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Choice of Initial Antiepileptic Drug for Older Veterans: Possible Pharmacokinetic Drug Interactions With Existing Medications

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Abstract

Objectives—Identify clinically-meaningful potential drug-drug interactions with antiepileptic drugs (AED-PDI), the AEDs and co-administered drugs commonly associated with AED-PDI, and characteristics of patients with increased likelihood of AED-PDI exposure.

Design—Five-year retrospective cohort study of veterans with new-onset epilepsy.

Setting—National VA and Medicare databases.

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Participants—Veterans age 66 years and older with a new diagnosis of epilepsy between October 1, 1999–September 30, 2004 (N=9,682).

Measurements—We restricted AED-PDI to clinically-meaningful potential drug interactions identified by prior literature review. AED-PDI were identified using participants' date of initial AED prescription and overlapping concomitant medications. Logistic regression analysis identified factors associated with AED-PDI including demographic characteristics, chronic disease states and diagnostic setting.

Results—AED-PDI exposure was found in 45.5% (4,406/9,682); phenytoin, a drug with many potential drug interactions, was the most commonly prescribed AED. Cardiovascular drugs, lipid-lowering medications and psychotropic agents were the most commonly co-administered AED-PDI medications. Individuals at higher likelihood of AED-PDI exposure had 1) hypertension (OR=1.46, 99% CI 1.24–1.82), 2) hypercholesterolemia (OR=1.40, 99% CI 1.24–1.57) and 3) were diagnosed in emergency or primary care vs. Neurology settings (emergency OR: 1.30 99% CI=1.08–1.58; primary care OR: 1.29 99% CI 1.12–1.49).

Conclusion—Exposure to AED-PDI was substantial, but less common in epilepsy patients diagnosed in a neurology setting. Because potential outcomes associated with AED-PDI include stroke and myocardial infarction in a population already at elevated risk, clinicians should closely monitor blood pressure, coagulation, and lipid measures to minimize adverse effects of AED-PDI. Interventions to reduce AED-PDI may improve patient outcomes.

Keywords

drug-drug interaction; epilepsy; geriatrics; antiepileptic drugs

Introduction

While many consider epilepsy a disease of childhood, the incidence of epilepsy is highest in the elderly, with prevalence estimates between 1.8 and 2%.¹ Management of epilepsy in older patients is clinically challenging. In addition to concern about assuring that seizures are controlled with minimal side effects, older patients tend to have a number of comorbid conditions which require medications,² many of which have the potential to interact with commonly used antiepileptic drugs (AEDs).

A number of published reviews on treatment of older patients with epilepsy highlight, but fail to quantify, the risk of potential pharmacokinetic drug-drug interactions (PDI) among individuals receiving older AEDs that are hepatically metabolized (e.g., phenytoin, carbamazepine, phenobarbital).^{3–5} These drug-drug interactions may cause AED toxicity or reduce the efficacy of the interacting drug.^{6,7} As many of the drugs with potential interactions with AEDs are used to treat hypertension, hyperlipidemia, and coagulation disorders, prolonged exposure to AEDs and potentially interacting drugs (AED-PDI) may be associated with adverse outcomes such as falls/fractures, stroke, myocardial infarction and mortality.^{8–10}

Recently, Gidal, et al., found that the majority of patients in all age groups received AEDs with the potential for pharmacokinetic drug-drug interactions, and that many also received medications that may interact with those AEDs.¹¹ It is unclear, though, the extent to which AEDs with the potential for these drug interactions were prescribed concomitantly with potentially interacting drugs. Thus, little is known about the extent to which AED-PDI actually occur, or whether clinicians were cognizant of, and avoided, potential interactions.¹¹

This study used national databases from the Department of Veterans Affairs, Veterans Health Administration (VA) to identify the extent to which older veterans with new onset epilepsy had AED-PDI exposure. While pharmacodynamic drug-drug interactions are also possible, this paper focuses exclusively on pharmacokinetic drug-drug interactions. We further identified 1) the duration of AED-PDI exposure, 2) older patients at greatest risk of AED-PDI exposure, and 3) those most likely to have the potentially interacting drug continued after starting AEDs.

