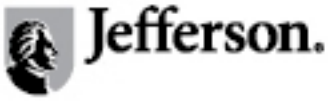

5-2014

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

Scott Mintzer
Thomas Jefferson University, scott.mintzer@jefferson.edu

Vittorio Maio
vittorio.maio@jefferson.edu

Kathleen Foley
Thomas Jefferson University, kathleen.a.foley@jefferson.edu

Use of Antiepileptic Drugs and Lipid-Lowering Agents in The United States

Scott Mintzer, MD, Vittorio Maio, PharmD, MSPH, Kathleen Foley, PhD

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 use of EIAEDs and subsequent new prescriptions for HMG-CoA reductase inhibitors ("statins") for hyperlipidemia.

Methods We queried the MarketScan® databases between July 2009 to 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 who were prescribed EIAEDs (phenytoin, carbamazepine, 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 non-inducing 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, a statin was newly prescribed in 66 of 496 (13.3%) EIAED-treated patients, and in 178 of 1930 (9.2%) non-inducing AED patients ($p < 0.007$). This difference remained significant after accounting for age and gender ($p=0.015$). A patient starting an EIAED was 46% more likely to be subsequently prescribed a statin than a patient started on a non-inducing AED (95% CI 1.08 - 1.98).

Conclusions EIAED 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 started in those newly-prescribed EIAEDs than to those given non-inducing AEDs. These preliminary data provides further evidence suggesting that EIAEDs elevate lipids in a clinically meaningful manner.

1. INTRODUCTION

Enzyme-inducing antiepileptic drugs (EIAEDs), including carbamazpine, 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. But 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 an 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 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 Commercial and Medicare Databases, which aggregate claims data from over 130 different carriers covering employees of more than 100 medium- and large-sized companies. The Medicare 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 de-identified 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 (pheno-

barbital, phenytoin, primidone, carbamazepine, valproate, gabapentin, lamotrigine, topiramate, oxcarbazepine, levetiracetam, zonisamide, or pregabalin) for at least 30 days; 4) follow-up in the database for at least 24 months subsequent to this prescription. We divided this population into two groups: those started on phenytoin, carbamazepine, phenobarbital or primidone comprised the EIAED group, while those started on any of the other AEDs were considered the non-inducing AED group. Any patient starting medications in both classes simultaneously was excluded.

After looking at patterns of AED prescription in this cohort, our next objective was to ascertain those who were prescribed statins for reduction of lipids. To do this, we limited the aforementioned cohort to those age 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 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 and those prescribed non-inducing AEDs.

Outcomes were calculated in a binary fashion for each patient over the whole 24 month follow-up period (i.e. new vascular diagnosis or not, new statin prescription or not). 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 non-inducing 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 non-inducing AED. Demographic data for the population are presented in the Table. 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 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 the Table.

3.2 *Statin use in AED-treated patients*

The analysis of subsequent statin use is shown in the Figure. Among all 11,893 patients, 7770 (65.3%) were age 25 years or older, and 4898 of those (63%) 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 non-inducing AEDs, and 50.8% of those taking EIAEDs ($p>0.10$). Among those in whom lipids were checked, 178 of the 1930 non-inducing AED patients (9.2%) were subsequently prescribed a statin, while 66 of the 496 EIAED-treated patients (13.3%) 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 non-inducing AEDs (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, 11]; 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 co-medications also increases substantially with age in the epilepsy population, as in all populations[6, 12]. There are also formal head-to-head studies indicating that non-inducing agents are equally effective, if not superior to, EIAEDs in the elderly, while avoiding drug interactions and other metabolic difficulties[7, 8]. Thus, we can find no cogent explanation for this finding, which is contrary to expert opinion[9]. 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 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[10]. 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 amongst 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 non-inducing AEDs. This finding persisted even after adjustment for age, and so cannot be attributed the EIAED group being older. While statins are commonly used for secondary prevention of cardiovascular disease and stroke even in the setting of normal cholesterol, we excluded any patient with a history of such disease from this portion of the analysis, so it is unlikely that many statin prescriptions in this cohort were for this purpose. Furthermore, a very similar fraction of patients had lipids checked in the inducing and non-inducing AED groups, so there was no evidence of ascertainment bias (e.g. more frequent lipid screening in those getting EIAEDs). Thus, the most likely explanation for this finding is that EIAEDs increase serum lipids to a degree that is judged clinically meaningful by practitioners, and thus worthy of treatment, in a statistically significant fraction of patients.

