REVIEW ARTICLE

Seizures and Choice of Antiepileptic Drugs Following Subarachnoid Hemorrhage: A Review

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ABSTRACT: Seizures are important complications following a subarachnoid hemorrhage (SAH). The evidence for the use of antiepileptic drugs (AEDs) in treatment and prevention of those seizures is conflicting. The purpose of this review is to provide an up-to-date evidence summary of the incidence and outcomes of seizures following an SAH as well as the use of different AEDs post-SAH in order to evaluate the need for seizure prophylaxis, the choice of AEDs, and their dosing considerations in SAH patients. A literature search of PubMed, Medline, Embase, and the Cochrane Library was performed. A total of 37 studies were reviewed, mostly observational. Definitions of seizures in temporal relation to initial hemorrhage were variable. Similarly, the rates of seizures varied in the literature, ranging from 0 to 31%. Given the reported adverse outcomes associated with AED usage, seizure prophylaxis is not warranted. Levetiracetam appears to be better tolerated than phenytoin in SAH patients, though further research is needed. Higher initial dosing of levetiracetam might be required due to its enhanced clearance in SAH patients. In conclusion, there is a lack of quality evidence to definitively recommend the use of one AED over another. Further prospective research comparing the use of different AEDs in patients with an SAH is needed.

RÉSUMÉ: Crises convulsives et choix de médicaments antiépileptiques suite à une hémorragie sous-arachnoïdienne : une revue. Les crises convulsives constituent des complications importantes après une hémorragie sous-arachnoïdienne (HSA). Les données en faveur de l'utilisation de médicaments antiépileptiques (MAE) dans le traitement et la prévention de ces crises sont contradictoires. Le but de cette revue est de présenter une mise-à-jour sommaire des données sur l'incidence et l'issue des crises suite à une HSA ainsi que sur l'utilisation de différents MAE post HSA afin d'évaluer la nécessité d'une prophylaxie et le choix et le dosage des MAE chez les patients atteints d'une HSA. Nous avons effectué une recherche de la littérature indexée dans PubMed, Medline, Embase et la Bibliothèque Cochrane. Nous avons revu 37 études, surtout des études d'observation. Les définitions des crises en relation temporelle avec l'hémorragie initiale étaient variables. De même, les taux de crises convulsives variaient dans la littérature, allant de 0 à 31%. Étant donné les résultats défavorables rapportés avec l'utilisation de MAE, la prophylaxie des crises convulsives n'est pas justifiée. Bien que des recherches supplémentaires soient nécessaires, le lévétiracétam semble être mieux toléré que la phénytoïne chez les patients atteints d'une HSA. Une dose supérieure initiale de lévétiracétam peut être requise à cause de sa clairance augmentée chez ces patients. Il existe un manque de données de qualité en faveur d'une recommandation de l'utilisation d'un MAE plutôt que d'un autre. De nouvelles études prospectives comparant l'utilisation de différents MAE chez les patients atteints d'une HSA devront être réalisées.

Keywords: Subarachnoid hemorrhage, seizures, antiepileptic drugs

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INTRODUCTION

Subarachnoid hemorrhage (SAH), a subtype of hemorrhagic stroke, accounts for approximately 5% of all strokes and has an overall annual incidence of 2–22 per 100,000 persons.[1,2] It is most commonly caused by a ruptured brain aneurysm and carries a high risk of morbidity and mortality. Known risk factors for an SAH include: female sex, hypertension, smoking, cocaine use, personal or family history of SAH, polycystic kidney disease, and alcohol abuse.[1] SAHs tend to occur in a younger population (mean age 55 years) compared to the more common ischemic stroke, and thus complications may have a devastating impact on patients' productive life years. Although mortality rates have declined from approximately 60% in the 1970s to 20–30% today as a result of early aneurysm repair and improvements in aggressive management of complications, roughly half of SAH survivors still incur some form of disability.[1] Complications may account for up to 25% of deaths following an SAH, and include, but are not limited to, aneurysm rebleeding, delayed cerebral ischemia (DCI) with consequential neurological and functional deficits, hydrocephalus, hyponatremia, fever, and seizures.[1] High-quality evidence guiding the management of many of these complications is lacking.[3,4]

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Seizures and epilepsy are important complications following an SAH. The rates of seizures and post-SAH epilepsy have been reported to range from 0 to 31% and 3.1 to 13%, respectively (Table 1). Seizures are a matter of concern for their potential association with such adverse outcomes as aneurysm rebleeding and additional cerebral injury, contributing to worsened long-term functional outcomes and increased mortality. Controversy exists in guiding decisions on the need for seizure prophylaxis in all patients versus only treating those who have actually experienced seizures.[5] In addition, the choice of antiepileptic drug (AED) therapy in SAH is a subject of debate due to a lack of quality prospective data to guide such a decision.[4] The purpose of this review is to provide an up-to-date summary of the evidence on the incidence and outcomes of seizures following an SAH as well as the use of different AEDs following an SAH in order to evaluate the need for seizure prophylaxis, the choice of AEDs, and their dosing considerations in SAH patients.

Methods

Search Strategy

A literature search of PubMed, Medline, EMBASE, and the Cochrane Library until 1 February 2017 was performed. The following keywords were used to complete the search: "subarachnoid h(a)emorrhage," "SAH," and all anticonvulsants, including: "acetazolamide," "brivaracetam," "carbamazepine," "clobazam," "clonazepam," "clorazepate," "diazepam," "divalproex," "eslicarbazepine," "ethosuximide," "felbamate," "fosphenytoin," "gabapentin," "ketamine," "lacosamide," "lamotrigine," "levetiracetam," "lorazepam," "midazolam," "oxcarbazepine," "paraldehyde," "pentobarbital," "perampanel," "phenobarbital," "phenytoin," "pregabalin," "primidone," "progabide," "propofol," "retigabine," "ezogabine," "rufinamide," "stiripentol," "sultiame," "sulthiame," "tiagabine," "topiramate," "valproic acid," "valproate," "vigabatrin," "zonisamide," "anticonvulsant," "antiepileptic," or "AED." Keywords were selected by both authors to cover any use of all currently available antiepileptic drugs in patients with an SAH.

