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Risk of Pharmacokinetic Interactions between Antiepileptic and Other Drugs in Older Persons and Factors Associated with Risk

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Abstract

Objective—To determine the frequency of older Americans with epilepsy receiving concomitant prescriptions for antiepileptic drugs (AEDs) and non-epilepsy drugs (NEDs) which could result in significant pharmacokinetic (PK) interaction, and to assess the contributions of racial/ethnic, socioeconomic, and demographic factors.

Methods—Retrospective analyses of 2008–2010 Medicare claims for a 5% random sample of beneficiaries ≥67 years old in 2009 augmented for minority representation. Prevalent cases had ≥1 ICD-9 345.x or ≥2 ICD-9 780.3x, and ≥1 AED. Among them, incident cases had no seizure/epilepsy claim codes nor AEDs in preceding 365 days. Drug claims for AEDs, and for the 50 most common NEDs within +/− 60 days of the index epilepsy date were tabulated. Interacting pairs of AEDs/NEDs were identified by literature review. Logistic regression models were used to examine factors affecting the likelihood of interaction risk.

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Conflicts of Interest/Financial Disclosures:

Dr. Faught has served as a consultant for Aprecia, Biogen, Eisai and UCB Pharma, and as a Data-Safety Monitoring Board member for Eisai, Lundbeck, SAGE, and SK Life Science. He has received research funding from Brain Sentinel, Neuropace, the University of Alabama at Birmingham, and UCB Pharma. He is on the editorial board of *Epilepsy Currents*, and was on the Medicare Evidence Development and Coverage Advisory Committee of the Center for Medicare and Medicaid Services 2011–2014, and was Chair of the Treatments Committee of the American Epilepsy Society 2012–15.

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Drs. Funkhouser, Richman, Piper, Pisu, and Ms. Juarez and Mr. Dai report no conflicts

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with these guidelines.

Results—Interacting drug pairs affecting NED efficacy were found in 24.5% of incident, 39% of prevalent cases. Combinations affecting AED efficacy were found in 20.4% of incident, 29.3% of prevalent cases. Factors predicting higher interaction risk included having ≥ 1 comorbidity, being eligible for Part D low Income Subsidy, and not living in the northeastern US. Protective factors were Asian race/ethnicity, and treatment by a neurologist.

Significance—A substantial portion of older epilepsy patients received NED-AED combinations that could cause important PK interactions. The lower frequency among incident vs. prevalent cases may reflect changes in prescribing practices. Avoidance of interacting AEDs is feasible for most persons because of the availability of newer drugs.

Keywords

Epilepsy; seizures; race; ethnicity; interactions; antiepileptic drugs

INTRODUCTION

We explored the frequency of potential pharmacokinetic interactions between antiepileptic drugs (AEDs) and commonly-used non-epilepsy drugs (NEDs). Drug interactions may be divided into two major types: pharmacokinetic (PK) and pharmacodynamic (PD). PK interactions alter the effective dose of one or both drugs reaching the biological target, and PD interactions are those which result from additive or subtractive effects of drug combinations on the same biological target. Most PK interactions are related to hepatic processing, but can be related to absorption, protein transport, or renal clearance. Many AEDs are subject to these interactions. PK interactions among AEDs are well-known, but interactions between AEDs and other classes of drugs are less recognized.[1] Older AEDs are more likely to participate in PK interactions, especially the hepatic enzyme-inducing drugs phenytoin, carbamazepine, and the barbiturates. These drugs increase hepatic metabolism and decrease the effect of drugs metabolized by the same pathway. Conversely, valproate is often an enzyme inhibitor, raising the effective levels of other drugs. Newer AEDs, instead, are relatively free of PK interactions, as are drugs like topiramate and oxcarbazepine which interact significantly only at high dosages.

