Pediatric Neurology 74 (2017) 32–40

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Trends in Antiepileptic Drug Use in Children and Adolescents With Epilepsy

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ABSTRACT

OBJECTIVE: We describe the trends in antiepileptic drug (AED) use in children and adolescents with epilepsy in the United States. **METHODS:** We undertook a cross-sectional study based on Medicaid Analytic eXtract data set from 26 US states. Children and adolescents aged three to 18 years with at least one year continuous Medicaid fee-for-service coverage after the second outpatient or the first inpatient diagnosis of epilepsy in each calendar year during 1999 to 2009 were included in the study; therefore, 11 cohorts were established. A patient was defined as being exposed to a specific AED if he or she had at least one-day supply of the AED during the 1-year follow-up period. The annual prevalence of AEDs was reported, stratified by gender and age. The trends in AED use were evaluated through linear regression. **RESULTS:** The sample sizes of the 11 cohorts ranged between 17,304 and 22,672. The annual prevalence of valproic acid use declined from 42.4% in 1999 to 26.5% in 2009, and the prevalence of carbamazepine use declined from 37.1% to 10.2%. Meanwhile, the prevalence of levetiracetam use increased from 5.1% to about 32.0% in 2009, and the prevalence of oxcarbazepine use increased from 1.3% to 19.1%. Since 2008, levetiracetam (29.6%) has replaced valproic acid (27.8%) as the most commonly used AED in children and adolescents with epilepsy. The prevalence of diazepam use increased from 11.6% to 28.1%. **SIGNIFICANCE:** Compared with first- and second-generation antiepileptic drugs, third-generation AEDs have fewer adverse side effects, resulting in increased patient treatment adherence. Equally important is the economic impact of these newer AEDs. This first-of-its-kind study underscores the need for large database studies that objectively assess the cost-effectiveness of third-generation AEDs versus first- and second-generation AEDs in the treatment of childhood epilepsy.

Keywords: antiepileptic drugs, epilepsy, children, adolescents, medicaid

Pediatr Neurol 2017; 74: 32-40

Introduction

Epilepsy is one of the most common neurological disorders in children and adolescents in the United States[1] and affects 0.5% to 1.0% of children younger than 16 years.[2] Antiepileptic drugs (AEDs) play an important role in the control of childhood seizures. Based on the time of introduction to the market, AEDs can be classified into three generations.[3] First- and second-generation AEDs include barbiturates (mephobarbital, phenobarbital, and primidone), benzodiazepines (clobazam, clonazepam, clorazepate, diazepam, and lorazepam), hydantoins (ethotoin, fosphenytoin, and phenytoin), succinimides (ethosuximide and methsuximide), acetazolamide, divalproex or valproic acid, and carbamazepine. Third-generation AEDs include felbamate, gabapentin, lamotrigine, lacosamide,

Disclosure statement: None of the authors has any conflict of interest to disclose.

Article History:
Received October 6, 2016; Accepted in final form May 22, 2017

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0887-8994/$ – see front matter © 2017 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2017.05.016

levetiracetam, oxcarbazepine, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide.

Over the past two decades, 14 new AEDs have been introduced to the market, accounting for more than half of the currently available AEDs.[4,5] Although third-generation AEDs are potentially safer and less likely to have drug-drug interactions, they are more costly and not necessarily more effective than first- or second-generation AEDs.[6] The UK National Institute for Health and Care Excellence (NICE) guidelines for epilepsy treatment discourages the use of some newer AEDs as first-line therapy because they are not cost effective.[7] Despite this fact, AED utilization studies from several countries[8-10] have revealed increased use of third-generation AEDs and decreased use of first- and second-generation AEDs. As drug policy, availability, and cost vary among countries, the trends in other countries may not apply to the United States. The use of AEDs in children and adolescents needs attention because the cause of epilepsy, its neuropathology, distribution of seizure types, and response to AEDs in children may differ from those in adults.[11-14] We conducted an AED utilization study to describe the trends in AED use in children and adolescents covered by Medicaid fee-for-service (FFS) programs in 26 US states from 1999 to 2010. This study underscores the need for guidelines for childhood epilepsy treatment that objectively takes into account multiple factors including efficacy, safety, and cost.

Methods

Data source

This is a cross-sectional study based on Medicaid Analytic eXtract (MAX) files from 26 US states from 1999 to 2010. Medicaid is a federal-state funded program of national health assistance that provides health care coverage to certain individuals and families with low income and resources.[15] As the largest public health insurance program for low-income patients in the United States, Medicaid has covered more than 50 million people as of December 2010. The MAX data set is originally generated for billing purposes and is then processed and assembled by the Centers for Medicare & Medicaid Services (CMS) for research purposes. In addition to demographic information, eligibility status, and billing records for outpatient and inpatient encounters, MAX details associated diagnoses, procedures, and pharmacy services. Health care services that are not associated with any claims are not included in the MAX data set, e.g., over-the-counter drugs.

