Epilepsy in Childhood

An Audit of Clinical Practice

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Background: It is not known how many children with epilepsy may not need treatment with antiepileptic drugs (AEDs), how many respond unsatisfactorily to subsequent treatment regimens, and how many achieve "acceptable control" despite lack of remission.

Methods: In a prospective multicenter hospital-based study, 494 children with a broad range of seizure types and types of epilepsy were followed up for at least 2 years. There was no standard treatment protocol. We describe the treatment strategies applied to these children by the neurologists in charge and outcome with respect to remission from seizures.

Results: Treatment was initially withheld in 29% of the children, and after 2 years 17% still had not received any AEDs. There were no serious complications caused by withholding treatment. Of the children treated with AEDs, 60% were still using the first AED after 2 years; 80% received monotherapy and 20%, polytherapy. Children with severe symptomatic epilepsies, such as the West or Lennox-Gastaut syndrome, received polytherapy early on in the course of treatment. When 3 regimens had failed, the chance of achieving a remission of more than 1 year with subsequent regimens was 10%. Nevertheless, 15 of 50 children receiving AEDs in whom the "longest remission ever" was less than 6 months did achieve acceptable seizure control according to the neurologist in charge of treatment. Hence, of 494 children, only 35 (7%) developed an intractable form of epilepsy, defined as failure to bring seizures under acceptable control.

Conclusions: A substantial percentage of children with new-onset epilepsy did not need treatment with AEDs. Chances of achieving a good outcome declined with subsequent treatment regimens. Not all children with recurrent seizures were suffering from intractable epilepsy; some had achieved acceptable control of seizures.

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TREATMENT strategies in childhood epilepsy are not simple and uniform. There is no universally applicable standard of treatment. Many unproved assumptions influence treatment decisions and may confound the perspective on important questions regarding the treatment of epilepsy. Publications that propose an algorithm of treatment in childhood epilepsy disagree on many issues. A basic point of discussion involves which children with seizures should be treated. It has been suggested that children with a first single seizure should not be treated, but children with few or minor seizures may not need treatment with antiepileptic drugs (AEDs) either.[1-3] It is not known what proportion of children can safely be left without treatment. When treatment is considered appropriate, only global guidelines are available to aid AED selection, although physicians may hold strong individual opinions.[4] Specific recommendations for treatment are only given for some specific seizure types, such as absences, infantile spasms, and myoclonic or atonic seizures.[5] There is

no evidence that indicates how to treat patients who fail to respond to an adequate first AED regimen, although most authors agree that for first- and second-choice therapy, monotherapy is generally preferable to polytherapy.[6-9] The usefulness of polytherapy, the correct moment to initiate it, and what combinations of AEDs to use are still matters of opinion rather than of comparative evidence.[7,10] At some point, when a number of AEDs have failed to provide complete control of seizures and when the consequences of seizures are not acceptable, the epilepsy can be classified as intractable. However, many different definitions to identify children with "intractable epilepsy" are being used. Most researchers[11,12] use operational criteria based only on seizure frequency or lack of remission. The essence of the concept of intractable epilepsy, however, is failure to bring seizures under "acceptable control."[13,14]

In the Dutch Study of Epilepsy in Childhood (DSEC),[15] a large prospective multicenter hospital-based study on the prognosis of newly diagnosed childhood epilepsy, the child neurologists were al-

PATIENTS AND METHODS

SETTING

The Departments of Child Neurology of 1 children's hospital, 1 general hospital, and 2 university hospitals in the Netherlands participated in the DSEC. All children in the study were treated by 1 of 4 child neurologists (W.F.M.A., H.S., O.F.B., or A.C.B.P.).

PATIENTS

Consecutive new referrals, aged 1 month to 16 years, who had had 2 or more idiopathic, cryptogenic, or remote symptomatic seizures were included. We excluded children with neonatal seizures only, acute symptomatic seizures, children referred from another hospital (to avoid selection bias toward unusually severe cases), and children with a history of epilepsy or treatment with AEDs (except for neonatal or febrile convulsions).