Methods

Data

After receiving approval from Institutional Review Boards at the University of Texas Health Science Center at San Antonio, and the Bedford and Hines VA Hospitals, we gathered national VA inpatient, outpatient, pharmacy and Medicare data October 1, 1999 to September 30, 2004 (FY00-FY04) linked with an encrypted identifier to identify older veterans (≥ 66 years) with new-onset epilepsy within the VA medical system. These data also allowed identification of the initial antiepileptic drug (AED) regimen received, concomitant medications received at the time of the first VA AED prescription, comorbid conditions, and demographic variables.

Population and Setting

We used an algorithm previously validated by Holden et al. 2005¹² and subsequently validated by Pugh et al.¹³ to identify elderly individuals with new-onset epilepsy. Using an algorithm described previously¹³ we identified older veterans with new-onset epilepsy using ICD-9-CM code for epilepsy (345.XX) or convulsion (780.39) in VA inpatient, outpatient and Medicare databases, and who also received an AED from the VA outpatient pharmacy within one year of the initial epilepsy diagnosis. Prior research found that, of those identified with epilepsy using this algorithm, 98% had documented epilepsy in the electronic medical record.¹³

Measures

Dependent Variable: Potential Drug Interactions—PDI were identified based on ‘clinically important drug interactions’ based on pharmacokinetic properties described by Patsalos and Perruca.⁶ Clinically important drug interactions include those potential drug interactions that may affect the clinical management of the patient, or that might have severe adverse outcomes for patients.¹⁴ We further restricted our assessment to drugs for chronic conditions such as hypertension, hypercholesterolemia, and mental health conditions rather than acute conditions such as infection. While there is a potential for interactions among AEDs, only a small number individuals received potentially interacting AEDs, and they also had AED-PDI. Thus we focus exclusively on the issue of AED-PDI in this paper. As such, these AED-PDI do not completely reflect the VA drug-drug interaction screening criteria, which are more broadly defined, and which include drug interactions defined as mild in nature¹⁵ and drug interactions that are not relevant to older patients (e.g., oral contraceptives). Table 1 provides a list of the most common potential drug interactions that are particularly relevant for older individuals, and the potential impact of each AED-PDI. Most AED-PDIs are associated with older AEDs that are cytochrome P450 inducers—phenytoin, carbamazepine, phenobarbital. Moreover, many of these AED-PDIs were defined as moderate in nature by Micromedex.¹⁵

We first identified the initial AED regimens prescribed within the VA. All AEDs prescribed the day of the initial VA prescription were considered in the assessment of PDI. Next we identified all unique medications in the current drug regimen the day of the AED

prescription. These drugs were determined by an algorithm which identified the initial fill date plus the day supply of that fill and all subsequent fills plus 30 days as most patients are not entirely compliant with medications and have some medications left over at the end of the fill period. For our initial approach, those receiving drugs for chronic conditions identified as having clinically meaningful drug interactions with the initial AED were classified as having AED-PDI.⁶ Because we could not accurately identify whether interacting drug prescriptions were discontinued, we restricted our final measure of AED-PDI to those who received a subsequent prescription of potentially interacting drugs after the initial AED prescription, which accounts for changes physicians made to drug regimens that may address the potential drug interaction. In order to further assess PDI exposure, we also determined the median duration of each AED-PDI for the year following the initial AED prescription. We calculated the day supply of medications during the year as long as the patient received both the AED and the potentially interacting drug.

Independent Variables

Demographic Characteristics: Using VA and Medicare data sources we identified the age, gender, and race of each patient. VA data were also used to identify marital status (married vs. not married). While race data is frequently missing in VA data, we supplemented Medicare data when VA data were missing for race, leaving less than one percent missing race data.

Diagnosis-related issues: Because prescribing patterns changed over the years of the study, with greater use of newer AEDs over time, we included the fiscal year of first AED prescription (FY 2000, 2001, 2002, 2003, 2004) in logistic regression analyses.¹³ Furthermore, since individuals in this cohort are generally eligible to receive health care through Medicare, we also identified whether the epilepsy diagnosis was first documented in VA or Medicare data since treatment may have been initiated outside of the VA setting.

