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REVIEW

Use of Prophylactic Anticonvulsants in Neurologic Critical Care: A Critical Appraisal

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Abstract Seizures are commonly encountered in the setting of brain injury in neurologic critical care. Though seizure prophylaxis with the use of antiepileptic drugs is frequently utilized in variety of brain injury paradigms, it is often not based on evidence and is controversial. Significant difficulties arise from interpretation of supporting literature due to lack of definitions for early-vs.-late-seizures, variable end points with seizure prophylaxis, as well as methodologic inconsistencies for seizure detection. This descriptive review summarizes the existing literature on the use of prophylactic anticonvulsants in clinical paradigms commonly encountered in neurologic critical care and highlights the important controversies concerning their use.

Keywords Seizures · Neurologic critical care · Anticonvulsants · Epilepsy

Seizures in the neurologic critical care setting are encountered in a variety of brain injury paradigms, can be devastating events, and have an adverse impact on outcome. Although critical care clinicians who manage this subset of critically ill patients are adept in the prompt recognition, diagnosis, and acute treatment of seizures, preventing these events from occurring remains the preferred method of seizure control.

The simplicity of the theory behind seizure prophylaxis belies the complexity and controversies that surround the topic. Prophylaxis with antiepileptic drugs (AED) is not without morbidity, and the balance between risk and benefit stands at the center of this debate. The literature is plagued by both a paucity of Class I evidence and by highly variable methodology. Inconsistent or absent monitoring of therapeutic levels of AEDs, the definitions of early and late seizures, the manner in which seizure activity is defined and diagnosed (electrophysiologic studies vs. clinical bedside observation), and lack of adequate follow-up are only a few of the examples of study flaws that run rampant in the current literature.

Most prophylactic use of AEDs is dogma based. Literature is reviewed here in various brain injury paradigms in an attempt to clarify whether the prophylactic use of AEDs is warranted. These conditions include traumatic brain injury (TBI), ischemic stroke, spontaneous intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), intracranial neoplasms (primary and metastatic), and other conditions (venous sinus thrombosis, meningitis, and encephalitis).

Traumatic Brain Injury (TBI)

Each year, more than 422,000 people in the United States are hospitalized with TBI, resulting in a significant number of patients who are affected by post-traumatic seizures [1]. The estimated number of new occurrences ranges from 5,000 to 30,000 per year. Some investigators have reported that approximately 20–25% of all patients who sustain

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severe TBI are expected to experience at least one post-traumatic seizure [2]. Retrospective analyses report that the overall standardized incidence ratio for development of new unprovoked seizures following TBI is 3.1 [3], with the highest rates occurring following penetrating TBI [4].

Many neurosurgeons routinely utilize prophylactic AEDs for patients with TBI. In a 1973 survey of neurosurgeons, 60% of respondents prescribed prophylactic AEDs for patients with TBI, giving several justifications for this practice [5]. One is the belief that seizures beget seizures and damage neural tissue, with corresponding deterioration of neurologic function, the so-called "kindling effect." Concern over acute consequences of seizures is another reason given to support the prophylactic administration of AEDs. A third justification is the fact that post-traumatic epilepsy (PTE) adversely affects quality of life, resulting in socioeconomic stress and often requiring life-long treatment. Finally, some respondents felt that failure to use prophylaxis for PTE may have medicolegal implications because of a widespread, though unsubstantiated, belief that, with proper treatment, PTE may be preventable.