A set of guidelines published in 2007, Quality Indicators for Epilepsy Treatment (QUIET), includes this recommendation: “If newly diagnosed patients are taking medications for other disorders, then a physician should minimize the risk of interactions between newly prescribed AEDs and concomitant medications.”[2] This is particular important among older adults for whom epilepsy is common,[3] and who are at high risk for drug interactions because they often take many drugs. Moreover, they are more subject to toxic effects because of lower capacities for hepatic and renal drug elimination.[4] Many NEDs are critical for health, and small variations in effect may have serious consequences. Data on the extent of use of drug combinations subject to significant interactions among older Americans with epilepsy is limited.

In our Quality of Epilepsy Treatment and Costs in Older Americans by Race (QUIET CARE) project, we examined quality care indicators for the Medicare population with epilepsy, focusing on differences in AED treatment by race/ethnicity because of previous

reports of treatment disparities.[5; 6] As part of this project, we examined the frequency and possible severity of interactions between AEDs and other commonly used drugs, and explored the concordance of epilepsy care with this QUIET indicator by race/ethnicity and by other demographic factors.

METHODS

Medicare is the U.S. medical insurance program covering older adults. We performed a retrospective analysis of Medicare claims data obtained from the Center for Medicare and Medicaid Services (CMS). The study was approved by the Institutional Review Board of the University of Alabama at Birmingham.

The base dataset included the 2008–2010 administrative claims for a 5% random sample of Medicare beneficiaries. To allow adequate comparisons between racial/ethnic groups, this was augmented with claims data for all beneficiaries with any claims related to seizures (780.3x) or epilepsy (345.xx) within that period who identified as African-American, Hispanic, Asian, or American Indian/Alaskan Natives (AI/AN). Inclusion criteria were age ≥67 in 2009, and with Part A Medicare coverage (hospital insurance), Part B (outpatient and physician visits), and Part D (prescription drugs) during the study period.

We identified epilepsy prevalent cases using the following criteria for 2009 claims: i) ≥ one claim (inpatient, outpatient or physician visit) with International Classification of Disease - version 9 (ICD-9) codes 345.xx (epilepsy), or ≥ two claims with 780.3x (seizures) at least 30 days apart, and ii) ≥ one prescription of 60 days or more for an AED. Similar definitions were found to have a positive predictive value of 94% for detecting cases of epilepsy among older veterans[7] and 70%–88% in a managed care population.[8] We defined the index date as the date of the first claim in 2009 that fulfilled the above criteria. To allow sufficient follow-up time to gather medication usage data, we included only beneficiaries who had at least one year of follow-up after the index date with continuous Part A and B coverage and not on managed care plans, which feature closed panels of providers and restricted drug formularies and for which claims data are not available. Among these prevalent cases, we classified as *incident* those with continuous Medicare coverage for the year before the index date, and no claims with ICD-9 codes for epilepsy or seizures, nor any filled AED prescriptions during that year (one-year “clean” period).

Outcomes

Using Part D claims for prescription drugs, we determined the 50 most common NEDs prescribed to persons with epilepsy for which they had a prescription on the index date (i.e., the epilepsy index date fell within the drug supply period). We then identified AED prescriptions filled within a window of ± 60 days around the index date.

The primary outcome event was the simultaneous presence of prescriptions for a combination of an AED and an NED with a risk for a PK interaction. We assessed risk for these AEDs: phenytoin, carbamazepine, phenobarbital, valproate, topiramate, and oxcarbazepine. We conducted a literature review to identify known interactions between these AEDs and the 50 most commonly prescribed NEDs in our population.

There is no definitive resource for drug interactions. Lists from reference sources often disagree.[9] We chose to use the FDA-approved labeled prescribing information (package insert) as our primary source, but supplemented it with other sources easily consulted by prescribers, including review articles[10; 11] and the Medscape interaction checker.[12] Lists of interactions from other proprietary services (Micromedex,[13] Clinical Pharmacology,[14] Lexicomp[15]) were also consulted, but these sources require paid subscriptions and are more difficult for practitioners to access.

Interaction risk of AEDs on NED efficacy was defined as *high* (potentially life threatening or liable to cause serious toxicity), *medium* (significant but effects less marked or may be delayed), or *probable but unspecified risk* (Table 1). *High and medium risk* interactions are usually, but not always, listed in prescribing information. For the category "risk probable but unspecified," no published interaction data were found, but a likely interaction was suspected because of their known common metabolic pathway. For other pairs of AEDs and NEDs, interactions were either proven not to exist from the literature or highly unlikely because of dissimilar metabolic pathways. This list of drug combinations is necessarily subjective, but we believe that it is conservative and consistent with the available literature.

