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Research Article

Antiepileptic Drugs and Suicidality in Veterans with Seizures

Shawniqua Williams Roberson[1]*, Rizwana Rehman[2] and Gabriel Bucurescu[3]

[1]*Department of Neurology, Vanderbilt University Medical Center, Nashville, Tennessee, USA*

[2]*Southeast Epilepsy Center of Excellence, Durham VA Medical Center, Durham, North Carolina, USA*

[3]*Department of Neurology, Corporal Michael J. Crescenz VAMC, Philadelphia, Pennsylvania, USA*

***Corresponding Author:** Shawniqua Williams Roberson, Department of Neurology, Vanderbilt University Medical Center, Nashville, Tennessee, USA.

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Abstract

Objectives: Veterans and patients with epilepsy are at higher risk of suicide than the general population. Some studies suggest that antiepileptic drugs (AEDs) further increase the risk of suicide. The nature of the relationship between suicidality and epilepsy treatment needs clarification. We examined this relationship in a cohort of veterans with seizures.

Methods: We performed a retrospective chart analysis of patients at the Philadelphia VA Medical Center with a diagnosis of seizure disorder between January 2000 and April 2007. Patients with suicidal ideation and/or suicidal behaviors were analyzed with respect to the following risk factors: age, history of traumatic brain injury (TBI), substance abuse and AED prescription.

Results: 526 charts were reviewed, 385 of which met inclusion criteria. Patients with substance abuse were more likely to have suicidal ideation (adjusted odds ratio 3.37, 95% CI 1.84 - 6.18). Risk decreased with age (adjusted odds ratio 0.94, 95% CI 0.92 - 0.97 for each year). There was no statistically significant relationship between suicidality and AED use or history of TBI.

Conclusion: In our population, AEDs were not associated with increased risk of suicidality, whereas substance abuse was associated with a substantial risk increase. The interactions among seizures, suicidality, substance abuse and other neuropsychiatric diseases are complex. Large-scale studies in patients with seizures are needed to understand the impact of individual drugs and other contributing factors. Providers should be cautious not to withhold potentially beneficial treatment, however patients with risk factors such as history of substance abuse should be followed closely after AED initiation or adjustment.

Keywords: *Antiepileptic Drugs; Adverse Effects; Veterans; Seizures; Suicide; Substance Abuse*

Abbreviations

AED, AEDs: Antiepileptic Drug(s); CPRS: Computerized Patient Record System; IRB: Institutional Review Board; SRB: Suicide-Related Behaviors; TBI: Traumatic Brain Injury; VA: Veterans Administration

Introduction

Suicide is a serious health problem among veterans, with rates 2 - 4 times those of the general population [1,2]. In 2008, the United States Food and Drug Administration (FDA) issued an alert stating that patients taking one or more of 11 antiepileptic drugs (AEDs) had twice the risk of suicide-related behaviors [3]. This claim is of particular concern in the Veterans Administration (VA) population given

that epilepsy is a significant cause of morbidity in veterans and the use of AEDs is high. In addition, AEDs are commonly prescribed for a number of psychiatric and pain conditions, for which veterans are also at high risk.

Concerns have been raised with the FDA alert, for example that not all AEDs were included in the analysis and that technical difficulties prevented differentiation among individual AEDs [4]. Subsequent studies have tried to identify individual drugs that conferred higher risk [5,6] or have pointed to the underlying indication as a potential confounding factor [7,8]. Indeed, Pugh and colleagues found an increase in suicide-related behaviors (SRB) in older veterans just before initiation of AEDs that appears to decrease after AED monotherapy [9]. Subgroup analysis in this study demonstrated increased SRB among new AED users with various psychiatric diseases but failed to find a similar increase among patients with epilepsy. This study included elderly veterans across multiple indications for AED initiation.

Aim of the Study

Our aim in this retrospective study was to determine if suicidality (defined as suicidal ideation and/or suicidal behavior) is associated with AED use in veterans treated for seizures at the Philadelphia VA, including younger patients and those on multiple AEDs. Our hypothesis was that the treatment with AEDs does not increase suicidality in veterans with seizures. We also investigated the effect of other commonly cited risk factors on suicidality in this population.

Materials and Methods

After obtaining approval from the institutional review board (IRB) at the Corporal Michael J. Crescenz VA Medical Center Philadelphia, medical records of patients treated for seizures were reviewed. The Computerized Patient Record System (CPRS) was searched to select patients treated between January 1, 2000 and April 3, 2007 for seizures. Initially patients who carried a diagnosis of "seizure disorder" (ICD-9:780.39) were identified and their medical records (526 patients) were examined. This was the most common diagnosis given to patients with any seizure type across all services during the specified time period, irrespective of clinical setting (e.g. emergency department, primary care clinic or neurology clinic).

