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Special Article

CME

Practice parameter: Antiepileptic drug prophylaxis in severe traumatic brain injury

Report of the Quality Standards Subcommittee of the American Academy of Neurology

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Abstract—*Objective:* To review the evidence regarding antiepileptic drug (AED) prophylaxis in patients with severe traumatic brain injury (TBI) in order to make practice recommendations. *Methods:* The authors identified relevant studies by searching multiple databases and reviewing reference lists of other sources. They included studies that prospectively compared post-traumatic seizure rates in patients given AED prophylaxis vs controls. Each study was graded (class I to IV) according to a standard classification-of-evidence scheme and results were analyzed and pooled. *Results:* Pooled class I studies demonstrated a significantly lower risk of early post-traumatic seizures (those occurring within 7 days after injury) in patients given phenytoin prophylaxis compared to controls (relative risk 0.37, 95% CI 0.18 to 0.74). Pooled class I and class II studies demonstrated no significant difference in the risk of late post-traumatic seizures (those occurring beyond 7 days after injury) in patients given AED prophylaxis compared to controls (relative risk 1.05, 95% CI 0.82 to 1.35). Serum AED levels were suboptimal in these studies and adverse effects were mild but frequent. *Conclusions:* For adult patients with severe TBI, prophylaxis with phenytoin is effective in decreasing the risk of early post-traumatic seizures. AED prophylaxis is probably not effective in decreasing the risk of late post-traumatic seizures. Further studies addressing milder forms of TBI, the use of newer AEDs, the utility of EEG, and the applicability of these findings to children are recommended.

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The Quality Standards Subcommittee (QSS) of the American Academy of Neurology (AAN) is charged with developing practice parameters for neurologists for diagnostic procedures, treatment modalities, and clinical disorders. Practice parameters are strategies for patient management that assist physicians in clinical decision-making. They comprise one or more recommendations based on analysis of evidence on a specific clinical problem. This report addresses the prophylactic use of antiepileptic drugs (AEDs) in patients with severe traumatic brain injury (TBI).

TBI is a common neurologic disorder, accounting for about 1.1 million emergency department visits and one hospitalization per 1,000 people each year in the United States.[1,2] Among all patients with head trauma who seek medical attention, about 2% develop post-traumatic seizures, although the number varies widely depending primarily on injury severity. About 12% of patients with severe TBI develop post-traumatic seizures, and the rate may be more than 50% for those with penetrating missile injuries.[3-5]

The use of AEDs to treat patients who have developed post-traumatic epilepsy is standard. However, the important question of whether to use AEDs prophylactically after TBI to prevent the development of post-traumatic seizures is unanswered. The development of seizures is both physically and psychologically debilitating, complicates acute management

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and subsequent rehabilitation, and contributes to the substantial cost associated with the care of the head-injured patient. However, the prophylactic use of AEDs carries with it the risk of adverse effects that may be especially disabling in this population.

There is substantial variability among clinicians in the practice of post-traumatic seizure prophylaxis. Two surveys of neurosurgeons reported that a majority prescribed AEDs for seizure prophylaxis at least some of the time, although the indications, choice of drug, and duration of treatment varied widely.[6,7] Similar variability was seen in the care of head-injured patients referred to a rehabilitation center.[8]

Published studies have addressed the issue of post-traumatic seizure prophylaxis, although they differ both in their methods and findings. We performed a systematic review and analysis of the literature on this topic and propose recommendations for the use of AED prophylaxis after severe TBI, based on the standard classification schemes of the AAN QSS.

Methods. We searched Medline, Science Citation Index, the Cochrane Database, and Current Contents by combining the search terms "head trauma," "head injury," or "brain injury" with the terms "seizure" or "epilepsy" (including all related terms and subheadings). A total of 928 references were identified in our search, updated as of November 2001. We screened these titles and found 125 that addressed either post-traumatic seizures or the use of AEDs in prophylactic settings. We reviewed the abstracts of these references to find those that reported on the clinical use of post-traumatic seizure prophylaxis in humans.

