Received: 22 October 2019 | Revised: 18 November 2019 | Accepted: 10 December 2019

DOI: 10.1111/epi.16420

Check for updates

Epilepsia®

FULL-LENGTH ORIGINAL RESEARCH

Hyperlipidemia in patients newly treated with anticonvulsants: A population study

Scott Mintzer[1] | **Misung Yi**[2] | **Sarah Hegarty**[2] | **Vittorio Maio**[3] | **Scott Keith**[2]

[1]Department of Neurology, Thomas Jefferson University, Philadelphia, Pennsylvania

[2]Division of Biostatistics, Department of Pharmacology, Thomas Jefferson University, Philadelphia, Pennsylvania

[3]School of Population Health, Thomas Jefferson University, Philadelphia, Pennsylvania

Correspondence
Scott Mintzer, Department of Neurology, Thomas Jefferson University, 901 Walnut Street, 4th Floor, Philadelphia, PA 19107.
Email: scott.mintzer@jefferson.edu

Funding information
This study was funded by UCB via an investigator-initiated grant to S.M.

Abstract

Objective: To determine the incidence of hyperlipidemia after first anticonvulsant treatment for seizures, using a large US administrative claims database.

Methods: We obtained data from the MarketScan Commercial and Medicare databases for 2005-2009 for all adult patients newly treated with an anticonvulsant for seizures who had no previous history of hyperlipidemia or treatment with a lipid-lowering agent. We divided the population based upon whether they were treated with an enzyme-inducing anticonvulsant (phenytoin, carbamazepine, phenobarbital, primidone) or a noninducing anticonvulsant (all others). The primary outcome measure was a new diagnosis of hyperlipidemia during subsequent follow-up. We accounted for a large number of demographic and clinical covariates.

Results: Of 11 374 subjects, 8778 (77%) were prescribed noninducers and 2596 (23%) were prescribed inducers. New hyperlipidemia diagnoses were seen in 14.6% of the patients started on inducing anticonvulsants and 10.7% of the patients started on noninducing anticonvulsants ($P < .001$). Both hyperlipidemia and the use of inducers were significantly associated with older age and male gender. After accounting for covariates, inducer prescription was still associated with 23% higher odds of a subsequent diagnosis of hyperlipidemia (odds ratio = 1.225, 95% confidence interval = 1.066-1.408, $P < .001$).

Significance: The use of enzyme-inducing anticonvulsants in patients with newly diagnosed epilepsy was associated with a significant increase in subsequent diagnoses of hyperlipidemia, suggesting that the lipid-elevating properties of these agents are of genuine clinical importance. This adds to the body of data demonstrating that these agents are likely associated with additional hassle, cost, and morbidity.

KEYWORDS

antiepileptic drugs, hyperlipidemia, incidence studies

1 | INTRODUCTION

Enzyme-inducing anticonvulsants—specifically phenytoin and carbamazepine—have been shown in many studies to increase serum lipids. On average, total cholesterol increases 20-25 mg/dL, and the large majority of this is in the atherogenic (non–high-density lipoprotein) fractions.[1,2] The amount of increase varies from patient to patient, and the various fractions increase more in some patients than others. This variability notwithstanding, the overall effect is significant in the substantial majority of studies, with a large

Statistical analysis was performed by Misung Yi, Sarah Hegarty, and Scott Keith.

© 2020 International League Against Epilepsy

enough effect size to indicate that it is a true pharmacologic property of the drugs.[3] However, the degree to which these increases are clinically meaningful remains uncertain—and is not an easy question to answer.

No absolute threshold can account for baseline risk having a major impact on whether a patient's lipid increase is meaningful; for example, an increase in serum cholesterol to 210 mg/dL in a healthy 23-year-old woman is not the same as an increase to 210 mg/dL in a 67-year-old man who has had coronary bypass surgery. The same may be said about a change of a certain magnitude; an increase of 20 mg/dL in the former patient is, once again, of less concern than it would be in the latter patient. Thus, any true determination of clinical significance must be individualized by those who care for the patient.

Our group made a preliminary attempt to investigate this issue by assessing whether lipid-lowering drugs were more commonly needed after the use of enzyme-inducing anticonvulsants in patients with newly diagnosed epilepsy.[4] Unfortunately, that study was limited by our inability to control for any covariates other than age and gender. In addition, the use of a drug prescription as an outcome measure is less than ideal, as prescriptions are themselves the product of clinical judgment and variability.

