experience seizure exacerbations. [44,175] For example, Callaghan et al. showed that generalized symptomatic epilepsy is a negative predictor of seizure remission in pharmacoresistant patients.[44] Berg et al. found that patients with a diagnosis of partial seizures were more likely to achieve seizure remission after resective surgery (RR=1.17-1.24).[175] No retrospective insurance claims studies in the literature sought to identify which epilepsy diagnoses may be associated with a higher likelihood of seizure exacerbations. However, four retrospective database studies that examined associations between bioequivalent switches and seizure exacerbations controlled for six main epilepsy diagnoses.[8-10,13] This study assessed if a specific seizure diagnosis was associated with a higher likelihood of seizure exacerbation. Table 9 presents six diagnosis categories that were examined as predictors for seizure occurrence.

Table 9 Seizure Diagnosis Categories

Seizure Type	ICD-9-CM Code
Generalized non-intractable	345.00-345.30
Generalized intractable	345.01-345.31
Partial non-intractable	345.40, 345.50, 345.70
Partial intractable	345.41, 345.51, 345.71
Other non-intractable	345.80, 345.90
Other intractable	345.81, 345.91

PRIOR SEIZURE

No retrospective insurance claims studies in the literature sought to identify the risk of seizure recurrence in patients who previously experienced a seizure. However, several retrospective database studies that examined the association between bioequivalent switches and seizure exacerbations included patients who did not experience seizures in the 180 days prior to the index date.[8-10,13] This study assessed the risk of seizure recurrence in patients who experienced a seizure in the 180-day pre-index period. The prior seizure predictor variable was coded as 0 (no prior seizure) and 1 (prior seizure), indicating the presence or absence of at least one prior seizure.

MENTAL HEALTH DIAGNOSIS

Studies in epilepsy and other conditions showed that the co-presence of mental health diagnoses increased both inpatient and outpatient healthcare utilization.[134,176] No studies using claims databases identified if presence of certain comorbid mental health conditions may be associated with seizure recurrence. Table 10 presents a list of mental health diagnoses that were included as predictor variables in this study. The list was based on a study of healthcare utilization of veterans with epilepsy and comorbid mental health conditions by Pugh et al.[134] In order to facilitate data analyses, these diagnoses were combined similarly to the methodology used in the Pugh et al. study.[134] The following five groups were formed: no mental health diagnosis, serious mental illness (schizophrenia, other psychosis, bipolar disorder), affective disorders (depression and anxiety, posttraumatic stress disorder (PTSD)), other mental illnesses and substance abuse. Pugh et al. placed PTSD into a separate category due to the high prevalence of this

condition among veterans. However, because the patient population of this study was civilian, it was not expected that the PTSD diagnosis would occur frequently. Thus, PTSD was grouped together with other affective disorders. Table 11 presents the grouped mental health diagnosis categories.

Table 10 Mental Health Diagnosis Categories

Mental Health Diagnosis[1]	ICD-9-CM Code
Schizophrenia	295.x excluding 295.5 (latent schizophrenia unspecified type)
Bipolar Disorder	296.0-296.2; 296.4-296.8
Other Psychosis	297-298
Depression	296.2-296.3; 311
Anxiety	300.00,300.02, 300.09
Posttraumatic Stress Disorder (PTSD)	309.81
Substance Abuse	291, 292, 303-305 excluding 305.1 (nondependent tobacco use)
Other mental illness	290-312 (excluding codes listed above)

[1]Categories were adapted from the study by Pugh MJ, Zeber JE, Copeland LA, Tabares JV, Cramer JA. Psychiatric disease burden profiles among veterans with epilepsy: the association with health services utilization. Psychiatr Serv. 2008 Aug;59(8):925-8.

Table 11 Grouped Mental Health Diagnosis Categories

Grouped Mental Health Diagnosis Category	Diagnoses Included
No mental health diagnosis	Absence of any mental health diagnoses
Serious Mental Illness	Schizophrenia, other psychosis, bipolar disorder
Affective Disorders	Depression, anxiety, PTSD
Substance Abuse	Substance abuse
Other mental illness	Other mental illness (codes 290-312, excluding the above)

COMORBIDITIES

Epilepsy is associated with other medical conditions or comorbidities.[177] It was shown that non-epilepsy related medical costs were responsible for about 80 percent of total medical costs in patients with epilepsy.[177] Studies in other chronic diseases such as chronic obstructive pulmonary disease (COPD) showed elevated healthcare utilization in patients with higher levels of comorbidities.[178,179] One common tool to measure comorbidity severity using ICD-9-CM diagnoses codes is the Charlson Comorbidity Index (CCI).[178-180] The CCI was validated for use in administrative claims databases.[181] The index includes 23 conditions where each condition is weighted based on a one-year mortality rate.[180] Table 12 presents the Charlson comorbidity conditions and their respective weights. Germane-Smith et al. developed and validated an epilepsy-specific comorbidity adjustment index based on the CCI and Elixhauser indexes for an epilepsy patient population in Canada.[129] This epilepsy-specific comorbidity index discriminated mortality slightly better than the CCI. However, because the epilepsy-specific index has not yet been widely used, this study selected the CCI as an instrument to measure comorbidity.

Table 12 Charlson Comorbidity Disease Categories with Weights

Condition	Weight
Congestive heart failure	1
Myocardial infarction	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Mild liver disease	1
Diabetes	1
Depression	1
Use of warfarin	1
Hypertension	1
Hemiplegia	2
Moderate or severe renal disease	2
Diabetes with end organ damage	2
Any tumor	2
Leukemia	2
Skin ulcer/cellulitis	2
Moderate or severe liver disease	3
Metastatic cancer	6
AIDS	6

Source: Table 3 in Charlson ME, Charlson RE, Peterson JC, Marinopoulos SS, Briggs WM, Hollenberg JP. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. J Clin Epidemiol. 2008 Dec;61(12):1234-40.

DEMOGRAPHIC COVARIATES: OPERATIONAL DEFINITIONS

PATIENT AGE

The prevalence of epilepsy increases with age.[182,183] The age of each patient was assessed in years at the time of the index date. Age was included as a continuous variable as well as a categorical variable with three categories: 18-30, 31-45, 46-64.

PATIENT GENDER

The prevalence of epilepsy differs between genders with a higher incidence found in women.[183] Gender was a dichotomous variable with the reference category being female (coded 0).

GEOGRAPHIC REGION

There is variation in patterns of care and outcomes in patients treated in different geographic regions.[151,184,185] The following four U.S. regions were used in previous retrospective database studies of patients with epilepsy: West, Midwest, South and Northeast.[8-10] Devine et al. used more specific U.S. census regions: New England, Mid Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain and Pacific.[13] This study used the four regions of West, Midwest, South and Northeast to aid data analysis and interpretation.

Table 13 provides a summary of dependent and independent variables that were modeled in this study, while Table 14 and 15 summarize the operational definitions of the study variables.

Table 13 Summary of Dependent and Independent Variables

Dependent Variable	Independent Variable
Seizure occurrence	Medication Independent Variables AED adherence Bioequivalent AED switch Presence of AED-interacting drugs Clinical Independent Variables Type of epilepsy diagnosis Prior seizure Mental health diagnosis Comorbidity Demographic Variables Age Gender Geographic region

Table 14 Operational Definitions of the Study Variables (I)

Variable	Operational Definition
Dependent	
Seizure occurrence	The ER visit, ambulance service use or hospitalization with the primary or secondary diagnosis of epilepsy coded with ICD-9-CM 345.XX over 365 days post-index : 0 = no epilepsy-related ER visit, ambulance service use or hospitalization 1 = epilepsy-related ER visit, ambulance ride or hospitalization with epilepsy code
Independent	
AED Medication adherence	Proportion of days covered (PDC) calculated post-index over 365 days: 0 = PDC<80% 1 = PDC≥80% For sensitivity analysis: 0 = PDC<60% 1 = PDC≥60%
Bioequivalent AED switch	Prescription claim for an AED with the same active ingredient and different manufacturer post-index: 0 = no switch over 365-days post-index 1 = switch over 365-days post-index
AED-interacting medications	Presence of one or more AED-interacting medications: 0 = no interacting medications over 365-days post-index 1 = one or more interacting medications over 365-days post-index

Table 15 Operational Definitions of the Study Variables (II)

Variable Independent	Operational Definition
Prior Seizure	The ER visit, ambulance service use or hospitalization with the primary or secondary diagnosis of epilepsy coded with ICD-9-CM 345.XX in the 180-day pre-index period: 0 = no ER visit, ambulance service use or hospitalization in the 180-day pre-index period; 1 = ER visit, ambulance ride or hospitalization in the 180-day pre-index period
Mental Health Diagnosis	Post-index mental health diagnosis: 0 = no mental health diagnosis (reference) 1 = serious mental illness 2 = affective disorders 3 = substance abuse 4 = other mental illness
Type of Epilepsy Diagnosis	0 = non-intractable 1 = intractable
Comorbidity	CCI post-index (claims within 180-day post-index) (dichotomous) 0 = no comorbidites (coded 0, reference) 1 = one or more comorbidities (CCI score of 1 or higher, coded 1)
Age	Age at index date (continuous) Age at index date (categorical): 0 = 18-30 (reference) 1 = 31-45 2 = 46-64
Gender	Gender of the patient: 0 = female (reference) 1 = male
Geographic Region	Patient geographic region of residence (extracted from the member file): 0 = South (reference) 1 = Northeast 2 = West 3 = Midwest

UNAVAILABLE VARIABLES

The Innovus Invision™ Data Mart dataset does not contain information on other possible predictors of seizures in medically treated patients with epilepsy. The following predictors have been shown in the literature to be associated with seizure events: race/ethnicity, epilepsy severity, duration of epilepsy, family history, as well as social determinants such as socioeconomic status, marital status and occupation.[3,93,186,187] However, since the study data source was limited to insurance claims, access to those variables was not available.

Statistical Analyses

Gender, age, geographic region and type of epilepsy diagnosis were assessed at index date. The presence of prior seizures was assessed during 180-day pre-index. The Charlson's Comorbidity Index and presence of comorbid mental health diagnoses were assessed during 180-day post-index. A logistic regression was used to test study hypotheses. There were no assumptions regarding distribution of the predictors except ensuring that independent variables were not highly correlated with each other to avoid estimation problems.[188] The analyses were conducted using SAS Enterprise Guide 4.3 (SAS Institute, Cary, NC) statistical software. All statistical analyses were two-sided with significance set a-priori at $p \leq 0.05$.

Sample Size Estimation

Generally, logistic regression requires about five to 10 events per predictor in the multivariate model.[189] Hosmer and Lemeshow recommend a sample size of at least 400 to conduct a multivariate logistic regression.[190] Since this study constructed four models for four antiepileptic agents, each model was required to have a minimum of 400 patients.

CHAPTER THREE

Results

GENERAL DATA SUMMARY

The pharmacy and medical claims data were available for the period between January 1, 2007 and September 30, 2010. The study time frame for identifying the index date was between July 1, 2007 and September 30, 2009 to allow assessment of 180-day pre-index period claims for inclusion criteria and to ensure each patient had a one-year post-index follow-up period. Initially, all available medical claims were examined to assess the number of claims with a primary or secondary diagnosis of epilepsy (ICD-9=345.XX). Table 16 presents a summary of medical claims with a primary or secondary epilepsy diagnoses for each year of data availability.

Table 16 Summary of Medical Claims

Year	Total Number of Medical Claims	Medical Claims with Diagnosis 1=345.XX Or Diagnosis 2 = 345.XX (%)
2007	212,301,356	216,846 (0.10)
2008	222,612,172	244,912 (0.11)
2009	227,667,156	262,949 (0.12)
2010	157,989,808	196,615 (0.12)
Total (n=117,016)	820,570,492	921,322 (0.11)

All medical claims with a primary or secondary epilepsy diagnosis over the period of data availability represented claims data for 117,016 unique patients. Table 17 presents the frequency distribution of medical service locations (Point of Service (POS) variable) for the 921,322 epilepsy-related claims.

Table 17 Medical Service Use: Frequencies*

Point-of-Service Code	Point-of-Service Description	Frequency	Percent
1, 2	**Office**	360,899	39.2
5, 6	*Inpatient hospital*	178,846	19.4
7, 8	**Outpatient hospital**	173,339	18.8
40, 41	Independent laboratory	122,650	13.3
9,11,12	*Emergency room*	34,409	3.7
3, 4	Home	32,525	3.6
42, 43, 44, 46, 47, 808, 1383	Other unlisted facility	12,551	1.3
18, 19	Skilled nursing facility	2226	0.3
22, 23	Hospice	849	0.1
24, 25	*Ambulance*	679	0.1
13, 14	Ambulatory surgical center	823	0.1
20	Nursing facility	765	0.1
21	Custodial care facility	205	≤0.1
32, 45	Residential substance abuse treatment facility	193	≤0.1
476	*Urgent care facility*	84	≤0.1
15, 16, 17 26, 27, 28, 29, 30, 35, 38, 109, 141, 297, 359, 453, 507, 525	Other facilities, including birthing center, military treatment center, federally qualified health center, inpatient psychiatric facility, psychiatric facility partial hospitalization, etc.	209	≤0.1
Total		921,322	100.00

*Outpatient visits are bolded; inpatient visits are italicized.

To facilitate data analysis, a new variable, healthcare service use (POS_rc or POS_recoded), was created with the following two categories: outpatient visit (coded 0-bolded in Table 17) that included either an office visit or an outpatient hospital visit, and inpatient visit (coded 1 - italicized in Table 17), that included inpatient, ER, urgent care facility visit or ambulance services. Due to rare occurrences of all other point-of-service categories and/or their irrelevance to the study purpose (e.g., laboratory services use), other rows of data were excluded from further analysis. Table 18 depicts the frequency distribution of the new POS_rc variable, type of healthcare service use across the time frame of data availability.

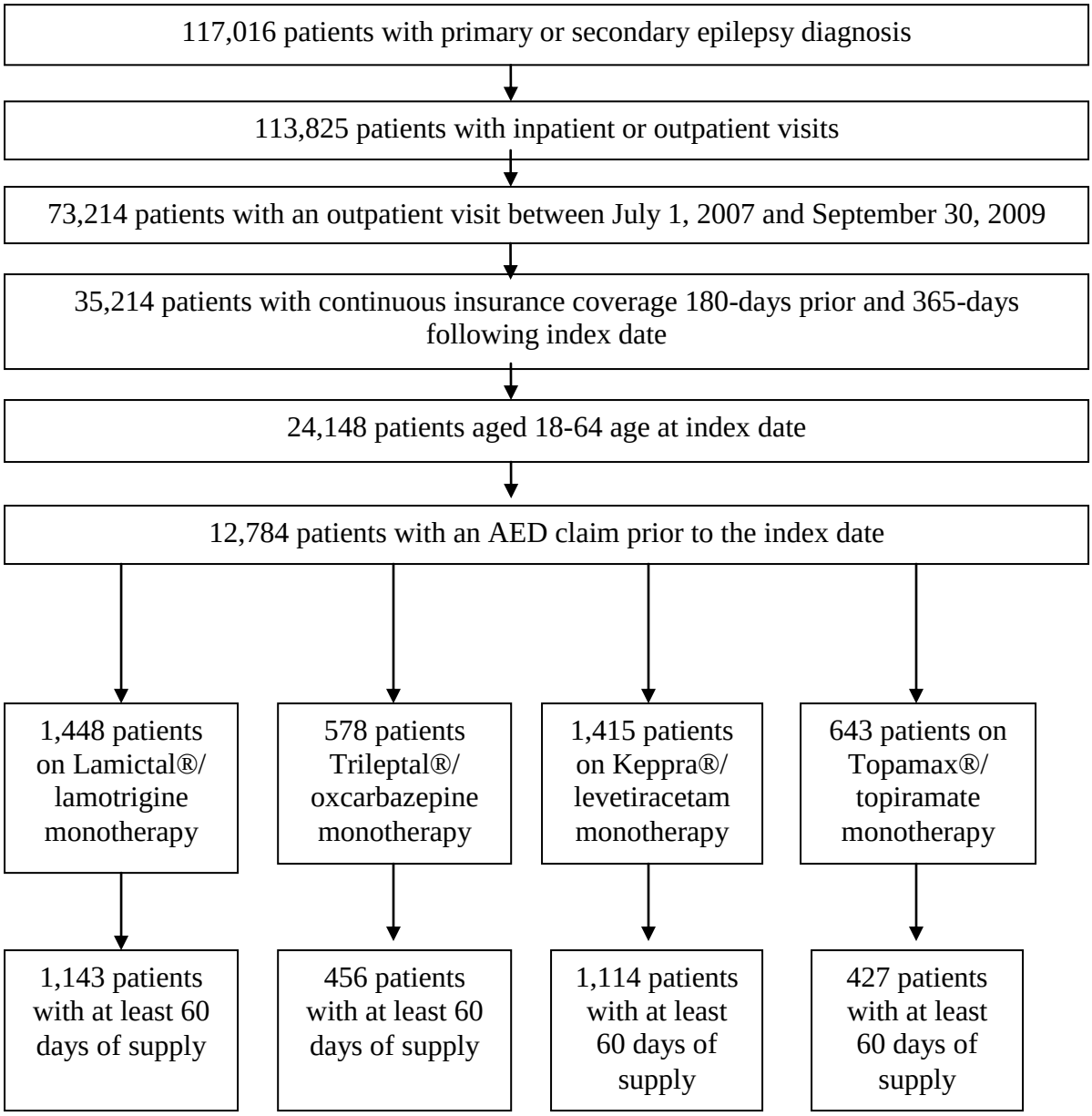
Table 18 Inpatient and Outpatient Service Use: Frequencies

Type of Healthcare Service*	**POS codes**	**Number of Claims**
Outpatient visit (code=0)	**1, 2, 7, 8**	**534,238**
Inpatient visit (code=1)	*5, 6, 9, 11, 12, 24, 25, 476*	*214,018*
Total		748,256 for 113,825 patients

*Outpatient visits are bolded; inpatient visits are italicized.