Fifty-four full-length articles were initially examined, as well as 12 others identified by reviewing the reference lists of the initial articles found and those of relevant review articles, meta-analyses, and book chapters. We selected studies that met the following eligibility criteria: 1) prospective design; 2) random or nonrandom assignment of TBI patients to a group receiving AED prophylaxis or a control group (placebo use not required); 3) reporting of post-traumatic seizure rates in the treated and control groups; and 4) publication in a peer-reviewed journal in any language (abstracts or publications reporting preliminary data only were excluded). In cases in which multiple publications reported ongoing results from the same study, we used the publication with the most complete data and longest duration of follow-up.

All studies meeting our criteria enrolled only patients considered by the studies' authors to have severe TBI (typically with loss of consciousness or amnesia for more than 12 or 24 hours, intracranial hematoma, depressed skull fracture, and/or brain contusion present on CT scan). This included patients with both penetrating and closed types of head injury. Also, all studies distinguished between early post-traumatic seizures (those occurring within and inclusive of 7 days of injury) and late seizures (those occurring thereafter). For each study, we extracted details on methodology and findings to the extent available in the publication. We then graded the quality of evidence provided by each study using the classification-of-evidence scheme in Appendix 1. Class I studies are judged to have a low risk of bias and class IV studies are judged to have a high risk of bias. The grading of each study was performed by consensus between the authors.

For each study, we compared the proportion of patients with early or late post-traumatic seizures in the treated group to that in the control group by calculating the relative risk (RR) and a 95% CI. When the appropriate data were available in the publication, we calculated these RRs based on intention to treat, analyzing all patients assigned to each treatment group as if they actually received that treatment. Comparisons between treated and control groups were performed using Fisher's exact test. When necessary, we pooled data from multiple studies to obtain more precise RRs, using general variance-based meta-analytic techniques.[9] Although there are limitations to the conclusions that can be drawn from combined evidence, we began by pooling class I studies first to minimize the risk of bias in our pooled comparisons.

We developed practice recommendations based on our analysis of the data according to the scheme in Appendix 2. Stronger recommendations were made when evidence showing a consistent and significant effect was derived from studies with lesser risks of bias. When combined evidence was used, we downgraded the strength of our recommendation to that appropriate for the lowest class of evidence (that with the highest risk of bias) included among the pooled studies.

Results. *Does AED prophylaxis decrease the risk of developing early seizures (those occurring within 7 days) in patients with severe TBI?* Study characteristics. Four eligible studies addressing the issue of early seizures were identified (table 1).[10-13] Two randomized placebo-controlled studies with masked assessment, both evaluating phenytoin given initially by IV load, were graded class I.[10,11] One study comparing carbamazepine to placebo was graded class II because treatment assignment was performed using a quasi-random method, based on patient birthdate.[12] One study comparing phenytoin to no treatment was graded class III because of nonmasked assessment.[13]

Prophylactic effect. One of the class I studies demonstrated a significantly lower rate of early post-traumatic seizure development among the group treated with prophylactic AEDs compared to the placebo group, with an RR of 0.25 (figure 1).[11] The other class I study, which evaluated a similar phenytoin regimen in a smaller but similar cohort, found no significant difference.[10] The latter study, however, reported a rate of early seizures in the placebo group of only 3.7%, which is much lower than the rates seen in other studies. Because the absolute seizure rates are so low in this study, the 95% CI for the RR

Table 1 *Prospective controlled studies of antiepileptic drugs (AED) for the prophylaxis of early post-traumatic seizures*

Reference	Class	Random	Masked	Placebo	Cohorts		Follow-up rate (at 1 wk), %	AED	Early seizure rate, %		RR (95% CI)
					AED	Control			AED	Control	
Young et al.[10]	I	Yes	Yes	Yes	137	108	100	DPH	3.6	3.7	0.99 (0.27, 3.58)
Temkin et al.[11]	I	Yes	Yes	Yes	208	196	94.6	DPH	3.4	13.3	0.25 (0.11, 0.57)
Glötzner et al.[12]	II	Quasi	Yes	Yes	75	76	100	CBZ	10.7	28.9	0.37 (0.18, 0.78)
Pechadre et al.[13]	III	Quasi	No	No	34	52	100	DPH	5.9	25.0	0.24 (0.06, 0.98)

Random = use of randomized assignment to treatment group; Masked = use of masked assessment in determining outcomes; Placebo = use of placebo in the control group; RR = relative risk of early seizures (AED/control); DPH = diphenylhydantoin; CBZ = carbamazepine.

