Review

Association between switching antiepileptic drug products and healthcare utilization: A systematic review☆,☆☆

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ABSTRACT

Aims: There is ongoing concern whether switching between different antiepileptic drug (AED) products may compromise patient care. We systematically reviewed changes in healthcare utilization following AED switch.
Methods: We searched MEDLINE and EMBASE databases (1980–October 2016) for studies that assessed the effect of AED switching in patients with epilepsy on outpatient visits, emergency room visits, hospitalization and hospital stay duration.
Results: A total of 14 articles met the inclusion criteria. All were retrospective studies. Four provided findings for specific AEDs only (lamotrigine, topiramate, phenytoin and divalproex), 9 presented pooled findings from multiple AEDs, and 1 study provided both specific (lamotrigine, topiramate, oxcarbazepine, and levetiracetam) and pooled findings. Three studies found an association between a switch of topiramate and an increase in healthcare utilization. Another three studies found that a brand-to-generic lamotrigine switch was not associated with an increased risk of emergently treated events (ambulance use, ER visits or hospitalization). The outcomes of the pooled AED switch studies were inconsistent; 5 studies reported an increased healthcare utilization while 5 studies did not.
Conclusion: Studies that have examined the association between an AED switch and a change in healthcare utilization report conflicting findings. Factors that may explain these inconsistent outcomes include inter-study differences in the type of analysis undertaken (pooled vs individual AED data), the covariates used for data adjustment, and the type of switch examined. Future medical claim database studies employing a prospective design are encouraged to address these and other factors in order to enhance inter-study comparability and extrapolation of findings.

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1. Introduction

Because breakthrough seizures significantly impact the quality of life and psychological wellbeing of patients with epilepsy, the main goal of antiepileptic drug (AED) therapy is to achieve seizure-cessation while minimizing adverse events [1–4].

The term 'AED switch' generally refers to the practice of changing from one product to another of the same AED, whether it is replacing a brand AED with a generic alternative (or vice versa), or changing between generic AED products made by different manufacturers [5]. AED switching is primarily driven by the lower cost of generic medication [6], and inconsistent availability from dispensing schemes [7]. However, there is concern that AED switching could compromise patient care, including: a) loss of seizure control [8–11] and increased seizure frequency [12,13], b) development of adverse effects [8,14,15], and c) hospitalization, longer hospital stays [16–18] and increased use of healthcare services [19,20].

Although bioequivalence is required for regulatory approval of generic AEDs from different manufacturers, it is unclear whether AED switch could compromise patient care and ultimately lead to increased healthcare utilization [19,20]. This is because some studies have suggested that AED bioequivalence does not necessarily infer therapeutic equivalence [21–24], that is, variability in serum levels within accepted bioequivalent limits may nonetheless compromise seizure control in

individual patients. As a result, a number of societies and regulatory agencies including the UK's Medicines and Healthcare products Regulatory Agency (MHRA) have recently provided guidance on switching of AEDs. Based on an anticipated risk related to switching, the MHRA has proposed 3 categories of AEDs (Table 1) [25].

Because unexpected seizure relapses often lead to more frequent outpatient visits, emergency room evaluation and/or hospitalizations to adjust AEDs and treat related injuries, healthcare utilization has been used as a surrogate to assess the effect of AED switching [17–19, 21]. A number of studies have used medical claim databases to assess the effect of AED switching on healthcare utilization [17–19,21, 26–34]; advantages of these studies include assessing the morbidity burden associated with an AED switch and the ability to do so with a large sample size and a control group. Previous systematic reviews on AED switching primarily focus on seizure frequency, seizure severity and adverse events [5,16,35]. Talati et al. [16] and Kesselheim et al. [5] included healthcare utilization measures in their findings; however, a systematic review focused solely on healthcare utilization outcomes has not been undertaken in recent years. The present review aimed to evaluate whether an AED switch is associated with greater healthcare utilization rates, that is, outpatient visits, emergency room (ER) visits, hospitalization and length of hospital stay.

2. Methods

2.1. Data sources and searches

We searched MEDLINE/PubMed and EMBASE for publication dates between January 1st 1980 and October 1st 2016, using predefined search terms. Three categories of search terms were used: 1) terms relating to epilepsy (seizure, convulsion, epilepsy, antiseizure, anticonvulsant, antiepileptic) and AEDs, including the generic and brand names of all relevant therapeutic agents, 2) terms relating to drug equivalency (bioavailability, bioequivalence, bioequivalent, substitution, switch) and the term "generic", and 3) terms relating to clinical outcomes of interest (outpatient, inpatient, ambulance, hospitalization, emergency room, healthcare utilization, resource utilization, medical care, duration, adverse effects). The search results were supplemented by additional manual mining of references from relevant articles.

