Effects of Switching from Brand Name to Generic Seizure Medication

Kim Dawson

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Effects of Switching from Brand Name to Generic Seizure Medication

By

Kim Dawson

A doctoral project submitted to the faculty of the Medical University of South Carolina in partial fulfillment of the requirements for the degree Doctor of Health Administration in the College of Health Professions

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Acknowledgment

First and foremost it is by God’s grace that I am able to complete this thesis. Though only my name appears on the cover of this dissertation, many people have contributed to its creation. I owe my gratitude to all the people who have made this dissertation possible and because of them my experience has been one that I will cherish forever. I would like to thank the members of my committee. To the chair of my committee, Dr. Kit Simpson, my sincere gratitude for her continuous support, patience, motivation and immense knowledge. Her guidance helped me formulate my research and opened my eyes to how to effectively research and work with data. Dr. Jillian Harvey was a voice of reason, stimulating discussion and always helping me to refine my approach. Dr. Vincent Omachonu taught me how to question thoughts and express ideas and his support helped me overcome many crisis situations and finish this dissertation. Finally, I must express my profound gratitude to my parents, Dr. Shirley Hall and William Hall, my children Symone and Desiree, my fiancée Clinton Williams and my siblings Melody, Keisha and Ty Hall for providing me with the unfailing support and continuous encouragement throughout my years of study and through the process of research and writing the thesis. This accomplishment would not have been possible without them. Thank you!
Approval Page

EFFECTS OF SWITCHING FROM BRAND NAME TO GENERIC SEIZURE MEDICATION

By

Kim Dawson

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Abstract of Doctoral Project Presented to the Executive Doctoral Program in Health Administration & Leadership Medical University of South Carolina
In Partial Fulfillment of the Requirements for the Degree of Doctor of Health Administration

EFFECTS OF SWITCHING FROM BRAND NAME TO GENERIC SEIZURE MEDICATION

By

Kim Dawson

Chairperson: Kit Simpson, DrPh, Professor Medical University South Carolina
Committee: Jillian Harvey, PhD, Assistant Professor Medical University South Carolina
Committee: Vincent Omachonu, PhD, Professor, University of Miami

Abstract

Generic drugs have been approved for use by the Food and Drug Administration (FDA) since 1984 on the basis of demonstrated bioequivalence as compared to the brand name version. Generic drugs constitute approximately two-thirds of all prescriptions dispensed in the US and account for <20% of total pharmaceutical expenditure (Patel et al., 2011). However, concerns about the safety and bioequivalence of the generic versions of specific drugs are raised regularly (Kesselheim et al., 2010). Despite evidence supporting bioequivalence, many observational studies have shown an increase in seizure occurrence with the use of generic drug formulations (Papsdorf et al., 2009; Berg et al.,
2008; for review see Yamada & Welty, 2010). These issues have not slowed the trend by medical insurance companies to mandate use of generic drugs over brand name drugs, and commercial and government insurance programs continue to prioritize the use of generics in most circumstances (Keenum et al., 2012). Although the use of generic medications can result in substantial savings for the American patient, anecdotal evidence indicates that beliefs concerning the safety and effectiveness of generic drugs compared to brand name medication may persist among patient subgroups as well as among medical practitioners (Figueiras et al., 2010; Ngo et al., 2013). While generic drug substitution may lead to immediate cost savings, these substitutions may be associated with additional expenses incurred due to increased adverse events, lack of adherence to therapy, and to the resulting failure of those therapies (Shin et al. 2014).

The purpose of this study is to examine: 1) the extent to which generic switch is practiced for privately insured US patients; 2) variations in adherence to AED medications for patients by brand name and generic AED and switching between the two, and 3) medical outcomes based on compliance to treatment. We examine factors associated with the use the antiepileptic brand drug Dilantin® manufactured by Pfizer, generic Phenytoin, and generic switch in 19-64 year old patients who have private insurance.

Keywords: Dilantin®, Phenytoin, generic, switch, compliance, epilepsy, seizure
Chapter 1: Introduction

Background and Need for the Study

Generic drugs have been approved for use by the Food and Drug Administration (FDA) since 1984 on the basis of demonstrated bioequivalence as compared to the brand name version. Generic drugs constitute approximately two-thirds of all prescriptions dispensed in the US and account for <20% of total pharmaceutical expenditure (Patel et al., 2011). Numerous studies (Andrade, 2015a; Andrade, 2015b; Davis et al., 2015; Jiang et al., 2015; Krauss et al., 2011) as well as general clinical acceptance and experience have validated this standard. However, concerns about the safety and bioequivalence of the generic versions of specific drugs are raised regularly (Kesselheim et al., 2010). Despite evidence supporting bioequivalence, many observational studies have shown an increase in seizure occurrence with the use of generic drug formulations in the treatment of epilepsy (Papsdorf et al., 2009; Berg et al., 2008; for review see Yamada & Welty, 2010). Yet the issues raised about the current bioequivalence standards have not slowed the trend by medical insurance companies to mandate use of generic drugs over brand name drugs in order to realize cost savings. Commercial and government insurance programs have prioritized the use of generics in most circumstances (Keenum et al., 2012). Additionally, the use of generic medications can result in substantial savings for the American patient due to the lower cost of generics compared to branded medications.
However, anecdotal evidence indicates that beliefs concerning the safety and effectiveness of generic drugs compared to brand name medication may persist among patient subgroups as well as among medical practitioners (Figueiras et al., 2010; Ngo et al., 2013). Studies have investigated patients’ perceptions of generics, and researchers report that although the consumer appreciates the cost savings from generics, some individuals are unwilling to use them, and medication compliance could be negatively affected (Kohli & Bueller, 2013, Shin et al., 2014).

In a 2009 study of commercially insured adults (Kohli & Bueller, 2013), 94% of patients agreed that generics are less expensive than brand name, yet only 37.6% of respondents would rather take a generic than a brand name medication. In the same study, researchers identified very different levels of acceptance of generic medications by individuals based on income and age (Kohli & Bueller, 2013). High-income patients were more likely than low-income patients to prefer generic medications. Older patients and more severely ill patients were more likely to report concerns about the safety of generics than healthy, high-income patients (Kohli & Bueller, 2013). Thus, while generic drug substitution may lead to immediate cost savings, it is possible that generic substitutions may be associated with additional expenses incurred due to increased adverse events, lack of adherence to therapy, and to the resulting failure of those therapies (Shin et al. 2014). This effect may be especially pronounced in subgroups of patients characterized by factors such as culture, social status, or personal and psychological characteristics. Indeed, studies continue to show that disadvantaged consumers may be reluctant to use generic drugs and may distrust generic medications (Keenum et al., 2012).
This distrust of generic substitutes may be especially dangerous for drugs that are essential for patient health and functioning. One example is the concern raised over generic substitution of drugs used for the management of epilepsy (Krauss et al., 2011; Kesselheim et al., 2010). The management of epilepsy requires anti-epileptic drugs (AEDs) in approximately 70-80% of patients, and some clinicians have raised concern that these patients may be at higher risk of non-adherence and seizures when switched from a brand name drug to generic AEDs (Kesselheim et al., 2010). This issue has raised such heated debate in the medical community that the FDA was requested by leading epilepsy organizations to issue a statement opposing mandatory switching from brand name drugs to generic AEDs. The FDA refused to issue a guidance statement on the matter, resulting in certain states (e.g. Hawaii, Tennessee) passing their own AED specific legislation. In these states, informed consent from both the provider and the patient is required before a generic substitution is permitted (Kesselheim et al., 2010). However, little is known about the current practice of switching from brand name to generic switch for AED. Table 1 outlines several organizations across the globe which have made legislation or strong recommendations regarding the use of generics in the treatment of epilepsy.

Table 1
Guidelines for generic prescription of AEDs (Atif et al., 2016)

<table>
<thead>
<tr>
<th>Country</th>
<th>Organization</th>
<th>Principal recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>AAN</td>
<td>The AAN argues the generic substitution of AEDs and advises to seek consent of attending physician</td>
</tr>
<tr>
<td></td>
<td>Epilepsy Foundation</td>
<td>Both physician and patient should give consent and to be notified upon substitution of AEDs</td>
</tr>
<tr>
<td></td>
<td>FDA</td>
<td>According to the FDA, a therapeutically equivalent</td>
</tr>
<tr>
<td>Country</td>
<td>Organization</td>
<td>Principal recommendations</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>American Epilepsy Society</td>
<td>product (either generic or brand) may be expected to have equivalent clinical effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The physicians involved in epilepsy treatment are trained for selection of appropriate AEDs and their dosages to minimize or eradicate seizures and to avoid adverse events</td>
</tr>
<tr>
<td></td>
<td></td>
<td>It is done by utilizing the best available scientific evidences and clinical expertise</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Also, the society contradicts the formulation substitution of AEDs without obtaining approval from the physician as well as the patient</td>
</tr>
<tr>
<td>England</td>
<td>NICE</td>
<td>Be precautious while generic substitution of AEDs having complex pharmacokinetics that may cause larger differences in therapeutic effects upon minor changes in drug absorption</td>
</tr>
<tr>
<td>Germany</td>
<td>German chapter of ILAE</td>
<td>A switch must be avoided for patients having well-controlled seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider a generic switch towards a lower cost AED only for the patients having poorly controlled seizures. It is better to initiate the treatment with a low-cost AED</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The serum drug levels should be monitored closely while switching and the patient should be informed about the potential risks</td>
</tr>
<tr>
<td>Italy</td>
<td>Italian chapter of ILAE</td>
<td>For patients exhibiting partial controlled seizures upon treatment with a brand AED, it might be appropriate to switch to a generic product</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The patient should be informed about the properties and nature of these products</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A switch is not recommended for the patients having well-controlled seizures</td>
</tr>
<tr>
<td>France</td>
<td>LFCE</td>
<td>AEDs belong to a class that may cause problems when substituted. It is recommended to avoid generic substitution of AEDs</td>
</tr>
<tr>
<td>Poland</td>
<td>Polish Society of Epileptology</td>
<td>Because of an increased risk of deterioration in epilepsy patients switching of formulations is</td>
</tr>
<tr>
<td>Country</td>
<td>Organization</td>
<td>Principal recommendations</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Scotland</td>
<td>Scottish Intercollegiate Guidelines Network</td>
<td>Generic substitution of AEDs should not be made as different available formulations of AEDs are not switchable</td>
</tr>
<tr>
<td>Sweden</td>
<td>Swedish Medicinal Products Agency</td>
<td>Switching between formulations may cause a poor control of seizures</td>
</tr>
<tr>
<td>Netherland</td>
<td>Netherlands Society of Child Neurology</td>
<td>The substitution of AEDs is not recommended</td>
</tr>
</tbody>
</table>

*Backg on Epilepsy*

Epilepsy is a heterogeneous, chronic and serious brain disorder with multiple manifestations. An epileptic seizure results from transient abnormal synchronization of neurons in the brain which disrupts normal patterns of neuronal communication, resulting in waxing and waning electrical discharges (Moshe et al., 2015). Epilepsy comprises many seizure types and epilepsy syndromes, some of which are life threatening (Schmidt & Schachter, 2014), and is defined as two or more unprovoked seizures. By this definition, epilepsy affects 45 million people worldwide and the incidence is approximately 26 to 40 per 100,000 person years (French & Pedley, 2008). The annual economic cost of epilepsy in the US in 2011 was $15.5 billion in direct healthcare associated costs as well as indirect costs due to employment loss, wage loss or reduction, and losses in productivity (Epilepsy at a Glance, 2011). Treatment has often been
empirically based on trial and error, and does not prevent or reverse the pathological process of the disorder (Schmidt & Schachter, 2014).