However, the diagnostic coding in the VA facilities was found to have shortcomings and inaccuracies up until the late 2000's, prompting the individual chart review for clinical confirmation of seizure diagnosis. We found that reliance solely upon ICD-9 coding was insufficient to accurately determine the diagnosis for some patients. To ensure that patients did indeed have a history of one or more seizures, each chart was investigated individually to determine how the diagnosis was made. The diagnosis of seizures was confirmed by review of the clinical notes in Primary Care and where available, Neurology or Psychiatry. If the diagnosis could not be confirmed based on chart review, then the record was excluded.

The flowchart of selection results is shown in figure 1. Charts were also investigated for diagnosis of TBI, substance abuse and suicidal ideation. The diagnosis of TBI was determined by assessing if patients had any history of head trauma or concussion in their problem list or in the medical history. Substance abuse was likewise assessed by examining the medical record for documented use of illicit substances and/or treatment for substance abuse (including abuse of alcohol, opiates and all illegal substances). Suicidal ideation was identified by documentation of diagnosis (ICD-9 codes: ideation V62.84 or tendencies 300.9) and/or mention of treatment for suicidality in clinical notes.

All charts were assessed for treatment with AEDs as well as visits to the Neurology clinic within one year of data collection. In addition, age of the patients at the time of chart review was recorded. Statistical analyses were performed using SAS 9.3 (SAS Institute Inc.; Cary NC). Binary logistic regression was carried out to determine factors associated with suicidality and to estimate effect sizes (odds ratios).

Results

Of the 526 total charts reviewed, 390 patients carried a clinical diagnosis of seizure disorder. Complete and relevant conclusive clinical data were available for 385 patients. Of these, 285 (74.3%) were prescribed AEDs and 99 (25.7%) were not. The clinical characteristics of the AED and non-AED groups are summarized in table 1. Patient ages at the time of evaluation ranged from 24 to 92 years, with a median of 62 years and an interquartile range of 55 to 74 years. Approximately one-third of all patients had a history of TBI and 40% had a history of substance abuse. The AED and non-AED groups did not differ significantly with respect to these characteristics. Only 29.9% of subjects had recent follow-up with neurology, however more patients on AED therapy were followed in neurology clinic than those off AEDs.

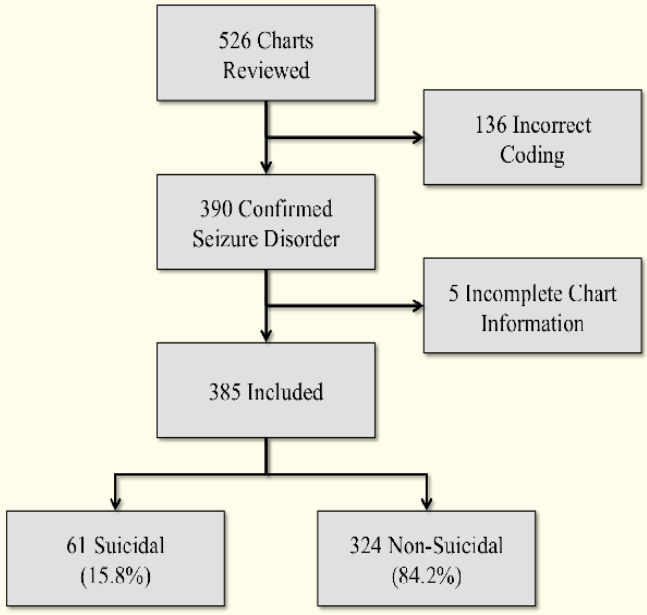

Figure 1: *Flowchart of included charts and breakdown of suicidal versus non-suicidal cases. Charts of patients evaluated for seizure disorder (ICD-9 780.39) between January 2000 and April 2007 were reviewed. Of the 385 charts with confirmed diagnosis of seizure and adequate information for inclusion in the study, 61 (15.8%) had history of suicide attempt, ideation or behaviors.*

