

Transient Risk of Breakthrough Seizures Associated with Phenytoin
Refilling and Switching

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Abstract

Background

Generic substitution is prevalent in the U.S.; however, clinicians and patients remain wary of use of generic products for drugs with narrow therapeutic indices. Epileptic seizure control is an example of a condition which requires consistent blood concentrations of medications; this cannot be assured when patients switch among medications from different manufacturers and even between product lots.

Objective

We aimed to quantify the transient risk of seizure activity attributable to refills and switches of phenytoin from same and different manufacturers.

Methods

We conducted a case-crossover study using administrative claims from the Truven MarketScan Commercial Claims and Encounters database in 2010-2012. We identified individuals who had at least 1 emergency room visit or hospitalization with a primary diagnosis of epilepsy or seizure. We required the cases to have epilepsy and at least 2 phenytoin prescription dispensed during the 6-months enrollment in their insurance plan before the first observed emergency room visit or hospitalization (index date). The case period was defined as the 7 days prior to the index date and the control period as 7 days prior to the case period. We used conditional logistic

regression to estimate the odds ratio.

Results

We identified 717 eligible individuals and 143 were discordant cases contributing to the analysis. 38% were females and the median age was 48 years old (interquartile range (IQR) 18 years). Individuals, who refilled phenytoin of the exact same dosage form and strength by the same manufacturer, had a 67% higher odds [odds ratio (OR) 1.67; 95% confidence interval (CI) (1.14-2.44)] of seizure-related events, when the prescription was filled in the 7 days prior to the index date rather than earlier. Individuals who switched phenytoin products had a non-significant 21% increased odds [OR 1.21; 95% CI (0.60-2.46)] of an event. The refill-adjusted risk for switching was close to the null [OR 0.73; 95% CI (0.33-1.63)].

Conclusions

Our results suggest that the period after refills and switches may be a high risk period for epileptic patients. Equal attention should be given to the cautious monitoring after refilling and switching and longer days of supply should be encouraged.

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1 Introduction

To balance the increasingly heavy economic burden of healthcare and gradually increased patients needs, generic substitution has been prevalently used in the US. In 2013, 86 percent of all prescriptions filled in the U.S were generic drugs. According to the legislation in 1984, there are 12 states where generic substitution is mandatory by law.¹

To ensure the bioequivalence to their innovators, FDA requires generic drug manufacturers to prove their products have equivalent bioavailability. FDA guidance has recommended that the confidence intervals for the area under the curve (AUC) and maximum concentration (C_{max}) of the generic drug should be within 80% to 125% of the confidence intervals of branded drug after log transformation, within which the difference in blood concentration for most drugs is considered not to be clinically significant.²

Despite of the stringent requirements by licensing agency, several surveys showed negative perceptions of generic drugs from consumers and prescribers for its efficacy and safety issues.³⁻⁷ This kind of concern is especially greater for drugs with narrow therapeutic index (NTI), of which small variation in dosage may result in a lack of efficacy or toxicity.

Phenytoin, as one of the mainstream antiepileptic drugs (AEDs), is commonly considered as an NTI drug. A slight change in its absorption will result in great adverse health outcomes.⁸⁻⁹ Besides, it has the characteristics of low water solubility

and non-linear pharmacokinetics, all risk factors to increase the likelihood of fluctuation in serum concentration and incidence of uncontrolled seizures when there is minor products change.¹⁰

As the fourth most common neurological disorder in the United States after migraine, stroke, and Alzheimer's disease, epilepsy is a complex spectrum of disorders that affects people of all ages. According to a report issued by IOM 2012, 2.2 million people in the United States have epilepsy. Each year 150,000 new cases of epilepsy are diagnosed and 1 in 26 people in the United States will develop epilepsy at some point in their lifetime.¹¹ A study in 2008 showed seizure accounts for 1 million Emergency Department (ED) visits annually [95% confidence interval (CI) (926,000–1,040,000)], or 1% of all ED visits in the US.¹² The contribution of “breakthrough seizures” among chronic epileptic patients to the burden of seizure care in the ED setting is unknown. A study suggested that only 6.8% of seizures in the ED were due to epilepsy.¹³ However, a smaller study in a different setting found that 46% of seizure visits to an urban ED were by individuals with known epilepsy.¹⁴

Although epilepsy is a chronic disorder that may not be cured, it can be controlled. The ultimate goal of treatment is to maintain the patients' normal lifestyle and reduce the epilepsy-related morbidity and mortality by the avoidance of seizures. Recent studies have shown that up to 70% of newly diagnosed individuals with epilepsy can be successfully treated (i.e. completely controlled seizures) with AEDs.¹⁵ When the long-term remission has been obtained, it becomes important to avoid even a single

breakthrough seizure. Previous studies showed that after a period of control, just a single breakthrough seizure can have great impact on patients' social and personal life, like loss of employment, loss of self-esteem, and even risk of death.¹⁶⁻²⁸ Therefore, epileptic treatment may have higher risk of negative health consequences when there is any slight loss of efficacy by changing product.¹⁰

Corresponding to the above mentioned aspects, the American Academy of Neurology opposes antiepileptic generic substitution without physician approval.²⁹ Breakthrough seizures have been attributed to switching prescriptions between brand-name and generic phenytoin.³⁰ In case reviews, participated in by sixty-nine physicians, fifty of their patients, whose conditions were well-controlled on a brand-name antiepileptic drug, subsequently experienced a breakthrough seizure or increased seizure frequency after switching to a generic without other provoking factors.³¹ Inconsistent evidence emerged from observational studies and clinical trials. The retrospective studies showed a significant association between generic substitution and increased utilization of healthcare sources, while prospective trials showed no significant difference in seizure frequency between brand-name and generic drugs.³²⁻³³