Epilepsy is one of many chronic diseases in which medication non-adherence is problematic. Studies estimate that between 30% and 60% of patients with epilepsy are non-adherent to their drug regimen, which can lead to higher seizure recurrence and increased medical resource utilization and costs (Davis et al., 2008).

**Treatment of Epilepsy**

The American Academy of Neurology, the American Epilepsy Society and the International League against Epilepsy have issued guidelines for the selection of pharmacologic therapy in patients with newly diagnosed epilepsy (French & Pedley, 2008)(Table 1). For these diagnosed patients, treatment with an antiepileptic drug is commonly recommended, especially if further seizures might result in serious morbidity or mortality (Schmidt & Schachter, 2014). Antiepileptic drugs should fully control seizures and be well tolerated with no long term safety problems, such as teratogenicity or hypersensitivity reactions (Schmidt & Schachter, 2014). The introduction of more than 15 antiepileptic drugs since 1980 has provided choice, but selecting the optimum drug, brand or generic, requires balancing of advantages and limitations to meet the patient's needs (Schmidt & Schachter, 2014).

**Drug Safety**

Drug safety is a major public health concern in the United States and both patients and health care providers must make sound decisions and be well informed of the potential benefits and harms of available treatment options. The efficacy and safety of
brand name prescription drugs continues to be examined in multiple randomized clinical trials conducted during drug development and Phase IV follow-up studies after FDA approval. Drug safety is the highest priority for patients and health providers, and the drug side effect profiles are key to many patients’ decision making about taking prescribed medications (Knapp et al., 2004).

Conventional methods of drug safety surveillance involve literature searches and individual analysis of reports of adverse events. Currently, the FDA data mines utilizing tools such as the Multi-item gama poisson shrinker (MGPS) in combination with their adverse event reporting system database (Ohno-Machado, 2015). In 2007, FDA Public law no: 110-85 mandated the use of observational data as part of the active drug safety surveillance system (FDA, 2015). These data sources explore pharmacoepidemiologic evaluation studies, yet statistical methods for screening observational data to generate hypothesis about potential drug effects have not been rigorously explored across mainstream data sources (Schneeweiss & Avorn, 2005).

**Problem Statement**

Epilepsy is a common neurological problem affecting 1-2% of the U.S. population, and has significant social and economic consequences, which can be minimized by optimal seizure control (McAuley et al., 2009). Medical research on epilepsy has explored the complexity of pharmacotherapy and has revealed intrinsic consequences from the pharmacokinetic and pharmacodynamic effects of medicating epileptic patients. Of particular concern is the increase in the number of prescriptions for patients aged 65 and older (Kohli & Bueller, 2013). Antiepileptic drugs provide satisfactory control of seizures for most patients with epilepsy, but the decision to start
drug treatment requires careful risk benefit analysis (Schmidt, 2009). Generic products are thought to be therapeutically interchangeable with brand name products and represent a cost effective alternative (Motola & DePonti, 2006). A controversial topic is the generic substitution of AED drugs, their interchangeability and equivalency to the brand name version. A growing number of observational studies have compared patients with epilepsy being treated with brand name AEDs to those patients switched to generics to determine seizure control and adverse events (Meyer et al., 2013), yet the results of these studies are conflicting (Yamada & Welty, 2011).

The purpose of this study is to examine: 1) the extent to which generic switch is practiced for privately insured US patients; 2) variations in adherence to AED medications for patients by brand name and generic AED; and 3) to assess medical outcomes of patients on generic or brand name AEDs.

**The Importance of the Study for Population Health**

Opportunities exist in the pharmaceutical, educational, and health care industries to assist research and public policy leaders to improve prescribing medication practices for epilepsy. Previous research has yielded mixed findings as to whether generic drugs are therapeutically interchangeable with their brand name counterpart. The present study is intended to contribute to the literature on the current topic of generic and brand medication switch in patients with epilepsy, as well as to help clarify issues that must be considered when requiring the use of generic drugs.

This study will investigate the differences in medication compliance between a generic and a non-generic AED medication, the rate of switching to a generic option
within this drug classification, and medical care outcomes for these patients using a large data set that reflects current practice in the US. The results will help inform the debate about regulations needed to circumscribe the practice of switching between brand-name and generic drugs for epilepsy. The results described here may also enable health care professionals to assume proactive roles in the initiation of a prescription drug reform for a special patient population, such as epilepsy. Furthermore, this analysis may contribute to the overall body of knowledge about important interactions between a common approach to cost savings and population health.

This study is both important and timely, as the topic of generic switching has become politically contentious, with some US states having recently passed AED specific legislation requiring informed consent from the prescriber and the patient raising concern about the safety of generic drugs (Kesselheim et al., 2010).

To better inform this issue, we will examine specific factors associated with the use the antiepileptic brand drug Dilantin® manufactured by Pfizer, comparing compliance rates for Dilantin® to those for the generic Phenytoin in 19-64 year old patients who have private insurance. Data from the MarketScan® database for 2013 will be used to examine switching behavior and medication adherence as measured by medication possession ratios, as well as medical care use in a one year period.

**Hypotheses:**

H1: Patients on generic Phenytoin have higher switch rates than patients on Dilantin®

H2: Patients on generic Phenytoin will have lower medication possession ratios over
a six month period than patients on branded Dilantin®

H3: Patients with lower medication possession ratios will be more likely to have medical care use indicative of seizure activity.
Chapter 2: Literature Review

Overview

A literature review was conducted to expand on the background and need for this study, analyze previous research, and review other study designs. The primary objectives of the literature review were to explore generic and brand drug interchange in the treatment of epilepsy, and to inform optimal study design.

Criteria for Selection of Literature

PubMed, Ovid, Scopus, and Google Scholar databases were searched for relevant articles for inclusion in this literature review. Three types of terminology were used in the completion of the literature search: (1) terms related to seizure treatment including: antiepileptic drug, anticonvulsant, Dilantin®, Phenytoin and (2) terms related to drug equivalency including: bioequivalence, substitution, and (3) the generic articles that had key words including each of the different search terms utilized were selected based on inclusion of human data, and published between 2008 and the present.

Significance of Epilepsy

It is estimated that 2 million people in the United States have epilepsy (CDC, 2015) and a recent report indicates that over 90% of patients with a seizure diagnosis have taken at least one drug for AED (CDC, 2015). Epilepsy is one of many chronic diseases in which medication non-adherence is problematic. Studies estimate that between 30% and 60% of patients with epilepsy are non-adherent to their drug regimen, which can lead to higher seizure recurrence and increased medical resource utilization and costs (Davis et al., 2008).
The FDA considers an approved generic product to be interchangeable with its brand counterpart as long as the mean area under the curve (AUC) and maximum concentration (C-max) are within 80-125% of the brand product (FDA, 2015). Generic drugs possess the same active ingredients, dosage form, strength, route of administration and labeling to meet the FDA’s approval standards without repeating Phase I, II, III clinical trials conducted by the original manufacturers (Kesselheim & Gagne, 2015). The FDA also maintains that all approved generic products are bioequivalent to each other, even though bioequivalence studies comparing generic AEDs are not always undertaken (Davit et al., 2009). As a result, stakeholders in the neurology community have explored generic substitution from the brand Dilantin® and have concluded that this practice may place patients with epilepsy at risk for loss of seizure control. The practice of switching a name brand medication for a generic one in patients with epilepsy is also discouraged by the American Epilepsy Society and the American Academy of Neurology (Kinikar et al., 2012). These organizations suggest that formulary driven generic interchange of AED medications should be avoided. Various health care payers have employed payment initiatives to drive down costs by incentivizing providers to increase the percentage of generic drugs used (Galanter, 2014).

**Treatment Compliance**

Leading authors in the field, such as Van Paesschen et al. (2008), Shin et al. (2014), Kesselheim et al. (2010), and Berg et al. (2008) agree that treatment failure of AED generic substitution can lead to a lack of treatment compliance, breakthrough seizures, bodily injuries, and job loss as several of the potential risks. The existing literature describes individual case reports confirming problems with generic AEDs
including Carbamazepine, Valproate, and Primidone, where some authors note wide-ranging variability in the bioavailability of these drugs, unlike other classes of chronic disorder medications (Berg et al., 2008; Kesselheim et al., 2010; Van Paesschen et al., 2008; Shin et al., 2014). Other factors, such as baseline seizure count and medication attitude influence the patient’s perception of seizure control, and can affect the patients’ decision making with regard to whether or not to switch to a generic AED medication (Bautista et al., 2011). Factors which may be involved in altering bioequivalence of generic drugs compared to brand name versions include low water solubility, narrow therapeutic window and drug interactions (Sankar et al. 2010). Non-bioequivalence of generic medications is thought to come primarily from differences in the manufacturing process, causing variability of the bioavailability of the generic preparation (Patel et al., 2012).

Additional individual case reports identified in the current review of the literature have confirmed problems with generic AED’s such as Phenytoin, Carbamazepine, Valproate, and Primidone. Some authors attribute these problems to reduced bioavailability of the generic AED (Berg et al., 2008; Kesselheim et al., 2010; Van Paesschen et al., 2008; Shin et al., 2014). Continued studies attempt to demonstrate and specify the problems associated with the generic substitution of AED medications, a matter that is believed to be both underreported and underestimated. Therefore, it is important for researchers to establish knowledge regarding the level of breakthrough seizures and or side effects that occur after switching to a generic product (Van Paesschen et al., 2008). Clinical and observational studies have provided updates to the body of literature over the years, illustrating that poor treatment compliance and
consequent failure of AED treatment can be promoted by generic substitution (Berg et al., 2008). Literature reviews by Kesselheim and colleagues (2010) and Yamada and Welty (2011) evaluated eight retrospective studies, which generally demonstrated that substitution of AED’s resulted in higher use of medical services in patients with epilepsy, with an apparent link between switching and increased incidences of seizure events associated with generic AED substitution (Hansen et al., 2013). However, individual study results remain inconclusive and conflicting, and thus additional evaluations of drug adherence following switching, and medical outcomes associated with generic switching are warranted.