A diagnosis of epilepsy (2 or more unprovoked seizures) was made by a committee of child neurologists (W.F.M.A., H.S., O.F.B., and A.C.B.P.), using predefined diagnostic criteria. Seizures were categorized according to the 1981 classification of the International League Against Epilepsy.[16] In case of multiple seizure types, classification was based on the most troublesome seizures. Epilepsy was classified according to the 1989 International League Against Epilepsy criteria, 2 years after study enrollment was completed.[17] Children were followed up at regular intervals for at least 2 years until the end point of the study.

TREATMENT

The neurologists were free to decide when to initiate AED treatment, and the time between patient enrollment and start of treatment was noted. A delay in treatment was defined as treatment initiated more than 3 months after enrollment in the study, because a short delay could often be attributed to diagnostic or unintentional logistic causes. Any marketed AED was available for initial and subsequent treatment, but it was agreed to use valproic acid or carbamazepine as principal first-choice AEDs and to use monotherapy as the first regimen. Polytherapy was to be selected only when at least 2 AEDs had failed as monotherapy. When polytherapy was considered appropriate, several first- and second-line AEDs could be combined. Initial medication and subsequent changes were noted on follow-up questionnaires. Polytherapy was defined as the concurrent use of 2 or more AEDs for more than 1 month; hence, a short overlap between 2 AEDs when one was gradually being replaced by another was not considered polytherapy. Temporary polytherapy for status epilepticus or an episode of corticotropin treatment in combination with a conventional AED was not included in the analysis as polytherapy. An AED regimen was considered to have failed when it was replaced by a new AED or a new combination of AEDs. In some children, when seizures were quickly and completely controlled, AED treatment was successfully discontinued during the follow-up period. These children were analyzed as if they were still receiving the discontinued AED therapy after 2 years. The results of discontinuation of AED therapy will be published separately.

OUTCOME

We analyzed the number of children not receiving any AED 2 years after enrollment in the study and until the end point of the study. For children receiving AEDs, we noted the number of subsequent treatment regimens that had been given after 2 years of medication and the number of children using monotherapy and polytherapy. We also studied the relationship between seizure type and the selection of the first AED and the reasons for failure of the first AED.

The duration of any remission from seizures was calculated from seizure calendars. Outcome with respect to seizure control was classified as *good* (terminal remission, as measured 2 years after the start of medication, more than 12 months), *fair* (terminal remission, between 6 and 12 months), or *poor* (terminal remission <6 months). When seizure calendars were considered unreliable, eg, when pseudoseizures were intermingled with genuine seizures, when patients were unavailable for follow-up, or when follow-up was less than 2 years after the start of medication, the outcome classification was discarded. In patients without medication, we assessed outcome 2 years after inclusion. Children with poor compliance were included in the analysis because the reasons for noncompliance were not systematically registered and may have included lack of efficacy or intolerable side effects and because their outcome was not different from the outcome of the entire group.

To identify cases with intractable epilepsy, we selected children in whom, despite treatment with AEDs, the "longest remission ever" was less than 6 months during the entire follow-up period. Within this group of children, we identified children who had received no new AEDs or increased dosage of AEDs during the last 6 months of follow-up. We explored the possibility that control of seizures had been "acceptable" in these children. For this purpose, we issued a retrospective questionnaire to the pediatric neurologist in charge. The neurologist was asked whether, in his/her opinion, the child had achieved acceptable control during the last 6 months of follow-up and, if so, whether this was attributable to a low seizure frequency, to an acceptable severity of seizures, or to other reasons. When seizure control was found not to be acceptable, the physician could confirm whether he/she had decided not to change the AED regimen because there were no reasonable alternatives left, or state other reasons.