Post-traumatic seizures (PTS) can be categorized into two types: early, or those occurring within 7 days of the ictus, and late, seizures that occur after the early period. Several reviews of the literature have demonstrated that, although AEDs appear to decrease the incidence of early PTS, they do not significantly alter the incidence of late PTS. Earlier non-randomized studies had suggested that the risk of late seizures following TBI was reduced with prophylactic AEDs [6, 7], but more recent and improved controlled studies do not support this inference. Young et al. conducted a randomized, double-blinded, placebo-controlled study to determine whether phenytoin administered soon after severe TBI decreases the incidence of early PTS [8] (Table 1). The percentage of patients who had early seizures was not significantly different between groups, and the intervals from injury to first seizure were not significantly different. The authors suggested that AEDs be given only after an early seizure has occurred. In contrast, another double-blind, randomized, placebo-controlled study of patients who suffered severe TBI and were given phenytoin within 24 h of injury and had phenytoin maintained at therapeutic levels for 1 year concluded that phenytoin exerted a beneficial effect by reducing seizures only during the first week following severe TBI [11]. More recent studies, including several meta-analyses, seem to corroborate the finding that early administration of prophylactic AEDs is associated with a decrease in the incidence of early PTS without a significant decrease in the incidence of late PTS. Interestingly, the decrease in the incidence of early PTS observed with phenytoin administration does not coincide with a decrease in mortality [14]. It has been suggested that early PTS are simply a marker of the severity of TBI and that the development of late PTS occurs via a different mechanism [15, 16]. However, it is important to note that early PTS predispose patients to the development of the more morbid late PTS [2].

Table 1 Evidence based recommendations for AED prophylaxis in TBI

Study and type	Results	Conclusions
Young et al. [8]; randomized, double-blind placebo-controlled; (n = 244)	No significant difference in the percentage of patients having early seizures in the phenytoin-treated and placebo groups	Suggested that AEDs be administered only after an early seizure has occurred
Glotzner et al. [9]; randomized, placebo-controlled trial; (n = 151)	Prophylaxis with carbamazepine significantly attenuated incidence of early post-traumatic seizures but not late seizures following TBI	Prophylactic AEDs (phenytoin and carbamazepine) recommended for up to 1 year following TBI
McQueen et al. [10]; randomized, double-blind, controlled trial (n = 164)	Low incidence of post-traumatic epilepsy (7% within 1 year and 10% between 1 and 2 years)	Larger clinical trials recommended
Temkin et al. [11]; randomized, placebo-controlled, double-blind trial (n = 404)	Seizure incidence of 3.6% in phenytoin-treated patients as compared to 14.2% in placebo-treated patients within 1 week of TBI	Phenytoin exerts a beneficial effect by reducing seizures only during the first week after severe head injury
Dickmen et al. [12]; randomized, placebo-controlled trial (n = 244)	In severe TBI, phenytoin significantly impaired functional performance at 1 month	Questions the use for long-term prophylaxis with phenytoin
Temkin et al. [13]; randomized, double-blind trial (n = 132)	Rates of early seizures were low and similar when using either valproate (4.5%) or phenytoin (1.5%). Trend toward a higher mortality rate in patients treated with valproate	Valproate demonstrated no benefit over short-term phenytoin therapy for prevention of early seizures and neither treatment prevented late seizures. Lack of additional benefit and the potentially higher mortality rate suggest that valproate should not be routinely used for the prevention of post-traumatic seizures

A major concern with the prophylaxis for PTE is the toxicity and safety profile of AEDs, in that these agents possess a high potential of adverse effects, reported to be as high as 22% in patients who receive monotherapy. These adverse events, which can be enhanced by the presence of brain injury, often require the withdrawal or substitution of the treating drug. Cognitive and behavioral abnormalities are common findings in patients with TBI, and these can often be exacerbated with the use of AEDs. These clinically observed neurobehavioral consequences of AEDs have been confirmed in experimental animal models and corroborated by clinical studies following treatment of epilepsy in other brain injury paradigms (ischemic stroke, ICH, SAH).

Pertaining to specific pathology in TBI, it is widely recognized that depressed skull fractures and intraparenchymal and subdural hematomas have an increased risk for the development of early seizures (~25%), while epidural hematomas have an incidence of ~4–10% [17, 18]. Over half of patients with intraparenchymal or subdural hematomas develop late seizures, with the incidence being ~20% in patients with epidural hematomas [2].

The general recommendation, supported by Class I evidence, is that prophylactic administration of AEDs should be instituted in patients with TBI for 7 days to decrease the incidence of early PTS.

Aneurysmal Subarachnoid Hemorrhage

Although, aneurysmal SAH (aSAH) has been linked to an increased risk of seizures, prophylactic administration of AEDs in this setting remains controversial. While the precise incidence of prophylactic AED use in this paradigm is unclear, an unpublished survey from the American Association of Neurological Surgeons indicates that 24% of respondents routinely utilized prophylactic AEDs for 3 months in patients with aSAH [19]. Although prophylactic treatment of seizures after aSAH may seem reasonable, it should be noted that the benefit of empiric AEDs has yet to be demonstrated in a prospective, randomized trial.