Study Selection

Human studies focusing on seizures and the use of AEDs following an SAH were included. Titles and abstracts were screened to exclude nonhuman studies, non-English studies that could not be easily translated into English using an online translator tool, and nonrelevant studies. Studies that included exclusively subjects with traumatic brain injury, brain malignancy, or ischemic stroke were also excluded. Only original primary research was included. Commentaries, editorials, conference abstracts, and reviews were also excluded. Then, the full texts of the selected articles were assessed for inclusion in our review. Lastly, a manual search for additional relevant studies was performed by analyzing the reference lists of the selected studies. In case of any discrepancies between the reviewers, further discussion was undertaken to reach a consensus.

Data Collection

Data collected included study type, year of publication, number of subjects with an SAH, seizure incidence, percentage of patients given AEDs, individual AEDs used, AED dosing, duration, pharmacokinetic characteristics, adverse reactions, outcomes assessed, and main study findings. The outcome data collected were mortality, rebleeding, disability at three months, and, when available, post-SAH epilepsy.

Results

The initial search of the databases identified 2,238 records. After removal of duplicate records, exclusion of nonhuman and non-English-language studies, and title and abstract screening, 101 records were identified. Following full-text screening, a total of 37 studies was included (Table 1). The majority of these studies were observational, 24 of which were retrospective. A total of 16 studies focused primarily on seizure incidence and outcomes, while 21 evaluated at least one aspect of AED use, including choice of AED, efficacy, comparison with other AEDs, adverse effects, dosing, and pharmacokinetics. Based on this, the available evidence was considered low or very low using the GRADE working group criteria.[6] As a result of the variability of the included studies' objectives, the outcome data assessed varied across studies (Table 1).

Discussion

Incidence and Impact of Seizures Following SAH

Seizures following an SAH may occur at onset, during a hospital stay (early or late), and/or after discharge (epilepsy). However, the definition of seizures and their temporal relation to the initial hemorrhage vary among studies, thus impeding accurate identification of seizure incidence. Most authors have defined onset seizures as occurring within 12 to 24 hours of the initial hemorrhage.[7-14] "Early" seizures have been defined as seizures occurring within 3 days, 7 days, and between 1 and 14 days from onset in three different studies.[11,15,16] Definitions of "late" seizures were equally variable. For example, late seizures have been defined as occurring between 24 hours and 6 weeks of the initial hemorrhage,[13] more than 1 week following surgery for an SAH,[7] 12 or more hours after hemorrhage but before surgical repair,[10] more than 14 days after the initial hemorrhage,[11,17] or as any seizures occurring after discharge. Alternatively, some have classified seizures in temporal relation to surgical repair, to the patient's hospital admission, or to initiation of AED therapy,[7,14,15,18-21] whereas others have simply reported an overall incidence of any seizures that occurred during the patient's hospital stay.[9,22-28] Furthermore, the definition of what constitutes a seizure was inconsistent among studies. Many identified seizures as focal or generalized rhythmic jerking or tonic–clonic contractions, as reported by bystanders, family members, or medical personnel.[7,9,13,14,17,19,20] This allows for potential subjective interpretation of the event. It has been suggested that nonepileptic tonic posturing occurring at the SAH ictus as a result of elevated intracranial pressure may often be incorrectly mistaken for a seizure, which would produce an overestimation of the incidence of onset seizures.[29,30] Establishment of standardized definitions in SAH is underway, and this will benefit future research by facilitating comparison of results across the literature.[31]

Onset Seizures

The prevalence of onset seizures has been reported to range from 2.8 to 19%,[7-14,21,22,32] with the majority occurring within 1–3 hours post-hemorrhage.[11,13,14] Several studies have yielded conflicting

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Table 1: Summary of included studies

First author, year of publication	Study design	Study population	Seizure incidence	Percentage given AED	AED dose/duration, adverse effects	Outcomes assessed, main finding(s)
Baker et al., 1995[18]	Retrospective	$N = 200$	Among SAH patients: 4.5% Early postop: 1.5% Late: 3%	All patients received AED on admission to ICU PHT 94.6% PHB 4.1% Other 1.3%	PHT LD: 900–1100 mg MD: 100 mg TID Average duration of AED prophylaxis: 5.5 days in SAH patients If postop seizures occurred, AED continued × 1 year	Seizure incidence Association between duration of AED therapy and seizures Most patients with SAH may safely receive AEDs restricted to the immediate postoperative period following surgical treatment as seizures were well-controlled with AEDs
Butzkueven et al., 2000[13]	Retrospective	$N = 412$	Onset: 7.8% Late: 4.1%	P and T both used 88% received AED; majority with PHT	PHT dose not reported	Mortality Factors associated with seizures Factors associated with disability at 6 weeks Onset seizures correlated with some amount of blood on initial CT scan and were predictive of disability and late seizures following an SAH
Byrne et al., 2003[8]	Prospective, observational	$N = 243$ Patients preferred for coil embolization only	Onset: 11% Late: 3% De novo, late: 0.85%	12% received AED AED choice not reported	Not reported	Factors associated with seizures Patients treated solely with coil embolization appeared to have a very low rate of late seizures following an SAH
Choi et al., 2009[7]	Retrospective	$N = 547$ Excluded patients treated with coil embolization	Overall incidence: 15.2% Onset: 7.9% Preop: 1.5% Postop: 6.2% Epilepsy 3.1%	P and T both used (IV loaded on presentation) 96.5% received AED: VPA 72.4% PHT 17.6% Other: PHB, CBZ, zonisamide, topiramate	AED therapy continued for 3 months following surgery ADR 23.4% (rash, fever, dizziness, thrombocytopenia, toxic hepatitis, hypotension, amenorrhea, vasospasm)	Factors associated with seizures and epilepsy Perioperative seizures did not appear to predict development of epilepsy, whereas cortical infarction and thick hemorrhage appeared to be risk factors
Chumnanvej et al., 2007[25]	Retrospective	$N = 453$	Overall: 1.3% in period I patients 1.9% in period II patients Late: 5.7% in period I patients 4.6% in period II patients	All patients received AED on presentation PHT 100%	Period I patients: LD PHT 1000 mg MD PHT 100 mg TID, until discharge (route of administration not specified) Period II patients: LD PHT 1000 mg MD PHT 100 mg TID for 3 days (route of administration not reported) ADR: Period I 8.9%; and 29% switched to CBZ due to PHT-induced fever Period II 0.5%	Rate of seizures in each group ADRs A 3-day course of PHT appeared to provide comparable seizure control and significantly fewer ADRs compared to an extended course of PHT
Claassen et al., 2003[38]	Prospective, observational	$N = 247$	In-hospital: 7% Unprovoked seizure within 12 months post-SAH: 11% New-onset epilepsy at 12 months post-SAH: 7%	All patients received AED on ICU admission FosPHT LD NCSE treated with midazolam infusion (first-line), or PHB or propofol (second-line)	FosPHT LD 20 mg/kg IV FosPHT MD 300 mg IV daily PHT continued after discharge if seizure occurred during hospitalization	Outcomes associated with seizures and epilepsy Factors associated with epilepsy Cerebral infarction and subdural hematoma appeared to predict the development of epilepsy post-SAH, and epilepsy was associated with poor functional recovery and QoL
De Marchis et al., 2016[24]	Retrospective	$N = 402$	Overall: 12%	All patients received AED therapy PHT was AED of choice until 2005; thereafter LEV became AED of choice SE treated with IV midazolam infusion	AED duration 1 week, unless patient experienced seizures	Incidence of nonconvulsive seizures and NCSE Factors associated with nonconvulsive seizures and NCSE Mortality rate Outcomes of increased seizure burden Increased seizure burden was associated with poor functional and cognitive outcomes 3 months post-SAH
Dennis et al., 2002[29]	Prospective, observational	$N = 26$ (comatose patients)	NCSE: 31%	All patients received FosPHT on admission to ICU If NCSE: LD FosPHT, VPA, or PHB ± midazolam	FosPHT: 300 mg IV daily If NCSE detected: LD FosPHT 10–20 mg/kg IV given if recent levels subtherapeutic; or LD VPA 30–60 mg/kg IV; or LD PHB 10–20 mg/kg IV.	Factors associated with NCSE Mortality rate in NCSE Management of NCSE required treatment with combination AED therapy, and patients with NCSE had a 100% mortality rate

