AMERICAN ACADEMY OF NEUROLOGY

Special Article

CME

Practice parameter: Treatment of the child with a first unprovoked seizure

Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society*

D. Hirtz, MD; A. Berg, PhD; D. Bettis, MD; C. Camfield, MD; P. Camfield, MD; P. Crumrine, MD; W.D. Gaillard, MD; S. Schneider, MD; and S. Shinnar, MD, PhD

Abstract—The Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society develop practice parameters as strategies for patient management based on analysis of evidence regarding risks and benefits. This parameter reviews published literature relevant to the decision to begin treatment after a child or adolescent experiences a first unprovoked seizure and presents evidence-based practice recommendations. Reasons why treatment may be considered are discussed. Evidence is reviewed concerning risk of recurrence as well as effect of treatment on prevention of recurrence and development of chronic epilepsy. Studies of side effects of anticonvulsants commonly used to treat seizures in children are also reviewed. Relevant articles are classified according to the Quality Standards Subcommittee classification scheme. Treatment after a first unprovoked seizure appears to decrease the risk of a second seizure, but there are few data from studies involving only children. There appears to be no benefit of treatment with regard to the prognosis for long-term seizure remission. Antiepileptic drugs (AED) carry risks of side effects that are particularly important in children. The decision as to whether or not to treat children and adolescents who have experienced a first unprovoked seizure must be based on a risk–benefit assessment that weighs the risk of having another seizure against the risk of chronic AED therapy. The decision should be individualized and take into account both medical issues and patient and family preference.

NEUROLOGY 2003;60:166–175

Population-based studies of the incidence of first unprovoked seizures suggest that there are between 25,000 and 40,000 children per year in the United States who experience a first unprovoked seizure.[1-4] Until relatively recently, it was common practice for physicians to begin long-term, daily antiepileptic drug (AED) therapy after a child or adolescent experienced a single seizure of any type. The rationale for this practice was based on the belief that all seizures were likely to recur and that seizures could be dangerous and cause brain damage. Furthermore, it was thought that if any recurrence were to take place, this would lead to progressively more seizures. It was also assumed that AED were safe, had few side effects, and were effective in prevention of seizure recurrences. These assumptions have undergone substantial modification over the last 20 years, leading to a more optimistic view about the nature of seizures and a more conservative approach to the use of treatment. However, no clear evidence-based guidelines have emerged regarding the initiation of treatment after a first unprovoked seizure in the pediatric population.

Practice parameters are developed by the Quality

Approved by the Quality Standards Subcommittee on April 16, 2002. Approved by the Practice Committee on August 3, 2002. Approved by the AAN Board of Directors on October 19, 2002.

This statement has been endorsed by the American Epilepsy Society; the American Academy of Pediatrics; and the Child Neurology Society.

*See the Appendix for a list of Committee members.

From the National Institute of Neurological Disorders and Stroke (Dr. Hirtz), NIH, Bethesda, MD; Department of Biological Sciences (Dr. Berg), Northern Illinois University, Dekalb; Boise (Dr. Bettis), ID; Department of Pediatric Neurology (Drs. C. Camfield and P. Camfield), IWK Health Center, Halifax, Nova Scotia, Canada; Department of Neurology (Dr. Crumrine), Children's Hospital of Pittsburgh, PA; Department of Neurology (Dr. Gaillard), Children's National Medical Center, Washington, DC; Riverside (Dr. Schneider), CA; and Departments of Neurology and Pediatrics (Dr. Shinnar), Montefiore Medical Center, Albert Einstein College of Medicine, New York, NY.

Received April 14, 2002. Accepted in final form July 19, 2002.

Address correspondence and reprint requests to QSS, American Academy of Neurology, 1080 Montreal Ave., St. Paul, MN 55116; e-mail: wedlund@aan.com

Table 1 *Evidence classification scheme of the American Academy of Neurology: rating of therapeutic article*

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required:

a. Primary outcome(s) is/are clearly defined.

b. Exclusion/inclusion criteria are clearly defined.

c. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias.

d. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above *or* a randomized, controlled trial in a representative population that lacks one criteria a–d.

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

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society and are evidence-based documents about diagnostic or prognostic evaluations and therapeutic interventions. These involve a systematic evaluation and classification of available evidence (table 1) that determine whether specific recommendations can be made and, if so, the strength of the recommendations (table 2).

This practice parameter reviews the current evidence about treatment with AED after a child experiences a first unprovoked seizure. We examine the risk of seizure recurrence and predictors that may affect that risk. We review and classify the published evidence on whether treatment prevents recurrences as well as chronic epilepsy. We also evaluate potential risks and side effects of AED commonly used to treat seizures in children.

This is the second of two parameters addressing a child's first unprovoked seizure; the first concerned the initial evaluation.[5] Febrile seizures have been addressed separately in recently published recommendations from the American Academy of Pediatrics[6] and are not included here. This parameter pertains to children and adolescents with first seizures only and does not include children diagnosed with epilepsy, defined as the occurrence of two or more seizures without acute provocation. For this reason, absence, myoclonic, and atonic seizures were excluded because they typically are not recognized until there have been multiple occurrences. The seizure types covered by this parameter include all partial seizures as well as generalized onset tonic-clonic or tonic seizures.

We defined the first seizure using the International League Against Epilepsy criteria to include multiple seizures within 24 hours with recovery of consciousness between seizures.[7] Children with a known immediate precipitating head trauma or those with previously diagnosed CNS infection, tumor, or other known acute precipitating causes such as hypoglycemia were excluded. We also excluded neonatal seizures ($\leq$28 days) and febrile seizures because these disorders are diagnostically and therapeutically different. Status epilepticus, defined as a seizure lasting $>$30 minutes without regaining of consciousness,[7] was included when data were available. Most articles describing pediatric studies covered up to age 18 years; studies including both adolescents and adults were also examined. The recommendations of this parameter pertain to children (excluding the neonate) and adolescents.