Incidence, Timing, and Predictors of Seizures Following aSAH

Over the past two decades, numerous groups have investigated the incidence of seizures following aSAH. Seizure risk has been linked to the thickness of the subarachnoid clot [20], to middle cerebral artery aneurysms [21], to the presence of a subdural hematoma, and to cerebral infarction [19]. In one study in patients with aSAH, variables associated with the development of epilepsy included a history of hypertension, cerebral infarction, and duration of impaired consciousness after the seizure [22].

Earlier studies have reported a 10–25% incidence of seizures following surgery for aSAH. For example, in a retrospective study (n = 177) of patients who were treated surgically for ruptured aneurysms, placed on phenytoin during surgery, and maintained on it for 2–3 months or longer, late seizures developed in 14% and were recurrent in 12% of all patients [23]. Most seizures were partial, secondary generalized, or generalized tonic–clonic (72%), and incidence of seizures was higher (33%) in Hunt & Hess (H&H) high-grade (3 and 4) patients compared to low-grade (1 and 2) patients (2.5%). This study concluded that patients who are H&H low-grade preoperatively have a very low risk for developing epilepsy and that treatment with phenytoin can be discontinued at 3 months following surgery if there are no accompanying risk factors (e.g., high admission H&H grade; middle cerebral artery aneurysm location; complications of aSAH, such as a large hematoma; vasospasm with infarction; shunt-dependent hydrocephalus; and persistent neurologic deficits, including hemiparesis, dysphasia, and visual field defects).

More recent studies report a lower rate of early seizures of 1.9–5% with surgery for aSAH [22, 24, 25]. A study of consecutive patients with aSAH (n = 100) who were followed for 4 years after surgery concluded that prophylactic phenytoin was not indicated, as only 3% of patients developed postoperative seizures, with no differences delineated in seizure incidence in patients with or without prophylactic AED use [26]. In another prospective study (n = 121) in which prophylactic AEDs were not utilized in surgically treated patients with aSAH unless they developed epilepsy (≥2 seizures), the overall risk for developing epilepsy was 7% and risk for a single seizure at 12 months was 2.5%. In light of this low incidence of seizures, this study concluded that prophylactic AEDs are not warranted following surgery for aSAH [27]. Based on these results, a large retrospective study was undertaken to evaluate the efficacy of perioperative, short-term prophylactic AEDs following craniotomies (n = 420) for cerebral aneurysms [25]. All patients were maintained on AEDs for 7 days following surgery (average of 3 days from surgery and 5 days of total treatment duration). Postoperative seizures occurred in 5.4% of patients (4.5% ruptured and 6.9% unruptured aneurysms). Early postoperative seizures (defined as within 14 days from surgery) occurred in 1.9% of patients (1.5% ruptured and 2.6% unruptured aneurysms), and late postoperative seizures occurred in 3.5% (3% ruptured and 4.4% unruptured aneurysms). Two-thirds of early postoperative seizures occurred in patients with significant intracranial pathology (hematomas or infarcts). Only one-third of patients had therapeutic levels of AEDs

when early seizures occurred, but all were reloaded and maintained on treatment for 1 year without any further seizures. Late seizures developed in 8 of 11 patients within 3 months of surgery and were readily controlled with AEDs. Multivariate analysis revealed that no association existed between total or postoperative duration of prophylactic treatment with AEDs and risk of early or late seizures. This study concluded that early postoperative seizures should always be evaluated for ongoing and accompanying intracranial pathology and recommended loading patients with AEDs the day before surgery, but not using AEDs for >7 days after surgery if peri-operative risk for seizures is considered to be low.