We therefore sought to readdress this issue, reasoning that a good proxy for clinically meaningful hyperlipidemia would be a new diagnosis of hyperlipidemia in the patient's chart; if the provider thought it was important enough to code, it was likely to be clinically relevant. We investigated how often a new diagnosis of hyperlipidemia appears in patients who are treated for seizures for the first time. Our hypothesis was that incident hyperlipidemia would occur more often in those started on inducing antiepileptic drug (AEDs) than in those started on noninducing AEDs.

Key Points

- Patients newly prescribed enzyme-inducing anticonvulsants were 23% more likely to be subsequently diagnosed with hyperlipidemia
- This indicates that the lipid-elevating properties of phenytoin, carbamazepine, et al are clinically relevant, not just "lab disease"
- This adds to the body of evidence showing that these drugs have profuse and problematic effects on metabolism
- Enzyme-inducing anticonvulsants are poor choices for those at risk for vascular disease and possibly for other patients as well

2 | MATERIALS AND METHODS

2.1 | Data source

We obtained administrative claims data from the MarketScan Research Databases (IBM Health), a very large collection of American administrative claims data. For this investigation, we queried both their commercial database, which aggregates data from >130 different insurance carriers covering employees of >100 companies, and the Medicare Supplemental Database, which includes data from patients with supplemental employer-sponsored Medicare insurance. A unique feature of this database is that when subjects switch carriers, they may remain in the database if their new carrier is also one that provides data to MarketScan; this helps reduce dropout from the "churn" of the private insurance market. Our initial data query focused on all subjects who appeared in the database in the 5-year period between 2005 and 2009 and had at least one inpatient or outpatient diagnosis code of epilepsy (International Classification of Diseases 9:345.xx) or seizure (780.3x). The initial query yielded 939 003 subjects from whom the more detailed investigation was structured.

2.2 | Inclusion/exclusion criteria

From this group, we considered a diagnosis of treated seizures to be confirmed if the subject had either (1) at least one admission with a seizure/epilepsy code, (2) at least one inpatient/outpatient service with an epilepsy code (345.xx), or (3) 2 distinct days of inpatient/outpatient services with a seizure code (780.3x). This fairly inclusive set of criteria was used for the main analysis, with the rationale that the point of the study was the long-term impact of anticonvulsant use for the treatment of seizures, rather than a diagnosis of epilepsy per se. As an internal sensitivity analysis, we also developed a set of more stringent criteria for epilepsy diagnosis, including patients who had (1) at least one admission with a seizure/epilepsy code or (2) 3 distinct days with inpatient/outpatient services carrying a seizure/epilepsy code. These criteria mirror those that were found to maximize sensitivity and specificity in a database validation study.[5] These latter criteria were used in a secondary analysis to see whether results varied depending upon how epilepsy was defined in the cohort. In either case, the date of diagnosis of epilepsy was defined as the date of the first epilepsy or seizure claim.

We then employed the following inclusion and exclusion criteria:

- We included subjects aged 18 years and older who had 12 months of continuous enrollment in the database prior to diagnosis to ensure that the vast majority of our cohort would be incident epilepsy.

- We included only those who were started on an anticonvulsant drug within 6 months of diagnosis.
- We excluded anyone who had been prescribed an anticonvulsant in the 12 months prior to the diagnosis, except for gabapentin or pregabalin; the latter were excepted because they are far more commonly used for pain or other conditions, and it was felt that exclusion on this basis would likely reduce our cohort unnecessarily.
- We excluded anyone who had a diagnosis of hyperlipidemia (272.1-4) or who had been prescribed a lipid-lowering agent during the 12 months prior to diagnosis.

2.3 | Drug exposure

Anticonvulsant drugs were divided into two categories: inducers and noninducers. Inducers included phenobarbital, primidone, phenytoin, and carbamazepine. Noninducers included valproate, ethosuximide, ethotoin, felbamate, gabapentin, pregabalin, lamotrigine, levetiracetam, zonisamide, rufinamide, oxcarbazepine, topiramate, tiagabine, and lacosamide. As it often takes time for a patient's therapy to be settled, we considered anticonvulsant prescriptions at 6 months following diagnosis; a subject taking a single anticonvulsant at that time was categorized in that class going forward. If the subject was taking two anticonvulsants, one inducer and one noninducer, the patient was excluded.