Before any treatment decisions are approached, it is critical to determine whether the event is truly a seizure and whether it is the child's first.[5] A detailed history from a reliable observer and careful medical history and neurologic examination may provide information allowing the physician to rule out nonepileptic events.

Description of process. A literature search was performed including Ovid Medline and Ovid Biosys and Current Contents for relevant articles published from 1980 to 2001 using the following key words: treatment, antiepileptics, medications, therapy, management, epilepsy, seizures, convulsions, child, newborn, and adolescent. Standard search procedures were used, and subheadings were applied as appropriate. These searches produced 948 titles of journal articles.

Titles and abstracts were reviewed for content re-

Table 2 *Evidence classification scheme of the American Academy of Neurology: recommendations*

Translation of evidence to recommendations	Rating of recommendation
Level A rating requires at least one convincing Class I study or at least two consistent, convincing Class II studies.	A = established as effective, ineffective, or harmful for the given condition in the specified population.
Level B rating requires at least one convincing Class II study or overwhelming Class III evidence.	B = probably effective, ineffective, or harmful for the given condition in the specified population.
Level C rating requires at least two convincing Class III studies.	C = possibly effective, ineffective, or harmful for the given condition in the specified population.
—	U = data inadequate or conflicting. Given current knowledge, treatment is unproven.

garding first unprovoked seizures in children and adults. Articles from the searches were identified as relevant, and additional articles from the references in these primary articles were included. Articles pertaining to children with both first seizures and established epilepsy were included but were excluded if they did not report data from either children or adults who had experienced only a single seizure. References were classified as to whether they contained data related to children and adults or just children. Articles were reviewed from searches, bibliographies, and suggestions by colleagues and committee members. In most reports pertaining to both children and adults, results were not categorized according to subsets of age groups.

A recently revised classification of evidence to determine the quality of data was used for the evaluation of reports of therapeutic studies (see table 1). Each article containing data regarding treatment was reviewed and classified by two or more reviewers. Abstracted data included numbers of subjects, study design, ages, seizure types, whether first seizures only or a mixture of single and multiple seizures, seizure recurrences, types of treatment, side effects, and measurement of compliance and length of follow-up. Methods of data analysis and power were noted when available. Recommendations were based on the level of evidence (see table 2).

What are the potential risks resulting from having a second seizure? Preventing seizure recurrences has been a concern ever since Gowers wrote: "The tendency of the disease is to self perpetuation; each attack facilitates the occurrence of another, by increasing the instability of the nerve elements."[8] This clinical belief has been supported by animal studies on kindling, an experimental technique for inducing epilepsy by a series of subclinical electrical stimulations of the temporal lobe that induce progressive intensification of evoked electrographic and behavioral seizures.[9-11] There is evidence from animal models that prolonged or recurrent seizures, under certain circumstances, cause neuronal injury and predispose to epilepsy.[12,13] There is recent evidence that seizures, some prolonged, that occur during critical periods of brain development in animals may alter neuronal activity and circuitry in a manner that may predispose to the later development of epilepsy.[14,15] The relevance of data from these animal models to seizures in humans is unclear.[10,11,16] Data from children indicate that even prolonged seizures rarely cause clinically discernible brain damage unless associated with an underlying acute neurologic insult.[17]

One reason why treatment may be considered is concern about the risk of physical injury or death from a subsequent seizure. Serious injury from a seizure in a child is a rare event, usually from a fall with loss of consciousness. To reduce that risk, restrictions are recommended that would apply to any young child, such as bicycling on a sidewalk rather than the street and always with a helmet and swimming only with a buddy. Showering rather than bathing is recommended for children and adolescents, unless they are supervised. Sudden unexpected death in children with epilepsy is, fortunately, very uncommon. When death occurs in children, it is nearly always related to an underlying neurologic handicap rather than the epilepsy.[18-20] One population-based study found that the risk of death in those with childhood-onset epilepsy is the same as that for the general population for children without significant neurologic handicap.[21] No studies were found that examined whether treating a child after a first unprovoked seizure would reduce the risk of either subsequent significant injury or sudden death.

Psychosocial considerations. The effect of taking daily medication on the child's self-perception may be a concern in some cases.[22,23] A child who is taking chronic medication is perceived to have a chronic illness by the child, family, and possibly others such as teachers. Additionally, chronic treatment to prevent seizure recurrence may affect the family's ability to obtain health insurance or day care. Issues in teenagers become more complicated as concerns about driving privileges and teratogenicity come into play.[24]

How likely is a second seizure? The probability of having a second seizure has been explored in several large, observational Class III studies with long-term follow-up. Results presented in table 3 are limited to studies that included children with or without adults. The cumulative risk of recurrence increases over time; however, in studies where the information is available, the majority of the recurrences occur early (within the first 1 to 2 years).[25-33] At any given time, the reported risk of recurrence is highly variable. For example, at 1 year, it ranges from a low of 14%[26] to a high of 65%.[33] In all these Class III studies, there is variability in the mix of patients, the nonrandomized use of treatment, and the distributions of important prognostic factors. Some methodologic differences in seizure identification, age ranges included, recruitment, and follow-up of study participants may also contribute to this variability.