DATA ANALYSIS

This is a primarily descriptive study. All data were analyzed using SPSS statistical software (SPSS Inc, Chicago, Ill). χ^2 Tests were used to analyze significance of differences between groups.

lowed to choose the medical treatment they considered the most appropriate for any particular child. The following options were available: (1) no medical treatment; (2) monotherapy with several first-line AEDs, preferably valproic acid or carbamazepine; and (3) combined therapy with first- and second-line AEDs.

Our primary purpose was to audit the treatment strategies chosen by the participating neurologists. We were interested in the following questions: How many children with epilepsy are not treated with AEDs? How does the selection between first-choice AEDs relate to seizure type? Which strategies are chosen in

Table 1. Epilepsy and Seizure Classification*			
	No. of Children		
	Total Group	**Untreated†**	**Treated†**
Epilepsy Classification			
Localization-related	194 [39]	32 (41) [6]	162 (39) [33]
Idiopathic (with age-related onset)	30 [6]	7 (9) [1]	23 (6) [5]
Symptomatic	71 [14]	9 (12) [2]	62 (15) [13]
Cryptogenic	93 [19]	16 (21) [3]	77 (19) [16]
Generalized	279 [56]	40 (51) [8]	237 (57) [48]
Idiopathic (with age-related onset)	205 [42]	36 (46) [7]	169 (41) [34]
Cryptogenic and/or symptomatic	74 [15]	4 (5) [1]	70 (17) [14]
Other/not classified	21 [4]	6 (8) [1]	15 (4) [3]
Total	**494 [100]**	**78 (100)** [16]	**416 (100)** [84]
Seizure Type			
Generalized tonic-clonic	297 [60]	57 (73) [12]	240 (58) [49]
Complex partial	49 [10]	7 (9) [1]	42 (10) [9]
Simple partial	26 [5]	5 (6) [1]	21 (5) [4]
Absences	61 [12]	5 (6) [1]	56 (14) [11]
Other/not classified	61 [12]	4 (5) [1]	57 (14) [11]
Total	**494 [100]**	**78 (100)** [16]	**416 (100)** [84]

*Numbers in brackets indicate percentages of the total group (494 children); numbers in parentheses, column percentages.

†Until the end point of the study, minimal follow-up of 2 years. Comparing treated and untreated children: differences in epilepsy classification were not significant; differences in seizure type were significant (P=.05).

case of failure of the first AED? Can we identify children who are not suffering from intractable epilepsy despite the lack of a substantial remission from seizures?

RESULTS

During the 4-year enrollment period, 494 children who had had 2 or more unprovoked seizures were included. Median age at enrollment was 5.5 years (range, 0.1-15.8 years); 239 (48%) were boys. Two hundred fifty-four children (51%) were referred by a general physician, 125 (25%) were referred by a pediatrician, and 78 (16%) came directly to an emergency department; the referral pattern was unknown in 37 (8%).

Seven children (1%) were unavailable for follow-up (2 without treatment, follow-up 1 and 18 months, respectively; 5 receiving AED treatment, follow-up 3 [n=2] and 12 [n=3] months after start of medication). Three children died during the follow-up period, all of whom were receiving AEDs. An additional 17 children were not followed up for 2 years after the initiation of AED treatment, because treatment was not started immediately after enrollment. Hence, they reached the end point of the study (August 1994) before they had been receiving medication for 2 years. Treatment analysis included these 17 children as if they had been followed up for 2 years after treatment. However, they were not included in the classification of outcome with respect to remission. The classification of epilepsy and seizures of the total cohort is given in **Table 1**.

