CHILDHOOD EPILEPSY:

ALTERNATIVE METHODS

FOR ASSESSING

TREATMENT STRATEGIES

AND OUTCOME

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ALTERNATIVE METHODS FOR ASSESSING TREATMENT STRATEGIES AND OUTCOME

(KINDEREPILEPSIE: ALTERNATIEVE METHODEN
OM BEHANDELINGSSTRATEGIE EN UITKOMST IN KAART TE BRENGEN)

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Cover: "Activities for which restrictions are often advised are bathing, swimming, climbing and riding a bicycle." (Chapter 7).

CONTENTS

1 INTRODUCTION

Epilepsy -defined as recurrent unprovoked seizures- is one of the most common neurological disorders in childhood and adolescence, with an incidence ranging from 50 to 100 per 100.000.[52] The severity of epilepsy intuitively ranges from 'mild' to 'severe', depending on various factors such as seizure frequency and severity, duration of illness, antecedent and concomitant illness, and response to treatment.

Most children with epilepsy are treated with antiepileptic drugs (AEDs). The purpose of treatment is to improve the child's quality of life (QoL) by suppressing the seizures. There is no evidence that all seizures require treatment because seizures cause brain damage, or because untreated epilepsy is a progressive disorder. Hence, the adverse consequences of treatment (e.g. side-effects) may outweigh the benefit of treatment (suppression of seizures). Most children with epilepsy respond very well to treatment with AEDs. However, in about one third of children with newly developed epilepsy a complete remission from seizures is not reached within a short period of time. For these children, it is especially difficult to find the best possible balance between seizure control and side-effects of medication. It is probable that 'acceptable control' can be achieved despite recurrent seizures, and that complete eradication of seizures -at the cost of more side-effects- is not always in the child's best interest.

Chapter 2 of this thesis addresses some controversies in the treatment of children with new onset epilepsy. It explores how many children in an inception cohort of the Dutch Study of Epilepsy in Childhood were not treated with AEDs, and describes the strategies followed by the clinicians when treatment with AEDs was considered necessary. An attempt was made to identify children with 'acceptable control' despite recurrent seizures. The description of outcome in this study was limited to retention on an AED or remission from seizures.

For a very long time, outcome assessment in epilepsy has been restricted to seizure frequency or duration of remission. The limitations of the traditional approach towards outcome assessment in epilepsy become apparent when we realize that 'the best possible balance between seizures and side-effects' or 'acceptable control' are essentially subjective terms. Therefore, outcome assessment in epilepsy may be more complete when measures addressing such subjective issues are included. In the past decade, some additional, alternative methods to improve outcome assessment in epilepsy have been proposed. We felt that the use of QoL instruments for outcome assessment was also appropriate for children

with epilepsy.

Chapter 3 provides a review of the literature on outcome assessment in epilepsy, with an emphasis on clinical issues such as the severity of seizures and side-effects of medication and their relation to quality of life. *Chapters 4,5,6 and 7* report our efforts to develop measures of seizure severity, severity of side-effects and disability due to restrictions in children with epilepsy as perceived by their parents. We provide data on the reliability and validity of these scales and their association with various clinical variables.

According to a recent Lancet Editorial, there is a trend in clinical research to make 'subjectivity scientific'.[82] Unfortunately, clinicians are often not familiar with the required psychometric techniques, which are provided by the social sciences. A comprehensive description of basic psychometric theory, which may help the reader to enjoy some of the chapters in this thesis, can be found elsewhere.[58,103]

2 EPILEPSY IN CHILDHOOD: AN AUDIT OF CLINICAL PRACTICE.

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2.0 ABSTRACT

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 epilepsies were followed 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% and after two years 17 % of the children still had not received any AED. There were no serious complications from withholding treatment. Of the children treated with AEDs, 60% were still using the first AED after 2 years. 80% received mono- and 20% polytherapy. Especially children with severe symptomatic epilepsies like the West or Lennox syndrome received polytherapy early on in the course of treatment. When three regimens had failed, the chance of achieving a remission of more than one year with subsequent regimens was 10%. 15 of 50 children receiving AEDs in whom the 'longest remission ever' was less than 6 months did, nevertheless, 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 regimes. Not all children with recurrent seizures were suffering from intractable epilepsy; some had achieved acceptable control of seizures.

2.1 INTRODUCTION

Treatment strategies in childhood epilepsy are not simple and uniform. There is no universally applicable standard of treatment. Many unproven assumptions influence treatment decisions and may confound the perspective on important questions regarding the treatment of epilepsy. Publications which propose an algorithm of treatment in childhood epilepsy disagree on many issues. A basic point of discussion is which children with seizures should be treated. It has been suggested that children with a first single seizure should not be treated, but also children with few or minor seizures may not need treatment with antiepileptic drugs (AEDs).[21,45,98] 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.[100] Specific recommendations for treatment are only given for some specific seizure types, like absences, infantile spasms, myoclonic or atonic seizures.[118] There is no evidence which 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.[36,39,46,91] The usefulness of polytherapy, the correct moment to initiate it, and with which combinations of AEDs, are still matters of opinion rather than of comparative evidence.[3,36] 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 [23,60] use operational criteria only based on seizure frequency or lack of remission. The essence of the concept of 'intractable epilepsy' is, however, failure to bring seizures under acceptable control.[19,20]

In the Dutch Study of Epilepsy in Childhood (DSEC), a large prospective multicenter hospital-based study on the prognosis of newly diagnosed childhood epilepsy, the child neurologists were allowed 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 valproate or carbamazepine. 3. Combined therapy with first- and second-line AEDs.

It is the primary purpose of this paper 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 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?

2.2 METHODS

2.2.1 Setting

The Departments of Child Neurology of one children's hospital, one general hospital and two university hospitals in The Netherlands participated in the DSEC. Children were treated by one of four child neurologists (HS, WFMA, OFB, ACBP).

2.2.2 Patients

Consecutive new referrals, aged 1 month to 16 years, who had had two 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 towards unusually severe cases), and children with a history of epilepsy or treatment with AEDs (except for neonatal or febrile convulsions).

A diagnosis of epilepsy (two or more unprovoked seizures) was made by a committee of child neurologists (HS, WFMA, OFB, ACBP), using predefined diagnostic criteria. Seizures were categorized according to the 1981 ILAE classification.[28] In case of multiple seizure types, classification was based on the most troublesome seizures. Epilepsy was classified according to the 1989 ILAE criteria, two years after intake.[29] Children were followed at regular intervals for at least two years until the endpoint of the study.

2.2.3 Treatment

The neurologists were free to decide when to start treatment with an AED, and the time between intake and start of treatment was noted. A delay in treatment was defined as treatment initiated more than 3 months after intake into 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 valproate or carbamazepine as principal first-choice AEDs and to use monotherapy as the first regimen. Polytherapy was to be selected only when at least two 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 two or more AEDs for more than one month; hence, a short overlap between two AEDs when one was gradually being replaced by another was not considered polytherapy. Temporary polytherapy for status epilepticus or an episode of ACTH treatment in combination with a conventional AED were not included in the analysis as polytherapy. An AED regimen was considered to have failed when it was re-

placed by a new AED or 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 on the discontinued AED after two years. Results of discontinuation of AEDs will be published separately.

2.2.4 Outcome

We analyzed the number of children not receiving any AED two years after intake and until the endpoint of the study. For children receiving AEDs, we noted how many subsequent treatment regimens had been given after two years of medication, and the number using mono- 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 two years after the start of medication, more than 12 months), 'fair' (terminal remission between 6 and 12 months) or 'poor' (terminal remission less than 6 months). When seizure calendars were considered unreliable, e.g., when pseudoseizures were intermingled with genuine seizures, when patients were lost to 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 two years after inclusion. Children with poor compliance were included in the analysis because the reasons for non-compliance 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 (Arts et al, submitted).

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 six 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 child neurologist in charge. The neurologist was asked whether, in his opinion, the child had achieved 'acceptable control' during the last six months of follow-up and, if so, whether this was due to a low seizure frequency or acceptable severity of seizures or to other reasons. When seizure control was found not to be 'acceptable', the physician could confirm whether he had decided not to change the AED regimen because there were no reasonable alternatives left, or state other reasons.

2.2.5 Data analysis

This is a primarily descriptive study. All data were analyzed using SPSS. Tests of significance of differences between groups were made using Chi-Square analysis.

2.3 RESULTS

During the 4-year intake period, 494 children who had had two or more unprovoked seizures were included. Median age at intake was 5.5 years (range 0.1-15.8); 239 (48%) were boys. 254 (51%) children were referred by a general physician, 125 (25%) by a pediatrician, 78 (16%) came directly to an emergency department and in 37 (8%) the referral pattern was unknown.

Seven children (1%) were lost to follow-up (2 without treatment, follow-up 1 and 18 months, respectively; 5 on AED treatment, follow-up 3 months after start of medication in 2 children, and 12 months in 3 children). Three children died during the follow-up period, all of whom were receiving AEDs. An additional 17 children were not followed for two years after the initiation of medication, because treatment was not started immediately after intake and hence they reached the endpoint of the study (August 1994) before they had been receiving medication for two years. Treatment analysis included these 17 children as if they had been followed for two 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 are listed in Table 2.1. Figure 2.1 shows the time between intake and start of any AED treatment for the entire group. Median time after intake until treatment was 18 days (25-75 percentiles: 2-58 days).

