SPECIAL ARTICLE

Seizure Prophylaxis in Neurocritical Care: A Review of Evidence-Based Support

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Seizures are a well-described complication of acute brain injury and neurosurgery. Antiepileptic drugs (AEDs) are frequently utilized for seizure prophylaxis in neurocritical care patients. In this review, the Neurocritical Care Society Pharmacy Section describes the evidence associated with the use of AEDs for seizure prophylaxis in patients with intracerebral tumors, traumatic brain injury, aneurysmal subarachnoid hemorrhage, craniotomy, ischemic stroke, and intracerebral hemorrhage. Clear evidence indicates that the short-term use of AEDs for seizure prophylaxis in patients with traumatic brain injury and aneurysmal subarachnoid hemorrhage may be beneficial; however, evidence to support the use of AEDs in other disease states is less clear.

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The use of antiepileptic drugs (AEDs) for seizure prophylaxis in neurocritical care patients is controversial. Because of the potential risk of seizures affecting outcomes in neurocritical care patients, practitioners have used AEDs for seizure prophylaxis in a variety of disease states including intracerebral tumors, traumatic brain injury (TBI), aneurysmal subarachnoid hemorrhage (aSAH), intracerebral hemorrhage (ICH), ischemic stroke, and for patients undergoing a craniotomy. However, the incidence of seizures and the AEDs used in these disease states vary greatly with the extent of neurologic injury, lesion location, and interventions performed.

In this article, the Neurocritical Care Society Pharmacy Section has reviewed literature related to the use of seizure prophylaxis in neurocritical care patients. The Neurocritical Care Pharmacy Section represents pharmacists practicing in

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clinical, educational, and research roles within the field of neurocritical care. The section supports the mission of the Neurocritical Care Society and strives to advance neurocritical care practice through the provision of quality patient care, professional collaboration, research, training and education, and advocacy. We believe this article will provide readers with a comprehensive review of the evidence behind the use of AEDs for seizure prophylaxis in neurocritical care patients.

Intracerebral Tumors

Seizures are extremely common in patients with brain tumors, occurring as the presenting symptom in ~40% of patients.[1] Seizure prophylaxis is often considered for these patients because 20–45% with no prior history of seizures will develop seizures during the course of their disease.[1, 2] The risk of developing seizures varies with tumor type and location. For example, seizures are more likely in the setting of a primary brain tumor than a metastatic lesion, more likely with a low-grade glioma than a high-grade glioma, and more likely with specific tumor types such as dysembryoplastic neuroepithelial tumors than with meningiomas.[2]

In 2000, the American Academy of Neurology (AAN) published a practice parameter regarding seizure prophylaxis in patients with newly diagnosed brain tumors based on 12 studies.[1] Four of the 12 studies provided level I evidence (e.g., randomized controlled trial or controlled clinical trials), and the remainder of the studies were level II evidence (well-designed observational studies). Among the AEDs studied were phenytoin, valproic acid, and phenobarbital. The median follow-up time in these trials varied from 5.44 to 19 months. Of all these studies, only a single retrospective trial showed a significant difference between patients receiving prophylaxis compared with no prophylaxis. In this trial, there were fewer seizures in the group receiving no prophylaxis. In the seven studies that followed AED serum concentration, many patients (42%) had subtherapeutic concentrations at the time of seizure, which may have blunted any positive treatment effect. Adverse effects were frequently noted in these trials, with 15% of patients experiencing rash; 5% experiencing nausea and vomiting, encephalopathy, ataxia, increased liver enzymes or gum pain; and 3% experiencing myelosuppression.[1] The AAN practice parameter concluded that AEDs are not effective in preventing seizures in patients with a newly diagnosed brain tumor and no prior history of seizures.

A meta-analysis published in 2004 evaluated five randomized controlled trials, three of which were evaluated in the previously mentioned AAN practice parameter.[3] The medications evaluated were phenobarbital (n=2), phenytoin (n=4), and valproic acid (n=1) versus either a placebo or no treatment. In three of the five trials, patients underwent surgical debulking or resection. Patients with both primary brain tumors and metastatic lesions were included. Four of the five trials showed no benefit of seizure prophylaxis in patients with brain tumors.[3] The fifth trial specifically evaluated the effect of phenytoin on the incidence of postoperative seizures in patients with brain tumors as well as others undergoing a craniotomy.[4] The trial utilized phenytoin 100 mg 3 times/day after a loading regimen of 250 mg twice/day started in the immediate postoperative period. Treatment with phenytoin was continued for 12 months. Of the 281 patients included in the analysis, only 81 patients had undergone surgery for a brain tumor (phenytoin group n=42, placebo group n=39). When evaluating high-risk patients (those with aSAH, TBI, and meningioma), this investigation concluded that phenytoin significantly reduced the incidence of seizures at day 30 (5 seizures vs 16 seizures; $p<0.05$) and day 343 (8 seizures vs 20 seizures; $p<0.05$). When patients with metastasis were also included in this analysis, no difference was observed in seizure rates between those treated with phenytoin and placebo.[4] Despite this one trial, the meta-analysis failed to find evidence to support the use of the agents just cited in patients without a history of seizures, regardless of tumor type.[3]