Comorbid Conditions: We used validated ICD-9-CM code algorithms to identify comorbid conditions the patient experienced **prior to** the date of the initial epilepsy diagnosis.¹⁶⁻¹⁹ Comorbidities identified included those that are commonly treated with drugs that interact with commonly used AEDs (e.g., hypertension, cardiovascular disease, diabetes, hypercholesterolemia, psychological disorders [any vs. no psychological disorders]) and those comorbidities that have been associated with epilepsy in epidemiological studies (e.g., stroke, dementia, brain tumors, head injury).²⁰⁻²³

Medication Burden: We tracked the number of unique medications for each individual the year prior to inclusion in the cohort and considered this as a proxy for overall medication burden.²⁴ Initially we classified medication burden by quartiles to ease interpretation of data. As odds ratios were the same for those in the second through fourth quartiles, we combined those groups to create a dichotomous measure: Low Medication Burden (1-5 medications) vs. High Medication Burden (≥ 6 medications).

Analysis

We calculated frequencies of demographic and clinical characteristics for the cohort, and identified the rate and duration of AED-PDI overall and by AED. We then conducted multivariable logistic regression analysis to identify factors that were associated with AED-PDI, and to identify characteristics of those for whom the offending drug was not renewed after initiation the AED. Because of the large cohort size, we used $p < 0.01$ as the level of significance. Interactions were included in the initial models; as none were statistically significant they were not included in the final model.

Results

Demographic characteristics

Our cohort consisted of 9,682 older veterans who met the criteria for new-onset epilepsy. Our cohort of new-onset epilepsy patients were mostly men (98%) and white (78.5%), representation of both blacks (15.8%) and Hispanics (4.9%; 0.8% other [Native American, Pacific Islander, Asian]) was similar for the overall elderly population.²⁵ Only 4.6% were over 85 years of age; 48.1% were 75-84 years and 47.3% were 66-74 years of age. The majority of the cohort (64.7%) was married.

Context of Epilepsy Diagnosis

Table 2 shows that the incidence of epilepsy was relatively consistent over the study period and that 61% (N=5,913) of patients had their initial epilepsy diagnosis documented first in Medicare data. The initial seizure diagnosis was identified in a VA neurology clinic or by a Medicare neurology provider for approximately 27% of patients.

Clinical Characteristics

Table 3 shows comorbid conditions and the unique number of drugs received the year before epilepsy diagnosis. Consistent with a new diagnosis of epilepsy, substantial numbers had prior diagnoses of stroke, dementia, and brain tumor. Moreover, this population had significant disease burden evidenced by high prevalence of cardiovascular disease (myocardial infarction, angina, and congestive heart failure), cardiac arrhythmias, chronic obstructive pulmonary disease, and diseases associated with metabolic syndrome such as hypertension, diabetes, and hypercholesterolemia. The population had a high prevalence of psychiatric comorbidity diagnosed prior to epilepsy diagnosis, with approximately half having at least one psychiatric diagnosis recorded in administrative data. The median number of unique drugs received the year prior to epilepsy diagnosis was eight.

Overall, 60.1% (N=5,822) of study subjects received a drug with potential for clinically significant interactions with the initial AED. Of those with AED-PDI exposure on the day of AED prescription, 24% (N=1,416) did not receive a subsequent refill of the potentially interacting drug, leaving 4,406 (45.5%) individuals as having AED-PDI.

Table 4 shows that rates of AED-PDI were highest for phenytoin, with 57.8% of new prescriptions associated with PDI. Over half of individuals prescribed phenobarbital (51.6%) or carbamazepine (55.5%) also received a potentially interacting drug. Approximately 94% of those with a persistent AED-PDI were accounted for by four groups of medications: cardiovascular drugs (e.g., metoprolol, felodipine), lipid-lowering drugs (e.g., simvastatin, lovastatin), psychotropic drugs (e.g., olanzapine, trazodone) and anticoagulants (e.g. warfarin, dicoumerol). Among the cohort, 26.4% had cardiovascular drug AED-PDI (N=2,552), 20.7% had lipid-lowering drug AED-PDI (N=2,007), 14.9% had psychotropic drug AED-PDI (N=1,444), and 6.2% had anticoagulant AED-PDI (N=601). Of those with a persistent AED-PDI, 48% had two or more concomitant AED-PDI.