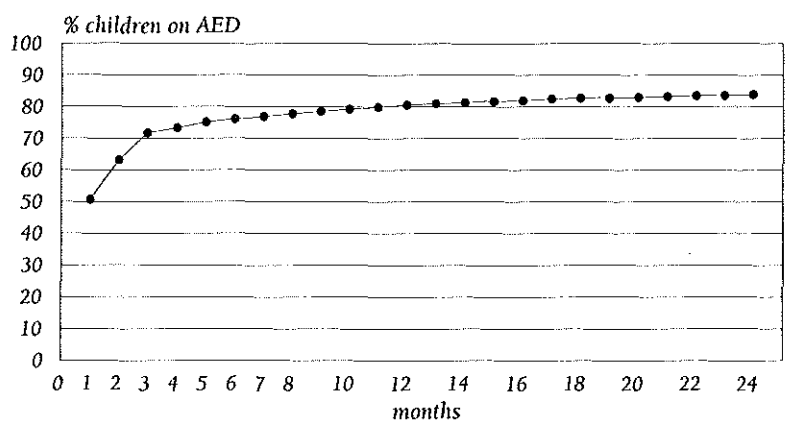

Figure 2.1 Time between intake into the study and start of any antiepileptic drug treatment of a cohort of children with newly developed epilepsy (N=494).

2.3.1 Untreated children

Three months after intake, 142 (29%) children were not receiving AEDs. Two years after intake, 82 (17%) had still received no AED treatment. Seventy-eight (16%) children were not given any AEDs until the endpoint 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 (see Table 2.1). The untreated group included more children with 'other/unclassified' epilepsies and fewer children with 'cryptogenic and/or symptomatic' generalized epilepsies than the treated group. There was a significant difference in seizure classification between the untreated and treated group (P=.05, see Table 2.1). 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 two years, 73 untreated children showed the following outcomes: good in 58 (79%), fair in 3 (4%), poor in 12 (16%). Outcome could not be classified in 5 children.

2.3.2 First-choice AED

In accordance with our protocol, the first AED regimen was monotherapy in all cases. Table 2.2 lists the AEDs used as first-choice medication and the distribution of seizure types per AED. 88% of the children were initially treated with valproate or carbamazepine.

Two years after the start of treatment, 250 (60%) children were still using the first-choice AED or had successfully discontinued it. Their outcomes with respect to terminal remission are listed in Table 2.3.

2.3.3 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 one alternative or additional AED. Reasons for failure of the first AED were recurrent seizures in 115 (28%) children; intolerable side-effects in 47 (11%) (with or without recurrent seizures); initial misclassification of seizures in two; and unknown in two children. Intolerable side-effects were allergic rashes in 15 (4%) children, 14 of whom were on carbamazepine (10% of all children who started with carbamazepine) and one on valproate; and other side-effects in 32 (8%), without substantial differences between AEDs.

Table 2.3 shows that there was a clear negative association between the number of AED regimens tried and the chance of achieving a substantial remission. When three 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 four or more AED regimens achieved a good outcome during the follow-up period.

2.3.4 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 two AEDs in 65 and three AEDs in 17 children. 25 (30%) of the 82 children who received polytherapy had tried two 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), valproate with carbamazepine, and valproate with ethosuximide.

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

2.3.5 '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 six 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 medication 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 and/or low seizure severity in 8 children. The reported lack of alternative options was attributed to poor compliance in one child. One child with 'acceptable control' had few and mild seizures, but seizures were also often self-induced and this was an additional reason for not having adjusted the medication further.

2.4 COMMENT

This analysis of data of the Dutch Study of Epilepsy in Childhood (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 epilepsies and epileptic syndromes, as seen in four primary referral centers.

2.4.1. No AED treatment

All children in the study had had at least two 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 two years after intake in the study, and only 4 children received their first AED more than two years after inclusion. Because there is no evidence that AEDs influence the natural course of epilepsy or that untreated epilepsy commonly evolves into a progressive disease,[37] 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.[21,45,98] 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 medication 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 one year points to a selection process during follow-up. A group of children with a relatively favourable prognosis for spontaneous remission was not treated initially, and most children who nevertheless had one or more recurrences were given medication at a later date.

2.4.2 First-choice treatment

The first-choice AED was retained for two years in 250 of 416 children (60%) and resulted in a terminal remission of > 1 year in 63%. In two randomized studies of children with epilepsy the allocated AED was successful in a somewhat larger percentage.[100,112] 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, valproate and carbamazepine were chosen as the main AEDs for initial treatment; a choice based on considerations of toxicity 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 valproate, and may be associated with more long-term side-effects.

We noted a trend to select valproate for children with generalized seizures and carbamazepine for children with partial seizures. This is probably common clinical practice [3,36,118] supported by the results of one comparative trial in adults.[72] Recent comparative studies in adults [53,92] and children [100,112] showed no significant differences in efficacy between valproate and carbamazepine for generalized or partial seizures, but these were published after the intake period of our study.

We included children with seizure types associated with severe symptomatic epilepsies, like infantile spasms or atonic seizures. In the majority of cases where a benzodiazepine, ACTH 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 registered 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, valproate and ethosuximide are probably equally effective and most other AEDs are ineffective. Valproate was used in almost all children with absences as the first AED, and ethosuximide was used as the second AED in case of failure of valproate. Some authors have recommended ethosuximide as first-choice AED for childhood absences because it is not associated with the possibility of severe hepatotoxicity.[21,36,118] We had no occurrences of valproate-induced hepatoxicity in our study. The advantage of valproate as first-choice AED in absences is its efficacy against tonic-clonic seizures, which may be associated with absences.

2.4.3 Failure of the first AED

The first AED failed in 166 of 416 treated children (40%). Recurrent seizures were the main reason to replace the first AED. On the whole, intolerable side-effects were relatively rare (11% of first AEDs). Verity et al reported intolerable side-effects related to the randomized AED in about 13% [112] and de Silva et al in about 4%.[100] However, many side-effects to AEDs are subjective and, because a standardized assessment in this and most other studies was lacking, results with respect to such side-effects are difficult to compare. It often remains unclear why a side-effect is considered 'intolerable'. In our study, allergic rashes occurred in 4% of the first AED regimens and were strongly associated with the use of car-

bamazepine. Others have suggested that such allergic reactions to carbamazepine are relatively rare in children compared with adults.[100,112] We noted a prevalence of allergic rashes associated with the use of carbamazepine comparable to that found in adult studies.[72,92]

After failure of the first AED, alternative or additional AEDs were prescribed in about 40% of the children. In two randomized studies, 29%[100] to 34%[112] of the children received alternative or additional AEDs. The inclusion here of epileptic syndromes with a poor prognosis may explain that our percentage of first AED failures was higher.

When designing our protocol, we agreed, whenever possible, to try two monotherapies before switching to polytherapy. There is no experimental evidence regarding the optimal number of monotherapy regimens before the patient can be considered as a candidate for polytherapy [70], but most authors recommend exhaustive [46] or at least two [3,35] monotherapy trials of first-line AEDs before initiating polytherapy. In our study, however, the percentage of children receiving polytherapy who had first tried two 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 epilepsies like the West or Lennox-Gastaut syndrome. These children may have received polytherapy already after failure of the first AED, because it is well known that combined medication, e.g., valproate and a benzodiazepine, is often necessary to achieve acceptable control in such epilepsies.[69]

In our study, a terminal remission of at least one year was achieved in 56 of the 166 (34%) children who failed on the first AED regimen. After failure of four AED regimens, a remission of more than one year was not achieved during our 2 year follow-up. In the first VA-multicenter study, failure of the first AED was followed by 'successful' alternative AED therapy in a somewhat higher percentage (46%) of adult patients.[74]

2.4.4 Acceptable control and intractable epilepsy

'Intractable epilepsy' is probably best defined as a subjective concept that implies failure to bring seizures under acceptable control[19], and what exactly is acceptable depends largely on the individual. 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 study directly the reasons for certain choices regarding treatment; more specific assessments of the impact of seizures and side-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 side-effects of medication.[26] In general, a broad outcome assessment, including measures of quality of life, is relatively complex compared to traditional measures, but will give better insight into the strategies chosen in the treatment of childhood epilepsy and their results.

Table 2.1. Epilepsy and seizure classification

Number of children	Total group 494 [100]	Untreated[1] 78 (100) [16]	Treated[1] 416 (100) [84]
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]
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]

( ) column percentages, [ ] percentages of the total group (494 children).

[1] until the endpoint of the study, minimal follow-up of two years

Comparing treated and untreated children: differences in epilepsy classification were not significant; differences in seizure type were significant (P= .05).