Characteristic	AED Prescribed (N = 286)	AED Not Prescribed (N = 99)	Overall Patients (N = 385)	Significance (AED vs No AED)
Mean (±SD) Age in Years	63.9 ± 12.8	64.9 ± 12.0	64.2 ± 12.6	p = 0.50
History of TBI	100 (35.0%)	26 (26.3%)	126 (32.7%)	p = 0.11
History of Substance Abuse	115 (40.2%)	40 (40.4%)	165 (40.3%)	p = 0.97
Recent Neurology Follow-up	106 (37.1%)	9 (9.1%)	115 (29.9%)	p < 0.01

Table 1: *Characteristics of veterans diagnosed with seizures.*

Clinical characteristics of patients diagnosed with seizures at the Philadelphia VA between January 2000 and April 2007, as a function of antiepileptic drug prescription status. Substance abuse includes both alcohol and illegal drugs. Percentages rounded to nearest one decimal digit. Age distributions of the two groups (AED vs no AED) were compared by pooled t-test (two tailed independent samples) and showed no significant difference. Chi-square tests between AED and non-AED subgroups with significance threshold $p \leq 0.05$ suggest that subgroups differed in terms of neurology clinic follow-up but not in terms of history of TBI or substance abuse.

TBI: Traumatic Brain Injury; AED: Antiepileptic Drugs.

Sixty-one patients were identified as having suicidal ideation or suicide-related behaviors. These comprised 48 (16.8%) of 286 patients on AED therapy and 13 (13.1%) of 99 patients not taking AEDs. Among the patients with suicidality, 78.6% were on AEDs, 36.1% had a prior TBI and 68.9% had a history of substance abuse. Among those without history of suicidality, 73.5% used AEDs, 32.1% had a prior TBI and only 34.9% had a substance abuse history. Rates of suicidality as a function of the three risk factors investigated (AED prescription status, TBI history, substance abuse) are shown in figure 2.

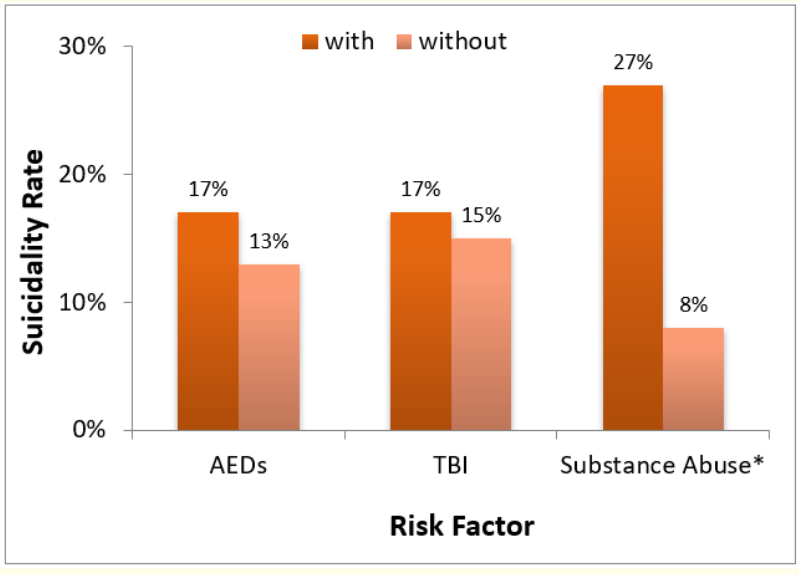

Figure 2: *Rates of suicidality among patients with seizures, by risk factor.*

*Observed suicidality rates with and without AED use, TBI history and substance abuse history among patients with seizures at the Philadelphia VA between January 2000 and April 2007. Binary logistic regression analysis demonstrated a significant association between substance abuse and risk of suicidality (*p<0.001). There was no statistically significant association between suicidality and AED use or TBI history.*

Binary logistic regression for outcome variable suicidality with binary categorical predictors substance abuse, history of TBI, AED prescribed and continuous variable age at the time of chart abstraction was carried out. C index (as a measure of goodness of fit) was 0.75 and p value of Hosmer-Lemeshow test was 0.84. All three Likelihood Ratio, Score and Wald tests for null hypothesis that all regression coefficients were zero showed statistical significance (all p values were less than 0.001). Using maximum likelihood estimates, substance abuse and age (both p values < 0.001) were significant predictors of suicidality; whereas AED prescribed (p value = 0.37) and TBI (p value = 0.59) were not statistically significant. Adjusted odds ratio for substance abuse yes vs. no was 3.37 (95% Wald confidence interval 1.84 to 6.18). For age the adjusted odds ratio was 0.94 (95% Wald confidence interval 0.92 to 0.97).