UNTREATED CHILDREN

Three months after enrollment, 142 children (29%) were not receiving AEDs. Two years after enrollment, 82 (17%) had still received no AED treatment. Seventy-eight children (16%) were not given any AEDs until the end point of the study. There was no significant difference in the overall epilepsy classification of children treated and not treated with AEDs if unclassified cases were omitted (Table 1). The untreated group included more children with "other/unclassified" epilepsy and fewer children with "cryptogenic and/or symptomatic" generalized epilepsy than the treated group. There was a significant difference in seizure classification between the untreated and treated groups (P=.05, Table 1). The untreated group included more children with generalized tonic-clonic seizures and fewer with absences and other/not classified seizures (including myoclonic and atonic seizures). After 2 years, 73 untreated children showed the following outcomes: good (n=58 [79%]), fair (n=3 [4%]), and poor (n=12 [16%]). Outcome could not be classified in 5 children.

FIRST-CHOICE AEDs

Median time after enrollment in the study until the start of treatment with an AED was 18 days (25-75 percentiles, 2-58 days). In accordance with our protocol, the first AED regimen was monotherapy in all cases. **Table 2** lists the AEDs used as first-choice medication and the distribution of seizure types per AED. Eighty-eight percent of the children were initially treated with valproic acid or carbamazepine.

Two years after the start of treatment, 250 children (60%) were still using the first-choice AED or had successfully discontinued treatment. Their outcomes with respect to terminal remission are listed in **Table 3**.

FAILURE OF THE FIRST AED: SUBSEQUENT TREATMENT STRATEGIES

Of the 416 children who were treated with AEDs, 166 (40%) did not respond successfully to their first AED and used at least 1 alternative or additional AED. Reasons for failure of the first AED were recurrent seizures (n=115 [28%]); intolerable side effects (n=47 [11%]) (with or without recurrent seizures); initial misclassification of seizures (n=2); and unknown (n=2). The intolerable side effects were rashes in 15 children (4%), 14 of whom were receiving carbamazepine (10% of all children who initially received carbamazepine) and 1 of whom was receiving valproic acid; there were other intolerable adverse effects in 32 children (8%), without substantial differences between AEDs.

Table 3 shows that there was a clear negative association between the number of AED regimens tried and the chance of achieving a substantial remission. When 3 regimens had failed, the chance of achieving a good outcome with subsequent regimens was only 10%. None of the children who had experienced failure with 4 or more AED regimens achieved a good outcome during the follow-up period.

Table 2. First Antiepileptic Drug (AED) Regimen: Selection of AED and Seizure Type*

AED	No. of Children	Seizure Type				
		GTC	CPS	SPS	Abs	Other
Valproate	221 (53)	122 (51)	14 (33)	5 (24)	53 (95)	27 (47)
Carbamazepine	147 (35)	100 (42)	24 (57)	16 (76)	1 (2)	6 (11)
Benzodiazepines	13 (3)	2 (1)	1 (2)	0	0	10 (18)
Phenytoin	12 (3)	8 (3)	2 (5)	0	1 (2)	1 (2)
Phenobarbital	9 (2)	7 (3)	0	0	0	2 (4)
Corticotropin	6 (1)	0	0	0	0	6 (11)
Ethosuximide	4 (1)	1 (0.5)	1 (2)	0	1 (2)	1 (2)
Vigabatrin	4 (1)	0	0	0	0	4 (7)
Total	**416**	**240** [58]	**42** [10]	**21** [5]	**56** [14]	**57** [14]

Numbers in parentheses indicate column percentages; numbers in brackets, row percentages; GTC (primary or secondary), generalized clonic-tonic seizure; CPS, complex partial seizure; SPS, simple partial seizure; Abs, absence; and Other, other or unclassified seizure type. Classification of seizures was based on ILAE guidelines.[15] In case of more than 1 seizure type, the most troublesome type is listed.

