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Brand name to generic substitution of antiepileptic drugs does not lead to seizure-related hospitalization: A population-based case-crossover study.

Running head: generic substitution of antiepileptic drugs

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Key points:

- There is still controversy on generic substitution in general, and specifically for antiepileptic drugs.
- We examined whether brand-to-generic antiepileptic drug substitution was associated with seizure-related hospitalization.
- With a narrow confidence interval, our results allow exclusion of a relevant association between brand-to-generic substitution and seizure-related hospitalization, in well-controlled, seizure-free patients.
- These findings may contribute to restoring confidence in generic antiepileptic drug formulations and more generally it might be reassuring for generic utilization, especially in stable patients with chronic disease.

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ABSTRACT (Word count: 232/250)

Purpose: There is still controversy on brand name to generic (B-G) antiepileptic drugs (AEDs) substitution.

Methods: To assess association between brand-to-generic (B-G) antiepileptic drug (AED) substitution and seizure-related hospitalization, we designed a case crossover using the French National Health Insurance Database. We identified a cohort of adult patients who filled a prescription in 2009-2011 for AEDs with at least one brand name and one generic form. The outcome date was defined as the date of hospitalization, coded G40.x or G41.x, with a G40/G41 hospitalization-free period of at least one year. Patients with a medical history of cancer and women who gave birth in 2009-2011 were excluded. We required individuals to have regular dispensations of AEDs within the year preceding the outcome date. Free patients were defined as patients who had only brand-name dispensations before the control period.

Results: 8,379 patients (mean age ± SD, 52.7 ± 18.8 years; sex ratio male/female, 1.27) were analyzed. Discordant pairs were 491 with B-G substitution in the control period only and 478 with B-G substitution in the case period only; OR (95%CI) 0.97 (0.86–1.10). No statistically significant interaction was detected among the four pre-specified subgroup analyses (gender, age strata, free or non-free and strict AED monotherapy or not). Controlling for non-seizure-related hospitalizations made no material difference. Sensitivity analyses yielded similar results.

Conclusions: B-G AED substitution was not associated with an elevated risk of seizure-related hospitalization.

INTRODUCTION

Generic drugs have been developed to control healthcare costs.

There are conflicting viewpoints regarding generic substitution, particularly towards antiepileptic drugs (AEDs). Potential difference in therapeutic response between bioequivalent products remains a concern, especially for older AEDs with a narrow therapeutic index (NTI) but also for newer, non-NTI AEDs [1-3]. Clinicians worry about possible therapy failure, especially in controlled patients, as even a single breakthrough seizure may have severe consequences such as loss of driving license, of employment or injuries [4].

Some US states and European countries recommend limiting the substitution of generic AEDs, the American Academy of Neurology opposing antiepileptic generic substitution without physician approval [1, 5-7]. It is also not recommended to switch AEDs in seizure-free patients [4].

Some studies argued for the association between generic substitution and a risk of breakthrough seizures: opinion studies among clinicians and patients [1, 8-11], observational cohort [12-15] or case-control studies [16-18]. These studies present several methodological limits and most of them were sponsored by brand medication manufacturers. In contrast, studies argued for a lack of association between generic substitution and a risk of seizure: meta-analysis of clinical trials, but included few patients and were underpowered to detect true clinical differences [19], observational cohort [20, 21], case-control [22, 23] and case-crossover studies [24, 25]. The study of Gagne et al [23] hypothesized that refilling a prescription for the same manufacturer's AED might itself be associated with risk of seizure-related events, due to confounders. The odds ratio (OR) was 2.75 (95% CI 0.88-8.64) for refills that involved switching, yielding a refill-adjusted OR for switching of 1.19 (95% CI 0.35-3.99).

All these studies did not provide a definite answer about the impact of brand-to-generic substitution on controlled epilepsy patients, especially for valproic acid, carbamazepine and lamotrigine, which are not extensively studied in the case-control studies. The aim of the GENEPI study ('GENeric substitution of antiEPIleptic drugs') was to further assess the association between seizure-related hospitalization and generic substitution and provide the necessary evidence to inform clinician and patient decisions.