(0.27 to 3.58) is very wide. This suggests that the study was not sufficiently powered to detect a clinically important difference in the seizure rates between the treated and control groups.

The class II study evaluating carbamazepine found a significantly lower rate of early seizures among the AED-treated group (RR 0.37).[12] The class III study evaluating phenytoin also showed a significant difference (RR 0.24), although the CI was wide (0.06 to 0.98).[13]

Combined evidence. Because the CI for one of the two class I studies was so wide, we pooled the data from the two studies to calculate a pooled RR for class I studies. This demonstrated a significantly lower rate of early seizures among the pooled AED-treated group compared to the pooled control group, with an RR of 0.37 (95% CI 0.18 to 0.74; see figure 1).

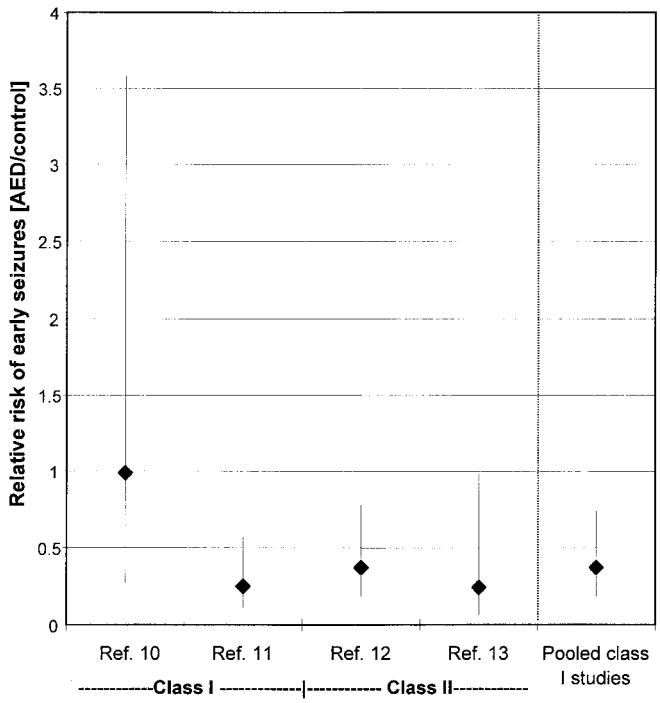

Figure 1. Outcomes of studies on prophylaxis of early post-traumatic seizures. AED = antiepileptic drugs.

Serum AED levels. All four studies addressing early seizures included testing of serum AED levels. In the class I study demonstrating a benefit of prophylaxis, 97% of phenytoin-treated patients had levels in or above the therapeutic range on the first day after injury, whereas 57% maintained such levels at 1 week.[11] All patients with early seizures had therapeutic levels on the day of their first seizure. In the class I study demonstrating no significant benefit of prophylaxis, more than 78% of patients maintained therapeutic levels through the first week, although only 60% of those who had an early seizure had a therapeutic level immediately afterward.[10]

In the class II study evaluating carbamazepine, average serum AED levels in the first week were in the therapeutic range.[12] In the class III study, levels were checked and doses adjusted accordingly but specific figures were not reported.[13]

Adverse effects. Few adverse effects specifically occurring within the first week of AED therapy were reported in these trials. In one class I study, 5.2% of patients stopped phenytoin and 9.2% stopped placebo in the first week owing to patient request or idiosyncratic and other reactions.[11] A secondary analysis of side effects in this cohort has been published separately.[14] The other class I study reported a rash in one patient during the first week of phenytoin therapy.[10] Neither the class II nor class III study commented on adverse effects.

Conclusions. An analysis using pooled evidence from two class I studies that evaluated phenytoin demonstrates a significantly lower rate of early post-traumatic seizures in patients given AED prophylaxis, compared to controls. Maintenance of therapeutic levels was suboptimal, but few adverse effects were reported. Therefore, using the scheme in Appendix 2, we conclude that prophylaxis with phenytoin in patients with severe TBI is *established as effective* in decreasing the risk of early post-traumatic seizures (those occurring within 7 days).