How likely are multiple recurrences in children who present with a first unprovoked seizure? A minority of children will go on to experience not just one but many recurrences. One study that enrolled 207 children with follow-up for 2 years found that in addition to an overall recurrence rate of 54%, 26% of the enrolled children were still experiencing one or more seizures during the last 6 months of the study follow-up, that is, >18 months after the index event.[27] Another study with longer follow-up enrolled 407 children and followed them for an average of >10 years. Of these, 46% had one or more recurrences during that period of time. Over the extended follow-up period, 19% of the children

Table 3 *Risk of recurrence after a first seizure*

Study	Age range	n	Treated, %	Risk of recurrence at different times since first seizure, %				
				6 mo	1 y	2 y	3 y	5 y
Children and adolescents only								
27	1–16 y	156	0	40	46	54	—	—
33	3–21 y	78	58	55	65	69	—	—
25,28	1 mo–19 y	407	14	22	29	37	—	42
29	2–16 y	119	61	22	29	—	32	—
30	1 mo–16 y	168	68	36	40	47	—	—
42	1 mo–7 y	284	—	—	—	—	—	69, up to 7 y
Children, adolescents, and adults								
31	All ages	424	?	30	36	45	48	—
32	All ages	564	?	27	37	43	46	—
26	All ages	208	≈80	—	14	25	29	34

enrolled experienced ≥4 seizures and only 10% experienced ≥10 seizure episodes.[28] Few of the children in either study met criteria for intractability.[34]

Are there factors that increase the recurrence risk? Certain factors may elevate the risk of experiencing a second seizure. The underlying etiology and whether the EEG is normal or abnormal are consistently related to the risk of recurrence.[35] The recurrence rate is higher in individuals who have a remote symptomatic etiology. In those with an idiopathic or cryptogenic etiology, it is significantly lower.[25-28,30,33] We use the term "remote symptomatic" to mean without immediate cause but with a prior identifiable major brain insult such as severe trauma or accompanying a condition such as cerebral palsy or mental retardation. Idiopathic seizures are not associated with a known CNS disorder and are of suspected genetic etiology (such as occur with benign rolandic epilepsy), and cryptogenic seizures occur in individuals otherwise normal with no clear etiology.[7] The estimates of risk at 2 years are highly variable. The extent to which treatment was used also varied and may have influenced, to some degree, the overall risk observed. For children with first seizures that are idiopathic/cryptogenic, the recurrence risk is generally between 30 and 50% by 2 years,[25,27-30] and for remote symptomatic seizures, the estimate of recurrence risk is generally above 50%.[25,27,28,30,33] An EEG performed after the initial seizure also helps to predict recurrence,[25-27,29-31,33] particularly if there is an epileptiform abnormality. Patients with remote symptomatic seizures and abnormal EEG were more likely to be treated than those with idiopathic/cryptogenic seizures and normal EEG. All of these studies addressing recurrence risk represent Class III evidence.

Are there special considerations if the first seizure is prolonged? Approximately 10 to 12% of children and adults with a first unprovoked seizure will present with a seizure lasting ≥30 minutes (status epilepticus) as their first seizure.[36] In the absence of an acute or progressive brain injury or disease, the morbidity and mortality of status epilepticus in children are relatively low.[17,37] Of 46 children with "idiopathic" seizures in a study of sequelae of status epilepticus in 193 children, 2 children had mental retardation, but they had been recruited retrospectively and details of the clinical circumstances were not clear. None of children studied prospectively had residual motor or cognitive disability.[17]

Evidence concerning the impact of status epilepticus on the risk of recurrence and, in particular, the risk of a prolonged recurrence is available from one Class III prospective observational study of 407 children with a first unprovoked seizure.[25,36] The overall recurrence risk following a prolonged first seizure was no different from the recurrence risk following a brief first seizure. However, if a child with an initial prolonged seizure did experience a seizure recurrence, it was more likely to be prolonged. Of 24 children with initial episodes of status epilepticus who had a recurrence, 5 (21%) had status epilepticus as a recurrence, whereas of 147 whose first seizures were brief and who had a recurrence, 2 (1%) had status epilepticus as their recurrence.[25] Thus, the risk of a recurrent seizure being prolonged is limited largely to those children whose first seizure was prolonged (Class III studies).

How effective is treatment after a first seizure in prevention of recurrences? *Evidence.* There are four randomized clinical trials including children and adolescents that have examined the efficacy of treatment after a first seizure.[38-41] Only one of these studies consisted solely of children randomized to treatment versus no treatment after a first nonfebrile seizure (Class II).[41] In this study with a total of 31 children, 2 of 14 children (14%) treated with carbamazepine (CBZ) experienced a recurrence compared with 9 of 17 (53%)

Table 4 *Recurrence rate by treatment in studies of children*

Study	Class	n	Recurrence rate, n (%)	Treated vs untreated	Length of follow-up, y
41	II	31	11/31	2/14 vs 9/17, 14.3% vs 52.9%	1
42	III	284	196/284 (69)	No difference	To 7
29	III	119	40/119 (32)	27% vs 38%, no difference	3
25	III	407	151/393 (38) at 2 y, 171/375 (46) at 5 y	No difference	6.3, mean
33	III	78, includes 12 symptomatic	54/78 at 2 y (69)	No difference	5.2

who were not treated. Follow-up was for 1 year, and compliance was monitored. Although the recurrence rate up to 1 year was significantly lower in the treated group, only 6 of 14 (43%) patients randomized to CBZ completed the year with no significant side effects or seizure recurrence and 7 of 17 (41%) assigned to no medication had no seizure recurrence.