Figure 3 depicts a flow diagram of subsequent patient selection according to study inclusion criteria. The four monotherapy cohorts were built from the sample of 12,784 patients on AEDs.

Figure 3 Flow Diagram of Patient Selection



The results examining each AED monotherapy patient cohort are presented in the following format: description of the patients according to their clinical, drug and demographic characteristics (focus of objective 1), followed by bivariate comparisons between each predictor variable and study dependent variable (presence of post-index seizure). Finally, the results of hypotheses testing for each respective AED monotherapy cohort are presented (focus of objective 2). The same format of results reporting is followed in the analysis of the four cohorts combined.

LAMICTAL®/LAMOTRIGINE MONOTHERAPY COHORT: OBJECTIVE 1

The Lamictal®/lamotrigine patient cohort consisted of 1,143 patients who were actively treated with 60 days or more of medication during the first 90 days of the post-index observation period. Table 19 summarizes insurance, clinical and medication characteristics of patients in the Lamictal®/lamotrigine monotherapy cohort. The average prescription strength was 135 mg (SD=51 mg; median=150 mg; range=25 mg-200 mg) with over 40 percent of prescriptions filled with the 100 mg strength of lamotrigine (42.0%), followed by 200 mg (28.7%) and 150 mg (22.5%). The suggested target daily dose upon completion of the titration period is between 100 and 200 mg.[6] The larger proportion of the Lamictal®/Lamotrigine monotherapy cohort was female (66.6%), and the average patient age (SD) was 39.9 (12.7) years old. The majority of patients had POS insurance (71.5%) and resided in the South (44.9%). The mean adherence measured with proportion of days covered was 0.73 (SD=0.25), or 73 percent. With the adherence threshold set at 80 percent, 54.4 percent of the Lamictatl®/lamotrigine cohort was adherent to their AED monotherapy. When the threshold was lowered to 60 percent, 72.5

percent of patients was adherent. The larger number of patients in the Lamictal®/lamotrigine cohort was treated for partial non-intractable seizures (29.3%), followed by other non-intractable (28.9%) and generalized non-intractable (26.3%) seizures. About 18 percent of patients were concomitantly taking interacting medications. Among patients with interacting medications, estrogen-containing hormonal products were prescribed most frequently (about 90 percent of all interacting prescriptions were for estrogen-containing oral contraceptives and hormone replacement products). Over 90 percent of patients in the cohort did not have a mental health diagnosis, while among those with such a diagnosis, affective disorders were most common (52.9%). The mean comorbidity score (SD) of patients in the cohort was 0.097 (0.39) with 92.3 percent of patients having no comorbidities accompanying their epilepsy condition. About 35 percent (n=403) of the cohort experienced bioequivalent formulation switches. A total of 45 patients (3.9%) experienced seizures post-index.

Table 19 Demographic, Insurance, Clinical and Medication Characteristics of Lamictal®/Lamotrigine Monotherapy Cohort

Characteristic	Lamictal®/Lamotrigine Monotherapy Cohort (n=1143)	
	N	%
Age (Mean±SD)	39.9±12.7	
18-30 y	303	26.5
31-45 y	434	38.0
46-64 y	406	35.5
Female gender	761	66.6
Insurance type		
POS	817	71.5
EPO	165	14.4
HMO	101	8.8
PPO	55	4.8
IND	5	≤0.5
One-year adherence		
Mean (SD) PDC[2]	0.73 ±0.25	
Median (range) PDC	0.82 (0.16-1.0)	
PDC≥60%	829	72.5
PDC≥80%	622	54.4
Region		
South	513	44.9
Midwest	292	25.6
West	205	17.9
Northeast	133	11.6
180-day Pre-index Seizure		
≥1	31	2.7
0	1112	97.3
365-day Post-index Seizure		
≥1	45	3.9
0	1098	96.1
Charlson Comorbidty Index Score		
Mean (SD)	0.097 (0.39)	
Median (range)	0 (0-6)	
18-30 y	0.03 (0.23)	
31-45 y	0.09 (0.35)	
46-64 y	0.16 (0.51)	
Score 0	1057	92.3
Score 1	62	5.4
Score 2	23	2.0
Score 6	1	≤0.1

Table 19 Demographic, Insurance, Clinical and Medication Characteristics of Lamictal®/Lamotrigine Monotherapy Cohort (Continued)

Characteristic	Lamictal®/Lamotrigine Monotherapy Cohort (n=1143)	
	N	%
Seizure type		
Partial non-intractable	335	29.3
Partial intractable	104	9.1
Generalized non-intractable	300	26.3
Generalized intractable	54	4.7
Other non-intractable	331	29.0
Other intractable	19	1.7
Comorbid Mental Health Diagnoses		
No mental health diagnosis	1075	94.0
Any mental health diagnosis	68	6.0
Mental Health Diagnosis Categories		
Affective disorders	36	52.9
Other mental health diagnoses	23	33.8
Serious mental illness	7	10.3
Substance abuse	2	2.9
Interacting Medications		
0	941	82.3
≥1	202	17.7
Bioequivalent Switch		
0	740	64.7
≥1	403	35.3

[1]POS-Point of Service; EPO-Exclusive Provider Organization; HMO-Health Maintenance Organization; PPO-Preferred Provider Organization; IND-Indemnity
[2]PDC-Proportion of Days Covered

BIVARIATE COMPARISONS OF SEIZURE INCIDENCE IN LAMICTAL®/LAMOTRIGINE MONOTHERAPY COHORT

The incidence of post-index seizures in the Lamictal®/lamotrigine cohort was 3.9 percent (n=45). For the purposes of bivariate comparisons, two independent categorical variables with more than two values had to be collapsed due to a low cell count in some

categories. The seizure type variable was dichotomized into two categories: (1) non-intractable epilepsy, including partial non-intractable, generalized non-intractable and other non-intractable (coded 0), and (2) intractable epilepsy, including partial intractable, generalized intractable and other intractable (coded 1). The mental health comorbidity variable was dichotomized into two categories: (1) absence of any comorbid mental health diagnosis (coded 0) and (2) presence of one or more mental comorbid diagnoses (coded 1).

Table 20 and 21 display the bivariate comparisons of incidence of post-index seizure by age, age group, gender, geographic region, prior seizure status, adherence, comorbidity, mental health comorbidity, seizure type, presence of interacting medications and presence of a bioequivalent switch. The mean age of patients in the two groups was not significantly different [t=-0.12 (df=1141);p=0.9]. Patients with a post-index seizure were 40.1 (±11.9) years old, while patients who did not have a post-index seizure were 39.9 (±12.7) years old. Although not statistically significant, chi-square analysis showed that more patients in the 31-45 age group experienced a seizure (5.5%) than patients in the two other age groups (3.2% [46-64 years] and 2.6% [18-30 years]) [χ^2=4.84 (df=2); p=0.09].

A chi-square analysis of incidence of post-index seizure-event and pre-index seizure status showed that more patients with a pre-index seizure experiences a seizure post-index seizure than patients without a pre-index seizure (29.0% vs 3.2%,

respectively) [χ^2=53.06 (df=1);p<0.0001]. A chi-square analysis of post-index seizure and patients' comorbidity status demonstrated that more patients with a CCI score of one or higher experienced a seizure post-index than those with a score of zero (8.1% vs 3.6%, respectively) [χ^2=4.34 (df=1);p=0.04]. A chi-square analysis of post-index seizure and patients' mental health comorbidity status demonstrated no association between mental health comorbidity and post-index seizure [χ^2=0.04 (df=1); p=0.83]. A chi-square analysis of post-index seizure and bioequivalent switch demonstrated no association between the two variables [χ^2=0.83 (df=1); p=0.36].

The mean adherence of patients in the two groups was not significantly different [t=-0.66 (df=1141); p=0.5]. Patients with a post-index seizure event had a mean PDC of 0.75 (SD=0.23) while patients who did not have a post-index seizure event had PDC of 0.73 (SD=0.25). A chi-square analysis between post-index seizure and geographic region of residence showed that more patients in the Northeast experienced a post-index seizure than patients in the South, Midwest or West (9.0% vs 2.7%, 3.8% and 3.9%, respectively) [χ^2=11.1 (df=3); p=0.01]. A chi-square analysis did not reveal any relationships between post-index seizures and gender, dichotomized adherence status (adherence set at 80% and 60%), interacting medications or seizure type (intractable vs non-intractable) (p>0.05).

Table 20 Bivariate Comparison of Incidence of Post-Index Seizure in Lamictal®/Lamotrigine Cohort by Age, Age Group, Gender, Adherence and Geographic Region

Independent Variable	Total		Seizure Event		No Seizure Event		t	df	p-value
	Mean	SD	Mean	SD	Mean	SD			
Age	39.9	12.7	40.1	11.9	39.9	12.8	-0.12	1141	0.9
Adherence (PDC)	0.73	0.25	0.75	0.23	0.73	0.25	-0.66	1141	0.5
	N=1143		n	%	n	%	X^2	df	p-value
Age group							4.84	2	0.09
18-30	303		8	2.6	295	97.4			
31-45	434		24	5.5	410	94.5			
46-64	406		13	3.2	393	96.8			
Gender							0.96	1	0.33
Female	761		33	4.3	728	95.7			
Male	382		12	3.1	370	96.9			
PDC							0.02	1	0.88
≥80%	622		25	4.0	597	96.0			
<80%	521		20	3.8	501	96.2			
PDC							0.02	1	0.90
≥60%	829		33	4.0	796	96.0			
<60%	314		12	3.8	302	96.2			
Region							11.1	3	0.01
South	513		14	2.7	499	97.3			
Midwest	292		11	3.8	281	96.2			
West	205		8	3.9	197	96.1			
Northeast	133		12	9.0	121	91.0			

Table 21 Bivariate Comparison of Incidence of Post-Index Seizure in Lamictal®/lamotrigine Cohort by Pre-Index Event, Comorbidity, Seizure Type, Mental Health Comorbidity, Presence of Interacting Medications and Presence of a Bioequivalent Switch

Independent Variable	Total	Seizure Event		No Seizure Event		Chi-square	df	p-value
	N=1143	n	%	n	%			
Pre-index event						53.06	1	<0.0001
0	1112	36	3.2	1076	96.8			
≥1	31	9	29.0	22	71.0			
CCI						4.34	1	0.04
0	1057	38	3.6	1019	96.4			
≥1	86	7	8.1	79	91.9			
Seizure Type						0.73	1	0.39
Non-intractable	966	36	3.7	930	96.3			
Intractable	177	9	5.1	168	94.9			
Mental Comorbidity						0.04	1	0.83
0	1075	42	3.9	1033	96.1			
≥1	68	3	4.4	65	95.6			
Interacting medications						0.61	1	0.44
0	941	39	4.1	902	95.9			
≥1	202	6	3.0	196	97.0			
Bioequivalent Switch						0.83	1	0.36
0	740	32	4.3	708	95.7			
≥1	403	13	3.2	390	96.7			

LOGISTIC REGRESSION ANALYSIS OF INCIDENCE OF POST-INDEX SEIZURES IN LAMICTAL®/LAMOTRIGINE MONOTHERAPY COHORT: OBJECTIVE 2

Objective 2 was to develop a prediction model of acute seizure events resulting in ER visits, ambulance service use or hospitalizations based on the factors identified as contributory to seizure recurrence in the initial bivariate analyses. For the Lamictal®/lamotrigine cohort, prior seizure and general comorbidity were included in the final regression model. Age, gender and geographic region covariates were included in the final model. Covariates age and gender though not significant in the bivariate analyses were included in all the final models as important non-modifiable seizure recurrence risk factors. Multiple logistic regression was used to address study objective 2.

The formula below was used to build the regression model:

$$logit\ (Y) = \ln\frac{\pi}{1-\pi} = \alpha + \beta 1X1 + \beta 2X2 + \beta 3X3 + \beta 4X4 + \beta 5X5$$

$$\pi = \frac{e^{\ \alpha+\beta 1X1+\beta 2X2+\beta 3X3+\beta 4X4+\beta 5X5}}{1+e^{\ \alpha+\beta 1X1+\beta 2X2+\beta 3X3+\beta 4X4+\beta 5X5}} \quad \text{where}$$

π= probability of seizure event;

α- the Y intercept
β1-β5- regression coefficients;
X1- prior seizure event;
X2- general comorbidity;
X3- gender;
X4- age
X5- geographic region.

The overall model with five predictors was significant [χ^2=38.0 (df=7);p<0.001]. The output for the model is presented in Appendix A. Mutlicollinearity between predictor variables was assessed using weighted regressions with COLLIN and COLLINOINT options.[191] Small condition indices suggested that there was no collinearity between independent variables in the model. The output of collinearity assessment is presented in Appendix B.

The results of hypotheses testing are presented below.

H1: AED nonadherence is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

There was no difference in AED adherence between patients with post-index seizures and those without a post-index seizure in the bivariate analysis. Hypothesis 1 was rejected in the Lamictal®/lamotrigine monotherapy cohort

H2: A bioequivalent medication switch is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

There was no difference in the frequency of switches between patients with post-index seizures and those without a post-index seizure in the bivariate analysis. Hypothesis 2 was rejected in the Lamictal®/lamotrigine monotherapy cohort.

H3: Presence of AED-interacting medications is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy

There was no significant association between post-index seizure and presence of AED-interacting medications in the bivariate analysis. Hypothesis 3 was rejected in the Lamictal®/lamotrigine monotherapy cohort.

H4: Type of epilepsy diagnosis is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

There was no significant association between post-index seizure and type of epilepsy (intractable versus non-intractable) in the bivariate analysis. Hypothesis 4 was rejected in the Lamictal®/lamotrigine monotherapy cohort.

H5: A prior acute seizure is a significant predictor of seizure recurrence in medically-treated patients with epilepsy.

The prior seizure variable was selected to be included in the final multivariate Lamictal®/lamotrigine model due to its significant association with post-index seizure incidence demonstrated in the bivariate analysis ($p<0.05$). Multiple logistic regression analysis showed that the odds of having a post-index seizure in patients with prior seizure was about 13 times higher than in patients with no prior seizures, while controlling for age, gender, general comorbidity and geographic region of residence ([OR]= 13.46; 95% CI, 5.55-32.66). Hypothesis 5 was accepted in the Lamictal®/lamotrigine monotherapy cohort.

H6: A mental health diagnosis is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

Due to the low number of cells with different categories of mental health diagnosis, hypothesis 6 was tested as the difference in seizure incidence between patients with no mental health diagnosis as compared to those having any mental health diagnosis. However, the variable was not included in the multivariate model because there was no significant association between post-index seizure and presence of a mental health diagnosis in the bivariate analysis. Hypothesis 6 was rejected in the Lamictal®/lamotrigine monotherapy cohort.

H7: Presence of comorbidity is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

The comorbidity variable was included in the multivariate model due to its significant association with post-index seizure incidence demonstrated in the bivariate analysis ($p<0.05$). In the multivariate analysis, patients with a CCI score of one or higher had over twice the odds of experiencing a post-index seizure than patients with a comorbidity score of zero, while controlling for age, gender, geographic region of residence and prior seizure ([OR]= 2.71; 95% CI, 1.10-6.66). Hypothesis 7 was accepted in the Lamictal®/lamotrigine monotherapy cohort.

H8: Higher age is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

There was no significant association between post-index seizure and age in the bivariate and multiple logistic regression analyses. Hypothesis 8 was rejected in the Lamictal®/lamotrigine monotherapy cohort.

H9: Female gender is a significant predictor of breakthrough seizures in medically treated patients with epilepsy.

There was no significant association between post-index seizure and gender in the bivariate and multiple logistic regression analysis. Hypothesis 9 was rejected in the Lamictal®/lamotrigine monotherapy cohort.

H10: U.S. Region is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

The geographic region of residence variable was included in the multivariate model due to its significant association with post-index seizure incidence demonstrated in the bivariate analysis ($p<0.05$). Patients residing in the Northeast had about three times higher odds of experiencing a post-index seizure than patients in the South (reference

group) ([OR] = 3.50; 95% CI, 1.52-8.04). There was no difference in the incidence of seizures between patients residing in the South and those residing in the West or Midwest. Hypothesis 10 was accepted in the Lamictal®/lamotrigine monotherapy cohort.

Table 22 summarizes results of the logistic regression analysis for the Lamictal®/lamotrigine patient cohort.