Subjects exposed to gabapentin and pregabalin were treated somewhat differently due to the overwhelming use of these two agents for pain. If the subject was taking two anticonvulsants, and one of them was gabapentin/pregabalin, the latter was ignored for this purpose, and the subject was classified according to the other drug (on the assumption that the former was likely being used for a pain indication). On the other hand, if the subject was taking gabapentin or pregabalin as the sole anticonvulsant, and it had been started subsequent to the epilepsy diagnosis, the subject was categorized as a non–inducer-treated patient.

We required that subject have at least 14 days of exposure to anticonvulsant medication, based upon prescription records, for inclusion. We set the threshold at such a brief level to be maximally inclusive in our patient population, knowing that doing so risked biasing our study toward the negative due to subjects who were on therapy fairly briefly (and thus would be unlikely to have any measured impact of the drug on metabolism). As a sensitivity analysis, we also looked at the fraction of the population who filled at least three anticonvulsant prescriptions for the drug category in which they were eventually assigned, with at least two of those being 30 days apart, indicating therapy for a minimum of a few months.

The start date for exposure was considered the first date of the prescription for the anticonvulsant category into which the patient was eventually sorted, or, if multiple anticonvulsants overlapped, the date at which the last prescription for the drug from the other category ran out. The end date was subsequently determined by either (1) loss of coverage and exit from the database; (2) gap in an anticonvulsant prescription of >30 days; (3) a new prescription for a drug from the other class, leading to censoring of data at that time; or (4) the end of the study period.

2.4 | Covariates

We attempted to control for histories of health conditions that might preferentially lead a clinician to prescribe a particular inducing or noninducing anticonvulsant. These included the following: obesity (278.0x); obstructive sleep apnea (327.23, used as a proxy for obesity); drug eruption (693.0); Axis I mood, anxiety, or psychotic disorder (295.x-298.x, 300.x); chronic back and spine conditions (722.x, 724.x); peripheral neuropathy (356.4, 356.8, 357.x); migraine (346.x); chronic renal insufficiency (585.x, 586); nephrolithiasis (592.x); hyponatremia (276.1); and chronic liver disease (571). We also calculated the Charlson Comorbidity Index score for each patient and incorporated this into analyses.

Year of diagnosis was also used as a covariate. In preliminary versions of the model, this was found to be associated with diagnosis of hyperlipidemia in a roughly linear fashion, with gradually decreasing incidence in advancing years (likely due to decreased follow-up time, with less time for the diagnosis to be made). Thus, in the final model, this was incorporated as a continuous variable.

Finally, we controlled for a number of sociodemographic measures, which were obtained from the first three digits of the subjects' ZIP codes, cross-referenced to data from the 2000 Census (the last year for which data were publicly available). The variables used included median household income, education (measured as percentage with high school degree or greater), percentage married, population density (measured as percentage living in an urban area), and race (measured as percentage white).

2.5 | Outcomes and analysis

Our primary outcome measure was the fraction of patients who obtained a new diagnosis of hyperlipidemia (272.0x-272.4x) during the follow-up period in those treated with inducing anticonvulsants and those treated with noninducing anticonvulsants. As an exploratory outcome measure, we also assessed the fraction of patients who obtained a

new diagnosis of cardiovascular disease (CVD), such as myocardial infarction, angina, or coronary artery disease during the follow-up period (codes 429.2x, 443.9x, 440.xx, 444.xx, 445.xx, 410.x0, 410.x1). For all outcomes, a single appearance of the code was considered positive for diagnosis. We considered this appropriate because the study was already biased toward a negative outcome simply because many patients may not have had their lipids measured, and therefore may have had elevated cholesterol that was never detected.

Demographic characteristics of subjects were compared between the two anticonvulsant groups with chi-square tests and *t* tests, as appropriate for categorical and continuous data. Odds of outcome diagnosis were compared between inducing and noninducing drug groups using logistic regression including age, gender, and all of the aforementioned covariates. This was done for the more inclusively defined cohort and, as a sensitivity analysis, for the more strictly defined cohort. In addition, as a further sensitivity analysis, we developed a propensity score model to predict each subject's likelihood of having serum lipids checked. This propensity was then also applied to the model, as a categorical covariate based upon quintiles of propensity score distribution, to see whether any difference found between groups could be explained simply on the basis of being less likely to have serum lipids checked. All statistical analyses were conducted using SAS v9.4 (SAS Institute), and the significance level of all tests was set a priori at $\alpha = .05$.