In studies involving both children and adults, outcome was not provided based on age. One Class I study in which 228 subjects were randomized to valproic acid (VPA) or placebo included 33 adolescents between the ages of 16 and 19.[38] The follow-up period for this trial was between 9 months and 5 years. Five (4%) of the treated group experienced a recurrence compared with 63 (56%) of those treated with placebo. However, these results were not found in another Class II randomized study (n = 419), in which 114 subjects were between 2 and 16 years old. Twenty-four percent of patients treated after a first seizure and 42% untreated patients had a recurrence by 1 year, but no difference by initial treatment assignment was seen after 2 years; 32% of those treated and 40% of those untreated had a recurrence by 2 years.[39]

In other studies in children (Class III), although the cohorts are prospectively followed, treatment was not randomly assigned and therefore baseline factors affecting risk of recurrence were not comparable.[25,29,33,42] None of these studies found a significant difference in recurrence rate in the treated and untreated children (table 4).

Summary. Studies of children and adults in which treatment assignment was randomized usually indicate that treatment with AED after a first seizure reduces the risk of seizure recurrence. The magnitude of the impact is variable, and the evidence from pediatric studies alone is weak (see table 4). Differences among the studies, the populations targeted, and the method in which treatment was administered may explain some of the variability. In the only randomized study restricted to the pediatric age group, the sample size is small and the confidence intervals are accordingly wide, ranging from 0 to 93% efficacy.[41]

Does treatment with AED after a first seizure change the long-term prognosis for seizure remission? *Evidence.* Although treatment after a first unprovoked seizure may reduce the risk of a second seizure, does treatment at this time make any difference in the patient's long-term prognosis for seizure control? This question is addressed in two randomized, prospective, but not placebo-controlled (Class II) first-seizure studies. One study had 419 subjects, of whom 114 were between 2 and 16 years of age.[39] This study compared the probability of experiencing a remission, that is, 1 or 2 seizure-free years, in patients treated after a first seizure versus in patients treated after a second seizure. Follow-up was for at least 3 years or a minimum of 2 years seizure-free. Patients treated after the first seizure and those treated after a second seizure had the same probability of achieving a 1- or 2-year seizure remission (68%, n = 215 versus 60%, n = 204) (risk of recurrence [RR] = 1.04, 95% CI = 1.30 to 0.82). Another smaller study[43] of 31 children randomized to CBZ (n = 14) or no treatment (n = 17) echoes the results of this large study. After a 15-year follow-up, the rate of 2-year terminal remission was the same in both the treated and the untreated groups (RR = 0.79, 95% CI = 0.3 to 2.1).

Summary. Two Class II studies provide no evidence of a difference when treatment is started after the first seizure versus after a second seizure in achieving a 1-or 2-year seizure remission.

What are the nature and frequency of side effects of AED commonly used after a first seizure in children? *Evidence.* AED may cause systemic side effects such as rash, hirsutism, and weight gain. Severe reactions such as hepatic toxicity, bone marrow toxicity, and Stevens–Johnson syndrome cannot be anticipated and require early recognition of symptoms. Side effects of AED occurring in children include effects on behavior and higher cortical function,[44] which are often dose related and may be under-recognized. Dose-related side effects may be highest initially and amenable to dosage reduction, but this may also limit the potential effectiveness of AED. If the patient is a teenage girl who may become pregnant, the risk of teratogenicity is an additional consideration.[24,45]

Trials that report data relating to efficacy do not always include data relating to side effects. Data regarding toxicity or side effects of AED are not specifically available for treatment after a first seizure. However, studies that include initial treatment of

Table 5 *Behavioral and cognitive side effects of antiepileptic drugs in children treated for epilepsy*

Study	Age, y	Follow-up	Medication (n)	Reported side effects
Class I				
50,51	5–14	1 y	CBZ (23)	Impaired recent recall, reported slow by teachers
			PHT (20)	Impaired information processing at 1 mo
			VPA (21)	No change
49	7–15	6 and 12 mo	CBZ (26)	No change
			PB (25)	Disturbed information processing (auditory event-related potentials prolonged)
			VPA (25)	No change
47	2–16	12 mo	CBZ (78)	29 of total of 116 had moderate/severe behavior problems
			PHT (38)	
48	6–14	6 mo	PB	Did less well on cognitive tests, more hyperactivity
			VPA	No change
53	—	None	CBZ (50)	No difference high vs. low level
54			VPA (46)	Low doses gave better accuracy and response time
55			PHT (50)	No difference high vs. low level
52	4–12	2 y	PB (51)	22% hyperactivity
			VPA (48)	13% hyperactivity
			PHT (52)	8% impaired school performance
Class 2				
56	3–16	3 y	PB (10)	6 withdrew owing to side effects
			PHT (50)	5 withdrew owing to side effects
			CBZ (54)	2 withdrew owing to side effects
			VPA (49)	2 withdrew owing to side effects
51	Average 9	12 mo	VPA (26)	Increase in IQ
			PB (23)	Significant impairment in learning
58	6–17	6 mo	CBZ (17)	No difference
			VPA (11)	No difference
			PHT (1)	No difference
59	7–12	12 mo	VPA (34)	No difference
			CBZ (29)	No difference
60	4–16	26–6 mo	CBZ (5)	No difference
		12–12 mo	VPA (3)	No difference
			Ethosuximide (4)	No difference

CBZ = carbamazepine; PHT = phenytoin; VPA = valproic acid; PB = phenobarbital.

children for epilepsy provide information that may be extrapolated to treatment after a first seizure.