Inclusion criteria were 1) articles containing at least one search term in each of the above three main categories, 2) randomized control trials, cohort studies, case–control studies or observational studies, and 3) at least one relevant healthcare utilization outcome defined above following a switch in AED product in patients with epilepsy only. Exclusion criteria were 1) case studies, surveys, case series, commentaries, conferences, congresses, debates, editorials, expert panel guidelines, review articles, letters, meta-analyses, and technical reports, 2) comparison of AED in different formulations (e.g. immediate-release vs extended-release) and evaluation of AED in different routes of administration, and 3) studies that provided pharmacodynamic analyses only or qualitative analyses of AED effectiveness or its evaluation for indications

other than epilepsy. Studies were also excluded if they were not written in English, were conducted in animals, or had only the abstract available. The final decision on the inclusion/exclusion of studies was made by the authors.

2.2. Data extraction and study quality

Two independent investigators extracted and reached agreement on data from included articles. Data extracted for each study included: study information (author, year, drugs studies), study design characteristics (subjects, study quality and trial design, covariates used to adjust data such as age, gender, comorbidities, and number of AEDs), and clinical information (stability of seizure control and mono/polytherapy rates if provided, healthcare utilization results and conclusions). The methodological quality of the studies was assessed using the 9-star Newcastle-Ottawa Scale [36], and the quality of evidence provided by the studies was assessed using the American Academy of Neurology (AAN) level of evidence classification [37] and the GRADE evaluation score (BMJ Clinical Evidence).

3. Results

The search identified a total of 2865 combined records from MEDLINE/PubMed and EMBASE. After title and abstract screening, 2825 were excluded, leaving 40 articles. After removing duplicate publications, 29 articles met criteria for detailed analysis. Of these, 14 articles met our inclusion criteria, and subsequently were included in the systematic review (Fig. 1). Details of the 14 included studies are provided in Table 2.

The included studies comprised 5 retrospective case–control studies, 3 retrospective case-crossover, and 6 retrospective open-cohort studies (Fig. 2A), with sample sizes ranging from 671 [18] to 33,625 [30] participants. The case–control studies examined patients with an emergently treated epilepsy event versus those who did not in order to assess the effect of an AED switch. In the case-crossover studies patients acted as their own controls while in the open-cohort studies, switch cohorts were compared to non-switch cohorts. Nine studies used US databases (MarketScan Research [26,27], Truven Health MarketScan [21], Thompson Healthcare MarketScan [29], PharMetrics Patient-Centric [30,33], Innovus Invision™ Data Mart [34], Ingenix LabRx [19], Medicaid Analytic Extract [38]), 4 studies used Canadian databases (Régie de

Table 1
Categories of antiepileptic drugs (AEDs) proposed by MHRA, based on anticipated risk relating to switching.

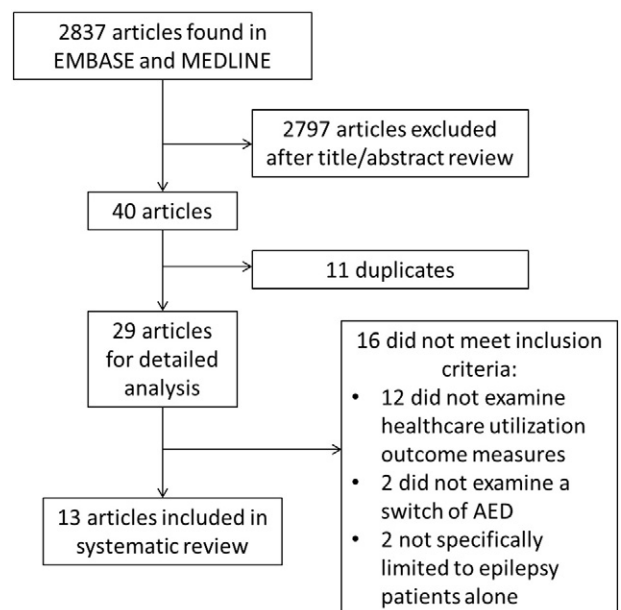| Categories	Description	Examples
Category 1	AEDs with definite concerns that need specific prescribing, supply and dispensing measures to ensure consistent supply	Phenytoin, carbamazepine, phenobarbital, primidone
Category 2	AEDs with possible concerns and where switching should be based on a clinician's judgment	Lamotrigine, valproate, topiramate, oxcarbazepine, zonisamide,
Category 3	AEDs with unlikely concerns where no specific measures are normally required	Levetiracetam, lacosamide, pregabalin, gabapentin

Fig. 1. Study selection.

