



Use of antiepileptic drugs and lipid-lowering agents in the United States



Scott Mintzer^{a,*}, Vittorio Maio^c, Kathleen Foley^b

^a Department of Neurology, Thomas Jefferson University, USA

^b Truven Health, Ann Arbor, MI, USA

^c School of Population Health, Thomas Jefferson University, Philadelphia, PA, USA

ARTICLE INFO

Article history:

Received 2 December 2013

Revised 4 March 2014

Accepted 7 March 2014

Available online 14 April 2014

Keywords:

Antiepileptic drugs
Enzyme induction
Lipid-lowering agents
United States

ABSTRACT

Introduction: The extent to which enzyme-inducing antiepileptic drugs (EIAEDs) are used as first-line treatment in the United States remains unknown. Studies suggest that EIAEDs produce elevation of serum lipids, which could require additional treatment. We assessed the current use of EIAED in monotherapy for epilepsy in the U.S., as well as the correlation between the use of EIAEDs and subsequent new prescriptions for HMG-CoA reductase inhibitors (“statins”) for hyperlipidemia.

Methods: We queried the MarketScan® databases between July 2009 and January 2013, covering 66 million patients with commercial or supplemental Medicare insurance. We identified individuals who had a diagnosis of seizures, continuous enrollment in the database from 6 months prior to 24 months after the epilepsy diagnosis, no utilization of an AED or a statin prior to that diagnosis, and at least 1 new AED prescription. We tabulated the fraction of subjects who were prescribed EIAEDs (phenytoin, carbamazepine, or barbiturates) and those prescribed all other AEDs. Rates of new statin prescription between 1 and 24 months after AED prescription were assessed among the two groups, restricted to those with no prior history of vascular disease who had lipid serology obtained subsequent to the new AED prescription.

Results: Of the 11,893 patients with newly treated epilepsy, 2425 (20.4%) were started on an EIAED, and 9468 (79.6%) were started on a noninducing AED. There was a consistent and significant trend for EIAEDs to be increasingly prescribed with increasing age ($p < 0.0001$).

Among patients meeting the criteria, 66 (13.3%) of 496 EIAED-treated patients and 178 (9.2%) of 1930 noninducing AED patients were newly prescribed a statin ($p < 0.007$). This difference remained significant after accounting for age and gender ($p = 0.015$). A patient who was started on an EIAED was 46% more likely to be subsequently prescribed a statin than a patient who was started on a noninducing AED (95% CI = 1.08–1.98).

Conclusions: Enzyme-inducing antiepileptic drug prescription for epilepsy appears to increase with increasing age in the U.S. despite the absence of a cogent rationale for this practice, suggesting a failure to appreciate the complications of EIAED therapy among U.S. physicians. Statins were more often prescribed to those newly treated with EIAEDs compared with those given noninducing AEDs. These preliminary data provide further evidence suggesting that EIAEDs elevate lipids in a clinically meaningful manner.

© 2014 Elsevier Inc. All rights reserved.

1. Introduction

Enzyme-inducing antiepileptic drugs (EIAEDs), including carbamazepine, phenytoin, and phenobarbital, are among the most commonly prescribed medications for seizures throughout the world. Mounting evidence indicates that these agents, probably via their widespread impact upon the cytochrome P450 system, engender a host of metabolic derangements [1,2], including elevations of serum lipids and other serologic markers of vascular risk [3]. These effects would be expected to materially increase the risk of vascular disease based upon estimation

from population studies in the cardiovascular literature [4] and additional surrogate markers [5].

Ideally, a direct assessment could be made to determine whether exposure to these drugs is associated with elevated incidence of vascular events. However, the hyperlipidemia caused by EIAEDs might easily and incidentally be picked up by primary care physicians performing routine health screening. If the lipid elevation is clinically significant, then treatment with a lipid-lowering agent may be initiated, often with no knowledge that the anticonvulsant is contributing to the problem. This may add to the costs and potential complications of care for patients.

Currently, there are little or no data to establish the extent to which EIAEDs are still being used as first-line therapy in the United States. Thus, the goals of this preliminary investigation were twofold: first, to

* Corresponding author at: 901 Walnut Street, 3rd Floor, Philadelphia, PA, USA. Tel.: +1 215 955 1222; fax: +1 215 955 0606.

assess patterns of new use of EIAEDs in the American epilepsy population; and second, to determine whether new AED therapy for probable epilepsy is associated with a higher incidence of subsequent initiation of treatment with an HMG-CoA-reductase inhibitor (“statin”). As our goal was to examine whether statins were needed for hyperlipidemia, we focused on the subset of patients who had a lipid panel drawn after AED initiation.

2. Methods

Our data source for this investigation is the Truven Health MarketScan® Research Databases (Truven Health, Ann Arbor, MI). In this investigation, we utilized the Medicare Supplemental Database, which aggregate claims data from over 130 different carriers covering employees of more than 100 medium- and large-sized companies. The Medicare Supplemental Database contains medical and prescription drug claims for patients with supplemental employer-sponsored Medicare insurance. The analysis used data from July 2009 to January 2013, encompassing 66 million unique individuals. All data are deidentified and include age, gender, outpatient and inpatient diagnoses, tests and procedures ordered, and prescriptions.