Table 1. *Continued*

First author, year of publication	Study design	Study population	Seizure incidence	Percentage given AED	AED dose/duration, adverse effects	Outcomes assessed, main finding(s)
Dewan et al., 2015[52]	Survey	*N* = 25 American centers with high volume of SAH cases	N/A	N/A	N/A	Assess respondents' beliefs on utility of AED prophylaxis in SAH and AED prescribing practices in SAH Levetiracetam appeared to be a first-line AED choice among respondents; 96% of respondents agreed that a trial comparing LEV to no AED is warranted
Dhakal et al., 2015[34]	Retrospective	*N* = 53	Overall incidence 7.5%	51% of patients received LEV Any patient with seizures received LEV treatment Gabapentin for headache, not for seizures	Any patient with clinical or EEG seizures received LEV 500 mg BID Gabapentin median dose 1200 mg/day	Headache improvement Seizure incidence No patients experienced seizures while weaning or discontinuing gabapentin therapy; unable to assess if seizure incidence was affected by gabapentin therapy
Drust et al., 2012[49]	Case report	*N* = 1	N/A	N/A	LEV up to 4000 mg/day	4000 mg/day of LEV was required to achieve seizure control and therapeutic levels in a patient with augmented renal clearance
Fung et al., 2015[9]	Retrospective	*N* = 425	Overall: 13.2% Early-onset: 9.6%	T 6.1% received AED treatment SE = VPA Self-limiting seizure = LEV	VPA dose not reported LEV dose not reported If no further seizures occurred, AED discontinued after 14 days from initiation	Factors associated with seizures Factors associated with poor functional outcomes Onset seizures associated with poor WFNS at admission and good functional outcome; occurrence of onset seizures appeared to influence grading of SAH
Hart et al., 1981[10]	Retrospective	*N* = 100	Overall: 26% Onset: 19% Late: 11.8%	Reported "highly variable" AED regimens PHT, PHB Patients considered to be AED-treated if received: > 250 mg PHT or >90 mg PHB daily for 24 hours before a seizure, or for >1/2 days before operation or discharge	Loading doses were not used; doses not reported	Outcomes associated with onset seizures Association between rebleeding and seizures Mortality Onset seizures did not appear to be a poor prognostic indicator. Seizures appeared to be related to either initial hemorrhage or aneurysm rebleed
Hasan et al., 1993[36]	Retrospective	*N* = 381	Overall: 9%	T most commonly PHT (percentage not reported)	PHT dose not reported	Mortality Factors associated with development of epilepsy Outcomes at 3 months post-SAH High cisternal blood score and rebleeding were associated with epilepsy
Huttunen et al., 2015[16]	Retrospective	*N* = 876	Acute: 15% Epilepsy: 13%	43% identified AED users	Not reported	Factors associated with seizures Outcomes associated with seizures Incidence of epilepsy Mortality rate and associated risk factors ICH >15 cm^3, Hunt–Hess III to V, and acute seizures were associated with development of epilepsy
Ibrahim et al., 2013[26]	Subgroup analysis of CONSCIOUS-1 trial	*N* = 413	Overall: 13.8%	T 37.5% treated with AEDs, 83% of which received PHT	Not reported	Factors associated with seizures Subarachnoid clot burden and subdural hematoma were associated with seizures
Karamchandani et al., 2014[20]	Retrospective	*N* = 259	Overall: 10% 8% prior to AED initiation 2% following AED initiation ("delayed")	All patients received AED on admission 17% received PHT exclusively, 66% of which were switched to LEV 51% received LEV exclusively No patients were switched from LEV to PHT	PHT dose: LD 20 mg/kg MD 4–6 mg/kg/day LEV dose: 250–500 mg BID, then adjusted per physician All patients started on AED at admission and tapered off within 30 days of discharge, unless they experienced a seizure	Comparison of rate of seizures, DCI, and functional outcomes between patients treated with PHT and LEV Factors associated with poor functional outcomes No significant difference in rate of delayed seizures, DCI, or poor functional outcomes was found between LEV- and PHT-treated patients; there was a high rate of crossover from PHT to LEV