Table 22 Logistic Regression Analysis of Variables Predicting Post-Index Seizure for 1143 Patients in Lamictal®/Lamotrigine Cohort

Variable	Likelihood of post-index seizure		
	OR	95% CI	p
Prior Seizure	13.46	5.55-32.66	<0.0001
Comorbidity Index ≥ 1	2.71	1.10-6.66	0.03
Age	0.99	0.97-1.02	0.73
Male	0.62	0.31-1.27	0.19
Geographic Regions (reference: South)			
Northeast	3.50	1.52-8.04	0.0032
West	1.79	0.72-4.45	0.21
Midwest	1.42	0.62-3.24	0.41

TRILEPTAL®/OXCARBAZEPINE MONOTHERAPY COHORT: OBJECTIVE 1

The Trileptal®/oxcarbazepine patient cohort consisted of 456 patients who were actively treated with 60 days or more of medication during the first 90 days of the post-index observation period. Table 23 summarizes insurance, clinical and medication characteristics of patients in the Trileptal®/oxcarbazepine monotherapy cohort. The average prescription strength was 394 mg (SD=164 mg; median=300 mg; range=150 mg - 600 mg) with over 50 percent of prescriptions filled with the 300 mg strength of oxcarbazepine active ingredient, followed by 600 mg (37 percent) and 150 mg (11 percent). The target daily dose for patients upon completion of titration period is between 900 and 1200 mg, while the initiation dose is between 300 and 600 mg per day.[6] Patients in the cohort were approximately equally distributed by gender (female=51%) and the average patient age was 40.7 (SD=13.3) years old, similar to patients in the Lamictal®/lamotrigine cohort. The majority of patients had point-of-service (POS) insurance (70.8 percent) and resided in the South (47.2 percent). The mean adherence measured with proportion of days covered was 0.78 (SD=0.24) or 78 percent. With the adherence threshold set at 80 percent, about 60 percent of the Trileptal®/oxcarbazepine cohort was adherent to their AED monotherapy. When the threshold was lowered to 60 percent, about 77 percent of patients were adherent. The larger number of patients in the Trileptal®/oxcarbazepine cohort was treated for partial non-intractable seizures (37.1 percent), followed by other non-intractable (28.7 percent) and generalized non-intractable (21.3 percent) seizures. About 6 percent of patients were concomitantly taking interacting medications. Among patients with interacting medications, thiazide diuretics (hydrochlorthiazide and chlorthalidone) were used most frequently, i.e. by 70.0 percent

of patients with interacting medications. Phenobarbital was used by 29.6 percent of patients with interacting medications. Over 90 percent of patients in the cohort did not have any mental health diagnosis, while among those with a diagnosis, affective disorders were most common (40 percent). The mean CCI score (SD) of patients in the cohort was 0.178 (0.59) with about 88 percent of patients having no comorbidities accompanying their epilepsy condition. A total 146 patients (32.0 percent) in the Trileptal®/oxcarbazepine cohort experienced a bioequivalent switch.

Table 23 Demographic, Insurance, Clinical and Medication Characteristics of Trileptal®/Oxcarbazepine Monotherapy Cohort

Characteristic	Trileptal®/Oxcarbazepine Monotherapy Cohort (n=456)	
	N	%[3]
Age (Mean±SD)	40.7 (±13.3)	
18-30 y	127	27.9
31-45 y	145	31.8
46-64 y	184	40.4
Female gender	231	50.7
Insurance type[1]		
POS	323	70.8
EPO	68	14.9
HMO	41	9.0
PPO	21	4.6
IND	3	≤1.0
One year adherence		
Mean (SD) PDC[2]	0.78 (±0.24)	
Median (range) PDC	0.90(0.17-1)	
PDC≥60%	352	77.2
PDC≥80%	275	59.6
Region		
South	215	47.1
Midwest	124	27.2
West	62	13.6
Northeast	55	12.1
180-day Pre-index Seizure		
≥1	17	3.7
0	439	96.3
365-day Post-index Seizure		
≥1	18	4.0
0	438	96.0
Charlson Comorbidity Index Score		
Mean (SD)	0.178 (±0.59)	
Median (range)	0 (0-6)	
18-30 y	0.118 (±0.43)	
31-45 y	0.166 (±0.60)	
46-64 y	0.228 (±0.67)	
Score 0	401	87.9
Score 1	37	8.1
Score 2	16	3.5
Score 6	2	0.5

Table 23 Demographic, Insurance, Clinical and Medication Characteristics of Trileptal®/Oxcarbazepine Monotherapy Cohort (Continued)

Characteristic	Trileptal®/Oxcarbazepine Monotherapy Cohort (n=456)	
	N	%[3]
Seizure Type		
Partial non-intractable	169	37.1
Partial intractable	44	9.6
Generalized non-intractable	97	21.3
Generalized intractable	8	1.8
Other non-intractable	131	28.7
Other intractable	7	1.5
Comorbid Mental Health Diagnoses		
No mental health diagnosis	431	94.5
Any mental health diagnosis	25	5.5
Mental Health Diagnosis Categories		
Affective Disorders	10	40.0
Other Mental Health Diagnoses	8	32.0
Serious mental illness	5	20.0
Substance Abuse	2	≤0.5
Interacting Medications		
0	429	94.1
≥1	27	5.9
Interacting Medications		
hydrochlorthiazide	18	66.7
chlortalidone	1	≤0.5
phenobarbital	7	25.9
Phenobarbital and hydrochlorthiazide	1	≤0.5
Bioequivalent Switch		
0	310	68.0
≥1	146	32.0

[1]POS-Point of Service; EPO-Exclusive Provider Organization; HMO-Health Maintenance Organization; PPO-Preferred Provider Organization; IND-Indemnity
[2]PDC-Proportion of Days Covered
[3]Some column totals may not add to 100% due to rounding

BIVARIATE COMPARISONS OF SEIZURE INCIDENCE IN TRILEPTAL®/OXCARBAZEPINE MONOTHERAPY COHORT

The incidence of post-index seizures in the Trileptal®/Oxcarbazepine cohort was 4 percent (n=18). For the purposes of bivariate comparisons, similarly to the Lamictal®/lamotrigine cohort, two independent categorical variables (type of epilepsy diagnosis and type of mental health diagnosis) had to be dichotomized due to a low cell count in some categories. Table 24 and 25 display the bivariate comparisons of incidence of post-index seizure by age, age group, gender, geographic region, prior seizure, adherence, general comorbidity, mental health comorbidity, type of epilepsy diagnosis, presence of interacting medications, and presence of a bioequivalent switch. The mean age of patients in the two groups was not significantly different [t=0.25 (df=454); p=0.8029]. Patients with a post-index seizure were 39.9 (±14.9) years old while patients who did not have a post-index seizure were 40.7 (±13.3) years old. Although not statistically significant, chi-square analysis showed that more patients in the 18-30 age group experienced a seizure (7.1 percent) than patients in the two other age groups (1.4 percent [31-45] and 3.8 percent [46-64)]) [χ^2=5.83 (df=2); p=0.0541]. A chi-square analysis of post-index seizure incidence and pre-index seizure showed that more patients with a pre-index seizure experienced a seizure post-index than patients without a pre-index seizure (17.6 percent vs 3.4 percent, respectively) [χ^2=8.74 (df=1);p=0.0031]. A chi-square analysis of post-index seizure and patients' comorbidity status demonstrated that more patients with a CCI score of one or higher experienced a seizure post-index than those with a score of zero (9.1 percent vs 3.2 percent, respectively) [χ^2=4.36

(df=1);p=0.0367]. A chi-square analysis of post-index seizure and patients' mental health comorbidity status demonstrated that more patients with a mental health comorbidity experienced a seizure post-index than patients without mental health comorbidities (24.0 percent vs 2.8 percent, respectively) [χ^2=28.05 (df=1); p<0.001]. A chi-square analysis of post-index seizure and concomitant administration of AED-interacting medications demonstrated that more patients with concomitant administration of AED-interacting medications experienced a seizure post-index than patients without records of interacting medications (11.1 percent vs 3.5 percent, respectively) [χ^2=3.88 (df=1);p=0.0487]. A chi-square analysis of post-index seizure and type of epilepsy diagnosis (intractable vs non-intractable) demonstrated that more patients with intractable epilepsies experienced a seizure post-index than patients with non-intractable epilepsies (10.2 percent vs 3.0 percent, respectively) [χ^2=6.92 (df=1);p=0.0085]. The mean adherence of patients in the two groups was not significantly different [t=0.77 (df=454); p=0.4433]. Patients with a post-index seizure had a mean PDC of 0.73 (±0.28) while patients who did not have a post-index seizure had a mean PDC of 0.78 (±0.24). A chi-square analysis did not reveal any relationships between post-index seizures and gender, dichotomized adherence status (adherence threshold set at 80 and 60 percent, respectively), bioequivalent switch or geographic region of residence (p>0.05).

Table 24 Bivariate Comparison of Incidence of Post-Index Seizure in Trileptal®/Oxcarbazepine Cohort by Age, Age Group, Gender, Adherence and Geographic Region

Independent Variable	Total		Seizure Event		No Seizure Event		t	df	p-value
	Mean	SD	Mean	SD	Mean	SD			
Age	40.7	13.3	39.9	14.9	40.7	13.3	0.25	454	0.0829
Adherence (PDC)	0.78	0.24	0.73	0.28	0.78	0.24	0.77	454	0.4443
	N=456		n	%	n	%	χ^2	df	p-value
Age group							5.83	2	0.0541
18-30	127		9	7.1	118	92.9			
31-45	145		2	1.4	143	98.6			
46-64	184		7	3.8	177	96.2			
Gender							1.92	1	0.1657
Female	231		12	5.2	219	94.8			
Male	225		6	2.7	219	97.3			
PDC							0.005	1	0.9433
≥80%	275		11	4.0	264	96.0			
<80%	181		7	3.9	174	96.1			
PDC							0.26	1	0.6081
≥60%	352		13	3.7	339	96.3			
<60%	104		5	4.8	99	95.2			
Region							2.11	3	0.5487
South	215		6	2.8	209	97.2			
Midwest	124		5	4.0	119	96.0			
West	62		4	6.5	58	93.5			
Northeast	55		3	5.5	52	94.5			

Table 25 Bivariate Comparison of Incidence of Post-Index Seizure in Trileptal®/Oxcarbazepine Cohort by Pre-Index Seizure, General Comorbidity, Seizure Type, Mental Health Comorbidity, Presence of Interacting Medications and Presence of Bioequivalent Switch

Independent Variable	Total	Seizure Event		No Seizure Event		χ^2	df	p-value
	N=456	n	%	n	%			
Pre-index event						8.74	1	0.0031
0	439	15	3.4	424	96.6			
≥1	17	3	17.6	14	82.4			
CCI						4.36	1	0.0367
0	401	13	3.2	388	96.8			
≥1	55	5	9.1	50	90.9			
Seizure Type						6.92	1	0.0085
Non-intractable	397	12	3.0	385	97.0			
Intractable	59	6	10.2	53	89.8			
Mental Comorbidity						28.05	1	<0.001
0	431	12	2.8	419	97.2			
≥1	25	6	24.0	19	76.0			
Interacting Medications						3.88	1	0.0487
0	429	15	3.5	414	96.5			
≥1	27	3	11.1	24	88.9			
Bioequivalent Switch						0.41	1	0.5238
0	310	11	3.5	299	96.5			
≥1	146	7	4.8	139	95.2			

LOGISTIC REGRESSION ANALYSIS OF INCIDENCE OF POST-INDEX SEIZURES IN TRILEPTAL®/OXCARBAZEPINE MONOTHERAPY COHORT: OBJECTIVE 2

Objective 2 was to develop a model predicting post-index seizures based on the factors identified contributory to seizure occurrence in the bivariate analyses: prior seizure, mental health comorbidity, general comorbidity, interacting medications, and seizure type. Age and gender covariates were included in the final model. Multiple logistic regression was used to address study objective 2.

The formula below was used to build the regression model:

$$logit\ (Y) = \ln\frac{\pi}{1-\pi} = \alpha + \beta 1X1 + \beta 2X2 + \beta 3X3 + \beta 4X4 + \beta 5X5 + \beta 6X6 + \beta 7X7$$

$$\pi = \frac{e^{\alpha+\beta 1X1+\beta 2X2+\beta 3X3+\beta 4X4+\beta 5X5+\beta 6X6+\beta 7X7}}{1+e^{\alpha+\beta 1X1+\beta 2X2+\beta 3X3+\beta 4X4+\beta 5X5+\beta 6X6+\beta 7X7}},$$ where

π= probability of seizure event;

α- the Y intercept

$\beta 1$-$\beta 7$- regression coefficients;

X1- prior seizure event;

X2-mental health comorbidity;
X3- general comorbidity;
X4- interacting medications;
X5- seizure type;
X6- gender;
X7- age.

The overall model with seven predictors was significant [χ^2=28.7 (df=7); p=0.0002]. The output for the model is presented in Appendix C. Mutlicollinearity between predictor variables was assessed using weighted regressions with COLLIN and COLLINOINT options.[191] Small condition indices suggested that there was no collinearity between independent variables in the model. The output of collinearity assessment is presented in Appendix D.

H1: AED nonadherence is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

This hypothesis was rejected in the Trileptal®/oxcarbazepine monotherapy cohort. There was no difference in adherence between patients who experienced post-index seizure and those who did not in the bivariate analysis.

H2: A bioequivalent medication switch is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

This hypothesis was rejected in the Trileptal®/Oxcarbazepine monotherapy cohort. There was no difference in frequency of switches between patients who experienced post-index seizure and those who did not in the bivariate analysis.

H3: Presence of AED-interacting medications is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy

The AED-interacting medications variable was selected to be included in the multivariate model due to its significant association with seizure incidence demonstrated in the bivariate analysis. However, in the final model there was no significant association between post-index seizure and interacting medications while controlling for age, gender, prior seizure, mental health comorbidity, general comorbidity and type of epilepsy diagnosis ([OR]= 1.57; 95% CI, 0.31-8.03). Hypothesis 3 was rejected in the Trileptal®/oxcarbazepine monotherapy cohort.

H4: Type of epilepsy diagnosis is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

The type of epilepsy diagnosis variable was selected to be included in the multivariate model due to its significant association with seizure incidence demonstrated in the bivariate analysis. In the final model there was a significant association between post-index seizure and type of epilepsy while controlling for age, gender, prior seizure event, mental health comorbidity, general comorbidity and interacting medications ([OR]= 4.06; 95% CI, 1.31-12.6). Patients with intractable epilepsy had about four-fold higher odds of experiencing post-index seizure than patients with non-intractable epilepsy. Hypothesis 4 was accepted in the Trileptal®/oxcarbazepine monotherapy cohort.

H5: A prior acute seizure is a significant predictor of seizure recurrence in medically-treated patients with epilepsy.

The prior seizure variable was selected to be included in the multivariate model due to its significant association with seizure incidence demonstrated in the bivariate analysis. Although the multiple logistic regression analysis showed that odds of having a post-index seizure in patients with prior seizure were four-fold higher than in patients with no prior seizures, the finding was not statistically significant while controlling for age, gender, mental health comorbidity, general comorbidity and type of epilepsy diagnosis

([OR]= 4.17; 95% CI, 0.85-20.56). Hypothesis 5 was rejected in the Trileptal®/Oxcarbazepine monotherapy cohort.

H6: A mental health diagnosis is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

The mental health comorbid diagnosis variable was selected to be included in the multivariate model due to its significant association with seizure incidence demonstrated in the bivariate analysis. The multiple logistic regression analysis showed that odds of having a post-index seizure in patients with mental health comorbidity were about ten times higher than in patients with no comorbid mental health diagnosis while controlling for age, gender, prior seizure, general comorbidity, presence of interacting medications and type of epilepsy diagnosis ([OR]= 10.84; 95% CI 3.19-36.82). Hypothesis 6 was accepted in the Trileptal®/oxcarbazepine monotherapy cohort.

H7: Presence of comorbidity is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy

The comorbidity was included in the multivariate model due to its significant association with seizure incidence demonstrated in the bivariate analysis. Although the multiple logistic regression analysis showed that odds of having a post-index seizure in patients with a comorbidity index of one or higher were about two and a half times higher than in patients with comorbidity index of zero, the finding was not statistically significant while controlling for age, gender, prior seizure, mental health comorbidity, presence of interacting medications and type of epilepsy diagnosis ([OR]= 2.51; 95% CI, 0.72-8.69). Hypothesis 7 was rejected in the Trileptal®/oxcarbazepine monotherapy cohort.

H8: Higher age is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

There was no significant association between post-index seizures and age in the bivariate analysis. Hypothesis 8 was rejected in the Trileptal®/Oxcarbazepine monotherapy cohort.

H9: Female gender is a significant predictor of breakthrough seizures in medically treated patients with epilepsy.

There was no significant association between post-index seizures and gender in the bivariate analysis. Hypothesis 9 was rejected in the Trileptal®/Oxcarbazepine monotherapy cohort.

H10: U.S. Region is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

There was no association between U.S. geographic region and post-index seizure incidence based on results of the bivariate analysis. Hypothesis 10 was rejected in the Trileptal®/oxcarbazepine monotherapy cohort.

Table 26 summarizes results of the logistic regression analysis for Trileptal®/oxcarbazepine patient cohort.