From this, we included individuals of all ages meeting the following criteria: 1) continuous enrollment in the database for at least 6 months without a diagnosis of epilepsy or seizures (ICD-9 codes = 345.xx or 780.39) and not on any treatment with an AED; 2) a diagnosis of epilepsy or seizures appearing on at least two occasions at least 1 day apart; 3) a new, filled prescription for an AED (phenobarbital, phenytoin, primidone, carbamazepine, valproate, gabapentin, lamotrigine, topiramate, oxcarbazepine, levetiracetam, zonisamide, or pregabalin) for at least 30 days; and 4) follow-up in the database for at least 24 months subsequent to this prescription. We divided this population into two groups: those who were started on phenytoin, carbamazepine, phenobarbital, or primidone comprised the EIAED group, while those who were started on any of the other AEDs were considered the noninducing AED group. A patient who was started on medications in both classes simultaneously was excluded.

After looking at the patterns of AED prescription in this cohort, we aimed to ascertain those who were prescribed statins for reduction of lipids. To do this, we limited the aforementioned cohort to those aged 25 and older who were not taking a statin prior to AED initiation, had no prior codes for any vascular disease of the heart brain or peripheral vessels (ICD-9 codes = 410–414, 433–438, 440, 443.9, and 444), and had a lipid panel obtained subsequent to the AED prescription. This was done to maximize the likelihood that the statin was prescribed for hyperlipidemia rather than for another purpose. We examined the incidence of new statin prescriptions in this subgroup beginning 30 days after AED prescription, comparing those prescribed EIAEDs to those prescribed noninducing AEDs.

Outcomes were calculated in a binary fashion for each patient over the whole 24-month follow-up period. Chi-squared tests for independence and trend were used to examine patterns of AED prescription by age and gender. A logistic regression model was utilized to examine whether statin use differed by type of AED prescribed, with gender and age as covariates and $p < 0.05$ used as the marker for significance. Limitations of use of the dataset precluded more extensive analysis of potential confounders. Data were analyzed using SAS (SAS Institute, Cary, NC).

3. Results

3.1. Overall use of inducing and noninducing AEDs

Over the study period, there were a total of 11,893 patients who met the inclusion criteria. Of these, 2425 (20.4%) were started on an EIAED, and 9468 (79.6%) were started on a noninducing AED. Demographic data for the population are presented in Table 1. The group prescribed

EIAEDs was significantly older (49 vs. 38, $p < 0.0001$). In fact, when patients were divided into age groups, there was a very significant trend to prescribe EIAEDs at a higher rate with increasing age (chi-squared test for trend, $p < 0.0001$). Male patients were significantly more likely to be started on an EIAED than female patients (22.6% vs. 18.5%, $p < 0.0001$). Variation in the use of EIAEDs among different geographic regions and different types of health plans is also seen in Table 1.

3.2. Statin use in AED-treated patients

The analysis of subsequent statin use is shown in Fig. 1. Among all 11,893 patients, 7770 (65.3%) were 25 years or older, and 4898 (63%) of those had no prior history of statin use or vascular diagnoses. A lipid panel was subsequently obtained in about half of these 4898 patients: 49.2% of those started on noninducing AEDs and 50.8% of those taking EIAEDs ($p > 0.10$). Among those in whom lipids were checked, 178 (9.2%) of the 1930 noninducing AED patients were subsequently prescribed a statin, while 66 (13.3%) of the 496 EIAED-treated patients were subsequently prescribed a statin. The difference in incident statin prescription was highly significant between the two groups ($p = 0.007$) and remained significant even after accounting for age and gender ($p = 0.015$). Patients started on an EIAED were 46% more likely to be subsequently treated with a statin than those started on a noninducing AED (95% CI = 1.08–1.98).

4. Discussion

Some noteworthy findings emerged from this investigation. First, we found that patients receiving a new AED in monotherapy were significantly more likely to be treated with an EIAED with increasing age in the United States. While it is known that elderly often receive EIAEDs, our finding was not restricted to the elderly population, showing instead a clear and consistent trend beginning with children and continuing through adults of all ages. To our knowledge, this has not been reported before and certainly not in the American population.

This finding is unexpected and somewhat difficult to explain. Concerns about the effects of EIAEDs on bone health have existed for over four decades, and more recent evidence has also suggested potential deleterious effects of these drugs on cholesterol and other cardiovascular markers [2,3,6]; these are conditions for which advancing age is a considerable risk factor. Furthermore, the propensity of EIAEDs to cause drug interactions has likewise been widely known for decades, and the use of comedications also increases substantially with age in those with epilepsy as in all populations [7,8]. There are also formal head-to-head studies indicating that noninducing agents are equally effective as EIAEDs in the elderly while avoiding drug interactions and other metabolic difficulties [9,10]. Thus, we can find no cogent explanation for this finding, which is contrary to expert opinion [11]. Further study is clearly necessary to determine whether this finding is valid and, if so, what might be driving this behavior.

We also found that females were less likely to receive EIAEDs less likely than males. Perhaps this is due to the cosmetic side effects of phenytoin, or it might reflect avoidance of the interaction between EIAEDs and oral contraceptives [12]. Variation in EIAED usage by geographic region is complex and may require in-depth analysis of physician and patient behavior to be properly understood. There was little apparent variation in EIAED use among different types of commercial insurance except for a significantly higher rate of EIAED use among those enrolled in comprehensive plans; the reasons for this are not apparent and also merit further exploration.

Another important finding from our study is that once patients receive new AED therapy for seizures, those prescribed EIAEDs are almost 50% more likely to be subsequently started on lipid-lowering therapy than those who receive noninducing AEDs. This finding persisted even after adjustment for age and thus cannot be attributed the EIAED group being older. While statins are commonly used for secondary

Download English Version:

<https://daneshyari.com/en/article/6012353>

Download Persian Version:

<https://daneshyari.com/article/6012353>

[Daneshyari.com](https://daneshyari.com)