Behavioral and cognitive side effects. Five Class I studies reported on behavioral and cognitive side effects in children with epilepsy treated with AED.[46-52] One study reported that 29 of 116 children treated with either CBZ or phenytoin (PHT) had moderate to severe behavioral or mood changes.[46,47] In a blinded, randomized, crossover study comparing phenobarbital (PB) with VPA, children taking PB had lower scores on four tests of cognitive function and had more behavior problems that were not dose related, particularly hyperactivity.[48] Although Wechsler Intelligence Scale for Children–Revised scores were not different, a study that included auditory event-related potentials found prolonged latencies indicating delayed information processing associated with PB.[49] In a Class I study of children with newly diagnosed epilepsy in which 23 children received CBZ, 20 received PHT, and 21 received VPA, those on CBZ and PHT were slower on tests of information processing, and children on CBZ showed increased irritability[50,51] (table 5).

A series of three Class I studies each designed to compare the cognitive effects of low versus high levels of one AED in children with epilepsy found no differences between low and high levels with either CBZ or PHT.[53,54] Children with a lower level of VPA performed better on specific cognitive tasks such as accuracy and response time than those with a higher level.[55] In one Class II study, 15 of 163 children assigned to AED withdrew because of intolerable side

Table 6 *Systemic side effects of antiepileptic drugs in children treated for epilepsy*

Study	n	Follow-up	Medication (n)	Side effects
Class I				
51	64	1 y	CBZ (23)	3 h/a, anorexia, nausea
			PHT (20)	1 depression, anorexia
			VPA (21)	0
47	116	1 y	CBZ (78)	9 n&v, 10 ataxia, 5 rash, 5 gingival hyperplasia
			PHT (38)	
52	151	29 mo, mean	PB (51)	17 patients including behavioral
			VPA (48)	15 patients, including behavioral
			PHT (52)	33 patients had at least 1, 30 gingival hyperplasia, 13 dose-related ataxia
Class II				
41	31	1 y	CBZ (14)	2 somnolence, 2 allergic rash
56	167	4 y	PB (10)	5 behavior, 1 drowsy
			PHT (54)	2 drowsy, 1 rash, 1 blood dyscrasia, 1 hirsutism
			CBZ (54)	1 drowsy, 1 blood dyscrasia
			VPA (49)	1 behavior problem, 1 tremor
61	260	1 y	VPA (130)	Half had adverse events, e.g., somnolence, ataxia, rash; 12% d/c owing to "adverse events" such as increased appetite, weight gain, alopecia
			CBZ (130)	7% d/c owing to side effects

CBZ = carbamazepine; PHT = phenytoin; VPA = valproic acid; PB = phenobarbital; h/a = headache; n&v = nausea and vomiting; d/c = discontinued.

effects,[56] and in another, children taking PB did not show an expected increase in IQ on retest.[57] In three other studies, which included 48 children taking VPA, 1 taking PHT, and 51 taking CBZ, evidence was not seen of behavioral or cognitive impairment[58-60] (see table 5).

A report from the American Academy of Pediatrics[44] regarding general recommendations for awareness of behavioral and cognitive effects of AED noted that high blood levels of some AED (PHT, PB, primidone) were significantly related to cognitive decline. Cognitive and behavioral effects of AED were described as subtle and affecting isolated functions. These effects were seen in conjunction with academic underachievement and neuropsychological impairment in children with epilepsy.

Systemic side effects. Systemic side effects other than behavioral or cognitive also occur in children placed on AED (table 6). In a Class I study of 116 children randomized to CBZ or PHT, 24 had one or more side effects including nausea and vomiting (9), ataxia (10), rash (5), gingival hyperplasia (3), and dizziness (3).[47] Another Class I study reported that of 23 children on CBZ, 3 experienced headache, anorexia, nausea or abdominal pain, and increased irritability. Systemic side effects were not reported for the 20 children on PHT or the 21 on VPA.[50,51] Dropout because of failure to comply with treatment, possibly due to side effects, occurred in several cases in all three groups.

In the one prospective, randomized, but not blinded study in children that pertains to first seizures only, 2 of 14 children on CBZ discontinued medication because of rash and 2 of 14 because of excessive somnolence.[41] When four drugs were compared in a Class II study of 167 children with newly diagnosed epilepsy, PB was dropped after 6 of 10 children had unacceptable side effects. Side effects occurred at a rate of 9% for PHT, 4% for CBZ, and 4% for VPA.[56] Included were behavioral problems, drowsiness, sleep problems, blood dyscrasia, hirsutism, and tremor. A randomized and blinded prospective study of 151 children with epilepsy found that 32% of children on PB, 19% of children on VPA, and 40% of children on PHT had more than one toxic side effect. Fifty-eight percent of those on PHT experienced gingival hyperplasia, and 25% had dose-related ataxia or sedation. Follow-up was 2 years.[52] In a Class II study of 130 children assigned to VPA and 130 assigned to CBZ, by 1 year, 13% discontinued VPA and 7% discontinued CBZ owing to adverse effects such as somnolence, fatigue, weight gain, headache, nausea, vomiting, and rash.[61]

In a Class III study of first seizures, four AED were used and an overall rate of side effects of 24% was reported. These were noted as behavior disorders, hyperkinesias, and sleepiness.[29] The exacerbation of seizures by CBZ has been reported in 11 of 129 cases of new-onset epilepsy.[62]

Several of the newer AED carry warnings or precautions for Stevens–Johnson syndrome (lamotrigine, zonisamide, felbamate), hepatic toxicity (lamotrigine, felbamate), aplastic anemia (felbamate), renal stones (topiramate, zonisamide), and

other rare medical complications such as hyperthermia secondary to hypohidrosis and hyponatremia (zonisamide and oxcarbazepine). The spectrum and incidence of medical ill effects of the newer AED in special populations such as children may not become apparent until after several years of use.[63] There are not yet adequate data on behavioral or cognitive side effects of newer AED in children, and they are not currently approved for monotherapy in children. A new form of treatment for acute seizure activity that may be used at home is diazepam administered in a rectal solution, but this is approved for use in selected refractory patients to control acute, repetitive seizure activity and is not used after a single unprovoked seizure.[64,65]

Summary. Whereas evidence from studies of treatment after only a single unprovoked seizure is lacking, Class I and II evidence concerning the AED accepted for use as first-line anticonvulsants in children (PB, PHT, VPA, CBZ) indicates that clinically relevant cognitive and behavioral effects may occur, particularly with PB. Parents and teachers may often overlook such cognitive and behavioral effects. In addition, one or more important systemic side effects such as rash, hirsutism, weight gain, or nausea may occur with a frequency ranging from 7 to 58%.