The duration of exposure was often quite long. Table 4 shows the median number of days of PDI prescription for the first year of epilepsy treatment. The day supply for AED-PDI was over 200 days, with medians ranging from 216-265 days.

Odds ratios and 99% confidence intervals from the multivariable logistic regression analysis predicting AED-PDI exposure are presented in Table 5. The strongest predictors of PDI were having hypertension or hypercholesterolemia and receiving 6 or more medications the year prior to epilepsy diagnosis.

Moreover, individuals initially diagnosed with epilepsy in an emergency department or primary care settings were significantly more likely to have AED-PDI exposure than were those initially diagnosed in a neurology setting. Individuals with a lower likelihood for AED-PDI exposure included those who were older and those with a diagnosis of liver disease.

Logistic regression analysis predicting renewal of interacting drug after initiation of AED (full data not shown) found that age, several chronic disease states, and year of initial AED prescription were significant predictors. Those who were 66-74 years were less likely to have an interacting drug renewed after the prescription of the initial AED than those who were 75-84 (OR 0.82; 99% CI 0.70-0.98, $p=.004$). Individuals with dementia (OR 0.80; 99% CI 0.66-0.97, $p=.002$), metastatic cancer (OR 0.64; 99% CI 0.47-0.86, $p<.001$), and chronic obstructive lung disease (OR 0.72; 99% CI 0.60-0.85, $p<.001$) were less likely to have interacting drugs renewed. Finally, those receiving their AED in FY04 were less likely to have the interacting drug renewed after the prescription of the initial AED than were individuals who received their AED in FY00 (OR 0.68; 99% CI 0.52-0.88, $p<.001$).

Discussion

Despite the availability of AEDs with low potential for AED-PDI, the majority of older epilepsy patients in the U.S. are treated with AEDs with high AED-PDI potential (phenytoin, carbamazepine and phenobarbital).^{11,13} The issue of AED-PDI been identified as a consideration in selecting AEDs for older patients in numerous review articles.³⁻⁶ To our knowledge, this is the first study that has systematically examined the scope of the AED-PDI problem in a geriatric population and further identified the patient characteristics (diagnostic setting, age, comorbidities) associated with an increase risk of AED-PDI. In our study nearly half of all older patients received an AED that interacted with existing, chronic medications. Among those with AED-PDI exposure, nearly half had multiple AED-PDI, and AED-PDI exposure was long, suggesting that health care providers need to increase their awareness of AED-PDI in caring for older adults.

Of the four classes of concomitant medications that accounted for 94% of AED-PDI, the most common were drugs used in the treatment of vascular disease. This is not surprising since stroke is the most common etiology associated with new onset epilepsy in older adults and 80% of elderly have been diagnosed with hypertension and hyperlipidemia.^{2,13} These potential interactions are of great clinical relevance since they may affect health outcomes. Potential interactions identified by this study may significantly reduce the efficacy of antihypertensive medications including beta blockers, calcium agonists, and angiotensin-receptor blockers, in some case without altering serum drug concentrations.²⁶⁻²⁹ In addition, previous research has found that co-administration of carbamazepine with orally administered simvastatin, a HMG-CoA reductase inhibitor used in the treatment of dyslipidemia, led to an 80% reduction in bioavailability of simvastatin.³⁰ This effect would require increasing the dose of simvastatin by a factor of four to achieve therapeutic blood concentrations. Lastly, warfarin related AED-PDI may result in altered anticoagulation properties of this drug leading to a prolongation of the prothrombin time. All of these AED-PDIs could potentially increase the risk for stroke and heart attack and hemorrhage leading to significant patient morbidity and mortality.

These data highlight the complexity of adding medications to the regimens of older patients with multiple medical conditions. Health care providers caring for older patients must be vigilant in the selection of an AED, especially in those with vascular disease, and closely monitor the treatment of hypertension, dyslipidemia and anticoagulation therapy. While our

data did not allow us to examine this clinical behavior, future research should consider the extent to which such monitoring is conducted.

