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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.

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

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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.

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

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

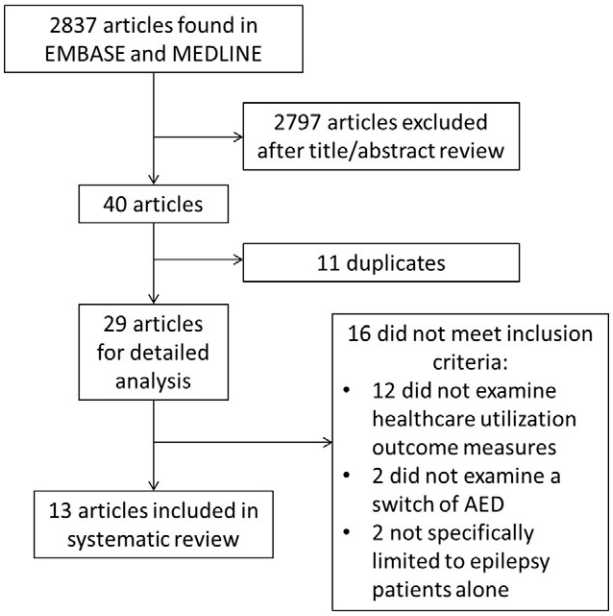

Fig. 1. Study selection.