We defined *any risk* as cases having high, medium, or probable but unspecified risk. Beneficiaries who had no prescriptions for drug combinations specified in Table 1 were considered to have no interaction risk. We also defined interaction risk for the NEDs altering the effect of AEDs: several NEDs inhibit the metabolism of AEDs, and a few increase the effect of AEDs (Table 1).

Analysis

We estimated the overall and race-specific frequency of incident and prevalent cases having any, high, medium, or probable but unspecified interaction risk of AEDs on NEDs, and the frequency of cases having interaction risk of NED on AED efficacy. Logistic regression was used to model any risk, high risk, and the combination high-medium interaction risk of AEDs on NEDs, and risk of drug combinations that affect AED efficacy, with adjustment for covariates.

Covariates considered included: 1) individual factors: race/ethnicity, age at the index epilepsy event, gender, number of comorbid conditions, and source of epilepsy care; i.e. having at least one claim for a visit with a neurologist or neurosurgeon in the time period from 45 days before to 60 days after the index date; 2) socio-economic factors: eligibility for Part D Low Income Subsidy, ZIP (postal) code indicators of poverty and 3) geography: US residence region (Northeast, West, Midwest, or South). Number of comorbid conditions were identified in the year before the index event based on those included in the calculations of the Charlson Comorbidity score.[16; 17] ZIP code information on poverty was obtained from the 2010 Census. We created indicators for high poverty corresponding to ZIP code levels with > 20% of households living below 100% of the Federal Poverty Line. All analyses were conducted with SAS version 9.4, Cary, NC.

RESULTS

Demographics

We identified 36,912 *prevalent* cases of epilepsy and 3706 *incident* cases (Table 2). *Prevalent* and *incident* epilepsy cases were demographically similar. Among the *incident* cases, 64.9% were female, 18% were white, 61.2% African American, 12.3% Hispanic, 6.6% Asian, and 2.0% AI/AN. By design, minorities were overrepresented (Table 2). Most (72.8%) saw a neurologist close to the index date (versus only 36.3% of prevalent cases), and other health problems were common: 41% had 1–3 and, 55.3% 4 or more comorbid conditions. Many were poor: 77.2% qualified for the Part D Low Income Subsidy. About half resided in the South and 18.8% in the Northeast.

Incident Cases

A drug combination with high, medium, and probable but unspecified risk of interaction was present in 6.9%, 10.3%, and 18.5% of *incident* cases, respectively (Table 3). A beneficiary could also have multiple interaction risks: overall, 75.5% had no interaction risk, and 24.5% were potentially at risk for some interaction (*any risk*). The proportion with *any risk* ranged from 30.4% for African Americans and 29.8% for AI/AN, to 21.5% for Asians. Moreover, 18% of incident cases, ranging from 18.7% of whites to 13.7% of Hispanics, also had drug interactions that increased the effect of the AED, while 2.4% had interactions that decreased the AED effect (Table 3).

Prevalent Cases

Among *prevalent* cases, 39% were taking a drug combination that could alter the efficacy of the NED (*any risk*) (Table 3). The proportion ranged from 41.7% of Hispanics to 32.7% of Asians. Moreover, 26.2% of prevalent cases had potential interactions that could increase the effect of AEDs, ranging from 27.6% of African Americans to 19.9% of Asians, and 3% had interactions that could decrease AED efficacy.

Specific Interacting Combinations Among Incident Cases

Table 4 lists NEDs, among the most common 50, that were prescribed to at least 5% of *incident* epilepsy cases and carry a documented or probable interaction risk with AEDs. Among cases taking each NED, Table 4 lists the percentage taking phenytoin and carbamazepine. Combinations with phenobarbital, valproate, topiramate, and oxcarbazepine are not reported due to low numbers. The most common NEDs were metoprolol and simvastatin with about 25% of cases filling prescriptions for these drugs. Among cases on simvastatin, 30.9% had prescriptions for phenytoin corresponding to 7.6% having this *probable but unspecified risk* drug combination. Prescriptions for warfarin were filled by 11% of cases, of which 33.3% were also on phenytoin, corresponding to 3.6% having this *high risk* drug combination.