Note should be made that the fraction of patients requiring a statin after epilepsy treatment is substantial, constituting 5% of the whole group and 10% of those in whom lipid serology was obtained; as lipids were only checked in 50% of patients, that 5% number could easily be much higher. Thus, our data would suggest that treating all epilepsy patients with EIAEDs results in 3 - 4% of the cohort requiring a statin prescription which would not have be needed had a non-inducing AED been used. The true impact of EIAEDs in this regard is likely much greater than this, of course, since we excluded all those who had a history of prior statin treatment; many of this latter group of patients may require either higher doses or the addition of another lipid-lowering agent because of both the native lipid-elevating effects of EIAEDs and the induction of metabolism of most statin drugs by EIAEDs[12]. This suggests that the use of EIAEDs may constitute not just an important health issue, but also an economic one.

The statin findings reinforce the difficulties inherent in assessing the potential atherogenic properties of EIAEDs. We looked preliminarily in this patient group, and after accounting for age did not find the incidence of vascular disease to be significantly higher among EIAED-treated patients (data not shown). However, our inability to account for differential prescription for statins, as well as a host of other covariates that are pertinent to vascular disease risk (e.g. use of antiplatelet agents, hypertension, diabetes), make this comparison of dubious utility. A fully-adjusted epidemiologic study, with a longer time horizon than the 24 months available to us in the present study, is greatly needed to address this crucial issue more definitively.

The present study has several important limitations. As mentioned previously, this was a preliminary analysis in which we were unable to account for co-variates other than age and gender. Adjustment for covariates may be relevant not just to statin use, but also to the choice of AED. The lack of covariates precluded us doing an appropriate examination of other factors such as subsequent disease incidence or hospital admission rates. We were also limited to a 2-year forward-looking time horizon and a 6-month backward-looking period during which there was no epilepsy diagnosis because of the dataset; ideally such a study should be able to exclude the diagnosis of epilepsy and the use of AEDs or statins for at least a year prior to the index date, but doing so would have abridged the time horizon even more. The findings here are limited to the population with commercial or supplemental Medicare insurance, and thus their generalizability to other segments of the U.S. population (e.g. those of lower economic status with Medicaid insurance) is uncertain. Another issue is that claims databases

do not have some pieces of data that may be relevant to prescribing choices (e.g. race, obesity, smoking), nor were the actual results of lipid panels available for review to document their elevation. Thus, while we may make a reasonably strong inference that most of the statin prescriptions were for hypercholesterolemia, we can be be certain of this. Finally, the choice of whether to take a drug, and what drug is chosen, depend upon many aspects of both patient and physician behavior that cannot be assessed in a study of this nature. Thus, the use of prescription choice as an outcome measure should always be interpreted cautiously, and whenever possible should be bolstered by objective criteria that do not depend upon the subjective choices of practitioners and patients. In this case, abundant serologic data attest to the lipid-elevating effects of EIAEDs[3], so that interpretation of the findings may be considered with this in mind.

Thus, caveats notwithstanding, we believe these data support the findings of serologic studies in implicating EIAEDs as a cause of significant hypercholesterolemia. Our data also suggest that a substantial education gap exists in U.S. physicians' knowledge of the dangers of EIAEDs. Programs to address this gap may be important to promote the second half of the oft-stated epilepsy treatment goal of "no seizures, no side effects."

TABLE. Use of enzyme-inducing antiepileptic drugs (EAIEDs) in various subsets of the American commerically-insured population.