Table 26 Logistic Regression Analysis of Variables Predicting Post-Index Seizure for 456 patients in Trileptal®/Oxcarbazepine Cohort

Variable	Likelihood of post-index seizure		
	OR	95% CI	p
Prior Seizure	4.17	0.85-20.56	0.079
Mental Health Comorbidity	10.84	3.19-36.82	0.0001
Comorbidity Index ≥1	2.51	0.72-8.70	0.15
Interacting Medications	1.58	0.31-8.03	0.58
Seizure Type = Intractable	4.06	1.31-12.60	0.02
Age	0.99	0.95-1.03	0.49
Male	0.45	0.15-1.33	0.15

KEPPRA®/LEVETIRACETAM MONOTHERAPY COHORT: OBJECTIVE 1

The Keppra®/levetiracetam patient cohort consisted of 1114 patients who were actively treated with 60 days or more of medication during the first 90 days of the post-index observation period. Table 27 summarizes insurance, clinical and medication characteristics of patients in the Keppra®/levetiracetam monotherapy cohort. The average prescription strength was 607 mg (SD=201 mg; median=500 mg; range=100 mg-1000 mg) with over 60 percent of prescriptions filled with the 500 mg strength of levetiracetam active ingredient, followed by 750 mg (18 percent) and 1000 mg (15 percent). The target daily dose for patients upon completion of the titration period is between 1000 and 2000 mg, while the initiation dose is between 250 and 500 mg per day.[6] Patients in the cohort were about equally distributed by gender (females 53.9 percent) and the average patient age was 43.5 (SD=13.2) years old, similar to patients in the Lamictal®/lamotrigine and Trileptal®/oxcarbazepine cohorts. The majority of patients had POS insurance (68.0 percent) and a larger number of patients resided in the South (46.2 percent). The mean adherence measured with proportion of days covered was 0.77 (SD=0.24) or 77 percent. With the adherence threshold set at 80 percent, 59.6 percent of the Keppra®/levetiracetam cohort was adherent to their AED monotherapy. When the threshold was lowered to 60 percent, 74.0 percent of patients were adherent. The larger number of of patients in the Keppra®/levetiracetam cohort was treated for partial non-intractable seizures (29.5 percent), followed by other non-intractable (29.4 percent) and generalized non-intractable (26.8 percent) seizures.

Levetiracetam is considered one of the least interacting AEDs, i.e. it binds minimally to plasma proteins (<10%) and does not inhibit or induce substrates of cytochrome P450.[108] However, the package insert indicates Risk C interaction (requiring therapy monitoring) of levetiracetam with ketorolac and mefloquine that may possibly diminish AED concentration. No patients in the cohort had prescription records for mefloquine and only 6 patients were prescribed Keppra®/levetiracetam concomitantly with ketorolac. About 4 percent of patients in the cohort (44 patients) had a mental health diagnosis, with affective disorders (depression, anxiety and PTSD) being the most common diagnosis type (n=26). The mean comorbidity score of patients in the cohort was 0.29 (SD=0.7) with about 80 percent of patients having no comorbidities accompanying their epilepsy condition. A total of 267 patients (24.0 percent) in the Keppra®/levetiracetam cohort experienced bioequivalent switches.

Table 27 Demographic, Insurance, Clinical and Medication Characteristics of Keppra®/Levetiracetam Monotherapy Cohort

Characteristic	Keppra®/Levetiracetam Monotherapy Cohort (n=1114)	
	N	%[3]
Age (Mean±SD)	43.5 (±13.2)	
18-30 y	234	21.0
31-45 y	330	29.6
46-64 y	550	49.4
Female gender	600	53.9
Insurance type[1]		
POS	758	68.0
EPO	147	13.2
HMO	152	13.6
PPO	47	4.2
IND	10	0.9
One year adherence		
Mean (SD) PDC[2]	0.77 (0.24)	
Median (range) PDC	0.89 (0.17-1)	
PDC≥60%	824	74.0
PDC≥80%	664	59.6
Region		
South	515	46.2
Midwest	354	31.8
West	128	11.5
Northeast	117	10.5
180-day Pre-index Seizure		
≥1	150	13.5
0	964	86.5
365-day Post-index Seizure		
≥1	88	7.9
0	1026	92.1
Charlson Comorbidty Index Score		
Mean (SD)	0.29 (0.7)	
Median (range)	0 (0-6)	
18-30 y	0.09 (0.4)	
31-45 y	0.28 (0.7)	
46-64 y	0.38 (0.8)	
Score 0	909	81.6
Score 1	107	9.6
Score 2	83	7.5
Score 3	12	1.1
Score 4	1	<0.1
Score 6	2	0.2

Table 27 Demographic, Insurance, Clinical and Medication Characteristics of Keppra®/Levetiracetam Monotherapy Cohort (Continued)

Characteristic	Keppra®/Levetiracetam Monotherapy Cohort (n=1114)	
	N	%[3]
Seizure Type		
Partial non-intractable	329	29.5
Partial intractable	85	7.6
Generalized non-intractable	299	26.8
Generalized intractable	35	3.1
Other non-intractable	327	29.4
Other intractable	39	3.5
Comorbid Mental Health Diagnoses		
No mental health diagnosis	1070	96.1
Any mental health diagnosis	44	3.9
Mental Health Diagnosis Categories		
Affective Disorders	26	59.1
Other Mental Health Diagnosis	12	27.3
Serious Mental Illness	3	6.8
Substance Abuse	3	6.8
Interacting Medications		
0	1108	99.5
≥1	6	0.5
Type of Interacting Medications		
Mefloquine	0	0.0
Ketorolac tromethamine	6	100.0
Type of Interacting Medications		
Mefloquine	0	0
Ketorolac tromethamine	6	100
Bioequivalent Switch		
0	847	76.0
≥1	267	24.0

[1]POS-Point of Service; EPO-Exclusive Provider Organization; HMO-Health Maintenance Organization; PPO-Preferred Provider Organization; IND-Indemnity
[2]PDC-Proportion of Days Covered
[3]Some column totals may not add to 100% due to rounding

BIVARIATE COMPARISONS OF SEIZURE INCIDENCE IN KEPPRA®/LEVETIRACETAM MONOTHERAPY COHORT

The incidence of post-index seizures in the Keppra®/levetiracetam cohort was about 8 percent (n=88). Similarly to bivariate analyses in Lamictal®/lamotrigine and Trileptal®/oxcarbazepine cohorts, two independent nominal variables (mental health comorbidity and type of epilepsy diagnosis) were dichotomized due to a low cell count in some categories. Tables 28 and 29 display the bivariate comparisons of incidence of post-index seizure by age, age group, gender, geographic region, prior seizure, adherence, general comorbidity, mental health comorbidity, type of epilepsy diagnosis, presence of interacting medications, and presence of a bioequivalent switch. The mean age of patients in the two groups was not significantly different [t=1.44 (df=1112);p=0.15]. Patients with a post-index seizure were 41.5 (±14.1) years old while patients who did not have a post-index seizure were 43.6 (±13.1) years old. Although not statistically significant, chi-square analysis showed that more patients in the 18-30 age group experienced a post-index seizure (10.3 percent) than patients in the two other age groups (7.0 percent [31-45] and 7.5 percent [46-64], respectively) [χ^2=2.33 (df=2); p=0.31]. A chi-square analysis of incidence of post-index seizure- and pre-index seizure showed that more patients with a pre-index seizure experienced a seizure post-index than patients without a pre-index seizure (19.3 percent vs 6.1 percent, respectively) [χ^2=31.15 (df=1); p<0.0001]. A chi-

square analysis of post-index seizure and comorbidity status demonstrated that more patients with a CCI score of one or higher experienced a seizure post-index than patients with a score of zero (16.6 percent vs 5.9 percent, respectively) [χ^2=26.05 (df=1); p<0.0001]. A chi-square analysis of post-index seizure and mental health comorbidity demonstrated that more patients with a mental health comorbidity experienced a post-index seizure than patients without a mental health comorbidity (31.8 percent vs 6.9 percent, respectively) [χ^2=36.0 (df=1); p<0.001]. A chi-square analysis of post-index seizure and bioequivalent switch demonstrated no significant association between the two variables [χ^2=1.03 (df=1); p=0.31]. The mean adherence of patients in the two groups was not significantly different [t=-1.45 (df=1112); p=0.15]. Patients with a post-index seizure had a mean PDC of 0.81 (±0.23) while patients who did not have a post-index seizure had a mean PDC of 0.76 (±0.24). A chi-square analysis of association between incidence of post-index seizure and presence of interacting medications was not conducted due to the low number of patients who had AED-interacting medications (n=6). A chi-square analysis did not reveal any differences between post-index seizure and gender, dichotomized adherence status (adherence threshold set at 80 and 60 percent, respectively), type of epilepsy diagnosis (intractable vs non-intractable) or geographic region of residence (p>0.05).

Table 28 Bivariate Comparison of Incidence of Post-Index Seizure in Keppra®/Levetiracetam Cohort by Age, Age Group, Gender, Adherence and Geographic Region

Independent Variable	Total		Seizure Event		No Seizure Event		t	df	p-value
	Mean	SD	Mean	SD	Mean	SD			
Age	43.5	13	41.5	14.1	43.6	13.1	1.44	1112	0.15
Adherence (PDC)	0.77	0.24	0.81	0.23	0.76	0.24	-1.45	1112	0.15
	N=1114		n	%	n	%	χ^2	df	p-value
Age group							2.33	2	0.31
18-30	234		24	10.3	210	89.7			
31-45	330		23	7.0	307	93.0			
46-64	550		41	7.5	509	92.5			
Gender							0.29	1	0.59
Female	600		45	7.5	555	92.5			
Male	514		43	8.4	471	91.6			
PDC							2.92	1	0.09
≥80%	664		60	9.1	604	91.0			
<80%	450		28	6.2	422	93.8			
PDC							1.54	1	0.21
≥60%	824		70	8.5	754	91.5			
<60%	290		18	6.2	272	93.8			
Region							4.3	3	0.23
South	515		33	6.4	482	93.6			
Midwest	354		36	10.2	318	89.8			
West	128		9	7.0	119	93.0			
Northeast	117		10	8.5	107	91.5			

Table 29 Chi-Square Comparison of Incidence of Post-Index Seizure in Keppra®/Levetiracetam Cohort by Pre-Index Event, Comorbidity, Seizure Type, Mental Health Comorbidity, Presence of Interacting Medications and Presence of a Bioequivalent Switch

Independent Variable	Total	Seizure Event		No Seizure Event		χ^2	df	p-value
	N=1114	n	%	n	%			
Pre-index event						31.15	1	<0.0001
0	964	59	6.1	905	93.9			
≥1	150	29	19.3	121	80.7			
CCI						26.05	1	<0.0001
0	909	54	5.9	855	94.1			
≥1	205	34	16.6	171	83.4			
Seizure Type						0.02	1	0.89
Non-intractable	955	75	7.9	880	92.1			
Intractable	159	13	8.2	146	91.8			
Mental Comorbidity						36.02	1	<0.0001
0	1070	74	6.9	996	93.1			
≥1	44	14	31.8	30	68.2			
Bioequivalent Switch						1.03	1	0.31
0	847	63	7.4	784	92.6			
≥1	267	25	9.4	242	90.6			

LOGISTIC REGRESSION ANALYSIS OF INCIDENCE OF POST-INDEX SEIZURES IN KEPPRA®/LEVETIRACETAM MONOTHERAPY COHORT: OBJECTIVE 2

Objective 2 was to develop a model predicting acute seizures based on the factors identified contributory to seizure recurrence in the bivariate analyses: prior seizure, mental health and general comorbidity. Age and gender covariates were included in the final model. Multiple logistic regression was used to address the study objective 2.

The formula below was used to build the regression model:

$$logit\ (Y) = \ln\frac{\pi}{1-\pi} = \alpha + \beta 1X1 + \beta 2X2 + \beta 3X3 + \beta 4X4 + \beta 5X5$$

$$\pi = \frac{e^{\alpha+\beta 1X1+\beta 2X2+\beta 3X3+\beta 4X4+\beta 5X5}}{1+e^{\alpha+\beta 1X1+\beta 2X2+\beta 3X3+\beta 4X4+\beta 5X5}}\ ,\ \text{where}$$

π= probability of seizure event;
α- the Y intercept;
$\beta 1$-$\beta 5$- regression coefficients;
X1- prior seizure event;
X2-mental health comorbidity,
X3- general comorbidity;
X4- gender;
X5- age.

The overall model with five predictors was significant [χ^2=65.3 (df=5); p<0.0001]. The output for the model is presented in Appendix E. Mutlicollinearity between predictor variables was assessed using weighted regressions with COLLIN and COLLINOINT options.[191] Small condition indices suggested that there was no collinearity between independent variables in the model. The output of collinearity assessment is presented in Appendix F.

H1: AED nonadherence is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

There was no difference in adherence between patients who experienced seizure post-index and those who did not in the bivariate analysis. Hypothesis 1 was rejected in the Keppra®/levetiracetam monotherapy cohort.

H2: A bioequivalent medication switch is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

There was no difference in frequency of switches between patients who experienced post-index seizure and those who did not in the bivariate analysis. Hypothesis 2 was rejected in the Keppra®/levetiracetam monotherapy cohort.

H3: Presence of AED-interacting medications is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

Hypothesis 3 was not tested in the Keppra®/levetiracetam monotherapy cohort due to the low number of patients with AED-interacting medications (n=6).

H4: Type of epilepsy diagnosis is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

The type of epilepsy diagnosis variable was not selected to be included in the multivariate model due to lack of significant association with post-index seizure incidence demonstrated in the bivariate analysis. Hypothesis 4 was rejected in Keppra®/levetiracetam monotherapy cohort.

H5: A prior acute seizure is a significant predictor of seizure recurrence in medically-treated patients with epilepsy.

The prior seizure variable was selected to be included in the multivariate model due to its significant association with post-index seizure incidence demonstrated in the bivariate

analysis ($p<0.05$). Patients with prior seizure had about three times higher odds of having a post-index seizure than patients who did not have a prior seizure while controlling for age, gender, mental health and general comorbidity ([OR]= 3.30; 95% CI, 1.98-5.50). Hypothesis 5 was accepted in the Keppra®/levetiracetam monotherapy cohort.

H6: A mental health diagnosis is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

The mental health diagnosis variable was selected to be included in the multivariate model due to its significant association with post-index seizure incidence demonstrated in the bivariate analysis ($p<0.05$). The multiple logistic regression analysis showed that odds of having a post-index seizure in patients with mental health comorbidity were about four and half times higher than in patients with no mental health comorbidity while controlling for age, gender, prior seizure and general health comorbidity ([OR]= 4.56; 95% CI 2.20-9.45). Hypothesis 6 was accepted in the Keppra®/levetiracetam monotherapy cohort.

H7: Presence of comorbidity is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy

The comorbidity index variable was selected to be included in the multivariate model due to its significant association with post-index seizure incidence demonstrated in the bivariate analysis ($p<0.05$). The multiple logistic regression analysis showed that odds of having a post-index seizure in patients with a CCI score of one or higher were about three times higher than in patients with a score of zero while controlling for age, gender, prior seizure and mental health comorbidity ([OR]= 3.24; 95% CI 1.96-5.37). Hypothesis 7 was accepted in the Keppra®/levetiracetam monotherapy cohort.

H8: Higher age is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

There was no significant association between post-index seizure and age in the bivariate analysis ($p>0.05$). However, as an important covariate age was included in the regression model. The results of logistic regression analysis showed that each one-year increase in age decreased patients' odds of having a post-index seizure by about 2 percent, while controlling for gender, prior seizure, mental health and general comorbidity (odds ratio [OR]= 0.98; 95% CI, 0.96-0.99). This finding was statically significant ($p=0.0068$). Hypothesis 8 was rejected in the Keppra®/levetiracetam monotherapy cohort. Older age

was associated with a slight reduction in the odds of having a post-index seizure. However, this finding may not be clinically significant.

H9: Female gender is a significant predictor of breakthrough seizures in medically treated patients with epilepsy.

There was no significant association between post-index seizure event and gender in the bivariate or multiple logistic regression analyses. Hypothesis 9 was rejected in the Keppra®/levetiracetam monotherapy cohort.

H10: U.S. Region is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

There was no association between U.S. geographic region and post-index seizure incidence based on results of the bivariate analysis. Hypothesis 10 was rejected in the Keppra®/levetiracetam monotherapy cohort.

Table 30 summarizes results of the logistic regression analysis for the Keppra®/levetiracetam patient cohort.

Table 30 Logistic Regression Analysis of Variables Predicting Post-Index Seizure for 1114 Patients in Keppra®/levetiracetam Cohort

Variable	Likelihood of post-index seizure		
	OR	95% CI	p
Prior Seizure	3.30	1.98-5.50	<0.0001
Mental Health Comorbidity	4.56	2.20-9.45	<0.0001
Comorbidity Index ≥1	3.24	1.96-5.37	<0.0001
Age	0.98	0.96-0.99	0.0068
Male	0.99	0.63-1.57	0.97

TOPAMAX®/TOPIRAMATE MONOTHERAPY COHORT: OBJECTIVE 1

The Topamax®/topiramate patient cohort consisted of 427 patients who were actively treated with 60 days or more of medication during the first 90 days of the post-index observation period. Table 31 summarizes insurance, clinical and medication characteristics of patients in the Topamax®/topiramate monotherapy cohort. The average prescription strength was 93.4 mg (SD=58.1 mg; median= 100 mg; range=25 mg-200 mg) with about 40 percent of prescriptions filled with the 100 mg strength of topiramate active ingredient (41.4 percent), followed by 50 mg (21.6 percent), 25 mg (18.8 percent) and 200 mg (18.3 percent). The target daily dose for patients upon completion of the titration period is between 100 and 200 mg, while the initiation dose is between 25 and 50 mg per day.[6] Patients in the cohort were predominantly female (76.8 percent). The average patient age was 40.7 (SD=12.4) years old, which is again similar to patients in the Keppra®/levetiracetam, Lamictal®/Lamotrigine and Trileptal®/Oxcarbazepine cohorts. The majority of patients had POS insurance (69.6 percent) and resided in the South (52.2 percent). The mean adherence measured with proportion of days covered was 0.64 (SD=0.27) or 64 percent, which was the lowest mean adherence value among the four monotherapy cohorts studied. With the adherence threshold set at 80 percent, about 40 percent of the Topamax®/topiramate cohort was adherent to their AED monotherapy. When the threshold was lowered to 60 percent, about 60 percent of patients were adherent. The larger number of patients in the Topamax®/topiramate cohort was treated for other non-intractable seizures (30.1 percent), followed by partial non-intractable (27.6 percent) and generalized non-intractable (26.9 percent) seizures.