Table 2.2. First AED regimen: selection of AED and seizure type

AED	Number 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)	0 (0)	10 (18)
Phenytoin	12 (3)	8 (3)	2 (5)	0 (0)	1 (2)	1 (2)
Phenobarbital	9 (2)	7 (3)	0 (0)	0 (0)	0 (0)	2 (4)
ACTH	6 (1)	0 (0)	0 (0)	0 (0)	0 (0)	6 (11)
Ethosuximide	4 (1)	1 (0.5)	1 (2)	0 (0)	1 (2)	1 (2)
Vigabatrin	4 (1)	0 (0)	0 (0)	0 (0)	0 (0)	4 (7)
Total	416 [100]	240 [58]	42 [10]	21 [5]	56 [14]	57 [14]

( ) column percentages, [] row percentages. AED= antiepileptic drug. Classification of seizures was based on ILAE guidelines.[28] GTC= (primary or secondary) generalized clonic-tonic seizure, CPS= complex partial seizure, SPS= simple partial seizure, Abs= absence, Other= other or unclassified seizure types.
In case of more than one seizure type, the most troublesome type is listed.

Table 2.3. Children receiving AEDs: Retention in subsequent treatment regimens and outcome with respect to terminal remission two years after the start of medication

	Treatment		Outcome				
	Monotherapy	Polytherapy	Total	Good	Fair	Poor	Not classified
AED regimen							
1st	250 [100%]	0 [0]	250 (51)	144 [63]	35 [15]	49 [22]	22
2nd	74 [80]	19 [20]	93 (19)	45 [51]	11 [13]	32 [36]	5
3rd	5 [17]	24 [83]	29 (6)	8 [29]	6 [21]	14 [50]	1
4th	4 [13]	26 [87]	30 (6)	3 [10]	3 [10]	24 [80]	0
5th	1 [11]	8 [89]	9 (2)	0 [0]	0 [0]	9 [100]	0
6th	0 [0]	4 [100]	4 (1)	0 [0]	0 [0]	4 [100]	0
7th	0 [0]	1 [100]	1 (0)	0 [0]	0 [0]	1 [100]	0
Total AED	334 [80]	82 [20]	416 (84)	200 [52]	55 [14]	133 [34]	28

( ) column percentages, [] row percentages. Outcome criteria: good=terminal remission > 12 months during two years of follow-up after the start of medication, fair=terminal remission > 6 and < 12 months, poor=terminal remission < 6 months. AED=antiepileptic drug.

Numbers and percentages of children in treatment regimes include 8 children who were followed < 2 years. Outcome was not classified in children who were lost to follow-up or followed < 2 years or when seizure calendars were unreliable. Outcome percentages only refer to children who could be evaluated.

3 REVIEW. OUTCOME ASSESSMENT IN EPILEPSY

AVAILABLE RATING SCALES FOR ADULTS AND METHODOLOGICAL ISSUES PERTAINING TO THE DEVELOPMENT OF SCALES FOR CHILDHOOD EPILEPSY.

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3.0 ABSTRACT

During the past decade, several scales have been developed to improve the assessment of outcome in epilepsy. These scales were developed for adults and their reliability, validity and usefulness have been established. However, there is also a need for alternative measures of outcome in childhood epilepsy, especially a measure of seizure severity (SS) and measures pertaining to quality of life (QoL).

Four of these adult scales are reviewed and compared to examine their applicability in childhood epilepsy. Two important methodological differences are discussed: a) patient self-report vs. physician-based scales, and b) generic vs. disease-specific scales. QoL in epilepsy is briefly reviewed. Severity of seizures and side-effects are relatively neglected areas of importance to QoL in epilepsy.

The existing scales for adults are not appropriate for children in their present form. Some specific methodological issues, which are relevant for the development of scales for children with epilepsy, are subsequently discussed. New scales pertaining to physical and psychosocial aspects of QoL in childhood epilepsy are being developed. In the near future, data on their reliability, validity and usefulness will become available. A combination of scales focusing on specific aspects of QoL, including SS and severity of side-effects, and more traditional clinical data may provide a more complete assessment of outcome in childhood epilepsy.

3.1. INTRODUCTION

Traditionally, outcome assessment in epilepsy has pertained to seizure frequency (SF). The limitations of this approach are obvious. Clearly, there are more variables that may be relevant for patients with epilepsy. In the past decade, several health measurement scales have been developed to improve assessment of outcome in epilepsy [15,32,40,116]. These alternative outcome measures were developed for adults with epilepsy. As such, they are probably inappropriate for children [93]. As epilepsy in childhood is relatively common and not always easy to control, the need for improvement of traditional measures of outcome for children with epilepsy is well recognized [27,35]. We studied the relevant literature on outcome measures in epilepsy, as a starting point for the development of scales for childhood epilepsy. Furthermore, we explored the specific problems relating to the development of outcome measures for childhood epilepsy. Although a wide spectrum of clinical and psychosocial problems applies to patients with epilepsy, this paper will only address the clinician's primary concerns in epilepsy treatment: seizures and adverse effects of medication.

Drug treatment will succeed in controlling seizures within a short period of time in about 70% of new onset patients [6,7,19,22]. In the remaining 30%, reasonable regimens fail to bring seizures under complete control. In 10-15 %, chances of remission are extremely poor [19,60]; these patients are referred to as 'intractable' [20]. In clinical practice, the aim in such cases is to find the optimal balance between seizure suppression and adverse effects of medication. Thus, a careful and complete assessment of the frequency and severity of seizures, as well as the prevalence and severity of side-effects, is necessary.

3.2 SCALES TO MEASURE THE CLINICAL SEVERITY OF EPILEPSY IN ADULTS

A comparison of four scales that have been developed to measure the severity of seizures and adverse effects in adult epilepsy demonstrates quite clearly the different strategies in the approach to outcome assessment in epilepsy. We selected these scales because they are well described in the literature. (1) Two physician-based scales will be described. (2) Two patient-based scales will be introduced which have been incorporated in quality of life (QoL) studies. The first three scales predominantly contain items which are specific for epilepsy, the last scale is a more generic measure. These differences in methodology will be discussed in subsequent sections.

3.2.1. Veterans Administration (VA) Rating Scales for Seizure Type and Frequency, Neurotoxicity and Systemic Toxicity (VA scale)

The VA scale provides a composite score intended to represent 'the overall effect of seizures and toxicity from medication on the QoL of a patient' [32]. It relates to SF, seizure type and severity, and severity of antiepileptic drug (AED) toxicity. This physician-based scale, developed in 1983 by Cramer et al., was used in an influential comparative trial of four AEDs [73]. A slightly modified scale has been validated in a Dutch population with epilepsy by Wijsman et al. [119]. This modified scale has been used for audit studies in adult epilepsy [66,120].

The design of the VA scale for Seizure Type and Frequency reflects the idea that the three most common seizure types in adults are not equally severe. Separate subscales provide ratings for generalized tonic-clonic seizures, complex partial seizures and simple partial seizures. The combination of type and frequency gives the basic score, with subsequent modifications for the presence of a useful aura, an avoidable precipitating factor, 'subtherapeutic' AED levels and specific patterns of seizures. Since seizure classification is a major factor in the determination of seizure severity (SS) in this scale, it has certain limitations, as discussed below (see Section 4.1). The VA scale has no rating for such generalized seizure types as absence and atonic seizures, which are rare in adults but not in children.

The VA scale takes the perspective of the medical-professional and does not measure patient perceptions. This causes concern about the relevance of the scale and the validity of the complex scoring system. For example, in the Systemic Toxicity Scale the same score is given to 'reduced platelet count (< 75000)' and to 'frequent vomiting'. As far as the patient is concerned, these are problems with an entirely different impact. As such, the VA scale is not adequate for assessments of QoL as we would define it today (see Section 3.1).

3.2.2. Chalfont SS Scale

This scale was designed by Duncan and Sander in 1991 and measures only SS [40]. It is completed by the physician, preferably during an interview with the patient and an eye-witness of the seizures, as detailed information about the seizures is requested. The physician has to make a medical-professional distinction between different seizure types in a patient. As in the VA scale, separate columns provide separate severity scores per seizure type. Individual item scores are modified according to the relative frequency of occurrence in a seizure type (e.g. when incontinence occurs in 25% of seizures, the incontinence score is quartered).

The Chalfont scale aims to measure aspects of SS that can be recorded objectively. Although the scale and weightings were based on interviews with

both patients and their close relatives, it does not necessarily reflect the individual patient's opinion.

To our knowledge, the Chalfont scale has not been validated in children.

3.2.3. Liverpool SS Scale

This epilepsy-specific scale was developed to measure the ('subjective') severity of seizures as perceived by the patient, although it includes some 'objective' items [15]. The scale consists of two subscales: perception of control and ictal and postictal events. Most items use a simple subjective four-point response scale, ranging from 1 (the patient perceived that aspect of the seizure to be no problem) to 4 (a severe problem). The patient may choose to complete different columns for his/her 'major' and 'minor' seizures. There is increasing evidence that this scale is reliable, valid and useful as an outcome measure in a clinical trial [14,105]. It has been included in a multidimensional model for QoL in epilepsy developed by Baker and colleagues [12,13]. A similar patient-based adverse event profile has been developed by the Liverpool research group (Baker et al, written communication).

Although these scales reflect the individual patient's perception, both the Liverpool SS Scale and the Adverse Events Profile agree well with the clinician's paradigm of the severity of epilepsy [51]. As these are self-report scales for adults, they would have to be modified to be applicable in a childhood population.