In contrast, another cohort study of patients with aSAH (n = 123) followed-up at 4–7 years found no evidence for the effectiveness of prophylactic AEDs [28]. In a more recent retrospective analysis (n = 217) of surgically treated patients with aSAH who were followed for an average of 78.4 months, 21.2% had at least one seizure. In the subgroup analysis, seizures in 7.8% were new-onset, 2.3% were preoperative, and 1.8% were postoperative. After the first postoperative week, 9.7% patients had at least one seizure, while incidence of late epilepsy was only 6.9%. The mean latency between the operative procedure and the onset of epilepsy was 8.3 months. Younger age (<40 years old), loss of consciousness of >1 h at ictus, and Fisher Grade 3 were factors that were significantly associated with seizures. In this study, all patients were treated with prophylactic phenytoin until the first outpatient visit (2–3 weeks post-surgery), at which time the dose was tapered off if no late seizures had occurred [26].

Several previous reports have investigated the *timing* of seizures and efficacy of AEDs in patients with aSAH. In a prospective study in patients with aSAH (n = 253), new-onset seizures occurred in 6.3% patients, and predictors included presence of hemiparesis, H&H grade >3, and higher Fisher grades (3 or 4) on admission. Aneurysmal re-rupture was more frequent in patients with seizures, but had no temporal relationship to seizures. Although mortality or severe disability at discharge was more frequent in these patients, seizures were not a significant predictor of prognosis. All patients with new-onset seizures were treated with phenytoin, and 25% of patients had recurrent seizures. Recommendations based on this study included prophylactic AED use during hospitalization in aSAH patients with new-onset seizures, but argued against long-term treatment [29]. A retrospective analysis (n = 95) reported that ~25% of seizures occurred prior to admission and that in-hospital seizures (4.1%) were not prevented by AEDs in 75% of patients [20]. Approximately 8% of the cohort had post-hospital discharge seizures, but none of the in-hospital patients had recurrent seizures following hospital discharge.

In another retrospective analysis (n = 412), new-onset seizures following aSAH that occurred in 7.8% of cohort correlated with a high Fisher grade on admission CT scan, but no significant correlation was seen with duration of loss of consciousness at onset, GCS, presence of aneurysm, or past history of hypertension or epilepsy. Disability 6 weeks after aSAH was independently predicted by initial GCS of <6 (OR, 13.7; $p < 0.01$) and new-onset seizure (OR, 7.8; $p = 0.04$) [21]. Based on this analysis, early and long-term treatment with AEDs in aSAH patients was recommended for patients with high Fisher grades and those with new-onset seizures [21]. However, this recommendation remains highly controversial because in preceding studies, early seizures were not predictive of their late recurrence, questioning the necessity of long-term AED use [30].

Seizure Detection

The methodology utilized for seizure detection may also play a critical role, in that routine "spot" electroencephalogram (EEG) may not be sensitive enough compared to continuous EEG (cEEG) monitoring. This sensitivity is illustrated in a study [31] of patients with aSAH (n = 101) who had unexplained coma or neurologic deterioration and underwent cEEG for at least 24 h. Eight of the 26 patients (all treated with prophylactic fosphenytoin) who underwent cEEG were found to be in non-convulsive status epilepticus (NCSE). Risk factors identified in this subset of patients included older age, external ventricular drainage, high H&H grade (4 and 5), and accompanying cerebral edema on CT scan. Also in this subset of patients, despite successful termination of NCSE in five patients following supplementary fosphenytoin administration or use of other AEDs (phenobarbital, valproate, or midazolam), only one patient had transient clinical improvement. All patients eventually died after a period of prolonged coma. This study highlights that cEEG may detect NCSE, particularly in comatose patients following aSAH. In a subsequent report, 9% of aSAH patients had in-hospital seizures or NCSE that were not predictive of subsequent incidence of seizures. After discharge, 4% of patients had one seizure and another 7% had ≥2 seizures.