Regarding interacting medications, no patients in the cohort had prescription records for mefloquine, whereas 9 patients were prescribed Topamax®/topiramate concomitantly with ketorolac. In addition, 7 patients were prescribed thiazide or thiazide-type diuretics concomitantly with their AED pharmacotherapy. About 8 percent of patients in the cohort (n=34) had a mental health diagnosis, with affective disorders (depression and anxiety) being the most common diagnosis type (n=15). The mean CCI score of patients in the cohort was 0.12 (SD=0.4), with about 90 percent of patients having no comorbidities accompanying their epilepsy condition. A total 48 patients (11.2 percent) in the Topamax®/topiramate cohort experienced bioequivalent switches.

Table 31 Demographic, Insurance, Clinical and Medication Characteristics of Topamax®/Topiramate Monotherapy Cohort

Characteristic	Topamax®/Topiramate Monotherapy Cohort (n=427)	
	N	%[3]
Age (Mean±SD)	40.7 (±12.4)	
18-30 y	104	24.3
31-45 y	163	38.2
46-64 y	160	37.5
Female gender	328	76.8
Insurance type[1]		
POS	297	69.6
EPO	52	12.2
HMO	55	12.9
PPO	22	5.2
IND	1	0.2
One year adherence		
Mean (SD) PDC[2]	0.64 (0.27)	
Median (range) PDC	0.74 (0.16-1.00)	
PDC≥60%	255	59.7
PDC≥80%	172	40.3
Region		
South	223	52.2
Midwest	108	25.3
West	52	12.2
Northeast	44	10.3
180-day Pre-index Seizure		
≥1	11	2.6
0	416	97.4
365-day Post-index Seizure		
≥1	15	3.5
0	412	96.5
Charlson Comorbidity Index Score		
Mean (SD)	0.12 (0.4)	
Median (range)	0 (0-2)	
18-30 y	0.06 (0.2)	
31-45 y	0.10 (0.3)	
46-64 y	0.17 (0.5)	
Score 0	383	89.7
Score 1	38	8.9
Score 2	6	1.4

Table 31 Demographic, Insurance, Clinical and Medication Characteristics of Topamax®/Topiramate Monotherapy Cohort (Continued)

Characteristic	Topamax®/Topiramate Monotherapy Cohort (n=427)	
	N	%[3]
Seizure Type		
Partial non-intractable	118	27.6
Partial intractable	35	8.2
Generalized non-intractable	115	26.9
Generalized intractable	22	5.2
Other non-intractable	129	30.2
Other intractable	8	1.9
Comorbid Mental Health Diagnoses		
No mental health diagnosis	393	92.0
Any mental health diagnosis	34	8.0
Type of Mental Health Diagnosis		
Affective Disorders	15	44.1
Other Mental Health Diagnosis	11	32.4
Serious Mental Illness	5	14.7
Substance Abuse	3	8.8
Interacting Medications		
0	411	96.3
≥1	16	3.7
Interacting Medications		
Ketorolac tromethamine	9	56
Mefloquine	0	0
Hydrochlorthiazide	6	37.5
Indapamide	1	6.3
Bioequivalent Switch		
0	379	88.8
≥1	48	11.2

[1]POS-Point of Service; EPO-Exclusive Provider Organization; HMO-Health Maintenance Organization; PPO-Preferred Provider Organization; IND-Indemnity
[2]PDC-Proportion of Days Covered
[3]Some column totals may not add to 100% due to rounding

BIVARIATE COMPARISONS OF SEIZURE INCIDENCE IN TOPAMAX®/TOPIRAMATE MONOTHERAPY COHORT

The incidence of post-index seizures in the Topamax®/topiramate cohort was 3.5 percent (n=15). Similar to the previous cohorts, two independent categorical variables (mental health comorbidity and type of epilepsy) with more than two categories were dichotomized due to a low cell count in some categories. Tables 32 and 33 display the bivariate comparisons of incidence of post-index seizures by age, age group, gender, geographic region, prior seizure, adherence, comorbidity, mental health comorbidity, type of epilepsy diagnosis, presence of interacting medications, and presence of a bioequivalent switch. The mean age of patients in the two groups was not significantly different [t=-1.05 (df=425); p=0.29]. Patients with a post-index seizure were 44.0 (±12.9) years old while patients who did not have a post-index seizure were 40.6 (±12.4) years old. Although not statistically significant, chi-square analysis showed that more patients I the age group 46-64 experienced a post-index seizure (5.0 percent) than patients in the two other age groups (3.7 percent [31-45] and 1.0 percent [18-30]) [χ^2=3.1 (df=2);p=0.22]. A chi-square analysis of the incidence of post-index seizure and pre-index seizure status showed no statistically significant relationships [χ^2=1.04 (df=1);p=0.31]. On the other hand, a chi-square analysis of post-index seizures and patients' comorbidity status demonstrated that more patients with a CCI score of one or

higher experienced a seizure post-index than patients with a score of zero (9.1 percent vs 2.9 percent, respectively) [χ^2=4.5 (df=1); p=0.034]. Although not statistically significant, chi-square analysis showed that more patients with mental health comorbidity experienced a seizure post-index than patients with no mental health comorbidities (8.8 percent vs 3.1 percent, respectively) [χ^2=3.07 (df=1);p=0.08]. A chi-square analysis of post-index seizures and bioequivalent switch status demonstrated that more patients with a bioequivalent switch experienced a seizure post-index than patients who did not have a switch (10.4 percent vs 2.6 percent, respectively) [χ^2=7.6 (df=1); p=0.0058]. The mean adherence of patients in the two groups was not significantly different [t=-0.7 (df=425); p=0.48]. Patients with a post-index seizure had a mean PDC of 0.69 (±0.2) while patients who did not have a post-index seizure had a mean PDC of 0.64 (±0.3). A chi-square analysis did not reveal any relationships between incidence of post-index seizure and gender, dichotomized adherence status (adherence set at 80% and 60%), interacting medications, type of epilepsy (intractable vs non-intractable) or geographic region of residence (p>0.05).

Table 32 Bivariate Comparison of Incidence of Post-Index Seizure in Topamax®/Topiramate Cohort by Age, Age Group, Gender, Adherence and Geographic Region

Independent Variable	Total		Seizure Event		No Seizure Event		t	df	p-value
	Mean	SD	Mean	SD	Mean	SD			
Age	40.7	12.4	44.0	12.9	40.6	12.4	-1.05	425	0.29
Adherence (PDC)	0.64	0.3	0.69	0.2	0.64	0.3	-0.7	425	0.48
	N=427		n	%	n	%	χ^2	df	p-value
Age group							3.1	2	0.22
18-30	104		1	1.0	103	99.0			
31-45	163		6	3.7	157	96.3			
46-64	160		8	5.0	152	95.0			
Gender							0.1	1	0.75
Female	328		11	3.4	317	96.6			
Male	99		4	4.0	95	96.0			
PDC							0.005	1	0.98
≥80%	172		6	3.5	166	96.5			
<80%	255		9	3.5	246	96.5			
PDC							0.31	1	0.58
≥60%	255		10	3.9	245	96.1			
<60%	172		5	2.9	167	97.1			
Region							3.66	3	0.30
South	223		9	4.0	214	96.0			
Midwest	108		3	2.8	105	97.2			
West	52		0	0.0	52	100			
Northeast	44		3	6.8	41	93.2			

Table 33 Chi-Square Comparison of Incidence of Post-Index Seizure in Topamax®/Topiramate Cohort by Pre-Index Event, Comorbidity, Seizure Type, Mental Health Comorbidity, Presence of Interacting Medications and Presence of a Bioequivalent Switch

Independent Variable	Total	Seizure Event		No Seizure Event		χ^2	df	p-value
	N=427	n	%	n	%			
Pre-index event						1.04	1	0.31
0	416	14	3.4	402	96.6			
≥1	11	1	9.1	10	90.9			
CCI						4.5	1	0.034
0	383	11	2.9	372	97.1			
≥1	44	4	9.1	40	90.9			
Seizure Type						0.04	1	0.84
Non-intractable	362	13	3.6	349	96.4			
Intractable	65	2	3.1	63	96.9			
Mental Comorbidity						3.07	1	0.08
0	393	12	3.1	381	96.9			
≥1	34	3	8.8	31	91.2			
Interacting Medications						0.37	1	0.54
0	411	14	3.4	397	96.6			
≥1	16	1	6.3	15	93.7			
Bioequivalent Switch						7.6	1	0.0058
0	379	10	2.6	369	97.4			
≥1	48	5	10.4	43	89.6			

LOGISTIC REGRESSION ANALYSIS OF INCIDENCE OF POST-INDEX SEIZURES IN TOPAMAX®/TOPIRAMATE MONOTHERAPY COHORT: OBJECTIVE 2

Objective 2 was to develop a model predicting acute seizures based on the factors identified contributory to seizure recurrence in the bivariate analyses in the Topamax®/topiramate cohort: comorbidity and bioequivalent switch. Since mental health comorbidity and post-index seizure bivariate analysis was approaching significance (p=0.08), the mental health comorbidity variable was also included in the final model. Among covariates, age and gender were included. Multiple logistic regression was used to address the study objective 2.

The formula below was used to build the regression model:

$$logit\ (Y) = \ln\frac{\pi}{1-\pi} = \alpha + \beta 1X1 + \beta 2X2 + \beta 3X3 + \beta 4X4 + \beta 5X5$$

$$\pi = \frac{e^{\alpha+\beta 1X1+\beta 2X2+\beta 3X3+\beta 4X4+\beta 5X5}}{1+e^{\alpha+\beta 1X1+\beta 2X2+\beta 3X3+\beta 4X4+\beta 5X5}},\ \text{where}$$

π= probability of seizure event;

α- the Y intercept
β1-β4- regression coefficients;
X1- comorbidity;
X2-bioequivalent switch;
X3-mental health comorbidity;
X4- age;
X5- gender.

The overall model with five predictors was significant [Chi-square=11.25 (df=5);p=0.0467]. The output for the model is presented in Appendix G. Mutlicollinearity between predictor variables was assessed using weighted regressions with COLLIN and COLLINOINT options.[191] Small condition indices suggested that there was no collinearity between independent variables in the model. The output of collinearity assessment is presented in Appendix H.

H1: AED nonadherence is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

There was no difference in adherence between patients who experienced a post-index seizure and those who did not in the bivariate analysis. Hypothesis 1 was rejected in the Topamax®/topiramate monotherapy cohort.

H2: A bioequivalent medication switch is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

Patients with a bioequivalent switch in the Topamax®/topiramate monotherapy cohort had about four times higher odds of having a post-index seizure than patients who did not experience a switch, while controlling for age, gender, general and mental health

comorbidity ([OR]= 4.52; 95% CI, 1.44-14.22). Hypothesis 2 was accepted in the Topamax®/topiramate monotherapy cohort.

H3: Presence of AED-interacting medications is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy

The AED-interacting medications variable was not selected for inclusion in the multivariate model due to its lack of significant association with post-index seizure incidence demonstrated in the bivariate analysis. Hypothesis 3 was rejected in the Topamax®/topiramate monotherapy cohort.

H4: Type of epilepsy diagnosis is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

The type of epilepsy diagnosis variable was not selected for inclusion in the multivariate model due to lack of significant association with post-index seizure incidence demonstrated in the bivariate analysis. Hypothesis 4 was rejected in Topamax®/topiramate monotherapy cohort.

H5: A prior acute seizure is a significant predictor of seizure recurrence in medically-treated patients with epilepsy.

The prior seizure variable was not selected for inclusion in the multivariate model due to lack significant association with post-index seizure incidence demonstrated in the bivariate analysis. Hypothesis 5 was rejected in the Topamax®/topiramate monotherapy cohort.

H6: A mental health diagnosis is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

There was no increased incidence of post-index seizures in patients with mental health comorbidity, while controlling for age, gender, general comorbidity status and bioequivalent switch ([OR] = 2.84; 95% CI 0.68-11.79). Hypothesis 6 was rejected in the Topamax®/topiramate monotherapy cohort.

H7: Presence of comorbidity is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy

The comorbidity variable was selected for inclusion in the multivariate model due to its significant association with post-index seizure incidence demonstrated in the bivariate

analysis ($p<0.05$). However, the multiple logistic regression analysis showed no association between post-index seizure incidence and comorbidity while controlling for age, gender, mental health comorbidity and bioequivalent AED switch ([OR]= 2.63; 95% CI 0.73-9.44). Hypothesis 7 was rejected in the Topamax®/topiramate monotherapy cohort.

H8: Higher age is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

There was no significant association between post-index seizure incidence and age in the bivariate and multiple logistic regression analyses. Hypothesis 8 was rejected in the Topamax®/topiramate monotherapy cohort.

H9: Female gender is a significant predictor of breakthrough seizures in medically treated patients with epilepsy.

There was no significant association between post-index seizure incidence and gender in the bivariate and multiple logistic regression analyses. Hypothesis 9 was rejected in the Topamax®/Topiramate monotherapy cohort.

H10: U.S. Region is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

There was no association between U.S. geographic region and post-index seizure incidence based on results of the bivariate analysis. Hypothesis 10 was rejected in the Topamax®/topiramate monotherapy cohort.

Table 34 summarizes results of the logistic regression analysis for Topamax®/topiramate patient cohort.

Table 34 Logistic Regression Analysis of Variables Predicting Post-Index Seizure for 427 patients in Topamax®/Topiramate Cohort

Variable	Likelihood of post-index seizure		
	OR	**95% CI**	**p**
Mental Health Comorbidity	2.84	0.68-11.78	0.15
Comorbidity Index ≥1	2.63	0.73-9.44	0.14
Bioequivalent Switch	4.52	1.44-14.22	0.0099
Age	1.02	0.98-1.07	0.37
Male	1.19	0.36-3.96	0.78

Table 35 presents a summary of hypotheses testing for each of the four AED monotherapy cohorts examined in the study.

Table 35 Summary of Hypotheses Testing for Four Monotherapy Cohorts

Hypothesis	Lamictal®/ Lamotrigine (n=1143)	Trileptal®/ Oxcarbazepine (n=456)	Keppra®/ Levetiracetam (n=1114)	Topamax®/ Topiramate (n=427)
H1: AED nonadherence is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.	Rejected	Rejected	Rejected	Rejected
H2: A bioequivalent medication switch is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.	Rejected	Rejected	Rejected	Accepted (presence of switch=positive predictor)
H3: Presence of AED-interacting medications is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy	Rejected	Rejected	Not tested	Rejected
H4: Type of epilepsy diagnosis is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.	Rejected	Accepted (intractable= positive predictor)	Rejected	Rejected

Table 35 Summary of Hypotheses Testing for Four Monotherapy Cohorts (Continued)

Hypothesis	Lamictal®/ Lamotrigine (n=1143)	Trileptal®/ Oxcarbazepine (n=456)	Keppra®/ Levetiracetam (n=1114)	Topamax®/ Topiramate (n=427)
H5: A prior acute seizure event is a significant predictor of seizure recurrence in medically-treated patients with epilepsy.	Accepted (prior seizure =positive predictor)	Rejected	Accepted (prior seizure =positive predictor)	Rejected
H6: A mental health diagnosis is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.	Rejected	Accepted (mental health diagnosis =positive predictor)	Accepted (mental health diagnosis =positive predictor)	Rejected
H7: Presence of a higher comorbidity score is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy	Rejected	Rejected	Accepted (CCI ≥1 =positive predictor)	Rejected
H8: Higher age is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.	Rejected	Rejected	Rejected	Rejected
H9: Female gender is a significant predictor of breakthrough seizures in medically treated patients with epilepsy.	Rejected	Rejected	Rejected	Rejected
H10: U.S. Region is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.	Accepted (Northeast =positive predictor)	Rejected	Rejected	Rejected

FOUR MONOTHERAPY COHORTS COMBINED

This section presents analyses of patients on AED monotherapy for the four cohorts combined: Lamictal®/lamotrigine, Trileptal®/oxcarbazepine, Keppra®/levetiracetam, and Topamax®/topiramate. This combined cohort included 3140 patients. Table 36 summarizes insurance, clinical and medication characteristics of patients in the combined monotherapy cohort.