The institutional review board (IRB) of Thomas Jefferson University formally verified that this investigation was exempt from IRB review.

3 | RESULTS

Application of our inclusion and exclusion standards to the dataset of 939 003 subjects yielded a total of n = 11 374 who met criteria for the primary analysis. When the more stringent definition of epilepsy was used, the number of subjects who met criteria decreased by about 10%, to n = 10 214. Mean follow-up time for all subjects was 1.2 years.

The drugs used by the patients are shown in Table 1; note that the total sums to more than three times the number of subjects, reflecting that many patients seem to be prescribed multiple drugs in the early period following diagnosis. The most commonly used agents, both in terms of number of subjects and total number of prescriptions, were levetiracetam and phenytoin, with gabapentin having about the same number of prescriptions as phenytoin (although in fewer patients). Other commonly used agents, in descending order, were valproate, lamotrigine, topiramate, pregabalin, oxcarbazepine, and carbamazepine.

When the subjects' drug exposures were analyzed according to our algorithm, there were n = 2596 subjects (23%) who were classified as inducer-treated, and n = 8778 (77%) who were classified as non–inducer-treated. Baseline differences in the two cohorts, in both demographic variables and medical comorbidities, are shown in Table 2. There were a number of significant differences between the two groups, the most noteworthy being that the inducer group averaged 8 years older and had a much higher percentage of male subjects (54% vs 38%). There were also a number of comorbid conditions that were seen more commonly in the noninducer

TABLE 1 Use of anticonvulsants in the studied population

Generic name	Prescriptions	Subjects	Drug class
Divalproex/valproate	17 957	3196	Noninducing
Ethosuximide	46	19	Noninducing
Felbamate	37	6	Noninducing
Lacosamide	205	75	Noninducing
Lamotrigine	24 005	3396	Noninducing
Levetiracetam	61 011	9429	Noninducing
Oxcarbazepine	11 189	1661	Noninducing
Tiagabine	163	51	Noninducing
Topiramate	17 700	3171	Noninducing
Zonisamide	3612	609	Noninducing
Carbamazepine	9454	1562	Inducing
Phenobarbital	1873	321	Inducing
Phenytoin	39 676	7709	Inducing
Primidone	808	173	Inducing
Gabapentin	39 577	4471	Noninducing
Pregabalin	16 573	2469	Noninducing

Note: Drugs used by ≤10 subjects are not shown.

TABLE 2 Baseline characteristics of two groups of anticonvulsant-treated subjects

Covariates	Inducing drug, n = 2596, 22.8%	Noninducing drug, n = 8778, 77.2%	*P*
Age, y, mean (SD)	54.3 (19.49)	46.6 (19.50)	<.001
Sex, male, n (%)	1391 (53.6%)	3346 (38.1%)	<.001
Follow-up time, y, mean (SD)	1.2 (0.88)	1.2 (0.82)	<.001
Median income, mean (SD)	$50 359 (11 800)	$52 524 (12 441)	<.001
% high school grad, mean (SD)	80.4 (6.53)	81.3 (6.39)	<.001
% married, mean (SD)	55.0 (6.39)	55.5 (6.21)	.005
% in urban metro area, mean (SD)	75.4 (23.23)	76.5 (22.59)	.073
% white race, mean (SD)	76.5 (16.51)	77.7 (15.30)	.006
Diagnosed 2006, n (%)	759 (29.2%)	1769 (20.2%)	<.001
Diagnosed 2007, n (%)	758 (29.2%)	2183 (24.9%)	—
Diagnosed 2008, n (%)	644 (24.8%)	2642 (30.1%)	—
Diagnosed 2009, n (%)	435 (16.8%)	2184 (24.9%)	—
Obesity, n (%)	51 (2.0%)	248 (2.8%)	.016
Sleep apnea, n (%)	32 (1.2%)	205 (2.3%)	<.001
Drug rash, n (%)	2 (0.1%)	20 (0.2%)	.125
Axis I psychiatric disorder, n (%)	438 (16.9%)	1914 (21.8%)	<.001
Chronic back/spine, n (%)	434 (16.7%)	1856 (21.1%)	<.001
Peripheral neuropathy, n (%)	21 (0.8%)	80 (0.9%)	.625
Migraine, n (%)	84 (3.2%)	771 (8.8%)	<.001
Renal insufficiency, n (%)	120 (4.6%)	213 (2.4%)	<.001
Nephrolithiasis, n (%)	41 (1.6%)	189 (2.2%)	.068
Hyponatremia, n (%)	92 (3.5%)	249 (2.8%)	.063
Chronic liver disease, n (%)	43 (1.7%)	146 (1.7%)	.981
Charlson index, mean (SD)	1.1 (1.50)	0.9 (1.34)	<.001