Surgical Clipping vs. Endovascular Coiling

Debate is emerging regarding the relative merits of endovascular coiling over surgical clipping for aSAH, specifically as it impacts comorbidities such as seizures. Theoretical considerations would suggest a relatively lower risk for seizures with endovascular coiling, resulting from a relative absence of accompanying retraction injury with craniotomy. In a prospective study (n = 243) in which

patients were treated with Guglielmi Detachable Coils and followed for up to 7.7 years [32], seizures occurred in 11% within 24 h of aSAH. In this study, 12% of patients received prophylactic AEDs following aSAH. Independent predictors for developing seizures included loss of consciousness, aneurysmal location (middle cerebral artery aneurysm), and treatment with AEDs. While 3% of patients developed late seizures, including three with preexisting epilepsy, only 1.7% developed new-onset seizures. None of the patients with late seizures presented within 30 days of the procedure and only half of these (0.85%) had recurrent seizures that required long-term AED use. Independent predictors of late seizures were a history of epilepsy before aSAH, cerebrospinal fluid shunting or drainage procedure, and AED use. Based on these results, the study inferred that periprocedural prophylactic AEDs are not indicated. Furthermore, the relative low incidence of late seizures does not justify recommending long-term prophylactic use of AEDs following aneurysmal coiling.

This proof of concept is further illustrated in the recently published 1-year outcomes of the International Subarachnoid Aneurysm Trial (ISAT) in which patients (n = 2,143) with aSAH were randomly assigned to aneurysmal clipping or endovascular coiling [33]. This study examined the risk of developing seizures as one of the secondary outcomes. Seizures occurred in the endovascular group in three patients, in 16 post-procedurally and prior to discharge, in 27 between discharge and 1 year, and in 14 after the first year, compared to 11, 33, 44, and 24, respectively, in the surgical arm. These data indicate a highly significant reduction in seizures in the endovascular arm compared to the surgical arm after the first procedure (RR, 0.52; 95% CI, 0.37–0.74). The inference from these results on the use of prophylactic AEDs after aSAH as it relates to choice of aneurysm therapy (clipping vs. endovascular coiling) remains unclear.

Prophylactic AEDs and Functional Outcomes in aSAH

Emerging evidence suggests that prophylactic AED use can lead to adverse functional outcomes. A meta-analysis of four prospective randomized, double-blinded, placebo-controlled trials conducted between 1991 and 1997 (n = 3,552) that examined the efficacy of older generation prophylactic AEDs (phenytoin, phenobarbital, carbamazepine) revealed worse outcome at 3 months with AED use [34]. In another report in patients with aSAH (n = 527), a calculated "phenytoin burden" (average serum level of phenytoin × time between the first and last serum level measurements) was associated with poor functional outcome at 14 days but not at 3 months and remained insignificant following a multivariate analysis. Higher quartiles of phenytoin burden were also associated with worse cognitive outcomes at both hospital discharge and at 3 months [35] (Table 2). Concomitant administration of other drugs is associated with other theoretical concerns. For example, nimodipine, a dihydropyridine calcium channel antagonist that is frequently given for vasospasm prophylaxis, is metabolized by the hepatic microsomal enzyme system (cytochrome P450 isoenzymes), the same metabolic pathway that is induced by drugs such as phenytoin, phenobarbital, and carbamazepine, theoretically resulting in the decreased bioavailability of nimodipine. In a single-dose pharmacokinetic study [37], half-life of orally-administered nimodipine was significantly attenuated when hepatic microsomal enzyme-inducing AEDs (carbamazepine, phenytoin, and phenobarbital) in patients with epilepsy as compared to controls. Conversely, patients on valproate did not demonstrate appreciable differences in half-lives [32]. The clinical import of these findings may be significant, in that, oral doses of nimodipine may have to be substantially increased to compensate for reduced

Table 2 Evidence based recommendations for AED prophylaxis in aSAH

Study and type	Results	Conclusions
Baker et al. [25]; retrospective; (n = 387)	Postoperative AEDs instituted for 3 days. Overall seizure rate was 5.4% (early—1.5% and long-term seizure disorder—3%)	AEDs may be safely restricted to the immediate post-operative period
Rhoney et al. [20]; retrospective; (n = 95)	Pre-hospital seizure incidence—17.9%; post-hospital discharge seizure incidence—8% (50% of patients on prophylactic AEDs)	Majority of seizures occurred prior to medical presentation. Thickness of cisternal clot predictive of seizures
Naidech et al. [35]; retrospective; (n = 527)	"Phenytoin burden" associated with poor outcome at 14 days and worse cognitive outcomes at 3 months	Treatment with prophylactic phenytoin predicts poor neurologic and cognitive outcomes
Chumnanvej [36]; Retrospective; (n = 453)	Three-day treatment with phenytoin resulted in similar seizure incidence (5.7%) as those treated until discharge (4.6%)	Three-day regimen of phenytoin prophylaxis is adequate to prevent seizures in aSAH

bioavailability and it is plausible that any neuroprotective effects of nimodipine are mitigated with concomitant administration of phenytoin in patients with aSAH [38].