In 2008, a Cochrane Review evaluated the same five randomized controlled trials as the previous meta-analysis.[5] The authors largely came to the same conclusion as the 2004 meta-analysis; however, they were more guarded in their recommendations. This review emphasized that the current evidence neither supports nor refutes the efficacy of prophylactic AEDs in patients with brain tumors, and it applies only to the agents included in these trials: phenobarbital, phenytoin, and valproic acid. In addition, the review highlighted a significant increase in adverse events for those patients who received prophylactic AEDs (risk ratio [RR] 6.10, 95% confidence interval [CI] 1.10–34.63). Two recent trials address the use of levetiracetam for

seizure prophylaxis in patients undergoing surgery for brain tumors. The first was a retrospective cohort of 78 patients surgically treated for primary and secondary brain tumors. Patients received between 1000 and 3000 mg of levetiracetam beginning in the perioperative period. Those patients who received levetiracetam had a seizure rate of 2.6% in the first week following surgery. The authors note that this is lower than the previously published rate of 15–20% in those patients who did not receive prophylactic AEDs. In addition, the authors saw a 6.4% rate (five patients) of adverse events in their cohort. These included progressive somnolence and reactive psychosis.[6] The second study describes a retrospective cohort of patients undergoing surgery for a variety of brain tumors, most commonly glioblastoma multiforme, meningioma, astrocytoma, and metastasis, who had not previously experienced a seizure. Patients received either phenytoin (n=154) or levetiracetam (n=81). Phenytoin was administered as a perioperative 750 mg loading dose and then continued for 24 hours as a continuous infusion of 30 mg /hour. This was followed by conversion to intravenous or oral phenytoin, which was tapered from 300 mg/day to 50 mg/day on postoperative day 5. Levetiracetam was given as a 1000-mg perioperative loading dose, followed by a second 1000-mg dose that day. It was then administered as 1000 mg twice/day and tapered to 500 mg twice/day by postoperative day number 5. There was no difference in the rate of postoperative seizures between the two groups, with 2.5% of the levetiracetam group experiencing a seizure compared with 4.5% in the phenytoin group (p=0.66). None of the patients in either cohort had a documented adverse event to the medications.[7] Although both of these studies are small and possibly underpowered, they suggest that levetiracetam may be a viable alternative to phenytoin to prevent seizures in those patients undergoing surgery for brain tumors.

Guidelines specifically addressing the use of prophylactic AEDs in patients with metastatic brain lesions were published in 2010.[8] They were developed on the basis of a subgroup analysis of a single randomized controlled trial that was also included in the previous meta-analysis and Cochrane review.[9] This trial included 60 patients with metastatic brain lesions who were randomized to treatment (either phenytoin or phenobarbital) or no treatment and found no difference in seizure incidence between the two groups. The authors observed that metastatic lesions are less likely to cause seizures than primary brain tumors. In addition, trials with mixed populations have not demonstrated a benefit, and it is unlikely that seizure prophylaxis would show a benefit in patients with metastatic brain lesions. Therefore, routine seizure prophylaxis with AEDs is not recommended in patients with metastatic brain lesions and no prior history of seizures.[8]

Since the publication of the 2010 guidelines regarding prophylactic AEDs for brain metastases, two key articles have been published. The first was a randomized controlled trial of short-course AED prophylaxis (7 days of phenytoin) versus no prophylaxis in patients with intraparenchymal brain tumors. Due to futility, the trial was terminated early. At closure, a total of 123 patients (77 with metastases and 46 with gliomas) were included. Overall, there was no difference in the seizure incidence between the prophylaxis and observational groups (24% vs 18%; p=0.51). However, there were a higher percentage of adverse events in the prophylaxis group as compared with the observational group (18% vs 0%; p<0.01). The adverse events reported in the study included rash, elevated liver enzymes, thrombocytopenia, confusion, aphasia, decreased level of consciousness, nausea, vomiting, dry itchy skin, ataxia, and photophobia. The authors concluded that the use of prophylactic AEDs for patients undergoing resection of intraparenchymal brain tumors does not improve the incidence of seizures but puts the patient at a higher risk of adverse drug events.[10] The second article was a meta-analysis of patients undergoing resection of supratentorial meningioma from 1979 through 2010. From 19 studies, a total of 553 patients were included in the AED group and 145 in the no-AED group. More than half of the included studies were retrospective (n=11) or case reports (n=5). The AED group was treated with a variety of AEDs including phenytoin, valproic acid, carbamazepine, lamotrigine, and levetiracetam. When the AED group and no-AED groups were compared with regard to early (1.4% vs 1.4%, p>0.05) or late seizures (8.8% vs 9.0%, p>0.05), there was no statistical difference. The authors of this meta-analysis concluded that their review does not support the routine use of prophylactic AEDs in patients undergoing supratentorial meningioma resection.[11] Both of these articles support earlier evidence against the use of prophylactic AEDs in patients with intraparenchymal brain tumors or supratentorial meningiomas

and that the use of prophylactic AEDS may increase adverse drug events.

Overall, current treatment guidelines and literature do not support the use of routine seizure prophylaxis in patients with primary brain tumors or metastatic lesions.[12] The use of AEDs is complicated in these patients because of the potential for significant drug interaction with commonly administered chemotherapeutic agents such as erlotinib, gefitinib, irinotecan, and temsirolimus, and the potential for serious cutaneous adverse events such as Stephens-Johnson syndrome and toxic epidermal necrolysis in patients undergoing cranial radiation therapy.[13, 14] Administration of enzyme-inducing AEDs should be avoided in patients receiving regimens containing these chemotherapeutic agents. However, perioperative administration of AEDs may be appropriate because enzyme induction occurs after the first 1–2 weeks of therapy. It remains unclear if newer AEDs, which do not require therapeutic drug monitoring, have fewer drug-drug interactions, and have a superior adverse effect profile, have a role in this patient population. There are ongoing investigations assessing the role of some of these newer AEDs. Table 1 summarizes the primary literature related to the use of AEDs in patients with intracerebral tumors.