Kim et al., 2015[48]	Prospective, observational	$N = 30$	Not reported	FosPHT 100%	FosPHT LD 20 mg/kg phenytoin equivalent at a rate of 150 mg/min PHT MD 300–350 mg/day × 24 hours Concomitant benzodiazepine or add-on AED was used if deemed clinically indicated No ADRs with FosPHT load	FosPHT levels at 0 min, 20 min, and 24 hours post-infusion of LD Most patients had supratherapeutic phenytoin levels for up to 20 minutes following loading with FosPHT, and loading was generally well-tolerated
Lin et al., 2008[11]	Retrospective	$N = 137$	Overall: 15% Onset: 3.6% Early: 5.8% Late: 5.8%	T 15% received AEDs PHT, PHB, VPA, gabapentin	81% received PHT Remaining patients received PHB, VPA, gabapentin, or PHT + VPA combination Doses not reported 43% of AED-treated patients experienced >1 ADR (rash, thrombocytopenia, anemia, abnormal LFTs, dyspepsia, ataxia, gingival hyperplasia)	Factors associated with seizures Outcomes associated with seizures Higher mean WFNS on presentation was predictive of seizures, but seizures were not predictive of poor functional outcomes at 1 year post-SAH
Lin et al., 2003[14]	Retrospective	$N = 217$	Overall: 21.2% Onset: 7.8% Preop: 2.3% Postop: 1.8% Late epilepsy: 6.9%	All patients received AED on admission 1st line: PHT 2nd line: CBZ, VPA	AED continued until 2–3 weeks postop if no further seizures occurred	Factors associated with seizures and development of epilepsy Outcomes associated with seizures Onset seizures were a significant predictor of persistent neurological deficits; perioperative seizures did not appear to predict the development of epilepsy
Little et al., 2007[35]	Retrospective	$N = 389$	NCSE: 3%	T (for NCSE) Unclear if other patients received AEDs PHT/FosPHT, LEV, PHB 2nd line: lorazepam or PHB infusion	Not reported	Factors associated with NCSE Mortality rate Control of NCSE required combination AED therapy, and NCSE was associated with significant morbidity and mortality
Mink et al., 2011[27]	Prospective, observational	$N = 35$ Included only patients with onset seizures and/or high risk for seizures	N/A	All patients received AED therapy with either IV LEV or IV VPA	Target dose for both LEV and VPA was 3 g/24 hours $n = 1$ discontinued VPA because of elevated LFTs	Rate of switching to another AED from VPA and from LEV Pharmacokinetic interactions with VPA and with LEV Conversion from IV to PO liquid LEV resulted in a reduction in plasma concentration; VPA concentrations decreased significantly when meropenem was given concomitantly
Murphy-Human et al., 2011[15]	Prospective, observational	$N = 442$ ($N = 297$ before protocol change; $N = 145$ after protocol change)	Overall: 12.4% In-hospital seizures: PHT group: 3.4% LEV group: 8.3% Late: PHT: 2% LEV: 5.5%	All patients received AED on presentation: 67% PHT 33% LEV	PHT LD 15–20 mg/kg IV; then PO MD not specified Continued PHT for duration of hospitalization LEV protocol: 500 mg PO BID × 3 days; extended beyond 3 days if patient experienced seizures 40% of PHT-treated patients were switched to LEV because of ADRs	Comparison of seizure incidence between patients treated with LEV and with PHT The rate of late seizures but not early seizures was significantly higher in patients treated with 3 days of LEV compared to an extended course of PHT
Naidech et al., 2005[22]	Prospective, observational	$N = 527$	Onset: 10% In-hospital seizures: 5%	All patients received AED on admission PHT	PHT LD 20 mg/kg Continued on PHT MD 5 mg/kg/day Duration of PHT therapy at the discretion of the attending physician	Relationship between "phenytoin burden" and functional outcomes Increased PHT burden was associated with worse functional outcomes at 14 days but not at 3 months post-SAH
Panczykowski et al., 2016[40]	Retrospective (propensity score matched analysis)	$N = 353$	Overall: 10% Onset: 4.5% Early: 3.4% Late: 1.7%	2005–2007 All patients received AED on admission: 81% PHT 19% LEV 2007–2010 No AEDs prophylaxis	PHT LD 1000 mg MD 100 mg every 8 hours LEV 1000 mg every 12 hours Duration 7–30 days	Comparison of seizure incidence between patients receiving AEDs prophylaxis vs. no prophylaxis AED prophylaxis did not influence incidence of seizures following an SAH
Pinto et al., 1996[12]	Prospective, observational	$N = 253$	Onset: 6.3%	T Most commonly PHT	PHT 300 mg/day	Factors associated with seizures Outcomes associated with seizures Rebleeding and severe disability or mortality at discharge were more common in patients with onset seizures; however, onset seizures were not a predictor of prognosis
Raper et al., 2011[21]	Retrospective	$N = 161$	Onset: 17% Early: 2% Late: 13%	P and T both used 57% received AED PHT; other AEDs not reported	5.8% of patients required switching or cessation of AED therapy due to ADRs Most common cause: elevated LFTs	Association(s) between timing of AED prophylaxis initiation and incidence of seizures The timing of AED therapy did not have an effect on the incidence of late or early seizures

