The development of seizures following spontaneous subarachnoid hemorrhage (SAH) is a well-documented phenomenon. Pathophysiologic processes involved in the development of post-SAH seizures include both acute biochemical dysfunction and delayed gliotic cellular reorganization. Seizure activity has been associated with secondary neurological injury, including reduced cerebral blood flow and increased intracranial pressure.1 Seizures occurring after SAH have been associated with clinical and radiographic markers of hemorrhage severity (higher SAH grade/extent of SAH blood burden, lower Glasgow Coma Scale score at presentation, etc), as well as rebleeding and delayed ischemic neurological deficits (DIND, or cerebral vasospasm).2,3 Literature has reported seizure rates to be as high as 27% in this population.4 These high rates of seizures, as well as concern over the possible consequences of a seizure in the setting of an unsecured aneurysm, has led to routine prophylactic administration of antiepileptic drugs (AEDs) after SAH in many centers.2,3

More recently published studies have found seizure rates to be significantly lower than previously described (1%–10%).2,5 Of added importance, newer literature has suggested increased adverse effects associated with posthemorrhagic AED exposure, including serious drug-related complications, as well as worse cognitive and functional outcomes.6 Systematic reviews examining AEDs and seizures after SAH found no recent literature supporting the effectiveness of AED prophylaxis.3,7 Furthermore, ≤21% of those receiving prophylactic AEDs had a similar likelihood of suffering seizures as those who did not (P=0.49).

The purpose of this study was to evaluate whether prophylactic administration of AEDs significantly decreased the incidence of post-SAH seizures. We hypothesized that the prophylactic AEDs would not be associated with a decreased risk of seizure occurrence in patients with spontaneous subarachnoid hemorrhage. (Stroke. 2016;47:1754-1760. DOI: 10.1161/STROKEAHA.116.013766.)

Key Words: antiepileptic drug ■ propensity score ■ SAH ■ seizure ■ subarachnoid hemorrhage
after SAH. To evaluate this, we performed a propensity score-matched analysis of patients with spontaneous SAH treated with or without prophylactic AEDs to assess the incidence of clinical and electrographic seizures during initial hospitalization.

**Methods**

**Patient Population**
We performed a retrospective review of prospectively collected data on all patients presenting to UPMC Presbyterian Hospital for spontaneous SAH from February 2005 to October 2010. The Institutional Review Board of the University of Pittsburgh approved this study (IRB No 021039), all participants (and their representative) gave informed consent, and all procedures were in accordance with institutional guidelines. Patients diagnosed with a cerebral aneurysm as well as those without an identifiable etiology for SAH on angiography were included for analysis. Patients were excluded if SAH was secondary to trauma, arteriovenous malformation or fistula, spontaneous intraparenchymal hemorrhage, or inflammatory vasculopathy. Baseline demographic information, clinical characteristics at presentation, aneurysm morphology and treatment modality, AED prescription characteristics (type, timing, and duration of use), and clinical course were all recorded prospectively and analyzed. A universally accepted grading scheme for hemorrhage severity does not exist, as such, cisternal SAH burden was defined as scant (≤1 mm of layering in ≤3 basal cisterns or <2 contiguous axial computed tomography slices), diffuse (≤1 mm in ≥3 basal cisterns on multiple slices), or severe (>1 mm in all basal cisterns on contiguous slices) as demonstrated on admission head computed tomography (standard axial noncontrast protocol performed at ≤5 mm slice thickness).

**Antiepileptic Drugs**
AED administration at our hospital or the referring facility was defined as either prophylactic (before documented clinical or electroencephalography [EEG] seizure activity) or therapeutic. Between February 2005 and July 2007, departmental protocol was to administer prophylactic AEDs upon presentation for all patients suffering spontaneous SAH. The dose and duration of treatment were left to the discretion of the attending neurosurgeon. Phenytoin was the predominant prophylactic AED administered (81%) and included a loading dose of 1000 mg followed by 100 mg every 8 hours. The remaining patients received prophylactic levetiracetam, given as 1000 mg doses every 12 hours. Prophylactic AEDs were administered for 7 to 30 days (mean 14±8 days) with the duration at the discretion of the treating neurosurgeon. As part of an institutional SAH Quality Improvement initiative and revision of departmental protocol in July 2007, patients presenting with spontaneous SAH no longer received prophylactic AEDs on admission, and AEDs initially administered at the referring hospital were immediately discontinued. Regardless of when or where the patient initially presented, those who received prophylactic AED were analyzed as the treatment cohort (including only a one-time bolus dose). Serum levels of AEDs administered for prophylaxis were not checked. Patients who did not receive AED were analyzed as controls. Clinical or electrographic seizure activity at UPMC was treated with an AED, with type, dose, and duration dependent on preferences of the managing physicians and response to medications. Patients undergoing craniotomy for aneurysm clipping and clot evacuation that received prophylactic AEDs postop were assigned to the treatment cohort; duration was at the discretion of the treating neurosurgeon (range 7–30 days).