Traumatic Brain Injury

Posttraumatic seizures (PTS) in TBI patients are classified as either early PTS, defined as a seizure within the first 7 days of injury, or late PTS, defined as a seizure occurring more than 7 days after injury. The incidence of early PTS in TBI patients has been correlated with the severity of the injury, with penetrating injuries having the highest incidence of PTS in ~50% of patients, and other high-risk patients (depressed skull fractures, subdural hematomas, intracerebral hematomas, Glasgow Coma Scale lower than 10, or cortical contusions) estimated to

Table 1. Selected Articles on the Use of Seizure Prophylaxis in Patients with Intracerebral Tumors

	Trial design and intervention	Total number of patients	Main outcomes and results
[3]	Meta-analysis of controlled trials regarding AED prophylaxis efficacy from 1966–2004	Five trials met inclusion criteria (n=403)	No benefit to AED use at 1 wk (OR 0.91; 95% CI 0.45–1.83) No benefit to AED use at 6 mo (OR 1.01; 95% CI 0.51–1.98) No effect on seizure prevention for primary glial tumors, cerebral metastases, and meningiomas
[4]	Double-blind, placebo-controlled trial of phenytoin vs placebo after supratentorial surgery PHT 250 mg IV twice/day, then 100 mg 3 times/day or matching placebo for 12 mo	PHT Group n=140; placebo group n=141	No difference in seizure rate at 12 mo in PHT and placebo groups (10 vs 6 seizures, p=NS) Lower seizure rate in PHT group up to 30 days postsurgery (8 vs 20 seizures; p<0.025) High-risk patients (those with aneurysms, head injury, or meningioma) in the PHT group had a lower rate of seizures at 30 days (5 vs 16, p<0.05) and at 365 days (8 vs 20, p<0.05)
[5]	Meta-analysis of controlled trials regarding AED prophylaxis efficacy from 1966–2007	Five trials met inclusion criteria	Regardless of intervention, there was no difference in prevention of first seizure (RR 0.94, 95% CI 0.55–1.61; p=0.82) Use of AED increased the risk of adverse event (OR 6.10, 96% CI 1.10–34.63, p=0.046)
[8]	Meta-analysis of trials regarding patients with solid brain metastases without a seizure from 1990–2008	One study met inclusion criteria (n=100)	No difference in seizure risk in patients treated with AEDs and no AEDs, p=0.9
[10]	RCT of PHT vs observation in patients undergoing resection of intraparenchymal tumors PHT load 15 mg/kg followed by 100 mg every 8 hrs for 7 days	Observation (n=61) (PHT n=62)	No difference in early seizure incidence (8% vs 10%, p=1.0) More adverse events in the prophylaxis group (0 vs 18%, p<0.01)
[11]	Meta-analysis of patients undergoing supratentorial meningioma resection	19 studies included	No difference in early seizures (1.4% vs 1.4%, p>0.05) or late seizures (8.8 vs 9.0, p>0.05)

AED = antiepileptic drug; OR = odds ratio; CI = confidence interval; PHT = phenytoin; IV = intravenous; NS = not significant; RR = risk ratio; RCT = randomized controlled trial.

range from 20% to 25%.[15] Investigators have reported that 20–25% of all patients who sustain a severe TBI (GCS lower than 8) will experience at least one PTS.[16]

For many years, the use of AEDs for early seizure prophylaxis was the standard of care after TBI, with phenytoin the most commonly prescribed AED. Previous retrospective analyses hypothesized that phenytoin would be effective at reducing PTS.[17, 18] In 1983, a prospective study found no difference in early seizure rates between patients who received phenytoin or placebo prophylactically.[19] Other earlier small randomized trials of carbamazepine and phenytoin also produced conflicting results with regard to reducing PTS in TBI.[20, 21] Most of these early studies were inconclusive either because of their retrospective design[17, 18] or had they had subtherapeutic drug concentrations.[19, 21]

A pivotal 1990 study was a randomized double-blind trial comparing a 20 mg/kg loading dose of phenytoin and doses adjusted thereafter to achieve therapeutic concentrations versus placebo in severe TBI patients. A total of 404 patients were included in the analysis. The authors found that the seizure incidence in the first week was significantly lower in the phenytoin-treated patients as compared with the placebo-treated patients (3.6% vs 14.2%, $p<0.001$, respectively). However, there was no decrease in the incidence of late seizures. In addition, a higher percentage of patients in the phenytoin group withdrew from the trial due to rash.[22] A follow-up study confirmed that long-term prophylaxis with phenytoin in severe TBI decreased functional performance at 1 month.[23]

In a randomized trial, valproate was shown to be as effective as phenytoin at reducing early PTS, but it had no effect on late PTS. The authors also noted a trend toward increased mortality in the valproate group.[24] Due to this risk, valproate is generally not recommended for the prophylaxis of PTS.

In 2001, a meta-analysis evaluating AEDs for seizure prophylaxis showed that only phenytoin and carbamazepine were effective in reducing early PTS but that no AED was effective at reducing late PTS.[25] In addition, a Cochrane systematic review of randomized clinical trials regarding seizure prophylaxis in TBI patients was conducted in 2010.[26] The review consisted of six trials including 1405 patients: four trials with phenytoin, one trial with carbamazepine, and one trial with phenobarbital. Two trials not previously analyzed in a review or meta-analysis were also included. One trial found benefit in preventing late PTS with therapeutic level phenytoin; the other found no benefit in late PTS from phenobarbital.[27, 28] This Cochrane review concluded that the use of AEDs was favorable for the prophylaxis of early PTS (0.34, 95% CI 0.21–0.54) and not favorable for late PTS (RR 1.28, 95% CI 0.90–1.81). However, seizure control in the acute phase showed no reduction in mortality or neurologic disability.[26]

