Potentially Inappropriate Antiepileptic Drugs for Elderly Patients with Epilepsy

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OBJECTIVES: To describe prescribing patterns for older veterans with epilepsy, determine whether disparity exists between these patterns and clinical recommendations, and describe those at greatest risk of receiving potentially inappropriate antiepileptic drugs (AEDs).

DESIGN: Retrospective administrative database analysis.

SETTING: All outpatient facilities within the Department of Veterans Affairs (VA).

PARTICIPANTS: All veterans aged 65 and older who had epilepsy diagnosed before the end of fiscal year 1999 (FY99) and who received AEDs from the VA in FY99 (N = 21,435).

MEASUREMENTS: National VA pharmacy data were used to determine the AED regimen based on the AEDs patients received during the year. Administrative data were used to describe demographic variables and to gauge disease severity and epilepsy onset.

RESULTS: Approximately 17% of patients received phenobarbital and 54% phenytoin. Patients classified as having newly diagnosed disease were less likely to receive phenobarbital monotherapy and combination therapy and more likely to receive gabapentin or lamotrigine monotherapy ($\chi^2 = 288.90$, $P < .001$). Logistic regression analyses indicated that, for all patients, those with more severe disease were less likely to receive phenobarbital monotherapy than other monotherapy and phenobarbital combinations than other combinations. Those who received specialty consultation were less likely to receive phenytoin monotherapy than AED monotherapy, which is consistent with clinical recommendations.

CONCLUSION: Most older veterans received potentially inappropriate AED therapy. Hence, the standard of care for older patients with epilepsy should be reevaluated, although the vast use of phenytoin in this population suggests that change in practice patterns may be difficult.
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Key words: epilepsy; drug therapy; adverse effects; quality of care; geriatrics

Medical treatment for epilepsy has changed considerably in the past 2 decades because of clinical research findings and the development of new antiepileptic drugs (AEDs). In 1983, a systematic assessment of the frequency and severity of adverse effects[1] showed differences between the standard AEDs (phenobarbital, primidone, phenytoin, carbamazepine, and valproate). Two landmark studies from the Department of Veterans Affairs (VA) extended this assessment by comparing AEDs in head-to-head randomized clinical trials. The first study[2,3] identified phenobarbital and primidone as undesirable first-line AEDs because of their higher burden of adverse effects. Although carbamazepine and phenytoin were similarly effective, phenytoin patients experienced significantly more adverse cognitive effects.[3] The second trial comparing carbamazepine and valproate[4] found equal efficacy but slightly different adverse-effect profiles. Thus, carbamazepine, phenytoin, and valproate have been favored for first-line use in the general population.[5–7]

In recent years, new AEDs that combine high efficacy with a low incidence of adverse effects have been developed (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide). Few studies have directly compared these new AEDs with standard AEDs,[5,6] and even fewer have examined these effects in the elderly,[8–10] but general studies of pharmacokinetics and pharmacodynamics suggest that the properties of the newer AEDs make them more suitable than phenytoin for use in elderly patients[5] because the pharmacokinetic profile of phenytoin

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requires careful dose adjustment in the elderly,[11,12] and the newer AEDs tend to have fewer adverse cognitive effects.[5,13–15]

The Scottish Intercollegiate Guidelines Network evidence-based guideline for treating epilepsy identified carbamazepine as the drug of choice for partial seizures (the most common type of seizures in the elderly), valproate as the drug of choice for primary (idiopathic) generalized seizures, and carbamazepine as the drug of choice for patients aged 25 and older with unclassified seizures.[16] A recent update to this guideline[6] identified lamotrigine as the AED of choice for the elderly. In the United States, 51 epilepsy experts evaluated treatment options for newly diagnosed patients[7] based on research evidence and professional experience. There was consensus that lamotrigine and valproate are first-line agents for idiopathic generalized epilepsy, and lamotrigine, gabapentin, carbamazepine, oxcarbazepine, and levetiracetam are first-line AEDs for partial epilepsy. Phenytoin and phenobarbital were identified as second- and third-line agents, respectively, for partial seizures and third-line agents (with carbamazepine) for idiopathic generalized seizures. These recommendations are for patients newly diagnosed; the expert panel did not address treatment for previously diagnosed patients on AEDs for some time.

The recommendation for phenytoin is a departure from the traditional treatment of epilepsy. Consequently, it is important to understand the status of epilepsy treatment for the elderly. The objectives of this study were to ascertain the prescribing patterns for older veterans with epilepsy receiving care in VA clinics, determine whether disparity exists between practice and the recent clinical recommendations, and describe the characteristics of patients most likely to receive phenobarbital and phenytoin.