Discussion

In this single center, retrospective study we sought to determine if AED use increases the risk of suicidality in a cohort of veterans with seizures at the Corporal Michael J. Crescenz VA Medical Center. We did not find a statistically significant association between AED usage and suicidality in this group. This is in contrast to previously reported results in elderly veterans [9,10] but consistent with those in civilian populations with epilepsy [7]. By contrast, the meta-analysis that prompted the original FDA alert suggested a 3.6-fold relative risk of suicidality among epilepsy patients taking AEDs by comparison to those on placebo. The patient populations of these studies were

distinct, in that our study focused on veterans of any age and only those with a confirmed history of one or more seizures. Ours was thus a predominantly male population with an age distribution younger than prior studies in veterans but older than studies of epilepsy patients in general. Overall, the findings support the notion that treatment with AEDs does not uniformly increase risk of suicidality across all patient populations.

We also found no significant association between history of traumatic brain injury (TBI)and suicidal ideation. We collected data on TBI history because of its increased prevalence among veterans and because people with a history of TBI are more likely than others to die by suicide [11,12]. Our data did not indicate any association between TBI and suicidal ideation, possibly because of our demographics-TBI-related suicide rates are highest in women and in persons between 21 and 60 years of age [12]. Neither of these demographics is well-represented in our study population.

There was however, a strong association between suicidal ideation and substance abuse. For any given age, TBI history and a known AED prescription status, the odds of being suicidal for patients with a history of substance abuse were more than triple the odds of patients who did not abuse drugs or alcohol. This is consistent with prior findings in the general population demonstrating an increase in suicide-related behaviors among persons with substance abuse [13]. It is not clear whether this association is causative-although substance abuse is associated with more impulsive behavior and more violent deaths of all causes, those with substance abuse also tend to have higher rates of mood and psychotic disorders and for many (including many veterans) the substance abuse is a method of self-medication for psychiatric symptoms. One way to investigate this further would be to study the specific types of substances abused, since various drugs of abuse have different mechanisms of action and may be associated with distinct patterns of psychiatric comorbidity and/or suicide risk. A detailed investigation of the types of drugs abused was, however, outside the scope of the current study.

We were not able to establish the age of onset of suicidal ideation for every patient in the cohort due to incomplete documentation. We found, however, that older age at the time of chart evaluation was associated with a slight decrease in the risk of history of suicidal ideation. This is consistent with prior studies showing that risk of death by suicide does not appear to increase with age among male veterans in general [2] and may even decrease slightly [14]. It does contrast with studies finding an increased risk of suicide with advancing age in the general population [15,13] and may be a function of increased rates of substance abuse in younger veterans [16]. Given that a diagnosis of suicidal ideation is unlikely to be retracted once established in a patient chart, the decreased longevity associated with suicidality may also be a contributing factor.

Epilepsy and suicidality

Suicidal ideation and suicidal behaviors are increased among persons with epilepsy [17-19] however the exact reason for this association is not clear. Epilepsy patients suffer a higher burden of depression and anxiety than the general population [20] as well as a higher burden of depression than comparably disabled controls [21]. These disorders are known to increase the risk of suicide in the general population [22-24]. Post-ictal psychosis also increases the risk of suicidality in patients with epilepsy [25]. It is important to note, however, that the increased risk of suicidality in epilepsy appears to be independent of comorbid psychiatric disorder [26]. An underlying pathophysiologic link has been postulated [27] but the detailed mechanism is yet poorly understood.

Importantly, the increased risk of suicidality among epilepsy patients and the frequency with which these patients are prescribed AEDs immediately upon diagnosis makes it difficult to disentangle the effects of epilepsy, comorbid mood disorder and frequently resultant socioeconomic stressors from that of antiepileptic drug prescriptions on suicidality. Pugh., *et al*. [9] addressed this question elegantly by demonstrating that, at least among elderly veterans initiating antiepileptic monotherapy, suicidal ideation is increased prior to AED initiation, is independent of treatment with AEDs and may gradually decrease over time after AED monotherapy. Though our study does not directly address the temporal relationship between AED initiation and onset of suicidality, our observations do raise the question of whether similar relationships hold when the entire age range of veterans with seizures is included.