AGE GROUP	COUNT	% OF CO-HORT	# ON EI-AEDs	% ON EIAEDs	# on non-inducers	% on non-inducers
0-17	2936	24.7%	259	8.8%	2677	91.2%
18-34	2106	17.7%	340	16.1%	1766	83.9%
35-44	1320	11.1%	294	22.3%	1026	77.7%
45-54	1801	15.1%	476	26.4%	1325	73.6%
55-64	1779	15.0%	495	27.8%	1284	72.2%
65+	1951	16.4%	561	28.8%	1390	71.2%
				p<0.0001		
GENDER						
Male	5453	45.9%	1235	22.6%	4218	77.4%
Female	6440	54.2%	1190	18.5%	5250	71.5%
				p<0.0001		
CENSUS DIVISION						
New England	534	4.5%	102	19.1%	432	70.9%
Middle Atlantic	1665	14.0%	342	20.5%	1323	79.5%
East North Central	2591	21.8%	549	21.2%	2042	78.8%
West North Central	542	4.6%	104	19.2%	438	70.8%
South Atlantic	2208	18.6%	398	18.0%	1810	72.0%
East South Central	926	7.8%	172	18.6%	754	71.4%
West South Central	1053	8.9%	239	22.7%	814	77.3%
Mountain	646	5.4%	137	21.2%	509	78.8%
Pacific	1683	14.2%	370	22.0%	1313	78.0%
Missing	45	0.4%	12	26.7%	33	73.3%
PLAN TYPE						
Comprehensive	1467	12.3%	418	28.5%	1049	71.5%
Exclusive Provider Organization	149	1.3%	29	19.5%	120	80.5%
Health Maintenance Organization	1999	16.8%	386	19.3%	1613	80.7%
Point-Of-Service	1006	8.1%	199	19.8%	807	80.2%
Preferred Provider Organization	5580	46.9%	1067	19.1%	4513	80.9%
Consumer-Driven Health Plan	539	4.5%	106	19.7%	433	80.3%
High-Deductible Health Plan	211	1.8%	32	15.2%	179	84.8%
Unknown	942	7.9%	188	20.0%	754	80.0%
Total Patients	11893	100.0%	2425	20.4%	9468	79.6%

FIGURE. Flow chart for analysis of subsequent statin prescription among patients with newly-treated epilepsy, divided by type of antiepileptic used for treatment.

CVD = cardiovascular disease (including stroke and peripheral vascular disease); EIAED = enzyme-inducing antiepileptic drug

REFERENCES

1. Mintzer S. Metabolic consequences of antiepileptic drugs. *Curr Opin Neurol*. 2010;23 (2):164-169.
2. Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D. Enzyme induction with antiepileptic drugs: cause for concern? *Epilepsia*. 2013;54 (1):11-27.
3. Lopinto-Khoury C, Mintzer S. Antiepileptic drugs and markers of vascular risk. *Curr Treat Options Neurol*. 2010;12 (4):300-308.
4. Mintzer S, Skidmore CT, Abidin CJ et al. Effects of antiepileptic drugs on lipids, homocysteine, and C-reactive protein. *Ann Neurol*. 2009;65 (4):448-456.
5. Chuang YC, Chuang HY, Lin TK et al. Effects of long-term antiepileptic drug monotherapy on vascular risk factors and atherosclerosis. *Epilepsia*. 2012;53 (1):120-128.
6. Gidal BE, French JA, Grossman P, Le Teuff G. Assessment of potential drug interactions in patients with epilepsy: impact of age and sex. *Neurology*. 2009;72 (5):419-425.
7. Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. *Epilepsy Res*. 1999;37 (1):81-87.
8. Rowan AJ, Ramsay RE, Collins JF et al. New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. *Neurology*. 2005;64 (11):1868-1873.
9. Karceski S, Morrell MJ, Carpenter D. Treatment of epilepsy in adults: expert opinion, 2005. *Epilepsy Behav*. 2005;7 Suppl 1: S1-64; quiz S65-7.
10. Harden CL, Leppik I. Optimizing therapy of seizures in women who use oral contraceptives. *Neurology*. 2006;67 (12 Suppl 4):S56-8.
11. Hamed SA, Nabeshima T. The high atherosclerotic risk among epileptics: the atheroprotective role of multivitamins. *J Pharmacol Sci*. 2005;98(4):340-53.
12. Candrilli SD, Manjunath R, Davis KL, Gidal BE. The association between antiepileptic drug and HMG-CoA reductase inhibitor co-medication and cholesterol management in patients with epilepsy. Epilepsy Res. 2010;91(2-3):260-6.