TABLE 3 Unadjusted results among patients treated with inducing or noninducing anticonvulsants

	All subjects		Inducers		Noninducers		
	n	%	n	%	n	%	*P*
Hyperlipidemia	1316	11.57%	379	14.60%	937	10.67%	<.0001
Cardiovascular diseases	682	6.00%	221	8.51%	461	5.25%	<.0001
Hyperlipidemia or cardiovascular diseases	1841	16.19%	546	21.03%	1295	14.75%	<.0001

group, including migraine; chronic back and spine conditions; and Axis I mood, anxiety, or psychotic disorders.

Unadjusted results are shown in Table 3. New hyperlipidemia diagnoses during the follow-up period were seen significantly more often in the inducer group than in the noninducer group (14.6% vs 10.7%, $P < .001$). New CVD diagnoses were also seen significantly more often in the inducer group (8.5% vs 5.3%, $P < .001$), as was the combined outcome of new hyperlipidemia or new CVD (21% vs 14.8%, $P < .001$).

Fully adjusted results for the primary outcome measure are shown in Table 4. After accounting for all baseline differences between the groups, subjects in the inducer group were 23% more likely to be subsequently diagnosed with hyperlipidemia than those in the noninducer group (odds ratio [OR] = 1.225, 95% confidence interval [CI] = 1.066-1.408, $P = .001$). There was an estimated 13% higher probability of CVD diagnoses in the inducer group, but this was not statistically significant (OR = 1.131, 95% CI = 0.942-1.362, $P = .19$). The odds of a combined outcome of new hyperlipidemia or CVD were 20% higher in the inducer group (OR = 1.198, 95% CI = 1.058-1.358, $P = .004$).

Of the other covariates, both increasing age and male sex were associated with significantly higher incidences of

TABLE 4 Fully adjusted analysis results for association of incident hyperlipidemia diagnoses in patients newly prescribed anticonvulsants

Effect	Odds ratio	95% CI, low-high	*P*
Inducing vs noninducing drug	1.225	1.066-1.408	.004[a]
Age, per 10-y increase	1.072	1.035-1.110	<.001[a]
Male sex	1.211	1.070-1.370	.002[a]
Year of diagnosis	0.824	0.777-0.873	<.001[a]
Income	1.000	1.000-1.000	.186
Education	0.993	0.977-1.009	.372
Marital status	1.003	0.986-1.020	.750
Population density	0.998	0.994-1.002	.239
Race	0.997	0.990-1.004	.396
Charlson index	0.960	0.913-1.010	.112
Obesity	1.045	0.723-1.509	.815
Sleep apnea	1.383	0.967-1.979	.076
Axis I psychiatric disorder	0.758	0.651-0.882	.001[a]
Chronic back/spine	0.980	0.849-1.131	.781
Migraine	0.880	0.693-1.116	.292
Renal insufficiency	1.013	0.719-1.428	.940

Note: See text for definition of income, education, marital, population density, and race variables.

Abbreviation: CI, confidence interval.

[a]Statistically significant difference.

hyperlipidemia diagnoses, as would be expected ($P < .001$ for each). Comorbid medical conditions had no association with the outcome, with one exception: those with an Axis I psychiatric diagnosis in the mood, psychosis, or anxiety categories were significantly less likely to be diagnosed with hyperlipidemia (OR = 0.758, 95% CI = 0.651-0.882, $P < .001$).