3.2.4. Epilepsy Surgery Inventory (ESI)-55

The ESI-55 was developed by Vickrey and colleagues in 1992 [116]. Like the Liverpool scales, the ESI-55 is a subjective patient-based scale. This self-report scale was developed for studies assessing the outcome of epilepsy surgery in adults. It consists of a generic core (the RAND 36-Item Health Survey) with additional items, providing an epilepsy-specific supplement. The items about physical function and pain do not specifically address the consequences of seizures or antiepileptic medication. When compared to the Liverpool scales, the ESI-55 is a more generic measure of QoL and its relation to epilepsy-specific clinical variables, like SS and severity of adverse effects, is not as direct as in the Liverpool scales. The ESI-55 has been applied to evaluate seizure-based outcome systems from studies addressing the outcome of epilepsy surgery [117].

Because the ESI-55 was designed for patients with a severe form of epilepsy who are candidates for epilepsy surgery, it may not be valid for less severe forms of epilepsy. For this reason, the ESI-55 was expanded for broader application as the QoL in Epilepsy (QOLIE) scale [69]. In their present form, as self-report scales for adults, they are not appropriate for children with epilepsy.

3.3. DEFINITIONS AND BASIC DIFFERENCES IN METHODOLOGY

The previous section has shown that there are important differences between existing health measurement scales for seizures and adverse effects of AED. Not surprisingly, none of these scales seems directly suitable for use in childhood epilepsy. However, they illustrate some important differences in methodology.

First, it seems appropriate to define two terms associated with assessment of outcome of chronic disorders: QoL and clinimetrics. Two basic methodological differences in the presented sample of scales are subsequently discussed.

3.3.1. QoL

Health-related QoL (or perceived health status) refers to a scientific analysis of the functional outcome of a disease and its treatment in a patient [96]. The goal is to quantify patient's perceptions as valid and reliable data [12]. According to Schipper et al., the questions included in the assessment may be drawn from the experience of patients, relatives and health care providers, but they should be answered from the patient's perspective [96]. Some authors, however, take a more restrictive - patient-centred - view [47]. Karnofsky and colleagues were the first in the literature to demonstrate the importance of assessment of the effects of disease on a patient's functional status [61]. The formal use of the term QoL developed later and its definition is still - to some extent - a matter of debate.

QoL is essentially a multidimensional concept, including physical, psychological, social and economic domains [96]. It is widely recognized as an important outcome measure in chronic disease [1]. The major drawback in the use of QoL assessments, is the lack of consensus on how it should be measured [47,48] and the complexity of most attempts to measure it.

3.3.1.1. QoL and Epilepsy

Epilepsy is a relative latecomer in the field of formal QoL studies [12,54]. A great deal of past psychosocial research on the impact of epilepsy might be appropriately termed 'QoL-research' [54,95]. QoL in epilepsy has been reviewed elsewhere [54,75,95,103]. From these reviews it becomes clear that the physical domain has been neglected as compared to the psychosocial domain. Many studies claiming to report QoL have only addressed psychosocial issues. Hermann identifies symptoms and functional status as underinvestigated areas of QoL in epilepsy [54].

As QoL is the ultimate outcome of medical treatment of any chronic disorder, there is no doubt that it is relevant in epilepsy and should be incorporated in trials comparing treatment regimes [33,35,75,121].

3.3.2. Clinimetrics

Clinimetrics refers to the use of rating scales which transform clinical data into a score. This allows the summation of different medical variables and, thus, facilitates statistical comparisons of a patient's status and the assessment of change after treatment [43]. This does not imply that the clinician is the only source of information. Clinimetric tools usually relate to severity of disease in medical terms, but can be a part of QoL research, when they quantify clinical data from the patient's perspective: a clinimetric approach to assessing QoL in epilepsy [31].

3.3.3. Methodological issues

A comparison of the scales in Section 2 indicates that there are important methodological differences between them. At least, we can make a distinction along two axes.

(1) Physician-based vs. patient-based scales (2.1 and 2.2 vs. 2.3 and 2.4).

(2) Epilepsy-specific vs. generic scales (2.1 to 2.3 vs. 2.4).

Clearly, two questions are of importance:

- Who determines the clinical severity of disease: the doctor or the patient?
- When should we use disease-specific scales and when a (more well known) generic profile?

3.3.3.1. Who determines disease severity?

Many authors agree that the patient is the most important authority regarding the effects of disease on his/her life [33,107]. At least, doctors and nurses are not able to assess overall QoL of their patients in a meaningful and reliable way [102]. This favours the assessment of subjective disease severity as perceived by the patient and QoL assessments are based on this principle. The openly subjective nature of QoL assessments, however, is a source of unease among some investigators [96]. In the opinion of some authors, physician-based scales are more 'scientific' than scales reflecting patient's perceptions [18].

Perhaps, a sharp division between 'patient-based' and 'physician-based' scales is too artificial. Any health measurement scale reflects patients' as well as doctors' opinions both in the development and selection of the scale as well as in the completion of the scale in an individual patient's case.

3.3.3.2. Generic and specific scales

Disease severity can be assessed with generic scales which are broadly applicable across different diseases and populations, or with disease- or population-specific scales [44,49,54,87]. A clear advantage of many generic scales is that they are well validated. This is especially important, since for most health measurement

scales there is no 'gold standard' to assess their validity in a simple way.

However, using such generic scales, one can easily miss important problems that relate only to a specific condition. If one focuses more accurately on a specific disease or population, this will result in increased responsiveness of a scale [49]. As epilepsy is not an 'average' disease, we agree with others that at least a fair amount of epilepsy-specific items should be included in any scale developed to assess treatment effects in clinical trials concerning epilepsy [103].

3.4. EPILEPSY-SPECIFIC SCALES: SEIZURES AND SIDE-EFFECTS

As the severity of uncontrolled epilepsy depends to a large extent on the frequency and severity of seizures and side-effects of AEDs, these variables should be addressed adequately in epilepsy-specific scales.

3.4.1. SF and type

Most clinical trials in intractable epilepsy are based on an assessment of change in SF. However, there is no consensus on how a change in SF should be measured or reported. A large number of different outcome systems, typically classifying patients into categories relating to SF, is used [8,32,117]. For some seizure types, reports of SF may be unreliable as they are difficult to quantify without sophisticated techniques [42].

The outcome systems used in most studies fail to recognize that the consequences of seizures determine the number of attacks which an individual patient will tolerate. At least for patients with several 'minor seizures' a day, the absolute quantity of seizures may not be clinically relevant, nor would a reduction in SF of 50% be very significant [20,45,117].

3.4.2. Seizure type and severity

SF is quite meaningless without at least information about seizure type. Clinicians will have some idea of the average severity of different seizure types. For example, seizure duration, an obvious indicator of SS, is related to seizure type [68,118]. Loss of consciousness during a seizure influences both classification and SS. However, the ILAE seizure classification [28] is not a complete and sensitive indicator of SS.

- It lacks content validity for this purpose: many factors that intuitively are relevant to SS, are not included: incontinence, injuries, postictal dysfunction etc.
- It lacks discriminative ability: within one seizure type, factors relating to severity may vary, e.g. a complex partial seizure lasting 15 s is less severe than a complex partial seizure lasting 8 min, despite identical classification.

- It is not adequately sensitive to change in SS: a change of SS can only be monitored if it results in a change in classification.
- It is not as practical as it might seem: especially, in the more complex childhood epilepsies seizure classification is not a simple matter [118].

In conclusion, for studies of uncontrolled epilepsy, a combination of a measure of SF and seizure classification is not sufficient. The development of a complete seizure-based outcome system should include a specific measure of SS.

In Section 2 we reviewed two scales, providing such a measure of SS: the Chalfont and the Liverpool SS scales (Section 2.2 and Section 2.3, respectively). Both scales include to a large extent the same variables, as shown in Table 3.1.

According to Cramer, the major problem inherent in assessing SS are dependence on patient recall and reporting, and observer documentation [31].

3.4.3. Timing, predictability and control of seizures

The VA and Chalfont scales include modifying factors for timing and/or predictability. The Liverpool SS scale has a subscale for this construct (Table 3.1), although it is less reliable and sensitive than the ictal subscale [105]. The common idea is that some degree of predictability and control makes seizures less likely to cause injuries and perhaps less severe.

3.4.4. Adverse effects of antiepileptic drug treatment

At present, in most studies, reports of adverse effects are descriptive and lack quantification [67,71]. Assessment of adverse effects is of great importance in epilepsy treatment [30,45,69]. Considerations regarding adverse effects influence the selection of an AED regimen [53,69,73,112]. Adverse effects are associated with high doses and the use of multiple AEDs [69,91]. Thus, patients with uncontrolled seizures are at risk for adverse effects, as they are often prescribed high doses or a combination of AEDs [97].