Table 1. *Continued*

First author, year of publication	Study design	Study population	Seizure incidence	Percentage given AED	AED dose/duration, adverse effects	Outcomes assessed, main finding(s)
Rejdak et al., 2008[47]	Case report	$N = 1$	N/A	N/A	Patient received phenytoin infusion at 15 mg/kg along with diazepam 10 mg × 2 Then, VPA LD 30 mg/kg; then MD 5 mg/kg/min infusion	Resolution of patient case and cessation of refractory seizure activity VPA successfully aborted seizures in a patient following failure of PHT and diazepam
Rhoney et al., 2000[19]	Retrospective	$N = 95$	Pre-hospital: 17.9% In-hospital: 4.1% Post-hospital: 8%	P and T both used 99% of patients received AED 45% of patients were discharged home on AED therapy: 74% PHT 19% CBZ 5% PHT + CBZ 2% CBZ + PHB Most common outpatient AED therapy: PHT followed by CBZ; then VPA	73% received PHT mean LD 13.1 mg/kg and then 99% received MD of 4.8 mg/kg Inpatient AED therapy given for median 12 days. ADRs occurred in 4.1%: CNS effects and rash	Factors associated with seizures Outcomes associated with seizures Effects of phenytoin therapy on seizures The majority of seizures occurred prior to presentation at hospital; thickness of cisternal clot was the only factor associated with seizures, and seizures did not appear to adversely affect outcomes
Rush et al., 2016[53]	Retrospective cohort analysis	$N = 12{,}647$	Overall: 10%	Not reported	Not reported	The impact of seizures on outcome in SAH patients Seizures in SAH are associated with increased mortality
Shah et al., 2009[32]	Retrospective	$N = 176$	Onset: 2.8%	All patients received PHT within 24 hours of symptom onset Switched to LEV if experienced ADR to PHT	PHT given as LD 20 mg/kg; then MD 5–7 mg/kg/day LEV given at 1500 mg BID (route not specified) 39.8% of patients switched from PHT to LEV, 81% of whom switched due to ADRs to PHT	Comparison of seizure incidence and ADRs between patients treated with LEV and PHT LEV appears to be better tolerated than PHT in patients with SAH
Spencer et al., 2011[45]	Prospective, open-label	$N = 10$	No patients experienced any seizures for the duration of the study	LEV 100%	LEV 500 mg IV Q12H No patients experienced ADRs from LEV that required discontinuation of therapy	Monte Carlo simulation to determine levetiracetam regimen most likely to achieve levels within defined reference range Dosing regimens with total daily doses of 3–4 g of LEV were the most likely to produce LEV trough concentrations within the suggested reference range
Sundaram et al., 1986[17]	Retrospective	$N = 131$	Overall: 24% Early: 20% Late 3.8%	Not reported	Not reported	Relationship between early and late seizures Early seizures did not appear to predict the occurrence of late seizures
Szaflarski et al., 2010[42]	Prospective, randomized, single-center, single-blinded	$N = 52$ Mainly TBI (6 SAH patients)	Early: 15%	All patients received AED: 65% LEV 35% PHT	PHT: LD 20 mg/kg; then MD 5 mg/kg IV Q12H LEV: LD 20 mg/kg; then MD 1000 mg IV Q12H All patients received AED therapy for 7 days; continued beyond 7 days if patient experienced seizures	Comparison of seizure incidence, functional outcomes, and ADRs between patients treated with PHT and LEV Patients treated with LEV appeared to have better long-term outcomes than those treated with PHT
Szaflarski et al., 2007[54]	Retrospective	$N = 102$	Not reported	All patients received AED: 35% LEV Other: PHT and others (not specified)	LEV: 500 mg BID × 1–3 days; then increase to 1000 mg BID PHT dosing not reported	Comparison between patients treated with LEV and PHT Treatment with LEV monotherapy was associated with fewer complications and shorter NSICU stay compared to other AEDs
Taylor et al., 2011[28]	Retrospective	$N = 26$	Overall: 2.4%	71% LEV 29% PHT	LEV 500–2000 mg/day PHT LD 15–20 mg/kg; then MD tailored to maintain therapeutic PHT levels	Comparison of seizure incidence and functional outcomes between patients treated with LEV and PHT Patients treated with LEV had a lower seizure incidence and better functional outcomes at discharge compared to patients treated with PHT
Yoon et al., 2015[37]	Retrospective	$N = 84$ Only included Hunt–Hess grades I - III without onset seizures	No seizures occurred during admission or at 6-month follow-up	P 52% received AED: 20% VPA 80% LEV	LEV 1000 mg/day VPA 900 mg/day Prescribed for at least 6 months (range 6–12 months)	Comparison of seizure incidence and functional outcomes between AED-treated and non-AED-treated patients Factors associated with poor functional outcomes No statistically significant differences in outcomes at discharge or 6-months post-SAH between AED-treated and non-AED-treated patients

Prophylaxis (P) refers to patients who were given AED therapy prior to any known seizure activity (including onset seizures). Treatment (T) refers to AED therapy initiated after any seizures (including onset) occurred.
ADR = adverse drug reaction; AED = antiepileptic drug; BID = twice daily; BP = blood pressure; CBZ = carbamazepine; DCI = delayed cerebral ischemia; DRS = disability rating scale; FosPHT = fosphenytoin; GOS = Glasgow Outcome Scale; GOSE = Glasgow Outcome Scale extended; ICH = intracranial hemorrhage; ICU = intensive care unit; LD = loading dose; LEV = levetiracetam; LFT = liver function test; LOS = length of stay; MD = maintenance dose; mRS = modified Rankin Scale; NCSE = nonconvulsive status epilepticus; NSICU = neuroscience intensive care unit; PHB = phenobarbital; PHT = phenytoin; PO = by mouth; QoL = quality of life; SE = status epilepticus; TID = three times daily; VPA = valproic acid or valproate; WFNS = World Federation of Neurological Surgeons.

findings regarding the association between onset seizures and negative outcomes. One study reported an association between onset seizures and increased risk of late seizures,[13] while several others have observed no such association.[7,8,14,15,19] Onset seizures have also been reported to be associated with disability at 6 weeks post-SAH, persistent neurological deficits more than 2 years post-SAH, rebleeding, and mortality.[12-14] In contrast, others have not found any link between onset seizures and rebleeding, residual deficits (though the authors' definition of "deficit" vs. "no deficit" was unclear), or mortality.[10] In addition, another study found that almost 70% of patients with onset seizures actually had favorable outcomes at follow-up, despite having identified an association between onset seizures and poor World Federation of Neurological Surgeons (WFNS) grade on admission.[9] The authors hypothesized that onset seizures distort patients' clinical picture on admission, resulting in an erroneously poor WFNS grading. Some researchers have proposed that onset seizures are merely a marker of SAH severity and that the associated deficits occur as a result of degree of acute insult, not due to seizure activity.[13,14] Study and population heterogeneity, variability in defining and identifying seizures, and small sample sizes with correspondingly low event rates may be potential explanations for the conflicting findings.