Murine animal models of brain ischemia and closed head injuries suggest that levetiracetam may be neuroprotective,[29, 30] and there is an increasing trend in using levetiracetam for PTS prophylaxis.[31] Levetiracetam offers some advantage over other AEDs in that it does not require serum concentration monitoring, has favorable pharmacokinetic properties, excellent bioavailability, and no known drug interactions. Although behavioral disturbances are associated with levetiracetam such as agitation, aggression, and anxiety (less than 10%), these disturbances are less than what was observed with carbamazepine.[32, 33] In a small underpowered pilot trial comparing levetiracetam (500 mg twice/day) to phenytoin (no dose given) for preventing seizures in the first week in 32 patients with TBI, there was no difference in seizure activity between levetiracetam and phenytoin (6.7% vs 0%; $p=0.556$).[34] Interestingly, when evaluating 1-hour electroencephalographs (EEGs) in the levetiracetam group and historical controls in the phenytoin group, abnormal EEGs were more frequent with the levetiracetam group (53.3% vs 0%; $p=0.003$). Due to the differences in measurement, the clinical significance of this finding was unclear.[34] Another study also prospectively examined seizure prophylaxis with levetiracetam (maximum dose 1500 mg twice/day) versus phenytoin (dose adjusted to achieve a maximum phenytoin concentration of 20 μg/ml) in a 2:1 randomized trial. There was no significant difference detected in adverse events between the groups. In addition, the authors did not detect a difference in early seizure rates (phenytoin group 3 of 18 vs levetiracetam 5 of 34; $p=1.0$). However, the authors did observe lower Disability Rating Scale scores at 3 and 6 months (11 vs 5; $p=0.006$ and 6 vs 3; $p=0.037$), and higher Extended Glasgow Outcomes Scale scores at 6 months (3 vs 5; 0.016) with levetiracetam.[35]

Current guidelines published by the Brain Trauma Foundation recommend that prophylactic AEDs be administered only for the first

7 days after injury (level II evidence).[36] In addition, the AAN recommends that prophylactic administration of phenytoin is "established as effective" for the prevention of early PTS.[37] Both of these guidelines were published before trials evaluating levetiracetam for seizure prophylaxis were published. Due to the potential for improved cognitive outcomes and a better adverse event profile, levetiracetam may be a reasonable alternative to phenytoin. Table 2 summarizes the primary literature related to the use of AEDs in patients with TBI.

Aneurysmal Subarachnoid Hemorrhage

The reported incidence of seizures after aSAH may be as high as 20%. This is in part due to the occurrence of seizures and seizure-like phenomena at the time of aneurysm rupture and their association with early complications such as rebleeding.[38–42] Following aneurysm treatment and discharge, the incidence of seizures appears low and may be related to the method the aneurysm was secured, thickness of the subarachnoid clot, aneurysm location, presence of

Table 2. Selected Articles on the Use of Seizure Prophylaxis in Patients with Traumatic Brain Injury

	Trial design and intervention	Total number of patients	Main outcomes and results
[22]	Prospective, randomized, placebo-controlled trial of PHT or matching placebo in patients with severe head injury	PHT group, n=208; placebo, n=196	Lower number of seizures within 7 days in the PHT-treated group (3.6 ± 1.3 vs 14.2 ± 2.6; p<0.001) No difference in the percentage of patients experiencing a seizure within 1 yr (PHT 21.5% ± 3.6% vs placebo (15.7%±3.2%; p>0.2) or at 2 yrs (PHT 27.5 ± 4.0 vs placebo 21.1 ± 3.7, p>0.2) More patients in the PHT group stopped taking study drug due to adverse events (p<0.01)
[24]	Prospective, randomized, single-center, parallel-group clinical trial of PHT and VPA in patients with severe head injury	PHT for 1 wk group, n=132 VPA for 1 mo group, n=120 VPA for 6 mo, n=127	No difference in treatment groups with regard to seizures rates within 7 days (PHT 1.5% vs combined valproate 4.5%; p=0.14) Survival analysis revealed no difference in late seizures between groups (p=0.19) Significantly higher AST levels in PHT group at day 4, 14, and 1 mo (p=0.0001–0.02) Lower platelet counts in the valproate group (p=0.0001–0.03); however, no difference in the fraction of patients below 100 000 platelets
[25]	A meta-analysis of trials regarding the use of AEDs for seizure prophylaxis	48 studies identified with 13 that included treatment for posttraumatic seizures	Treatment with PHT (OR 0.3, 96% CI 0.9–0.59) and carbamazepine (OR 0.39, 95% CI 0.17–0.92) decreased the risk of early seizures in brain injury Treatment with phenobarbital (OR 0.3, 95% CI 0.03–2.81) and phenytoin plus phenobarbital (OR 0.15, 95% CI 0.01–2.94) did not reach a statistical difference for prevention of early seizures; no AED or combination of AEDs reached significance for prevention of late seizures
[34]	A prospective historical control clinical trial comparing 7 days of LEV with a historical control of patients receiving PHT	LEV group, n=15 PHT group, n=12	Increased rate of seizure tendency in the LEV group (0% vs 46.7%, p=0.007) No difference in seizure activity (0% vs 6%, p=0.556) More abnormal EEG interpretations in LEV group (0% vs 53.3%, p=0.003)
[47]	Prospective, single-center, randomized, single-blinded comparative trial of LEV and PHT for seizure prophylaxis in patients with severe head injury	LEV group, n=34 PHT group, n=18	Better functional outcome at 3 mo as measured by the disability rating score in the LEV group (p=0.042) No difference in seizure occurrence during continuous EEG monitoring (p=1.0), at 6 mo (1.0) or in mortality (0.227)

PHT = phenytoin; VPA = valproic acid; AST = aspartate aminotransferase; AED = antiepileptic drug; OR = odds ratio; CI = confidence interval; LEV = levetiracetam; EEG = electroencephalography.

subdural hematoma, and secondary cerebral infarction.[39, 41, 42] After a 14-year follow-up period, data from the International Subarachnoid Aneurysm Trial demonstrated a higher incidence of posttreatment seizures in patients who underwent surgical clipping compared with endovascular coiling (13.6% vs 8.3%, p=0.014).[40]