It is possible to classify adverse effects along different axes, such as relationship to duration of therapy (early vs. late adverse effects) or relationship to dose (idiosyncratic vs. dose-dependent adverse effects) or by organ system [36]. The most frequent adverse effects are dose-related, not dangerous and quite subjective [69]. They may come and go when the dose is changed or when the patient's tolerance to the drug changes [41]. Therefore, an individual, subjective measure for these 'subtle' adverse effects seems useful. Clinically severe adverse effects are a rare and clear medical-professional problem and the patient's perception in such cases is less relevant. Behavioural and cognitive adverse effects are usually evaluated with standardized psychological tests [5,76]. As these psychological tests are not easily administered, especially in children, a more simple (screening) tool may be useful [30].

3.5. HEALTH MEASUREMENT SCALES IN CHILDHOOD EPILEPSY

It is not surprising that health measurement scales developed for an adult population are seldom appropriate for children [93]. We concluded that the reviewed scales for adult epilepsy patients in their present form are inappropriate for childhood epilepsy. Let us look at the reasons for this conclusion and at some specific issues relating to scales for children and childhood epilepsy.

3.5.1. Who determines disease severity in children?

Children are a problematic group for self-report scales. Self-report scales for children require separate scales at least for different age groups. Probably sex groups should be analyzed separately at different developmental stages, as during the school age period, girls may have relatively superior language and social skills [62]. All this makes it difficult to compare results.

Second, any researcher developing a self-report scale for children should be aware of their structurally different way of thinking about disease [63]. A model of severity of epilepsy that makes sense to adults, may not agree with the ideas that children have.

Third, for children who develop epilepsy, the parents play a crucial role in relation to rationalization and as suggested by Scambler, the opinions of young children about their epilepsy may in fact be very similar to their parents' opinions [94]. This raises the question: Is it worthwhile developing a childhood self-report scale if the same information can be collected more easily by questioning the parents?

In most studies on disease severity in children, information comes from the parents, even when the aim is to assess the children's QoL [93]. Apparently, many researchers believe that the parents are so close to their child that their perception of disease severity approaches the child's perspective. Furthermore, such an approach rightly recognizes parents as experts on their own children [80]. Self-report scales in childhood epilepsy are usually aimed at adolescents. Ratings by adolescents and their parents may well disagree [10].

When subjective assessments of disease severity are used, one must consider the possibility of biased assessments. For example, when parents or clinicians are asked to quantify the severity of specific aspects of a child's epilepsy, they may be biased by the overall disease severity and may have difficulties to focus on the specific issue addressed in a scale. Anxiety and coping difficulties may bias ratings by the parents in severe cases of epilepsy. In some cases, clinicians may feel the parents have produced 'idiosyncratic' scores, which are totally out of line with the clinician's view. Health measurement scales are to be used to supplement the standard clinical information and results should always be inter-

preted in this context. Nevertheless, it is not always within the physician's competence to judge at what point ratings by the parents become exaggerated and such a conclusion should, therefore, be reached with caution.

3.5.2. Specific characteristics of childhood epilepsy

The need for a childhood epilepsy-specific scale is further emphasized by the following specific characteristics of childhood epilepsy.

Childhood epilepsy is often more complex than adult epilepsy. Children with chronic epilepsy frequently have polymorphous seizure disorders.

Many children with chronic epilepsy are mentally retarded or have other impairments [16,60]. In polyhandicapped patients, it is more difficult to determine to what extent the epilepsy contributes to the overall impairment [38].

The incidence and nature of adverse effects reported in children are different from those in adults [70,112]. A scale to assess the presence and severity of adverse effects of AEDs in children should be adjusted to the specific characteristics of adverse effects in this population.

Daily life and responsibilities in children are clearly different from those of adults and, thus, the consequences of seizures are different [85]. Hence, the extent to which epilepsy is a handicapping disorder or causes disabilities [122] differs in adults and children.

3.6. IMPROVEMENT OF OUTCOME MEASURES FOR CHILDHOOD EPILEPSY: ON-GOING PROJECTS

Most research into improvement of outcome assessment and QoL in childhood epilepsy is of very recent date and only preliminary reports are available. Studies addressing QoL are focused on psychosocial, rather than physical or clinical factors. For this reason a discussion of projects addressing physical aspects of QoL in childhood epilepsy has to be brief.

Baker et al.[12] proposed a multidimensional model to assess QoL in childhood epilepsy, including measures of SS, severity of adverse effects, mood and behaviour, intellectual function and physical co-ordination. A questionnaire based on this model was used in a study of lamotrigine in children with severe epilepsy and learning difficulties (Baker, written communication).

In 1993, the Dutch Study Group of Epilepsy in Childhood has embarked on a project to improve outcome assessment in childhood epilepsy. It was decided to focus on the physical domain of QoL, specifically on SS and severity of side-effects. Subjective parent-completed scales were developed. Furthermore, a

scale was developed to measure the severity of disabilities due to restrictions in activities of daily life.

Austin et al. have compared the QoL of children with asthma and children with epilepsy, using more generic and predominantly psychosocial measures [11]. Children with epilepsy had a more compromised QoL in the psychological, social and school domain, children with asthma in the physical domain. Furthermore, social activities and parental supervision of children with new-onset epilepsy were studied [9]. Reduced child activity was found to be related to SF.

Hoare and Russel[37] published a pilot validation study with a newly developed parental QoL questionnaire measuring the impact of illness on children with epilepsy and their families. No data to support the scale's reliability were given. Their scale reflects a generic approach, as it was intended to be valid for children with other disabilities as well.

In conclusion, the perfect assessment of outcome in childhood epilepsy will perhaps never be achieved, but in our opinion a combination of well validated and reliable measures pertaining to specific physical and psychosocial aspects of QoL, with medical-professional outcome variables in epilepsy, would seem an important step forward. In the near future, such new measures of outcome will become available. However, the final proof of their usefulness must come from clinical trials.

Table 3.1 Comparison of variables included in two scales measuring seizure severity (SS).

Liverpool SS Scale	Chalfont SS Scale
Perception subscale	
Timing	
Aura	Warning before loss of awareness
Predictability	
Prevention	
Clustering	
Control	
Day-to-day activity	
Occurrence in sleep	Nocturnal seizures only: divide score by 2
Ictal and postictal subscale	
Overall severity of seizures	
Loss of consciousness	Loss of awareness
Duration of loss of consciousness	Duration of seizure
Lip smacking/fidgeting	Automatisms
Postictal confusion	
Duration of postictal confusion	Time to return to normal from onset
Falling	Fall to ground
Headache	
Incontinence	Incontinence
Tongue-biting	Injury, including tongue-biting
	Drop, spill a held object
	Convulsion (clonic jerking of limbs)

4 PARENT-COMPLETED SCALES FOR MEASURING SEIZURE SEVERITY AND SEVERITY OF SIDE-EFFECTS OF ANTIEPILEPTIC DRUGS IN CHILDHOOD EPILEPSY: DEVELOPMENT AND PSYCHOMETRIC ANALYSIS.

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4.0 ABSTRACT

We have developed two outcome measures for childhood epilepsy: a seizure severity (SS) scale and a side-effects (SE) scale. Both scales have been designed for completion by parents. The scales were tested in two pilot phases and the results of this stepwise analysis are described here. The final scales' psychometric properties were assessed in a group of 80 children with active epilepsy, representative of the population at whom the scales were aimed: children with chronic epilepsy, aged 4-16 years, including all seizure types and epilepsies, as well as children with neurological comorbidity.

Both scales showed good internal consistency and test-retest stability. Although there was a significant positive correlation between the scales, this was low, indicating that the scales measure a different clinical trait. The SE scale consisted of two subscales: a Toxic subscale, measuring the severity of dose-related side-effects, and a Chronic subscale, measuring the severity of long-term behavioural and cognitive side-effects. These subscales for side-effects showed a high correlation, and can be used as a joint scale. The SS and SE scales have the potential to improve outcome assessment in childhood epilepsy, and they can be used to assess important aspects of quality of life in this population.

4.1 INTRODUCTION

During the past decade, several tools have been developed to improve the assessment of treatment outcome in epilepsy. These efforts have focused on epilepsy in adults. The high prevalence of epilepsy in children [52] and the fact that about 30% does not achieve total seizure control [19,50], suggest that the development of similar measures of outcome for a childhood epilepsy population is indicated. Such measures can prove useful in research and clinical practice.

The purpose of treating epilepsy is to improve the child's life. It is important to assess the effects of treatment on an individual basis. In the words of Freeman: "We need to treat seizures when, for that individual, the risk of having seizures and the consequences of having more seizures are worse than the risks and consequences of the treatment itself" [45]. For clinicians concerned with epilepsy, the most important variables are frequency and severity of seizures, and prevalence and severity of side-effects of antiepileptic drugs (AEDs). How can a clinician determine whether an acceptable balance is achieved between seizure suppression and toxicity? In childhood epilepsy, a reliable and valid inventory of the child's health-related quality of life (QoL) [66], would probably provide useful answers [33,35].

QoL is generally seen as a multidimensional concept. In most studies addressing QoL in epilepsy, physical symptoms are neglected compared to psychosocial issues [54]. Measures of seizure severity and severity of side-effects are important aspects of the physical domain of QoL in epilepsy [12]. The methodological difficulties of self-report QoL assessments in a population of children with epilepsy (see previous chapter) suggest that the use of parent-report instead of self-report scales is justified. The majority of children with chronic epilepsy lacks the skills required for reliable self-report, because they are mentally retarded [60] or simply too young.