The risk was not only elevated when patients switched among medications from different manufacturers but even when refilled between different product lots from the same manufacturer. A case-crossover was conducted by Gagne et al in 2010 to evaluate the risk for breakthrough seizures associated with both refilling and

switching. In their study, switching was treated as a special case of the refilling process. Enabled by the unique study design, they showed that refilling itself significantly increased the transient risk of seizure-related events. An elevated risk was also observed in switching, but the association was no longer significant in this much smaller group. And the risk was similar after comparing the risk for switching to that for refilling.³⁴

In this study we aimed to use a standard unidirectional case-crossover design to quantify the transient risk of seizure activity attributable to refills and switches of phenytoin from same and different manufacturers and of same or different dosage form and strength. We first tested the hypothesis that patients, who refill a phenytoin product of the exact same dosage form and strength by the same manufacturer, have a higher risk of seizure-related emergency room visits or hospitalizations when the refilling occurs during the case period than during the control period. We further tested the hypothesis that patients who switch to a phenytoin product of different dosage form, strength or manufacturer have a higher risk of seizure-related outcomes when the switching occurs during the case period than during the control period. At last, we examined the hypothesis that the risk associated with switching is greater than the risk with refilling.

2 Methods

2.1 Data source

We used Truven Health MarketScan Commercial Claims and Encounters Database from 2010 to 2012. It contains data from active employees, early retirees, Consolidated Omnibus Budget Reconciliation Act (COBRA) continuees, and dependents insured by employers-sponsored plans (i.e., persons not eligible for Medicare) in the United States. The dataset captures individual-level information about clinical utilization, expenditures and enrollment across inpatient, outpatient and prescription drug services in all 8 tables. Patients were identified in inpatient admission table and outpatient services table, which contain data including diagnostic codes and date on which service incurred. An outpatient pharmaceutical claims table was also used to identify medication refill records. All tables used were linked by a personal enrollment identification number unique to each enrollee. The MarketScan data are completely de-identified to protect patient confidentiality; their use is considered exempt from review by institutional review board of the Johns Hopkins Bloomberg School of Public Health.³⁵

2.2 Study Design

A case-crossover (CCO) study was used to examine the relationship between the seizure-related emergency room visits or hospitalization and phenytoin refilling and switching. CCO is a retrospective observational study. It is a kind of case-only design which restricts to cases, that is, only people who experienced the outcome of interest

at least once during the follow-up were included in the study. The term “crossover” is used because the analysis is restricted to people who had both exposed and unexposed person-time and therefore crossed between two or more exposure levels.³⁶ Instead of selecting matched controls based on some measured covariates or time points, CCO uses cases as their own controls, by assuming an exposure risk window proximate to the event as the case period and the time beyond (either earlier or even after the event) as the control-period. The investigator then compares the exposure distribution in the case periods to the control periods. The CCO method has been commonly used to assess the transient effects of eruptive or intermittent exposure like prescription refilling and switching, or vaccination. This design by nature accounts for the measured and unmeasured time-invariant confounders such as sex and race, and some time-variant but not fast-changing confounders like age would be weak enough to be ignored if the exposure risk window is very short and the case period is close to the control period.³⁷⁻³⁹

In our study, we used a standard CCO, in which time was viewed relative to the date of the outcome event and only one control-period was selected from the time before the case-period.

2.3 Study population

We started by identifying patients who had at least one emergency room visit or hospitalization with a primary diagnosis of International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9) codes 345.xx (epilepsy and recurrent

seizures) or 780.3x (convulsions), but not code 345.6x (infantile spasms), between 2010 and 2012 in the outpatient or inpatient data files. The first identified hospitalization or emergency visit was considered to be the index date for all analyses. Individuals whose index date was in the first 6 months in 2010 were excluded to ensure that exposure and covariates data were available for the 180 days prior to the index date for each case. To make sure that phenytoin was used for treatment of epilepsy, rather than prevention of seizures such as after surgery or trauma, we further required individuals to have had at least one outpatient visit (not to emergency rooms) with the above mentioned ICD-9 codes prior to the index date. Lastly, we required at least two prescriptions of anticonvulsant hydantoin derivatives dispensed on separate days during the 180-days of constant enrollment prior to the index date. Relevant medications were identified by their National Drug Classification (NDC) codes. Patients who were concurrently using a medicine from a different class of AEDs but who did not initiate, terminate, or change the medicine during the case and control periods were included in the study. Patients with changes in these other AEDs medications in the relevant time periods were excluded. A grace period of 2 days was granted to the gap between the two refills and the patients who had a medication discontinuation larger than 2 days were excluded from the analysis.