Relationship of Interaction Risk to Demographic Factors

In adjusted logistic regression models, factors associated with lower likelihood of *any risk* in the *incident* population were: 1) being Asian compared to white (OR 0.64, CI 0.43–0.96);

and 2) treatment by a neurologist (OR 0.56, CI 0.48–0.67) (Table 5). Factors associated with higher likelihood of *any risk* were: 1) having one comorbidity or more (1–3 vs 0 comorbidities OR 2.14, CI 1.26–3.64, and 4+ vs 0 comorbidities OR 2.73, CI 1.61–4.64), and 2) residence outside the Northeast. Results were similar when considering high and high-medium risk: however, for these risk stratifications, being eligible for Part D low income subsidies was associated with a higher likelihood of having high (OR 2.05, CI 1.36–3.09) and high-medium risk (OR 1.44, CI 1.10–1.88). Moreover, the same factors were also associated with the likelihood of drug combinations that affected NED efficacy (OR 1.34, CI 1.08–1.65). Age, sex, and residence in a high-poverty ZIP (postal) code were not significantly associated with any type of risk.

DISCUSSION

Many older Americans receive AEDs, especially phenytoin, which are involved in PK interactions with drugs commonly used for the treatment of other conditions.[1] Almost a quarter of our *incident* cases received at least one such combination. Moreover, one in five had a drug combination that altered the effect of the AED. The proportion of beneficiaries with interaction risk was higher among prevalent cases. Our hypothesis that quality of care by this measure would vary markedly by race/ethnicity was not supported: we only found that Asian Americans were at slightly lower risk by some measures. A more important factor was income status: persons designated as low-income, because eligible for the Part D low income subsidy, were more likely to have a high risk, or a high-medium drug combination. This individual measure of income status is likely more accurate than one measured at the ZIP code of residence: in fact, our measure of poverty at the ZIP code level was not associated with interaction risk. This finding calls into question studies that assess quality of care by race/ethnicity without controlling for income levels. In addition, we found that having more comorbid conditions was associated with a higher risk of having interacting drug combinations, while having care by a neurologist was associated with lower risk, suggesting the importance of specialty care.

It is encouraging that prescribers seem to be more averse to prescribing high risk drug combinations than combinations we rated as either medium risk or probable but unspecified risk (Table 3). However, the latter category does not necessarily imply low risk, just a risk not yet quantified in the literature. Overall, the problem of drug interactions with AEDs may be improving. The 24.5% proportion of older adults with new-onset seizures who started on medication during 2009 with interacting NED-AEDs was lower than the 39% found among the prevalent cases. Furthermore, it was lower than the 45.5% rate among new cases reported by Pugh et al. for an older veteran population treated from 1999–2004.[18] This is in line with a reduction in the prescription of older enzyme-inducing AEDs. In our incident population we found that about 44% were prescribed enzyme-inducing AEDs[19] compared to about 60% of a cohort of older veterans with new-onset seizures who began on medication in 2006.[20]

Some drug interactions are quite dangerous and present immediate risk. It is reassuring that the combination of warfarin and phenytoin was used in only 3.6% of incident cases. The effect of phenytoin on warfarin is unpredictable and may vary over time, so either bleeding or clotting may ensue. Digoxin plus phenytoin was prescribed in 2.5% of incident cases: this

combination could increase the risk of heart failure because phenytoin enhances hepatic elimination of digoxin. Finally, 2.4% were taking both quetiapine and phenytoin where the reduced effect of quetiapine could cause decompensation of psychiatric conditions. Other risks accumulate over time - phenytoin increases both metoprolol and simvastatin metabolism, effects which could eventually lead to higher risks of vascular disease.[21] Most of these interactions involve reduction of the effect of the NED by simultaneous use of an enzyme-inducing AED. A few have the opposite effect: phenytoin and carbamazepine strongly inhibit metabolism of sertraline, a common antidepressant, which could cause adverse serotonergic effects. However, citalopram, another common antidepressant, has a diminished effect when taken with these AEDs. Thus, the choice of antidepressant can be important in persons with epilepsy.[22]