**Outcomes**
The primary end point was seizure occurrence diagnosed clinically and through EEG during the initial hospitalization period. A neurologist, neurosurgeon, and neurointensivist must have witnessed clinical seizure activity to be recorded as clinically positive. As such, it was impossible for adjudication of clinical seizure to be performed without knowledge of AED treatment status (ie, masked). Clinical seizure activity included intermittent twitching, paroxysmal autonomic signs, or motor automatism with suspicion of seizure. Electroencephalographic monitoring was performed in all patients unable to be followed clinically because of depressed mental status or in whom a high clinical suspicion of seizure activity existed. Initial monitoring was performed over a 2-hour period for acute evaluation and repeated 12 to 24 hours later if clinical suspicion of seizure activity remained. Patients suffering electrographically confirmed seizures were continuously monitored until epileptiform activity was controlled. EEG output was recorded digitally using 21 scalp electrodes placed according to the international 10 to 20 system. Results were interpreted by an attending neurophysiologist/neurologist without knowledge of AED treatment status (ie, masked). Positive seizure activity was defined as focal or generalized epileptiform discharges according to 2012 American Clinical Neurophysiology Society Standardized Critical Care EEG Terminology. Consequently, generalized spike and wave patterns slower than 3 s and evolving discharges that remained slower than 4 s were not recorded as positive.

**Statistical Analysis**
Acceptable Type I error was set as a priori at α=0.05 for all statistical tests. Patients with missing and incomplete clinical, radiographic, or outcome data were excluded from all analyses. Continuous demographic characteristics were assessed for normality using Kolmogorov–Smirnov test; normally distributed data were analyzed by t test, whereas the remainders were compared using the Wilcoxon Rank–sum test. Categorical data were analyzed with Pearson’s chi-squared or Fisher exact test. Univariable logistic regression analysis was performed to assess for predictors of seizure activity. Multivariable logistic regression was used to adjust for variables identified by univariate analysis to be marginally different between the outcomes (the probability value for inclusion was set at P<0.2). Secondary end points, including DIND, were analyzed using multivariable logistic regression, adjusting for known predictors of functional outcome.

Because prophylactic AED treatment was not randomly assigned, the decision was made a priori to perform analyses using propensity score matching to account for clinical covariates associated with prophylactic AED administration. The covariates used to generate this propensity score were clinical characteristics (admission Hunt–Hess score, cisternal SAH thickness, intraventricular hemorrhage, and intraparenchymal hemorrhage), procedural characteristics (aneurysm occlusion modality, craniotomy for hemorrhage evacuation), and monitoring characteristics (use of EEG monitoring). After propensity score generation, patients underwent 1:1 nearest neighbor (Greedy-type) matching of the logit of the propensity score with a caliper width of 0.25. Matching between those receiving prophylactic AEDs (treatment) and those who did not (control) was performed without replacement, and unpaired treated and control patients not meeting matching criteria were excluded. Each propensity score–derived matched pair was assigned a unique pair ID. Improvement in covariate balance after matching was determined using conditional logistic regression, conditioned on the pair ID. Occurrence of seizure was then compared between treatment and control propensity-matched patients using univariate statistics. Data were analyzed using Stata version 14 (StataCorp, College Station, TX).

**Results**

**Baseline Characteristics**
From July 2005 through October 2010, 353 patients were admitted with a diagnosis of spontaneous SAH. Baseline clinical characteristics for these patients are displayed in Table 1.
by prophylactic AED status. Forty-three percent (n=152/353) of patients received prophylactic AEDs either on admission or after craniotomy (Figure). Clinical characteristics that varied significantly between those receiving prophylactic AEDs or not included age, aneurysmal etiology, and presence of acute hydrocephalus (all \( P < 0.01 \)). The remaining baseline demographic characteristics, as well as clinical and radiographic surrogates of SAH severity (Hunt–Hess score, cisternal SAH burden, intraventricular hemorrhage, intraparenchymal hemorrhage, etc) were not significantly different between treatment cohorts.