2.4 Case and control periods definition

In the primary analysis, for both refilling and switching, we defined a 1-day induction period as the minimum time needed to experience a seizure-related outcome

(one emergency room visit or hospitalization with a primary diagnosis of epilepsy or seizures) after the exposure in the population, which was consistent with a former study.³⁴ We used a prespecified 7-day risk window immediately preceding the induction period as the case period and another 7-day risk window right before the case period as the control period (Figure 1). This was chosen based on the pharmacokinetics characteristics of phenytoin and a study in the past.⁴⁰⁻⁴¹

2.5 Exposure definition

A *refill* was defined as a filled phenytoin prescription for a given NDC code that was preceded by a filled prescription with the identical NDC code, indicating dispensing a phenytoin product of the same dose and strength by the same manufacturer. A *switch* was defined as a filled phenytoin prescription with a given NDC code that was preceded by a filled prescription for the same medication but with a different NDC code, indicating dispensing a phenytoin product of a different dose, strength or manufacturer. The date of refilling or switching was defined as the date of dispensing the second or subsequent prescription and it must be covered by the previous prescription. Days-covered by a prescription was defined as the date of refilling or switching of a prescription plus its days supply plus a 2-day grace period. Branded and generic phenytoin were distinguished by a generic drug indicator variable in the MarketScan data.

2.6 Confounders definition

To control for the confounding by indication in the observational study, the number

of visits to neurologists was used as a proxy for the disease severity of epilepsy and measured in both case and control periods. Another important source of confounding was the drug and drug interaction. The interaction caused by the concurrent initiation or termination of other classes of AEDs during the case and control periods was handled by the restriction in study design; the concurrent initiation or termination of medication for non-epileptic conditions (i.e. Non-AEDs) was controlled in the analysis. It was identified by different values of a therapeutic class variable between the two refills. This therapeutic class variable is a 3-digit code that indicates the therapeutic/pharmacologic category of the drug product based on the American Hospital Formulary Service Classification Compilation (AHFSCC) Therapeutic Class with a range of value from 1 to 999.

2.7 Statistical methods

Conditional logistic regression was used to calculate the risk of seizure-related outcomes associated with phenytoin refilling and switching before and after controlling for the confounding by physician visits and concurrent medications change of Non-AEDs, under the assumption that they were not affected by their previous status.⁴² The dependent variable in the model followed a binomial distribution and was given a value of 1 for case period and 0 for control period. The independent variable, “exposure”, was a dichotomous indicator for exposure status, which was given a value of 1 when a refill or switch occurred and a value of 0 when neither refill nor switch occurred during the case or control period. An interaction

term between “exposure” and “group” was also added to the right side of the model, where “group” was a dichotomous indicator for switching status, and had a value of 1 when a switch occurred and a value of 0 when a refill occurred during the case or control period; Thus the coefficient of “exposure” was an estimate of the odds ratio (OR) of seizure-related outcomes associated with refilling only, and the summation of the coefficients of “exposure” and “group” was an estimate of the OR of seizure-related outcomes associated with switching alone, on log scale. The use of this product term enabled us to adjust for the within-manufacturer between-lot variability and other factors involved in the prescription refilling or switching process and generated a refill-adjusted estimate of the risk of seizure-related outcomes associated with switching. Number of physician visits to neurologists was included to the adjusted model as an ordinal variable and concurrent medication change of Non-AEDs was included as a binary variable. The performances of crude and adjusted models were compared by Likelihood Ratio Test (LRT). Statistical packages SAS 9.3 and STATA 12.0 were used for all the analyses.

2.8 Sensitivity analysis

For sensitivity analyses, we first varied the case and control periods from 7 days to 10 days. The grace period was not extended because we believed that any gap greater than 2 days between 2 sequential refills would lead to a substantial change in blood concentration of phenytoin and that subsequent seizures would be attributable to medication non-adherence. This stringent definition of medication compliance was

chosen based on the narrow therapeutic range of phenytoin.⁴¹ Secondly, we limited the analysis to individuals using phenytoin as monotherapy during the case and control periods, that is, patients who did not have concurrent AEDs in other classes. In the third sensitivity analysis, we adjusted the dates of refilling or switching for the stacked (or left-over) pills among patients who refilled or switched while there was still medication on hand from the previous prescription. Lastly, we excluded the switches between different dosages or strengths.

3 Results

A total of 717 cases were identified in the MarketScan data. Their characteristics are summarized in Table 1. The patients were predominantly middle-aged men who had one physician visit to their neurologists and one phenytoin prescription dispensed during the case and control periods. As in a matched case-control study, only the cases with discordant exposure status between the case and control periods contributed information to the analysis. Therefore, 143 of 717 individuals were included in the primary analysis. The majority were also middle-aged men, who had one phenytoin dispensed, but most of them didn't have any concurrent medication change of non-AEDs or physician visits to their neurologists during the periods (Table 1). The distribution of phenytoin refills and switches in the 180 days prior to the index date was shown in Figure 2 and 3. Only the refill or switch closest to the index date of each 717 individual was counted.

The results of our primary analyses are shown in Table 2. Both individuals who refilled phenytoin and those who switched among phenytoin products within the case window had increased odds of a seizure-related emergency room visit or hospitalization relative to those who refilled or switched outside of the case window. In the crude analysis, the OR related to a refill alone was 1.67 with 95% CI (1.14-2.44) and for a switch alone the OR was 1.21 [95% CI (0.60-2.46)].

Accounting for the risk associated with a refilling process, i.e., between-lot variability and other factors, a medication switch had 0.73 times the risk of

seizure-related outcomes than the risk associated with refilling and the 95% CI for this refill-adjusted OR was (0.33-1.63).

