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

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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.

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
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 Pediatrics6 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 tonic 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 (=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-
Regarding 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.” 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. There is evidence from animal models that prolonged or recurrent seizures, under certain circumstances, cause neuronal injury and predispose to epilepsy. 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. The relevance of data from these animal models to seizures in humans is unclear. Data from children indicate that even prolonged seizures rarely cause clinically discernible brain damage unless associated with an underlying acute neurologic insult.

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. 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. 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. 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.

**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). At any given time, the reported risk of recurrence is highly variable. For example, at 1 year, it ranges from a low of 14% to a high of 65%. 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. 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
enrolled experienced ≥4 seizures and only 10% experienced ≥10 seizure episodes. Few of the children in either study met criteria for intractability.

### 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. 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. 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. 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, and for remote symptomatic seizures, the estimate of recurrence risk is generally above 50%. An EEG performed after the initial seizure also helps to predict recurrence, 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. In the absence of an acute or progressive brain injury or disease, the morbidity and mortality of status epilepticus in children are relatively low. 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.

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. 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 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. 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. Only one of these studies consisted solely of children randomized to treatment versus no treatment after a first nonfebrile seizure (Class II). 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%)
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. 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.

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. 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.

### 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. 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 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 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, 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.

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...
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 irritability50,51 (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 effects.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Age, y</th>
<th>Follow-up</th>
<th>Medication (n)</th>
<th>Reported side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50,51</td>
<td>5–14</td>
<td>1 y</td>
<td>CBZ (23)</td>
<td>Impaired recent recall, reported slow by teachers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PHT (20)</td>
<td>Impaired information processing at 1 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VPA (21)</td>
<td>No change</td>
</tr>
<tr>
<td>49</td>
<td>7–15</td>
<td>6 and 12 mo</td>
<td>CBZ (26)</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PB (25)</td>
<td>Disturbed information processing (auditory event-related potentials prolonged)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VPA (25)</td>
<td>No change</td>
</tr>
<tr>
<td>47</td>
<td>2–16</td>
<td>12 mo</td>
<td>CBZ (78)</td>
<td>29 of total of 116 had moderate/severe behavior problems</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PHT (38)</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>6–14</td>
<td>6 mo</td>
<td>PB (26)</td>
<td>Did less well on cognitive tests, more hyperactivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VPA</td>
<td>No change</td>
</tr>
<tr>
<td>53</td>
<td>6–12</td>
<td>12 mo</td>
<td>CBZ (50)</td>
<td>No difference high vs. low level</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VPA (46)</td>
<td>Low doses gave better accuracy and response time</td>
</tr>
<tr>
<td>54</td>
<td>6–15</td>
<td>12 mo</td>
<td>PHT (50)</td>
<td>No difference high vs. low level</td>
</tr>
<tr>
<td>55</td>
<td>4–12</td>
<td>2 y</td>
<td>PB (51)</td>
<td>22% hyperactivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VPA (48)</td>
<td>13% hyperactivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PHT (52)</td>
<td>8% impaired school performance</td>
</tr>
<tr>
<td>Class 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>3–16</td>
<td>3 y</td>
<td>PB (10)</td>
<td>6 withdrew owing to side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PHT (50)</td>
<td>5 withdrew owing to side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CBZ (54)</td>
<td>2 withdrew owing to side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VPA (49)</td>
<td>2 withdrew owing to side effects</td>
</tr>
<tr>
<td>51</td>
<td>Average</td>
<td>12 mo</td>
<td>VPA (26)</td>
<td>Increase in IQ</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td></td>
<td>PB (23)</td>
<td>Significant impairment in learning</td>
</tr>
<tr>
<td>58</td>
<td>6–17</td>
<td>6 mo</td>
<td>CBZ (17)</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VPA (11)</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PHT (1)</td>
<td>No difference</td>
</tr>
<tr>
<td>59</td>
<td>7–12</td>
<td>12 mo</td>
<td>VPA (34)</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CBZ (29)</td>
<td>No difference</td>
</tr>
<tr>
<td>60</td>
<td>4–16</td>
<td>26–6 mo</td>
<td>CBZ (5)</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>12–12 mo</td>
<td></td>
<td>VPA (3)</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ethosuximide (4)</td>
<td>No difference</td>
</tr>
</tbody>
</table>

CBZ = carbamazepine; PHT = phenytoin; VPA = valproic acid; PB = phenobarbital.
and in another, children taking PB did not show an expected increase in IQ on retest.\textsuperscript{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 impair-
ment\textsuperscript{58-60} (see table 5).

A report from the American Academy of Pediatrics\textsuperscript{44} regarding general recommendations for aware-
ness of behavioral and cognitive effects of AED noted that high blood levels of some AED (PHT, PB, primi-
done) were significantly related to cognitive decline. Cognitive and behavioral effects of AED were de-
scribed as subtle and affecting isolated functions. These effects were seen in conjunction with academic
underachievement and neuropsychological impair-
ment in children with epilepsy.

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

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

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

effects,\textsuperscript{56} and in another, children taking PB did not show an expected increase in IQ on retest.\textsuperscript{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 impair-
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done) were significantly related to cognitive decline. Cognitive and behavioral effects of AED were de-
scribed as subtle and affecting isolated functions. These effects were seen in conjunction with academic
underachievement and neuropsychological impair-
ment 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).\textsuperscript{47} Another Class I study reported that of 23 children on CBZ, 3 experienced headache, an-
orexia, nausea or abdominal pain, and increased irri-
tability. Systemic side effects were not reported for
the 20 children on PHT or the 21 on VPA.\textsuperscript{56,51} Drop-
out because of failure to comply with treatment, pos-
sibly 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 sei-

zures only, 2 of 14 children on CBZ discontinued medication because of rash and 2 of 14 because of
excessive somnolence.\textsuperscript{41} When four drugs were com-
pared 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.\textsuperscript{56} Included were behavioral problems,
drowsiness, sleep problems, blood dyscrasia, hirsut-
ism, and tremor. A randomized and blinded prospec-
tive 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 experi-
enced gingival hyperplasia, and 25\% had dose-
related ataxia or sedation. Follow-up was 2 years.\textsuperscript{52}

In a Class II study of 130 children assigned to VPA
and 130 assigned to CBZ, by 1 year, 13\% discontin-
ued VPA and 7\% discontinued CBZ owing to adverse
effects such as increased appetite, weight gain, alopecia
and CBZ/H11005

CBZ/H11005 carbamazepine; PHT/H11005 phenytoin; VPA/H11005 valproic acid; PB/H11005 phenobarbital; h/a/H11005 headache; n&v/H11005 nausea and vomiting; d/c/H11005 discontinued.

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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. 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.

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 (≥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.

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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 Aschwal, MD; Richard M. Dubinsky, MD; Jacqueline French, MD; Gary H. Friday, MD; Michael Gantz, MD; James Levesque, 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; Bhavan P. Garg, MD; Brian Grabert, MD; Annette Grefe, MD; Michael Goldstein, MD; David Griessemer, MD; Betty Koo, MD; Edward Kovnar, MD; Leslie Anne Morrison, MD; Colette Parker, MD; Ben Renfroe, MD; Anthony Riel, MD; Michael Shevell, MD; Shlomo Shinnar, MD; Gerald Silverboard, MD; Russell Snyder, MD; Dean Timms, MD; Greg Yim, MD; Mary Anne Whelan, MD.

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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*

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