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Clinical and economic burden of breakthrough seizures

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ABSTRACT

Purpose: The purpose of this study was to measure health-care resource utilization and costs in treatment-adherent, previously seizure-free patients with epilepsy who were treated in the inpatient/emergency room (ER) setting for new-onset seizures, compared with matched controls.
Methods: The study used a retrospective case/control study design using administrative claims from the IMS PharMetrics™ database. We identified adult patients with epilepsy with 1 + ER visit/hospitalization with primary diagnosis of epilepsy between 1/1/2006 and 3/31/2011, preceded by 6 months of seizure-free activity and anti-epileptic drug (AED) treatment adherence (≥80% of days covered by any AED); the first observed seizure defined the "breakthrough" seizure/index event. Treatment-adherent patients with epilepsy without any ER/hospital admission for seizures served as controls: an outpatient epilepsy-related medical claim within the selection window was chosen at random as the index date. The following were continuous enrollment requirements for all patients: ≥12-month pre- and ≥6-month postindex. Each case matched 1:1 to a control using propensity score matching. All-cause and epilepsy-related (epilepsy/convulsion diagnosis, AED pharmacy) resource utilization and unadjusted and adjusted direct health-care costs (per person, 2012 US dollars (USD)) were assessed in a 6-month follow-up period.
Principal results: There were 5729 cases and 14,437 controls eligible. The final sample comprised 5279 matched case/control pairs. In unadjusted analyses, matched cases had significantly higher rates of all-cause hospitalization and ER visits compared to controls and significantly higher total all-cause direct health-care costs (median $12,714 vs. $5095, $p < 0.001$) and total epilepsy-related costs among cases vs. controls (median $7293 vs. $1712, $p < 0.001$), driven by higher inpatient costs. Among cases, costs increased with each subsequent seizure (driven by inpatient costs). Cases had 2.3 times higher adjusted all-cause costs and 8.1 times higher adjusted epilepsy-related costs than controls (both $p < 0.001$).
Conclusion: Inpatient/ER-treated breakthrough seizures occurred among 28.4% of our treatment-adherent study sample and were associated with significant incremental health-care utilization and costs, primarily driven by hospitalizations. Our findings suggest the need for better seizure control via optimal patient management and the use of effective AED therapy, which can potentially lower health-care costs.
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1. Introduction

Epilepsy is a chronic brain disorder characterized by recurrent seizures caused by abnormal neuronal activity, impacting more than 2.3 million adults in the US [1]. Therapeutic options for better seizure control include antiepileptic drug (AED) therapies such as sodium channel blockers and gamma-aminobutyric acid (GABA) enhancers, and in the case of drug-resistant epilepsy, surgical therapies such as vagal nerve stimulation (VNS) and focal resection [2,3]. Treatment choice is primarily based on the efficacy of an AED for a specific seizure type, but other factors such as tolerability, age, sex, and comorbidities are also important to consider [4,5].

Approximately two-thirds of newly diagnosed patients with epilepsy will become seizure-free with AED therapy (typically defined as seizure-free for ≥1 year), and for most, seizure control will be achieved with the use of their first or second AED regimen [2]. However, at least one-third of patients may continue to experience seizures, sometimes referred to as "breakthrough seizures". Breakthrough seizures have been described in the literature as seizures that happen suddenly and

Abbreviations: AED, antiepileptic drug; ER, emergency room; USD, US dollars; GABA, gamma-aminobutyric acid; VNS, vagal nerve stimulation; HIPAA, Health Insurance Portability and Accountability Act; PDC, proportion of days covered; CCI, Charlson Comorbidity Index; FM, family medicine; GP, general practitioner; GPI, general product identifier; GEE, generalized estimating equation; IM, internal medicine; POS, partial onset seizure.

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unexpectedly after a period of seizure freedom [6], but a clear clinical definition within guidelines is lacking [4,7–9]. Breakthrough seizures are most often discussed as a potential consequence of a change in AED, or nonadherence to prescribed AEDs; however, other potential precipitants include onset of an infection, sleep deprivation, severe emotional stress, and provocative environmental factors such as flashing lights or playing video games [6,10,11]. There can be severe consequences of breakthrough seizures including risk of accidents, fractures or head injuries, emergency room (ER) visits, and hospitalization, as well as an associated increase in health-care costs.

The economic burden of epilepsy is well established in the literature [12]. Higher health-care costs have also been associated with increasing number of seizures from initial epilepsy diagnosis [13]. Patients with refractory epilepsy (defined as use of ≥3 AEDs in a calendar year) have been found to have higher costs compared to patients with well-controlled epilepsy among patients with partial onset seizures (POS) [14]. Patients with uncontrolled epilepsy (defined as addition of an AED to an existing regimen) have been found to have higher costs compared to patients with stable epilepsy [15]. Patients with uncontrolled epilepsy (defined as ≥2 changes in AED therapy, followed by ≥1 epilepsy-related ED visit/hospitalization within 1 year) have been found to have higher costs compared to patients with well-controlled seizures (no AED change and no epilepsy-related ER visit/hospitalization) [16]. Additionally, one study assessed patients who received epilepsy-related treatment in emergent care settings after a period of AED adherence and seizure control and found higher costs in the 6 months following the event compared to the 6 months prior [17].