Table 2
Description of trials examining healthcare utilization following an antiepileptic drug switch.

Author	Drugs studied (MHRA category[a])	Type of AED switch	Subjects, N (mean age, year)	Study design (Newcastle Ottawa Scale score[b])	Stability of seizure control and mono/poly-therapy rates if provided	Covariates used in an adjusted analysis	Results	Conclusion
Duh et al. [17]	Topiramate (2)	Brand-to-generic and generic to generic	948; branded users: 875, single generic users: 331 and multiple generic users: 99 (33.7–37.5)	Retrospective open-cohort (7)	Not provided	Gender, age, comorbidities, treatment characteristics (dose change, polytherapy, switch to topiramate after being treated with another drug of the same class, switch from topiramate to another drug in the same class)	Adjusted incidence rate ratio (95% CI): *Brand vs single generic switch* Hospitalizations = 1.08 (0.88, 1.34), outpatient visits = 0.99 (0.94, 1.04), length of hospital stay = 1.12 (1.03, 1.23). *Brand vs multiple generic* Hospitalizations = 1.65 (1.28, 2.13); outpatient visits = 0.95 (0.88, 1.02); length of hospital stay = 1.43 (1.27, 1.60).	Patients receiving multiple-generic versions of topiramate had a higher risk of greater healthcare utilization. Those receiving a single generic version of topiramate did not.
Paradis et al. [31]	Topiramate (2)	Brand-to-generic [c]	1164 (39.8)	Retrospective open-cohort (8)	78.9% were polytherapy	Gender, age, comorbidities, AED polytherapy	Incidence rate ratio (95% CI) of: *Unadjusted* hospitalizations = 1.22 (1.07, 1.38) [p = 0.0021], outpatient visits = 1.02 (0.99, 1.05) [p = 0.2559], hospitalization duration = 1.26 (1.20, 1.33) [p < 0.0001]. *Adjusted* hospitalizations 1.17 (1.03, 1.33) [p = 0.0149], outpatient visits 0.99 (0.96, 1.03) [p = 0.7427], hospitalization duration 1.21 (1.15, 1.28) [p < 0.0001].	Periods of treatment with generic topiramate were associated with significantly higher healthcare utilization (hospitalizations and hospitalization duration)
Shcherbakova et al. [34]	lamotrigine (2), oxcarbazepine (2), levetiracetam (3), topiramate (2)	Any bioequivalent AED switch – no further detail provided	3140 (41.4)	Retrospective cohort (8)	All patients were on monotherapy	Not applicable	Odds ratio (95% CI) of an ER visit, ambulance use or inpatient hospitalization: all patients combined = 1.13 (0.79–1.63) [p = 0.51], lamotrigine cohort = 0.63 (0.31–1.29) [p = 0.21], oxcarbazepine = 0.45 (0.13–1.65) [p = 0.23], levetiracetam = 0.18 (0.07–0.46) [p = 0.0004], topiramate = 4.38 (1.28–14.97) [p = 0.0185]	AED switch did not appear to have a relationship with healthcare utilization
Erickson et al. [27]	Phenytoin (1), divalproex (2), lamotrigine (2)	Brand-to-generic	Phenytoin: 745 switch, 745 no switch (61.2, 60.8); lamotrigine 995 switch, 995 no switch (17.8, 17.6); divalproex 399 switch, 399 no switch (43.3, 41.8)	Retrospective cohort (8)	Patients had at least 1 ER visit, 1 hospital stay or 2 outpatient visits in the year preceding the index date. 29–35% utilized 2 AEDs during the preindex period, 6–11% utilized 3 and 2% utilized 4 or more	Not applicable	Event related ratio (95% CI) for all-cause ER visit or hospitalizations: phenytoin cohort = 0.96 (0.80–1.16), lamotrigine cohort = 0.97 (0.80–1.17), divalproex cohort = 0.84 (0.66–1.06)	Patients who switched from brand to generic phenytoin, divalproex (valproate), or lamotrigine did not have greater all-cause ER visits or hospitalizations
LeLorier et al. [18]	Lamotrigine (2)	Brand-to-generic	671 (39)	Retrospective open-cohort (8)	17.3% of patients were monotherapy, 82.7% were polytherapy	Gender, age, comorbidities and polytherapy	Adjusted rate ratio (95% CI): total medical service visits (inpatient plus outpatient visits) = 1.13 (1.09, 1.18) [p = 0.0001], inpatient visits = 1.14 (0.96, 1.35) [p = 0.1264], average hospital stay = 1.48 (0.96, 1.35) [p < 0.0001], outpatient visits = 1.13 (1.09, 1.18) [p < 0.0001].	An AED switch to generic lamotrigine was significantly associated with increased physician visits and hospitalizations, and longer hospital stays
Devine et al. [26]	Not provided	Brand-to-generic, generic-to-brand, generic-to-generic	2949 cases, 8847 controls (42, 44)	Nested case–control (9)	Stable epilepsy and AED use for 6 months. Patients with a recent	Age, comorbidities, number of AEDs, new interacting medications, change in	Odds ratio (95% CI) for hospitalizations: unadjusted = 1.51 (1.3–1.8), adjusted = 1.08 (0.91–1.3), adjusted	After adjusting for confounders, no evidence was found that AED switching was associated with