Drug interactions are frequently predictable. We chose to list as *probable but not specified* those combinations that share metabolic pathways, even when no primary literature quantifying the interaction was found. Thus, drug pairs sharing the cytochrome P450 3A4 pathway, such as carbamazepine and escitalopram, are included in our list. As new drugs are introduced to the market, such interactions can be predicted and warnings should be placed in product information and electronic references. For existing drugs, many electronic medical record systems generate warnings when interacting combinations are prescribed, but these warnings can be overridden. Sometimes this is necessary because it is medically appropriate to prescribe the interacting pair, but there may be better alternatives. There is no evidence that the older, interacting AEDs are more effective in general populations[23] or in older persons,[24] so there is no efficacy advantage to starting with one of these older drugs.

There are limitations to our study. First, any list of drug interactions and any qualitative ranking of their potential severity reflects the judgment of the authors. Second, we only measured concomitant use of the 50 most-often prescribed NEDs for this Medicare population. There are thousands of other drugs that could interact with AEDs. AEDs may participate in serious interactions with important classes of drugs which are not among the 50 most common NEDs prescribed to our Medicare cohort. These critical drugs include antivirals and antineoplastic agents. Thus, our numbers should be considered low estimates. Our goal was not to identify all possible drug interactions with AEDs, but to get a sense of the magnitude of the problem for older persons of different races and demographic descriptions. Third, we did not assess interactions among AEDs, which are numerous and quantitatively significant. However, in our cohort of incident cases less than a quarter had more than one AED in the follow-up period.[25] Fourth, we did not evaluate pharmacodynamic interactions, which are common but difficult to quantify. Fifth, the number of comorbidities may be underestimated because we did not identify psychiatric conditions, although psychiatric drugs are included in our analyses. Consequently, we may have not accurately estimated the effect of this number on the likelihood of interaction risk, and if different across demographic groups, we may have not appropriately adjusted for confounding of the association between demographics and interaction risk. Sixth, our study included only older Medicare recipients enrolled with Part D prescription plans. Medicare beneficiaries with other or no drug coverage were not included in our sample. We should emphasize that our study population was not intended to be representative of the entire older Medicare population because we oversampled minority groups. However, because we found

only small differences across racial groups, we believe that our results are likely applicable to the general population of older persons.

In conclusion, in this population of older Americans, one in four with new onset epilepsy may have received care that did not "minimize the risk of interactions between newly prescribed AEDs and concomitant medications" in line with QUIET indicators. However, fewer were receiving drug combinations that have evidence of high or medium risk of interaction. Most newer AEDs are less likely to be involved with PK interactions, and, therefore, may be more appropriate choices for older persons.[26] If use of an interacting AED is unavoidable, careful monitoring for side effects is necessary and, in some cases, serum drug level measurements of the NED or AED may be needed. Warnings built into electronic prescribing programs and provider education may mitigate this problem. Referral to specialty care with a neurologist or epilepsy specialist to address the complexities of treatment of older adults with epilepsy may be desirable.

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Key Points

1. One in four older Americans with incident epilepsy, and more than a 1/3 with prevalent epilepsy, received an AED which could reduce the effect of the non-epilepsy drug.
2. Smaller proportions had drug combinations with evidence of high or medium risk of interaction.
3. One in five incident cases received a drug combination that could alter the effect of the AED and potentially cause toxicity.
4. Having interacting drug pair combinations was more likely for those with comorbid conditions or eligible for a low-income subsidy, while having care from neurologists, being Asian and living in the northeastern US was protective.