The average patient age was 41.4 (SD=13.0) years old. The majority of patients had POS insurance (69.9 percent) and the larger number of patients resided in the South (46.7 percent). The mean adherence of combined monotherpay cohorts measured with PDC was 0.74 (SD=0.25) or 74 percent. With the adherence threshold set at 80 percent, about 55 percent of patients in the combined cohort were adherent to their respective type of AED monotherapy. When the threshold was lowered to 60 percent, about 72 percent of patients were adherent. The majority of patients were treated for partial non-intractable seizures (30.3%), followed by other non-intractable (29.2%) and generalized non-intractable (25.8%) seizures. About eight percent of patients in the combined cohort had medications that may have possibly interacted with their respective antiepileptic agents. Only about five percent of patients in the combined cohort (n=171) had any type of a mental health diagnosis. The mean comorbidity score of patients in the combined cohort was 0.18 (SD=0.6) with 87.6 percent of patients having no comorbidities accompanying their epilepsy condition. A total of 864 patients (27.5 percent) in the combined cohort experienced bioequivalent switches.

Table 36 Demographic, Insurance, Clinical and Medication Characteristics of Combined Monotherapy Cohort

Characteristic	Combined Monotherapy Cohort (n=3140)	
	N	%[3]
Age (Mean ± SD)	41.4 (±13.0)	
18-30 y	768	24.5
31-45 y	1072	34.1
46-64 y	1300	41.4
Female Gender	1920	61.2
Insurance Type[1]		
POS	2195	69.9
EPO	432	13.8
HMO	349	11.1
PPO	145	4.6
IND	19	0.6
One Year Adherence		
Mean (SD) PDC[2]	0.74 (0.25)	
Median (range) PDC	0.82 (0.16-1)	
PDC≥60%	2260	72.0
PDC≥80%	1733	55.2
Region		
South	1466	46.7
Midwest	878	28.0
West	447	14.2
Northeast	349	11.1
180-day Pre-index Event		
≥1	209	6.7
0	2931	93.3
365-day Post-index Event		
≥1	166	5.3
0	2974	94.7

Table 36 Demographic, Insurance, Clinical and Medication Characteristics of Combined Monotherapy Cohort (Continued)

Characteristic	Combined Monotherapy Cohort (n=3140)	
	N	%[3]
Charlson Comorbidty Index Score		
Mean (SD)	0.18 (0.6)	
Median (range)	0 (0-6)	
18-30 y	0.07 (0.3)	
31-45 y	0.16 (0.5)	
46-64 y	0.26 (0.6)	
Score 0	2750	87.6
Score 1	244	7.8
Score 2	128	4.1
Score 3	12	0.4
Score 4	1	<0.1
Score 6	5	0.2
Seizure Type		
Partial non-intractable	951	30.3
Partial intractable	268	8.5
Generalized non-intractable	811	25.8
Generalized intractable	119	3.8
Other non-intractable	918	29.2
Other intractable	73	2.3
Comorbid Mental Health Diagnoses		
No mental health diagnosis	2969	94.6
Any mental health diagnosis	171	5.5
Interacting Medications		
0	2889	92.0
≥1	251	8.0
Bioequivalent Switche		
0	2276	72.5
≥1	864	27.5

[1]POS-Point of Service; EPO-Exclusive Provider Organization; HMO-Health Maintenance Organization; PPO-Preferred Provider Organization; IND-Indemnity
[2]PDC-Proportion of Days Covered
[3]Some column totals may not add to 100% due to rounding

BIVARIATE COMPARISONS OF SEIZURE INCIDENCE IN THE COMBINED MONOTHERAPY COHORT

The incidence of post-index seizure in the combined cohort was 5.3 percent (n=166). Tables 37 and 38 demonstrate the bivariate comparisons of the incidence of post-index seizure by age, age group, gender, geographic region, prior seizure, adherence, general comorbidity, mental health comorbidity, seizure type, presence of interacting medications, presence of a bioequivalent switch and type of AED medication. The mean age of patients in the two groups was not significantly different [t=0.2 (df=3138); p=0.85]. Patients in the combined cohort with a post-index seizure were 41.2 (±13.5) years old while patients who did not have a post-index seizure were 41.4 (±13.0) years old. A chi-square analysis of the incidence of post-index seizure and pre-index seizure showed that more patients with a pre-index seizure experienced a seizure post-index than patients without a pre-index seizure (20.1 percent vs 4.2 percent, respectively) [χ^2=98.07 (df=1); p<0.0001]. A chi-square analysis of post-index seizure incidence and patients' general comorbidity status demonstrated that more patients with a CCI score of one or higher experienced a seizure post-index seizures than those with a score of zero (9.1 percent vs 2.9 percent, respectively) [χ^2=50.48 (df=1); p<0.0001]. A chi-square analysis of post-index seizure incidence and mental health comorbidity showed that more patients with mental health comorbidities experienced a seizure post-index than patients without mental health comorbidities (15.2 percent vs 4.7 percent, respectively) [χ^2=35.53 (df=1); p<0.0001]. A chi-square analysis of post-index seizure incidence and type of AED

medication demonstrated that more patients on Keppra®/levetiracetam monotherapy experienced a seizure post-index seizures than patients on other AED monotherapy regimens (7.9 percent vs 3.9 percent, 4.0 percent and 3.5 percent, respectively) [χ^2=23.66 (df=1);p<0.0001]. The mean adherence of patients in the two groups was not significantly different [t=-1.85 (df=3138); p=0.06]. Patients in the combined cohort with a post-index seizure had a mean PDC of 0.77 (±0.2) while patients who did not have a post-index seizure had a mean PDC of 0.74 (±0.3). A chi-square analysis of post-index seizure incidence and geographic region of residence demonstrated that more patients in the Northeast U.S. experienced a seizure post-index than patients in other geographic areas (8.0 percent vs 4.2 percent, 6.3 percent and 4.7 percent, respectively) [χ^2=10.48 (df=1); p=0.0149]. A chi-square analysis of the combined cohort did not reveal any differences between incidence of post-index seizures and gender, dichotomized adherence status (adherence threshold set at 80 and 60 percent, respectively), presence of interacting medications, type of epilepsy diagnosis (intractable versus non-intractable) or presence of a bioequivalent switch (p>0.05).

Table 37 Bivariate Comparison of Incidence of Post-Index Seizure in the Combined Cohort by Age, Age Group, Gender, Adherence and Geographic Region

Independent Variable	Total		Seizure Event		No Seizure Event		t	df	p-value
	Mean	SD	Mean	SD	Mean	SD			
Age	41.4	13.0	41.2	13.5	41.4	13.0	0.2	3138	0.85
Adherence (PDC)	0.74	0.25	0.77	0.2	0.74	0.3	-1.85	3138	0.06
	N=3140		n	%	n	%	χ^2	df	p-value
Age group							0.1	2	0.95
18-30	768		42	5.5	726	94.5			
31-45	1072		55	5.1	1017	94.9			
46-64	1300		69	5.3	1231	94.7			
Gender							0.006	1	0.93
Female	1920		101	5.3	1819	94.7			
Male	1220		65	5.3	1155	94.7			
PDC							2.77	1	0.10
≥80%	1733		102	5.9	1631	94.1			
<80%	1407		64	4.6	1343	95.5			
PDC							1.34	1	0.25
≥60%	2260		126	5.6	2134	94.4			
<60%	880		40	4.6	840	95.6			
Region							10.48	3	0.0149
South	1466		62	4.2	1404	95.8			
Midwest	878		55	6.3	823	93.7			
West	447		21	4.7	426	95.3			
Northeast	349		28	8.0	321	92.0			

Table 38 Bivariate Comparison of Incidence of Post-Index Seizure in the Combined Cohort by Pre-Index Seizure, Comorbidity, Seizure Type, Mental Health Comorbidity, Presence of Interacting Medications, Presence of Bioequivalent Switch and AED Medication

Independent Variable	Total	Seizure Event		No Seizure Event		χ^2	df	p-value
	N=3140	n	%	n	%			
Pre-index event						98.07	1	<0.0001
0	2974	124	4.2	2807	95.8			
≥1	166	42	20.1	124	79.9			
CCI						50.48	1	<0.0001
0	2750	116	2.9	2634	95.8			
≥1	390	50	9.1	340	87.2			
Seizure Type						1.64	1	0.20
Non-intractable	2680	136	5.1	2544	94.9			
Intractable	460	30	6.5	430	93.5			
Mental Comorbidity						35.53	1	<0.0001
0	2969	140	4.7	2829	95.3			
≥1	171	26	15.2	145	84.8			
Interacting Medications						0.92	1	0.34
0	2889	156	5.4	2733	94.6			
≥1	251	10	4.0	241	96.0			
Bioequivalent Switch						0.60	1	0.44
0	2276	116	5.1	2160	94.9			
≥1	864	50	5.8	814	94.2			
AED medication						23.66	3	<0.0001
Lamictal/lamotrigine	1143	45	3.9	1098	96.1			
Keppra/levetiracetam	1114	88	7.9	1026	92.1			
Trileptal/oxcarbazepine	456	18	4.0	438	96.0			
Topamax/topiramate	427	15	3.5	412	96.5			

LOGISTIC REGRESSION ANALYSIS OF INCIDENCE OF POST-INDEX SEIZURES IN THE COMBINED COHORT: OBJECTIVE 2

Objective 2 was to develop a combined model predicting acute seizures based on the factors identified contributory to seizure recurrence in the bivariate analyses: pre-index seizure, general comorbidity, mental health comorbidity and type of AED medication. Age, gender and geographic region covariates were included in the final model. Multiple logistic regression was used to address the objective.

The formula below was used to build the regression model:

$$logit\ (Y) = \ln\frac{\pi}{1-\pi} = \alpha + \beta 1X1 + \beta 2X2 + \beta 3X3 + \beta 4X4 + \beta 5X5 + \beta 6X6 + \beta 7X7$$

$$\pi = \frac{e^{\alpha+\beta 1X1+\beta 2X2+\beta 3X3+\beta 4X4+\beta 5X5+\beta 6X6+\beta 7X7}}{1+e^{\alpha+\beta 1X1+\beta 2X2+\beta 3X3+\beta 4X4+\beta 5X5+\beta 6X6+\beta 7X7}},$$ where

π= probability of seizure;
α- the Y intercept;
$\beta 1$-$\beta 7$- regression coefficients;
X1- prior seizure event;
X2- general comorbidity;
X3- mental health comorbidity;
X4- AED medication;
X5- gender;
X6- age;
X7- geographic region.

The overall model with seven predictors was significant [χ^2=130.97 (df=11); p<0.0001]. The output for the model is presented in Appendix I. Mutlicollinearity between predictor variables was assessed using weighted regressions with COLLIN and COLLINOINT options.[191] Small condition indices suggested that there was no collinearity between independent variables in the model. The output of collinearity assessment is presented in Appendix J.

H1: AED nonadherence is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

There was no difference in adherence between patients who experienced seizure event and those who did not in the bivariate analysis (p>0.05). Hypothesis 1 was rejected in the combined monotherapy cohort.

H2: A bioequivalent medication switch is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

The bioequivalent switch variable was not selected for inclusion in the multivariate model due to its lack of significant association with seizure incidence demonstrated in the bivariate analysis ($p>0.05$). Hypothesis 2 was rejected in the combined monotherapy cohort.

H3: Presence of AED-interacting medications is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy

The AED-interacting medications variable was not selected for inclusion in the multivariate model due to its lack of significant association with seizure incidence in the bivariate analysis ($p>0.05$). Hypothesis 3 was rejected in the combined monotherapy cohort.

H4: Type of epilepsy diagnosis is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

The type of epilepsy diagnosis variable was not selected for inclusion in the multivariate model due to lack of significant association with seizure incidence demonstrated in the

bivariate analysis ($p>0.05$). Hypothesis 4 was rejected in the combined monotherapy cohort.

H5: A prior acute seizure event is a significant predictor of seizure recurrence in medically-treated patients with epilepsy.

The prior seizure variable was selected for inclusion in the multivariate model due to its significant association with post-index seizure incidence demonstrated in the bivariate analysis ($p<0.05$). Patients with prior seizure had about four times higher odds of having a post-index seizure than patients without a prior seizure while controlling for age, gender, geographic region, general and mental health comorbidity, and AED medication ([OR]= 4.29; 95% CI, 2.81-6.53). Hypothesis 5 was accepted in the combined cohort.

H6: A mental health comorbidity is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

A mental health comorbidity was selected for inclusion in the multivariate model due to its significant association with seizure incidence demonstrated in the bivariate analysis ($p<0.05$). Patients with mental health comorbidity had about three times higher odds of having a post-index seizure than patients without mental health comorbidity, while

controlling for age, gender, geographic region, general comorbidity, prior seizure, and type of AED medication ([OR]= 3.41; 95% CI, 2.09-5.54). Hypothesis 6 was accepted in the combined monotherapy cohort.

H7: Presence of comorbidity is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy

The comorbidity variable was selected for inclusion in the multivariate model due to its significant association with seizure incidence demonstrated in the bivariate analysis ($p<0.05$). The multiple logistic regression analysis showed that odds of having a post-index seizure in patients with a comorbidity index of one or higher were more than twice higher than in patients with a comorbidity index of zero, while controlling for age, gender, geographic region of residence, prior seizure, mental health comorbidity and AED medication ([OR]= 2.88; 95% CI 1.96-4.24). Hypothesis 7 was accepted in the combined monotherapy cohort.

H8: Higher age is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

There was no significant association between post-index seizure incidence and age in the bivariate analysis ($p>0.05$). However, as an important covariate age was included in the regression model. With each year increase in age, patients had about 1 percent lower odds of having a post-index seizure, while controlling for gender, geographic region of residence, prior seizure, mental health comorbidity, general comorbidity and AED medication ([OR]= 0.987; 95% CI, 0.974-0.999). This finding was statically significant ($p=0.0413$). Hypothesis 8 was rejected in the combined monotherapy cohort. Older age was associated with slight reduction in the odds of having a post-index seizure. However, this finding may not be clinically significant.

H9: Female gender is a significant predictor of breakthrough seizures in medically treated patients with epilepsy.

There was no significant association between post-index seizure incidence and gender in the bivariate and multiple logistic regression analyses ($p>0.05$). Hypothesis 9 was rejected in the combined monotherapy cohort.

H10: U.S. Region is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

The geographic region of residence variable was included in the multivariate model due to its significant association with post-index seizure incidence demonstrated in the bivariate analysis ($p<0.05$). Patients residing in the Northeast had about two times higher odds of experiencing a post-index seizure than patients in the South while controlling for age, gender, mental health and general comorbidity, prior seizure and AED medication ([OR] = 1.92; 95% CI, 1.19-3.10). There was no difference in the incidence of seizures between patients residing in the South and those residing in the West or Midwest ($p>0.05$). Hypothesis 10 was accepted in the combined monotherapy cohort.

H11: Type of AED medication is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.

The AED medication was included in the multivariate model due to its significant association with post-index seizure incidence demonstrated in the bivariate analysis in the combined cohort ($p<0.05$). Patients on Keppra®/levetiracetam monotherapy had 54 percent higher odds of experiencing a post-index seizure than patients on Lamicatl®/lamotrigine monotherapy while controlling for age, gender, geographic region of residence, mental health and general comorbidity, and prior seizure ([OR] = 1.54;

95% CI, 1.03-2.31). There was no difference in the incidence of seizures between patients on Lamictal®/lamotrigine and those on Trileptal®/oxcarbazepine or Topamax®/topiramate treatment regimens, respectively (p>0.05). Hypothesis 11 was accepted.

Table 39 summarizes results of the logistic regression analysis for the combined monotherapy cohort. Table 40 presents an overall summary of hypotheses testing for each of the four AED monotherapy cohorts as well as the combined cohort.