METHODS

Data source

We used data from the French national health insurance system (Système National d'Information Inter-Régimes de l'Assurance Maladie, SNIIR-AM with comprehensive data for all health spending reimbursements of affiliated subjects linked by a unique personal health number to the French hospital discharge database (Programme de Médicalisation des Systèmes d'Information; PMSI). The SNIIR-AM database contains basic demographic patient data such as age and gender of about 65 million individuals (99% of the French population). We used data covering the period 2009 to 2011.

Ethics

The Institute on Health Data (Institut des Données de Santé) approved this study (No. 28, September 2011), as well as the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés [DE-2012-111]).

Design

We used a case-crossover design [26-28]. We arbitrarily chose a 3-day induction period and a 3-month exposure window (i.e. "case period") for primary analyses. The control period was then defined as the 3 months immediately preceding the case period in primary analyses.

Study population

We used data from all adult patients affiliated to the French national health insurance scheme, aged 18 years or more on January 2009, who had at least one reimbursement between 2009 and 2011 for at least one of the following AEDs: carbamazepine, lamotrigine, levetiracetam, topiramate, or valproic acid, referred to as selected AEDs. These drugs had a brand name and at least one "A-rated" generic form available on the French market by this time (2009-2011) and were widely prescribed for epilepsy, allowing identification of epilepsy patients. They were extracted from the SNIIR-AM databases using anatomical therapeutic chemical (ATC) classification codes (N03AF01, N03AX09, N03AX14, N03AX11 or N03AG01). Targeted AEDs, i.e. AEDs with at least one generic form available on the French market, were defined as the above selected AEDs plus oxcarbazepine (N03AF02) which is mostly used in combination.

Patients with a medical history of cancer (all ICD-10 codes for cancer with LTD) and women who gave birth (hospitalization with ICD-10 codes O80-O84) within the study

period were excluded because of the high risk of repeated seizures as well as patients receiving fatty acid derivatives through formulations registered as mood-stabilizing drugs such as valpromide (DEPAMIDE) or divalproex sodium (DEPAKOTE) who may be not epilepsy patients.

Case ascertainment

Cases were identified, using the PMSI database, as individuals with a seizure-related hospitalization between January 2010 and December 2011. We used ICD-10 codes G40.x (epilepsy) or G41.x (*status epilepticus*) as codes of interest in primary or secondary hospital discharge diagnosis position. The index event date was defined as the date of occurrence in the PMSI database of one of the abovementioned codes of interest with an hospitalization-free (for ICD-10 G40.x or G41.x) period of at least one year preceding the index event date (controlled epilepsy patients). We further required individuals to have regular dispensations of the same product for each targeted AED within the year preceding the index event date; this was defined as the dispensation of products having the same International Non-proprietary Name (INN) at the same strength per unit with the same number of units per box and the same dosage form. Regular dispensation (a proxy for medication adherence) was defined as at least ten dispensation claims within a year, keeping in mind that those dispensations are on a monthly basis in France. Thus, we excluded events that occurred in 2009 to ensure that exposure and hospitalization data were available for the 365 days prior to the index date for each case.

Exposure and covariate assessment

A generic substitution (switch from brand to generic) was defined as a dispensation of a generic drug that was preceded by a dispensation of a product having the same INN at the same strength per unit with the same number of units per pack and the same dosage form but corresponding to the brand-name counterpart. Of note, in France, drugs are delivered by pharmacist using individual pack with blisters; pharmacists are not filling individual patient containers like in the US. Branded and generic drugs are distinguishable in the SNIIR-AM database using the French drug identification numbers (CIP, Presentation Identifying Code), which are specific to each drug product marketed by each manufacturer; The CIP (7-digit code) identifies the various existing presentations (INN, market authorization holder, strength per unit, number of units per pack and dosage form).