**What is Known About the Issue?**

Epilepsy is a common and chronic disorder where lifetime treatment is often required. According to the latest estimates, about 1.8% of adults aged 18 years or older have had a diagnosis of epilepsy or seizure disorder (CDC, 2015). Concerns about medication cost and drug safety have increased, resulting in an increased notoriety regarding the clinical equivalence of generic drugs (Kesselheim et al, 2010). Helmers and colleagues (2010) report, in a retrospective analysis of over 33,000 patients, direct health care costs during periods of generic use versus brand AED medications were significantly higher. Epilepsy related medical costs were also higher during periods of generic treatment, representing 28% of all cause cost difference, due to increased utilization of both hospital and outpatient services (Helmers et al., 2010). As the use of generic antiepileptic drugs increases, the highly debated topic among healthcare professionals continues to raise concerns, and remains controversial. According to Crawford and associates (1996), doubts about the safety of generic prescribing for epilepsy arose in
1968 after reports of Phenytoin intoxication among patients with epilepsy, yet safety evidence for epilepsy prescribing is still not conclusive. Scientists have shown that a relatively small decrease in serum concentrations could result in breakthrough seizures due to the narrow therapeutic range of AED medications (Shin et al., 2014). The FDA only requires bioequivalence testing for the original product and not of corresponding generic substitutions (FDA, 2015). Additionally, a positive or negative 20% difference in bioavailability is permitted when licensing generics compared with branded drugs, a level that may be acceptable for most drugs (Crawford et al., 1996). However, small changes in bioavailability of AEDs specifically may result in poorer control of seizures with potentially serious implications. There may also be a large difference in bioavailability among the range of generics, especially those generic AED medications that have a narrow therapeutic index, which in turn may affect clinical outcomes (Shin et al., 2014). Although a variety of concerns have been raised regarding the FDA requirements for bioequivalence, the most urgent appears to be clinicians’ belief that an 80-125% range is too broad for narrow therapeutic range conditions such as epilepsy (Berg et al., 2008).

Consequently, a great deal of research has focused on the unreliability of interchanging brand name and generic AED medications, which has raised additional concern about the fact that more generic medications are being used. This increase in the use of generic medications is thought to be due to either expiry of patent protection, or because generics drugs are sold at prices below their brand name counterparts, and thus can contribute to reduced healthcare spending (Kesselheim et al., 2011). Crawford (2006) reports that formulary committees, health policy makers, and consumer groups may see the increased use of generic products as an important tool to battle healthcare
costs, yet the true costs of generic prescribing must also include the cost of additional hospital and physician visits and cost of treatment failure, which overall could offset the savings of the generics.

Concern has been noted with regard to the role of the medical legal environment if adverse consequences arise from generic substitution, particularly when informed consent is involved (Crawford et al. 2006). The legal responsibility of the occurrence of a breakthrough seizure is complicated when the patient’s medication has been switched to another treatment, considered by regulatory authorities to be equivalent, without informed consent of the patient. Informed consent is a prerequisite to the inclusion in clinical studies, however not a legal obligation for switching preparations (Crawford et al., 2006), further complicating the issue of legal responsibility of any adverse effects.

Prescription drug substitution is addressed in state legislatures. Some legislation will support the use of generics while other bills have been submitted seeking to restrict substitution of certain classes of drugs, notably antiepileptic drugs and immunosuppressants (Shaw & Hartman, 2010). There are variations in both existing and proposed legislation, but in general these bills aim to prohibit a pharmacist from substituting or interchanging any AED without prior notification and/or signed consent from the prescriber and patient (Shaw & Hartman, 2010).
Table 2

<table>
<thead>
<tr>
<th>Antiepileptic Drug Substitution Legislation</th>
</tr>
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<tbody>
<tr>
<td><strong>Hawaii</strong></td>
</tr>
<tr>
<td><strong>Illinois</strong></td>
</tr>
<tr>
<td><strong>Tennessee</strong></td>
</tr>
<tr>
<td><strong>Utah</strong></td>
</tr>
</tbody>
</table>

(Shaw & Hartman, 2010)

The Role of Phenytoin in Treatment of Epilepsy

The treatment of epilepsy has a very broad degree of complexity which can be complicated by the unreliability of interchanging brand and generic AED medications. This study reviews Phenytoin, which has been the most widely used generic medication to treat seizures over the past twenty years, even though a variety of new compounds have been released (Das et al., 2013). Phenytoin was first synthesized in 1908 at the University of Kiel in Germany and marketed under the trade name Dilantin® (Das et al., 2013).
**Effect of Using Generics on Government Spending**

In 2007, the congressional budget office (CBO) examined the use of generic drugs in Medicare’s outpatient prescription drug benefit for senior citizens and people with disabilities (Part D), using the claims data from Centers for Medicare and Medicaid Services (CMS) plans for ten million prescriptions. At that time, about 65% of Part D prescriptions were filled with generics. The CBO’s goal was to analyze how much was saved as a result of the use of generic drugs, as well as assess the potential for savings associated with increasing the use of generics. The CBO also examined savings from generic substitution. Among Part D prescriptions, of those brand drugs that had a generic version available more than 90% were filled with the generic option (CBO, 2014).

In a separate analysis by the Department of Health and Human Services (Office of Inspector General) generic drugs were dispensed 88% of the time when available (OIG, 2007). For Part D, there was a strong financial incentive to encourage the use of generic drugs, yet there was little data to reflect how the patients felt about the use of such generic drugs.

**Influence of Patient Illness on Perception of Generics and Brand**

In addition to the prescribing habits and protocols of healthcare providers, decisions about the choice of generic or brand name medicines may also be influenced by patients’ perceptions and beliefs about treatment, side effects, as well as their illness (Figueiras et al., 2010). The literature suggests that patients develop beliefs about the necessity of a specific type of medication for maintaining their health status. Subsequently, beliefs about illness and medicines are interconnected, and may influence compliance and outcomes (Omojasola et al., 2012). According to Horne and Weinman
(1999), literature is scarce regarding how patients make decisions concerning their medications, or about their preferences for one drug or another. However, there is evidence that levels of knowledge about medicines in general may influence consumer attitudes and beliefs about medicines for particular illnesses (Horne & Weinman, 1999), suggesting that perceptions concerning efficacy and safety of generic prescriptions may depend on the medical condition being treated. Illness and treatment beliefs may also play a crucial role in patients’ decisions about the choice between generic and brand medicines (Figuerias et al., 2008). Figuerias (2008) and authors have argued that the nature of the illness threat is influenced by the illness label and the interpretation of symptoms.

According to a study conducted by Dohle and Siegrist (2014), the consumers’ perceptions of an illness was the main determinant of satisfaction with generic drug use, rather than beliefs regarding the equivalence of brand versus generic medicine. Another study investigated whether consumers were more likely to utilize a generic medication or a brand prescription for minor or more serious health problems (Figuerias et al., 2008). The results indicated that patients are less likely to take generic drugs for chronic and serious conditions like epilepsy, even when they have had positive experiences with them and believed they were equal in quality to brand name products (Figuerias et al., 2008). Decisions not to take generics appeared to be driven by a fear of health loss, which increased with the seriousness of a disorder, rather than the belief that generics were in general equivalent to brand name drugs (Omojasola et al., 2012). These and other findings indicate that the consumer’s perception of their illness also influences the preference for a medicine (Omojasola et al., 2012). Although we can expect that
preferences for medicines may differ between the general population and those who experience a condition, we can assume that the perceptions of illness severity as well as patient beliefs and knowledge about medicines will all have an important roles in decisions about the use of generic or brand name treatments (Figueiras et al., 2010).

**Conceptual Model**

A review of the multidisciplinary literature on seizure outcomes following use of brand versus generic antiepileptic drugs reveals a lack of comprehensive theoretical framework for understanding these events and their complexities (Berg et al., 2008; Hansen et al., 2009; Shin et al., 2014). Berg (2008) argues that definitive evidence on the effects of generic AED medication substitution is lacking, and it is important for physicians to take more accountability, reporting any cases involving breakthrough seizures to the FDA directly. Conversely, other experts have pointed out that a 2010 systematic review provided no evidence of loss of seizure control with generic substitution for many AED medications (Kesselheim et al., 2010). The topic itself is wrought with confusion, and studies indicate unclear consensus to guide clinicians (Privitera, 2013). Applying a process of conceptual framework analysis, as shown in Figure 1, will provide a theoretical framework to shed new light on the feasibility of implementing sustainable prescribing practices. This study will contribute important information to the current database on generic switch, and help clarify the issues that must be considered when prescribing or switching to generic drugs.
Figure 1: Representation of the conceptual framework developed for interpretation of proposed hypotheses.

Past Studies

Literature identified in this review suggests that the majority of studies have primarily relied on retrospective analysis to show increase in breakthrough seizure occurrence when switching from brand name to generic drug use in the treatment of epilepsy (Hansen et al., 2009; Kinikar et al., 2012; Shin et al., 2014; Zachry et al., 2009; Rascati et al., 2009; Labiner et al., 2010). However, several prospective studies have also found significant increase in pharmacokinetic outcomes affecting bioequivalence (Olling et al., 1999; Revankar et al., 1999). Several authors have reported an increase in switchback rates from generic to brand AED medications using claims databases as their primary source of data (Lelorier et al., 2008).
A review of selected study designs suggests that the current approaches do not appear to have become more advanced or sophisticated over the years. Researchers have primarily applied existing case control designs and either longitudinal, prospective, or retrospective analysis (Yamada & Welty, 2011). Most trials identified by this search were short-term evaluations of small populations and were powered to assess differences in pharmacokinetic parameters rather than clinical outcomes (Kesselheim et al., 2010). Future studies could potentially improve external validity and generalizability based on the sampling model. Providing data about the degree of similarity between the various study groups utilizing different locations, people, and times of day might continue to frame the ability to generalize findings.

**The Next Step in Study Design**

Analyses of administrative insurance claims data to assess the prevalence of generic switches and adherence has been widely used in a variety of chronic disease studies. The utilization of claims data presents a good opportunity to provide information regarding patterns of medication dispensing and may be more generalizable than observational studies in controlled clinical trials (Kinikar et al., 2012).

A limitation of current clinical research is that controlled trials are frequently comprised of participants that are not randomly selected, and therefore may be atypical of real world practice settings (Davis et al., 2008). Data may then be viewed as non-representative of the general population, and study design must be augmented in some way to address this matter. To this end, it is recommended that future studies of administrative data to assess medication adherence of generic AED medications are needed to support previous work using trial-based data (Davis et al., 2008).
It should be further noted that there is also a pressing need for additional studies to determine whether there is bioequivalence and therapeutic equivalence between the brand name medication Dilantin® and the generic medication Phenytion, both of which are currently available in the market (Jankovic & Ignjatovic Ristic, 2014). Currently, the FDA (2015) states that there is no adequate data indicating that current testing for generic medications is faulty, even with drugs that have narrow therapeutic range conditions. It is unclear if reported problems are due to underreporting, or if there is actually no problem to report with generic preparation of AED medications (Berg et al., 2008). Some drug products may have unique structural or functional attributes that necessitate product specific approaches to therapeutic equivalence determinations (Kesselheim & Gagne, 2015). Tests to demonstrate therapeutic equivalence following generic approval using product-specific pathways along with active surveillance studies would be useful in promoting appropriate use of lower cost generic drugs (Kesselheim & Gagne, 2015). This is a critical issue that warrants further review.