Table 3. Children Receiving Antiepileptic Drugs (AEDs): Retention in Subsequent Treatment Regimens and Outcome With Respect to Terminal Remission 2 Years After Initiation of Therapy*

AED Regimen	Treatment			Outcome			
	Monotherapy	Polytherapy	Total	Good	Fair	Poor	Not Classified
First	250 [100]	0 [0]	**250** (51)	144 [63]	35 [15]	49 [22]	22
Second	74 [80]	19 [20]	**93** (19)	45 [51]	11 [13]	32 [36]	5
Third	5 [17]	24 [83]	**29** (6)	8 [29]	6 [21]	14 [50]	1
Fourth	4 [13]	26 [87]	**30** (6)	3 [10]	3 [10]	24 [80]	0
Fifth	1 [11]	8 [89]	**9** (2)	0 [0]	0 [0]	9 [100]	0
Sixth	0 [0]	4 [100]	**4** (1)	0 [0]	0 [0]	4 [100]	0
Seventh	0 [0]	1 [100]	**1** (0)	0 [0]	0 [0]	1 [100]	0
Total No. of AEDs	**334** [80]	**82** [20]	**416** (84)	**200** [52]	**55** [14]	**133** [34]	**28**

Numbers in brackets indicate row percentages; numbers in parentheses, column percentages; good, terminal remission more than 12 months during 2 years of follow-up after initiation of therapy; fair, terminal remission more than 6 months and less than 12 months; and poor, terminal remission less than 6 months. Numbers and percentages of children in treatment regimens include 8 children who were followed up for less than 2 years. Outcome was not classified in children who were unavailable for follow-up or followed up for less than 2 years or when seizure calendars were unreliable. Outcome percentages only refer to children who could be evaluated.

MONOTHERAPY/POLYTHERAPY

Two years after the start of treatment, 334 (80%) of the 416 children receiving AEDs were treated with monotherapy and 82 (20%) with polytherapy. Polytherapy regimens consisted of 2 AEDs in 65 children and 3 AEDs in 17 children. Twenty-five (30%) of the 82 children who received polytherapy had tried 2 monotherapy regimens.

In total, 42 different AEDs or combinations of AEDs were used. The most frequently chosen combinations of AEDs were valproate with a benzodiazepine (clobazam was used more than other benzodiazepines), valproic acid with carbamazepine, and valproic acid with ethosuximide.

The classification of epilepsy of the 82 children receiving polytherapy at 2 years included a greater proportion with symptomatic/cryptogenic epilepsy as compared with the group as a whole. Of the cases of localization-related epilepsy, 2 were classified as idiopathic and 29 as symptomatic/cryptogenic; of the cases of generalized epilepsy, 17 were classified as idiopathic and 34 as symptomatic/cryptogenic.

ACCEPTABLE CONTROL DESPITE LACK OF A REMISSION

Fifty children had a longest remission ever of less than 6 months despite treatment. Hence, these children were suffering from intractable epilepsy when this concept was defined as lack of remission alone. Of these 50 children, 32 had had adjustments in their AED regimen during the last 6 months, suggesting that their seizure control had not been acceptable. Eighteen children had had no change in their AED regimen (including increased dosages) during the last 6 months of follow-up. Thus, we explored whether seizures had been acceptably controlled despite the lack of a substantial remission in these 18 children.

In response to our retrospective questionnaire concerning these 18 children, the neurologists stated that the AED was not changed because acceptable control was achieved in 15 children and because there were no further options for treatment in 3 children. They attributed acceptable control to low seizure frequency in 12 children and/or low seizure severity in 8 children. The reported lack of alternative options was attributed to poor

compliance in 1 child. One child with acceptable control had few and mild seizures, but the seizures were also often self-induced, and this was an additional reason for not having adjusted the therapy further.

COMMENT

This analysis of data of the DSEC provides a descriptive overview of the treatment strategies chosen by the neurologists in charge. Our cohort comprised children with all seizure types and a broad variety of types of epilepsy and epileptic syndromes, as seen in 4 primary referral centers.