					inpatient or ER claim with a primary diagnosis of epilepsy were excluded	diagnosis from baseline, new AEDs in 90 days pre index date and a change in epilepsy diagnosis from baseline	for those being treated with 3 or more AEDs = 3.19 (2.55–4.01)[d]	increased acute epilepsy exacerbations
Gagne et al. [28]	Multiple AEDs (including category 1, 2, and 3 drugs)	Brand-to-generic and generic-to-generic	1762 (35)	Case-crossover (8)	At least one diagnosis of epilepsy or seizure in the year preceding the index date	Risk associated with refilling the same agent	Odds ratio (95% CI) of an ER visit or hospitalization: unadjusted = 2.75 (0.88–8.64), refill-adjusted odds ratio = 1.19 (0.35–3.99)	After adjustment for the risk associated with refilling the same agent, the harmful effect of AED switching is either negligible or much lower than that found in other studies
Hansen et al. [29]	Multiple AEDs (including category 1, 2, and 3 drugs)	Brand-to-generic, generic-to-brand, generic-to-generic	757 cases, 2271 controls (36.9, 39.9)	Case–control (9)	Patients with a recent ambulance use, inpatient or ER claim with a primary diagnosis of epilepsy were excluded	Gender and total number of AED prescriptions	Odds ratio (95% CI) of an ambulance trip, ER visit or hospitalization: unadjusted = 1.78 (1.35–2.36), adjusted for gender and total number of AED prescriptions filled = 1.57 (1.17–2.10).	Switching AEDs is associated with an increased risk of emergently treated epilepsy-related events
Hansen et al. [21]	Multiple AEDs (including category 1, 2, and 3 drugs)	Brand-to-generic, ggeneric-to-brand, generic-to-generic	4555 cases, 4555 controls	Case–control (9)	Patients with a recent ambulance use, inpatient or ER visit with a primary diagnosis of epilepsy were excluded	Age, diagnosis category and total number of AED prescriptions filled	Odds ratio (95% CI) of a seizure-related event: unadjusted = 1.38 (1.25–1.52), adjusted for age, epilepsy diagnosis category and AED = 1.27 (1.14–1.41)	Switching AEDs is associated with a modest increase in seizure-related events
Kesselheim et al. [38]	Multiple AEDs (including category 1, 2, and 3 drugs)	Generic-to-generic	5200 (34.1)	Case-crossover (8)	Patients with a seizure related hospitalization or ER visit in the previous 6 months were excluded	Adjustment for the process of refilling	Odds ratio (95% CI) of an ER visit or hospitalization for seizures: unadjusted = 1.09 (1.03–1.15), refill-adjusted odds ratio = 1.00 (0.94–1.07)	After adjusting for the refilling process, there was no association between switching among generic manufacturers and an increase in healthcare utilization
Labiner et al. [30]	Multiple AEDs (including category 1, 2, and 3 drugs)	Brand-to-generic [c]	18,125 stable, 15,500 unstable (52.5, 49.1)	Retrospective open-cohort (8)	54% of patients were stable (2 or less outpatient services per year on average and no ER visit) and 46% unstable patients (all other patients)	Gender, age, comorbidities, treatment characteristics (stable epilepsy, polytherapy), switch to study drug from another AED (either brand or generic), geographical region	Incidence rate ratio (95% CI) for all patients (stable and unstable): *Adjusted* hospitalization = 1.24 (1.19–1.30), outpatient visits = 1.14 (1.13–1.16), length of hospital stay = 1.29 (1.27–1.32). *Unadjusted* hospitalization = 1.29 (1.23–1.35), outpatient visits = 1.16 (1.15–1.17), length of hospital stay = 1.34 (1.32–1.37).	Generic AED use was associated with significantly greater healthcare utilization in both stable and unstable patients
Polard et al. [32]	Multiple AEDs (including category 1, 2, and 3 drugs)	Brand-to-generic	8379 (52.7)	Case-crossover (9)	Controlled epilepsy patients: hospitalization-free period of 1 year proceeding the index event	Non-seizure related hospitalizations during case and control periods	Odds ratio (95% CI) for hospitalizations: unadjusted = 0.97 (0.86–1.10), adjusted = 0.97 (0.85–1.10)	There was no association between a brand to generic switch and seizure-related hospitalizations in well-controlled, seizure-free patients
Rascati et al. [33]	Multiple AEDs (MHRA categories not provided)	Brand-to-generic, generic-to-brand, generic-to-generic	991 cases, 2973 control (35.6, 39.2)	Case–control (9)	Stable epilepsy patients with no acute epileptic event (epilepsy related ambulance use, ER visit or hospitalization) in the 6 months prior to the index event	Not applicable	Odds ratio (95% CI) for ambulance use, emergency care or hospitalization: 1.84 (1.44, 2.36).	Patients who had an acute epileptic event requiring an ambulance, emergency care or hospitalization were more likely to have had an AED switch than matched controls
Zachry et al. [19]	Multiple AEDs (including category 1, 2, and 3 drugs)	Brand-to-generic, generic-to-brand, generic-to-generic	416 cases, 1248 controls	Retrospective case–control (9)	No inpatient/emergency epilepsy care in the 6 months prior to the index date	Not applicable	Odds ratio (95% CI) of an ER visit, ambulance service use or inpatient hospitalization claim: 1.81 (1.25–2.63).	Epilepsy patients who had an epilepsy related ambulance trip, ER visit or hospitalization had a greater odds of having had an AED switch in the previous 6 months