Risk of Seizure Following Propensity Score Adjustment

The risk for seizure development was analyzed in relation to prophylactic AED treatment using propensity score matching and calculated for each patient using a logistic regression model with 6 covariates (Hunt–Hess grade, SAH burden, intraventricular hemorrhage, intraparenchymal hemorrhage, etc).
intraventricular hemorrhage, intraparenchymal hemorrhage, hydrocephalus, craniotomy, and aneurysmal etiology). Following 1:1 matching, 152 treated and 201 control patients were matched to at least one patient of the other treatment cohort based on similarities in clinical characteristics previously listed. There were no nonmatched cases in either treatment or control groups. Following matching, all covariates were statistically indistinguishable between the prophylactic AED treatment and control cohorts.

After propensity score matching, prophylactic AED treatment did not significantly impact the incidence of seizure after SAH (P=0.49). Similarly, the incidence rate of seizure activity by diagnostic modality (clinical or EEG) was also not significantly different in those receiving prophylactic AEDs (P=0.86). Adjusted analyses for secondary outcome measures suggested that prophylactic AED treatment was significantly associated with DIND (OR 1.21, 95% CI 1.05–1.40), however, not 12-month functional outcome. As well, diagnosis of seizure by any means was also not significantly associated with worse 12-month neurological outcome after adjustment for known predictors of poor outcome (P=0.15).

Post hoc analysis was performed to explore the significant association observed between prophylactic AED treatment and the development of DIND. Multivariable logistic regression analysis of AED type (phenytoin versus levetiracetam) adjusting for known predictors of DIND (age, aneurysmal SAH etiology, and cisternal SAH burden) revealed that the risk of DIND was significantly greater among those following prophylactic levetiracetam compared with phenytoin or no AED treatment whatsoever (levetiracetam 45% versus phenytoin 29% versus 12%; OR 2.10, 95% CI 1.02–4.35).

**Discussion**

This retrospective analysis of prospectively collected data revealed that the administration of prophylactic AEDs after spontaneous SAH was not associated with a significant change in seizure incidence. This finding persisted despite adjustment for clinical characteristics, which have been consistently associated with a higher risk of seizure occurrence, including severity of neurological injury, higher hemorrhage burden, and need for craniotomy. Previous studies have identified several risk factors for the development of seizures during the acute hospitalization period after spontaneous SAH, including aneurysmal etiology, middle cerebral artery aneurysms, thickness of SAH clot, associated intracerebral hematoma, rebleeding, infarction, and poor neurological grade.²,³,¹⁰ Univariate and adjusted logistic regression analyses of this sample parallel these prior findings; in our study, poor neurological grade on admission, cisternal SAH burden, and intraventricular hemorrhage were all significant predictors of seizure occurrence.

Prior recommendations for prophylactic AED treatment after spontaneous SAH had been based on the concern for

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**Table 2. Distribution of Seizure Characteristics and Secondary Outcomes**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No AEDs, % (n=201)</th>
<th>AEDs, % (n=152)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures, % overall</td>
<td>9 (22)</td>
<td>11 (22)</td>
<td>0.59</td>
</tr>
<tr>
<td>Seizures, % of those monitored</td>
<td>14 (11)</td>
<td>15 (8)</td>
<td>0.84</td>
</tr>
<tr>
<td>Poor outcome, %</td>
<td>32 (50)</td>
<td>25 (33)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

AED indicates antiepileptic drug; DIND, delayed ischemic neurological deficits; EEG, electroencephalography; IQR, interquartile range; and mRS, modified Rankin Scale.