Does AED prophylaxis decrease the risk of developing late seizures (those occurring after 7 days) in patients with severe TBI? Study characteristics. Eight eligible studies addressing the issue of late seizures

Table 2 *Prospective controlled studies of antiepileptic drugs (AEDs) for the prophylaxis of late post-traumatic seizures*

Reference	Class	Random	Masked	Placebo	Cohorts		AED	Treatment duration	Follow-up duration	Follow-up rate, %	Late seizure rate, %		RR (95% CI)
					AED	Control					AED	Control	
McQueen et al.[15]	I	Yes	Yes	Yes	84	80	DPH	1 y	2 y	98.8	9.5	8.8	1.09 (0.41, 2.86)
Young et al.[16]	I	Yes	Yes	Yes	119	95	DPH (PB if not tolerated)	18 mo	18 mo	93.0	10.9	8.4	1.29 (0.56, 3.00)
Glötzner et al.[12]	II	Quasi	Yes	Yes	75	76	CBZ	2 y	2 y	92.0	18.6	26.3	0.78 (0.51, 1.22)
Temkin et al.[11]	II	Yes	Yes	Yes	208	196	DPH	1 y	2 y	76.0	21.2	17.0	1.25 (0.79, 1.96)
Temkin et al.[17]	II	Yes	Yes	Yes (after DPH for 1 wk)	247	132	VPA	1 mo or 6 mo	2 y	88.6	15.8	12.9	1.23 (0.72, 2.08)
Manaka et al.[18]	III	Yes	No	No	50	76	PB	2 y	5 y	NC	16.0	10.5	1.52 (0.61, 3.79)
Pechadre et al.[13]	III	Quasi	No	No	34	52	DPH	3 mo or 1 y	2 y	100	5.9	42.3	0.14 (0.04, 0.55)
Servit and Musil[19]	III	No	No	No	143	24	DPH + PB	At least 2 y	At least 8 y	73.7	2.1	25.0	0.08 (0.02, 0.31)

Random = use of randomized assignment to treatment group; Masked = use of masked assessment in determining outcomes; Placebo = use of placebo in the control group; RR = relative risk of late seizures (AED/control); DPH = diphenylhydantoin; PB = phenobarbital; CBZ = carbamazepine; VPA = valproate; NC = not calculable based on available data.

were identified (table 2).[11-13,15-19] In three cases, the studies also addressed the issue of early seizures within the same cohort of patients[11-13]; in one case late seizures were assessed in a subset of the cohort studied for early seizures.[16]

Two randomized placebo-controlled trials with masked assessment, both evaluating phenytoin, were graded class I.[15,16]

Three studies were graded class II. One, comparing phenytoin to placebo, was graded class II due to a 24.0% loss to follow-up at time of analysis at 2 years; this study was graded class I for the purposes of our early seizure analysis because only 5.4% of patients had been lost to follow-up at the end of the first week.[11] Another randomized placebo-controlled study with masked assessment evaluating valproate was graded class II because of an 11.4% loss to follow-up at 2 years.[17] This study compared patients given valproate for 1 month or 6 months to those given phenytoin for 1 week followed by placebo. We included this study in our late seizure analysis because the control group received placebo from 1 week onward. The third class II study used a quasi-random assignment method based on patient birthdate.[12]

Finally, three studies were graded class III because of nonmasked assessment.[13,18,19]

Prophylactic effect. Neither of the two class I studies demonstrated a significant difference in late seizure rates between the treated group and control group, although for both studies the 95% CI of the RRs was quite wide (figure 2).[15,16] In both studies the RR for late seizures was actually greater than 1.00 (that is, the treated group had a higher rate of late seizures than the control group), and the CI reached higher than 2.50. One of the two trials enrolled patients who met at least one criterion for severe TBI,[15]