In the adjusted analysis, after controlling for two confounders, the OR related to refilling decreased to 1.47 [95% CI (0.93-2.30)]. The OR associated with switching also declined to 1.10 [95% CI (0.53-2.29)]. The refill-adjusted OR was 0.76 [95% CI (0.33-1.69)], quite close to the crude analysis. The likelihood ratio test indicated that the adjusted model fit no better than the crude model ($p=0.56$), so only unadjusted models were used in the subgroup and sensitivity analyses below.

Regardless of whether the refill was a refill of a branded product or a refill of a generic phenytoin product, the risk of seizure-related outcomes was higher when the refilling occurred during the 7-day case period than during the 7-day control period, but this relationship was only statistically significant for the more prevalent generic refilling. For different subcategories of switching, the highest risk, an OR 3.00 [95% CI (0.61-14.86)], was observed for individuals switching between different generic products. The risk was also elevated for those switching from a generic product to a branded phenytoin, with an OR of 1.25 [95% CI (0.34-4.65)]. ORs of 0.83 [95% CI (0.25-2.73)] and 0.50 [95% CI (0.05-5.51)] were seen, respectively, among individuals switching between branded phenytoin products, and switching from a branded product to a generic phenytoin (Table 3).

Table 4 includes all the results from our sensitivity analyses. After extending the risk period from 7 to 10 days, a similar increased risk was observed. The OR for

refilling alone was 1.40 [95% CI (1.01-1.93)] and for switching alone 1.11 [95% CI (0.59-2.10)]. The refill-adjusted OR was 0.79 [95% CI (0.39-1.59)].

By excluding the individuals that were on other classes of AEDs along with phenytoin during the case or control period, the OR among individuals on phenytoin monotherapy was 1.46 [95% CI (0.96-2.22)] for refilling and 1.00 [95% CI (0.43-2.31)] for switching, when the 7-day risk windows were used in case and control periods. The refill-adjusted OR was 0.69 [95% CI (0.27-1.74)]. Comparable results were seen when 10-day risk windows were applied.

We also adjusted the date of refilling or switching from the actual refill or switch date, on which a patient filled his/her prescription at pharmacies, to the date, on which the last dose of his/her previous prescription was supposed to be taken, if the patient refilled or switched phenytoin earlier than the day of last dose. Refilling alone was associated with 1.09 [95% CI (0.86-1.38)] times risk of seizures-related outcomes and switching alone was associated with 0.82 times of the risk of refilling [95% CI (0.41-1.65)], when 7-day risk windows were used, and similar results were observed in 10-day risk periods.

Last, after excluding cases whose refill or switch involved a change in dosage form or strength or both, the OR for seizure-related outcomes associated with refilling alone was 1.67 [95% CI (1.14-2.44)] and 1.50 [95% CI (0.25-8.98)] for switching alone, when using 7-day risk windows. The refill-adjusted OR was 0.90 [95% CI (0.14-5.61)]. In 10-day risk windows, the OR for a refill was 1.40 [95% CI

(1.01-1.93)] and a switch was 2.00 [95% CI (0.37-10.92)]. The refill-adjusted OR increased to 1.43 [95% CI (0.25-8.06)]. Although the point estimates of refill-adjusted OR for switching were seen on different sides of 1 depending on the length of the risk window, their wide 95% confidence intervals largely overlapped.

4 Discussion

In this study, we found that individuals, who refilled a phenytoin product of the exact same dosage form and strength by the same manufacturer, were at a 67% increased risk of seizure-related events during a short period after refilling than the time beyond during which they continued taking their current prescription. Although after adjustment for plausible confounders, this point estimate was no longer statistically significant and moved towards the null with a widened confidence interval, the LRT test gave more credibility to the results from the crude analysis and it supported a statistically increased risk associated with refilling. A similarly elevated risk, albeit with a wide confidence interval, was also seen when switching to a phenytoin product of different dosage form, strength or manufacturer. After accounting for the risk associated with refilling process, switching alone did not pose additional increased risk of seizure-related outcomes, for the refill-adjusted OR was around 1.

The possible mechanism for this observation was proposed in a previous study by Gagne et al in 2010. Two of main explanations they discussed were the within- and between-manufacturer variability in bioavailability and the patients' behavioral aspects which trigger pharmacotherapy discontinuity.³⁴ The between-manufacturer variability between approved generic drugs and their innovators has been reviewed in a study funded by the US Food and Drug Administration (FDA) in 2009. Bioequivalence was measured by the evaluation of Cmax and AUC,

representing drug rate and extent of absorption. A small difference was found. The average difference of Cmax and AUC between generic drugs and their innovators was 4.35% and 3.56%, respectively.⁴⁶ However, some researchers argued that bioequivalence implies but does not guarantee that a drug will have the same therapeutic and adverse effects as the reference drug, due to the permitted range of bioavailability for generics, small numbers of relatively young healthy volunteers in the evaluation methods as well as individual variation in the response to the drug.²⁰ Similar fluctuations in the bioavailability and other attributes may be expected between different lots of an identical product manufactured by the same company.⁴⁷⁻⁵⁰ Patients are also vulnerable to non-adherence during the refilling and switching process; confusion and mistrust caused by the change of drug appearance may lead to medication discontinuation and result in breakthrough seizures.⁴³⁻⁴⁵