*Percentages calculated from matched pairs.*

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**Table 3. Overall Seizure Risk by Clinical Characteristic**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age‡</td>
<td>1.02; 0.99–1.05</td>
<td>0.09</td>
</tr>
<tr>
<td>Female</td>
<td>1.29; 0.62–2.66</td>
<td>0.48</td>
</tr>
<tr>
<td>Aneurysmal SAH etiology</td>
<td>1.92; 0.57–6.52</td>
<td>0.30</td>
</tr>
<tr>
<td>Aneurysm location, anterior vs posterior circ.</td>
<td>1.15; 0.93–1.42</td>
<td>0.19</td>
</tr>
<tr>
<td>Severe Hunt–Hess score§</td>
<td>2.24; 1.54–3.24</td>
<td>0.01</td>
</tr>
<tr>
<td>Severe SAH burden</td>
<td></td>
<td>4.41; 1.03–18.9</td>
</tr>
<tr>
<td>Intraparenchymal hemorrhage</td>
<td>1.62; 0.74–3.57</td>
<td>0.22</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>2.40; 1.15–5.03</td>
<td>0.02</td>
</tr>
<tr>
<td>Acute hydrocephalus</td>
<td>1.67; 0.79–3.49</td>
<td>0.17</td>
</tr>
<tr>
<td>Treatment period, no prophylactic AEDs#</td>
<td>0.86; 0.43–1.75</td>
<td>0.68</td>
</tr>
<tr>
<td>Aneurysm treatment</td>
<td>1.15; 0.52–2.57</td>
<td>0.73</td>
</tr>
<tr>
<td>Seizure prophylaxis</td>
<td>AED administration</td>
<td>0.70; 0.33–1.46</td>
</tr>
<tr>
<td>AED duration</td>
<td>1.01; 0.93–1.10</td>
<td>0.85</td>
</tr>
</tbody>
</table>

AED indicates antiepileptic drug; CI, confidence interval; circ., circulation; CT, computed tomography; OR, odds ratio; and SAH, subarachnoid hemorrhage.

*Significant predictors (P≤0.05) are reported as odds ratio and 95% CI.

**Panczykowski et al Antiepileptics in SAH**

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seizure in the setting of an unsecured aneurysm and the possible impact of seizures on long-term functional outcomes. Compounding this, early observational trials also reported seizure rates to be high as 20% to 30%. However, this current study exhibited seizure occurrence in only 10% of our sample population, a finding consistent with many other recent trials. One such analysis of the Nationwide Inpatient Sample database identified a 10% to 11% incidence of seizures or epilepsy after clipping or coiling of ruptured intracranial aneurysms, further corroborating the results of our trial. Despite data such as these, surveys suggest that ≤84% of practitioners routinely use prophylactic AEDs after aneurysmal SAH, with nearly a quarter of neurosurgeons prescribing AEDs ≤3 months after SAH.

Continued justification for prophylactic AEDs has focused on the unsubstantiated risk of seizures contributing to aneurysmal rerupture, a finding that has not been chronologically proven as the cause rather than the product of aneurysmal rerupture. In this current study, only 4.5% of patients suffered acute, postictal seizures (<24 hours after SAH), and of these patients, only 12% (n=2/16) suffered documented rerupture. Importantly, neither the incidence of acute seizure nor the occurrences of aneurysm rerupture significantly differed between AED treatment cohorts (P=0.26); at the same time, sensitivity analysis did not reveal an underlying interaction. These findings, along with other literature reported that seizure rates as low as 3% in the acute postictal period do not support routine prophylaxis even for the short-term in the current era of early aneurysm control.

Moreover, the efficacy of routine prophylactic use of AEDs in patients with SAH has never been proven in a randomized control trial. Prior recommendations for routine administration were based on retrospective trials evaluating patients undergoing elective craniotomy for aneurysm clipping and studies on delayed epilepsy. Previous retrospective studies and systematic reviews specifically evaluating prophylactic AED therapy have failed to demonstrate a clear benefit for prophylactic use of AED after aneurysmal subarachnoid hemorrhage. A Cochrane systematic review found insufficient evidence to support the routine use of prophylactic AEDs; however, the trials reviewed all lacked cohorts not receiving prophylactic AEDs. This current study contains the largest reported patient sample not treated with prophylactic AEDs after SAH.

Further confounding the results of prior trials, use and duration of AED therapy were associated with severity of SAH, suggesting that there may have been bias in who was selected for AED treatment. To solve these previous shortcomings, we implemented propensity-matched analysis to reduce the possibility of selection bias contributing to our findings (eg, bias from factors that may have made it more likely that a patient would have been administered prophylactic AEDs). Propensity matching mimics randomization by sampling a treatment cohort that is comparable across these factors to a control cohort who did not receive the treatment. In this study, 6 covariates found in early trials to be associated with AED administration were used: Hunt–Hess grade, SAH burden, intraventricular hemorrhage, intraparenchymal hemorrhage, hydrocephalus, craniotomy, and aneurysmal etiology. Propensity score–matched analyses revealed that prophylactic AED treatment did not significantly impact the incidence of seizure after spontaneous SAH, providing the most robust support to date for discontinuing the routine, prophylactic administration of AED after spontaneous SAH.