AED, antiepileptic drug; ER, emergency room; MHRA, Medicines and Healthcare products Regulatory Agency.

[a] MHRA categorizes AEDs into 3 categories based on the risk related to switching: Category 1, AEDs with definite concerns; Category 2, AEDs with possible concerns; and Category 3, AEDs with unlikely concerns.

[b] The methodological quality of the studies was assessed using the 9-star Newcastle-Ottawa scale [36].

[c] Generic-to-generic switches may have been included in the analysis but this is not explicitly stated in the methodology section.

[d] For individuals taking 2 or ≥3 AEDs, the adjusted odds ratio of hospitalization for epilepsy was higher: 1.95 (95% CI: 1.7–2.2) and 2.96 (95% CI: 2.48–3.49), respectively.

l'Assurance-Maladie du Québec [17,18,31], and PharmaNet [28]) and 1 study used a French database [32] (Système National d'Information Inter-Régimes de l'Assurance Maladie) (Fig. 2B). No randomized study was identified. The studies scored between 7 and 9 on the 9-point Newcastle-Ottawa Scale but only achieved a CLASS III level of evidence according to the American Academy of Neurology (AAN) classification [37] and a very low quality of evidence according to the GRADE score (-1).

According to details provided in each study, 5 studies evaluated brand-to-generic switches only [18,27,30–32], 1 examined generic-to-generic switches only [38], 2 examined brand-to-generic and generic-to-generic switches [17,28], 5 examined brand-to-generic, generic-to-brand and generic-to-generic switches [19,21,26,29,33], while 1 study did not provide any detail on the type of switch evaluated [34].

Four studies analyzed specific AEDs only (lamotrigine [18,27], topiramate [17,31], phenytoin [27], divalproex [27]) while nine studies performed pooled analyses for multiple AEDs (Fig. 2C) [19,21,26,28–30, 32,33,38]. One study undertook an analysis of both specific AEDs (lamotrigine, topiramate, oxcarbazepine and levetiracetam) and a pooled analysis [34].