Table 1

Combination of antiepileptic (AEDs) and non-antiepileptic (NEDs) drugs at risk for pharmacokinetic interactions

	Antiepileptic Drug (AED)					
	phenytoin	**carbamazepine**	**phenobarbital**	**valproate**	**topiramate**	**oxcarbazepine**
Combinations affecting NEDs						
High risk	warfarin quetiapine	warfarin simvastatin quetiapine mirtazapine risperidone	warfarin	quetiapine		
Medium risk	atorvastatin mirtazapine digoxin levothyroxine	citalopram trazodone levothyroxine	metoprolol levothyroxine	warfarin	digoxin risperidone	diltiazem
Risk probable but unspecified	simvastatin furosemide sertraline diltiazem prednisone donepezil	sertraline diltiazem prednisone escitalopram	simvastatin donepezil carvedilol quetiapine			omeprazole clopidogrel donepezil atorvastatin prednisone
Combinations affecting AEDs						
Increased effect	omeprazole clopidogrel warfarin sertraline diltiazem trazodone allopurinol nitrofurantoin risperidone	diltiazem propoxyphene quetiapine trazodone risperidone	omeprazole propoxyphene	sertraline	metoprolol	
Decreased effect	quetiapine					

Table 2

Characteristics of Medicare beneficiaries with epilepsy, 2009

	Prevalent epilepsy cases N = 36,912	Incident epilepsy cases N = 3,706
White	19.2	18.0
African American	62.5	61.2
Hispanic	11.3	12.3
Asian	5.0	6.6
AI/AN	2.0	2.0
Female	61.6	64.9
Age		
66–74	41.5	34.9
75–84	36.1	37.3
85+	22.4	27.8
Comorbid conditions		
0	8.3	3.7
1–3	45.7	41.0
4+	46.0	55.3
Neurologist visit close to index event	36.3	72.8
LIS eligible	82.0	77.2
Region of residence		
South	50.2	49.2
West	13.3	15.1
Midwest	17.7	17.0
Northeast	18.7	18.8

AI/AN = American Indian/Alaskan Native; LIS = Part D Low Income Subsidy; South = DE, DC, FL, GA, MD, NC, SC, VA, WV, AL, KY, MS, TN, AR, LA, OK, TX; West = AZ, CO, ID, NM, MT, UT, NV, WY, AK, CA, HI, OR, WA; Midwest = IN, IL, MI, OH, WI, IA, NE, KS, ND, MN, SD, MO; Northeast = CT, ME, MA, NH, RI, VT, NJ, NY, PA

Table 3

Prevalence of risk of pharmacokinetic interactions among older adults with epilepsy by race/ethnic group

	Overall	White	AA	Hispanic	Asians	AI/AN
Incident Cases (N = 3,706)						
Interaction risk of AED on NED						
Any risk	24.5	25.4	30.4	24.2	21.5	29.8
High risk	6.9	7.1	6.8	7.1	3.9	0.0
Medium risk	10.3	11.0	10.0	9.9	9.0	*
Probable but unspecified risk	18.5	16.6	18.5	16.9	11.6	16.4
No risk	75.5	74.6	69.6	75.8	78.5	70.2
Interaction risk of NED on AED						
Increased AED efficacy	18.0	18.7	17.9	14.8	13.7	14.9
Decreased AED efficacy	2.4	2.0	2.4	3.1	*	0.0
Prevalent cases (N = 36,912)						
Interaction risk of AED on NED						
Any risk	39.0	38.6	41.5	41.7	32.7	39.7
High risk	11.4	11.8	11.6	11.9	8.1	9.1
Medium risk	16.3	19.5	15.3	17.5	13.8	17.4
Probable but unspecified risk	27.6	24.6	28.8	29.0	21.6	26.5
No risk	61.0	61.4	58.5	58.3	67.3	60.3
Interaction risk of NED on AED						
Increased	26.2	23.5	27.6	26.4	19.9	25.8
Decreased	3.1	2.4	3.3	3.7	1.7	2.4

AA = African American; AI/AN = American Indian/Alaskan Native; AED = antiepileptic drugs; NED = non-epilepsy drugs; High risk = potentially life threatening or liable to cause serious toxicity; Medium risk = significant risk but effects less marked or may be delayed; Probable but unspecified risk = no published interaction data but interaction suspected based on common metabolic pathway;

*Omitted due to low numbers

Table 4

Specific drug combinations among 3,706 probable incident cases of epilepsy in older adults which may cause significant interactions.