Post-Admission Seizures

The overall reported rate of postadmission seizures in SAH have ranged from 0 to 31%.[7,9-11,14,15,17,20,24-26,28,29,33-37] The highest reported rate (31%) was observed by Dennis et al.[29] in patients with nonconvulsive seizures detected by electroencephalogram (EEG). On the other hand, the study that did not report any seizures excluded patients with onset seizures and included only patients with SAH Hunt–Hess grades of I to III.[37] This finding raises the question of whether AED prophylaxis is beneficial in low-grade SAH patients presenting without onset seizures. Several studies have reported worse outcomes with postadmission seizures. One study of 402 patients, more than half of whom had a Hunt–Hess grade of IV or V, identified a relationship between increased seizure burden (hours of epileptic activity detected on EEG) and unfavorable cognitive and functional outcomes. Every 1 hour of seizure activity was associated with 1.1 times higher odds of disability or mortality at 3 months.[24] These findings encourage the use of cEEG in poor-grade SAH patients with risk factors for nonconvulsive status epilepticus (NCSE), especially when NCSE has been reported to be associated with very poor prognosis and high mortality rates (82–100%).[29,35,38] Associations between postadmission seizures and aneurysm rebleeding,[10] longer hospital length of stay (LOS),[15,19] and mortality at 12 months have also been observed.[38] On the other hand, some studies have found no association between seizures and poor Glasgow Outcome Scale (GOS) score at 1 year post-SAH,[11] or poor functional outcomes.[16,20]

Epilepsy

Post-SAH epilepsy is an important outcome in the SAH population given its link to functional disability, poor quality of life, and increased anxiety.[38] The reported incidence has ranged from 3.1 to 13%.[7,14,16,38] Although Huttunen et al.[16] found that acute seizures (within 7 days of initial hemorrhage) were a risk factor for development of epilepsy, the remainder of the studies did not find a similar association,[7,11,14,36,38] suggesting that long-term AED therapy following SAH may not be necessary.

Risk Factors of Seizures Following SAH

Several factors have been found to be associated with seizures following an SAH. Table 2 summarizes the risk factors for seizures and epilepsy in SAH patients.

Is Seizure Prophylaxis Needed?

Historically, most patients presenting with an SAH would receive AED therapy in an effort to avoid the apparent harmful effects of seizures.[7,13,14,19,39] However, growing evidence of poor outcomes with AED therapy has made clinicians more hesitant to initiate AED prophylaxis, and this was reflected in the most recent SAH guidelines.[1,39] For example, one study that found poor long-term outcomes in patients who developed epilepsy by 12 months post-SAH (94% of whom were on AED therapy) suggested that the negative outcomes could be a result of the epilepsy itself or of the adverse effects from the AEDs used to treat the epilepsy.[38] Additionally, two retrospective studies did not find a difference in seizure incidence with AED prophylaxis.[21,40] Therefore, the role of AEDs in preventing seizures in patients with an SAH remains unclear, especially considering the shortfalls of retrospectively gathered observational data, which comprises the majority of the findings. Therefore, weighing the benefits of preventing detrimental outcomes associated with seizures against the risks of adverse effects of AEDs and their potential long-term sequelae might need to be considered. Generally, seizure prophylaxis is not warranted given the currently available evidence. However, an awareness of the risk factors for seizures (Table 2) may aid in determining which patients are most likely to benefit from seizure prophylaxis following an SAH. In addition, identification of patients with risk factors for epilepsy may aid in deciding about in which patients long-term AED therapy might be indicated.

Choice of Antiepileptic Drugs for Seizures Following an SAH

The choice of initial AED therapy in SAH is a subject of great debate due to a lack of quality prospective data to guide such a decision.[4] Though most studies have specified which AEDs were used, some have reported outcomes in general terms of AED-treated versus non-AED-treated patients. In studies that specified AED use, selection of AED has been variable. Phenytoin, fosphenytoin, phenobarbital, levetiracetam, valproic acid, carbamazepine, zonisamide, and topiramate have been reported in the SAH population (Table 1). The advantages must be weighed against the disadvantages unique to each AED in the context of an SAH when selecting appropriate AED therapy. Phenobarbital use has generally fallen out of favor as a first-line agent, as newer, safer, and less-sedating AEDs have been developed. Carbamazepine has been used in a few studies,[7,14,19] but the evidence for its use is scarce, and it is not easily or quickly loaded in emergency situations.[41] Phenytoin, levetiracetam, and valproic acid appear to be the most-studied agents in the SAH literature, and these will be discussed in detail below.

Phenytoin

Phenytoin, a hydantoin group compound, was one of the first AEDs discovered and approved for use in 1953. Phenytoin can be given enterally (by various formulations) or parenterally. Phenytoin has the advantage of being able to be loaded rapidly to

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Table 2: Number of studies identifying risk factors for different types of seizures post-SAH

Risk factors	Onset seizures	Postadmission seizures (including NCSs)	NCSE	Epilepsy
Demographics				
Female sex		1[24]	1[35]	
Male sex		1[19]		
Older age		1[24]	2[29,35]	
Age < 40 years	2[7,14]			
Presentation				
Amount of blood on initial CT scan (e.g., Fisher score of III to IV)	4[7,12-14]	3[16,19,26]	1[35]	3[7,16,36]
Higher Hunt–Hess score	2[7,12]		2[29,35]	
Loss of consciousness at ictus	2[8,14]			1[14]
WFNS grade	1[9]	1[11]		
MCA location of aneurysm	1[8]			
Intraventricular hemorrhage		1[16]		
Subdural hematoma		1[26]		1[38]
Complications				
Hydrocephalus/CSF shunt/drain	1[7]	1[8]	1[29]	
Rebleeding	1[7]	2[10,13]		1[36]
Hemiparesis	1[12]			
Cortical infarction				2[7,38]
Abnormal cerebral angiogram			1[35]	
Cerebral edema			1[29]	
Seizures				
History of seizures prior to admission		1[8]		
Onset seizures		1[13]		
Acute seizures within 1 week of SAH				1[16]
GOS score 2-4				1[14]