In summary, a randomized, placebo-controlled trial is warranted to assess the effect of prophylaxis with AEDs on the prevalence of early and late seizures in patients with aSAH. Such a trial would ideally incorporate predefined stratification based on focal parenchymal pathology, aneurysm location, aSAH grade, age, and history of hypertension [39].

Brain Neoplasms

New-onset seizures and epilepsy represent common comorbidities of brain tumors, with an incidence of ~35% in the literature [40]. Several conclusions can be drawn regarding the association of various tumor types with seizures: high-grade tumors tend to be associated with acute, isolated seizures, whereas low-grade tumors (e.g., gangliogliomas) are associated with the development of epilepsy; cortically based tumors, particularly those in the temporal and parietal lobes, are more epileptogenic [40, 41]. The topic of use of prophylactic AEDs has been raised, but a firm consensus has not been reached, though the American Academy of Neurology has devised a practice parameter against the use of prophylactic AEDs in adults with newly diagnosed brain tumors [42]. Several prospective, randomized trials have been performed to investigate if prophylactic AEDs prevent the development of early and late seizures in the setting of brain tumors. A recent meta-analysis [43] clearly summarizes the findings of five prospective, randomized trials that analyzed the prophylactic use of a various AEDs (phenytoin, valproic acid, and phenobarbital) in various tumor types (meningiomas, metastatic disease, and primary intracranial neoplasms) in patients with negative seizure history. This review of the literature found little evidence to support the use of AED prophylaxis with phenobarbital, phenytoin, or valproic acid in adult patients with brain tumors and no history of seizures. These AEDs failed to prevent the development of seizures occurring within 1 week of intervention and seizures occurring within 6 months of follow-up. In addition, tumor pathology failed to show any effect on response to prophylactic AEDs. Surgery has often been quoted to be a factor in the development of seizures. However, in three studies in which patients underwent tumor resection, surgery did not influence seizure prevention with AEDs despite the potential epileptogenic risks of bleeding and iatrogenic edema.

The risk of adverse effects with the use of AEDs is one that is not unique to the cancer population. Seizures and AED therapy may cause cognitive and social constraints on work or school performance and driving. Serious adverse effects such as Stevens–Johnson syndrome can occur with the use of AEDs. One retrospective study cited a 25% incidence of rash with phenytoin use and 26% incidence in patients who harbored malignant gliomas and were taking carbamazepine [43–46]. Similarly, carbamazepine, phenobarbital, phenytoin, and valproic acid all have potential hematologic effects when used alone; when any of these drugs are used concomitantly with antineoplastic agents, these effects can be exaggerated [47–49]. In addition, as stated above, most current AEDs induce the cytochrome P450 system that represents a metabolic pathway shared with many AEDs. It remains to be seen whether contemporary anticonvulsant medications interact less with antineoplastic regimens.

In summary, Class I evidence suggests that the prophylactic use of AEDS in patients with intracranial neoplasms who do not have a history of seizures is ineffective.

Intracerebral Hemorrhage (ICH)

Intracerebral hemorrhage is a devastating event that is associated with the development of early and late seizures. Rates of developing immediate seizures (usually described as occurring within 24 h of the ictus) range from 1.4 to 17% [50]. The cumulative risk of experiencing a seizure is also higher within the first 5 days, compared to the first 30 days. In addition, a review of the literature reveals that, of the patients who experience seizures following non-traumatic ICH, up to 14% manifest their seizure disorder as status epilepticus. It has also been reported that with the use of continuous electroencephalography, 28% of comatose or stuporous patients with ICH were in status epilepticus [51]. The epicenter of the ICH appears to play a role in epileptogenesis, and it is widely recognized that patients with a cortically based nidus are more likely to experience a seizure.