Our results are consistent with the study by Gagne et al., but their results showed a greater magnitude of risk, in which refilling alone was associated with around 2.1- to 2.3- fold increase in the odds of seizure-related outcomes, and a 4% to 19% increase in risk associated with the refill-adjusted effect of switching between products from different manufacturers. However, there are several differences between these 2 studies that should be noted. Their study was conducted using an administrative database from Canada with data from 1996-2005. Different manufacturing practices in 1990s may prevent the application of their results to the patients today. Besides, the utilization patterns in their study were very different from what we observed in the US

dataset. In our data, most patients received 30-day supplies of the drug; the majority of their prescriptions fills were with 90-day supplies. This enabled them to have the power to examine the relationship in a much longer risk window, 21/28 days, compared to the 7 days in our study. Their study population was older and had more females than our study. Moreover, as they mentioned in their paper, the bioequivalence requirements of the US FDA are more stringent than those of Health of Canada. The requirements established by FDA was intended to ensure that the differences in bioavailability between bioequivalent products, i.e., the between-manufacturer variation are no greater than between-lot within-manufacturer variation.⁵¹⁻⁵² This would result in our seeing fewer difficulties at the time of refill than what was seen in the Canadian study. Besides, Gagne et al included refilling and switching of multiple classes of antiepileptic drugs with different pharmacokinetic characteristics and the 21/28-day risk window was applied despite of classes.³⁴ They also defined “switch” more strictly than we did since they required the dosage form and strength to be held constant, so cases who switched could only be included if the product came from different manufacturers. Other similar results to the risk for switching was found in a nested case-control study, in which a crude OR of 1.51 [95% CI (1.29-1.76)] and an adjusted estimate of 1.08 [95% CI (0.91-1.29)] were calculated.⁵³

There are several limitations we would like to point out in our study. First, by using ICD-9 codes from emergency room visits and hospitalizations to identify our cases,

only the breakthrough seizures severe enough to require inpatient care were recorded; seizures at home would not be captured. The accuracy or correctness of the ICD-codes recorded by healthcare providers is unknown but is likely to be highly sensitive and specific in a population of patients with epilepsy. The record of a patient's refilling or switching in the claims data does not necessarily indicate what the patient was taking and how complete was his/her adherence. Even if a patient refilled medication at the end of previous prescription, he/she may not take the medication immediately. Lastly, the size of our study population was relatively small, especially the group that switched among products. This lack of power brought wide confidence intervals to our estimation and added more uncertainty to some of our results.

However, our study also has the following strengths. Although our sample size was relatively small, we began with a claims data from 70 million individuals. It is unlikely that other data would allow investigator to identify many more patients meeting the specified criteria. We chose to use a case-crossover design, which is considered to be efficient on its own. According to a review by Maclure et al., fewer than half as many subjects may be needed in a case-crossover study as in a traditional case-control study because the same results may be obtained without the need to select traditional controls and each case can provide at least one control time.³⁸ Another difference from the traditional case-control study is its unidirection design, in which the control period is selected to be before the time of the case period only,

which makes the results less affected by reverse causality.³⁶ Although this design is susceptible to exposure-trend bias, our decision to use a short risk window in the case and control periods, as well as their close placement to each other, should make this risk negligible. Our selection of one single control-period from the time before the case-period was the most efficient control sampling strategy in terms of our prespecified length of the risk window and induction period, the degree of within-person confounding and the quality of data available.⁵⁴ Our study more carefully controlled for the confounding from drug-drug interactions by taking the termination of a drug into consideration, apart from initiation. In our study, only one class of anti-epileptics was studied and the prespecified risk-window was defined based on the drug's pharmacokinetic characteristics, hopefully reducing misclassification of the exposures.⁴⁰ This single class design also prevented the transient effect of refilling or switching from being offset by variations of pharmacological characteristics among different classes, if the effects of these variations were in opposite directions. Despite of the relatively small sample size, there was no empty cell in any subcategory of refilling and switching. This enabled us to show the individual risk associated with each subcategory in the subgroup analysis.

Based on our findings, we suggest that patients with epilepsy and healthcare providers should be cautious during the first 7-10 day after phenytoin refilling and switching as this is a higher risk period for severe seizure activity. Clinicians and payers should encourage the extension of the commonly prescribed 30 days of supply

to 90 days of phenytoin to reduce the refill frequency. The results of our study are expected to be relevant to European patients as well, considering the European Medicines Agency has the same requirements of bioequivalence as the US FDA.⁵⁵

To conclude, we found an increased risk of seizure-related outcomes when refilling a phenytoin product of the exact same dosage form and strength by the same manufacturer. Switching to a phenytoin product of a different dosage form, strength or manufacturer has much in common with the refilling process and was also found to be associated with an elevated risk of seizure-related events. However, extra risk arising from between-manufacturer differences, which is a concern of patients and physicians, was not seen in our study.

5 Tables

5.1 Table 1 Characteristics of study population and discordant cases in the primary analysis

Characteristic	Study population ^a	Discordant cases ^b
Age at index date, median (IQR ^c)	48 (18)	47 (19)
Female, n (%)	271 (37.8%)	49 (34.3%)
Number of phenytoin dispensed during primary 14-day study period, median (IQR)	1 (0)	1 (0)
No concurrent medication change of non-AEDs ^d during 7-day case period, n (%)	414 (57.7%)	136 (95.1%)
No concurrent medication change of non-AEDs during 7-day control period, n (%)	418 (58.3%)	138 (96.5%)
Number of physician visits during 7-day case period, median (IQR)	1 (0)	0 (0)
Number of physician visits during 7-day control period, median (IQR)	1 (0)	0 (0)

a. Number of study population, N_s=717.

b. Number of discordant cases contributed to the analysis, N_a=143.

c. IQR, interquartile range.

d. Non-AEDs, non-antiepileptic drugs.