This study provides a unique opportunity to assess the extent of non-adherence and or generic switch behavior with currently approved generic AED medications within a managed care environment. There is a potential opportunity to extrapolate the association between AED medication non-adherence and future healthcare utilization. In addition, the identification of specific factors associated with the occurrence of increased seizures and adverse effects when switching from brand name to generic AED medications will provide insight into the potential ways in which positive healthcare behaviors may be fostered, and result in decreased utilization of outpatient and hospital services (Baustista et al., 2011). This additional information could also aid clinicians and
health policymakers to better identify instances where prescribing brand AED medications would improve patient outcomes.

We use a retrospective analysis of archival statistics utilizing data from the MarketScan® database for 2013, which contains all billing records for approximately four million covered individuals. It will be used to examine switching behavior and medication adherence as measured by medication possession ratios in patients with epilepsy. Selection bias will be controlled through statistical modeling.

Summary

Chapter 2 provided a review of relevant literature. An overview of relevant material to the research study at hand was presented, and the implementation of a conceptual model was discussed, along with the necessity for its use. The different study designs used in research related to this field of study were reviewed, and the issues with past study designs were discussed. Information was pulled from these studies regarding the recommended course of action for future study designs. The criteria for the selection of literature included within this review are presented. Chapter 3 will offer a description of the methodology to be used in the completion of this study.
Chapter 3: Methodology

Study Objective

A retrospective cross sectional analysis of administrative data about the utilization of generic and brand medications in epilepsy and seizure disorder was conducted. Large health care utilization databases are frequently used in variety of settings to study the use and outcomes of therapeutics. Their size allows the study of infrequent events, and their representativeness of routine clinical care makes it possible to study real-world effectiveness and utilization patterns (Schneeweiss 2005).

This study’s primary objectives are to examine:

1) The extent to which generic switch is practiced for privately insured US patients; and

2) Variations in adherence to anti-epileptic medications (AEDs) for patients switched from brand name and generic AEDs.

3) Medical care use for patients on brand name and generic AEDs.

Hypotheses

We hypothesize that:

● H1: Patients on generic Phenytoin will have higher switch rates than patients on Dilantin®

● H2: Patients on generic Phenytoin will have lower medication possession ratios over a one year period than patients on branded Dilantin®
H3: Patients with lower medication possession ratios will be more likely to have medical care use indicative of seizure activity

For the purposes of this study, the use of the antiepileptic brand drug Dilantin® manufactured by Pfizer will be assessed to measure these effects, and the rates of compliance will be compared for Dilantin® and the generic medication Phenytoin in 19-64 year old privately insured patients. Data from the MarketScan® database for 2013, which contains all billing records for approximately four million covered individuals, will be used to examine switching behavior and medication adherence as measured by medication possession ratios.

Data Collection

The Medical University of South Carolina (MUSC) College of Health Professions (CHP) purchased rights to the use of the Truven Health Analytics MarketScan® database. The SAS statistical system was used to gather and summarize the data and then present for analysis to this author.

The blinded dataset lacks personal health information linked to any specific patient. Due to the data's lack of individual identifiers, the MarketScan® data was deemed Non-human research by the Medical University of South Carolina Institutional Review Board.

Data Population

The International Classification of Diseases-9-Clinical Modification (ICD-9-CM) codes were used to search the MarketScan® National database. Patients with the ICD-9-CM diagnosis code: 345.9, 345.0, 345.1, 345.4, 345.5 representing seizure activity served
as the primary inclusion criteria. The new data set was refined by selecting from patients who had the following ICD-9-CM codes: 345.9, 345.0, 345.1, 345.4, 345.5. All information from the SID databases for each patient was carried over to the new database, respectively. Multiple hospitalizations for the same individual counted as separate occurrences.

De-identified patient data were included in the analysis if they (1) were prescribed Phenytoin for seizure disorder, (2) experienced some form of interchange through the use of at least one generic Phenytoin prescription in 2010, (3) were at least 19 years of age or older at the time the medication interchange occurred, and (4) had a continuous membership in their primary insurance plan for six months before and after the medication interchange. Patients were excluded if they received Phenytoin for neuropathy or for a pain diagnosis, as opposed to being prescribed the drug for a seizure diagnosis. The data for the sample was extracted using the following final diagnosis for any patient in the dataset: ICD-9-CM coded encounter of a seizure disorder: 345, 345.9, 345.0, 345.1, 345.4, 345.5

**Description of Variables**

The project independent variable was the brand Dilantin® or generic Phenytoin medication. The first dependent (y) variables are that of medication possession for each of the following:

1. Generic Phenytoin switch - Yes/No
2. Dilantin® switch- Yes/No
The dependent variables identified for a medical care use were:

1. General admission to inpatient hospital (may or may not seizure related)
2. Hospital inpatient admission due to seizure
3. Outpatient visit due to seizure
4. Emergency department (ED) visit due to seizure

Data Set and Statistical Methods

The raw dataset contained exposure and outcome variables for 6681 patients followed for 1 year. Data collected from patients on generic Phenytoin or brand name Dilantin® were used to determine which of these patients had higher switch rates, medication possession ratios, and medical care events. The following statistical analyses were conducted: summary statistics are reported as numbers and percentages for categorical variables and medians and ranges for continuous variables. For hypothesis 1, Chi-square tests were used to assess statistical significance between groups. Logistic regression was used to calculate odds ratios, confidence intervals and P-values. This analysis assessed which patient classes had higher switch rates. For hypothesis 2, the Kruskal-Wallis nonparametric test assessed the difference in average medication possession ratios for four groups of treatment switched or non-switched patients. This analysis determined if patients on generic Phenytoin had lower medication possession ratios than patients on branded Dilantin®, and if switching from one treatment to another affected medication possession ratios over a one year period.

Groups were defined as follows:

Group 1: Start on Generic, end on Generic

Group 2: Start on Generic, switch to Dilantin®
Group 3: Start on Dilantin®, switch to Generic

Group 4: Start on Dilantin®, end on Dilantin®

For hypothesis 3, medication possession was the exposure variable and the analysis assessed whether patients with lower medication possession ratios were more likely to have medical care use indicative of seizure activity. Specifically, compliance was defined for a patient with a ratio > 1 and non-compliant had a ratio < 1. Logistic regression and poisson regression were used to calculate odds ratios and relative risk, respectively. The outcomes we identified were as mentioned above: inpatient admissions, epilepsy related inpatient admissions, outpatient visits, and ED visits.

Study Importance

The studies investigating bioequivalence and interchangeability of brand name and generic anti-convulsant drugs are sparse, and their results are conflicting. Few studies have investigated change in seizure control after switching from brand name drugs to generic medications, a central question in the field of research and treatment. Steady state plasma concentrations of anticonvulsants and their fluctuations are directly linked to seizure control, so a study that explores therapeutic equivalence of brand name and generic was needed. This study provides insight into the "switchability" issues of brand name and generic anticonvulsants. It serves to provide clinicians with useful data to evaluate and take into consideration when prescribing anticonvulsants to their patients with epilepsy, and those patients who are being considered for a switch from brand named to generic anticonvulsants. This study will contribute important information to the
current knowledge of effects of generic switches, and help clarify issues that must be considered when requiring or suggesting the use of generic drugs.

Limitations

The key limitation of this study is the utilization of administrative claims data. Administrative database research creates potential risks that can make the study uninterpretable or biased (Walraven 2012). Concerns about database studies include data validity, lack of detailed clinical information, and a limited ability to control confounding variables (Schneeweiss & Avorn, 2005). While most guidelines for assessing the validity of observational studies apply to administrative database research, the unique characteristics of this data source must be accounted for in the study design to avoid results that are biased or uninterpretable (van Walraven et al., 2012). Minimization of risk by providing robust description of data and variables utilizing ICD-9-CM codes will be important. Employing quality criteria to ensure the accuracy of diagnostic and procedural codes, distinguishing between clinical and statistical significance and analyzing data properly to explore the influence of population definitions on study outcomes is key to providing valid and useful results (van Walraven et al., 2012). Physician beliefs and prescribing ability to treat epilepsy could influence the patient’s outcomes, thus it is likely that within provider correlation may exist. This effect must be examined using statistical methods that control for within provider correlation, if needed. The adoption of evidence based clinical care pathways and increased education evolves from the strength of the study and the ability to generalize the results. Accuracy of administrative data is dependent on the accuracy of the physician documentation as well as the skill of the medical records professional coding the disease (Tu et al., 2014). The term seizure
disorder and epilepsy can be used with similar frequency, and including both terms to identify patients with this condition is recommended (Tu et al., 2014). This study is unadjusted for possible imbalances for demographics.
Chapter 4: Results

Hypothesis 1

Data were analyzed using statistical software (R®; Vienna, Austria). The total number of patients identified as having epilepsy or epileptic syndrome, as well as currently prescribed generic Phenytoin or Dilantin® in the MarketScan® database were 6681. For H1, logistic regression was conducted to examine the difference in switch rates between patients who started treatment on Phenytoin versus those who started treatment on Dilantin®. Of the 6681 patients identified, 4704 patients started treatment with Phenytoin, and 1977 patients began their treatment with Dilantin®. Data show that 6312 of these patients did not switch treatments, while 369 patients had switched, resulting in a 5.5% switch rate in this sample overall. Within the group who started treatment on Phenytoin, 4566 patients did not switch and 138 patients switched, a switch rate of 2.9%. The switch rate for the group of patients who started on Dilantin® was 11.7%, where 1746 patients did not switch from Dilantin®, and 231 patients did switch. A Pearson’s Chi-squared test with Yates’ continuity correction revealed a significant difference in switch rates between patients who started treatment on Phenytoin compared to those who started on Dilantin® $\chi^2 (1, N = 507) = 202.60$, $p < 0.001$. Patients who began treatment on Dilantin® were more likely to switch treatments than those who started their treatment with Phenytoin. The difference between these rates was statistically significant (OR = 4.38, 95% CI [3.52-5.44], $p < 0.001$) and can be seen in Figure 2. Additional data from the analysis can be found in Table 3.
Figure 2: Results of logistic regression analysis on medication switch rates among epilepsy patients who began treatment on generic Phenytoin, compared to those who began treatment on Dilantin®. The analysis revealed significant differences in switch rates between the two groups. Chi-square, odds ratio were significant at $p < 0.001$. CI = confidence interval.
Table 3
Logistic regression coefficients of prescription switch rates in epileptic patients prescribed generic Phenytoin or Dilantin® in 2013

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Estimate</th>
<th>Std. error</th>
<th>z value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>-3.50</td>
<td>0.09</td>
<td>-40.50</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dilantin®</td>
<td>1.48</td>
<td>0.11</td>
<td>13.28</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>( \chi^2 )</td>
<td>202.60</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>4.38 (3.52-5.44)</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>df</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>507</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hypothesis 2**