A trend in Medicaid programs that profoundly affects the use of MAX data set for research purposes should be noted, which is called "Medicaid managed care penetration." As of July 1, 2013, managed care accounted for more than 50% of Medicaid enrollees in 27 states.[16] Medicaid managed care programs are characterized by capitation payments, and the benefits of Medicaid enrollees are delivered by managed care organizations. Because Medicaid managed care encounter data are unavailable, incomplete, or not validated in a large number of states, we selected for this study 26 states that retain enough FFS enrollees under comprehensive managed care penetration from 1999 to 2010. The FFS part of MAX data set has been used in many epidemiological studies,[17-19] and the data quality is satisfactory.

Study population

Children aged three to 18 years with at least two outpatient visits with the diagnosis of epilepsy or one hospitalization for epilepsy (The International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes: 345.xx), followed by at least one year of continuous Medicaid FFS coverage, were included in this study. Outpatient visits had to be at least 30 days but no more than two years apart. We did not include ICD-9-CM codes of 780.3x because the target population is not patients with probable epilepsy but those with epilepsy; thus a higher positive predicted value (PPV) is preferred. Combining 345.xx and 780.3x has a lower PPV than using 345.xx alone.[13] We did not require more than two diagnoses because this may shrink the sample size dramatically, although requiring four diagnoses may elevate the PPV to almost 100%.[13] We required at least two outpatient claims or one inpatient claim of epilepsy to balance PPV and sample size. We did not require any AED use to identify the study population because the aim of the study is to describe the use of AED in children and adolescents with epilepsy; requiring any AED prescriptions would bias the results by overestimating AED exposure.

Demographic characteristics (gender, race, and date of birth) were ascertained from enrollment data, which also provided reasons for Medicaid eligibility, allowing the determination of foster care, families receiving cash assistance, poverty, and disability.

The epilepsy subtype was determined by the second outpatient diagnosis or the first inpatient diagnosis in each calendar year, whichever came first. The date of the claim defined the index date. If the first inpatient claim and second outpatient claim occurred on the same day, the inpatient claim was set to override the outpatient claim. As one claim might include multiple epilepsy diagnoses, the diagnoses with specific types and severity were set to override those without it, and the principal diagnoses were set to override secondary diagnoses. The subtypes are categorized as follows[20]: generalized nonconvulsive epilepsy or petit mal status (345.0x, 345.2x), generalized convulsive epilepsy or generalized tonic-clonic status (345.1x, 345.3x), focal epilepsy (345.4x and 345.5x), and other types or unclassified epilepsy (345.6x, 345.7x, 345.8x, and 345.9x). Validation studies have shown that ICD-9-CM coding to identify generalized tonic-clonic status (345.3x) and partial epilepsy with complex partial seizures (345.4x) had PPVs >75%, but the PPVs for other types of epilepsy are low or unavailable.[21] Therefore the misclassification of epilepsy subtypes in claims databases should be considered when interpreting the results. We used the fifth digit of the ICD-9-CM codes to categorize epilepsy severity, including nonintractable (345.x0), intractable (345.x1), and unspecific (345.x9, or missing the fifth digit). By the same token, misclassification of epilepsy severity in claims database should be considered when interpreting the results.

We excluded children who stayed in the hospital for more than 30 days because the drug exposure during hospitalization is not documented in claims databases (unmeasurable period). Although during the remaining time the patients may have had outpatient visits and filled prescriptions, the total follow-up time for them is shorter than those without long hospitalizations. To make the study population have the same length of follow-up, we decided to remove the patients with long hospitalizations. This decision may limit the generalizability of the study as it excludes the sickest.

Measurement of antiepileptic drug exposure

We measured AED exposure based on active ingredient identified with national drug code, prescription filling date, and days' supply. The dosage form was ignored. The follow-up period is one year after the second outpatient visit or the first hospitalization with the diagnosis of epilepsy (Fig 1). Children with at least one AED prescription filled during the follow-up period were defined as being exposed to this AED in the specific year. A patient can contribute to multiple years of follow-up as long as he or she met the inclusion criteria.

We studied the trends of using the following AEDs in this study. The first- and second-generation AEDs include barbiturates (mephobarbital, phenobarbital, primidone), benzodiazepines (clobazam, clonazepam, clorazepate, diazepam, lorazepam), hydantoins (ethotoin, fosphenytoin, phenytoin), succinimides (ethosuximide, methsuximide), acetazolamide, divalproex or valproic acid, and carbamazepine. The third-generation AEDs include felbamate, gabapentin, lamotrigine, lacosamide, levetiracetam, oxcarbazepine, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide.

We did not include ezogabine and perampanel in the AED list because they were approved by the US Food and Drug Administration in 2011 and 2012, respectively, and were therefore not available during our study period (1999 to 2010). For AEDs approved after 1999, study periods