5.2 Table 2 Odds ratios (95% CIs) for the relationship between phenytoin refilling and switching and seizure-related outcomes for primary analyses*

	Crude analysis ^a		Adjusted analysis ^b	
	Odds ratio (OR)	95% Confidence interval (CI)	Odds ratio (OR)	95% Confidence interval (CI)
Refill^c	1.67	(1.14-2.44)	1.47	(0.93-2.30)
Switch^d	1.21	(0.60-2.46)	1.10	(0.53-2.29)
Refill-adjusted odds ratio for switching	0.73	(0.33-1.63)	0.76	(0.33-1.69)
Number of Physician visits			0.88	(0.33-2.29)
No concurrent medication change of non-AEDs^e			1.39	(0.75-2.58)

* N_s=717; N_a=143.

a. Unadjusted model in the primary analysis:

$$Outcome = \beta_0 + \beta_1 \times Exposure + \beta_2 \times Exposure \times Group.$$

b. Adjusted model in the primary analysis: $Outcome = \beta_0 + \beta_1 \times Exposure + \beta_2 \times Exposure \times Group + \beta_3 \times Number\ of\ physician\ visits + \beta_4 \times Non - AEDs\ medication\ change.$

c. Refill of phenytoin for the same strength, and dosage form from the same manufacturer.

d. Switch to a different strength, dosage form or manufacturer.

e. Non-AEDs, non-antiepileptic drugs.

5.3 Table 3 Odds ratios (95% CIs) for the relationship between phenytoin refilling and switching and seizure-related outcomes for subgroup analyses *

Exposure type	N _a	Odds ratio (95% CI)
Refill		
Generic (GG)	74	1.74 (1.08-2.79)
Branded (BB)	38	1.53 (0.80-2.94)
Switch		
Generic – Branded (GB)	9	1.25 (0.34-4.65)
Branded – Generic (BG)	3	0.50 (0.05-5.51)
Generic – Generic (GG')	8	3.00 (0.61-14.86)
Branded – Branded (BB')	11	0.83 (0.25-2.73)

* Unadjusted model in the subgroup analysis only: $Outcome = \beta_0 + \beta_1 \times GG \text{ indicator} + \beta_2 \times BB \text{ indicator} + \beta_3 \times GB \text{ indicator} + \beta_4 \times BG \text{ indicator} + \beta_5 \times GG' \text{ indicator} + \beta_6 \times BB' \text{ indicator}$.

5.4 Table 4 Odds ratios (95% CIs) for the relationship between phenytoin refilling and switching and seizure-related outcomes for sensitivity analyses *

		Refill		Switch		Refill-adjusted odds ratio for switching
Number of days in case/control period	N _s	N _a	Odds ratio (95% CI)	N _a	Odds ratio (95% CI)	Odds ratio (95% CI)
Extended number of days in case and control periods						
7 ^a	717	112	1.67 (1.14-2.44)	31	1.21 (0.60-2.46)	0.73 (0.33-1.63)
10	703	151	1.40 (1.01-1.93)	40	1.11 (0.59-2.10)	0.79 (0.39-1.59)
Phenytoin monotherapy						
7	510	91	1.46 (0.96-2.22)	22	1.00 (0.43-2.31)	0.69 (0.27-1.74)
10	738	157	1.42 (1.03-1.94)	41	1.16 (0.63-2.14)	0.82 (0.41-1.63)
Adjusted refill/switch dates						
7	1137	278	1.09 (0.86-1.38)	36	0.89 (0.47-1.72)	0.82 (0.41-1.65)
10	1114	393	0.97 (0.80-1.19)	62	0.82 (0.50-1.36)	0.84 (0.49-1.45)
Excluded switches between different dosage forms or strengths						
7	691	112	1.67 (1.14-2.44)	5	1.5 (0.25-8.98)	0.90 (0.14-5.61)
10	669	151	1.40 (1.01-1.93)	6	2.00 (0.37-10.92)	1.43 (0.25-8.06)

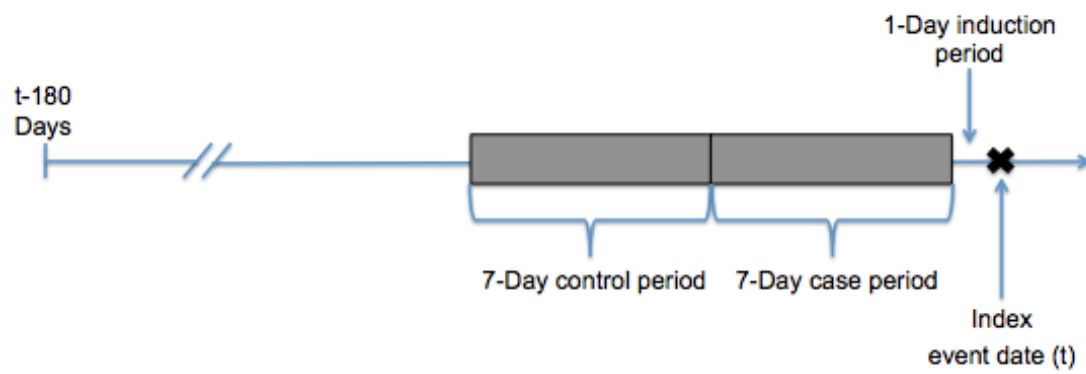
* Unadjusted model in the sensitivity analysis only:

$$Outcome = \beta_0 + \beta_1 \times Exposure + \beta_2 \times Exposure \times Group.$$

a. Results from the crude primary analysis in Table 2.