Substitution was first considered as any substitution of at least one targeted AED. Due to the late availability on the French market of levetiracetam generic form (August, 2011), we excluded patients who switched before the index date from the levetiracetam brand to the generic. Substitution was then classified into two groups: narrow therapeutic index (carbamazepine and valproic acid) or not (lamotrigine, oxcarbazepine, topiramate).

AED-free patients were defined as patients who had only targeted AED brand name dispensations before the control period; which means no prior exposure to AED generics before the control period. Conversely, patients who had at least one dispensation of the generic drug before control period were defined as AED non-free patients.

Strict monotherapy was defined as dispensations of only one targeted AED and without any concurrent use of other AEDs during the year preceding the index event date. These other (non-targeted) AEDs were as follows: barbiturates, benzodiazepines (clonazepam, clobazam, diazepam), phenytoin, GABA analogs (gabapentin, pregabalin). No generic formulation of these drugs was available in the French market (e.g. phenytoin) or they were not specifically dedicated to epilepsy treatment (e.g. gabapentin). They were identified by their CIP number.

We defined psychiatric disease based on selected ICD-10 codes justifying LTD inscription for psychiatric disorder (LTD 23). We also collected the occurrence of hospitalizations not related to seizure during both control and case periods.

Statistical analysis

Data were analyzed using standard methods for matched case-crossover data. Odds ratios (ORs) and 95% confidence intervals (95% CIs) for seizure-related hospitalizations were estimated using conditional logistic regression models.

We introduced an interaction term between switch occurrence and user profile (AED-free patient or not), strict monotherapy or not, age strata, or gender. Age strata were defined according to first and third quartiles. Statistical models were first built without any adjustment and then with adjustment for non-seizure-related hospitalizations during case and control periods. All analyses were conducted using the SAS statistical package (version 9.3; SAS Institute, Cary, N.C., USA).

Sensitivity analyses

We reduced case and control periods to 28 days and we tested 1-day and 5-day induction periods. Analyses were also performed for B-G substitution of any targeted AEDs or narrow therapeutic index AEDs (carbamazepine and valproic acid).

RESULTS

A total of 812,314 adults with at least one reimbursement between 2009 and 2011 for one of the selected AEDs, were identified in the SNIIRAM, of whom 132,927 were excluded because they had a diagnosis of cancer or had been pregnant or had received fatty acid derivatives through formulations registered as mood-stabilizing drugs (Figure 1). Of the remaining 679,387 patients [median age (quartiles) 51 years (38-66); sex ratio male/female, 0.85], 66,315 had been hospitalized for seizure; 21,879 were excluded because of inadequate date(s) of hospitalization(s), too early (hospitalization in 2009) or too close, thus a one-year period free of seizure-related hospitalization was not observed. Of the remaining 44,436 patients, 8,407 had regular dispensation of targeted AEDs in the year preceding the index date. Subsequently, 28 patients with a substitution involving levetiracetam before the index date were excluded.

Main analysis

8,379 patients [median age (quartiles) 52 years (40-69); sex ratio male/female, 1.27] were included in the primary analysis (Tables 1 and 2). Table 1 depicts patients' characteristics and AED patterns. The targeted AED claims were mainly valproic acid, followed by lamotrigine and carbamazepine. Two-thirds of our population received only one targeted AED, with 41% of patients on strict monotherapy. Mean numbers of accounting lines related to any healthcare provisions during the six month case-control period were quite similar between free and non-free patients: 38.8 ± 45.5 vs. 39.4 ± 47.0. Of note healthcare provision encompassed all claims being reimbursed: not only physician visits, but also nurse visits, physiotherapy session, biological measurements and drug dispensation.

The distributions of brand-to-generic antiepileptic drug (B-G AED) substitution in the six-month period preceding the index event dates are displayed in Tables 2 and 3.

There were 969 discordant pairs: 491 with B-G substitution in the control period but not in the case period, and 478 with B-G substitution in the case period but not in the control period: odds ratio 0.97 (95% CI: 0.86–1.10). Results were consistent across the different AEDs (Table 3). A post-hoc power analysis showed that 969 discordant pairs provided 93% power at the 5% level of significance to detect an odds ratio of 1.25.