NO AED TREATMENT

All children in the study had had at least 2 unprovoked seizures. Nevertheless, treatment was initially withheld in 29%, and this approach could be continued in more than 50% of these children. In 17%, no AEDs were given during a follow-up of 2 years after enrollment in the study, and only 4 children received their first AED more than 2 years after enrollment. Because there is no evidence that AEDs influence the natural course of epilepsy or that untreated epilepsy commonly evolves into a progressive disease,[18] AED treatment might essentially be palliative. It has been suggested that most children with epilepsy should receive an AED only when the impact of recurrent seizures outweighs the possible adverse effects of medication.[1-3] Our data provide a minimum estimation of the proportion who may not need AEDs, because in most children we have not tried to withhold treatment. We know of no other comparable data indicating how many children with epilepsy may not need treatment with AEDs. Our data suggest that both parents and neurologists of the children in our sample have reservations about starting drug therapy early on in the disease, but we had no detailed information about their motivation not to start treatment in individual cases. There were no adverse events such as seizure-related serious injuries or deaths in the untreated group. The high percentage of untreated children achieving a terminal remission of more than 1 year points to a selection process during follow-up. A group of children with a relatively favorable prognosis for spontaneous remission were not treated initially, and most children who nevertheless had 1 or more recurrences were given medication at a later date.

FIRST-CHOICE TREATMENT

Use of the first-choice AED was retained for 2 years in 250 (60%) of 416 children and resulted in a terminal remission of more than 1 year in 63%. In 2 randomized studies of children with epilepsy, the allocated AED was successful in a somewhat larger percentage.[4,19] However, an important difference between our population and those of the randomized studies is that we have included children with all seizure types, rather than only children with simple, complex partial, or generalized tonic-clonic seizures. This difference clearly pertains to the choice of AED therapy and to the prognosis.

In the study protocol, valproic acid and carbamazepine were chosen as the main AEDs for initial treatment, a choice based on considerations of toxic effects and pharmacokinetics. At the time we embarked on our study, phenobarbital was already recognized as a relatively toxic AED, and in the present investigation, it was used only as a first AED in exceptional cases. Phenytoin has a more complex pharmacokinetic profile than carbamazepine or valproic acid and may be associated with more long-term adverse effects.

We noted a trend to select valproic acid therapy for children with generalized seizures and carbamazepine therapy for children with partial seizures. This is probably common clinical practice[5,7,10] supported by the results of one comparative trial in adults.[20] Recent comparative studies in adults[21,22] and children[4,19] showed no significant differences in efficacy between valproic acid and carbamazepine therapy for generalized or partial seizures, but the findings were published after the enrollment period of our study.

We included children with seizure types associated with severe symptomatic epilepsy, such as infantile spasms or atonic seizures. In the majority of cases in which a benzodiazepine, corticotropin, or vigabatrin was chosen as the initial treatment, children had one of these seizure types; many of them had the West or Lennox-Gastaut syndrome. Vigabatrin was licensed in the Netherlands in 1991, and only children who were included after this date could be treated with this AED.

Furthermore, we included children with absences. For this seizure type, valproic acid and ethosuximide are probably equally effective and most other AEDs are ineffective. Valproic acid was used as the first AED in almost all children with absences, and ethosuximide was used as the second AED in case of failure of valproic acid therapy. Some authors have recommended ethosuximide as first-choice AED for childhood absences because it is not associated with the possibility of severe hepatotoxic effects.[2,5,9] We had no occurrences of valproic acid–induced hepatotoxic effects in our study. The advantage of using valproic acid as the first-choice AED in absences is its efficacy against tonic-clonic seizures, which may be associated with absences.