Risks and benefits of epilepsy treatment in veterans

Veterans with epilepsy are at a higher risk of death than other veterans [28]. Although the 2 - 3 fold increase in mortality among epilepsy patients is not entirely due to the direct effect of seizures, approximately 6 - 10% of epilepsy deaths in developed countries are seizure-related [29] and could potentially be avoided with optimal seizure control. By comparison, suicide accounts for less than 2% of epilepsy deaths in community studies [30]. This suggests care must be taken to weigh risks and benefits of starting treatment. Although suicide is an important cause of death among veterans as a whole, we argue that the benefits of epilepsy treatment may outweigh the risks in veterans with epilepsy. Subpopulations that are at higher risk for suicidality (e.g. those with substance use disorders) may require a higher threshold for AED initiation. These veterans should be followed closely when new AEDs are started and may benefit from referral for psychiatric evaluation. This is consistent with the 2013 consensus statement by the Task Force on Therapeutic Strategies of the International League Against Epilepsy (ILAE) Commission on Neuro psychobiology, which a) pointed out that the risk of stopping or refusing to start AEDs can result in serious harm, b) recommended that this risk be weighed carefully against the risk of suicidality and c) patients with "positive suicidal risks" should be referred for psychiatric evaluation but should not have AEDs withheld [31].

Limitations of the Study

There were several limitations to this study that should be kept under consideration. First, due to technical and resource constraints it was not possible to search across multiple diagnostic codes in the electronic medical record. To address this, we searched on the most commonly used diagnostic code in our center for epilepsy patients. It is possible that not all epilepsy patients treated during the designated time span were captured in the analysis, although typically patients with more specific diagnoses (e.g. 345.XX) also had our selected ICD-9 code. It is also possible that some of the patients included in our study did not have a significant ongoing seizure burden. Indeed, this may partly explain the substantial percentage of patients not on AED therapy at the time of our evaluation. Nevertheless, we believe we have captured a reasonable cross-section of the population of veterans with epilepsy in general and those for whom suicidal behaviors have been identified in particular. It is hoped that ongoing technological advances in electronic medical record management will make such an analysis feasible on an even larger scale in future studies.

In addition, it is possible that a select few AEDs contribute to increased risk of suicidality while others were associated with a decreased risk. The FDA meta-analysis included 11 drugs and anticipated that the observed risk extends to all AEDs. Subsequent studies have demonstrated inconsistent results for individual drugs, although valproate and lamotrigine appear to have the strongest consensus for negative effect [6,32]. We did not collect data on individual AED usage for our study population and believe this would be an important consideration for future investigation.

Likewise, as previously mentioned, details of the nature of TBI (e.g. blast vs. focal); type, severity and age of onset of seizures; and the specific substances abused were out of the scope of this study. Furthermore, data were not collected on comorbid mood and psychotic disorders, nor on social demographics such as race and marital status, factors that also impact the risk of suicide-related behaviors in the general population. Future studies with larger cohorts of veterans with seizures can allow stratification by these factors and would serve to further clarify cohorts that are at highest risk and thus require closer follow-up and/or psychiatric evaluation upon initiation of AED therapy.

We did not expect the time of onset of suicidality to be reliably documented in the clinical charts and an assessment of the date of initial AED prescription was outside the scope of our study. Thus, the temporal relationship between cited risk factors and suicidality was not assessed. It is possible that in some patients, suicidal ideation preceded AED use, TBI incidence and/or substance abuse. Refinement of our data to exclude these cases could potentially yield different results. Future prospective studies would do well to consider evidence of suicidality prior to initiation of AEDs.

Finally, this retrospective study was performed at a single VA medical center. As such, despite including patients treated over a broad range of years, the size of our cohort remained relatively small. A multicenter study could likely capture many more times the number of veterans with seizures and may shed more light on the relative risks of suicidality with and without AEDs. Caution must be taken, however, to optimize consistency of diagnostic criteria and clinical data capture across multiple centers.

Conclusion

Patients with epilepsy have an increased risk of suicide compared to the general population. The risk of suicidality is climbing among veterans and factors that increase suicide risk warrant careful consideration. Although some studies suggest that certain antiepileptic

drugs are associated with increased risk of suicide, these findings are by no means conclusive. Our study examined this question retrospectively in a cohort of veterans with seizures and did not find a relationship between the use of antiepileptic drugs as a whole and the risk of suicidality. Likewise, there was no relationship between suicidality and traumatic brain injury. However, substance abuse conferred a more than three-fold risk of suicidality. Finally, we saw that suicidality risk decreased slightly with increasing age. Given the complex relationships among these and other factors, we agree with other authors that a blanket labeling of all AEDs as increasing the risk of suicide may be counterproductive and that further investigation with large-scale studies is appropriate.

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Conflicts of Interest

The authors declare no conflict of interest exists, financial or otherwise, with respect to this work.

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