METHODS

Population

VA administrative (inpatient and outpatient) and pharmacy data were used to select veterans who were aged 65 and older, had an *International Classification of Diseases* diagnosis of epilepsy (345.XX), convulsion (780.3), or late effect of brain injury (907.0) in VA facilities between fiscal years (FY) 1997 and 1999, and received an AED from the VA pharmacy in FY99. (Although the 780.3 code is less specific, it was the only available "check-off" diagnosis indicative of epilepsy on many clinic encounter forms and thus frequently used for pragmatic reasons.) Patients who received only AED medications not examined in this study (e.g., clonazepam, ethosuximide), had infantile spasm (incompatible with veteran status) as the only epilepsy diagnosis, or had a single diagnosis of 780.3 or 907.0 with a comorbidity of neuropathic pain were excluded.

Outcomes

Data from the national VA Pharmacy Benefits Management database in FY99 were used to ascertain prescribing patterns. Regimens included all AEDs received that year regardless of duration (e.g., may have been discontinued because of adverse effects). AED regimens included phenobarbital monotherapy; phenytoin monotherapy; carbamazepine monotherapy; valproate monotherapy; gabapentin or lamotrigine monotherapy; combination therapy with phenobarbital (phenobarbital combinations); combination therapy with phenytoin but no phenobarbital (phenytoin combinations); and combinations consisting only of carbamazepine, gabapentin, or lamotrigine (recommended combinations). These regimens were further combined, creating comparison groups for use in logistic regression analyses: phenobarbital monotherapy versus all other monotherapy, phenobarbital combinations versus other combinations (phenytoin and recommended combinations), and phenytoin monotherapy versus recommended monotherapy (carbamazepine, gabapentin or lamotrigine, and sodium valproate monotherapy). Phenytoin combinations were not compared with recommended combinations.

Independent Variables

Independent variables included characteristics of the patient (demographics and clinical status) and care received.[17] Demographic characteristics (age, sex, and race) were obtained from VA administrative data. Age was categorized as younger-old (65–74) and older-old ($\geq$75). Race was categorized as white and nonwhite (findings were similar for nonwhite groups).

Clinical Status

Patients with more-severe seizures are more likely to require emergency and hospital care for epilepsy, so disease severity was measured by counting the number episodes requiring emergency and hospital care for epilepsy in the VA during FY99. The distribution was skewed, so disease severity was dichotomized ($\geq$1 vs 0). Although type of seizure may also influence treatment, diagnostic data were not specific enough to accurately classify seizure type (partial, generalized, status epilepticus), but the major drugs of interest (phenobarbital, phenytoin, carbamazepine, gabapentin, and lamotrigine) are all equally effective for partial seizures—the type of seizures most common in adult onset epilepsy.[5,18] Only lamotrigine is recommended for both partial and generalized seizures.

Onset of epilepsy was identified using outpatient and inpatient administrative data; pharmacy data were not available until FY99. Patients with epilepsy first diagnosed in VA files during FY99 and who previously received VA outpatient or inpatient care (FY96–98) were classified as newly diagnosed. Patients with a first diagnosis of epilepsy in FY99 without previous outpatient or inpatient care were classified as new to VA. Those diagnosed before FY99 were identified as previously diagnosed.

Characteristics of Care

Characteristics of care were classified using outpatient data. Care was defined as only primary care if patients had no neurology clinic visits (FY97–99) and neurology care if patients also received at least one neurology consultation.

Statistical Analyses

Chi-square (χ^2) analyses determined whether onset of epilepsy was associated with AED regimen. Haberman's adjusted residual (HAR) values identified statistically significant cells (HAR with absolute value $\geq$1.96; $P<.05$).[19]

The likelihood of receiving phenobarbital and phenytoin was assessed using separate logistic regression analyses for those classified as newly and previously diagnosed. Analyses for those classified as new to the VA are not reported. Significant interactions between age, race, specialty care, and disease severity are reported. Approval for this study was obtained from the Bedford VA Hospital institutional review board.

RESULTS

Characteristics of the Population

A cohort of 21,435 older veterans received phenobarbital, phenytoin, carbamazepine, valproate, or newer AEDs (gabapentin or lamotrigine). Approximately half of these patients (n = 10,778) were identified using the less-specific 780.3 (convulsion) code. Because those with a single diagnosis are more likely to be inaccurately identified, those cases were further examined. Only 299 had a single 780.3 code, and one had a single 907.0 code. All of these patients were newly diagnosed or new to the VA, and those with the 780.3 code were less likely to have neurology consultations (44% vs 59%; $\chi^2 = 261.07$, $P < .001$) than patients with an epilepsy-specific code. The cohort was primarily male and white (63% white, 15% African American, 4% Hispanic, 2% other, 16% unknown), with most being aged 65 to 74. More than half of these patients received primary care only. Eighty percent received a regimen including phenobarbital or phenytoin, and 20% received a regimen consistent with current clinical recommendations. Ten percent (n = 2,157) were classified as newly diagnosed, 82.5% (n = 17,683) as previously diagnosed, and 7.4% (n = 1,595) as new to the VA. Table 1 provides descriptive statistics for these groups.