We describe two newly developed scales for parents of children with epilepsy: The Hague Seizure Severity scale (HASS) and The Hague Side-Effects scale (HASES). These scales were designed to measure the parents' perception of these two basic aspects of severity of epilepsy in children.

4.2 METHODS

4.2.1. Subjects

Children were recruited from the outpatient populations of the departments of child neurology of two hospitals in The Hague (one children's hospital

and one general hospital) and the University Hospitals of Rotterdam, Leiden and Utrecht, four cities in the most densely populated area of the Netherlands. Parents were asked to participate by their child's own doctor and, after giving informed consent, they were asked to complete a mailed questionnaire, including both scales, at home. All questions referred to the child's condition during the previous three months. All parents completed the HASS. The HASES was completed only by parents of children who were treated with AEDs.

The treating physicians -experienced child neurologists- classified the seizures and epilepsies according to the current ILAE Classifications [28,29].

4.2.2.1. Inclusion criteria

Children aged 4-16 years, with a diagnosis of epilepsy and having experienced at least one seizure in the past three months were included, regardless of seizure type or syndrome diagnosis. The physicians were asked to select parents with sufficient Dutch-reading skills to complete a questionnaire, thus, excluding most immigrant parents.

4.2.2. Content

We developed scales to measure the parents' perception of the severity of seizures (HASS) and of side-effects of AEDs (HASES) in children with epilepsy. A 19-item pilot HASS was based on the Liverpool Seizure Severity scale -a valid and reliable self-report scale for adults [15]- to which new items were added as suggested by the child neurologists who participated in the study. The definitive 13-item HASS is presented in Appendix A. Questions 2, 3, and 7-13 have been translated from the Liverpool SS scale and subsequently modified to allow completion by the parents. The Liverpool scale includes some items with precise rather than subjective responses. We felt it was more consistent to include only items with subjective answer categories.

The pilot HASES was based on items suggested by the child neurologists. It also included an open question inviting the parents to suggest alternative or additional items which they considered important within the scope of the scale.

Ten sets of parents of children with uncontrolled epilepsy were asked to comment on the items and content of the pilot scales. Some questions were subsequently added or rephrased. To some items in the HASS and all items in the HASES, a response category "unknown" was added, to allow completion in case of a permanent impairment (like mental retardation or cerebral palsy). When a child is always incontinent or unable to express certain complaints, it seems impossible for the parents to answer a question about such problems occurring during or after a seizure, or because of AED treatment. The most severe score possible on both scales for children with (severe) permanent impairments was

consequently lower than for children without those impairments.

Next, the scales were tested in two phases: (1) a pilot study in 25 patients, after which a preliminary psychometric evaluation was done; (2) a subsequent study in a larger population of 80 children and their parents, followed by a more extensive data analysis. We have chosen not to construct these scales on the basis of factor analysis, but first of all to construct the most homogeneous scales possible as suggested by Nunally [81].

4.2.3. Psychometric and statistical analyses (SS and SE Scales)

4.2.3.1. Item analysis

Two steps of item analysis were performed. (1) Corrected item-total correlations (CITCs) -the correlation between the item and the rest of the scale- were calculated, and items with a CITC < 0,20 were deleted. (2) Frequency distributions of answers were computed, and items where one alternative was chosen in > 95% of cases were left out.

4.2.3.2. Reliability analysis

Crohnbach's alpha was computed as a measure of internal consistency of the final scales. A scale has sufficient internal consistency for research purposes, when alpha is at least 0.8 [103].

Test-retest reliability: of 22 consecutive parents who were asked to complete a second questionnaire 14 days after the first, 18 parents responded. Pearson's R was used as a measure of test-retest stability.

4.2.3.3. Distribution of the scores

Items consisted of 4 or 5 point adjectival questions. A simple scoring system was adopted with ratings ranging from 1 (most favourable) to 4 or 5 (most unfavourable) points for each item.

Scale mean scores, SD values and frequency distributions of scores were established as these measures indicate the scales' potential to measure change.

4.2.3.4. Correlations between scales and correlations with seizure frequency

Spearman's rank correlation coefficient (Rs) was used as a measure of the relationships between the scales and of each scale with seizure frequency. We used an estimation of seizure frequency in the preceding three months by the parents.

4.3 RESULTS

In the final study, 81 children and their parents were included. The parents of one child did not return the questionnaire. The analysis of the HASS was, thus, based on 80 completed questionnaires. The parents of 75 children completed the HASES, as 5 children were not treated with AEDs. The overall availability of data was excellent. None of the parents had any serious problems completing the scales.

Demographic and clinical characteristics of the children included in the study are shown in Table 4.1. The majority of the children can be considered to be patients with intractable epilepsy. In 75% of the children, seizures were not under control after at least one year of therapy. Many children had symptomatic epilepsies and seizure types which are difficult to control. Mild to severe mental retardation was present in 37 (46%) children. The distribution of the number of AEDs/child reflected current clinical practice as monotherapy dominated and some children were not treated with an AED despite recurrent seizures. However, as one might expect in this sample, 40% of the children were treated with polytherapy.

4.3.1. HASS

4.3.1.1. Analysis after the pilot study

One item concerning active seizure control by the child was left out. All 25 parents answered negatively. No other changes were found necessary after the analysis of the pilot results.

4.3.1.2. Final HASS

After the item-analysis, we further reduced the number of items in the HASS. Items deleted because of a low CITC related to the following symptoms. Interruption of activities by the seizure, disability to speak during the seizure and seizure-related faecal incontinence. For several items relating to the same symptoms, we made a choice based on the best CITC. The final HASS comprised 13 items (Appendix A).

The items represent the following areas of content. Consciousness (4 questions), motor symptoms (2), incontinence (1), injuries/pain (3) and overall SS (3). Ictal symptoms are addressed in 9 and predominantly postictal symptoms in 4 questions. The CITC values are listed in Appendix A. CITC values ranged from 0.22 to 0.70. The highest CITC, indicating the item most representative of what the scale measures, was found for Q3 (How severe have the seizures been overall?).

Table 4.2 presents the results of reliability analysis, which indicate good internal consistency (Crohnbach's alpha 0.85) and a high test-retest correlation of 0.93. Some scores were obtained on the lower extreme of the scale, which implied that for these children the scale could not measure any improvement. No scores were produced in the upper extreme range of the scale. The mean score was > 2 SD values higher than the lowest possible score and 3 SD values lower than the highest possible score.

4.3.2. HASES

4.3.2.1. Analysis of the pilot study

The pilot HASES was revised completely because of ambiguity of certain items and insufficient internal consistency. We frequently found an inconsistency in the parents' response to a question concerning the presence of side-effects (12/24 parents reported 'no side-effects') and the subsequent responses on a list of items representing the most common side-effects (10 of these 12 parents responded positively to at least 1 item). Many parents added items to the pilot list of side-effects. Some of these items were included in a new 29-item pool.

4.3.2.2. Final HASES

After testing the new pool of 29 items, three items were deleted: one with 100% negative response (concerning vomiting), two with a low CITC (concerning sleeplessness and increase of appetite/obesity). Subsequently, three subscales were formed, based on a clinical classification of the side-effects. The subscales were called 'Toxic' (14 items relating to dose-dependent gastro-intestinal and neurotoxic side-effects), 'Idiosyncratic' (6 items relating to gum hyperplasia, rash, hirsutism, hair loss, acne/pimples, itching), and 'Chronic' (6 items relating to cognitive and behavioural side-effects). We felt it was appropriate to analyze the internal consistency of these subscales first, before defining the final HASES.

Internal consistency analysis of the subscales (n=75) resulted in the following alpha scores: Toxic 0.87; Idiosyncratic 0.47; Chronic 0.81. Alpha of the Idiosyncratic subscale was below the limit of 0.8, this subscale was consequently not included in the subsequent analysis.

Test-retest stability of the HASES was good (Table 4.2). On the HASES many children produced a score in the lowest possible range and the mean score was < 1 SD from the scale's lowest value. Very few children obtained scores in the high range of the HASES.

The definitive HASES is presented in Appendix B, including a list of CITC values. The CITC values ranged from 0.24 to 0.77. The item with the highest

CITC in the Toxic subscale was "Fatigue" (0.77) and in the Chronic subscale "Decreased concentration" (0.64).

4.3.3. Correlations

Correlations between the HASES, its Toxic and Chronic subscales and the HASS are shown in Table 4.3. These indicate that the HASS and the HASES measured a different trait, as we found a low correlation between them. The Toxic and Chronic subscales largely measured the same clinical trait.

There was a significant correlation between seizure frequency and the score on the HASS: Rs was -0.33 (P=0.004), meaning that frequent seizures were less severe. The correlation between seizure frequency and the score on the HASES was not significant: Rs was 0.18 (P=0.12).