A (non-parametric) logistic regression was conducted on the data for H2, which also yielded highly significant results. The overall distribution of the sample can be seen in Figure 3. For this hypothesis, data from the 6681 identified patients in the MarketScan® database was used to compute medication possession ratios for each group of interest (Group 1: Start on Generic, end on Generic; Group 2: Start on Generic, switch to Dilantin®; Group 3: Start on Dilantin®, switch to Generic; Group 4: Start on Dilantin®, end on Dilantin®). The median medication possession ratio for the total sample \( (N = 6681) \) was 99.4 \( (IQR = 79.65-107.80) \). The numbers of patients in each group were as follows; Group 1: 4566 patients, Group 2: 138 patients, Group 3: 231...
patients, Group 4: 1746 patients. The analysis showed significant differences in rates of compliance, as measured by possession ratios, among the groups; Group 1: \( Mdn = 98.21, IQR = 76.92-107.20 \), Group 2: \( Mdn = 98.41, IQR = 69.45-113.70 \), Group 3: \( Mdn = 100.30, IQR = 86.56-111.40 \), Group 4: \( Mdn = 101.7, IQR = 86.96-108.30, p < 0.001 \). This data suggests that patients who start treatment on Dilantin® and stay on Dilantin® are the most compliant, while those who start on Phenytoin and switch to Dilantin® are the least compliant. Additionally, Figure 4 shows that both groups who started treatment on Dilantin® were more compliant than those starting treatment on Phenytoin. As can also be seen in Figure 4, the greatest variability in medication compliance, as measured by medication possession ratios, occurred in Group 2 patients who had switched from generic Phenytoin to Dilantin® \( (IQR = 69.45-113.70) \), followed by those patients in Group 1 who were taking generic Phenytoin only without switching \( (IQR = 76.92-107.20) \). Alternatively, the least variability in compliance was seen in Groups 4 and 3, the Dilantin® only group \( (IQR = 86.96-108.30) \), and the Dilantin® switched to Phenytoin group 3 \( (IQR = 86.56-111.40) \), respectively. This suggests that patients who began treatment with Dilantin® overall showed less variability in compliance than those who started treatment on Phenytoin. Finally, these data also reveal unexpected findings with regard to outliers. Group 1 and Group 4 had the greatest number of outliers, followed by Group 3. However, all groups with the exception of Group 4, contained outliers only in the direction of lesser compliance. Group 4 (treated with Dilantin® only) is the only group to contain outliers that reached and exceeded the target compliance. This means that not only were patients in this group the most compliant of all groups, but even the
outlying patients from this group were uniquely exhibiting 100% compliance with their medication regime.

Figure 3. Histogram representing the overall distribution of computed medication possession ratios for the total sample \((N = 6681)\) of epileptic patients prescribed generic Phenytoin or Dilantin® in 2013. The data is not normally distributed, leading to the use of non-linear logistic regression analyses. A large number of patients are non-compliant with their medication taking regime. Frequency refers to the number of patients from the total sample.
Figure 4. Box plot representation of compliance rates, as measured by medication possession ratios, for epilepsy patients in all four groups over one year (2013). Group 1, Gen/Gen includes patients who started treatment on generic Phenytoin and ended on generic Phenytoin (no switch from generic Phenytoin); Group 2, Gen/Dil includes patients who started treatment on generic Phenytoin and ended on Dilantin® (switched from generic Phenytoin to Dilantin®); Group 3, Dil/Gen included patients who started treatment with Dilantin® and ended on generic Phenytoin (switched from Dilantin® to generic Phenytoin); Group 4, Dil/Dil includes patients who started treatment on Dilantin® and ended on Dilantin® (no switch from Dilantin®). The dashed horizontal line represents the target value of 100 (representing 100% compliance). Black bars
indicate the median value for each group. Red boxes represent the extent of the
interquartile range (1\textsuperscript{st} and 3\textsuperscript{rd} interquartile values). Outliers are represented by empty
circles.

Table 4

Logistic regression analysis of medication possession ratios in epileptic patients by
Group in 2013

<table>
<thead>
<tr>
<th>Group</th>
<th>Min.</th>
<th>1\textsuperscript{st} Quart.</th>
<th>Median</th>
<th>Mean</th>
<th>3\textsuperscript{rd} Quart.</th>
<th>Max.</th>
<th>Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 4566)</td>
<td>0.00</td>
<td>76.92</td>
<td>98.21</td>
<td>88.12</td>
<td>107.20</td>
<td>148.00</td>
<td>30.26</td>
</tr>
<tr>
<td>2 (n = 138)</td>
<td>17.96</td>
<td>69.45</td>
<td>98.41</td>
<td>91.70</td>
<td>113.70</td>
<td>147.10</td>
<td>30.76</td>
</tr>
<tr>
<td>3 (n = 231)</td>
<td>0.00</td>
<td>86.56</td>
<td>100.30</td>
<td>96.28</td>
<td>111.40</td>
<td>142.40</td>
<td>23.36</td>
</tr>
<tr>
<td>4 (n = 1746)</td>
<td>0.00</td>
<td>86.96</td>
<td>101.70</td>
<td>95.61</td>
<td>108.30</td>
<td>148.00</td>
<td>23.92</td>
</tr>
</tbody>
</table>

Kruskal-Wallis

$\chi^2$  73.46

$Df$  3

$p <$

$p$-Value  0.001

N  6681
Hypothesis 3

Dichotomized Variable Analysis

Total Sample

The third hypothesis tested various medical outcomes associated with compliance as measured by medication possession ratios. Data for the overall sample was initially dichotomized by “compliance” and “non-compliance”, where patients were coded 0 (compliant) if their medication possession ratio was \( \geq 100 \), and coded 1 (non-compliant) when their medication possession ratio was < 100, 100 therefore being the target value indicating 100% compliance. This revealed that from the total sample of 6681 epilepsy patients prescribed generic Phenytoin or Dilantin®, there were a 3216 compliant and 3465 non-compliant patients. This dichotomization was also confirmed by analyses for each group (Compliant: \( \text{Mdn} = 108.1, IQR = 103.70-116.40 \); Non-compliant: \( \text{Mdn} = 80.84, IQR = 56.57-92.44 \))

Of the 6681 patients in the total sample, data from MarketScan® reported 642 patients requiring in-patient hospital admissions, 173 patients with epilepsy related admissions, 433 patients having had outpatient visits, and 5832 attending the emergency department (ED).

The mean number of ED visits was similar among compliant and non-compliant patients, \( M = 1.9 \) and \( M = 2.15 \), respectively. However, the range of ED visits showed variability, with a greater range in the number of ED visits for non-compliant (range = 0.00-37.00) patients than for compliant patients (range = 0.00-19.00). Over a one year period, we observed on average a range of 0-19 visits for the compliant and 0-37 visits
for the non-compliant patients with an overall average of approximately two emergency room visits for both groups with a slight increase in the non-compliant group.

**In-Patient Visits by Compliance**

Logistic regression analyses and Pearson’s Chi-squared tests were used to assess the dichotomized variable data. Data from the MarketScan® database for 2013 showed that 233 of the 3216 compliant patients required in-patient hospital admissions, compared to 409 of the 3465 non-compliant patients. These values result in a 7.25% admission rate for compliant patients, and an 11.80% admission rate for non-compliant epilepsy patients, a difference that was statistically significant, $\chi^2 (1, N = 442) = 39.38, p < 0.001$. Logistic regression showed that non-compliant patients were 71% more likely to require in-patient services than compliant patients, $\text{OR} = 1.71$, 95% CI (1.45-2.02), $p < 0.001$. These results and additional logistic regression coefficient values are presented in Figure 5 and Table 5.
Figure 5. In-patient admission rates for compliant and non-compliant epileptic patients, according to medication possession ratios. These data were statistically significant, $p < 0.001$. 

Odds Ratio = 1.71
95% CI = 1.45 to 2.02

- Compliant: 7.2%
- Non-Compliant: 11.6%

n=6681
Table 5

Logistic regression coefficients of inpatient visits in compliant and non-compliant epileptic patients prescribed generic Phenytoin or Dilantin® in 2013

<table>
<thead>
<tr>
<th>Group</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>z value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliant</td>
<td>-2.55</td>
<td>0.07</td>
<td>-37.48</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Non-compliant</td>
<td>0.54</td>
<td>0.09</td>
<td>6.26</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

**Epilepsy Related Hospital Admissions by Compliance**

Data was also collected from the MarketScan® database regarding the number of epilepsy related hospital admissions for compliant and non-compliant epileptic patients prescribed Phenytoin or Dilantin® in 2013. These data showed that 58 compliant epileptic patients had epilepsy related hospital admissions during the one year period, while 115 non-compliant patients were admitted for epilepsy related reasons during the same year. The admission rates for compliant vs. non-compliant patients were 1.80% and 3.32%, respectively. This difference was statistically significant, $\chi^2 (1, N = 173) = 14.59$, $p < 0.001$. As is shown in Figure 6, non-compliant patients were 87% more likely to have had an epilepsy related hospital admission than compliant patients, OR = 1.87, 95% CI (1.36-2.57), $p < 0.001$. Additional data from this analysis is also provided in Table 6.
Figure 6. Epilepsy related hospital admission rates for compliant and non-compliant patients, according to medication possession ratios. These data were statistically significant, $p < 0.001$. 

Epilepsy Admission Rates

Odds Ratio = 1.87
95% CI = 1.36 to 2.57

Compliant: 1.8%
Non-Compliant: 3.3%

n=6681
Table 6

Logistic regression coefficients for epilepsy related hospital admissions in compliant and non-compliant epileptic patients prescribed generic Phenytoin or Dilantin® in 2013

<table>
<thead>
<tr>
<th>Group</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>z value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliant</td>
<td>-3.99</td>
<td>0.13</td>
<td>-30.17</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Non-compliant</td>
<td>0.63</td>
<td>0.16</td>
<td>3.84</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

Outpatient Visits by Compliance

Poisson regression was used to analyze the data on outpatient and ED visit data described below. Data on the number of outpatient visits in 2013 showed 188 episodes of outpatient visits for compliant epilepsy patients as a group. Non-compliant patient data revealed that 439 episodes of outpatient visits were required in this group. Data also revealed that, for compliant patients, the incidence rate of outpatient visits was 58 per 1000 person years; for the non-compliant patients, the incidence rate of outpatient visits was 127 per 1000 person years (RR = 2.17, 95% CI [1.83-2.57], p < 0.001). This data suggests that if 1000 compliant patients were followed for one year, there would be a total of 58 outpatient visits within that year. Alternatively, for 1000 non-compliant patients, the total number of outpatient visits would equal 127 in one year. This also suggests that non-compliant patients have greater than twice the risk of requiring outpatient services than do compliant patients. These differences, shown in Figure 7,
were statistically significant. Poisson regression coefficients are shown in Table 7.