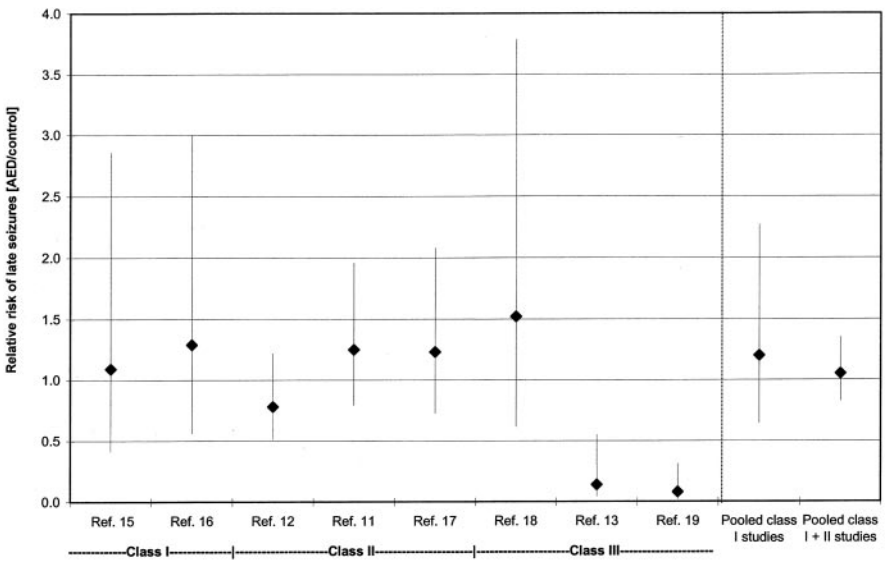

Figure 2. Outcomes of studies on prophylaxis of late post-traumatic seizures. AED = antiepileptic drugs.

whereas another enrolled patients estimated to have a >15% chance of developing late seizures, although the exact criteria by which this was determined were not reported.[16]

None of the three class II studies demonstrated a significant difference in the rate of late seizures between the treated and control groups. The carbamazepine study had high rates of late seizures in both treated and control groups, and an RR of 0.78.[12] The other class II studies both had RRs greater than 1.0.[11,17]

Finally, of the three studies graded class III, two demonstrated a significant decrease in late seizure rate among the treated patients compared to control patients.[13,19] These were the only studies we identified that reported such a difference. In one case the rate of late seizures in the control group was very high (42.3%) and AED prophylaxis reduced the late seizure rate substantially (RR 0.14).[13] In the other case the late seizure rate was more than 90% lower in the treated group (RR 0.08).[19] Neither of these studies employed truly random assignment, masked assessment, or the use of placebos in the control group. The third class III study showed no significant difference between treated and control groups.[18]

Combined evidence. Because the CIs for the two class I studies were so wide, we pooled the data from the two studies to calculate a pooled RR for class I studies. However, the CI was still wide enough to include a clinically significant effect in either direction (either a doubling of or a 33% decrease in the late seizure rate with AEDs), so we pooled data from the five studies graded either class I or II in order to obtain a more precise RR, at the expense of including studies that had a higher risk of bias. This pooled RR was 1.05 (95% CI 0.82 to 1.35), demonstrating no significant effect of AEDs in preventing late post-traumatic seizures (see figure 2).

Serum AED levels. Both class I studies included testing of serum AED levels. One found that only 48% of patients had a therapeutic phenytoin level on at least one occasion.[15] In the other class I study 28% of patients had therapeutic levels at 18 months, although levels were checked in only a minority of treated patients.[16]

Among the three class II studies, one reported that average carbamazepine levels were in the low therapeutic range,[12] another reported that 70% of patients had phenytoin levels at least in the therapeutic range at follow-up visits after the first week and 78% of those with late seizures were therapeutic on the day of their first seizure,[11] and the third reported a 90% rate of therapeutic valproate levels at 1 month and an 85% rate at 6 months.[17]

Two class III studies reported that AED levels were checked and doses adjusted accordingly but did not report specific figures,[13,18] whereas levels were not checked in the third class III study.[19]

Adverse effects. One class I study reported that 6.0% of patients in the phenytoin group developed a rash, compared to 1.2% in the placebo group.[15] In the other class I study, 17.6% of the phenytoin-treated patients were changed to phenobarbital within the 1-year treatment period because they could not tolerate phenytoin.[16]