3.1. Topiramate

Three studies analyzed healthcare utilization following a brand-to-generic switch of topiramate, a MHRA Category 2 AED [17,31,34]. In a retrospective open-cohort study, patients switching to multiple different generic products of topiramate had a higher risk of hospitalization (incidence rate ratio [IRR] 1.65; 95% CI 1.28–2.13) and longer hospital stays (IRR 1.43; 95% CI 1.27–1.60) than those treated with brand topiramate alone [17]; this effect was less pronounced for those with a single brand-to-generic switch (hospitalization: IRR 1.08; 95% CI 0.88–1.34, and length of stay: IRR 1.12; 95% CI 1.03–1.23) [17]. Another open-cohort study also found higher hospitalization rates (adjusted IRR 1.17; 95% CI 1.03–1.33) and longer hospital stays (adjusted IRR 1.21; 95% CI 1.15–1.28) following a brand-to-generic topiramate switch but an examination of the effect of the number of generic switches undertaken was not carried out [31]. Neither of these studies found an association between switching and frequency of outpatient visits [17,31]. A third study reported a significant association between a switch to generic topiramate and an increase in a composite score of ER visit, ambulance use or inpatient hospitalization (odds ratio 4.38, p = 0.02) [34].

3.2. Lamotrigine

Three studies investigated healthcare utilization following a switch from brand-to-generic lamotrigine, another MHRA category 2 AED [18,27,34]. One retrospective open-cohort study found that switching was associated with an increased rate ratio of outpatient visits (1.13, p < 0.0001) and hospitalization duration (1.48, p < 0.001) but not inpatient visits (1.14, p = 0.1264) [18]. The other 2 studies did not find an increased likelihood of ER visits or hospitalizations (odds ratio 0.97) [27], or ER visits, ambulance use or inpatient hospitalizations (odds ratio 0.63, p = 0.21) [34], following an AED switch.

3.3. Phenytoin, divalproex, oxcarbazepine and levetiracetam

Two of the three studies that provided findings on lamotrigine also provided data on other AEDs [27,34]. No increase in event related ratio for ER visits or hospitalizations was found for generic switches of either phenytoin (0.96) or divalproex (0.84), MHRA category 1 and 2 AEDs, respectively [27]. Similarly, there was no increase in odds ratio for an ER visit, ambulance visit or inpatient hospitalization following a generic switch of either oxcarbazepine (0.45) or levetiracetam (0.18), MHRA category 2 and 3 AEDs, respectively [34].

3.4. Pooled AED analyses

The remaining studies detailed in Table 2 provide pooled results on several AEDs (spanning MHRA categories 1, 2 and 3) as opposed to a single AED from a single drug category. Five of these studies found increased healthcare utilization following an AED switch [19,21,29,30,33], while another 5 studies (including a pooled analysis by Shcherbakova et al.) reported no such association [26,28,32,34,38]. Labiner et al. stratified patients with stable and unstable epilepsies using multiple AEDs and found that generic AED use was associated with greater healthcare utilization regardless of epilepsy stability (findings for stable and unstable patients combined were: hospitalizations (IRR 1.24; 95% CI 1.19–1.30), outpatient visits (IRR 1.14; 95% CI 1.13–1.16), and length of hospital stay (IRR 1.29; 95% CI 1.27–1.32)) [30]. In a case–control study involving patients with no recent emergently treated seizures, Hansen et al. [29] found a 57% increased likelihood of an emergently treated event following an AED switch when patients were matched for age, seizure diagnosis, gender and total number of AED prescriptions filled (adjusted odds ratio 1.57; 95% CI 1.17–2.10). The same author found a moderate association between switching and emergently treated seizure-related events in an additional study (adjusted odds ratio 1.27; 95% CI 1.14–1.41), and the risk of healthcare utilization increased as the number of co-morbidities increased [21]. Two further case–control studies assessed a composite endpoint of ER visit, ambulance service utilization or hospitalization [19,33]. Rascati et al. [33] found that epilepsy patients who required acute healthcare were approximately 80% more likely than matched controls to have had an AED switch (odds ratio 1.84; 95% CI 1.44–2.36). Similarly, Zachry et al. also found that acute healthcare use was approximately 80% more likely for those who had an AED switch versus those who had not (odds ratio 1.81; 95% CI 1.25–2.63) [19].