Subgroup analyses and secondary analysis

No statistically significant interaction was detected among the four pre-specified subgroup analyses (Table 4). The p value was equal to 0.11 for the interaction term between substitution and free/non-free status: OR (95%CI) 1.20 (0.90–1.61) for free patients and 0.93 (0.81-1.07) for non-free patients. Non-free patients had a mean ± SD number of B-G AED substitution within the 6 months prior to the control period of 0.95 ± 1.36, which remains a rare event. In addition, substitution was evenly distributed in the 6-month, case-control period.

Less than 25% of patients had a non-seizure related hospitalization in the 6-month, case-control period: 22.4% in free patients and 24.7% in non-free patients. When we considered a non-seizure-related hospitalization as an exposure, the OR (95%CI) was 1.30 (1.18–1.44), $p < 0.0001$. Controlling for this covariate made no material difference to the effect estimates for B-G AED substitution (Table 4).

Sensitivity analyses

Sensitivity analyses yielded results similar to primary analysis (Table 4 and Table 5).

DISCUSSION

Based on the largest set of data to date, our findings support the absence of association between brand-to-generic antiepileptic drug substitution and the risk of seizure-related hospitalization for AEDs with or without a narrow therapeutic index in the target population for clinicians (i.e. seizure-free patients, controlled by a stable treatment). This result supports that the bioequivalence between generics and their branded counterparts means clinical equivalence and is consistent with the bioequivalence requirements established by the Food and Drug Administration (identical to those of the European Medicines Agency) which are intended to ensure that differences in bioavailability between generics and their brand-name counterparts are not greater than between-lot variations from a single manufacturer [23, 29].

By seeking an association in patients receiving stable therapy who had been seizure-free for at least one year, this provides the best possible conditions to assess the impact of substitution on the clinical state of patients. Patients for whom loss of seizure control has the most serious medical and social consequences (e.g. injury, loss of driving license, loss of employment…) are stable patients. In our study, the eligibility of seizure-free patients is warranted by the absence of any G40/G41 ICD-10 codes within the year preceding the index date and by continuous brand or generic use, resulting in only adherent patients being captured. Indeed, non adherence has been shown to be associated with increased seizure risk and a significantly higher incidence of hospitalization [20]. Furthermore, the number of AEDs dispensed is a strong predictor of seizure-related events [24] and multiple AEDs are generally reserved for patients with more severe forms of epilepsy, thus making multiple AEDs a potential proxy for disease severity [22]. Yet at least 40% of patients in our study sample were on strict AED monotherapy, mainly valproic acid. In a previous study [30], it was reported that AED monotherapy was the rule in stable epilepsy patients. The fact that the association remains non-significant in stable patients following strict monotherapy gives the result even more value.

An individual's risk for epilepsy exacerbations may increase with co-morbidities [22], which is confirmed when we considered a non-seizure-related hospitalization as an exposure. However, our results are unchanged when controlling for this covariate.

In the study of Zachry et al [16], the percentage of patients experiencing a switch in the case group was highest in the three months prior to the index event (emergent

epilepsy-related care) whereas this percentage in the control group was highest only in the first month prior to the index event, with no discernible pattern thereafter. In our study, the switches were evenly distributed throughout the case and control periods and sensitivity analyses, by varying the duration of the case and control periods and the induction period, confirming the robustness of the results.

It is of note that the analysis based on the 28-day case and control period gave consistent results but a less precise estimation.

As regards confounding the advantage of the case-crossover method is that the influence of factors that vary among the participants, such as fixed between-person confounders, is removed. Previous studies [16-18] which found an association between A-rated formulations of AEDs and an increased risk of inpatient/emergency epilepsy care were limited by confounding on account of the severity of epilepsy. Using a short study period, confounding by time-varying factors is thought to be limited or unlikely. Imbalances were still possible in transient individual factors. Specifying the risk period requires particular caution as the estimator may be biased toward the null. Sensitivity analyses by modifying the end and duration of the risk period and control periods verified the robustness of our results. Generic AEDs have been available on the French market since 2000, thus no time-trend in exposure was anticipated excepted for levetiracetam. Using electronic health records allowed completeness and timeliness of information regarding drug dispensation and hospitalization dates. As regards selection bias, the completeness of the SNIIR-AM files narrowed concerns about external generalizability.