Table 39 Logistic Regression Analysis of Variables Predicting Post-Index Seizure for 3140 Patients in the Combined Monotherapy Cohort

Variable	Likelihood of post-index seizure		
	OR	95% CI	p
Prior Seizure	4.29	2.81-6.53	<0.0001
Mental Health Comorbidity	3.41	2.10-5.54	<0.0001
Comorbidity Index ≥ 1	2.88	1.96-4.24	<0.0001
AED Medication (reference: Lamictal®/lamotrigine)			
Keppra®/levetiracetam	1.54	1.03-2.31	0.04
Trileptal®/oxcarbazepine	0.93	0.52-1.64	0.79
Topamax®/topiramate	0.80	0.44-1.48	0.48
Age	0.99	0.97-0.999	0.04
Male	0.83	0.59-1.17	0.28
Geographic region (reference: South)			
Northeast	1.92	1.19-3.10	0.008
West	1.21	0.72-2.04	0.46
Midwest	1.29	0.87-1.91	0.20

Table 40 Overall Summary of Hypotheses Testing

Hypothesis	Lamictal®/ Lamotrigine (n=1,143)	Trileptal®/ Oxcarbazepine (n=456)	Keppra®/ Levetiracetam (n=1114)	Topamax®/ Topiramate (n=427)	Combined Cohort (n=3,140)
H1: AED nonadherence is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.	Rejected	Rejected	Rejected	Rejected	Rejected
H2: A bioequivalent medication switch is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.	Rejected	Rejected	Rejected	Accepted (presence of switch=positive predictor)	Rejected
H3: Presence of AED-interacting medications is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy	Rejected	Rejected	Not tested	Rejected	Rejected
H4: Type of epilepsy diagnosis is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.	Rejected	Accepted (intractable= positive predictor)	Rejected	Rejected	Rejected

Table 40 Overall Summary of Hypotheses Testing (Continued)

Hypothesis	Lamictal®/ Lamotrigine (n=1143)	Trileptal®/ Oxcarbazepine (n=456)	Keppra®/ Levetiracetam (n=1114)	Topamax®/ Topiramate (n=427)	Combined Cohort (n=3,140)
H5: A prior acute seizure event is a significant predictor of seizure recurrence in medically-treated patients with epilepsy.	Accepted (prior seizure =positive predictor)	Rejected	Accepted (prior seizure =positive predictor)	Rejected	Accepted (prior seizure =positive predictor)
H6: A mental health diagnosis is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.	Rejected	Accepted (mental health diagnosis =positive predictor)	Accepted (mental health diagnosis =positive predictor)	Rejected	Accepted (mental health diagnosis =positive predictor)
H7: Presence of a higher comorbidity score is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy	Rejected	Rejected	Accepted (CCI ≥1 =positive predictor)	Rejected	Accepted (CCI ≥1 =positive predictor)
H8: Higher age is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.	Rejected	Rejected	Rejected	Rejected	Rejected
H9: Female gender is a significant predictor of breakthrough seizures in medically treated patients with epilepsy.	Rejected	Rejected	Rejected	Rejected	Rejected
H10: U.S. Region is a significant predictor of breakthrough seizures in medically-treated patients with epilepsy.	Accepted (Northeast =positive predictor)	Rejected	Rejected	Rejected	Accepted (Northeast =positive predictor)

CHAPTER FOUR

DISCUSSION AND CONCLUSIONS

OBJECTIVE 1

The current study examined the prevalence of acute seizures in medically treated patients with epilepsy, and also assessed the demographic, clinical and medication characteristics of patients, including mental and general health comorbidity, types of epilepsy diagnosis, AED medication adherence, prevalence of concomitant use of AED-interacting medications and bioequivalent AED switches. Examinations of the combined patient cohort (n=3,140) showed the prevalence of acute seizures in medically treated patients on AED monotherapy was about 5 percent. The findings of acute seizure prevalence in the 1-year follow-up period were similar across three of the four cohorts at 3.5, 3.9, and 4.0 percent for the Topamax®/topiramate, Trileptal®/oxcarbazepine and Lamictal®/lamotrigine cohorts, respectively. The prevalence for Keppra®/levetiracetam cohort was higher, at 8.0 percent. When controlling for other demographic, clinical and medication variables, patients on Keppra®/levetiracetam monotherapy appeared to have about 50 percent higher odds of experiencing a seizure during the one-year follow-up period (OR= 1.54; 95% CI, 1.03-2.31) than patients in other monotherapy cohorts. This higher seizure event occurrence in patients on Keppra®/levetiracetam monotherapy has not been previously documented in prospective or retrospective studies. However,

studies assessing monotherapy outcomes of levetiracetam as well as levetiracetam compared with other agents showed comparable effectiveness of the former in seizure reduction rates with that of the other products.[165,167,192]

For example, previous retrospective studies that examined treatment outcomes primarily in adults (one study [Scotland] included patients ≥ 12 years old) initiated on levetiracetam monotherapy (both newly treated and converted from other AEDs) at epilepsy centers or physician offices in France, Scotland, and the U.S. found that 46.8 (total n= 579), 49.1 (total n=228), and 54.0 (total n=46) percent of patients achieved 6-months seizure freedom at 1-year follow-up.[167,168,192] Meanwhile, a recent randomized open-label prospective study in Germany that aimed to compare treatment outcomes in newly diagnosed patients (age ≥ 12 years) with partial or generalized epilepsy initiated on lamotrigine versus patients started on levetiracetam did not find a difference in seizure-free status in the two patient groups.[165] The proportion of seizure-free patients at study completion (26 weeks) was 45.2 percent for levetiracetam and 47.8 percent for lamotrigine. In addition, there was no difference in the incidence of adverse events ($p>0.05$). However, a randomized clinical trial of patients newly initiated on topiramate monotherapy (n=470) showed slightly higher seizure reduction rates of 59 and 76 percent of patients being seizure-free at 12 months on 50 mg/day and 400 mg/day, respectively.[193] Meanwhile, a study of oxcarbazepine in patients with medically refractory partial epilepsy found that about 6.6 percent of patients achieved completed

remission.[194] However, the oxcarbazepine low seizure reduction rate may be due to the focus of the study on solely pharmacoresistant patients.

A possible explanation behind the finding of higher likelihood of seizure events in patients on Keppra®/levetiracetam may be related to the regulatory status of the product being non-FDA-approved for monotherapy. Patients placed on this treatment regimen may be more likely to seek ER or hospital services if they are aware of potential risks involved with off-label prescribing.[195,196]

The overall prevalence of seizure events in studied populations (5%) was lower than in other studies. However, it is important to exercise caution when comparing this seizure events rate with other studies. First, there was no access to certain important variables, i.e., age of seizure onset and total duration of monotherapy as in some prospective or chart review studies. Second, only the most severe cases of acute events were counted as seizures in this study due to the nature of database research that does not allow the capture of events that did not result in medical services use. In addition, when this dissertation study results were compared to the findings of similar retrospective database studies, the prevalence of seizure exacerbations remained lower in this investigation than in some of the studies reporting the rate of acute events. For example, two claims database studies reported acute seizures in medically-treated epilepsy patient populations at 14.0 (Manjunath et al., n=18,073) and 57.4 percent (Davis et al., n=10,892), respectively.[7,97] It is of note, that patients in both studies were sicker, with

mean CCI scores of 1.04 (2.02) and 0.93 (SD not reported) versus 0.18 (0.6) in this study. In addition, both studies included all medically-treated epilepsy patients, rather than patients treated with monotherapy. It appears that monotherapy patients with epilepsy in this study's moderately large sample (n=3140) tend to have had their disease under better control, as suggested by the low prevalence of acute events requiring ER visits, ambulance services or hospitalizations. Another study of healthcare utilization of patients with epilepsy (n=46,857) by Kurth et al., using Thomson-Reuters' MarketScan database, compares better with the seizure event rates found in this study. The authors reported that epilepsy-related healthcare utilization was low, with mean (SD) annual epilepsy-related hospitalizations, ER visits and transportation use at 0.07 (0.31), 0.30 (1.91) and 0.37 (1.24), respectively.[197] The patient distribution by gender was slightly skewed toward females (61.2 percent in the combined cohort) in this study, whereas in the Kurth et al. study, females comprised 52.6 percent of included epilepsy patients. The average age of patients in the Kurth et al. cohort was 41.0 years – similar to our population (41.4 years). Regarding patient distribution by type of epilepsy, Kurth et al. reported that patients with generalized, partial and other epilepsies comprised 45.8, 33.0 and 21.0 percent of their cohort, respectively, as compared to 29.6, 38.3 and 31.5 percent in this study, respectively. This difference may be in part due to the classification method, i.e., Kurth et al. did not include patients with an ICD-9 of 345.9X (epilepsy unspecified) in their analysis, whereas in this study it was combined with ICD-9 345.8X into the 'other' category.[197]

The prevalence of mental health comorbidities in the current study (combined cohort) was 5.5 percent, which is lower than reported in previous studies in Canada (23.5 percent) and the U.S. (48 percent, in veteran patient population).[132,134] A possible reason for the lower prevalence of mental health disorders in the studied patient population may be due to study inclusion criteria (i.e., monotherapy patients) and consequently selection bias (i.e., less severe/ more controlled disease). Patients on polytherapy tend to have treatment-refractory, i.e. pharmacoresistant, epilepsy more often, and that in turn may be accompanied with a higher prevalence of mental health comorbidities.[198] With regard to AED adherence of all four cohorts combined, 55.2% of the patients were adherent (PDC$\geq$ 80%), which is slightly lower than in two similar database studies of patients with epilepsy, 60.7 percent (Davis et al.) and 60.8 percent (Briesacher et al.), but comparable to about 50 percent in another study (Manjunath et al.).[7,96,97]

OBJECTIVE 2

This study identified predictors of acute seizures in medically-treated patients with epilepsy within each studied AED monotherapy cohort as well as for the four monotherapy cohorts combined. For the combined cohort (n=3140), significant predictors of post-index seizures were prior seizure (seizure occurring in the 180-day period before the index date) ([OR]= 4.29; 95% CI, 2.81-6.53), the presence of a mental health comorbidity ([OR]= 3.41; 95% CI, 2.09-5.54), a general comorbidity score (CCI) of at

least 1 (odds ratio [OR]= 2.88; 95% CI 1.96-4.24), monotherapy with Keppra®/levetiracetam (odds ratio [OR] = 1.54; 95% CI, 1.03-2.31), age ([OR]= 0.987; 95% CI, 0.974-0.999) and Northeast geographic region of residence ([OR] = 1.92; 95% CI, 1.19-3.10). One study of predictors of seizure recurrence in Norway (Lossius et al.; n=669) conducted via chart reviews found that age over 50 years and polytherapy were the only independent predictors.[18] On the other hand, gender, etiology and comorbidity were not predictive. It is possible that the smaller sample size of Lossius et al. study as well as a different methodology of defining comorbidity may have contributed to the divergent from this study result regarding comorbidity predictor. As for the predictive role of age over 50 in the Norway study, omitting polytherapy patients who may be older and sicker may have contributed to the lack of a similar finding in this dissertation study.

Unlike some other database studies examining large populations of patients with epilepsy, rate of adherence and the presence of bioequivalent AED switches were <u>not</u> associated with an increased risk of seizures. For example, in the case of adherence, there was no relationship with seizure occurrence post-index within each of the monotherapy cohorts or for the combined cohort, while controlling for other clinical, demographic, medication factors and covariates ($p>0.05$). The studies by Davis et al. and Manjunath et al. reported between an 11 to 21 percent increased risk of seizures in the non-adherent patients (MPR<0.8). Both authors included all medically-treated patients, rather than patients on monotherapy. In relation to bioequivalent switches, the results from the combined cohort demonstrated no relationship between switches and post-index seizures

($p>0.05$). Because the methodology of this study was different from the designs of most other retrospective investigations that examined the association between switches and acute seizures, comparing the results is problematic. The methodologically closest study in the literature, by Erickson et al., that assessed only one of the AEDs (lamotrigine) examined in this study, also did not identify an increased likelihood of seizures in patients with bioequivalent switches. Another, more recent study, by Hartung et al., examined lamotrigine switches in a Medicaid patient population and did not find relationships between conversion to a generic product and ER visits or hospitalizations.[199]

Although the findings from the overall cohort did not demonstrate any association between switches and acute seizures in this study, it was found that patients with bioequivalent switches in the Topamax®/topiramate cohort tended to have higher odds of experiencing a post-index seizure ([OR]= 4.52; 95% CI, 1.44-14.22) than patients without bioequivalent switches. Given the low prevalence of seizures in the Topamax®/topiramate cohort (3.5 percent) as well as small sample size (n=427), this finding warrants further investigation as to the reasons behind the identified relationships for patients on Topamax®/topiramate monotherapy but not on three other monotherapies using a larger sample size.

The finding with regard to patients in the Northeast appearing to be at a higher likelihood of acute seizure events demonstrates that there possibly exists a geographic variation in epilepsy care. Although no studies documented a similar finding in patients

medically treated with epilepsy, Pugh and co-authors showed that less than 50 percent of recommendations from the Quality Indicators in Epilepsy Treatment (QUIET) measure were performed in a medical center in New England.[73] Hence, the finding from this dissertation study further underscores possible quality of care differences across geographic regions of the U.S.

LIMITATIONS

Like other database investigations, this study has several limitations. Any error in diagnosis coding may have caused the exclusion of patients with relevant diagnoses or inclusion of those who may not have had actual epilepsy. However, the second is unlikely, given the study inclusion criteria being based not only on medical codes but also specific drug utilization. Given the nature of claims data, detailed information was not available on the severity of a patient's epilepsy (i.e., measured via common severity assessment self-reported instruments). However, the study relied on four-digit diagnosis codes that classified each epilepsy diagnosis into groups by type (partial, generalized, other) and severity (intractable and non-intractable) which was used as a proxy for severity status.

Prescription claims data were used to estimate adherence by assuming that if patients had their prescriptions filled, they took their medication appropriately. Given the large patient population examined in this study, prescription claims analysis may be the most practical method to examine adherence, as opposed to serum concentration measurement, pill counts or medication electronic monitoring systems use. Several important demographic, clinical and psychosocial variables were unavailable (i.e., age of epilepsy onset, duration of AED monotherapy, ethnicity, income, living conditions,

alcohol misuse, sleep deprivation). The paucity of robust demographic and clinical variables is a common limitation of most database studies.

The population in the current study represented commercially-insured patients - hence the findings may only generalize to similar commercially-insured patient populations. The findings in economically disadvantaged patients with no insurance or low-income patients on Medicaid may be different from those reported in this study. Finally, the study did not include patients older than 64 years because of the lack of complete data about their healthcare utilization due to dual eligibility status with Medicare.

CONCLUSIONS

This study was conducted within a conceptual framework of modifiable and non-modifiable risk factors hypothesized to affect seizure recurrence in patients with epilepsy. Among non-modifiable risk factors that were available to be examined, it was found that mental and general health comorbidities indeed had a relationship with seizure recurrence in the hypothesized direction. Patient's age, which was another non-modifiable risk factor examined, did show a small but significant association with seizure recurrence, albeit in the opposite direction than hypothesized. However, this finding is unlikely to be clinically meaningful. Type of epilepsy diagnosis was associated with seizures in only one of the four patient cohorts examined. Patients in the Trileptal®/oxcarbazepine cohort

with intractable epilepsy were more likely to experience seizures post-index than patients with non-intractable epilepsy. However, when the combined cohort was examined, the type of epilepsy was not associated with seizure recurrence ($p>0.05$). Among modifiable risk factors examined, it appears that patients on monotherapy, which is considered the rational and preferred mode of pharmacotherapy in epilepsy, as a whole tend to experience a much lower rate of acute seizures (5 percent) than patients taking more than one AED. Patients stabilized on one medication may have a lower severity of the disease overall, so selection bias may be a problem in this study since only monotherapy patients were assessed. Contrary to the hypothesized relationships which were based on previous findings, it appeared that treatment adherence was not associated with acute seizure recurrence.

Overall, the findings from this study provide important clinical insights. First, patients on monotherapy tend to have relatively low likelihood of acute seizure events requiring medical services utilization. Second, patients with mental and general comorbidities, as well as patients with previous acute seizures, should be closely monitored with appropriate pharmacotherapy and lifestyle modifications in order to reduce the likelihood of seizure recurrences. In addition, bioequivalent switches in patients on monotherapy did not appear to have a relationship with occurrence of acute seizure events. Finally, there was little to no relationship between seizure recurrence and demographic variables such as age and gender, indicating the need for monitoring of all patients without regard to age or gender.

FUTURE RESEARCH

Epilepsy is a type of disorder that affects patients regardless of their socioeconomic status. One of the avenues for future research in identifying predictors of seizure recurrence in patients with epilepsy may possibly lie in replicating the study in low-income patient populations as well as in a dataset with access to ethnicity categories. Ethnic differences in health outcomes are well-documented in multiple disease states. It is important to identify ethnic and socioeconomic disparities in epilepsy care in order to build awareness among practitioners and create interventions to address the disparities. Future research involving prospective studies that incorporate qualitative types of investigation coupled with quantitative modeling may help address the domains of epilepsy care and outcomes rarely captured in traditional clinical or databases studies, i.e., how patients' experiences of stigma, psychosocial adjustment, and social support affect health outcomes - as well as health-related quality of life. Finally, a possible avenue of further investigating the impact of bioequivalent switches on seizure events may lie in designing a study that would control for a specific manufacturer of the AED and ensure that, for example, switch to an authorized generic (a brand-name drug sold as a generic)[200] would be considered a continuation of a brand-name therapy rather than a switch.

APPENDICES

APPENDIX A

Logistic Regression Output for Lamictal®/Lamotrigine Monotherapy Cohort

The LOGISTIC Procedure

Model Information	
Data Set	WORK.LTL_MODEL_RC
Response Variable	post_event
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	1143
Number of Observations Used	1143

Response Profile		
Ordered Value	post_event	Total Frequency
1	1	45
2	0	1098

Probability modeled is post_event=1.