While Gagne et al. found an increased risk of an ER visit or hospitalization following an AED switch (odds ratio 2.75; 95% CI 0.88–8.64), after adjusting for the risk associated with refilling an AED prescription per se, the effect of a switch was much reduced (odds ratio 1.19; 95% CI 0.35–3.99) [28]. Similarly, Kesselheim et al. found no increased risk of a seizure-related event after adjusting for the process of refilling (odds ratio 1.00; 95% CI 0.94–1.07) and thus no association between switching and seizure-related hospital visits [38]. Devine et al. found a notable increase in ER visits or hospitalization in an unadjusted analyses (odds ratio 1.51; 95% CI 1.29–1.76), but this was greatly reduced (odds ratio 1.08; 95% CI 0.91–1.29) after adjusting for confounders such as age, comorbidity index, total number of AEDs, presence of new AEDs, drug interactions, and change in epilepsy diagnosis [26]. Even after adjusting for confounders, however, the odds ratio of an ER visit or hospitalization was higher for those who had 2 (odds ratio 1.95; 95% CI 1.7–2.2) or ≥3 (odds ratio 2.96; 95% CI 2.48–3.49) AED switches. Moreover, Devine et al. [26] included patients who were not taking any AED at index date (12% of cases and 19% of controls), which makes their results more difficult to interpret. Finally, a recent case-crossover trial of controlled epilepsy patients did not find an increase in hospitalizations following a brand-to-generic AED switch [32].

4. Discussion

The findings of studies that examined an association between an AED switch and a change in healthcare utilization are conflicting.

Inter-study methodological differences may, at least in part, explain the inconsistent outcomes observed:

(a) Seven of the 14 reviewed studies used pooled data from several AEDs and as a result, individual AED findings may have been masked. In the pooled findings of Shcherbakova et al. for example, switching was found to have no effect on healthcare utilization but when data for topiramate were analyzed independently
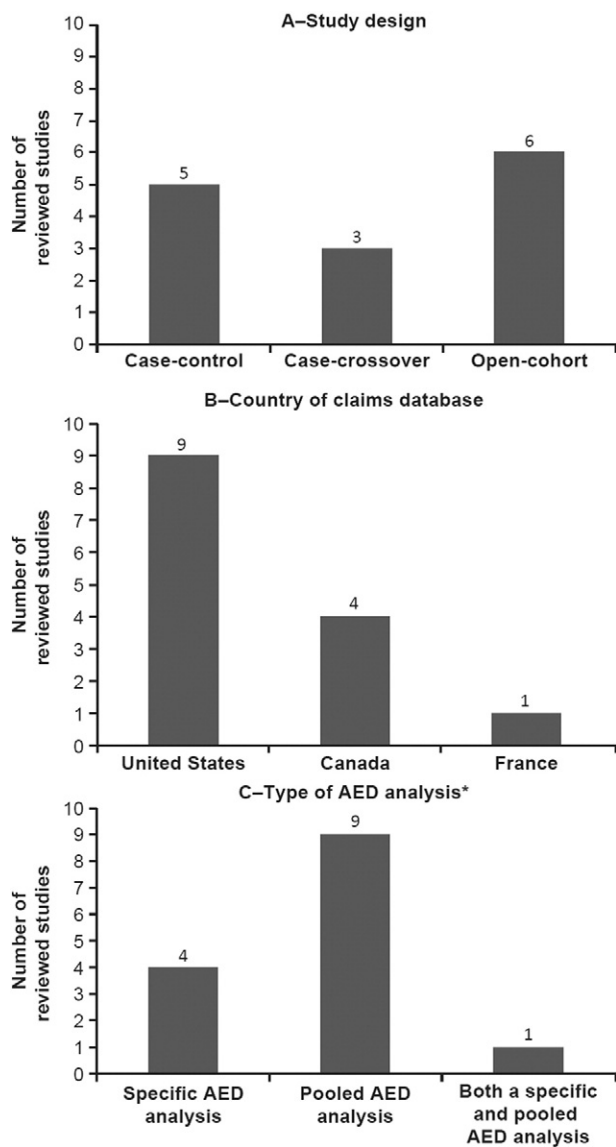
Fig. 2. Breakdown of the included studies by design, country of claims database and type of AED analysis. *Some studies examined the effect of switching in a specific AED e.g. topiramate, whereas others examined the effect of switching in a pooled analysis of multiple AEDs.

there was evidence of an increased risk of healthcare utilization for that AED [34].

(b) There was a lack of consistency among the reviewed studies in terms of the covariates used for adjustment (Table 2). None of the studies that reported an increase in healthcare utilization following an AED switch appear to have adjusted for the risk associated with simply refilling the same agent. Gagne et al. and Kesselheim et al. found that after such an adjustment, the harmful effect of AED switching was much reduced or negligible [28, 38].