We also have to consider ICD code accuracy and misclassification bias. However, these should be limited, given that most instances of seizures are readily evident for healthcare providers. Other users of AEDs for conditions such as bipolar disorder, neuropathic pain or migraine may also have been included in our study population (i.e. 24% of our patients have a previous psychiatric diagnosis). Nevertheless, AEDs indicated for diseases other than epilepsy were not selected, such as gabapentin. Moreover, studies have shown that the use of a combination of diagnosis codes and pharmacy claims of AEDs can correctly classify 90% of epilepsy cases [31] and the most accurate algorithm to identify epilepsy cases in administrative health data is IDC-10 codes G40/G41 [32].

The relevance of the choice of our outcome should be discussed: it is a highly specific outcome, which does not allow generalization of our results, because not all

patients with breakthrough seizures are hospitalized, some of them could be managed in an outpatient setting [16, 17, 24]. These results are only applicable to serious exacerbations of epilepsy, as claims databases capture only the most serious events [17, 21]. However we assume, as other researchers, that stable patients experiencing unexpected breakthrough seizures are likely to seek care in emergency and inpatient settings more often than in ambulatory settings[16-18].

Switches are usually characterized as one of three types: brand to generic, generic to brand or generic to generic [16, 17, 24]. As many healthcare providers focus on problems related to brand-to-generic switching, our survey has studied this type of switch, but the results could not be extended to switches among different generic formulations.

Results were consistent across all targeted AEDs, either NTI AEDs or non-NTI AEDs, which is reassuring for the use of valproic acid or carbamazepine generic formulations. Nevertheless, no conclusion for phenytoin, another NTI AED, could be drawn because no generic formulation of phenytoin is marketed in France.

Conclusion

Previous studies suggested that switching AED medication may result in adverse events although the differences could be attributable to confounders which were not well accounted for. Our results allow exclusion of an association between a brand-to-generic substitution and seizure-related hospitalization, in well-controlled, seizure-free patients. These findings may restore confidence in AED generic formulations, keeping in mind that substitution should not be performed without physician and patient agreement.

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AUTHOR CONTRIBUTIONS

E.P, E.N, E.O. wrote the manuscript. E.O. designed the research. E.P, E.N, A.H., and E.O. performed the research. E.P, E.N, A.H., A.B., and E.O. analyzed the data.

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Table 1 Patients' characteristics and antiepileptic drug (AED) treatment patterns

Variable		All patients n = 8 379	Free patients n = 4 088	Non free patients n = 4 291
Age at index date, median (Q1-Q3)		52 (40-69)	52 (38-70)	52 (40-67)
Gender, n (%)	Male,	4,689 (56%)	2 165 (53%)	2,524 (59%)
	Female	3,690 (44%)	1,923 (47%)	1,767 (41%)
Previous psychiatric diagnosis, n (%)		2,004 (24%)	808 (20%)	1196 (28%)
Targeted AEDs, n (%)	Carbamazepine	1,907 (23%)	1,104 (27%)	803 (19%)
	Lamotrigine	1,888 (23%)	766 (19%)	1,122 (26%)
	Levetiracetam	2,182 (26%)	1,646 (40%)	536 (12%)
	Oxcarbazepine	239 (3%)	121 (3%)	118 (3%)
	Topiramate	588 (7%)	396 (10%)	192 (4%)
	Valproic acid	3,892 (46%)	1,176 (29%)	2,716 (63%)
Other AEDs, n (%)		4,163 (50%)	2,083 (51%)	2,080 (48%)
Only one targeted AED, n (%)		6,338 (76%)	3,103 (76%)	3,235 (75%)
Strict monotherapy, n (%)		3,462 (41%)	1,649 (40%)	1,813 (42%)

AED-free patients were defined as patients who had only targeted AED brand name dispensations before the control period; which means no prior exposure to AED generics before the control period. Conversely, patients who had at least one dispensation of the generic drug before control period were defined as AED non-free patients.