Conclusions. The majority of children who experience a first unprovoked seizure will have few or no recurrences. Only approximately 10% will go on to have many ($\geq$10) seizures regardless of therapy. Treatment with AED after a first seizure as opposed to after a second seizure has not been shown to improve prognosis for long-term seizure remission (Class II evidence).

Treatment has been shown in several studies combining both children and adults to reduce the risk of seizure recurrence (Class II evidence). There is a relative paucity of data from studies involving only children after a first seizure. AED therapy in children who have epilepsy (at least two seizures) has potential serious pharmacologic and psychosocial side effects (Class I evidence). No separate data exist specifically for treatment side effects in children who have experienced only a single seizure.

There is no evidence about whether treatment specifically after the first seizure alters the risk of sudden unexpected death in epilepsy patients in children.

Recommendations. The decision as to whether or not to treat with AED following a first unprovoked seizure in a child or adolescent must be based on a risk–benefit assessment that weighs the risk of another seizure (both the statistical risk of recurrence and the potential consequences of a recurrence) against the risk (cognitive, behavioral, and physical as well as psychosocial) of chronic AED therapy. This decision must be individualized and take into account both medical issues and patient and family preference. Therefore, the following recommendations are made for children and adolescents who have experienced a first seizure:

1. Treatment with AED is not indicated for the prevention of the development of epilepsy (Level B).
2. Treatment with AED may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial side effects (Level B).

Future research recommendations. Although evidence reviewed in this practice parameter does not support the routine treatment of every child who presents with a first unprovoked seizure, a minority of children (approximately 10%) will develop difficult-to-control and protracted epilepsy. Prediction of who these children will be is currently not possible; the prognosis becomes evident only after months or years have passed. Research is needed to identify these children after a first seizure and to determine which treatment and management options are best. Imaging studies may help determine if and under what circumstances children may sustain neuronal injury due to seizure. Identifying genetic, immune, or imaging markers may improve prediction of prognosis.

More research is needed on the efficacy and side effects in children of the new AED. Behavioral and cognitive side effects need to be better evaluated, especially for new AED, and individual risks as well as group differences assessed on tests of cognition. A goal of pharmacogenetics will be to minimize the likelihood of adverse events from medication. Identification of children at risk for idiosyncratic adverse reactions to AED and understanding the pharmacogenetics of responders to specific AED may improve our ability to identify those children who should be treated and to use only those treatments to which they are likely to respond.

Determinants of psychosocial factors involved in seizures and AED therapy must be better understood for the different ages of children and their families, so that overall best possible quality of life is the goal of management. Research on seizure disorders in the next decade will be focused on "no seizures, no side effects" and, most importantly, toward strategies for prevention and cure of the underlying process.[66]

Acknowledgment

The authors thank Wendy Edlund and Alison Nakashima at the American Academy of Neurology for their superb assistance in coordinating this project and Francine Hill for preparing the manuscript.

Disclaimer: This statement is provided as an educational service of the American Academy of Neurology (AAN) and the Child Neurology Society (CNS). It is based on an assessment of current scientific and clinical information. It is not intended to include 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 and CNS recognize that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

Appendix

American Academy of Neurology Quality Standards Subcommittee members: Gary Franklin, MD, MPH (co-chair); Catherine Zahn, MD (co-chair); Milton Alter, MD, PhD (ex officio); Stephen Ashwal, MD; Richard M. Dubinsky, MD; Jacqueline French, MD; Gary H. Friday, MD; Michael Glantz, MD; Gary Gronseth, MD; Deborah Hirtz, MD; Robert G. Miller, MD; David J. Thurman, MD, MPH; and William J. Weiner, MD. *Child Neurology Society Practice Committee members:* Carmela Tardo, MD (chair); Bruce Cohen, MD (vice-chair); Elias Chalhub, MD; Roy Elterman, MD; Murray Engel, MD; Bhuwan P. Garg, MD; Brian Grabert, MD; Annette Grefe, MD; Michael Goldstein, MD; David Griesemer, MD; Betty Koo, MD; Edward Kovnar, MD; Leslie Anne Morrison, MD; Colette Parker, MD; Ben Renfroe, MD; Anthony Riela, MD; Michael Shevell, MD; Shlomo Shinnar, MD; Gerald Silverboard, MD; Russell Snyder, MD; Dean Timmns, MD; Greg Yim, MD; Mary Anne Whelan, MD.