The class II study evaluating phenytoin found that 34.1% of phenytoin-treated patients stopped the drug between the first week and the end of the first year for either idiosyncratic reactions or patient request, compared to 20.9% in the placebo group.[11] Rash was the most common idiosyncratic reaction. The class II study evaluating valproate reported two events that the authors felt were probably related to treatment: a decreased neutrophil count in one valproate-treated patient and a rash in one patient who received a week of phenytoin.[17] Of the patients assigned to receive valproate for 6 months, 11.0% discontinued their medication due to side effects during that period, compared to 15.2% in the placebo group. Lethargy and fatigue were the most common side effects reported. There was a trend toward higher mortality in the valproate-treated group. More detailed analyses of cognitive side effects in these two class II studies have been reported separately.[20,21] The class II study evaluating carbamazepine did not comment on adverse effects.[12]

Finally, one class III study reported that no adverse effects were seen,[19] whereas the other two did not comment on adverse effects.[13,18]

Conclusions. An analysis using pooled evidence from class I and class II studies that evaluated phenytoin, carbamazepine, and valproate demonstrates no significant difference in the late post-traumatic seizure rate between patients receiving AEDs and controls. Maintenance of therapeutic levels was suboptimal in some studies, but there was no obvious difference in outcomes when compared to studies with higher rates of therapeutic levels. Adverse effects were mild but fairly frequent, prompting medication change or discontinuation in a sizable number of patients in some studies.

Therefore, using the scheme in Appendix 2, we conclude that prophylaxis with phenytoin, carbamazepine, or valproate in patients with severe TBI is *probably not effective* in decreasing the risk of late post-traumatic seizures (those occurring after 7 days).

Practice recommendations. For adult patients with severe TBI (typically with prolonged loss of consciousness or amnesia, intracranial hematoma or brain contusion on CT scan, and/or depressed skull fracture):

Prophylactic treatment with phenytoin, beginning with an IV loading dose, should be initiated as soon as possible after injury to decrease the risk of post-traumatic seizures occurring within the first 7 days (Level A).

Prophylactic treatment with phenytoin, carbamazepine, or valproate should not routinely be used beyond the first 7 days after injury to decrease the risk of post-traumatic seizures occurring beyond that time (Level B).

These recommendations are generally consistent with those from other national specialty organizations,[22-24] as well as with the findings on post-traumatic seizures from a recent meta-analysis of AED prophylactic effect in a variety of epileptogenic conditions.[25]

Recommendations for future research. In a number of areas, we did not find sufficient evidence in the analyzed studies upon which to base a comment or recommendation, and here we discuss some of these topics, as well as other recommendations for future studies.

Mild and moderate TBI. One limitation of the selected studies is their exclusion of patients with milder forms of head trauma. Such patients have lower rates of post-traumatic seizures[3] and their mechanisms of injury are often different. Therefore, it is difficult to generalize our analysis to the population of patients with mild or moderate TBI, and we recommend that studies of early seizure prophylaxis in these patients be performed.

The utility of EEG. Although some clinicians may obtain an EEG before deciding whether to use AED prophylaxis, we found no data in our analyzed studies upon which to base a recommendation regarding the use of EEG. Only one of the studies[19] reported that EEGs were obtained routinely in the early post-traumatic period, and the findings were not reported in detail. In the future, subgroup analyses of TBI patients with EEG abnormalities might allow for a better differentiation of patients' post-traumatic seizure risk.

Pediatric population. Two of the early seizure studies[10,13] and four of the late seizure studies[13,15,16,18] allowed enrollment of patients below 14 to 16 years of age. However, only one of these studies specifically reported findings in the pediatric subgroup, in a separate publication.[26] This report demonstrated no significant difference in late seizure rates between treated children and controls, but the 95% CI for the RR was quite wide (data not shown). Therefore, we recommend that further studies directed at the pediatric population be performed.

Therapeutic AED levels. Relatively high rates of subtherapeutic AED levels were reported in a number of studies analyzed here, particularly in cohorts followed for late post-traumatic seizures. This is a common finding in clinical trials of patients with epilepsy and reflects the reality of clinical practice.[27] The rate at which therapeutic AED levels are achieved in the routine care of patients with TBI is likely to be even lower than that seen in trials in which patients are closely monitored. Therefore, our recommendations are of practical clinical use despite the suboptimal therapeutic levels found in some trials. Future studies should measure and report levels systematically during the late seizure phase and ensure achievement of therapeutic levels to the extent possible.