Class Level Information				
Class	Value	Design Variables		
georegion	0	0	0	0
	1	1	0	0
	2	0	1	0
	3	0	0	1

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	Intercept Only	Intercept and Covariates
AIC	381.332	357.302
SC	386.373	397.633
-2 Log L	379.332	341.302

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	38.0303	7	<.0001
Score	68.6704	7	<.0001
Wald	43.9400	7	<.0001

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
prior_event	1	33.0769	<.0001
char_rc	1	4.6908	0.0303
age	1	0.1212	0.7278
gender	1	1.7017	0.1921
georegion	3	8.9922	0.0294

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-3.6221	0.5686	40.5827	<.0001
prior_event		1	2.6000	0.4521	33.0769	<.0001
char_rc		1	0.9954	0.4596	4.6908	0.0303
age		1	-0.00440	0.0126	0.1212	0.7278
gender		1	-0.4725	0.3622	1.7017	0.1921
georegion	1	1	1.2520	0.4246	8.6950	0.0032
georegion	2	1	0.5841	0.4641	1.5836	0.2082
georegion	3	1	0.3493	0.4222	0.6846	0.4080

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
prior_event	13.464	5.551	32.659
char_rc	2.706	1.099	6.661
age	0.996	0.971	1.021
gender	0.623	0.307	1.268
georegion 1 vs 0	3.497	1.522	8.038
georegion 2 vs 0	1.793	0.722	4.454
georegion 3 vs 0	1.418	0.620	3.244

Association of Predicted Probabilities and Observed Responses

Percent Concordant	70.0	Somers' D	0.440
Percent Discordant	26.0	Gamma	0.458
Percent Tied	4.0	Tau-a	0.033
Pairs	49410	c	0.720

APPENDIX B

Collinearity Diagnostics Output for Lamictal®/Lamotrigine Monotherapy Cohort

Collinearity Diagnostics								
			Proportion of Variation					
Number	Eigenvalue	Condition Index	Intercept	prior_event	char_rc	age	gender	georegion
1	3.10274	1.00000	0.00765	0.00522	0.01515	0.00831	0.03341	0.03204
2	0.97225	1.78642	0.00001987	0.91309	0.07521	0.00004517	0.00188	0.00078575
3	0.88440	1.87304	0.00161	0.07301	0.86082	0.00075237	0.00134	0.03480
4	0.64903	2.18645	0.00078497	0.00016915	0.01766	0.00080767	0.72691	0.20089
5	0.34629	2.99333	0.03675	0.00851	0.01861	0.06087	0.22910	0.69927
6	0.04530	8.27612	0.95319	1.63253E-9	0.01255	0.92921	0.00737	0.03221

Collinearity Diagnostics (intercept adjusted)							
			Proportion of Variation				
Number	Eigenvalue	Condition Index	prior_event	char_rc	age	gender	georegion
1	1.20186	1.00000	0.00888	0.30302	0.29114	0.16216	0.04851
2	1.04193	1.07401	0.05142	0.09484	0.10704	0.18645	0.50916
3	1.00101	1.09574	0.89371	0.00792	0.02343	0.05616	0.01498
4	0.91291	1.14740	0.01505	0.02378	0.02810	0.59113	0.42640
5	0.84229	1.19453	0.03094	0.57044	0.55029	0.00410	0.00094812

APPENDIX C

Logistic Regression Output for Trileptal®/Oxcarbazepine Monotherapy Cohort

The LOGISTIC Procedure

Response Profile		
Ordered Value	post_event	Total Frequency
1	1	18
2	0	438

Probability modeled is post_event=1.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	Intercept Only	Intercept and Covariates
AIC	153.636	138.945
SC	157.759	171.925
-2 Log L	151.636	122.945

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	28.6910	7	0.0002
Score	47.7125	7	<.0001
Wald	27.2664	7	0.0003

Analysis of Maximum Likelihood Estimates					
Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-3.2833	0.8897	13.6176	0.0002
prior_event	1	1.4280	0.8140	3.0776	0.0794
mental_dich	1	2.3835	0.6237	14.6055	0.0001
char_rc	1	0.9198	0.6341	2.1040	0.1469
interact	1	0.4557	0.8302	0.3013	0.5830
seizure_rc	1	1.4012	0.5778	5.8813	0.0153
age	1	-0.0140	0.0201	0.4850	0.4862
gender	1	-0.8095	0.5597	2.0916	0.1481

Odds Ratio Estimates			
Effect	Point Estimate	95% Wald Confidence Limits	
prior_event	4.170	0.846	20.559
mental_dich	10.843	3.194	36.816
char_rc	2.509	0.724	8.695
interact	1.577	0.310	8.027
seizure_rc	4.060	1.308	12.599
age	0.986	0.948	1.026
gender	0.445	0.149	1.333

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	80.4	Somers' D	0.629
Percent Discordant	17.5	Gamma	0.642
Percent Tied	2.1	Tau-a	0.048
Pairs	7884	c	0.814

APPENDIX D

Collinearity Diagnostics Output for Trileptal®/Oxcarbazepine Monotherapy Cohort

Collinearity Diagnostics										
			Proportion of Variation							
Number	Eigenvalue	Condition Index	Intercept	prior_event	mental_dich	char_rc	interact	seizure_rc	age	gender
1	3.12523	1.00000	0.00719	0.00878	0.01206	0.02100	0.01247	0.01976	0.00800	0.02994
2	0.99231	1.77467	0.00243	0.00982	0.45757	0.04767	0.25827	0.04179	0.00217	0.02907
3	0.95992	1.80436	0.00041681	0.72451	0.00565	0.03347	0.19196	0.00809	0.00072745	0.00046350
4	0.92089	1.84220	0.00077797	0.15228	0.03440	0.12857	0.19547	0.38640	0.00057783	0.02853
5	0.81899	1.95345	0.00022960	0.00660	0.43902	0.42709	0.14793	0.03171	0.00001400	0.01739
6	0.75119	2.03970	0.00159	0.09744	0.04415	0.30151	0.14760	0.46582	0.00144	0.04386
7	0.38654	2.84342	0.02562	0.00012485	0.00120	0.03614	0.03964	0.04496	0.05376	0.76864
8	0.04494	8.33928	0.96174	0.00045247	0.00595	0.00454	0.00666	0.00147	0.93331	0.08210

Collinearity Diagnostics (intercept adjusted)									
			Proportion of Variation						
Number	Eigenvalue	Condition Index	prior_event	mental_dich	char_rc	interact	seizure_rc	age	gender
1	1.29300	1.00000	0.02612	0.04316	0.12779	0.20392	0.04555	0.21841	0.08308
2	1.13276	1.06839	0.14344	0.30802	0.10606	0.00001097	0.01740	0.07572	0.21179
3	1.03971	1.11518	0.21814	0.00210	0.12257	0.00025747	0.55745	0.04600	0.00002542
4	0.99822	1.13812	0.26773	0.20716	0.16359	0.27569	0.00611	0.05351	0.00193
5	0.90831	1.19312	0.08874	0.11773	0.03603	0.02680	0.10835	0.07711	0.62331
6	0.85014	1.23326	0.25559	0.06662	0.23309	0.23561	0.26358	0.04254	0.05266
7	0.77787	1.28928	0.00024174	0.25521	0.21086	0.25771	0.00156	0.48670	0.02721

APPENDIX E

Logistic Regression Output for Keppra®/Levetiracetam Monotherapy Cohort

The LOGISTIC Procedure

Model Information	
Data Set	WORK.KEPPRA_JUNE27_FINAL
Response Variable	post_event
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	1114
Number of Observations Used	1114

Response Profile		
Ordered Value	post_event	Total Frequency
1	1	88
2	0	1026

Probability modeled is post_event=1.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	Intercept Only	Intercept and Covariates
AIC	617.612	562.317
SC	622.628	592.411
-2 Log L	615.612	550.317

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	65.2950	5	<.0001
Score	86.5726	5	<.0001
Wald	65.5062	5	<.0001

Analysis of Maximum Likelihood Estimates					
Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-2.0924	0.3944	28.1441	<.0001
prior_event	1	1.1953	0.2603	21.0889	<.0001
ment	1	1.5170	0.3721	16.6173	<.0001
char_rc	1	1.1768	0.2567	21.0179	<.0001

age	1	-0.0244	0.00902	7.3374	0.0068
gender	1	-0.00859	0.2332	0.0014	0.9706

Odds Ratio Estimates			
Effect	Point Estimate	95% Wald Confidence Limits	
prior_event	3.304	1.984	5.504
ment	4.559	2.198	9.454
char_rc	3.244	1.962	5.365
age	0.976	0.959	0.993
gender	0.991	0.628	1.566

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	71.2	Somers' D	0.440
Percent Discordant	27.3	Gamma	0.446
Percent Tied	1.5	Tau-a	0.064
Pairs	90288	c	0.720

APPENDIX F

Collinearity Diagnostics Output for Keppra®/Levetiracetam Monotherapy Cohort

Collinearity Diagnostics								
			Proportion of Variation					
Number	Eigenvalue	Condition Index	Intercept	prior_event	ment	char_rc	age	gender
1	3.08618	1.00000	0.00700	0.02471	0.00980	0.02988	0.00725	0.03458
2	0.95119	1.80127	0.00188	0.04709	0.85992	0.00063502	0.00199	0.01955
3	0.78714	1.98009	0.00065717	0.89653	0.08450	0.07120	0.00069527	0.00719
4	0.71415	2.07882	0.00483	0.02532	0.04307	0.85767	0.00253	0.06237
5	0.42034	2.70962	0.02494	0.00614	0.00063567	0.01840	0.03480	0.84836
6	0.04100	8.67563	0.96070	0.00020626	0.00206	0.02222	0.95274	0.02794

Collinearity Diagnostics (intercept adjusted)							
			Proportion of Variation				
Number	Eigenvalue	Condition Index	prior_event	ment	char_rc	age	gender
1	1.29839	1.00000	0.14834	0.07770	0.27749	0.18747	0.04922
2	1.04223	1.11614	0.12313	0.30056	0.04680	0.32145	0.14139
3	0.98904	1.14576	0.02472	0.25799	0.00752	0.00463	0.70401
4	0.90437	1.19820	0.68495	0.26591	0.11099	0.00506	0.01322
5	0.76597	1.30196	0.01887	0.09785	0.55720	0.48139	0.09215

APPENDIX G

Logistic Regression Output for Topamax®/Topiramate Monotherapy Cohort

The LOGISTIC Procedure

Model Information	
Data Set	WORK.TPMAX_MODEL_RC
Response Variable	post_event
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	427
Number of Observations Used	427

Response Profile		
Ordered Value	post_event	Total Frequency
1	1	15
2	0	412

Probability modeled is post_event=1.

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	Intercept Only	Intercept and Covariates
AIC	131.929	130.683
SC	135.986	155.024
-2 Log L	129.929	118.683

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	11.2456	5	0.0467
Score	14.9699	5	0.0105
Wald	12.2555	5	0.0315

Analysis of Maximum Likelihood Estimates					
Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-4.8349	1.0762	20.1833	<.0001
char_rc	1	0.9654	0.6531	2.1854	0.1393
age	1	0.0206	0.0227	0.8203	0.3651
gender	1	0.1746	0.6129	0.0811	0.7757

switch	1	1.5080	0.5849	6.6474	0.0099
mental	1	1.0423	0.7265	2.0584	0.1514

Odds Ratio Estimates			
Effect	Point Estimate	95% Wald Confidence Limits	
char_rc	2.626	0.730	9.444
age	1.021	0.976	1.067
gender	1.191	0.358	3.958
switch	4.518	1.436	14.215
mental	2.836	0.683	11.778

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	74.3	Somers' D	0.511
Percent Discordant	23.3	Gamma	0.523
Percent Tied	2.4	Tau-a	0.035
Pairs	6180	c	0.755

APPENDIX H

Collinearity Diagnostics Output for Topamax®/Topiramate Monotherapy Cohort

Collinearity Diagnostics								
			Proportion of Variation					
Number	Eigenvalue	Condition Index	Intercept	mental	char_rc	switch	age	gender
1	2.74399	1.00000	0.00930	0.02204	0.02679	0.02529	0.00936	0.03955
2	1.02735	1.63430	0.00101	0.35429	0.27565	0.13630	0.00103	0.05268
3	0.84511	1.80191	0.00087933	0.00094457	0.08904	0.64914	0.00074654	0.24851
4	0.74940	1.91353	0.00120	0.60799	0.39236	0.10607	0.00253	0.01437
5	0.59180	2.15330	0.02050	0.00251	0.20816	0.08243	0.02104	0.64355
6	0.04236	8.04875	0.96711	0.01222	0.00799	0.00077853	0.96529	0.00134

Collinearity Diagnostics (intercept adjusted)							
			Proportion of Variation				
Number	Eigenvalue	Condition Index	mental	char_rc	switch	age	gender
1	1.20011	1.00000	0.30129	0.42902	0.00062975	0.06361	0.00052862
2	1.07136	1.05838	0.12058	0.00334	0.20665	0.47572	0.11031
3	1.00552	1.09248	0.10677	0.02534	0.00107	0.04891	0.80139
4	0.97953	1.10688	0.04531	0.00000228	0.79115	0.15594	0.02183
5	0.74347	1.27052	0.42606	0.54230	0.00050664	0.25583	0.06593

APPENDIX I

Logistic Regression Output for Combined Monotherapy Cohort

The LOGISTIC Procedure

Model Information	
Data Set	WORK.FOUR_COHORTS
Response Variable	post_event
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	3140
Number of Observations Used	3140

Response Profile		
Ordered Value	post_event	Total Frequency
1	1	166
2	0	2974

Probability modeled is post_event=1.

Class Level Information				
Class	Value	Design Variables		
georegion	0	0	0	0
	1	1	0	0
	2	0	1	0
	3	0	0	1
type_drug	0	0	0	0
	1	1	0	0
	2	0	1	0
	3	0	0	1

Model Convergence Status
Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics		
Criterion	Intercept Only	Intercept and Covariates
AIC	1301.142	1192.170
SC	1307.194	1264.794
-2 Log L	1299.142	1168.170

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq

Likelihood Ratio	130.9722	11	<.0001
Score	185.1170	11	<.0001
Wald	140.3252	11	<.0001

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
prior_event	1	45.8663	<.0001
ment	1	24.3991	<.0001
char_rc	1	29.0618	<.0001
type_drug[1]	3	8.1473	0.0431
age	1	4.1638	0.0413
gender	1	1.1582	0.2818
Georegion[2]	3	7.1487	0.0673

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-3.1245	0.3125	99.9523	<.0001
prior_event		1	1.4551	0.2149	45.8663	<.0001
ment		1	1.2261	0.2482	24.3991	<.0001
char_rc		1	1.0588	0.1964	29.0618	<.0001
type_drug	1	1	0.4335	0.2065	4.4070	0.0358
type_drug	2	1	-0.0782	0.2928	0.0713	0.7894
type_drug	3	1	-0.2190	0.3106	0.4971	0.4808
age		1	-0.0132	0.00649	4.1638	0.0413
gender		1	-0.1867	0.1734	1.1582	0.2818
georegion	1	1	0.6511	0.2457	7.0224	0.0080
georegion	2	1	0.1940	0.2654	0.5345	0.4647
georegion	3	1	0.2550	0.1989	1.6449	0.1996

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
prior_event	4.285	2.812	6.529
ment	3.408	2.095	5.543
char_rc	2.883	1.962	4.237
type_drug 1 vs 0	1.543	1.029	2.312
type_drug 2 vs 0	0.925	0.521	1.642
type_drug 3 vs 0	0.803	0.437	1.477
age	0.987	0.974	0.999
gender	0.830	0.591	1.166
georegion 1 vs 0	1.918	1.185	3.104
georegion 2 vs 0	1.214	0.722	2.042

georegion 3 vs 0	1.291	0.874	1.906

Association of Predicted Probabilities and Observed Responses			
Percent Concordant	71.6	Somers' D	0.452
Percent Discordant	26.4	Gamma	0.461
Percent Tied	2.0	Tau-a	0.045
Pairs	493684	c	0.726

[1]Coding categories for type_drug variable (type of AED medication): Lamicatal®/lamotrigine (coded 0,=reference), Keppra®/levetiracetam (coded 1); Trileptal®/oxcarbazepine (coded 2), Topamax®/topiramate (coded 3)

[2]Coding categories for georegion (geographic region of residence) variable: South (coded 0, =reference), Northeast (coded 1); West (coded 2), Midwest (coded 3)

APPENDIX J

Collinearity Diagnostics Output for Combined Monotherapy Cohort

Collinearity Diagnostics										
			Proportion of Variation							
Number	Eigenvalue	Condition Index	Intercept	prior_event	ment	char_rc	type_drug	age	gender	georegion
1	3.89756	1.00000	0.00431	0.00770	0.00588	0.01276	0.01920	0.00499	0.02004	0.01960
2	0.94149	2.03465	0.00115	0.10510	0.72598	0.07444	0.00933	0.00118	0.01017	0.01066
3	0.91356	2.06551	0.00044987	0.75263	0.19887	0.02959	0.00818	0.00019339	0.00000559	0.00264
4	0.80509	2.20026	0.00046563	0.12441	0.05968	0.84564	0.00280	0.00005360	0.00027007	0.00966
5	0.59137	2.56725	0.00032560	0.00229	0.00350	0.00540	0.04083	0.00061159	0.78818	0.14815
6	0.51932	2.73956	0.00015176	0.00416	0.00070760	0.00109	0.46956	0.00024127	0.02129	0.47492
7	0.28899	3.67242	0.04745	0.00299	0.00067963	0.01261	0.42346	0.09451	0.14237	0.31018
8	0.04262	9.56308	0.94570	0.00072141	0.00469	0.01848	0.02664	0.89822	0.01766	0.02419

Collinearity Diagnostics (intercept adjusted)									
			Proportion of Variation						
Number	Eigenvalue	Condition Index	prior_event	ment	char_rc	type_drug	age	gender	georegion
1	1.26104	1.00000	0.13861	0.02192	0.30413	0.00826	0.23017	0.05427	0.01015
2	1.04142	1.10040	0.05934	0.05898	0.01217	0.51254	0.00073029	0.01864	0.29333
3	1.02194	1.11084	0.00594	0.56775	0.00046978	0.00534	0.07398	0.09614	0.22072
4	1.01309	1.11568	0.03247	0.12923	0.00320	0.02962	0.16366	0.48941	0.12787
5	0.94173	1.15718	0.27287	0.10849	0.07156	0.39295	0.06420	0.03266	0.10714
6	0.92574	1.16713	0.49035	0.00285	0.02534	0.04860	0.00038331	0.26340	0.23864
7	0.79504	1.25942	0.00042255	0.11077	0.58314	0.00269	0.46688	0.04549	0.00217

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