FAILURE OF THE FIRST AED

The first AED failed in 166 (40%) of 416 treated children. Recurrent seizures were the main reason to replace the first AED. On the whole, intolerable side effects due to first AEDs were relatively rare (11% of cases). Verity et al[19] reported intolerable side effects related to the randomized AED use in about 13% of cases and de Silva et al[4] in about 4%. However, patient reports of many adverse effects due to the use of AEDs are subjective and, because a standardized assessment in this and most other studies was lacking, results with respect to such adverse effects are difficult to compare. It often remains unclear why an effect is considered intolerable. In our study, rashes occurred in 4% of the children receiving their first AED regimen and were strongly associated with the use of carbamazepine. Others have suggested that such allergic reactions to carbamazepine are relatively rare in children compared with adults.[4,19] We noted a prevalence of rash associated with the use of carbamazepine comparable with that found in adult studies.[20,21]

After failure of treatment with the first AED, alternative or additional AEDs were prescribed in about 40% of the children. In 2 randomized studies, 29%[4] to 34%[19] of the children received alternative or additional AEDs. The inclusion here of epileptic syndromes with a poor prognosis may explain why our percentage of first AED failures was higher.

When designing our protocol, we agreed, whenever possible, to try 2 monotherapies before switching to polytherapy. There is no experimental evidence regarding the optimal number of monotherapy regimens before the patient can be considered a candidate for polytherapy,[23] but most authors recommend exhaustive[9] or at least 2[10] monotherapy trials of first-line AEDs before polytherapy is initiated. In our study, however, the percentage of children receiving polytherapy who had first tried 2 first-line AEDs as monotherapy was only 30%, despite our initial intentions. The use of polytherapy as the second step in treatment was associated with poor control of seizures and symptomatic epilepsy such as the West or Lennox-Gastaut syndrome. These children may have already received polytherapy, after treatment with the first AED failed, because it is well known that it is often necessary to combine drugs, eg, valproic acid and a benzodiazepine, to achieve acceptable control in such cases.[24]

In our study, a terminal remission of at least 1 year was achieved in 56 (34%) of the 166 children whose first AED regimen failed. After failure of 4 AED regimens, a remission of more than 1 year was not achieved during our 2-year follow-up. In the first Department of Veterans Affairs multicenter study, failure of the first AED therapy was followed by "successful" alternative AED therapy in a somewhat higher percentage (46%) of adult patients.[25]

ACCEPTABLE CONTROL AND INTRACTABLE EPILEPSY

Intractable epilepsy is probably best defined as a subjective concept that implies failure to bring seizures under acceptable control,[13] and what exactly is acceptable depends largely on the individual case. Clearly, it is difficult to translate such a definition into scientific data. In our study, 50 of 416 children treated with AEDs achieved no substantial remission, but our data suggest that acceptable control was nevertheless achieved in 15 of these children. Thus, only 35 children (7% of the cohort) were really suffering from intractable epilepsy.

We have not been able to focus on the reasons for certain choices regarding treatment; more specific assessments of the impact of seizures and adverse effects of AEDs in individual cases would have been useful. Such data may also be helpful in properly identifying children with intractable epilepsy. We have developed subjective parent-completed scales quantifying the severity of seizures and adverse effects of medication.[26] In general, a broad outcome assessment, including measures pertaining to quality of life, is relatively complex compared with traditional measures, but will give better insight into the strategies chosen in the treatment of childhood epilepsy and their results.