Onset of Epilepsy

Analysis indicated that AED regimens were associated with the classification of epilepsy onset ($\chi^2 = 288.90$, $P < .001$) (Table 1). Patients with previously diagnosed epilepsy were more likely to receive phenobarbital monotherapy (6.5% vs 4.7%, $P < .001$) and phenobarbital combinations (12.4% vs 4.7%, $P < .001$) and less likely to receive gabapentin or lamotrigine monotherapy (3.5% vs 7.8%, $P < .001$) than those newly diagnosed with epilepsy.

Newly Diagnosed with Epilepsy

Logistic regression analyses indicate that race and disease severity were strong predictors of receiving phenobarbital monotherapy versus other monotherapies for patients with newly diagnosed epilepsy. See Table 2 for odds ratios and 95% confidence intervals for analyses of phenobarbital and phenytoin regimens. Patients were twice as likely to receive phenobarbital monotherapy if they were white and if they received no emergency or hospital care in the VA. Characteristics of care and disease severity were the strongest predictors of receiving phenobarbital combination therapy. Patients receiving phenobarbital combinations were less than half as likely to have seen a neurologist and less than one-third as likely to receive emergency or hospital care in the VA. Finally, the data suggest that race and characteristics of care were significant predictors of receiving phenytoin monotherapy. White veterans and those receiving neurology consultation were half as likely to receive phenytoin monotherapy as recommended AED monotherapies. The younger-old were also somewhat less likely to receive phenytoin monotherapy.

Previously Diagnosed with Epilepsy

Results for patients previously diagnosed (Table 3) were similar to those for patients newly diagnosed with epilepsy, with generally smaller effect sizes. Whites and those receiving no VA emergency or hospital care were more likely to receive phenobarbital monotherapy than other monotherapy. Younger patients, patients receiving neurology consultation, and those receiving VA emergency or

Table 1. Descriptive Statistics

Patient Characteristic	Previous Diagnosis* (n = 17,683)	New Diagnosis† (n = 2,157)	New to VA‡ (n = 1,595)
	n (%)		
Demographic			
Male	17,426 (98.5)	2,110 (97.8)	1,577 (98.9)
White§	11,378 (64.3)	1,436 (66.6)	595 (37.3)
Received neurology care	7,711 (43.6)	981 (45.5)	531 (33.3)
Required VA emergency or hospital care	1,987 (11.2)	374 (17.3)	240 (15.0)
Medication regimen			
Phenobarbital monotherapy	1,147 (6.5)	102 (4.7)	83 (5.2)
Phenytoin monotherapy	9,447 (53.4)	1,229 (57.0)	915 (57.4)
Carbamazepine monotherapy	1,883 (10.6)	209 (9.7)	168 (10.5)
Valproate monotherapy	762 (4.3)	121 (5.6)	124 (7.8)
Gabapentin or lamotrigine monotherapy	618 (3.5)	169 (7.8)	70 (4.4)
Phenobarbital combination	2,200 (12.4)	102 (4.7)	119 (7.5)
Phenytoin combination	1,220 (6.9)	168 (7.8)	90 (5.6)
Recommended combination	406 (2.3)	57 (2.6)	26 (1.6)

Age, mean ± standard deviation: *73.13 ± 5.43; †73.60 ± 5.64; ‡73.52 ± 5.43.
§16.6% unknown for previously diagnosed epilepsy, 11% for newly diagnosed epilepsy, 54% for new to Veterans Affairs (VA).