The objective of this study was to evaluate the direct cost impact of breakthrough seizures among AED-adherent patients. We identified patients with epilepsy in a US managed care population with and without evidence of a breakthrough seizure after a period of sustained control and compared all-cause and epilepsy-related health-care resource utilization and direct health-care costs between matched cohorts in the 6-month follow-up period. Additionally, we evaluated the impact of seizure frequency on all-cause health-care resource utilization and direct costs among cases. These findings would help quantify the frequency of breakthrough seizures as well as the direct clinical and economic consequences caused by breakthrough seizures, currently missing from existing literature.

2. Materials and methods

2.1. Data source

This retrospective database analysis utilized data from the IMS LifeLink Health Plan Claims database (PharMetrics™), comprising fully adjudicated medical and pharmaceutical claims for approximately 70 million unique patients from over 70 health plans across the US at the time of the study. Enrollees represented include those covered by employer-sponsored plans and government-sponsored but commercially administered Medicaid and Medicare plans as well as individuals purchasing coverage in the marketplace. Among payer types for all enrollees, 79% have a commercial plan while 10% are self-insured. The remaining 11% comprise Medicaid, Medicare Cost, Medicare Risk, or State Child Health Insurance. The PharMetrics database is most represented by the Midwest (34%) and South (31%), followed by the Northeast (19%) and then West (16%). The database is overrepresented by the Midwest and slightly underrepresented by the South and West: compared to the 2010 US census, the US population was highest in the South (37%), followed by the West (23%) and Midwest (22%), and then the Northeast (18%) [18]. Records are representative of the national, commercially insured population on demographic measures, including age and gender. Data elements include patient and plan type/enrollment, as well as inpatient and outpatient diagnoses (in ICD-9-CM format) and services/procedures, and both retail and mail order prescription records. Allowed, charged, and paid amounts are available for all services rendered as well as dates of service for all claims. The data are longitudinal, with an average member continuous enrollment period of more than two years, providing complete data capture. Patient data are de-identified following the Health Insurance Portability and Accountability Act (HIPAA); therefore, this study was exempt from Institutional Review Board review.

2.2. Cohort selection

Medical and pharmacy claims were assessed to identify adult (18+ years) cases and controls based on seizure activity within the sample selection window (July 1, 2006 to March 31, 2011). Because there is no single clinical definition or clinical diagnosis code for breakthrough seizure, we developed our definition based on a review of the literature and clinical input. We used our breakthrough seizure definition as a proxy to identify the subset of patients who experience breakthrough seizures and receive inpatient/ER care. Similar to two studies by Zachry et al., our breakthrough seizure definition required an epilepsy-related inpatient or ER admission following a combined period of seizure control and AED adherence [17,19]. Breakthrough seizures were identified as an ER or inpatient admission with a primary diagnosis of epilepsy (ICD-9-CM code 345.x excluding 345.6 [infantile spasms]), occurring in patients who had no evidence of a seizure and with ≥80% of days covered by any AED (proportion of days covered (PDC)) during the 6-month preindex period (80% adherence is a commonly used measure of "good" adherence within the literature). Patients meeting the criteria for a breakthrough seizure were identified as cases. The first seizure eligible as a breakthrough seizure within the sample selection window was chosen as the index date for cases. These requirements help provide confidence that the observed breakthrough seizure, occurring after a period of sustained seizure control and medication adherence, more likely resulted due to AED inefficacy rather than nonadherence.

The control group consisted of patients with epilepsy who had no evidence of a seizure in their entire available time within the database and who met the same AED adherence requirements as cases. A random outpatient medical claim (i.e., physician or facility visit) containing a primary diagnosis of epilepsy during the selection window was selected as the index date for controls in order to help ensure that controls were captured in all stages of the disease.

All patients were required to have ≥12-month preindex continuous health plan enrollment with ≥1 epilepsy diagnosis within that period. Patients were further required to have ≥6-month continuous health plan enrollment postindex (the follow-up period). The continuous health plan enrollment criteria were required to eliminate the impact of insurance coverage interruptions and to ensure visibility into a patient's health-care utilization and costs under his or her plan's coverage. Patients with incomplete health plan data (e.g., Medicare Fee-for-Service plan) were excluded.

Propensity score matching was utilized on the final eligible sample to control for demographic and clinical factors which may otherwise impact resource utilization and costs, aside from the event of interest (seizure activity resulting in ER/inpatient care). Propensity score matching is a common regression modeling technique used in retrospective database analysis to adjust for differences between study cohorts. After examining unadjusted baseline patient characteristics, cases and controls were matched 1:1 using a "nearest neighbor" approach, defined by a minimal difference (e.g., <0.001) in the fitted probability of experiencing a breakthrough seizure on the following characteristics: age group, gender (although not significant), payer type, physician specialty, and the following characteristics measured over the 6-month preindex: Charlson Comorbidity Index, essential hypertension, and all-cause health-care costs (in the 6-month preindex).

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