The use of prophylactic AEDs in the perioperative setting is common, although controversial.[43] The incidence of seizures appears low, the influence of seizures on outcomes is unclear, and many risk factors for seizures have been identified with little consistency.[39, 41, 42, 44] Randomized controlled trials demonstrating the safety and efficacy of prophylactic AEDs in patients with aSAH are lacking. Additionally, studies have demonstrated worse neurologic outcomes with prophylactic AEDs.[43, 45]

The literature examining the efficacy of prophylactic AEDs is mostly observational and predominantly focuses on phenytoin. A 1995 article describes the early use of a short perioperative course of phenytoin (900–1100 mg load followed by 300 mg/day) for seizure prophylaxis. Low-risk patients—defined as those without a history of seizure disorder, cerebral ischemia, parenchymal clot, postoperative hematoma, or concomitant arteriovenous malformation (AVM) resection–received an average of 5.3 days of therapy. The authors noted a low overall seizure incidence of 5.4% after an average of 2.4 years of follow-up and thus advocated no more than 7 days of phenytoin prophylaxis for low-risk patients.[38] Other researchers took these data a step further and compared their practice of phenytoin prophylaxis (1000 mg loading dose followed by 300 mg/day) through hospital discharge (average 14 days) to prophylaxis for 3 days. This retrospective analysis of 453 patients found a similar incidence of seizures between the two groups during hospitalization (discharge vs 3 days: 1.3% vs 1.9%, p=0.6) and at follow-up (5.7% vs 4.6%, p=0.6), which ranged from 3 to 12 months. They also observed a significant reduction in the incidence of drug reactions (8.8% vs 0.5%, p=0.002).[46] A subsequent study further examined the association between phenytoin exposure and harm by quantifying phenytoin burden (average phenytoin concentration x time between first and last serum concentration measurement) and then investigating its impact on outcomes. This study included 527 patients and identified increasing phenytoin burden as an independent predictor of poor functional outcome at 14 days (OR per quartile 1.5, 95% CI 1.2–1.9) and was associated with poor cognitive outcome at 3 months (p=0.003).[45] The effect of phenytoin exposure on outcome was also assessed by researchers who examined data collected in 3552 patients who participated in four randomized placebo-controlled trials investigating tirilazad. Sixty-five percent of patients received at least one AED, of which phenytoin was the most common (52.8%). Phenobarbital (18.7%) and carbamazepine (2.3%) were the other commonly used AEDs in this study. Adjusting for study center, World Federation of Neurologic Surgeons grade, age, and admission systolic blood pressure, AED therapy was found to be an independent predictor of unfavorable 3-month outcome using the Glasgow Outcome Scale (OR 1.56, 95% CI 1.16–2.10; p=0.003). Patients treated with AEDs also had a higher incidence of delayed ischemic neurologic deficit, neurologic worsening, cerebral infarction, and fever.[43] In addition, there is significant potential for a drug-drug interaction between phenytoin and nimodipine, a commonly used medication to prevent delayed cerebral ischemia in patients experiencing aSAH. This drug-drug interaction is due to the cytochrome P450 enzyme-inducing nature of phenytoin and would be more significant with long-term administration (more than 7 days). In a single-dose pharmacokinetic study of nimodipine, patients chronically taking enzyme-inducing AEDs (including phenytoin) had a greater than 70% decrease in the nimodipine area under the curve.[47]

Given the association between phenytoin and adverse outcomes, many have advocated for alternative prophylactic agents. To date, trials comparing AEDs are scarce. Levetiracetam is the focus of most research efforts, and the body of evidence supporting its use is growing. A large retrospective study compared extended duration phenytoin (15–20 mg/kg loading dose followed by maintenance dose; average 13.7 days) to short-course levetiracetam (500 mg twice/day; average 3.6 days) in 442 patients with aSAH.[48] One study found a higher incidence of in-hospital seizures in the levetiracetam group compared with phenytoin (8.3% vs 3.4%, p=0.026); however, the lack of levetiracetam loading dose, short course of therapy, and small study size limit its generalizability. However, those patients who received levetiracetam showed a trend toward a lower incidence of poor outcome (death or discharge to nursing home) (16% vs

24%, p=0.06), although this was statistically insignificant.[48]

The lack of randomized controlled trials in this population is reflected in the 2011 guidelines developed by the Neurocritical Care Society (NCS) and the 2012 American Heart Association/American Stroke Association (AHA/ASA) guidelines. The NCS recommends against the use of phenytoin as prophylaxis, although recognizing that the effects of other AEDs are unclear. Both state that prophylaxis "may be considered" in the immediate posthemorrhagic period (AHA/ASA) for a short 3- to 7-day course (NCS). The AHA/ASA states that a longer duration may be considered in patients who have experienced a prior seizure, parenchymal hematoma, infarct, or middle cerebral artery aneurysms.[49] The NCS also advocates an extended duration of therapy for patients who experience a seizure after presentation.[50]

Many questions remain regarding the role of prophylactic AEDs following SAH. Some data suggest that administration of these medications has consequences and that outcomes beyond seizure incidence need to be considered in future studies. It is not clear whether prophylaxis is needed. Until data from randomized controlled trials become available, it appears prudent to limit phenytoin exposure; 3 days of therapy may be sufficient. The role of newer AEDs is undefined and will likely be the subject of future research efforts. Table 3 summarizes the primary literature related to the use of AEDs in patients with SAH.

Craniotomy

The incidence of postoperative seizures varies widely depending on procedure performed and underlying pathology. As discussed elsewhere in this review, guidelines for the prophylaxis of postoperative seizures exist for TBI, brain tumor resection, ICH, and aSAH; however, guidance for general neurosurgical patients is limited.