4.4 DISCUSSION

4.4.1. HASS

The 13-item HASS was easy to administer and reliable in terms of internal consistency and retest stability. The distribution of scores obtained in this sample suggested the scale has adequate potential to measure both positive and negative change in seizure severity. Its validity cannot be demonstrated using an external gold standard. However, face and content validity were appropriately established. Furthermore, the question with the highest CITC clearly addressed SS, supporting the idea that the scale measured what it was intended to measure. The negative correlation between seizure frequency and the score on the HASS is in accordance with clinical intuition and suggests that parents were able to separate seizure frequency and severity. Further evidence of construct validity must be obtained from subsequent clinical studies.

It is well-recognized that assessment of SS adds to the overall reliability, sensitivity and clinical relevance of research on treatment outcome in uncontrolled epilepsy [15,20,27,104,117]. In addition to a measure of seizure frequency, the HASS can provide a more complete seizure-based outcome system for studies in uncontrolled childhood epilepsy. It is likely that, for children with recurrent seizures, it provides useful information pertaining to their QoL.

4.4.2. HASES

The HASES and its subscales have adequate internal consistency and retest stability. Mean scores were very close to the best possible scores. This indicates

that prevalence and severity of side-effects in the majority of the study population were limited. This easily administered scale seems a useful and valid screening tool for identifying children with gastro-intestinal and neurotoxic side-effects. It is important to emphasize that the HASES was tested in an unselected sample of patients who have been treated for a long time. Tolerance to dose-dependent side-effects may have reduced the scores on side-effects as addressed in the Toxic subscale [41,59]. Probably, if children had been selected shortly after starting new medication, higher scores for dose-dependent side-effects might have resulted.

The Idiosyncratic subscale failed the standard of internal consistency. This means that the symptoms and signs grouped in this subscale do not represent a homogeneous construct. The summation of scores over a number of items is appropriate only if all items are measuring the same trait [103]. Although the validity of this subscale seems strong, we can not confidently conclude that a summation of scores on the items addressing idiosyncratic side-effects is appropriate. They may be useful as single items addressing idiosyncratic side-effects. One might argue that the Idiosyncratic subscale's low internal consistency is even supportive of the validity of the individual items.

The considerable correlation between the Toxic and Chronic subscales makes it appropriate to use one HASES including the items of both subscales, instead of separate subscales. We found no significant correlation between seizure frequency and the score on the HASES. This suggests that parents are able to separate seizures from side-effects. However, the complex relations between seizures and side-effects clearly warrant further studies.

A quantification of subjective adverse effects is of importance in epilepsy treatment. Using a scale listing the most frequent side-effects may be a particularly informative approach. In our pilot study, the majority of parents, reporting "no side-effects" to a global question, did report complaints on a subsequently presented list of side-effects. As such, the HASES may contribute to a better screening for the presence of side-effects, as well as to the assessment of their severity.

Acknowledgements

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Table 4.1 Demographic and clinical variables of the sample

Number of children	80
Mean age (SD)	9.6 years (3.4)
Sex	34 (43%) girls
Mean duration of epilepsy (SD)	4.7 years (4.0)
Epilepsy classification	*localization-related* - idiopathic with age-related onset: 12 (15%) - symptomatic: 31 (39%) *generalized* - idiopathic with age-related onset: 11 (14%) - generalized idiopathic or symptomatic: 18 (23%) *unclassified*: 8 (10%)
Seizure classification*	simple partial: 18 complex partial: 24 secondary generalized: 15 absences: 14 myoclonic: 3 clonic: 1 tonic: 3 tonic-clonic: 9 atonic: 7
Number of AEDs per patient	no AED: 5 (6%) 1 AED: 43 (54%) 2 AEDs: 21 (26%) 3 AEDs: 10 (13%) 4 AEDs: 1 (1%)

* In the preceding 3 months; 13 children had more than 1 seizure type.

Table 4.2 Results of reliability analysis of the scales for seizure severity (HASS) and side-effects (HASES) and its subscales for toxic side-effects and chronic side-effects.

Scale	Alpha	Retest
HASS (13 items)	0.85	0.93
HASES (20 items)	0.88	0.91
HASES subscales:		
Toxic (14 items)	0.87	
Chronic (6 items)	0.81	

Alpha: Crohnbach's alpha (internal consistency). Retest: Pearson R between first test score and retest score after 14 days.

Table 4.3 `Correlations between scores on the scales for seizure severity (HASS), side-effects (HASES) and subscales for toxic side-effects and chronic side-effects (Spearman rank correlation).

	HASES	toxic subscale	chronic subscale
HASS	0.25 *p=0.027*	0.20 *p=0.080*	0.23 *p=0.048*
toxic subscale			0.58 *p<0.001*

n = 75

Appendix A: THE HAGUE SEIZURE SEVERITY SCALE and CITC values in 80 children.

Questions relate to your child's seizures in the past 3 months.

Q1. How often do you notice a decrease of consciousness during a seizure in your child? *(CITC = 0.33)*

a. always
b. usually
c. sometimes
d. never

Q2. How long does such a decrease of consciousness last? (From time of onset to time of normal consciousness) *(CITC = 0.59)*

a. very long
b. long
c. short
d. very short

Q3. How severe have the seizures been overall? *(CITC = 0.70)*

a. very severe
b. severe
c. mild
d. very mild

Q4. Are there any muscle jerks or cramps in the arms or legs during an attack? *(CITC = 0.48)*

a. always
b. usually
c. sometimes
d. never

Q5. How long do the jerks or cramps last during an attack? *(CITC = 0.54)*

a. very long
b. long
c. short
d. very short
e. does not apply, there are no jerks or cramps

Q6. How noticeable are the seizure symptoms? *(CITC = 0.64)*

a. very noticeable, everyone will notice an attack
b. fairly noticeable, most people will notice an attack
c. not very noticeable, most people will not notice
d. not at all noticeable, you have to be very alert to notice an attack

Q7. During or after an attack, how often does your child seem Confused? *(CITC =0.49)*

a. always
b. usually
c. sometimes
d. never

Q8. During an attack, how often does your child wet him/herself? *(CITC = 0.41)*

a. always
b. usually
c. sometimes
d. never or unknown, my child is permanently incontinent

Q9. During an attack, how often does your child bite his/her tongue? *(CITC 0.49)*

a. always
b. usually
c. sometimes
d. never

Q10. How often does your child become injured during an attack (other than biting the tongue)? *(CITC = 0.22)*

a. always
b. usually
c. sometimes
d. never

Q11. After the attack has finished, is your child sleepy? (Including sleepiness caused by the use of rescue medication like Diazepam) *(CITC = 0.67)*

a. always
b. usually
c. sometimes
d. never

Q12. After an attack, does your child complain of sickness, headache and/or pain in the muscles? *(CITC = 0.43)*

a. always
b. usually
c. sometimes
d. never or unknown, my child would not be able to complain about that

Q13. After an attack, how long does it take, until your child can resume normal activity? *(CITC = 0.65)*

a. very long
b. long
c. short
d. very short or direct after an attack

Appendix B: THE HAGUE SIDE-EFFECTS SCALE and CITC values in 75 children.

The following questions concern possible side-effects of the medication for epilepsy. To explain: If your child has trouble walking, and you believe that this is caused by the medication, this is called a side-effect. If this difficulty with walking has another (probable) cause, eg. a handicap or a broken leg, this does not count as a side-effect.

Have you noticed any of the following side-effects of antiepileptic medication in your child during the past three months?

a= yes, it is a very serious problem
b= yes, it is a moderately serious problem
c= yes, it is a mild problem
d= no or not applicable or cannot be assessed because of impairment

			CITC
1	drowsiness, sleepiness	a. b. c. d.	0.62
2	dizziness	a. b. c. d.	0.48
3	uncertainty when walking	a. b. c. d.	0.66
4	falling	a. b. c. d.	0.56
5	sickness	a. b. c. d.	0.43
6	difficulty with defecation	a. b. c. d.	0.31
7	diarrhoea	a. b. c. d.	0.24
8	shaking, trembling	a. b. c. d.	0.45
9	speech difficulties	a. b. c. d.	0.41
10	double or blurred vision	a. b. c. d.	0.49
11	headache	a. b. c. d.	0.55
12	fatigue	a. b. c. d.	0.77
13	loss of appetite	a. b. c. d.	0.40
14	depression	a. b. c. d.	0.54
15	hyperactivity	a. b. c. d.	0.31
16	temper tantrums, aggression	a. b. c. d.	0.32
17	slowness	a. b. c. d.	0.61
18	poorer school results	a. b. c. d.	0.63
19	decreased concentration	a. b. c. d.	0.64
20	behavioural disturbance	a. b. c. d.	0.57

Note: CITCs relate to the full HASES, which addresses toxic side-effects (items 1-14), and chronic side-effects (items 15-20).

5 SEIZURE SEVERITY IN CHILDREN WITH EPILEPSY: A PARENT-COMPLETED SCALE COMPARED WITH CLINICAL DATA.

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Epilepsia 1997;38:346-352.