References

1. Verity CM, Ross EN, Golding J. Epilepsy in the first ten years of life: findings of the child health and education study. Br Med J 1992;305: 857–861.
2. Camfield CS, Camfield PR, Gordon K, Wirrell E, Dooley JM. Incidence of epilepsy in childhood and adolescence: a population-based study in Nova Scotia from 1977 to 1985. Epilepsia 1996;37:19–23.
3. Hauser W, Annegers J, Kurland L. Incidence of epilepsy and unprovoked seizures in Rochester, Minnisota, 1935–1984. Epilepsia 1993;34: 453–468.
4. Jallon P, Goumaz M, Haenggeli C, Morabia A. Incidence of first epileptic seizures in the canton of Geneva, Switzerland. Epilepsia 1997;38: 547–552.
5. Hirtz D, Ashwal S, Berg A, et al. Practice parameter: evaluating a first nonfebrile seizure in children. Neurology 2000;55:616–623.
6. Academy of Pediatrics, Committee on Quality Improvement, Subcommittee on Febrile Seizures. Practice parameter: long-term treatment of the child with simple febrile seizures. Pediatrics 1999;103:1307–1309.
7. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. Epilepsia 1993;37:592–596.
8. Gowers WR. Epilepsy and other chronic convulsive diseases: their causes, symptoms and treatment. London: J & A Churchill, 1881:242.
9. Goddard GV, Mc Intyre DC, Leech CK. A permanent change in brain function resulting from daily electrical stimulation. Exp Neurol 1969; 25:295–330.
10. Berg AT, Shinnar S. Do seizures beget seizures? An assessment of the clinical evidence in humans. J Clin Neurophysiol 1997;14:102–110.
11. Wasterlain CG. Recurrent seizures in developing brain are harmful. Epilepsia 1997;38:728–734.
12. Meldrum B. Physiological changes during prolonged seizures and epileptic brain damage. Neuropaediatrie 1978;9:203–212.
13. Cavazos JE, Das I, Sutula TP. Neuronal loss induced in limbic pathways by kindling: evidence for induction of hippocampal sclerosis by repeated brief seizures. J Neurosci 1994;14:3106–3121.
14. Chen K, Baram TZ, Soltesz I. Febrile seizures in the developing brain result in persistent modification of neuronal excitability in limbic circuits. Nat Med 1999;5:888–894.
15. Schmid R, Tandon P, Stafstrom CE, Holmes GL. Effects of neonatal seizures on subsequent seizure-induced brain injury. Neurology 1999; 53:1754–1761.
16. Camfield PR. Recurrent seizures in the developing brain are not harmful. Epilepsia 1997;38:735–737.
17. Maytal J, Shinnar S, Moshé SL, Alvarez LA. Low morbidity and mortality of status epilepticus in children. Pediatrics 1989;83:323–331.
18. Harvey AS, Nolan T, Carlin JB. Community-based study of mortality in children with epilepsy. Epilepsia 1993;34:597–603.
19. Callenbach PM, Westendorp RG, Geerts AT, et al. Mortality risk in children with epilepsy: the Dutch study of epilepsy in childhood. Pediatrics 2001;107:1259–1263.
20. Donner EJ, Smith CR, Snead OC. Sudden unexplained death in children with epilepsy. Neurology 2001;57:430–434.
21. Camfield CS, Camfield PR, Veugelers P. Death in children with epilepsy: a population-based study. Lancet 2002;315:1891–1895.
22. Austin JK, Dunn DW. Assessing children's concerns about epilepsy. Clin Nurs Practice Epilepsy 1996;3:11–12.
23. Austin JK. Concerns and fears of children with seizures. Clin Nurs Practice Epilepsy 1993;1:4–10.
24. O'Dell C, Shinnar S. Initiation and discontinuation of antiepileptic drugs. Neurol Clin 2001;19:289–311.
25. Shinnar S, Berg AT, Moshe SL, et al. The risk of seizure recurrence after a first unprovoked febrile seizure in childhood: an extended follow-up. Pediatrics 1996;98:216–225.
26. Hauser WA, Rich SS, Annegers JF, Anderson VE. Seizure recurrence after a first unprovoked seizure: an extended follow-up. Neurology 1990;40:1163–1170.
27. Stroink H, Brouwer OF, Arts WF, Geerts AT, Peters AC, van Donselaar CA. The first unprovoked, untreated seizure in childhood: a hospital based study of the accuracy of the diagnosis, rate of recurrence, and long term outcome after recurrence. Dutch Study of Epilepsy in Childhood. J Neurol Neurosurg Psychiatry 1998;64:595–600.
28. Shinnar S, Berg AT, O'Dell C, Newstein D, Moshe SL, Hauser WA. Predictors of multiple seizures in a cohort of children prospectively followed from the time of their first unprovoked seizure. Ann Neurol 2000;48:140–147.
29. Boulloche J, Leloup P, Mallet E, Parain D, Tron P. Risk of recurrence after a single, unprovoked, generalized tonic-clonic seizure. Dev Med Child Neurol 1989;31:626–632.
30. Camfield PR, Camfield CS, Dooley JM, Tibbles JAR, Fung T, Garner B. Epilepsy after a first unprovoked seizure in childhood. Neurology 1985; 35:1657–1660.
31. Annegers JF, Shirts SB, Hauser WA, Kurland LT. Risk of recurrence after an initial unprovoked seizure. Epilepsia 1986;27:43–50.
32. Hart YM, Sander JWAS, Johnson AL, Shorvon SD. National general practice study of epilepsy: recurrence after a first seizure. Lancet 1990; 336:1271–1274.
33. Martinovic Z, Jovic N. Seizure recurrence after a first generalized tonic-clonic seizure in children, adolescents and young adults. Seizure 1997; 6:461–465.
34. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, Beckerman B. Early development of intractable epilepsy in children: a prospective study. Neurology 2001;56:1445–1452.
35. Berg AT, Shinnar S. The risk of seizure recurrence following a first unprovoked seizure: a quantitative review. Neurology 1991;41:965–972.
36. Shinnar S, Berg AT, Moshe SL, Shinnar R. How long do new-onset seizures in children last? Ann Neurol 2001;49:659–664.
37. Dodson WE, De Lorenzo RJ, Pedley TA, Shinnar S, Treiman DM, Wannamaker DB. The treatment of convulsive status epilepticus: recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. JAMA 1993;270:854–859.
38. Chandra B. First seizure in adults: to treat or not to treat. Clin Neurol Neurosurg 1992;94:S61–S63.
39. Musicco M, Beghi E, Solari A, Viani F. Treatment of first tonic-clonic seizure does not improve the prognosis of epilepsy. Neurology 1997;49: 991–998.
40. Das CP, Sawhney IMS, Lal V, Prabhakar S. Risk of recurrence of seizures following single unprovoked idiopathic seizure. Neurol India 2000;48:357–360.
41. Camfield P, Camfield C, Dooley J, Smith E, Garner B. A randomized study of carbamazepine versus no medication after a first unprovoked seizure in childhood. Neurology 1989;39:851–852.
42. Hirtz DG, Ellenberg JH, Nelson KB. The risk of recurrence of nonfebrile seizures in children. Neurology 1984;34:637–641.
43. Camfield PR, Camfield CS, Dooley JM, Smith S, Smith E. Long-term outcome is unchanged by anti-epileptic drug treatment after a first seizure: a 15-year follow-up from a randomized trial in childhood. Epilepsia 2002;43:662–663.
44. American Academy of Pediatrics. Behavioral and cognitive effects of anticonvulsant therapy (RE9537). Pediatrics 1995;96:538–540.
45. Yerby MS. Teratogenic effects of antiepileptic drugs: what do we advise patients? Epilepsia 1997;38:957–958.
46. Canadian Study Group for Childhood Epilepsy. The cognitive and behavioral effects of clobazam and standard monotherapy are comparable. Epilepsy Res 1999;33:133–143.
47. Canadian Study Group for Childhood Epilepsy. Clobazam has equivalent efficacy to carbamazepine and phenytoin as monotherapy for childhood epilepsy. Epilepsia 1998;39:952–959.
48. Vining EP, Mellits ED, Dorsen MM, et al. Psychologic and behavioral effects of antiepileptic drugs in children: a double-blind comparison between phenobarbital and valproic acid. Pediatrics 1987;80:165–174.
49. Chen YJ, Kang WM, So WCM. Comparison of antiepileptic drugs on cognitive function in newly diagnosed epileptic children: a psychometric and neurophysiological study. Epilepsia 1996;37:81–86.
50. Berg I, Butler A, Ellis M, Foster J. Psychiatric aspects of epilepsy in childhood treated with carbamazepine, phenytoin or sodium valproate: a random trial. Dev Med Child Neurol 1993;35:149–157.
51. Forsythe I, Butler R, Berg I, McGuire R. Cognitive impairment in new cases of epilepsy randomly assigned to carbamazepine, phenytoin and sodium valproate. Dev Med Child Neurol 1991;33:524–534.
52. Thilothammal N, Banu K, Tatnam RS. Comparison of phenobarbitone, phenytoin with sodium valproate: Randomized, double-blind study. Indian Pediatr 1996;33:549–555.
53. Aman MG, Werry JS, Paxton JW, Turbott SH. Effects of phenytoin on cognitive–motor performance in children as a function of drug concen-