Presence of previous psychiatric diagnosis is based on inscription in long-term disease (LTD) with an ICD-10 code corresponding to a psychiatric disorder

Targeted anti-epileptic drugs (AEDs), i.e. AEDs with at least one available generic form on the French market, were: carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, topiramate and valproic acid.

Strict monotherapy was defined as dispensations of only one targeted AED without any concurrent use of other AEDs during the year preceding the index event date. These other (not targeted) AEDs were the following: barbiturates, benzodiazepines (clonazepam, clobazam, diazepam), hydantoins, GABA analogs (gabapentin, pregabalin). They were identified by their CIP number. They belong to the following ATC classes: N03AA, N03AB, N03AD, N03AE, N05BA09, N05BA01, N03AF03, N03AF04, N03AG04, N03AG05, N03AG06, N03AX12, N03AX15, N03AX16, N03AX17 and N03AX18.

Table 2 Number of patients according to the occurrence of brand to generic substitution in case and control periods

Generic substitution		Case period	
		No	Yes
Control period	No	7222	478
	Yes	491	188

Table 3 Number of patients experiencing a brand-generic substitution according to antiepileptic drug, user profile (generic-free or not) and period as well as number of occurrence of non-seizure related hospitalization according user profile (generic-free or not) and period.

	Free patients N = 4 088		**Non free patients N = 4 291**	
	Control period	**Case period**	**Control period**	**Case period**
AED substitution				
Carbamazepine	15	21	98	87
Lamotrigine	31	32	153	155
Oxcarbazepine	2	1	9	7
Topiramate	8	12	17	11
Valproic acid	54	60	317	304
Any of them	107	124	572	542
Non-seizure related hospitalization	496	601	584	687

AED-free patients were defined as patients who had only targeted AED brand name dispensations before the control period; which means no prior exposure to AED generics before the control period. Conversely, patients who had at least one dispensation of the generic drug before control period were defined as AED non-free patients.

Table 4 Crude and non-seizure-related-hospitalization-adjusted odds ratios (OR) relative to brand-to-generic substitution (any targeted antiepileptic drug (AED) or narrow therapeutic index AEDs) for different subgroups of patients

Any targeted AEDs ***Narrow therapeutic index***	**Unadjusted analysis**		**Adjusted analysis**	
Population	**Conditional OR (95% CI)**	**p-value**	**Conditional OR (95% CI)**	**p-value**
All patients	0.97 (0.86–1.10) *0.95 (0.82–1.11)*		0.97 (0.85–1.10) *0.95 (0.81–1.10)*	
Men	1.02 (0.86–1.20) *1.01 (0.83–1.22)*	0.42 *0.37*	1.01 (0.86–1.20) *1.00 (0.82–1.21)*	0.44 *0.39*
Women	0.92 (0.76–1.11) *0.88 (0.69–1.11)*		0.91 (0.76–1.11) *0.87 (0.68–1.11)*	
Free patients	1.20 (0.90–1.61) *1.21 (0.84–1.75)*	0.111 *0.160*	1.20 (0.90–1.61) *1.20 (0.83–1.73)*	0.107 *0.171*
Non free patients	0.93 (0.81–1.07) *0.91 (0.77–1.07)*		0.92 (0.80–1.06) *0.90 (0.77–1.06)*	
Patients following a strict monotherapy	0.95 (0.77–1.16) *0.90 (0.70–1.15)*	0.73 *0.55*	0.93 (0.76–1.15) *0.88 (0.69–1.13)*	0.67 *0.48*
Patients not following a strict monotherapy	0.99 (0.84–1.16) *0.99 (0.82–1.19)*		0.99 (0.84–1.16) *0.99 (0.82–1.19)*	
Patients < 40 years old at index date	1.07 (0.84–1.35) *0.99 (0.74–1.31)*		1.06 (0.84–1.35) *0.98 (0.74–1.31)*	
Patients 40-69 years old at index date	0.97 (0.81–1.16) *0.99 (0.81–1.22)*	0.54 *0.49*	0.97 (0.81–1.15) *0.99 (0.81–1.21)*	0.52 *0.45*
Patients ≥ 70 years old at index date	0.87 (0.66–1.15) *0.78 (0.55–1.12)*		0.86 (0.65–1.14) *0.77 (0.54–1.10)*	