A controversial topic has been the effect of aneurysm treatment on the risk of seizure after SAH. Craniotherapy and clip occlusion for aneurysm treatment has been inconsistently associated with a higher seizure risk in the perioperative period, whereas those treated solely by coil embolization have been shown to suffer no additional seizures in the perioperative period (despite an 11% incidence of acute, postictal seizures). Interestingly, this current study did not corroborate these findings. After controlling for the higher rate of postoperative prophylactic AED treatment after craniotomy through both adjusted logistic regression and propensity-matched analysis, aneurysm treatment modality was not associated with seizure risk.

Recent trials have shown that prophylactic AED themselves may contribute to poor outcome. Prior recommendations for routine administration were based on retrospective trials evaluating patients undergoing elective craniotomy for aneurysm clipping and studies on delayed epilepsy. Previous retrospective studies and systematic reviews specifically evaluating prophylactic AED therapy have failed to demonstrate a clear benefit for prophylactic use of AED after aneurysmal subarachnoid hemorrhage. A Cochrane systematic review found insufficient evidence to support the routine use of prophylactic AEDs; however, the trials reviewed all lacked cohorts not receiving prophylactic AEDs. This current study contains the largest reported patient sample not treated with prophylactic AEDs after SAH.

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may have also suffered from detection bias because not all the patients underwent EEG monitoring. The incidence of nonconvulsive seizure activity in conscious SAH patients is unknown, and it is highly unlikely that these patients would not display even subtle neurological findings prompting further work-up; 28% of good-grade patients underwent EEG monitoring and only 9% of which revealed seizure activity. Of greater concern is the incidence of nonconvulsive seizure/epilepsy in obtunded or comatose patients. A meta-analysis evaluating the diagnostic ability of continuous EEG in SAH found that nonconvulsive seizure and epilepsy was diagnosed in 3% to 18% of poor-grade SAH patients, most occurring by postbleed day 9 (interquartile range 4–17 days).23 In our study, poor neurological-grade patients (n=79) who did not improve after 24 hours underwent continuous EEG monitoring; 22% of these patients suffered seizures (5 diagnosed clinically, 12 suffered electrographic seizures). Despite this increased seizure incidence, AEDs were not associated with lower risk in this patient subset, a finding corroborated by other reports.21,22 Sensitivity analyses were also performed to evaluate and control for characteristics that may have increased the likelihood of having EEG monitoring (ie, interaction effects). Detection method was again not associated with treatment, nor did it correlate with rate of seizure detection, suggesting that any detection bias may be inconsequential in this situation.

Phenytoin was generally used for seizure prophylaxis in our series, an agent only recently recommended against by AHA/Stroke Guidelines.15 Subgroup analysis from this study did not find an association between type of prophylactic AED and seizure risk; however, levetiracetam or other newer agents may yet prove to be more effective without an increase in side effects. The use of phenytoin as a first-line prophylactic AED is hampered by its unpredictable, nonlinear pharmacokinetics, requiring assessment of serum phenytoin levels. Unfortunately, the general practice during both treatment epochs was not to routinely assess phenytoin levels. Unfortunately, the general practice during both prophylactic AED administration because phenytoin may take up to 1 week to achieve steady-state serum concentrations, well outside the peak postictal seizure period.23 Instead, serum levels were drawn only in the setting of suspected or confirmed seizures, and analyzing these levels in isolation would introduce significant bias. Antiepileptic burden (dose and number of days administered) is a surrogate covariate for AED exposure; however, sensitivity analyses in this study did not show a significant interaction between duration of AED administration and risk of seizure (all patients administered phenytoin received the same loading and maintenance dose).

Summary/Conclusions

In a sample of patients suffering spontaneous SAH, the risk of seizure during the acute hospitalization period was low. The utilization of propensity score–matched analysis suggests that prophylactic AED therapy did not significantly reduce the risk of seizure occurrence. After controlling for markers of SAH severity, patients receiving prophylactic AED therapy did display an increased risk of DIND; however, AEDs were not associated with overall neurological outcome. There is no substantial evidence to support the routine administration of prophylactic AEDs in patients with aneurysmal SAH.

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Disclosures

None.

References


Prophylactic Antiepileptics and Seizure Incidence Following Subarachnoid Hemorrhage: A Propensity Score–Matched Analysis
David Panczykowski, Matthew Pease, Yin Zhao, Gregory Weiner, William Ares, Elizabeth Crago, Brian Jankowitz and Andrew F. Ducruet

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