tration, seizure type, and time of medication. Epilepsia 1994;35:172–180.
54. Aman MG, Werry JS, Paxton JW, Turbott SH, Steward AW. Effects of carbamazepine on psychomotor performance in children as a function of drug concentration, seizure type, and time of medication. Epilepsia 1990;31:51–60.
55. Aman MG, Werry JS, Paxton JW, Turbott SH. Effect of sodium valproate on psychomotor performance in children as a function of dose, fluctuations in concentration, and diagnosis. Epilepsia 1987;28:115–124.
56. De Silva M, MacArdle B, McGowan M, et al. Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy. Lancet 1996; 347:709–713.
57. Calandre EP, Dominguez-Granados R, Gomez-Rubio M, Molina-Font JA. Cognitive effects of long-term treatment with phenobarbital and valproic acid in school children. Acta Neurol Scand 1990;81:504–506.
58. Williams J, Bates S, Griebel ML, et al. Does short-term antiepileptic drug treatment in children result in cognitive or behavioral changes? Epilepsia 1998;39:1064–1069.
59. Stores G, Williams PL, Styles E, Zaiwalla Z. Psychological effects of sodium valproate and carbamazepine in epilepsy. Arch Dis Child 1992; 67:1330–1337.
60. Mandelbaum DE, Burack GD. The effect of seizure type and medication on cognitive and behavioral functioning in children with idiopathic epilepsy. Dev Med Child Neurol 1997;39:731–735.
61. Verity CM, Hosking G, Easter DJ. A multicentre comparative trial of sodium valproate and carbamazepine in pediatric epilepsy. Dev Med Child Neurol 1995;37:97–108.
62. Prasad AN, Setfanelli M, Nagarajan L. Seizure exacerbation and developmental regression with carbamazepine. Can J Neurol Sci 1998;25: 287–294.
63. Dreifuss FE, Langer DH, Moline KA, Maxwell JE. Valproic acid hepatic fatalities. II. US experience since 1984. Neurology 1989;39:201–207.
64. Dreifuss FE, Rosman NP, Cloyd JC, et al. A comparison of rectal diazepam gel and placebo for acute repetitive seizures. N Engl J Med 1998;338:1869–1875.
65. Morton LD, Rizkallah E, Pellock J. New drug therapy for acute seizure management. Semin Pediatr Neurol 1997;4:51–63.
66. Jacobs MP, Fischbach GD, Davis MR, et al. Future directions for epilepsy research. Neurology 2001;57:1536–1542.