The examination of risk factors for AED-PDI and likelihood of having an interacting drug renewed suggest that clinicians in Neurology clinic may have a heightened awareness of AED-PDI compared to providers in primary care or the emergency department. The data also suggested more caution on the practitioner's part with regard to medication problems among patients who might be considered frail. The oldest-old (85 years and older) and individuals with dementia and liver disease were less likely to have AED-PDI exposure compared to their younger counterparts and those without such disease. The finding regarding age is consistent with previous findings from studies of suboptimal prescribing in the elderly.³¹⁻³³ The consistency of these findings to more general studies of suboptimal prescribing in the elderly suggest that providers are generally more cautious when making changes to medication regimens in these more vulnerable patients. Regarding liver disease, it is possible that providers preferentially prescribed gabapentin—a drug that is primarily renally cleared and has no significant drug interactions—for those with impaired liver function.³⁴

Our findings must be interpreted in light of several unique features of this study. First, it examined only AED-PDI in those with new-onset epilepsy. This “incident case” approach allows us to better understand the extent to which providers are aware of, and consider, AED-PDI in their initial AED prescribing decision and early on in treatment since AEDs are rarely changed once seizures are successfully controlled unless the patient experiences adverse drug events. While we did exclude individuals who did not have interacting medications continued after the initial AED prescription in our analysis, our method did not examine changes made to prescriptions that were continued. It is possible that clinicians altered dosage or increased monitoring in response to the AED-PDI. Future research should examine this possibility.

A second feature is that this study was based in a single integrated health care system (the VA health care system) in which most of the cohort had a co-pay waiver due to poverty or severe disability. Thus, the generalizability of our findings to other settings is unclear. Other systems with a fee for service model or multi-tiered formulary may actually have higher rates of AED-PDI during the study period since AEDs with fewer PDI tended to be more expensive than phenytoin or carbamazepine. Because, prescribing patterns for AEDs appears similar to those presented by Gidal, et al.¹¹ and this cohort included those whose first diagnosis (and possibly AED prescription) occurred in the context of a non-VA Medicare provider, we believe this bias is minimized. However, it is possible that AED-PDI patterns are different among women since studies have found different patterns of suboptimal prescribing among women³⁵ so further exploration of AED-PDI among older women is needed.

Moreover, our analysis included only medications dispensed by the VA. However, during the time of this study most older veterans who receive prescription drugs through VA received few prescription drugs from outside sources,³⁶ thus we believe this potential bias is limited.

Finally, these data reflect prescribing patterns several years ago. Increasing use of automatic, computerized medication alerts at the time of prescribing within the VA have occurred since this time, and may be reflected in the significant reduction of AED-PDI between October 1, 1999 and September 30, 2004, and the finding that individuals with AED-PDI were more likely to have the interacting drug dropped in FY04 than in FY00. Examination of more

contemporaneous data is needed to examine changes in AED patterns and concomitant changes in AED-PDI.

These data suggest that exposure to AED-PDI is highly prevalent among older patients newly diagnosed with epilepsy, primarily due to the high rates of use of phenytoin, and to a lesser extent carbamazepine. Despite evidence of slowly growing awareness of this patient safety problem, there is substantial room for improvement. Because pharmacologic data suggests that AED-PDI may reduce the efficacy of the interacting drug or cause AED toxicity, prolonged AED-PDI exposure has the potential to result in adverse outcomes such as falls/fractures, stroke, myocardial infarction, excessive anticoagulation or even death.^{6,7} Thus, it is time to consider implementing interventions to reduce AED-PDI in older patients with epilepsy. Data from prior studies suggests that integrating neurology³⁷ and/or clinical pharmacy consultation³⁸ combined with electronic medical records systems that alert clinicians to potential drug interactions,³⁹ may improve care quality and outcomes in this vulnerable population.