Figure 7. Incidence rates of outpatient visits for compliant and non-compliant epileptic patients prescribed generic Phenytoin or Dilantin® in 2013
Table 7

Poisson regression coefficients for outpatient visit incidence rates in compliant and non-compliant epileptic patients prescribed generic Phenytoin or Dilantin® in 2013

<table>
<thead>
<tr>
<th>Group</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>z value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliant</td>
<td>-2.84</td>
<td>0.07</td>
<td>-38.93</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>Non-compliant</td>
<td>0.77</td>
<td>0.09</td>
<td>8.87</td>
<td>$p &lt; 0.001$</td>
</tr>
</tbody>
</table>

**Emergency Department Visits by Compliance**

The number of ED visits in 2013 for compliant and non-compliant epilepsy patients were alarmingly high. Compliant patients exhibited 6110 ED visits overall as a group, while non-compliant patients attended the ED 7440 times as a group within this one year period. The incidence rates of ED visits for compliant and non-compliant patients were 1900 and 2147 per 1000 person years, respectively (RR = 1.13, 95% CI [1.09-1.17], $p < 0.001$). This data, represented in Figure 8, also suggests that non-compliant patients have a 13% greater risk of attending the ED than do compliant patients. These results were also statistically significant, and corresponding Poisson regression coefficients are shown in Table 8.
Figure 8. Incidence rates of emergency department visits for compliant and non-compliant epileptic patients prescribed generic Phenytoin or Dilantin® in 2013
Table 8

Poisson regression coefficients for emergency department visit incidence rates in compliant and non-compliant epileptic patients prescribed generic Phenytoin or Dilantin® in 2013

<table>
<thead>
<tr>
<th>Group</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>z value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliant</td>
<td>0.64</td>
<td>0.012</td>
<td>50/17</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Non-compliant</td>
<td>0.12</td>
<td>0.017</td>
<td>7.09</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**Continuous Variable Analyses**

**In-patient Visits**

Logistic regression analyses were used to assess the continuous variable data for medication possession from the MarketScan® database for 2013. These analyses revealed that a 1% positive change in compliance resulted in a statistically significant 1% decrease in the number of in-patient hospital admissions, OR = 0.99, 95% CI (0.98-0.99), p < 0.001. Additionally, a 10% positive change in compliance corresponded to a 12% decrease in in-patient hospitalization which was also statistically significant, OR = 0.88, 95% CI (0.86-0.90), p < 0.001.

**Epilepsy Related Hospital Admissions**

Analyses of the continuous variable medication possession with regard to epilepsy related hospital admissions also showed statistically significant results. A 1% positive change in compliance resulted in a 2% decrease in epilepsy related hospital admissions, OR = 0.98, 95% CI (0.98-0.98), p < 0.001. A 10% positive change in compliance was
related to a 16% decrease in epilepsy related admissions, OR = 0.84, 95% CI (0.81-0.88), \( p < 0.001 \).

**Outpatient Visits**

Continuous data on outpatient visits indicated that a 1% positive change in compliance resulted in a statistically significant 1% decrease in the number of outpatient visits (OR = 0.99, 95% CI [0.98-0.99], \( p < 0.001 \)), while a 10% positive change in compliance resulted in a 13% decrease in outpatient visits which was also statistically significant (OR = 0.87, 95% CI [0.85-0.89], \( p < 0.001 \)).

**Emergency Department Visits**

Logistic regression conducted on the data regarding the number of ED visits in epilepsy patients revealed that a 1% positive change in compliance corresponded to a less than 1% decrease in the number of ED visits, yet this change was statistically significant, OR = 1.00, 95% CI (1.00-1.00), \( p < 0.001 \). A 10% positive change in compliance resulted in a statistically significant 3% decrease in ED visits, OR = 0.97, 95% CI (0.96-0.97), \( p < 0.001 \). These data, despite their significance, suggest that ED visits may be the least affected by increased compliance.
Chapter 5: Discussion

Substantial concerns continue to be expressed about potential problems arising from switching epileptic patients between generic and brand AED drugs. This study was designed to provide an assessment of brand name Dilantin® and generic Phenytoin, comparing switch rates, compliance, and seizure related outcomes, as there is growing concern about the efficacy and safety of generic AED’s (Haskins et al., 2005). Changing health policy and managed care practices focus on cost containment and may encourage the use of generics because they are less expensive than their branded counterparts. What may be greatly underestimated are the additional unexpected costs associated with switching drugs which can cause both an increase in adverse events and increased medical use, such as hospitalization and emergency room visits.

Results from this large managed care database demonstrated that patients treated with Phenytoin had a switch rate of 2.9%, while those patients who started treatment on Dilantin® showed a switch rate of 11.7%. These initial results appear to support the body of evidence suggesting that patients who begin treatment on a branded AED (i.e. Dilantin®) are more likely to switch treatment to a generic. However, an unexpected finding in our study suggests that those who start on Phenytoin and switch to Dilantin® are the least compliant compared to other groups in our analyses, as measured by medication possession ratios. Study investigators initially hypothesized that switches from generic to brand name Dilantin® would prove better compliance outcomes, yet this
switch showed the opposite effect and is inconsistent with previous studies conducted in this area. The greatest rates of compliance were evident in the Dilantin® treated patients who experienced no switch, and therefore remained on the brand name drug during our
one year review period. In a recent study, Gagne (2015) showed differing results with regard to brand/generic interchange, and reported confirmation that generics were more effective than their brand counterparts. Gagne (2015) provided opposing evidence that adherence was better for generic AED’s than their branded versions, and better medication adherence was associated with better patient outcomes.

In the present study, a confirmed relationship between brand or generic AED’s and compliance, inpatient hospital use, outpatient services, and ED visits was established. Non-compliant patients were 71% more likely to require in-patient services than compliant patients, had greater than twice the risk of requiring outpatient services than compliant patients, and were at a 13% greater risk for attending the ED than compliant patients. These results are in line with previous research such as observational studies by Zachry et al. 2009, which provide further evidence that AED substitution may increase use of health care services (hospitalization, ED) and strengthen the association between switching and adverse outcomes.

Equally important is the attention given to the complexity of pharmacokinetics between brand and generic AED’s. This influence has proven to be critical to the implication of AED switching. In 2011, a systematic review of the current evidence on generic substitution of AEDs was conducted by Yamada and Welty (2011), including a retrospective and prospective controlled study analysis of generic substitution of AEDs. The authors found that the majority of past retrospective studies had indicated that generic AED substitution resulted in higher use of medical services in patients with epilepsy. Similarly, our study also suggests that switching to generic may be associated with increased rates of health services utilization and lower medication possession ratios.
It is important to ensure that patients, pharmacists, prescribers and policy decision makers are aware of the potential risks of AED switching.

Although the present study had some limitations, our analyses support the existence of viable concerns and challenges associated with AED switching, for both patients and health care providers. Until formal guidelines are administered by regulatory authorities, many epilepsy patients will continue to experience the negative effects of AED switching. It is clear from our literature review and previously conducted research that many physicians are concerned about the efficacy and safety associated with unhampered substitution of generic AEDs, but may inaccurately underestimate how often generic substitution occurs (Wilner, 2002). Policies that include mandatory substitution or substitution without informed consent to both patient and provider are clearly passionate topics and warrant further discussion (Maliepaard et al., 2009). Strong recommendations regarding generic substitution from The Epilepsy Society and The American Academy of Neurology as well as other advocacy and medical authorities detail anecdotal evidence as well as clinical concerns regarding generic substitution. Several states have issued laws regarding generic substitution, while other states are considering implementation of similar legislation (Meyer et al., 2013). These groups aim to scrutinize the need for continued robust studies to evaluate generic AED substitution, and to directly examine the clinical effects of brand to generic substitution in controlled trials. Supplementing the existing body of knowledge, The Agency for Healthcare Research and Quality conducted a comparative effectiveness review in December 2011 which evaluated the effectiveness and safety of AEDs in patients with epilepsy. The review states that patients who initiate treatment with and AED have no substantive
differences in benefits or harms associated with the use of generics versus brand name products (Talati et al., 2011). The review also acknowledges that switching from a brand name AED to a generic AED may increase health care utilization, but recognizes that “this is based on controlled observational study data, which has inherent limitations substantially reducing the strength of evidence” (Talati et al., 2011).

**Study Considerations and Recommendations**

The results of this study provide additional substance and contributory evidence regarding epilepsy treatment, switching, and associated medical events, yet has its limitations. The first major limitation was the use of observational data from a managed care database, and not utilizing a randomized controlled trial design which might have included additional patient data such as disease characteristics, seizure frequency, disease duration or patients identified on multiple AED’s. Our research falls short of specifically identifying whether generic AED’s directly affect the risk of breakthrough seizures, however does include important results regarding compliance and medical care use. This study reinforces evidence showing that when an AED formulation switch occurs, additional patient monitoring is necessary and patients should be considered individually regarding the appropriateness for changes in treatment formulation. There remains important considerations when substituting AED’s as compared to other chronic or acute medications that need to be underscored. It is clear that further clinical studies are needed to determine outcomes or possible pitfalls of generic substitution to guide treatment decisions. Fortunately, there are a growing number of observational studies comparing outcomes of patients with epilepsy being treated with brand name AEDs or switched to generic to determine if there are differences in seizure control or seizure-related adverse
events. Unfortunately, however, the results of these studies are conflicting, with some showing an increased risk of seizures and medical outcomes when generic AED products were switched with brand name products (Zachary et al., 2009), and other studies showing no difference in seizure control (Gagne et al., 2015). More prospective studies analyzing the pharmacokinetics of brand to generic substitution are needed to assess the true variability of generic products. It is important to ensure that every patient with epilepsy is receiving the best health care possible, prescribers and policy makers should be aware of the current state of disease management including prescribing patterns of generic AEDs. Our observational data suggest that brand to generic switching may be associated with increased rates of health services utilization which could increase national healthcare costs. When any medication change occurs, physicians should consider intense monitoring of these patients in the absence of conclusive data that challenge the utilization of generic substitution as there is little evidence to conclude discontinued use of generic AED’s (Kesselheim et al., 2010). Based on the current knowledge and attitudes toward generic AED formulations, we conclude that both patients and physicians need to advocate for education and policy that would help better inform and enrich the medical community.
Switching and Compliance Between Brand Name and Generic Seizure Medication

Kim Dawson, DHA candidate, Medical University South Carolina
Kit Simpson, DrPh, Professor Medical University South Carolina
Jillian Harvey, PhD, Assistant Professor Medical University South Carolina
Vincent Omachonu, PhD, Professor, University of Miami

Objective: The purpose of this study is to examine: 1) the extent to which treatment switch is practiced for privately insured US patients; 2) variations in adherence to anti-epileptic drugs (AED) by brand name and generic AED switching, and 3) medical outcomes based on compliance to treatment.

Methods: A retrospective cross sectional analysis was conducted. Data were included in analyses if patients (1) were prescribed phenytoin or Dilantin® for seizure disorder, (2) experienced interchange through the use of at least one generic phenytoin prescription, (3) were at least 19 years of age or older at the time of medication interchange, and (4) had a continuous membership in their primary insurance plan for six months before and after medication interchange. Analyses assessed which patient classes had higher switch rates, medication possession ratios and medical care events.