Other AEDs. Animal models of epileptogenesis, such as the kindling model, have been used to evaluate the ability of AEDs to prevent the development of an epileptic process, rather than merely suppress seizures. It is reasonable to assume that an AED with antiepileptogenic properties would be most likely to be beneficial in the prophylaxis of late seizures. Phenytoin and carbamazepine, the drugs used in four out of the five late seizure studies graded class I or class II, do not appear to be antiepileptogenic in animal models and may actually exhibit some proepileptogenic properties.[28,29] Interestingly, the three class I and class II studies that evaluated phenytoin all showed a trend toward a higher rate of late seizures in the treated group, although CIs were quite wide. Valproate and phenobarbital, however, which are antiepileptogenic in animal models,[28,29] showed a similar trend toward a higher rate of late seizures in the clinical trials in which they were tested. Ideally, other AEDs with demonstrated antiepileptogenic properties and mechanisms of action should be tested in randomized controlled trials of post-traumatic seizure prophylaxis.

In addition, other AEDs may be more tolerable than those tested in the studies analyzed. For example, given the improved safety profile and ease of administration of fosphenytoin compared to phenytoin, the former should also be evaluated in the prophylaxis of early post-traumatic seizures. Some investigators have also noted that many medications used in the care of head-injured patients, including phenytoin, have deleterious effects in animal models of TBI.[30] Further work in this area may help provide clinicians with additional information on which to base their decision regarding the relative risks and benefits of AED prophylaxis in this population.

Definition of early seizures. The distinction between early and late post-traumatic seizures at 7 days after injury is widely used but arbitrary.[31] Unlike the development of later seizures, the occurrence of seizures soon after severe TBI does not necessarily imply the presence of an underlying epileptogenic process. Indeed, early seizures do not appear to be an independent predictive factor for the occurrence of late seizures.[3] However, the highest rate of late seizures is present within the first few weeks after injury,[32] and some have classified early seizures as those occurring within 1 month if the acute injury is complicated by a protracted illness.[3] It is reasonable to wonder whether seizures occurring within the first few weeks may have the same implications as those occurring within the first 7 days. Data on post-traumatic seizure timing are needed to allow for identification of the point after which the occurrence of a seizure *does* predict future seizures. This would be a rational dividing point between early and late seizures, and studies of AED prophylaxis for early seizures could then evaluate a longer duration of prophylaxis, if appropriate.

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all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

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Appendix 1: Definitions for classification of evidence

Class I. Evidence provided by a randomized, controlled clinical trial (RCT) with masked outcome assessment in a representative population. The following are required: a) primary outcomes are clearly defined; b) exclusion and inclusion criteria are clearly stated; c) there is adequate accounting of dropouts and crossovers with numbers sufficiently low to have minimal potential for bias; and d) relevant baseline characteristics are substantially equivalent among treatment groups. For the purposes of this parameter, a loss-to-follow-up rate of <10% was required to meet criterion c.

Class II. Evidence provided by a prospective matched group cohort study in a representative population with masked outcome assessment that meets a through d above or an RCT that lacks one criterion a through d.

Class III. All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population where outcome assessment is independent of patient treatment.

Class IV. Evidence from studies not assessing outcomes independent of treatment, uncontrolled studies, case series, case reports, or expert opinion.

Appendix 2: Definitions for strength of recommendations

Level A. Established as effective, ineffective, or harmful for the given condition in the specified population. Usually, an "A" recommendation requires that the pooled result from two or more distinct class I studies demonstrates a consistent, significant, and important effect.

Level B. Probably effective, ineffective, or harmful for the given condition in the specified population. Usually, a "B" recommendation requires that a single class I study demonstrates a significant and important effect or the pooled result from two or more distinct class II studies demonstrates a consistent, significant, and important effect.

Level C. Possibly effective, ineffective, or harmful for the given condition in the specified population. Usually, a "C" recommendation requires that a single class II study demonstrates a significant and important effect or the pooled result of two or more distinct class III studies demonstrates a consistent, significant, and important effect.

Level U. Data are inadequate or conflicting. Given current knowledge, treatment is unproven and an evidence-based recommendation cannot be made.

Appendix 3

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