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Appendix

Elements of Financial/ Personal Conflicts	MJVP		ACVC		MAS		EMM		MEA		CPW		JEK		DRB	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		✓		✓		✓		✓		✓		✓		✓		✓
Grants/Funds		✓	✓			✓		✓		✓		✓		✓		✓
Honoraria		✓		✓		✓		✓		✓		✓		✓		✓
Speaker Forum		✓		✓		✓		✓		✓		✓		✓		✓
Consultant		✓		✓		✓		✓		✓		✓		✓		✓
Stocks		✓		✓		✓		✓		✓		✓		✓		✓
Royalties		✓		✓		✓		✓		✓		✓		✓		✓
Expert Testimony		✓		✓	✓			✓		✓		✓		✓		✓
Board Member		✓		✓		✓		✓		✓		✓		✓		✓
Patents		✓		✓		✓		✓		✓		✓		✓		✓
Personal Relationship		✓		✓		✓		✓		✓		✓		✓		✓

*Authors can be listed by abbreviations of their names; Yes = written explanation; No = Check (✓) mark

Table 1
Clinically Meaningful Drug Interactions

Drug Class/Drug	Anticonvulsant	Interaction/Potential outcomes
Cardiovascular drugs		
disopyramide, mexilitine, & quinidine	CBZ, PHT, PB	decreased antiarrhythmic concentrations
propranolol, metoprolol	CBZ, PHT, PB	may require increase dosage of beta blocker
nifedipine, felodipine & nimodipine	CBZ, PHT, PB	may nullify effects of the calcium channel blocker
diltiazem	CBZ, PHT	increase AED plasma concentration
nimodipine	VPA	increase plasma concentrations of nimodipine
verapamil	CBZ	CBZ toxicity
atorvastatin, fluvastatin, lovastatin, & simvastatin	CBZ, PHT, PB	may reduce statin efficacy
ticlopidine	PHT, CBZ	CNS toxicity by elevated AED plasma concentration
Hematological agents		
warfarin	CBZ, PHT	decreased anticoagulant effect
Central nervous system agents		
amitriptyline	CBZ, VPA	increases metabolism of & reduces plasma concentration of amitriptyline
bupropion, paroxetine	PHT, PB	reduced plasma concentrations of the antidepressant
nefazodone	CBZ	contraindicated; CBZ toxicity and reduced effectiveness of nefazodone
nortriptyline, clomipramine, & amitriptyline	PHT	concurrent use can result in PHT toxicity
nortriptyline, clomipramine	VPA	may inhibit metabolism of antidepressant causing elevated plasma concentrations
chlorpromazine, clozapine, haloperidol, ziprasidone, olanzapine, quetiapine, mesoridazine, risperidone	CBZ, PHT	decreased antipsychotic plasma concentrations can result in therapeutic failure
Gastrointestinal agents		
cimetidine	CBZ, PHT	AED toxicity
sucralfate	PHT	decreased phenytoin effectiveness
omeprazole	CBZ, PHT	AED toxicity

AED = antiepileptic drug; CBZ = carbamazepine; PB = phenobarbital; PHT = phenytoin; VPA = valproic acid

Source: Patsalos and Perucca (2003).

Table 2
Context of initial seizure diagnosis

Variable	N (%)
Year of Diagnosis	
2000	1,843 (19.0)
2001	1,978 (20.4)
2002	1,947 (20.1)
2003	2,153 (22.2)
2004	1,761 (18.2)
Source of Initial Diagnosis	
Neurology	2,646 (27.3)
Primary Care	2,870 (29.6)
Other Specialty	997 (10.3)
Hospital	1,718 (17.7)
Emergency	1,299 (13.4)
Other/Missing	152 (1.6)
System of First Diagnosis	
VA	3,769 (38.9)
Medicare	5,913 (61.1)

Study Cohort N=9,682

Table 3
Clinical Characteristics

Variable	N (%)
Medical Cormorbidities Associated with Epilepsy	
Cerebrovascular disease	5,538 (57.2)
Dementia	2,439 (25.2)
Brain Tumor	458 (4.7)
Other Neurological Conditions	1,684 (17.4)
Other Medical Comorbidities	
Heart Disease ^	4,472 (46.2)
Cardiac arrhythmias	3,655 (37.8)
Hypertension	8,240 (87.0)
Diabetes	3,741 (38.5)
Renal failure	1,249 (12.9)
Liver disease	216 (2.2)
Hypercholesterolemia	5,631 (58.2)
Chronic Obstructive Pulmonary Disease	4,337 (44.8)
Psychiatric Comorbidity	
Zero	5,883 (60.8)
One	2,293 (23.7)
Two or more	1,506 (15.6)
Unique Drugs	
Q-1 0 to 5	2,848 (29.4)
Q-2 6 to 8	2,533 (26.3)
Q-3 9 to 11	1,883 (19.5)
Q-4 12+	2,418 (25.0)
Potential Drug Interaction	4,406 (45.5)