We performed several variants of the analysis to check the importance of some of the assumptions that were made. First, when we applied the more stringent definition of epilepsy to our cohort, the association between inducer use and hyperlipidemia remained significant (OR = 1.161, 95% CI = 1.004-1.342, $P = .044$). Second, we applied our propensity score variable to the original logistic regression model, which attempted to account for the likelihood that a subject would have their lipids checked in the first place, and the association between inducer treatment and hyperlipidemia diagnoses remained nearly identical. Finally, we took the latter model, which included the propensity score variable, and looked only at subjects who had filled three anticonvulsant prescriptions (with at least two that were ≥30 days apart) in the drug class to which they ended up being assigned; once again, the association between inducer use and hyperlipidemia diagnosis remained almost exactly the same. (Data for all sensitivity analyses are not shown.)

After seeing the strong negative correlation between Axis I psychiatric diagnosis and hyperlipidemia, we hypothesized that the use of valproate in the population could be responsible, as there are several studies suggesting that valproate can reduce serum cholesterol.[6–8] Thus, we performed one final analysis in which we separated outpatients treated with valproate to see whether the former might be less likely to be diagnosed with hyperlipidemia. Using the remaining noninducer patients for comparison, valproate patients did have a lower incidence of subsequent hyperlipidemia, but the difference was not significant (OR = 0.831, 95% CI = 0.643-1.073, $P = .1563$).

4 | DISCUSSION

Confirming our hypothesis, we found that adults being treated for new onset seizures are about 23% more likely to be subsequently diagnosed with hyperlipidemia if they are treated with an enzyme-inducing anticonvulsant (such as phenytoin or carbamazepine) than they are if treated with a noninducing anticonvulsant. This not only reinforces the numerous serologic studies showing that inducers increase serum cholesterol[1,2,6,8–11]; it demonstrates that these changes are of clinical significance. Clinicians are unlikely to bother coding for a mere laboratory abnormality unless it is pertinent to the patient's health and engendered some discussion with the patient. A new diagnosis of hyperlipidemia suggests that the clinician will almost certainly be checking serum lipids again in the future, and may also recommend lipid-lowering measures, whether dietary or pharmacologic. This leads to expenditure of time, effort, and worry by patients, side effects from additional lipid-lowering treatments, and additional costs.

It is worth noting that incident hyperlipidemia was not a rare outcome in this cohort, occurring in about 12% of patients, so that the increased incidence seen with inducers is noteworthy even in absolute terms. Furthermore, our data almost certainly underestimate both the incidence of hyperlipidemia and the magnitude of the difference between the two groups, for a number of reasons. First, this is an observational study, and many subjects had not had their serum lipids checked at all, which precludes making such a diagnosis. The period of follow-up was quite limited, averaging only 1.2 years, and a longer follow-up time would undoubtedly have resulted in many more subjects getting screening lipid serology and being diagnosed with elevated cholesterol. Second, we employed very relaxed criteria for drug exposure; even our more stringent algorithm required treatment with the appropriate drug class for only a few months. We did this to be maximally inclusive and conservative in our methods, but in doing so we effectively created something akin to an "intention-to-treat" study; it is likely that some patients came off

their seizure medications after months, having already been classified in an anticonvulsant-treated group, so that when lipids were eventually checked, they were no longer affected by the seizure medication. Third, coding for a new diagnosis of hyperlipidemia is probably highly specific for clinically relevant lipid elevation, but the sensitivity is likely far less, as busy practitioners may not bother to code for everything of clinical importance during a visit. All of these factors would serve to reduce the overall incidence of hyperlipidemia in this population; the first factor alone would put the true incidence substantially higher (and the others suggest that it is likely higher still). As the increase in incidence would be seen preferentially in the inducer-treated patients, the difference between the two groups is likely to be larger as well.

Although we did not find a significant difference in CVD outcomes between the two groups, this is not surprising, as this was only an exploratory outcome, and the study was not designed for this. In particular, much longer follow-up would likely be required, as hyperlipidemia takes many months to years to produce cholesterol plaques, which then must enlarge or rupture to produce clinical CVD. Some evidence has suggested that inducers may be associated with CVD,[12,13] but interpretation of the studies has not always reflected this, and it is clear that more work is very much needed to examine this in light of our primary findings.