A retrospective cohort analysis evaluated the use of phenytoin and levetiracetam for patients undergoing supratentorial neurosurgery for a wide range of disease states. Patients were included in the study if they did not have epilepsy and had at least a 7-day follow-up. The study included a total of 315 patients. Prior to surgery, 31% of patients in the levetiracetam group and 45% of the patients in the phenytoin group experienced seizures. Patients received levetiracetam 500 mg to 3000 mg/day or phenytoin 200 mg to 800 mg/day; the most common doses were levetiracetam 1000 mg/day and phenytoin 300 mg/day. Postoperatively, the incidence of early seizures (within 7 days) was 1% and 4.3% in the levetiracetam and phenytoin groups, respectively (p=0.17). The incidence of late-onset seizures (within 30 days) was also low in both the levetiracetam and phenytoin groups (1.9% vs 5.2%, p=0.23). In those patients with a history of preoperative seizures, no difference was noted in the incidence of postoperative seizures between the levetiracetam and phenytoin groups (0% vs 1.8%, p=0.56). However, patients in the levetiracetam group had fewer adverse events prompting a change in therapy (1% vs 18%, p<0.001).[51] Although this study had a retrospective design, it is worth noting that in neurosurgical patients, the effect of different AEDs may influence the risk of an adverse event rather than efficacy.

This risk of adverse events from AEDs has been observed in other studies as well. One study reported that 9% of all adverse events in a neurosurgical intensive care unit were associated with AEDs, most of which were due to phenytoin (56%).[52] This increase in phenytoin-related adverse events may be biased because of the prevalent use of phenytoin as a prophylactic AED in neurosurgical patients. Despite the paucity of evidence, the advent of newer AEDs may offer a potentially safer alternative to older AEDs.

Another area of controversy is the postoperative use of prophylactic AEDs following direct surgical, endovascular, or radiosurgical management of intracranial AVMs. New-onset seizure is the presenting symptom in 20–25% of patients with an AVM.[53] The American Stroke Association has a guideline for the management of AVM; however, they do not give specific recommendations on the most appropriate postoperative anticonvulsant or duration of therapy.[53] No studies have compared the effectiveness of currently available AEDs for postoperative seizures following surgery for an AVM. However, a recent study evaluated the seizure risk from cavernous malformation (CM) or AVM. This was a prospective observational study of 368 adults (CM 139, AVM 229) over a 5-year period. The investigators observed a low incidence of developing seizures after an incidental diagnosis of CM or AVM (0.9% and 2%).[54] This would support a recommendation that AEDs not be prescribed prophylactically prior to a seizure. Thus the patient with new-onset seizures following AVM surgery should be evaluated and treated as a patient with new-onset epilepsy.

Table 3. Selected Articles on the Use of Seizure Prophylaxis in Patients with Aneurysmal Subarachnoid Hemorrhage

	Trial design and intervention	Total number of patients	Main outcomes and results
[38]	Retrospective cohort analysis of high-risk and low-risk patients postcraniotomy for cerebral aneurysm 94.6% received PHT, 4.1% received phenobarbital, 1.3% received other	High-risk patients n=33 Low-risk patients n=305	Seizure rate of all patients was 5.4% over 2.4 yrs Seizure rates immediately postoperatively was 1.9%
[43]	Meta-analysis of four randomized controlled trials evaluating tirilazad 52.8% of the 65% who received an AED received phenytoin	3552 patients evaluated Treated with any AED, n=2313 Not treated with an AED, n=1239	Unfavorable 3-mo Glasgow Outcome Scale (OR 1.56, 95% CI 1.16–2.1, p=0.003) Increased risk of vasospasm (OR 1.87, 95% CI, 1.43–2.44), high temperature (OR 1.36, 95% CI, 1.03–1.80), cerebral infarction (OR 1.33, 95% CI 1.01–1.74) and neurologic worsening (OR 1.61, 95% CI 1.25–2.06) with AED use
[44]	Retrospective cohort analysis of patients with SAH 73% received loading doses of PHT, 99% received maintenance doses of PHT	95 patients	Prehospital seizure rate (17.9%); in-hospital seizure rate (4%); posthospital seizure rate (8%; of which 50% were receiving prophylaxis) No difference in seizure risk despite AED treatment Thickness of cisternal clot was predictor of seizure risk
[45]	Prospective observational study All patients received PHT	527 patients	Higher PHT burden resulted in a higher risk of poor functional outcome at 14 days by 1.5 per quartile of PHT burden (95% CI 1.2–1.9) Multivariate analysis revealed that fever (OR 2.9, 95% CI 1.6–5.0), stroke of any cause (OR 2.9, 95% CI 1.6–5.0), age in years (1.05, 95% CI 1.03–1.07), NIHSS ≥ 10 (OR 19.7, 95% CI, 7.4–52.7), rebleeding of aneurysm (OR14.5 95% CI, 1.7–121.5), clinical vasospasm (OR 3.4, 95% CI 1.6–2.1), and hydrocephalus (OR 2.5, 95% CI 1.3–4.7) were associated with increased risk of functional dependence or worse at hospital discharge.
[46]	Retrospective analysis 3 days of treatment with PHT vs PHT treatment during complete hospitalization	Entire hospitalization treatment, n=79 3-day treatment, n=374	Decreased rate of drug-adverse reactions in the 3-day treatment group (8.8% vs 0.5%, p=0.002) No difference in seizure rate when 3-day group compared with entire hospitalization group (1.3% vs 1.9%, p=0.603)
[48]	Retrospective analysis Comparing short-course LEV (3 days) to extended course of PHT (7 days)	PHT, n=297 LEV, n=145	Significantly more in-hospital seizures in the LEV group as compared with the PHT group (8.3% vs 3.4%, p=0.026) LEV group remained associated with an increased risk of seizures when adjusting for age, clinical grade, history of prior seizures, and aneurysm treatment (OR 2.3, 95% CI 0.97–5.6, p=0.054)

PHT = phenytoin; AED = antiepileptic drug; OR = odds ratio; CI = confidence interval; SAH = subarachnoid hemorrhage; NIHSS = National Institutes of Health Stroke Scale; LEV = levetiracetam.