^ Congestive Heart Failure, Myocardial Infarction, or Angina

Study Cohort N=9,682

Table 4

Potential Drug Interaction by Antiepileptic Drug (AED)

AED	AED N (%)	Initial Approach N (%)	Conservative Approach N (%)	Median Day Supply for all PDI year following AED prescription	Most Common Interacting Drugs
Phenytoin	6477 (66.9)	4,965 (76.7)	3,721 (57.5)	239	metoprolol, digoxin, felodipine, sertraline
Phenobarbital	246 (2.5)	167 (67.9)	127 (51.6)	265	simvastatin, metoprolol, warfarin
Carbamazepine	824 (8.5)	565 (68.6)	457 (55.5)	216	simvastatin, metoprolol, warfarin
Valproate	545 (5.6)	119 (21.8)	97 (17.0)	232	sertraline, paroxetine, amitriptyline,
Totals	9,682 (100)	5,822 (60.1)	4,406 (45.5)		

AEDs with fewer than 11 potential drug interactions are not presented due to VA data security requirements. Initial approach includes all individuals who received an AED with a clinically meaningful drug interaction with ongoing medication on the day of the initial AED prescription. Conservative approach includes only those individuals with a subsequent prescription of interacting medications.

Table 5
Logistic Regression: Predictors of Potential Antiepileptic Drug-Drug Interaction

Variable	Odds Ratio (99% Confidence Interval)	p-value
Demographic Characteristics		
Age (vs. 66-74 years)		
75-84	0.86 (0.77-0.96)	<.001
85 years	0.69 (0.53-0.91)	<.001
Race (vs. White)		
Black	1.02 (0.87-1.19)	.72
Hispanic	1.00 (0.77-1.29)	.98
Other	0.87 (0.48-1.58)	.55
Female (vs. Male)	0.79 (0.53-1.19)	.14
Married (vs. Not Married)	1.11 (0.98-1.24)	.03
Context of Epilepsy Diagnosis		
Year (vs. 2000)		
2001	0.91 (0.77-1.08)	.16
2002	0.89 (0.75-1.06)	.08
2003	0.85 (0.72-1.01)	.02
2004	0.83 (0.69-0.99)	.01
Diagnosis in Medicare (vs. Diagnosis in VA)	1.02 (1.01-1.04)	<.01
Setting of Epilepsy Diagnosis (vs. Neurology)		
Emergency Department,	1.30 (1.08-1.58)	<.001
Hospital	1.08 (0.91-1.28)	.26
Other Specialty Care	1.20 (1.00-1.45)	.01
Primary Care	1.29 (1.12-1.49)	<.001
Clinical Characteristics		
Cerebrovascular Disease	1.22 (1.08-1.36)	<.001
Dementia	0.94 (0.82-1.07)	.22
Brain Tumor	0.86 (0.66-1.10)	.08
Other Neurological Conditions	1.01 (0.87-1.17)	.86
Cardiovascular Disease [^]	1.04 (0.92-1.17)	.86
Cardiac Arrhythmia	1.05 (0.93-1.18)	.31
Hypertension	1.46 (1.24-1.82)	<.001
Diabetes	0.91 (0.81-1.03)	.04
Renal Failure	0.91 (0.77-1.07)	.13
Liver Disease	0.70 (0.50-0.98)	.01
Hypercholesterolemia	1.40 (1.24-1.57)	<.001
Chronic Obstructive Pulmonary Disease	0.91 (0.81-1.11)	.03

Variable	Odds Ratio (99% Confidence Interval)	p-value
Psychiatric Conditions: One or more (vs. none)	0.99 (0.88-1.11)	.76
High Medication Burden (≥ 6 medications)	1.36 (1.20-1.55)	<.001

N for multivariate analysis = 9624

^ Congestive Heart Failure, Myocardial Infarction, or Angina