Non-Antiepileptic Drug (NED)	% taking NED	% on NED taking AEDs below*	
		Phenytoin	Carbamazepine
METOPROLOL	27.3	32.5	1.8
SIMVASTATIN	24.7	30.9	2.0
FUROSEMIDE	19.6	34.2	3.0
DONEPEZIL	17.7	29.2	2.1
OMEPRAZOLE	17.6	33.0	3.7
CLOPIDOGREL	17.0	33.7	2.2
LEVOTHYROXINE	13.7	26.4	**
WARFARIN	11.1	33.3	**
ATORVASTATIN	9.4	32.1	**
CARVEDILOL	8.8	33.2	**
QUETIAPINE	6.5	37.2	**
SERTRALINE	6.5	33.8	**
DIGOXIN	6.3	39.9	**
ESCITALOPRAM	5.6	29.3	**
CITALOPRAM	5.5	40.1	**
DILTIAZEM	5.3	36.4	**
MIRTAZAPINE	5.2	34.2	**

* Only phenytoin and carbamazepine included, other AED- NED combinations omitted due to low numbers

** Omitted due to low numbers

Table 5

Adjusted logistic regression on the likelihood of having drug combinations with risk of pharmacokinetic interactions among incident cases (N = 3,706)

	Odds Ratio (Confidence Interval) of			
	Interaction risk of AED on NED			Interaction risk of NED on AED
	Any	High	High-Medium	
White	1.00	1.00	1.00	1.00
AA	1.00 (0.80–1.26)	0.73 (0.5–1.06)	0.76 (0.58–0.998)	0.80 (0.63–1.03)
Hispanic	0.93 (0.68–1.26)	–	0.74 (0.51–1.06)	0.72 (0.52–1.01)
Asian	0.64 (0.43–0.96)	–	0.57 (0.35–0.93)	0.63 (0.41–0.96)
AI/AN	0.86 (0.47–1.57)	–	0.41 (0.17–0.99)	0.71 (0.36–1.38)
Non AA or White	–	0.61 (0.39–0.97)	–	
Female	1.07 (0.91–1.27)	0.77 (0.59–1.02)	1.09 (0.89–1.34)	0.95 (0.79–1.14)
Age				
66–74	1.00	1.00	1.00	1.00
75–84	1.16 (0.96–1.39)	0.90 (0.66–1.23)	1.13 (0.90–1.41)	1.16 (0.95–1.41)
85+	1.02 (0.83–1.25)	1.05 (0.75–1.48)	1.18 (0.92–1.50)	0.90 (0.72–1.13)
Comorbid conditions				
0	1.00	1.00	1.00	1.00
1–3	2.14 (1.26–3.64)	2.82 (0.87–9.10)	2.16 (1.07–4.36)	2.08 (1.12–3.86)
4+	2.73 (1.61–4.64)	3.80 (1.19–12.2)	2.85 (1.42–5.71)	2.92 (1.58–5.38)
Neurologist close to diagnosis	0.56 (0.48–0.67)	0.66 (0.5–0.87)	0.61 (0.50–0.75)	0.64 (0.53–0.77)
LIS eligible	1.19 (0.96–1.47)	2.05 (1.36–3.09)	1.44 (1.10–1.88)	1.62 (1.27–2.07)
Region not Northeast	1.34 (1.08–1.65)	1.19 (0.83–1.69)	1.39 (1.07–1.80)	1.25 (0.99–1.57)
High poverty ZIP code	1.08 (0.92–1.27)	0.99 (0.76–1.31)	1.11 (0.91–1.34)	1.02 (0.85–1.21)

AED = antiepileptic drugs; NED = non-epilepsy drugs; High risk = potentially life threatening or liable to cause serious toxicity; Medium risk = significant risk but effects less marked or may be delayed; AA = African American; AI/AN = American Indian/Alaskan Native; LIS = Part D Low Income Subsidy