(c) Different types of AED switch were examined in the studies (Table 2) but findings from Devine et al. [26] and Duh et al. [17] suggest that the effect of switching on healthcare utilization may be particularly pronounced for certain types of switch i.e. multiple generic switches. Erickson et al. [27] and Polard et al. [32], who found no association between a switch and healthcare utilization, only examined brand-to-generic switches.

(d) The included studies did not take into account potential variations in the quality of generic formulations. This may be a relevant issue because the standards for bioequivalence differ, especially in

developing countries [35,39]. The reviewed studies also lack data on potentially important confounding factors that could influence outcome, including disease severity, duration and type of epilepsy, and the reason for an AED switch [18]. A medical record review could provide such information and thus enhance these studies.

Given the heterogeneity of methodologies and findings among the included studies, an examination of the average effect across studies (a meta-analysis) was not undertaken. While the Newcastle-Ottawa rating of the included studies indicated they were generally of good quality (i.e. in terms of the selection and comparability of the study groups, and the identification of the exposure/outcome of interest), the level of evidence and strength of recommendations from the studies were considered to be very low (GRADE score and AAN classification). Fundamental limitations in medical claims analyses, such as their open-label, observational nature and a lack of randomization or blinding, can explain these findings. It is encouraging that higher-level evidence is now emerging from double-blind, randomized controlled trials in this area. Two studies on lamotrigine have recently been published for example. The EQUIGEN trial assessed the US FDA bioequivalence standards by studying the effects of switching between two generic lamotrigine products in patients with epilepsy using a randomized, double-blind, crossover study design [40]. No detectable differences in seizure control were found, supporting the bioequivalence of the two generic products. Another randomized, double-blind study compared brand and generic lamotrigine and found that few subjects had seizure exacerbations with switching [41]. These findings support those of the healthcare utilization studies included in our review where a brand-to-generic lamotrigine switch was not associated with an increased risk of emergently treated events (ambulance use, ER visits or hospitalization) [17,25,32].

Whether the findings regarding lamotrigine can be extrapolated to other AEDs is open to question. Support in doing so may be based on the argument that the same regulatory standard is applied to generic products of all AEDs. However, differences between individual drugs and types of switches may exist. For instance, the topiramate studies included in our review revealed a trend toward increased healthcare utilization with a switch to generics, particularly when multiple generic switches were undertaken [17,31,34]. Hence, ideally, similarly high quality evidence should be obtained for the other AEDs, although this may not be feasible due to the high costs of clinical trials.

The conflicting evidence regarding the association between an AED switch and a change in healthcare utilization rates is reflected by inconsistency in recommendations from different professional and regulatory bodies. Existing guidelines from a number of professional bodies advocate a cautious approach [25,42–44]. For instance, the AAN opposes the generic substitution of AEDs for the treatment of epilepsy without the approval of a physician in general [42], while the MHRA provided guidance for individual AEDs according to the anticipated risk. However, based on the findings of the lamotrigine studies [31,32], the American Epilepsy Society (AES) has recently revised its position and states that switching to a FDA-approved generic product does not compromise efficacy. There is a need for harmonization of guidelines which should be updated as new evidence emerges.

A final word should be reserved for the putative confounding role of epilepsy severity in healthcare utilization related to AED switch. As briefly alluded to above, reviewed studies fail to take this key aspect into account. Clinicians need not be reminded of the difficulties and nuances associated with the achievement of an acceptable level of seizure control in patients with severe epilepsies. Interference with such a delicate balance may be inevitable with AED switch and its impact in this specific population constitutes an urgent matter of study.

5. Conclusion

This systematic review provides a comprehensive overview of the available studies that examined the effect of an AED switch on outpatient visits, emergency room (ER) visits, hospitalization and length of hospital stay, and provides recommendations for future research directions in this area. Studies that have examined the association between an AED switch and a change in healthcare utilization report conflicting findings. Factors that may explain this lack of consistent outcome include inter-study differences in the type of analysis undertaken (pooled vs individual AED data), the covariates used for data adjustment, and the type of switch examined. Future medical claim database studies in this area are encouraged to address these and other factors in order to enhance inter-study comparability and extrapolation of findings. The recent demonstration of bioequivalence between generic products of lamotrigine in studies using a randomized, double-blind design is encouraging. Similar well designed, prospective studies are needed for the other AEDs.

Acknowledgement

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