REFERENCES

1. Freeman JM. A clinical approach to the child with seizures and epilepsy. *Epilepsia*. 1987;28(suppl 1):S103-S109.
2. Bourgeois BFD. Pharmacologic intervention and treatment of childhood seizure disorders: relative efficacy and safety of antiepileptic drugs. *Epilepsia*. 1994;35 (suppl 2):S18-S23.
3. Shinnar S, O'Dell C. Treating childhood seizures: when and for how long? In: Shinnar S, Amir N, Branski D, eds. *Childhood Seizures: Pediatric and Adolescent Medicine*. Vol 6. Farmington, Conn: S Karger AG; 1995:100-110.
4. de Silva M, MacArdle B, McGowan M, et al. Randomized comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy. *Lancet*. 1996;347:709-713.
5. Wallace SJ. Seizures in children. In: Laidlaw J, Richens A, Chadwick DW, eds. *A Textbook of Epilepsy*. 4th ed. New York, NY: Churchill Livingstone Inc; 1993:77-164.
6. Reynolds EH, Shorvon SD. Monotherapy or polytherapy for epilepsy? *Epilepsia*. 1981;22:1-10.
7. Dodson WE. Principles of antiepileptic drug therapy. In: Shinnar S, Amir N, Branski D, eds. *Childhood Seizures: Pediatric and Adolescent Medicine*. Vol 6. Farmington, Conn: S Karger AG; 1995:78-92.
8. Duncan JS. Modern treatment strategies for patients with epilepsy: a review. *J R Soc Med*. 1994;84:159-162.
9. French J. The long-term therapeutic management of epilepsy. *Ann Intern Med*. 1994;120:411-422.
10. Aicardi J. Clinical approach to the management of intractable epilepsy. *Dev Med Child Neurol*. 1988;30:429-440.
11. Huttenlocher PR, Hapke RJ. A follow-up study of intractable seizures in childhood. *Ann Neurol*. 1990;28:699-705.
12. Camfield PR, Camfield CS. Antiepileptic drug therapy: when is epilepsy truly intractable? *Epilepsia*. 1996;37(suppl 1):S60-S65.
13. Berg AT, Hauser WA, Shinnar S. The prognosis of childhood-onset epilepsy. In: Shinnar S, Amir N, Branski D, eds. *Childhood Seizures: Pediatric and Adolescent Medicine*. Vol 6. Farmington, Conn: S Karger AG; 1995:93-99.
14. Blume WT. Uncontrolled epilepsy in children. *Epilepsy Res*. 1992;9(suppl 5):19-24.
15. Brouwer OF, Van Donselaar CA, Stroink H, Arts WFM, Geerts AT, Peters ACB. The Dutch Study of Epilepsy in Childhood: design of the study. *Epilepsia*. 1995; 36(suppl 3):S28.
16. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia*. 1981;22:489-501.
17. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia*. 1989;30:389-399.
18. van Donselaar CA, Brouwer OF, Geerts AT, Arts WFM, Stroink H, Peters ACB. Clinical course of untreated tonic-clonic seizures in childhood: prospective, hospital-based study. *BMJ*. 1997;314:401-404.
19. Verity CM, Hosking G, Easter DJ, the Paediatric EPITEG Collaborative Group. A multicentre comparative trial of sodium valproate and carbamazepine in paediatric epilepsy. *Dev Med Child Neurol*. 1995;37:97-108.
20. Mattson RH, Cramer JA, Collins JF, and the Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. *N Engl J Med*. 1992;327:765-771.
21. Richens A, Davidson DLW, Cartlidge NEF, Easter DJ. A multicentre comparative trial of sodium valproate and carbamazepine in adult onset epilepsy. *J Neurol Neurosurg Psychiatry*. 1994;57:682-687.
22. Heller AJ, Chesterman P, Elwes RDC, et al. Phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed adult epilepsy: a randomised comparative monotherapy trial. *J Neurol Neurosurg Psychiatry*. 1995; 58:44-50.
23. Mattson RH. Drug treatment of uncontrolled seizures. *Epilepsy Res*. 1992;5 (suppl):29-35.
24. Mattson RH. Selection of drugs for the treatment of epilepsy. *Semin Neurol*. 1990; 10:406-413.
25. Mattson RH, Cramer JA, Collins JF, VA Epilepsy Cooperative Study Group. Success with alternate antiepileptic drug selection. *Epilepsia*. 1986;27:645.
26. Carpay JA, Vermeulen J, Stroink H, et al. Parent-completed scales for measuring severity of seizures and side effects of antiepileptic drugs in childhood epilepsy: development and psychometric analysis. *Epilepsy Res*. 1996;24:173-181.