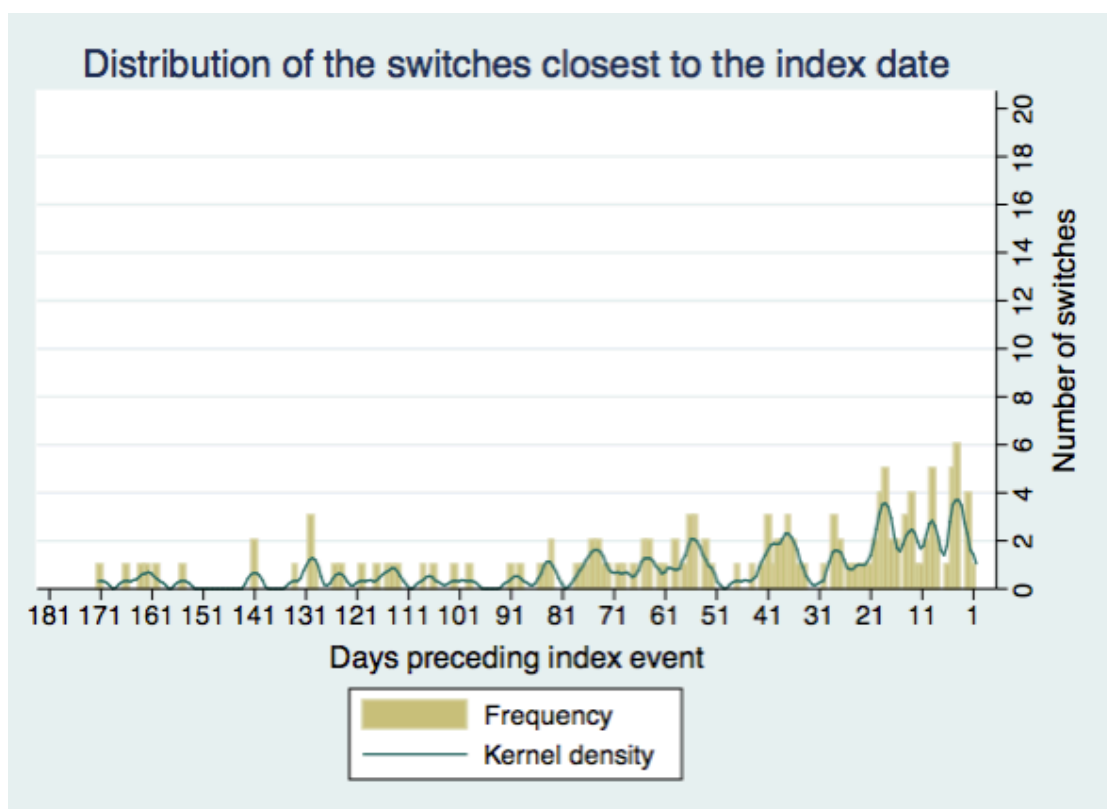
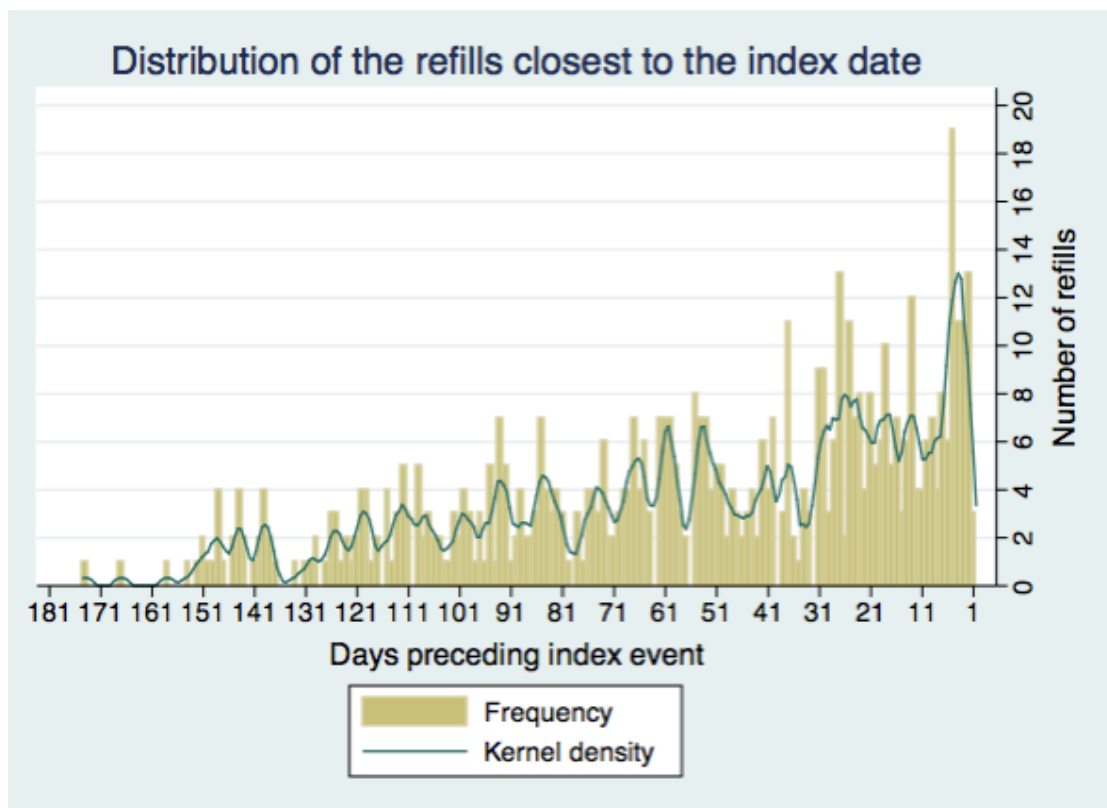
6 Figures

6.1 Figure 1 Case-crossover study design*



* Case and control periods were defined as 7 days in the primary analysis.