Table 2. Logistic Regression Predicting Antiepileptic Drug Choice for Older Veterans with Newly Diagnosed Epilepsy: Likelihood of Receiving Potentially Inappropriate Drug Regimens

Independent Variable	Phenobarbital Monotherapy vs Other Monotherapy	Phenobarbital Combinations vs Other Combinations	Phenytoin Monotherapy vs Recommended Monotherapy
	Odds Ratio (95% Confidence Interval)		
White	1.88 (1.05–3.39)	1.56 (0.78–3.09)	0.54 (0.41–0.71)*
Male	0.70 (0.21–0.23)	0.17 (0.03–0.98)	1.81 (0.89–3.64)
Aged 65–74	1.34 (0.86–2.08)	1.26 (0.73–2.16)	0.79 (0.63–0.99)
≥1 emergency department or hospital care	0.47 (0.22–0.98)	0.29 (0.13–0.70)*	1.15 (0.86–1.55)
Received neurology care	0.81 (0.52–1.26)	0.45 (0.27–0.76)	0.49 (0.39–0.61)*

*$P < .001$.

hospital care were less likely to receive phenobarbital combination therapy than other combinations. Finally, patients who were white, younger, and received neurology consultation were less likely to receive phenytoin monotherapy than recommended AEDs.

DISCUSSION

Epilepsy is an increasingly common neurological disorder in the elderly,[14,20,21] so the effect of suboptimal treatment for older patients with epilepsy will increase as society ages. Evidence has gradually accumulated suggesting that phenobarbital and phenytoin are less desirable alternatives than carbamazepine[1–4] and newly developed AEDs.[9] This information was recently synthesized in the form of evidence-based clinical recommendations and expert consensus statements advocating use of carbamazepine, lamotrigine, gabapentin, and other newly developed AEDs rather than phenytoin and phenobarbital as first-line AEDs for newly diagnosed patients.[6,7,14,15] Although clinical studies suggest that phenobarbital is more problematic than phenytoin,[2] these recommendations suggest that both are potentially inappropriate for older patients, because the elderly are more susceptible to the adverse cognitive effects of these drugs.[5,9,22]

Overall, 80% of the cohort received an AED regimen including phenobarbital or phenytoin. Although most patients were taking phenytoin, approximately 18.9% of patients with previously diagnosed epilepsy and 9.4% of patients with newly diagnosed epilepsy received phenobarbital. The latter finding was particularly surprising because research over the past 15 years has clearly shown phenobarbital to be a potentially inappropriate drug.[2,3,23] Reasons for continued use of phenobarbital in newly diagnosed patients are unclear. Consequently, additional research is needed to explore the reasons behind this practice.

Analyses indicate that patients receiving phenobarbital were more likely to have previously diagnosed epilepsy than were patients on other AED regimens and that they tended to have less-severe disease than patients who received other monotherapy or combination therapies regardless of disease onset. However, findings for phenytoin suggest that patients receiving phenytoin monotherapy had a similar degree of disease severity as those who received currently recommended monotherapy. Patients on phenytoin monotherapy were twice as likely to be seen only in primary care setting as veterans who received recommended AED monotherapy, suggesting the possibility of delay in dissemination of clinical research to primary care providers. Neurologists may have greater access to the few studies comparing effects of different AEDs on the elderly,[24] but the scarcity of studies providing direct comparisons of phenytoin with recommended AEDs is also implicated. Alternatively, this finding might imply a more stable population. The finding of similar levels of disease severity in these groups reduces the likelihood of this explanation.

Table 3. Logistic Regression Predicting Antiepileptic Drug Choice for Older Veterans with Previously Diagnosed Epilepsy: Likelihood of Receiving Potentially Inappropriate Drug Regimens

Independent Variable	Phenobarbital Monotherapy vs Other Monotherapy	Phenobarbital Combinations vs Other Combinations	Phenytoin Monotherapy vs Recommended Monotherapy
	Odds Ratio (95% Confidence Interval)		
White	1.33 (1.13–1.56)*	1.04 (0.88–1.22)	0.61 (0.55–0.68)*
Male	0.55 (0.36–0.85)	1.25 (0.71–2.22)	1.38 (0.98–1.96)
Aged 65–74	0.94 (0.82–1.07)	0.83 (0.71–0.96)	0.84 (0.77–0.92)*
≥1 emergency department or hospital care	0.56 (0.43–0.73)*	0.58 (0.47–0.72)*	0.96 (0.84–1.10)
Received neurology care	1.06 (0.93–1.22)	0.40 (0.35–0.47)*	0.49 (0.45–0.53)*

*$P < .001$.