Based on current evidence, levetiracetam may have a better side-effect profile and may be a reasonable alternative to phenytoin for preventing early-onset seizures in patients undergoing a craniotomy. More research is needed on the cost effectiveness and outcomes associated with the use of newer AEDs for seizure prophylaxis following craniotomy. Table 4 summarizes the primary literature related to the use of AEDs in patients undergoing a craniotomy

Ischemic Stroke

The association of seizures and acute ischemic stroke (AIS) has been well recognized for many years. Cerebral infarction is considered the most

Table 4. Selected Articles on the Use of Seizure Prophylaxis in Patients Who Have Undergone Craniotomy

	Trial design and intervention	Total number of patients	Main outcomes and results
[51]	Retrospective cohort analysis of patients who underwent supratentorial surgery and received either PHT or LEV	LEV group, n=105 PHT group, n=210	No significant difference in 7-day seizure rate between groups (LEV 0.95% vs PHT 4.2%, p=0.17) Greater percentage of adverse events requiring a change in therapy in PHT group (0.95% vs 18.1%, p<0.0001) No difference in rate of epilepsy development (p=0.34)
[52]	Retrospective analysis of adverse drug reactions in a neurosurgical population	3496 patients during a 3-yr period	Adverse drug events were reported at a higher rate in the neurosurgical population as compared with the nonneurosurgical cohort (4% vs 10%, p<0.001) AEDs, histamine antagonists, antibiotics, and analgesics were the most commonly reported medications causing adverse drug reactions.

PHT = phenytoin; LEV = levetiracetam; AED = antiepileptic drug.

common cause of epilepsy in elderly patients.[55] Depending on the study design, the reported incidence of postischemic stroke seizures can range from 4% to 23%,[56, 57] and the definition for early- or acute onset versus late-onset seizures can be from 24 hours up to 4 weeks.[58, 59]

Although the exact underlying pathophysiology of post-AIS seizures is not clear, it is thought that edema and cytotoxicity induced by an ischemic insult are responsible for early seizures, whereas scar tissue formed after anoxia and deformation of dendrites is responsible for late seizures.[58, 60] There is no consensus on how well the size of an infarct correlates with the incidence of seizures and which subtype of stroke has more tendencies to develop recurrent seizures or epilepsy. However, there is a general agreement that ischemic stroke is less epileptogenic than hemorrhagic stroke.[58, 60]

Due to the lack of data regarding the prophylactic administration of AEDs, the AHA/ASA *Guideline for the Early Management of Adults with Ischemic Stroke* recommends that "prophylactic administration of anticonvulsants is not recommended (III/C). Recurrent seizures should be treated (I/B)."[61] In addition, there is a paucity of data regarding the use of newer, less toxic AEDs in patients with post-AIS seizures. Based on this, the routine use of prophylactic AEDs in the post-AIS setting should be avoided. Table 5 summarizes the primary literature related to the use of AEDs in patients with ischemic stroke.

Intracerebral Hemorrhage

ICH is a frequent cause for admission to the neurocritical care unit. A number of observational studies have evaluated the incidence, risk factors, and outcomes associated with seizures in this patient population.[62–70] The results of these trials vary greatly due to study design, patient inclusion and exclusion criteria, patient population, definitions, and length of follow-up. One consistent finding is that hemorrhage within or proximal to the cortex is associated with a high risk of seizure.[62–68, 70]

Patients with ICH are at the greatest risk of seizure within the first few days after ictus, with over half occurring in the first 24 hours.[62–70] Early seizures after ICH are not fully understood, but they are considered to be a result of the immediate metabolic and physical distur-

Table 5. Selected Articles on the Use of Seizure Prophylaxis in Patients with Ischemic Stroke

	Trial design and intervention	Total number of patients	Main outcomes and results
[56]	Community-based stroke registry used to evaluate the occurrence of seizures in patients who have experienced a first stroke	675 patients followed for 2 yrs	52 patients had a seizure during the follow- up period. After excluding those patients with a history of epilepsy and a seizure just prior to death, the 5-yr actuarial risk of poststroke seizure was 11.5% (95% CI 4.8–18.2%

CI = confidence interval.

bances within the brain.[66, 67, 71] The incidence of early seizures has been reported in 7.4–17% of patients with ICH. When continuous EEG monitoring was utilized for seizure diagnosis, the rate increased to 28–31%, with clinical seizures observed in 5.5–24% of patients.[65, 70]

Late seizures occur less often after ICH and are attributed to epileptogenic effects of gliotic scarring.[64, 66, 71] The incidence is reported to occur in 2.6–10.2% of patients with ICH.[62, 64–74] Recurrent seizures after ICH have been reported; however, incidence and risk factors cannot be accurately reported due to the lack of high-powered longitudinal studies.[64, 67, 68] Seizure prophylaxis in the patient with ICH is controversial. Although one study reports seizures are associated with a longer hospital stay, the impact of clinical seizures in patients with ICH has not been associated with worsened neurologic outcomes or mortality.[62, 64, 69] There are currently no randomized placebo-controlled trials listed in clinicaltrials.gov evaluating the efficacy and safety of prophylactic AED therapy in patients with ICH.[72]