The finding that Axis I psychiatric conditions were associated with significantly less hyperlipidemia is interesting and unexpected. We thought that the use of valproate in this population might explain this; valproate is a potent inhibitor of many cytochrome P450 enzymes and therefore might be expected to reduce serum cholesterol,[14] and there is evidence from a few quarters that lipids may be lower in valproate-treated patients.[6–8] This is likely part of the explanation, but our data here did not show a difference that was significant in valproate-treated patients, and in any case, it would not seem to explain the phenomenon entirely. One possibility is that psychiatrists, who have become very attuned to the long-term metabolic effects of their agents, monitor their patients carefully for such derangements and may head this problem off to some extent. More work is clearly necessary to see if this finding is reproducible in other studies.

Our results confirm and extend those of our prior study, which looked at new prescriptions for lipid-lowering agents following anticonvulsant treatment.[4] Because of data restrictions, that study did not allow for measurement of and adjustment for covariates other than age and sex. In the present study, we were able to adjust for many variables, both demographic and medical, in an effort to reduce confounding that might impact the decision to prescribe an anticonvulsant. Although there were a host of factors that differed between the groups, very few of these had a significant effect in the multivariate analysis aside from age and gender, and the correlation between inducer use and hyperlipidemia remained highly significant.

The main limitation of this study is that it is observational, and therefore nonrandomized, which means that we cannot exclude the presence of residual confounders in producing the result. However, we explored a large number of variables, almost all of which had no impact on the association; even a detailed propensity score model aimed at ascertaining the likelihood of lipid screening left the magnitude of the primary finding unchanged. Furthermore, our findings correspond with the serologic data in this area, as previously mentioned. Thus, we think it is unlikely that an unmeasured confound could explain our results.

Another important limitation is that neither hyperlipidemia nor the diagnosis of epilepsy has been validated in this database. With regard to the latter, we tested a second version of epilepsy diagnosis that has been validated in other databases and recommended for widespread use,[5] and it did not change the finding. More importantly, however, it does not necessarily matter whether a subject has an epilepsy diagnosis for the purpose of this study; our goal was simply to ensure that the patient was being treated with the drug for seizures rather than primarily for another condition (eg, migraines, bipolar disorder) to avoid confounding by indication. The effects of the drugs on lipid metabolism are unlikely to differ depending upon whether the patient has had a single seizure or many. With regard to the former, as mentioned in the introduction, determination of whether an elevation of lipids is clinically significant is itself subjective and requires the judgment of the practitioner. Thus, this is an outcome that may not be readily "validatable" in the sense in which this term is usually used. What is germane to our result is the question of whether there might be any tendency of practitioners to preferentially apply this code to one group or another; as mentioned, extensive examination of potential covariates yielded nothing in that regard.

In a similar vein, another limitation is that we went back only 12 months to ensure that each subject had not been diagnosed with seizures or epilepsy. Although this should produce a cohort largely comprised of incident cases, there may be some who had a pre-existing diagnosis. We did this because the data we obtained were for a limited slice of time, and using a 2-year "clean period" would have reduced the size of our cohort substantially. As with the points above, this limitation is unlikely to have affected the analysis, because we also excluded patients who had taken an anticonvulsant during that time, and what truly matters is not so much that they had incident epilepsy, but whether they had any lingering effects of treatment. Having had no prescriptions filled for 1 year is certainly enough to ensure that any metabolic effects from a seizure medication would not be present, such that the subject could be considered treatment-naive.

In summary, we find that patients treated with inducers are more likely to be subsequently diagnosed with hyperlipidemia, indicative of a clinically important lipid problem. On a larger scale, the finding had an effect size such as to constitute a legitimate clinical practice issue, particularly when one also considers the many other difficulties engendered by the use of inducing anticonvulsants.[15] The use of inducers rather than noninducers is likely to produce additional comorbidity for patients, along with more utilization of resources, more hassle, and additional costs. This work adds to the body of data strongly suggesting that enzyme-inducing anticonvulsants should not be used as first-line therapy. Given the many studies showing equivalent efficacy among anticonvulsant drugs,[16–20] further consideration should be given to the question of whether those already taking inducing agents should remain on them.