In addition, a variety of factors has slowed the acceptance of newly developed AEDs for use as first-line treatment. First, phenytoin is one of the few AED formulations available for rapid intravenous administration during emergencies; consequently, it is continued in oral form after intravenous administration. Second, phenytoin is less expensive than newly developed AEDs. Cost is a concern both for patients who must pay for drugs and for providers whose formulary costs are affected by prescribing patterns. Thus, treatment usually starts with a standard AED such as phenytoin and steps up to a new drug only as needed for improved efficacy or better tolerability. Moreover, the titration schedule of lamotrigine must be gradual, and it thus may be initially inappropriate for those requiring quick seizure control.[21]

Finally, reasons underlying lower rates of use for carbamazepine are not entirely clear because the cost of phenytoin is comparable and both have been used for more than 20 years. The extensive use of phenytoin may be associated with dosing. Phenobarbital, phenytoin, and divalproex (extended-release valproate) offer once-daily dosing. Carbamazepine's requirement for multiple daily doses may limit its use because patient compliance is associated with fewer daily doses.[25] Carbamazepine's metabolism results in enzyme induction and consequently complicated drug interactions, but a similar process occurs with phenytoin, although phenytoin also has the unfavorable feature of nonlinear pharmacokinetics.[11,20] Thus, dosing of phenytoin can be more problematic in the elderly than carbamazepine.

The finding of racial differences was intriguing. Whites were more likely to receive phenobarbital, and nonwhites were more likely to receive phenytoin. Frequency of dosing is unlikely the origin of this finding, because both drugs may be given once per day. Consequently, additional research is necessary to understand these results.

Although these findings suggest that most older veterans with epilepsy receive potentially inappropriate AEDs, the homogeneous nature of the cohort might limit generalization to other elderly populations. It is likely that similar treatment is provided in non-VA care, but additional research is necessary to ascertain these patterns of care. Veterans receive medications associated with a service-connected disability for free and pay a small copayment ($2 at the time of this study) for drugs related to non–service-connected conditions. Many elderly Americans pay a copayment that is higher for branded drugs or pay the entire cost of their medications. Newer AEDs do not have generic forms, and the cost of these AEDs could be prohibitive for those with low incomes. Thus, it is important to verify patterns of care for other populations.

The data are also limited because they do not include emergency, hospital, or outpatient care received outside the VA. Consequently, patients might have epilepsy diagnosed and have received care outside the VA, which could affect the classification of disease onset and disease severity. However, examination of the findings indicates that they are theoretically consistent with expectations. Patients on combination therapy were more likely to be described as having more-severe disease, and patients with newly diagnosed epilepsy were more likely to receive monotherapy and newly developed AEDs. These findings suggest that, although not exact, the measures provide reasonable estimates for severity and epilepsy onset. Further research will allow for further refinement of these methods and improvement of these measures.

The consistency of clinical recommendations and expert consensus for treatment of epilepsy suggest that the treatment of older patients with epilepsy should be reevaluated. Although recommendations advise providers to avoid using phenobarbital and phenytoin for newly diagnosed epilepsy, the course of action for those who have been on these drugs long-term is less clear. Patients may gradually habituate to the adverse effects of these AEDs, and changes in pharmacokinetics and pharmacodynamics that occur with age may lead to additional subtle changes that are not apparent to patient or provider and that become apparent only when the AED is discontinued. These subtle effects could increase patients' risk of falls,[26] accidents,[27] or diminished quality of life.[28] Thus, long-term patients—particularly those on phenobarbital—might benefit from a yearly reevaluation of AED regimen, as recommended in the geriatrics literature.[29]

The complexity surrounding the extensive use of phenytoin suggests that change in treatment patterns for older patients with epilepsy might be difficult to attain because it would require a shift from prescribing phenytoin, a medication that has been used for more than 40 years and with which providers feel comfortable, to unfamiliar medications. To change such ingrained practice, it is likely that providers will want more evidence documenting the problems these AEDs pose for their patients.[30] Results from the soon-to-be-released VA Cooperative Study comparing the efficacy and effect of carbamazepine, lamotrigine, and gabapentin (VACS 428) will provide insight regarding the initial therapy for epilepsy with these drugs,[14] but it will not clarify the role of phenytoin. Unfortunately, there are no long-term effectiveness studies providing direct comparisons of various AEDs on older patients' health status that could help gauge the risk associated with long-term use of phenobarbital and phenytoin in the elderly and help clinicians determine whether the risks of continued treatment outweigh the risks associated with changing AED regimens for their patients

It is clear that most older veterans receive less-than-desirable medications, but changing drugs for those already on AEDs is complicated by drug-drug interactions and the risk of breakthrough seizures during this change. However, the potential effect of these suboptimal AEDs suggests that we must, at minimum, begin by altering prescribing practices for those who have newly diagnosed epilepsy. The magnitude of phenytoin use suggests a great need to educate providers about the less-burdensome adverse-effect profiles of the newer AEDs before change will occur in the community. Effectiveness studies and interventions might also be necessary; without such efforts, older patients with epilepsy may continue to receive AEDs with adverse cognitive effects,[5,22] which increase their dependence on others and the healthcare system.[26–28]

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