The value of AED therapy was assessed in a long-term prospective observational study of 761 nontraumatic, nonaneurysmal patients with ICH.[68] Patients who survived ICH without seizure in the first 24 hours were grouped by ICH location (n=650). In patients with lobar ICH (n=268), prophylactic AED therapy with phenobarbital significantly reduced the risk of early seizures when compared with patients not treated (5.9% vs 13.6%). It was concluded that AED therapy initiated immediately after onset of ICH and continued through the acute and subacute phases may benefit patients with lobar ICH.[68]

Other researchers have analyzed data from the placebo arm (n=295) of a multicenter randomized trial of a neuroprotectant in patients with ICH.[73] The purpose of this analysis was to determine whether prescriber-driven AED therapy was associated with severe disability or death, using the modified Rankin Scale. At 90 days, the AED group had a significantly higher rate of poor outcomes (65% vs 28%). The authors concluded that prophylactic AED therapy following acute ICH was strongly associated with poor outcomes, independent of other known risk factors. The authors also noted that phenytoin was the primary AED used in this study, suggesting these results might not be replicated with other AEDs.[73]

Another study predicted that the use of AEDs in patients with ICH would result in more complications and worse outcomes.[74] This hypothesis was based on previously described data reporting poor outcomes with the use of AEDs in patients with subarachnoid hemorrhage. Patients were treated with phenytoin, levetiracetam, or both. Prophylactic AED therapy was not associated with reduced risk of seizure. Phenytoin was associated with more fever, worse scores on the National Institutes of Health Stroke Scale at 14 days and worse scores on the modified Rankin Scale over 3 months compared with levetiracetam. The authors acknowledged that larger ICH volume in the phenytoin group may have contributed to the poorer outcomes. They concluded that prophylactic phenytoin was associated with more fever and poorer outcomes in patients with ICH; however, the observational nature of this study makes it impossible to establish causation.[74]

AHA/ASA guidelines for the management of ICH recommend that "prophylactic anticonvulsant medication should not be used."[75] This recommendation is a class III; level of evidence b recommendation and based on the studies described earlier as well as studies that were unable to associate clinical seizures with worsened outcomes and mortality.[75]

The current available evidence is observational and represents a heterogeneous group of patients, comorbidities, and severity of illness. Because phenytoin was the only AED correlated with poor outcomes, it seems critical to investigate the use of other AEDs for seizure prophylaxis in ICH patients. A large well-designed, multicenter randomized trial is needed not only to determine the efficacy and safety of prophylactic AED therapy in patients with ICH patients, but also to determine which patients might benefit from this intervention. Table 6 summarizes the primary literature related to the use of AEDs in patients with ICH.

Conclusions

There is great disparity in the use of prophylactic AEDs in neurocritical care. In the case of TBI and aSAH, there may be benefit to using short-course seizure prophylaxis to prevent early seizures. In other disease states, the benefit is not as clear. In addition, currently available AEDs have a wide range of pharmacologic properties and should not be considered equal when used for seizure prophylaxis. Older AEDs, such as phenytoin, phenobarbital, carbamazepine, and valproic acid, are associated with

Table 6. Selected Articles on the Use of Seizure Prophylaxis in Patients with Intracerebral Hemorrhage

	Trial design and intervention	Total number of patients	Main outcomes and results
[68]	Prospective, observational study AED prophylaxis vs none Compare location of ICH	650 patients Phenobarbital, n=423 No AED, n=227	Prophylactic AED therapy significantly reduced early seizures in patients with lobar ICH (13.6% vs 5.9%; OR, 0.62; 95% CI 0.40–0.96; p=0.033), but it did not modify the risk of early seizures in patients with deep ICH and deep ICH with lobar extension
[73]	Subanalysis of the placebo arm of an RCT AED vs prophylaxis	295 patients enrolled after excluding patients previously treated with AED. Poor outcome (n=82) Good outcome (n=209) 23 patients without documented seizures were treated with AEDs during the first 10 days post-ICH PHT, n=18 VPA, n=4 Lamotrigine, n=1	Univariate analysis of baseline patient characteristics suggested AED use was associated with poor outcome at 90 days (18% vs 4%; p<0.001) as did multivariable logistic regression incorporating all factors significant in the univariate analysis (OR 6.8; 95% CI 2.2–21.2, p=0.001) Factors influencing the initiation of AED include a change in the NIHSS of ≥4 from baseline to 72 hrs, lobar location of hematoma, and neurosurgical interventions. When adding these factors to the multivariable model, AED use remained significantly associated with poor outcome (OR = 11.45, 95% CI 2.7–48.6, p=0.001)
[74]	Prospective, observational study	98 patients enrolled 58 patients not treated (59%) 40 patients treated with AED LEV, n=12 PHT, n=22 LEV + PHT, n=6	Patients who received PHT or LEV + PHT were more likely to have an ICH with a larger volume (p=0.03) Seizure was associated with increased administration of PHT including duration and serum-free level (≤0.002) LEV was not associated with seizures or any demographic characteristic (p>0.1) AED therapy was not associated with a reduced risk of seizures (p>0.1) The number of febrile days was associated with duration of PHT use and total administered PHT dose (p=0.03 and 0.04, respectively) as well as worse NIHSS at 14 days (p=0.01) PHT use was associated with worse NIHSS at 14 days and discharge (23 vs 11; p=0.003) as well as worse modified Rankin Scale at 14 and 28 days; 3-mo LEV was not associated with poor outcomes

AED = antiepileptic drug; ICH = intracerebral hemorrhage; OR = odds ratio; CI = confidence interval; RCT = randomized controlled trial; NIHSS = National Institutes of Health Stroke Scale; PHT = phenytoin; VPA = valproic acid; LEV = levetiracetam.

adverse drug events and clinically significant drug-drug interactions. With the advent of newer AEDs such as levetiracetam and lacosamide, many of these adverse events can be minimized. However, more studies are needed of these newer AEDs to fully support their use for seizure prophylaxis.

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