Patients who have suffered an ICH might benefit from the prophylactic administration of AEDs, but thus far, no prospective, randomized trial has been performed to assess the existence of beneficial effects from prophylaxis. However, the American Heart Association has provided guidelines that recommend the prophylactic administration of AEDs in selected patients (level V evidence V, grade C recommendation) [52]. These guidelines are based on an observational study in which prophylactic administration of phenytoin demonstrated a risk reduction in patients with lobar hemorrhages vs. those with deeper subcortical hemorrhages. Interestingly, though these patients experienced a reduction in the incidence of early seizures, no effect on mortality was observed; this effect was explained by the fact that cortically based hemorrhages tended to be smaller

and thus inherently have better outcomes. This study suffers from inadequate monitoring of serum AED levels and the lack of diagnostic electrodiagnostic studies [53].

In summary, paucity of literature surrounding seizure prophylaxis for patients with ICH underscores the need for prospective, randomized trials. Ideally, these trials would stratify hemorrhages based upon their location and size, whether the patient underwent surgical evacuation of the hematoma, use of electroencephalography, and rigorous monitoring of serum AED levels.

Ischemic Stroke

Ischemic stroke is considered to be the most common cause of epileptic seizures in the elderly, with one study stating that 45% of seizures starting after the age of 60 were due to ischemic cerebral infarction [54]. The frequency of post-stroke seizures reported in the literature varies from 2.3 to 43% [55, 56]. This variation reflects differences in the patient populations studied, definition of the terms "post-stroke seizures" and "post-stroke epilepsy," study design and methods, and duration of follow-up. By using multivariate analyses, a variety of factors have been found to predict post-stroke seizures, including stroke severity, ICH, and cortical location of the stroke [57–62]. Age at stroke onset has not been found to predict post-stroke epilepsy [63].

Currently no prospective, randomized trials are being conducted to examine the use of prophylactic AEDs to reduce seizure incidence, though several small observational studies suggest that an isolated early seizure after cerebral infarction does not require treatment or can be easily controlled with a single drug [64–66]. A prospective cohort study of gabapentin monotherapy in patients with a first, late post-stroke seizure found that 81% had excellent seizure control with no seizure recurrence after 30 months [67]. Since the study did not include a control group, no assessment can be made as to whether this result is better than would have occurred in patients who did not receive treatment or who received treatment with an alternative AED.

Rampant controversy continues regarding the safety of AEDs in this patient population. As demonstrated in laboratory animal studies of focal and global ischemia, AEDs may also act as neuroprotectants [68]. For example, phenytoin, benzodiazepines, lamotrigine, topiramate, levetiracetam, and zonisamide have neuroprotective properties and may therefore have beneficial effects when used to treat seizures in the setting of hyperacute stroke. However, no clinical data validate these theoretical benefits, and the comparative risks and benefits of the various AEDs have not been well studied in the stroke population. In fact, some concern exists that the use of phenytoin, phenobarbital, and benzodiazepines may actually impair recovery after stroke. One retrospective cohort study compared the motor recovery of stroke patients who received one or a combination of theoretically detrimental drugs, including benzodiazepines and phenytoin, with the recovery of a similar group of patients who were not given any of these medications [69]. Those who received these drugs had poorer recovery than controls, an effect that remained constant even after controlling for other contributing factors. This potentially deleterious effect on motor recovery was also found in a separate cohort of patients who were control subjects in a prospective acute interventional stroke trial [70]. Since these analyses were retrospective in nature, the impact of the individual drugs could not be determined because of sample-size limitations, nor were analyses of dose or timing effects possible. Clinical studies are consistent with laboratory experiments and suggest that phenytoin, phenobarbital, and benzodiazepines be avoided during the post-stroke recovery period.

In summary, no available data demonstrate that administration of AEDs after stroke prevents the later development of epilepsy. In addition, current literature suggests that the administration of these drugs to this particular patient population can be potentially injurious.