6.2 Figure 2 and 3 Distribution of refills and switches in the 180 days before the index date*



* $N_s=717$.

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Curriculum Vitae

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PROFILE

Master of Health Science candidate with strong methodological and analytic skills in epidemiology, biostatistics and health services research. Research assistant familiar with coding systems in electronic health records and experienced in manipulation and analysis of large longitudinal data in SAS and other statistical packages. Integrative medicine professional with clinical training. Fluent in English and Chinese.

EDUCATION

Master of Health Science in Epidemiology, GPA: 3.82/4.00 Expected May 2015

Concentration: Clinical Epidemiology

Johns Hopkins Bloomberg School of Public Health (JHSPH), Baltimore, MD

Relevant Coursework: Epidemiology Methods I-IV; Statistical Methods in Public Health I-IV;

Principles of Clinical Epidemiology; Introduction to Clinical Trials; STATA Programming;

Introduction to the SAS Statistical Package; Introduction to R for Public Health Researcher; Advanced Methods for Design and Analysis of Cohort Study; Survival Analysis; Analysis of Longitudinal Data.

Certificate in Pharmacoepidemiology and Drug Safety Expected May 2015

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Relevant Coursework: Pharmacoepidemiology Methods; Pharmacoepidemiology: Utilization; Principles of Drug Development; Causal Inference in Medicine and Public Health; Introduction to Comparative Effectiveness and Outcomes Research; Assessing Health Status and Patient Outcomes; Introduction to Economic Evaluation; Health Management Information Systems.

Bachelor of Medicine, GPA: 3.70/4.00

June 2013

Beijing University of Chinese Medicine (BUCM), Beijing, China

Major: Traditional Chinese Medicine

Honors: First Class Scholarship, BUCM 2011; Merit Student, BUCM 2011; Second Class Scholarship, BUCM 2010; Merit Student, BUCM 2010; National Scholarship, Ministry of Education of the People's Republic of China 2009

RESEARCH EXPERIENCE

Student Investigator

Nov 2014 – Present

Johns Hopkins Center for Drug Safety and Effectiveness, Baltimore, MD

Project: *Transient Risk of Breakthrough Seizures Associated with Phenytoin Refilling and Switching*

• Collaborated with a faculty member to develop a case-crossover study

- Conducted data management on Truven MarketScan Commercial Claims and Encounters database in SAS
- Used NDC codes and diagnosis codes to identify important variables
- Performed conditional logistic regression to examine the transient risk of prescriptions refilling/switching

Research Assistant

June 2014 – March 2015

Johns Hopkins Center for Drug Safety and Effectiveness, Baltimore, MD

Project: Adverse Events Associated with Testosterone Use: Systematic Review and Meta-analysis

- Coordinated project meeting and established working timeline
- Collaborated with a librarian to built up search strategy and assisted with inclusion and exclusion criteria
- Prepared project protocol ready to be submitted
- Conducted title and abstract screening in EndNote and Excel

Project: Impact of Opioids Use on Statins Adherence and Persistence

- Assisted with study design
- Conducted data cleaning of IMS claims data in SAS
- Performed survival analysis to evaluate the impact of opioids use on statins adherence

Research Assistant

February 2014 – June 2014

The Welch Center for Prevention, Epidemiology and Clinical Research, Baltimore, MD

Project: Five Nuts and Beans

- Administered dietary questionnaires and conducted data cleaning in STATA
- Analyzed longitudinal data to assess the association between dietary pattern and cardiovascular disease

Research Assistant

March 2012 – June 2013

Dongzhimen Hospital, Beijing, China

Project: The Effects of Chinese Formula Fufang Xiaokuxin Tang Granules on Mouse Models of Bleomycin-Induced Pulmonary Fibrosis

- Collaborated with other researchers on the study design
- Assisted in laboratory operation and data collection

CLINICAL EXPERIENCE

Intern

July 2012 – June 2013

Dongzhimen Hospital, Beijing, China

- Rotated through 10 departments: Pediatrics, Dermatology, Nephrology, Pneumology, Cardiology, Neurology, Gynaecology and Acupuncture, Emergency and Surgery.
- Practiced patients admission, history taking, physical examinations, interpretation on

lab results, making medical records and ancillary procedures, such as electrocardiograms.

VOLUNTEER EXPERIENCE

Treasurer, International Society for Pharmacoepidemiology Student Chapter, 2014-2015

Student Mentor, Johns Hopkins Bloomberg School of Public Health, 2014-2015

Activity Coordinator, Medical School Class of 2013, BUCM, 2009-2013

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PROFESSIONAL DEVELOPMENT

Language Skills: Fluent English and Chinese; Professional translation of traditional Chinese medicine

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PUBLICATIONS/PRESENTATIONS

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