Results: A higher switch rate was apparent for patients who started on Dilantin® over patients who started treatment on phenytoin, \( p < 0.001 \), and significant differences in rates of compliance were apparent. Non-compliant patients were 71% more likely to require in-patient services than compliant patients, \( p < 0.001 \), and 87% more likely to
have had an epilepsy related hospital admission, \( p < 0.001 \). The incidence rate of outpatient visits was 58 per 1000 person years for compliant patients; for the non-compliant patients, the incidence rate of outpatient visits was 127 per 1000 person years, \( p < 0.001 \). Non-compliant patients have a significant 13% greater risk of attending the ED than compliant patients.

**Significance:** It is important to ensure that patients, pharmacists, prescribers and policy decision makers are aware of the potential risks of AED switching. When medication change occurs physicians should consider intense monitoring of these patients. We conclude that both patients and physicians need to advocate for education and policy related to AED switching.

**Key Points:**

- Little is known about the current practice of switching from brand name to generic for anti-epileptic drugs
- Higher switch rates occur for epileptic patients initially prescribed brand name drugs than those on generic drugs
- Significant differences in rates of compliance occur based on whether patients are taking brand name or generic treatments
- Non-compliant patients were 71% more likely to require in-patient services than compliant patients, and 87% more likely to have had an epilepsy related hospital admission
- Non-compliant patients have a significant 13% greater risk of utilizing the ED than compliant patients.
- It is important to ensure that patients, prescribers, and policy decision makers are aware of the potential risks of AED switching

**Introduction**

Generic drugs have been approved for use by the Food and Drug Administration (FDA) since 1984 on the basis of demonstrated bioequivalence as compared to the brand name version. Generic drugs constitute approximately two-thirds of all prescriptions dispensed in the US and account for <20% of total pharmaceutical expenditure (Patel et al., 2011). However, concerns about the safety and bioequivalence of the generic versions of specific drugs are raised regularly (Kesselheim et al, 2015). Despite evidence supporting bioequivalence, many observational studies have shown an increase in seizure occurrence with the use of generic drug formulations (Papsdorf et al., 2009; Berg et al., 2008; Yamada & Welty, 2010). These issues have not slowed the trend by medical insurance companies to mandate use of generic drugs over brand name drugs, and commercial and government insurance programs continue to prioritize the use of generics in most circumstances (Keenum et al., 2012). Although the use of generic medications can result in substantial savings for the patient, anecdotal evidence indicates that beliefs concerning the safety and effectiveness of generic drugs compared to brand name medication may persist among patient subgroups as well as among medical practitioners (Figueiras et al., 2010; Ngo et al., 2013). Studies investigating patient perceptions of generics show that although the consumer appreciates the cost savings from generics, some are unwilling to use them, and medication compliance could be negatively affected (Kohli & Bueller, 2013, Shin et al., 2014). For example, in a study of commercially
insured adults, 94% of patients agreed that generics are less expensive than brand name, yet only 37.6% of respondents would rather take a generic than a brand name medication (Kohli et.al, 2013). This effect may be especially pronounced in subgroups of patients characterized by factors such as culture, social status, or personal and psychological characteristics, as studies also show that disadvantaged consumers may be reluctant to use generic drugs and may distrust generic medications (Keenum et. al, 2012).

While generic drug substitution may lead to immediate cost savings, these substitutions may be associated with additional expenses incurred due to increased adverse events, lack of adherence to therapy, and to the resulting failure of those therapies (Shin, 2014). Little is known about the current practice of switching from brand name to generic (G-switch) for anti-epileptic drugs (AED).

Epilepsy is one of many chronic diseases in which medication non-adherence is problematic. Studies estimate that between 30% and 60% of patients with epilepsy are non-adherent to their drug regimen, which can lead to higher seizure recurrence and increased medical resource utilization and costs (Davis, 2008).

Generic products are thought to be therapeutically interchangeable with brand name products and represent a cost effective alternative (Motola, 2006). A controversial topic is the generic substitution of AED drugs, their interchangeability and equivalency to the brand name version. A growing number of observational studies have compared patients with epilepsy being treated with brand name AEDs to those patients switched to generics to determine seizure control and adverse events, (Meyer, 2013) yet the results of these studies are conflicting (Yamada, 2011).
The purpose of this study is to examine: 1) the extent to which G-switch is practiced for privately insured US patients; 2) variations in adherence to AED medications for patients by brand name and generic AED and switching between the two, and 3) medical outcomes based on compliance to treatment. We examine factors associated with the use the antiepileptic brand drug Dilantin® manufactured by Pfizer, generic phenytoin, and generic switch in 19-64 year old patients who have private insurance.

**Methods**

Data from the 2013 MarketScan® database was used to examine switching behavior and medication adherence as measured by medication possession ratios. A retrospective cross sectional analysis of 2013 administrative data from patients covered by commercial health insurance in the United States was conducted. The MarketScan® database was used in this setting to study the use and outcomes of therapeutics. Their size allows the study of infrequent events, and their representativeness of routine clinical care makes it possible to study real-world effectiveness and utilization patterns (Schneeweiss, 2005).

For the purposes of this study, data from the MarketScan® database calendar year 2013, containing all billing records for approximately four million covered individuals, were utilized. Eligible patients were identified according to International Classification of Diseases-9-Clinical Modification (ICD-9-CM) epilepsy diagnosis, as well as treatment by a medical professional. ICD-9-CM diagnosis codes 345.9, 345.0, 345.1, 345.4, 345.5 representing seizure activity served as the primary inclusion criteria. De-identified patient
data were included in analyses if patients 1) were prescribed phenytoin or Dilantin® for seizure disorder, 2) experienced some form of interchange through the use of at least one generic phenytoin prescription in 2010, 3) were at least 19 years of age or older at the time the medication interchange occurred, and 4) had a continuous membership in their primary insurance plan for six months before and after the medication interchange. Patients were excluded if they received phenytoin for neuropathy or for a pain diagnosis, as opposed to being prescribed the drug for a seizure diagnosis. Patients who were not treated for seizure disorder with a primary care physician were not considered for inclusion within the sample. All information from the original databases for each patient was carried over to the new database. Multiple hospitalizations for the same individual counted as separate occurrences. The raw dataset contained exposure and outcome variables for 6681 patients followed for one year. Summary statistics are reported as numbers and percentages for categorical variables, and medians and ranges for continuous variables. A Chi-square test was used to assess statistical significance between groups. Logistic regression was used to examine the relationship between independent variable Dilantin and generic phenytoin and dependent variables hospital inpatient admission due to seizure, general hospital inpatient, outpatient visit due to seizure, and emergency department visit due to seizure. This analysis assessed which patient classes had higher switch rates. The Kruskal-Wallis nonparametric test assessed the difference in average medication possession ratios for 4 groups. Groups were defined as follows: Group 1, Start on Generic, end on Generic; Group 2, Start on Generic, switch to Dilantin®; Group 3, Start on Dilantin®, switch to Generic; Group 4, Start on Dilantin®, end on Dilantin®. This analysis determined if patients on generic phenytoin had lower
medication possession ratios than patients on branded Dilantin® over a one year period. In analyses of health outcomes, medication possession was the exposure variable and the analyses assessed whether patients with lower medication possession ratios were more likely to have medical care use indicative of seizure activity. Specifically, compliance with medication was defined for a patient with a ratio > 1 and non-compliant had a ratio < 1. Logistic regression and poisson regression were used to calculate odds ratios and relative risk, respectively. Compliance for this study, obtained from medication possession rates, was used to analyze patients on generic phenytoin or Dilantin® to determine if these patients had higher switch rates, medication possession ratios and medical care events. The medical care event outcomes identified were: total inpatient admissions, epilepsy related inpatient admissions, outpatient visits, and emergency department (ED) visits.

All analyses were performed using R statistical software (Vienna, Austria), and statistical significance was determined at the 0.05 level. The SAS statistical system was used to gather and summarize the data.

**Results**

Of the 6681 patients identified, 4704 patients started treatment with phenytoin, and 1977 patients began their treatment with Dilantin®. Data show that 6312 of these patients did not switch treatments, while 369 patients had switched, resulting in a 5.5% switch rate in this sample overall. Within the group who started treatment on phenytoin, 4566 patients did not switch and 138 patients switched, a switch rate of 2.9%. In the group of patients who started on Dilantin®, 1746 patients did not switch from Dilantin®,
and 231 patients did switch, resulting in a switch rate of 11.7%. This revealed a significant difference in switch rates between patients who started treatment on phenytoin compared to those who started on Dilantin® $\chi^2 (1, N = 507) = 202.60, p < 0.001$. Patients who began treatment on Dilantin® were more likely to switch treatments than those who started their treatment with phenytoin. The difference between these rates was statistically significant (OR = 4.38, 95% CI [3.52-5.44], $p < 0.001$) as shown in Figure 1.

Figure 1: Results of logistic regression analysis on medication switch rates among epilepsy patients who began treatment on generic phenytoin, compared to those who began treatment on Dilantin®. Chi-square, odds ratio were significant at $p < 0.001$. CI = confidence interval.
Data from the 6681 identified patients in the MarketScan® database was used to compute medication possession ratios for each group of interest (Group 1: Start on Generic, end on Generic; Group 2: Start on Generic, switch to Dilantin®; Group 3: Start on Dilantin®, switch to Generic; Group 4: Start on Dilantin®, end on Dilantin®). The median medication possession ratio for the total sample (N = 6681) was 99.4 (IQR = 79.65-107.80). The numbers of patients in each group were as follows; Group 1: 4566 patients, Group 2: 138 patients, Group 3: 231 patients, Group 4: 1746 patients. Analysis showed significant differences in rates of compliance, as measured by possession ratios, among the groups (Group 1: Mdn = 98.21, IQR = 76.92-107.20, Group 2: Mdn = 98.41, IQR = 69.45-113.70, Group 3: Mdn = 100.30, IQR = 86.56-111.40, Group 4: Mdn = 101.7, IQR = 86.96-108.30, p < 0.001).
Figure 2. Box plot representation of compliance rates, as measured by medication possession ratios, for epilepsy patients in all 4 groups over one year (2013). Group 1, Gen/Gen includes patients who started treatment on generic phenytoin and ended on phenytoin (no switch from generic phenytoin); Group 2, Gen/Dil includes patients who started treatment on generic phenytoin and ended on Dilantin® (switched from generic phenytoin to Dilantin®); Group 3, Dil/Gen included patients who started treatment with Dilantin® and ended on generic phenytoin (switched from Dilantin® to generic phenytoin); Group 4, Dil/Dil includes patients who started treatment on Dilantin® and ended on Dilantin® (no switch from Dilantin®). The dashed horizontal line represents the target value of 100 (representing 100% compliance). Black bars indicate the median.
value for each group. Red boxes represent the extent of the interquartile range (1\textsuperscript{st} and 3\textsuperscript{rd} interquartile values). Outliers are represented by empty circles.