CSF = cerebral spinal fluid; CT = computerized tomography; GOS = Glasgow Outcome Scale; ICH = intracranial hemorrhage; MCA = middle cerebral artery; NCSE = nonconvulsive status epilepticus; NCSs = nonconvulsive seizures; WFNS = World Federation of Neurological Surgeons scale.

achieve steady-state concentrations in emergency situations. Historically, phenytoin was the most commonly used AED in SAH for many years. In studies that reported the use of phenytoin in SAH, the proportion of patients who received phenytoin ranged from 17 to 100%.[7,15,18-20,25,26,28,42] Though many studies have reported using phenytoin in patients, they did not elaborate on the effects of phenytoin on seizure frequency or further outcomes. In a study where 95% of the patients were treated with phenytoin and 67% had "therapeutic levels," 4.5% experienced seizures.[18] The authors found no association between total duration of postoperative AED therapy and risk of late seizures, and they concluded that patients might benefit from therapeutic levels of anticonvulsant drugs in the immediate postoperative period following an SAH. Similarly, in another study where 88% of the study population received AED therapy "mostly" with phenytoin, 4.1% of the entire population experienced late seizures.[13]

The duration of phenytoin therapy was studied by Chumnanvej et al.[25] They compared patients treated with a phenytoin loading dose (LD) of 1000 mg followed by a maintenance dose (MD) of 100 mg three times daily from admission until discharge (as per the institutional protocol prior to 1999), to patients treated with a 3-day course (based on a change in the protocol in 1999). Serum phenytoin levels were not monitored, and so it is unclear if patients were receiving appropriately therapeutic doses. The incidence of seizures and mortality rate did not differ between the two groups; however, there was a significant reduction in occurrence of adverse effects in patients who received the 3-day course of phenytoin. This led the authors to conclude that a 3-day course of phenytoin "prophylaxis" is sufficient for patients with an SAH. Further, Naidech et al.[22] published findings that raised concerns about the use of phenytoin in patients with an SAH. Patients with SAH were appropriately loaded with phenytoin on admission and continued on maintenance doses of 5 mg/kg/day, and those with a higher "phenytoin burden" (defined as the patient's average serum phenytoin level multiplied by the duration of phenytoin therapy to a maximum of 14 days) were found to be more likely to have poor functional and cognitive outcomes at 14 and 30 days post-SAH than those with a lower burden.

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Many adverse effects attributed to phenytoin have been reported, ranging from 4 to 81%.[11,15,19,32] Reported adverse reactions in addition to difficulty maintaining therapeutic serum levels include difficulty optimizing cognitive recovery, rash, thrombocytopenia, anemia, abnormal liver function tests, ataxia, and fever.[11,20,32] When adverse effects were observed more frequently in patients treated with phenytoin compared to levetiracetam, a corresponding crossover rate to levetiracetam ranging from 40 to 66% has been reported.[20,32] These findings suggest that patients may tolerate levetiracetam better than phenytoin. Furthermore, clinicians need to be aware of the many significant drug/drug interactions involving phenytoin. Phenytoin is a strong inducer of CYP 2C and 3A, which are both responsible for the metabolism of many other medications. Such enzyme induction often results in a clinically significant decrease in serum levels of other medications, which may in turn warrant a dose increase or even contraindicate the use of one or another drug. Of importance in SAH is the interaction between phenytoin and nimodipine. Phenytoin induces the metabolism of nimodipine, which has been shown to result in an 86% reduction in nimodipine exposure.[43] Although this finding has been reported in non-SAH patients on long-term phenytoin therapy, enzyme induction may occur as early as 4 days following initiation of phenytoin therapy, and that is within the highest risk period for DCI in most SAH patients.[44]

Levetiracetam

The body of evidence for levetiracetam use in SAH is growing. Levetiracetam is available as oral and parenteral formulations and can be rapidly loaded. The parenteral formulation is not manufactured in Canada but can be obtained through the Health Canada Special Access Program. Levetiracetam displays linear elimination kinetics; therefore, dose changes produce relatively predictable changes in serum concentrations. In addition, levetiracetam has minimal drug/drug interactions.[41]

Several studies have compared the use of phenytoin and levetiracetam in patients with SAH.[15,20,28,32,42] A trend toward similar or lower seizure incidence has been reported in levetiracetam-treated patients.[20,28,32,42] On the other hand, Murphy-Human et al.[15] reported a higher rate of late seizures in levetiracetam-treated patients compared to phenytoin. However, the dose given was 500 mg twice daily, which may arguably be considered "subtherapeutic" in light of an analysis of levetiracetam elimination kinetics in neurocritical care patients (see the next section).[45] The mild and tolerable side effects of levetiracetam have also been shown to favor its use over phenytoin. Several studies have shown a lower incidence of such adverse effects as gastrointestinal upset, worsened neurological status, elevated liver function tests, thrombocytopenia, and fever in patients treated with levetiracetam compared to phenytoin,[32,42] as well as a high rate of crossover from phenytoin to levetiracetam.[15,20,32] Given the retrospective nature and low power of most of the studies, conflicting findings have been reported. While improved GOS scores and functional outcomes following discharge have been reported in patients treated with levetiracetam compared to phenytoin,[28] other researchers have found no difference in functional outcomes, hospital length of stay, and mortality.[15,20,42]

An appropriate duration of levetiracetam following an SAH has yet to be determined. A study[15] comparing a three-day course of levetiracetam to an extended course of phenytoin found a higher incidence of late seizures in the levetiracetam group. However, it is difficult to ascribe the difference in late seizure incidence to subtherapeutic dosing, inadequate duration of therapy, or possibly both. To follow up, a recent randomized open-label study[46] presented as a conference abstract compared a three-day course of levetiracetam to an extended course in patients with an SAH. Interestingly, these results showed that the extended course of levetiracetam was associated with worse functional outcomes than the three-day course. Furthermore, a post-hoc analysis of a recent retrospective study reported that levetiracetam prophylaxis may be associated with a higher risk of delayed neurological deficits than no prophylaxis.[40] This contributes to the evidence suggesting that seizure prophylaxis may contribute to detrimental outcomes.