Other Conditions

Data from several reports support the observation that the risk of seizures in *cerebral venous and sinus thrombosis* (CVST) is considerable. In a multinational, multi-centered, prospective, observational study in patients with CVST (n = 624), the incidence of seizures was 10.6% [71]. In a prospective study (n = 194) in patients with acute CVST [72], symptomatic seizures were found in 44.3%, with status epilepticus in 12.8% of patients. In a multivariate analysis, motor deficit, ICH, and cortical vein thrombosis were independent risk factors for early seizures. In an earlier study [73] of a prospective registry (n = 91), 34% of patients had early symptomatic seizures, with the presenting feature in 31.9%. In this study, early symptomatic seizures occurred more frequently in motor and sensory deficits and in those with focal ischemic or hemorrhagic strokes on admission neuroimaging studies. Seizures were a direct cause of death in two patients. Late seizures occurred in 9.5% of patients and were more frequent in patients with early symptomatic seizures and ICH on admission. However, neither early nor late seizures were related to functional outcomes. In summary, patients with CVST are at significant risk for early- and late-onset seizures. In the absence of data from a randomized clinical trial, a case can be made for the use of prophylactic AEDs

in this subset of patients, particularly in those with neurologic focal deficits and focal abnormalities on neuroimaging (CT/MRI).

The incidence of seizures is ~5% in community-acquired acute bacterial meningitis [74], and prophylactic AED use is not recommended in this population. Seizures are a common accompaniment of herpes simplex encephalitis; its precise incidence is not known. In a 12-year follow-up of children (n = 322) with encephalitis, 5% were secondary to herpes simplex and seizures occurred in 44% of these cases [74]. Although refractory NCSE has been reported in this setting [75], presently, no clear consensus exists based on existing literature as to the use of prophylactic AEDs in herpes encephalitis.

Choice of Anticonvulsants

Selecting the appropriate anticonvulsant medication from a large catalog of AEDs, each with its own side effect profile and cost, is a daunting task for the treating clinician. Despite the variety of choices, studies that compare the efficacy of different AEDs in the critical care setting are strikingly few. Phenytoin continues to dominate the literature in studies that investigate seizure prophylaxis.

In the setting of PTE, Temkin et al. conducted a double-blinded study of valproate for the prevention of late PTE [76]. In their study, 132 patients were randomized to a 1-week course of phenytoin, 120 were randomized to a 1-month course of valproate, and 127 were randomized to a 6-month course of valproate. The entry criteria consisted of immediate PTS, depressed skull fracture, penetrating brain injury, or evidence of cortical contusion or subdural, epidural, or ICH on CT. Patients received AEDs for 1 year, after which they were followed until 24 months after injury. No differences were delineated between the phenytoin-treated and valproate-treated groups in the frequency of early PTS.

Antiepileptic drugs target multiple sites pre- and post-synaptically, decrease excitatory transmission, or enhance neuronal inhibition. With this mechanistic premise, AEDs have been proposed as neuroprotective agents, particularly following cerebral ischemia [77]. The newer AEDs with more desirable toxicity profiles than the older generation AEDs (benzodiazepines, phenytoin, Phenobarbital) hold promise for clinical use in seizure prophylaxis as well as neuroprotectants in ischemic stroke and other brain injury paradigms. For example, levetiracetam (keppra), an AED utilized as adjunctive therapy for partial-onset seizures is safe and well tolerated with minimal side effects when instituted both via the enteral and intravenous routes with comparable pharmacokinetics [78]. While, clinical data on the use of levetiracetam as first-line AED is limited, a recent study demonstrated its efficacy and safety in treatment of repetitive seizures in hospitalized patients that included 30% of patients with ischemic stroke [79]. Similarly, rapid intravenous infusion of valproate (depacon) is efficacious in patients with new-onset seizures with no hemodynamic compromise and minimal side effects (injection site pain, dizziness, and somnolence) [80].

In clinical practice, in absence of Class I evidence, the physician should institute prophylactic AEDs based on established predictors for seizures in various brain injury paradigms. Newer AEDs such as levetiracetam and valproate hold promise for utility as first-line agents, although this requires further study.

Conclusions and Future Directions

The use of prophylactic AEDs remains controversial in various brain injury paradigms. While their use is recommended in patients with TBI based on Class I evidence, their utility in aSAH, ICH, and ischemic stroke currently depends on the individual patient and is largely dependent on clinical practices. Large, randomized clinical trials are necessary to address many of these practices in this subset of patients.

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