Data regarding medical outcomes associated with compliance as measured by medication possession ratios was initially dichotomized by “compliance” and “non-compliance”. This dichotomization of the data revealed that from the total sample of patients prescribed generic phenytoin or Dilantin®, 3216 were compliant and 3465 were non-compliant.

Data from MarketScan® also showed 642 patients requiring in-patient hospital admissions, 173 patients with epilepsy related admissions, 433 patients having had outpatient visits, and 5832 attending the emergency department (ED).

The mean number of ED visits was similar among compliant and non-compliant patients, $M = 1.9$ and $M = 2.15$, respectively. However, the range of ED visits showed variability, with a greater range in the number of ED visits for non-compliant (range = 0.00-37.00) patients than for compliant patients (range = 0.00-19.00).

Analyses showed that 233 of the 3216 compliant patients required in-patient hospital admissions, compared to 409 of the 3465 non-compliant patients. These values result in a 7.25% admission rate for compliant patients, and an 11.80% admission rate for non-compliant epilepsy patients, a difference that was statistically significant, $\chi^2 (1, N = 442) = 39.38, p < 0.001$. Non-compliant patients were 71% more likely to require in-patient services than compliant patients, OR = 1.71, 95% CI (1.45-2.02), $p < 0.001$. These results are presented in Figure 3.
Figure 3. In-patient admission rates for compliant and non-compliant epileptic patients, according to medication possession ratios. These data were statistically significant, $p < 0.001$.

Data regarding the number of epilepsy related hospital admissions for compliant and non-compliant epileptic patients showed that 58 compliant epileptic patients had epilepsy related hospital admissions during the one year period, while 115 non-compliant patients were admitted for epilepsy related reasons during the same year. The admission rates for compliant vs. non-compliant patients were 1.80% and 3.32%, respectively. This difference was statistically significant, $\chi^2 (1, N = 173) = 14.59, p < 0.001$. As is shown in
Figure 4, non-compliant patients were 87% more likely to have had an epilepsy related hospital admission than compliant patients, OR = 1.87, 95% CI (1.36-2.57), \( p < 0.001 \).

Figure 4. Epilepsy related hospital admission rates for compliant and non-compliant patients, according to medication possession ratios. These data were statistically significant, \( p < 0.001 \).

Compliant patients experienced 188 outpatient visits overall, while non-compliant patients experienced 439 outpatient visits. Data also revealed that, for compliant patients, the incidence rate of outpatient visits was 58 per 1000 person years; for the non-compliant patients, the incidence rate of outpatient visits was 127 per 1000 person years.
(RR = 2.17, 95% CI [1.83-2.57], p < 0.001). These differences, shown in Figure 5, were statistically significant.

Figure 5. Incidence rates of outpatient visits for compliant and non-compliant epileptic patients prescribed generic phenytoin or Dilantin® in 2013

Compliant patients exhibited 6110 ED visits overall as a group, while non-compliant patients attended the ED 7440 times as a group within this one year period. The incidence rates of ED visits for compliant and non-compliant patients were 1900 and 2147 per 1000 person years, respectively (RR = 1.13, 95% CI [1.09-1.17], p < 0.001).
This data, represented in Figure 6, also suggests that non-compliant patients have a significant 13% greater risk of attending the ED than do compliant patients.

**Figure 6. Incidence rates of emergency department visits for compliant and non-compliant epileptic patients prescribed generic phenytoin or Dilantin® in 2013**

Continuous variable data for medication possession revealed that a 1% positive change in compliance resulted in a statistically significant 1% decrease in the number of in-patient hospital admissions, OR = 0.99, 95% CI (0.98-0.99), p < 0.001. Additionally, a 10% positive change in compliance corresponded to a 12% decrease in in-patient
hospitalization which was also statistically significant, $OR = 0.88$, 95% CI (0.86-0.90), $p < 0.001$. Similarly, a 1% positive change in compliance resulted in a 2% decrease in epilepsy related hospital admissions, $OR = 0.98$, 95% CI (0.98-0.98), $p < 0.001$. A 10% positive change in compliance was related to a 16% decrease in epilepsy related admissions, $OR = 0.84$, 95% CI (0.81-0.88), $p < 0.001$. Analyses of continuous outpatient visit data indicated that a 1% positive change in compliance resulted in a statistically significant 1% decrease in the number of outpatient visits ($OR = 0.99$, 95% CI [0.98-0.99], $p < 0.001$), while a 10% positive change in compliance resulted in a 13% decrease in outpatient visits which was also statistically significant ($OR = 0.87$, 95% CI [0.85-0.89], $p < 0.001$). Data regarding the number of ED visits in epilepsy patients revealed that a 1% positive change in compliance corresponded to a less than 1% decrease in the number of ED visits, yet this change was statistically significant, $OR = 1.00$, 95% CI (1.00-1.00), $p < 0.001$. A 10% positive change in compliance resulted in a statistically significant 3% decrease in ED visits, $OR = 0.97$, 95% CI (0.96-0.97), $p < 0.001$. These data, despite their significance, suggest that ED visits may be the least affected by increased compliance.
Discussion

This study was designed to provide an assessment of brand name Dilantin® and generic phenytoin, comparing switch rates, compliance, and seizure related health outcomes, as there is growing concern about the efficacy and safety of generic AED’s (Haskins et. al, 2005). Health policy and managed care practices often focus on cost containment and may encourage the use of generics because they are less expensive than their branded counterparts. What may be greatly underestimated are the additional unexpected costs associated with switching drugs and drug taking compliance, which can cause both an increase in adverse events and increased medical use, such as hospitalization and emergency room visits.

Results from this large managed care database demonstrated that patients treated with phenytoin had a lower switch rate than those patients who started treatment on Dilantin®. These initial results support existing evidence suggesting that patients who begin treatment on a branded AED (i.e. Dilantin®) are more likely to switch treatment to a generic. However, an unexpected finding in our study suggests that those who start treatment on phenytoin and switch to Dilantin® are the least compliant compared to other groups in our analyses. Study investigators initially hypothesized that switches to brand name Dilantin® would prove better compliance outcomes, yet this switch showed the opposite effect, a finding which is inconsistent with previous studies conducted in this area. The greatest rates of compliance were evident in the Dilantin® treated patients who experienced no switch, and therefore remained on the brand name drug during our one year review period. A recent study by Gagne and colleagues (2015) showed differing results with regard to brand/generic interchange. This group reported that adherence was
better for generic AED’s than their branded versions, and that better medication adherence was associated with better patient outcomes. Additionally, these authors noted that generics were more effective than their brand name counterparts, further alluding to the need for additional research in this area.

Additionally, the present study confirmed a relationship between brand or generic AED compliance and inpatient hospital use, outpatient services, and ED visits. Non-compliant patients were significantly more likely to require in-patient services than compliant patients, had greater than twice the risk of requiring outpatient services than compliant patients, and were at a significantly greater risk for attending the ED than compliant patients. These results are in line with previous research (Zachry et.al, 2009) which provide further evidence that AED substitution may increase use of health care services and strengthen the association between switching and adverse outcomes.

Furthermore, a systematic review of the current evidence on generic substitution of AEDs (Yamada et al., 2011) including both retrospective and prospective controlled study analyses of generic substitution of AEDs, found that the majority of retrospective studies had indicated that generic AED substitution resulted in higher use of medical services in patients with epilepsy. Our study, as well as those noted here, suggest that switching to generic may be associated with increased rates of health services utilization and lower medication possession ratios. It is important to ensure that patients, pharmacists, prescribers and policy decision makers are aware of the potential risks.

Our analyses support existing concerns and challenges associated with AED switching, for both patients and health care providers. Until formal guidelines are administered by regulatory authorities, many epilepsy patients will continue to
experience the negative effects of AED switching. It is clear from our literature review that many physicians are concerned about the efficacy and safety associated with unhampered substitution of generic AEDs, but may inaccurately underestimate how often generic substitution occurs (Wilner, 2002). Policies that include mandatory substitution or substitution without informed consent to both patient and provider are clearly passionate topics and warrant further discussion (Maliepaard et al., 2009). Strong recommendations regarding generic substitution from The Epilepsy Society and The American Academy of Neurology as well as other advocacy and medical authorities detail anecdotal evidence as well as clinical concerns regarding generic substitution. Several states have issued laws regarding generic substitution, while other states are considering implementation of similar legislation (Meyer et al., 2013). Supplementing the existing body of knowledge, The Agency for Healthcare Research and Quality conducted a comparative effectiveness review in December 2011, which evaluated the effectiveness and safety of AEDs in patients with epilepsy. The review states that patients who initiate treatment with and AED have no substantive differences in benefits or harms associated with the use of generics versus brand name products (Talati et al., 2011). The review also acknowledges that switching from a brand name AED to a generic AED may increase health care utilization, but recognizes that “this is based on controlled observational study data, which has inherent limitations substantially reducing the strength of evidence” (Talati et al., 2011). These groups aim to scrutinize the need for continued robust studies to evaluate generic AED substitution, and to directly examine the clinical effects of brand to generic substitution in controlled trials.
The results of this study provide additional substance and contributory evidence to the area of research regarding epilepsy treatment, switching, and associated medical events. Our study, however, does have its limitations. The first major limitation was the use of observational data from a managed care database, and not utilizing a randomized controlled trial design, which might have included additional patient data such as disease characteristics, seizure frequency, disease duration or patients identified on multiple AED’s. Our research falls short of specifically identifying whether generic AED’s directly affect the risk of breakthrough seizures, however does include important results regarding compliance and medical care use.

This study reinforces evidence showing that when an AED formulation switch occurs, additional patient monitoring is necessary and patients should be considered individually regarding the appropriateness for changes in treatment formulation. There remain important considerations when substituting AED’s as compared to other chronic or acute medications that need to be underscored. It is clear that further clinical studies are needed to determine outcomes or possible pitfalls of generic substitution to guide treatment decisions. Fortunately, there are a growing number of observational studies comparing outcomes of patients with epilepsy being treated with brand name AEDs or switched to generic to determine if there are differences in seizure control or seizure-related adverse events. Unfortunately, however, the results of these studies are conflicting, with some showing an increased risk of seizures and negative medical outcomes when generic AED products were switched with brand name products (Zachry et al., 2009) and other studies showing no difference in seizure control (Gagne et al., 2015). More prospective studies analyzing the pharmacokinetics of brand to generic
substitution are needed to assess the true variability of generic product use and switch. It is important to ensure that every patient with epilepsy is receiving the best health care possible, and thus prescribers and policy makers should be aware of the current state of disease management including prescribing patterns of generic AEDs. When any medication change occurs, physicians should consider intense monitoring of these patients in the absence of conclusive data that support or challenge the utilization of generic substitution (Kesselheim et al., 2015). Based on the current knowledge and attitudes toward generic AED formulations, we conclude that both patients and physicians need to advocate for education and policy that would help better inform and enrich the medical community.
References


Epilepsy at a Glance,