CONFLICT OF INTEREST

S.M. reports participating on advisory boards, consultation, and speaking for Eisai, Greenwich Biosciences, UCB, and Abbvie. The other authors have no relevant financial relationships to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Scott Mintzer https://orcid.org/0000-0002-3285-5666

REFERENCES

1. Mintzer S, Skidmore CT, Abidin CJ, et al. Effects of antiepileptic drugs on lipids, homocysteine, and C-reactive protein. Ann Neurol. 2009;65:448–56.
2. Mintzer S, Miller R, Shah K, et al. Long-term effect of antiepileptic drug switch on serum lipids and C-reactive protein. Epilepsy Behav. 2016;58:127–32.
3. Lopinto-Khoury C, Mintzer S. Antiepileptic drugs and markers of vascular risk. Curr Treat Options Neurol. 2010;12:300–8.
4. Mintzer S, Maio V, Foley K. Use of antiepileptic drugs and lipid-lowering agents in the United States. Epilepsy Behav. 2014;34C:105–8.
5. Tu K, Wang M, Jaakkimainen RL, et al. Assessing the validity of using administrative data to identify patients with epilepsy. Epilepsia. 2014;55:335–43.
6. Calandre EP, Rodriquez-Lopez C, Blazquez A, Cano D. Serum lipids, lipoproteins and apolipoproteins A and B in epileptic patients treated with valproic acid, carbamazepine or phenobarbital. Acta Neurol Scand. 1991;83:250–3.
7. Green MW, Giordano S, Jiang P, Jafari M, Smith TB. Effect of divalproex on metabolic parameters is dose related in migraine prophylaxis. Headache. 2005;45:1031–7.
8. Nikolaos T, Stylianos G, Chryssoula N, et al. The effect of long-term antiepileptic treatment on serum cholesterol (TC, HDL, LDL) and triglyceride levels in adult epileptic patients on monotherapy. Med Sci Monit. 2004;10:MT50-2.
9. Bramswig S, Sudhop T, Luers C, von Bergmann K, Berthold HK. Lipoprotein(a) concentration increases during treatment with carbamazepine. Epilepsia. 2003;44:457–60.
10. Chuang Y-C, Chuang H-Y, Lin T-K, et al. Effects of long-term antiepileptic drug monotherapy on vascular risk factors and atherosclerosis. Epilepsia. 2012;53:120–8.
11. Isojarvi JI, Pakarinen AJ, Myllyla VV. Serum lipid levels during carbamazepine medication. A prospective study. Arch Neurol. 1993;50:590–3.
12. Olesen JB, Abildstrom SZ, Erdal J, et al. Effects of epilepsy and selected antiepileptic drugs on risk of myocardial infarction, stroke, and death in patients with or without previous stroke: a nationwide cohort study. Pharmacoepidemiol Drug Saf. 2011;20:964–71.
13. Renoux C, Dell'Aniello S, Saarela O, Filion KB, Boivin J-F. Antiepileptic drugs and the risk of ischaemic stroke and myocardial infarction: a population-based cohort study. BMJ Open. 2015;5:e008365.
14. Kandutsch AA, Chen HW, Heiniger HJ. Biological activity of some oxygenated sterols. Science. 1978;201:498–501.
15. Mintzer S. Metabolic consequences of antiepileptic drugs. Curr Opin Neurol. 2010;23:164–9.
16. Baulac M, Brodie MJ, Patten A, Segieth J, Giorgi L. Efficacy and tolerability of zonisamide versus controlled-release carbamazepine for newly diagnosed partial epilepsy: a phase 3, randomised, double-blind, non-inferiority trial. Lancet Neurol. 2012;11:579–88.
17. Brodie MJ, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group. Lancet. 1995;345:476–9.
18. Brodie MJ, Perucca E, Ryvlin P, Ben-Menachem E, Meencke HJ. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. Neurology. 2007;68:402–8.
19. Bill PA, Vigonius U, Pohlmann H, et al. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy. Epilepsy Res. 1997;27:195–204.
20. Baulac M, Rosenow F, Toledo M, et al. Efficacy, safety, and tolerability of lacosamide monotherapy versus controlled-release carbamazepine in patients with newly diagnosed epilepsy: a phase 3, randomised, double-blind, non-inferiority trial. Lancet Neurol. 2017;16:43–54.

How to cite this article: Mintzer S, Yi M, Hegarty S, Maio V, Keith S. Hyperlipidemia in patients newly treated with anticonvulsants: A population study. *Epilepsia*. 2020;00:1–8. https://doi.org/10.1111/epi.16420