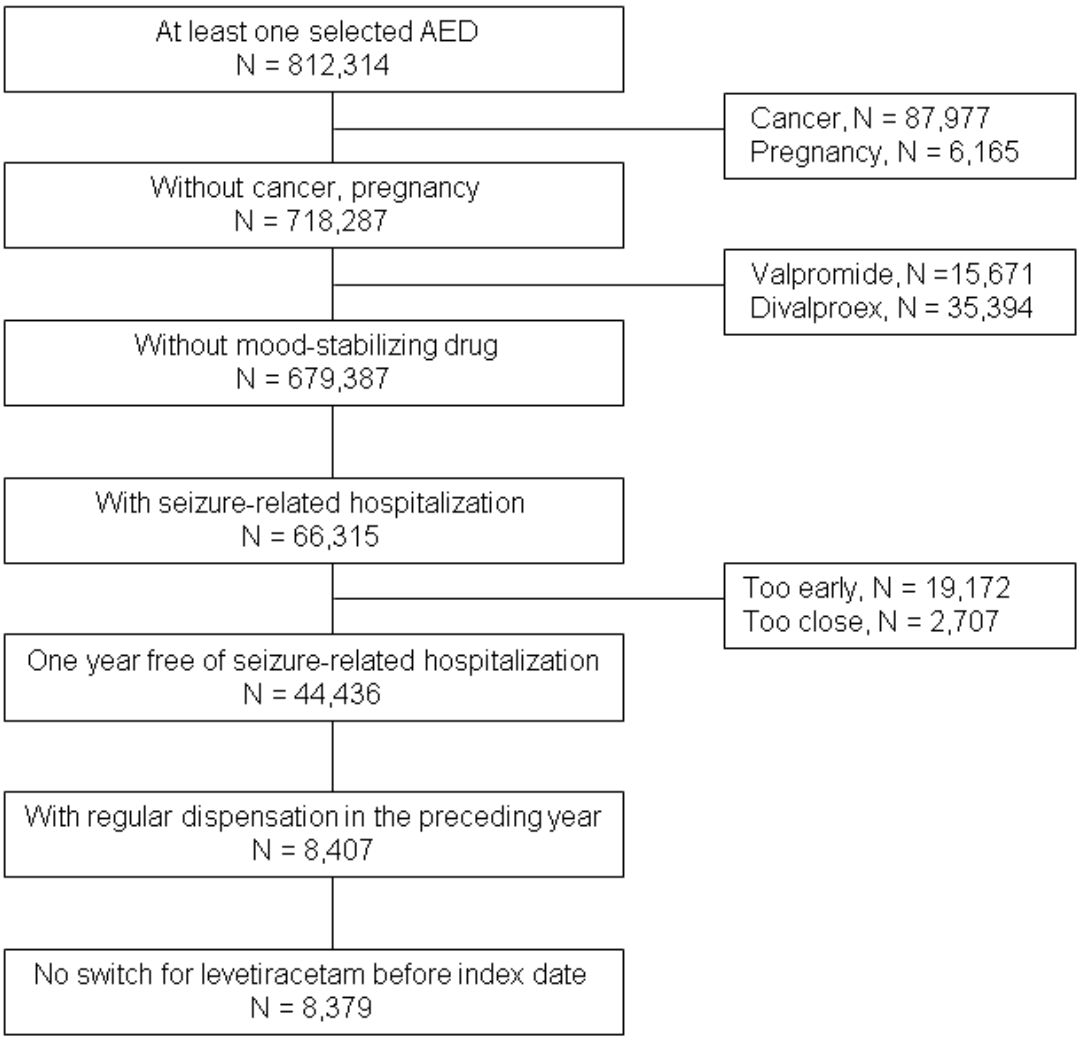
P values are for homogeneity testing;
AED-free patients were defined as patients who had only targeted AED brand name dispensations before the control period; which means no prior exposure to AED generics before the control period. Conversely, patients who had at least one dispensation of the generic drug before control period were defined as AED non-free patients.