Valproic acid

Several studies have reported the use of valproic acid (VPA) in patients with an SAH.[7,9,27,37,47] In a small prospective trial comparing the use of VPA to levetiracetam in SAH,[27] no difference was observed in the incidence of seizures between the two groups.[27] However, 65% of patients on VPA were switched to another AED, whereas only 22% of patients on levetiracetam required switching. The reasons for switching included having plasma concentrations below the reference range, occurrence of seizures, elevated liver function tests, or evidence of clinical coagulopathy. Another study,[7] where 72% of AED-treated patients received VPA, reported an incidence of adverse effects of 23% among the AED-treated patients (e.g., rash, fever, dizziness, thrombocytopenia, hepatitis, hypotension, and vasospasm). Based on very limited evidence, VPA appears to be associated with a higher incidence of adverse effects than levetiracetam. If further use of VPA in SAH is to be considered, then prospective research comparing its efficacy and safety to other AEDs (such as phenytoin or levetiracetam) would be warranted. However, VPA could be useful as a second-line agent to control refractory seizures.[47]

In conclusion, phenytoin has been used most commonly in SAH, though its use has been linked to poor long-term cognitive outcomes and increased rates of adverse drug reactions. Studies comparing the use of levetiracetam and phenytoin in SAH have reported mixed findings regarding seizure occurrence, but many have suggested that levetiracetam is better tolerated than phenytoin.

Dosing and Monitoring Antiepileptic Drugs in SAH

Phenytoin Dosing and Monitoring

Kim et al.[48] explored the pharmacokinetics of fosphenytoin loading in patients with SAH. They found that total phenytoin serum concentrations remained above the reference range upper limit of 80 μmol/L in 28/30 patients for the first 20 minutes following infusion of a 20-mg/kg dose over 150 mg/min. The mean serum concentration at 24 hours following the loading dose was 48 μmol/L (reference range = 40–80 μmol/L). Although 4 patients experienced a drop in mean blood pressure greater than 20 mmHg, none experienced serious adverse reactions.[48] Similarly, Rhoney et al.[19] reported that, following administration of a mean loading dose of 13.1 mg/kg, 20% of patients had supratherapeutic phenytoin levels (>80 μmol/L), 50% were within the reference range, and 30% were subtherapeutic (<40 μmol/L). Subtherapeutic phenytoin levels were not associated with in-hospital seizures. In addition, patients who received a loading dose were less likely to

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have seizures than those who did not. Based on that, regular phenytoin initial dosing is suggested in SAH patients.

Phenytoin displays nonlinear Michaelis–Menten kinetics, meaning that the rate of elimination is dose-dependent: as the dose increases, the rate of phenytoin metabolism becomes saturated and the elimination half-life increases.[41] As a result, small dose changes yield disproportionate and unexpected changes in serum concentrations. This, combined with large interindividual variability, warrants meticulous monitoring of serum phenytoin levels in addition to clinical/EEG monitoring of patients.

Levetiracetam dosing and monitoring

Augmented renal clearance (ARC), defined as a creatinine clearance (CrCl) exceeding 130 ml/min, has been reported in patients with an SAH, given the young age at onset.[49,50] Levetiracetam renal clearance has been reported to be directly related to creatinine clearance in SAH, resulting in a need for higher than regular doses to achieve seizure control in patients with ARC.[45] A Monte Carlo simulation conducted by Spencer et al.[45] based on pharmacokinetic data obtained from 12 patients (10 of whom had an SAH) showed that the regimen most likely to achieve serum levetiracetam levels within the suggested reference range (6–20 μg/mL) was 1000 mg IV Q8H. In addition, the regimen least likely to achieve levels within the reference range was 500 mg IV Q12H. Furthermore, Drust et al.[49] reported an SAH patient who required a total levetiracetam daily dose of 4 g to maintain therapeutic levels and remain seizure-free. This has been attributed to the patient's ARC (CrCl ~ 160 mL/min).

In addition to enhanced levetiracetam clearance, it seems that the oral bioavailability of levetiracetam may also be reduced, further affecting drug exposure. It has been reported that switching intravenous levetiracetam to an oral liquid in SAH patients resulted in a mean decline of 30% in levetiracetam plasma concentrations.[27] The authors hypothesized that critically ill patients may have altered absorption of the medication, suggesting that clinicians might consider increasing the dose of levetiracetam by 30% when converting from parenteral to oral liquid dosing.[27] Further evaluation of the pharmacokinetics of levetiracetam in patients with an SAH is needed. Until then, clinicians choosing to use levetiracetam in this setting may consider an initial regimen of 1000 mg IV/PO Q8–12.[45]

Monitoring levetiracetam concentrations is generally unnecessary given its linear and predictable pharmacokinetics and minimal drug interactions. However, given the altered pharmacokinetics in the SAH population, serum levetiracetam level may be of value, especially in patients with refractory seizures. In addition to clinical/EEG monitoring, close monitoring of renal function in patients on levetiracetam is essential given its renal elimination. The adverse effects of levetiracetam are minimal, with sedation being the most common—and usually transient. The more rare psychiatric and behavioral side effects should serve as a precaution for use in patients with preexisting psychiatric comorbidities.[51]

Conclusions

The current evidence is largely derived from retrospective and observational data and thus has limited validity due to unaccounted-for biases and confounders. However, clinicians are left with the available evidence on which to base their decisions. Given the reported adverse outcomes associated with AED use, seizure prophylaxis is not warranted; however, it might need to be considered in SAH patients with risk factors for seizure recurrence. The duration of AED therapy remains a point of debate, but it seems that continuation of AEDs post-discharge is not strongly supported unless the patient develops post-SAH epilepsy. Levetiracetam appears to be better tolerated than phenytoin in SAH patients. Ideally, a randomized controlled trial comparing the use of phenytoin, levetiracetam, and placebo in SAH powered to detect a meaningful difference in seizures and adverse effects would provide a more clear direction for deciding which AED is best to use in patients with SAH. Also, the utility of other AEDs in SAH has not as yet been explored. In addition, further studies are needed to characterize and confirm levetiracetam pharmacokinetics in SAH patients.

Disclosures

The authors do not have anything to disclose.

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