Table 5 Sensitivity analyses

3-days induction **1-day induction** **5-days-induction**	**3-months case and control period**		**28-day case and control period**	
Population	**Conditional OR (95% CI)**	**p-value**	**Conditional OR (95% CI)**	**p-value**
All patients	0.97 (0.86–1.10) 0.99 (0.87–1.12) 0.98 (0.86–1.11)		1.07 (0.88–1.30) 1.12 (0.92–1.35) 1.01 (0.84–1.23)	
Men	1.02 (0.86–1.20) 1.01 (0.86–1.20) 1.04 (0.88–1.23)	0.42 0.63 0.28	1.03 (0.79–1.33) 1.07 (0.83–1.39) 0.96 (0.74–1.24)	0.63 0.65 0.51
Women	0.92 (0.76–1.11) 0.95 (0.79–1.15) 0.90 (0.74–1.09)		1.13 (0.84–1.51) 1.17 (0.88–1.56) 1.09 (0.81–1.47)	
Free patients	1.20 (0.90–1.61) 1.28 (0.96–1.70) 1.22 (0.91–1.64)	0.11 0.05 0.09	1.12 (0.74–1.71) 1.21 (0.81–1.83) 1.10 (0.72–1.68)	0.80 0.64 0.68
Non free patients	0.93 (0.81–1.07) 0.93 (0.81–1.07) 0.93 (0.81–1.07)		1.06 (0.85–1.31) 1.09 (0.88–1.35) 0.99 (0.80–1.23)	
Patients following a strict monotherapy	0.95 (0.77–1.16) 0.96 (0.78–1.18) 0.97 (0.79–1.19)	0.73 0.70 0.92	0.97 (0.71–1.34) 1.01 (0.73–1.40) 0.84 (0.62–1.16)	0.47 0.47 0.15
Patients not following a strict monotherapy	0.99 (0.84–1.16) 1.01 (0.86–1.18) 0.98 (0.84–1.15)		1.13 (0.89–1.44) 1.18 (0.93–1.49) 1.13 (0.89–1.44)	
Patients < 40 years old at index date	1.07 (0.84–1.35) 1.07 (0.85–1.36) 1.04 (0.82–1.32)		1.11 (0.77–1.60) 1.41 (0.98–2.03) 1.05 (0.73–1.52)	
Patients 40-69 years old at index date	0.97 (0.81–1.16) 1.00 (0.84–1.19) 0.97 (0.81–1.16)	0.54 0.45 0.74	0.98 (0.75–1.28) 0.94 (0.72–1.22) 0.95 (0.73–1.23)	0.57 0.16 0.71
Patients ≥ 70 years old at index date	0.87 (0.66–1.15) 0.85 (0.65–1.13) 0.90 (0.68–1.19)		1.29 (0.83–2.03) 1.29 (0.83–2.00) 1.17 (0.75–1.84)	

P values are for homogeneity testing; AED-free patients were defined as patients who had only targeted AED brand name dispensations before the control period; which means no prior exposure to AED generics before the control period. Conversely, patients who had at least one dispensation of the generic drug before control period were defined as AED non-free patients.

Figure 1 Flow chart



Selected antiepileptic drug (AED): carbamazepine, lamotrigine, levetiracetam, topiramate, or valproic acid;
Seizure-related hospitalization: ICD-10 codes G40.x (epilepsy) or G41.x (*status epilepticus*) as codes of interest in primary or secondary hospital discharge diagnosis position;
Too early: only hospitalized in 2009; Too close: several hospitalizations but no period greater than or equal to 1 year between two subsequent hospitalizations;
Regular dispensation: at least ten dispensations within a year