5.0 SUMMARY

Purpose- We wished to compare a parent-completed scale quantifying seizure severity (SS) in children with various seizure types with the clinicians' impression of SS and other clinical data.
Methods- The parents of 117 children with recurrent seizures completed a 13-item, subjective scale (The Hague Seizure Severity Scale, HASS). Eight treating neurologists quantified SS on a 10-point Visual Analog Scale (VAS) and supplied other clinical data.
Results- Both the HASS and the VAS assessments of SS showed considerable variation within one seizure type. Significant differences were found between groups with 1) absences and simple partial seizures, 2) complex partial seizures, and 3) generalized tonic-clonic seizures. The correlation coefficient between the neurologists' and the parents' scores was 0.45 but did not exceed 0.26 after stratification for seizure type. The parents' score was not substantially influenced by various other clinical variables. The neurologists' score was correlated with resistance to treatment and presence of mental retardation.
Conclusions- The SS ratings of the parents and the neurologists were not substantially correlated. The consideration that parents, as eye-witnesses to the seizures, are probably better judges of SS than clinicians may favour the use of a parent-completed scale to quantify SS. The HASS is a valid and reliable measure of parent-perceived SS that can be useful as an outcome measure in childhood epilepsy.

5.1 INTRODUCTION

Seizures in epilepsy are of variable severity. Because one quarter to one third of children with new onset epilepsy will not become seizure free in a short time, measures of seizure severity (SS) may contribute to a more complete assessment of the outcome after treatment [27]. A SS scale should measure the components of seizures that concern patients and their carers [31] and has its place in assessments of quality of life (QoL) in epilepsy [12]. Since the 1980s, several specific scales to measure SS have been developed, including self-report [15] and physician-based scales [32,84]. As scales developed for adults, they are not appropriate for children [24]. The development of self-report scales for children raises a number of specific methodological problems [35,93], e.g., children's lack of understanding of disease [68]. The use of a parent-based instrument in childhood epilepsy allows the inclusion of children who obviously lack the ability to participate in self-report assessments, such as mentally retarded or very young children. Furthermore, amnesia for seizures could make results using self-report scales less useful. Alternatively, a physician-based scale may be used to assess seizure severity.

We performed a study using a parent-completed scale specifically developed for use in childhood epilepsy: the Hague Seizure Severity scale (HASS scale) [26]. We compared results with a standardized assessment of the neurologists' global impression of seizure severity, using a Visual Analogue Scale (VAS) (for a brief introduction of this technique see, e.g., Streiner and Norman [103]). Our intention was to explore the relationship between seizure severity scores as assigned by parents and neurologists and seizure type. Because clinicians and patients perceive differences in global seizure severity for specific seizure types [15,31,84], we used this analysis as a method of validation of the parents' and neurologists' assessments. We also wished to determine if the variability in reported seizure severity per seizure type would justify the effort of a specific measurement of seizure severity. Furthermore, we intended to provide a systematic comparison between the parents' and the neurologists' assessments of seizure severity and various clinical data.

5.2 MATERIALS AND METHODS

5.2.1 Parental HASS scale

The HASS scale is shown in Table 5.1; the full scale and its development were published previously [26]. The HASS scale quantifies the parents' opinion on the severity of 13 possible ictal and postictal problems in the previous three

months. It was based partly on items derived from the Liverpool SS scale [15], with subsequent modifications to allow for completion by the parents, and on items suggested by parents and neurologists in a pilot study. From a pool of pilot items, the most appropriate items were selected based on item-analysis, (aimed at constructing a homogeneous scale) and content validity analysis. An assessment of reliability indicated good internal consistency (Crohnbach's alpha 0.85) and retest stability (r=0.93) of the HASS scale [26].

5.2.2 VAS and clinical data

The treating neurologist classified the seizures according to the 1981 ILAE Classification [28]. Because children were treated in an outpatient setting, the neurologists based their judgements on a description of the seizures by the parents or other eyewitnesses. Furthermore, the neurologists were asked to rate 'global seizure severity' on a 10-point VAS, with 1 representing the least severe seizure imaginable and 10 representing the most severe seizure. Previous discussions in our group had shown that there was good agreement about the clinical factors that were related to seizure severity. The neurologists had no knowledge of the parents' score on the HASS scale. The medical records of all children were reviewed for information about the following variables: age, sex, duration of epilepsy, current treatment with antiepileptic drugs (AEDs), and schooling level.

5.2.3 Setting and subjects

Children and their parents were recruited from the outpatient populations of the child neurology departments of three university hospitals, one paediatric hospital, and one general hospital. Eight paediatric neurologists participated in the study. The study protocol was approved by the ethics committees of the participating centres.

Children aged 4-16 years with a diagnosis of epilepsy and at least one seizure in the previous three months were included. The neurologists selected parents with sufficient written Dutch language skills to be able to complete a questionnaire. The parents were asked by their regular specialist to participate and received written information about the study. They were requested to complete the questions on the HASS scale at home. Parents were also asked how many different types of seizures they had observed in the previous three months, to estimate the seizure frequency, and to describe the differences between seizures in case of multiple seizure types. Irrespective of the number of reported seizure types, parents were not asked to complete separate questionnaires for different seizure types.

5.2.4 Construct validity

Clinicians and patients perceive similar global differences in severity between seizures types [15,31,84]. For example, generalized tonic-clonic (GTC) seizures are considered to be at the severe end of the spectrum. We studied the ability of both the HASS scale and the neurologists' VAS-assessments to detect these differences, which would support their validity. We created three subgroups: (in order of increasing seizure severity) Minor, Intermediate and Major. The Minor subgroup consisted of children with absences and simple partial seizures, the Intermediate subgroup of complex partial seizures and the Major subgroup of GTC seizures. To avoid mixed responses, we included only children who had one single seizure type. Children with more than one seizure type, e.g., those with a combination of complex partial seizures and secondarily GTC seizures or of different generalized seizure types were not included. To decide if the child had one or more seizure types, we considered information obtained from both the neurologist and the parents.

To provide additional data on the HASS scale's and VAS's relation with clinical data and discriminant validity -which means that these measures should not be correlated substantially with measures of different entities than seizure severity-, we determined whether the scores were independent of the child's age, sex, duration of epilepsy, seizure frequency, schooling level and mono- or polytherapy. We expected a negative correlation between seizure frequency and seizure severity in the total group, because seizure type and frequency are associated variables: Children with absences -seizures at the least severe end of the spectrum- have a much higher seizure frequency than children with other seizure types. After stratification for seizure type, however, the scores should not be substantially correlated with seizure frequency. We had no reason to expect significant correlations between scores reflecting seizure severity and the remaining demographic or clinical variables of the children.

5.2.5 Statistical methods

Correlations were computed with Pearson's r-value. To analyze group differences we used Student's t-test or analysis of variance (ANOVA) with post hoc Scheffé test. A significance level of $P < 0.05$ was chosen. The distribution of scores in the seizure type subgroups was plotted and compared with the distribution of scores in the total group, and a plot was constructed showing the relationship between the parents' and neurologists' scores.

5.3 RESULTS

One hundred and twenty children were selected for the study, and 117 (97.5 %) questionnaires were returned. The HASS scale was completed by the mother in 58, the father in 8, both parents in 49, and other caregivers in 2 cases. The overall availability of data was excellent, reflecting that parents had no serious problems in completing the questionnaire. Demographic and clinical characteristics of the 117 children are shown in Table 5.2. Most of the children included had had recurrent seizures for > one year despite treatment. Of the 117 children, 99 children had had one single seizure type, and 18 had had more than one seizure type in the previous three-month period. Of the children with more than one seizure type nine had an encephalopathic epilepsy with a combination of generalized seizures (Lennox Gastaut syndrome) and nine a combination of partial or secondary generalized seizure types.

5.3.1 Validity

The three subgroups of children with only one seizure type (n=92) based on their assumed difference in seizure severity were the following: 1. Minor subgroup: 33 children with either simple partial seizures, all experiencing motor symptoms or absences and in our opinion representing a category of least severe seizures; 2. Intermediate subgroup: 30 children with complex partial seizures; and 3. Major subgroup: 29 children with secondary generalized or primary GTC, representing the highest level of seizure severity.

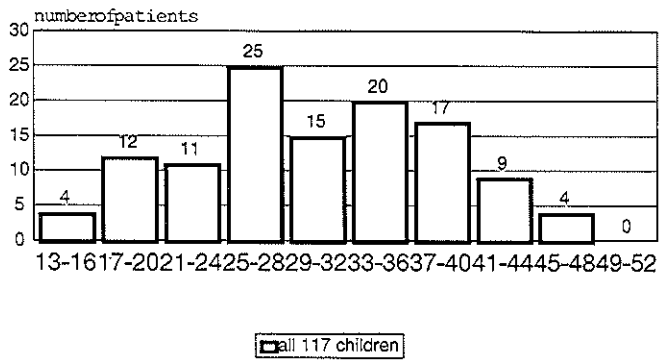
The differences in mean VAS scores were significant between the Minor, Intermediate and Major subgroups (ANOVA, D.F. 2, F ratio 18.6, $P< 0.0001$ for overall difference, with the Scheffé test showing a significant difference between all three subgroups). Mean HASS scale scores in these three subgroups were also significantly different (ANOVA, D.F. 2, F ratio 34.4, $P< 0.0001$ for overall difference, Scheffé test showing a significant difference between all three subgroups).

5.3.2 Seizure severity and seizure type

A plot of HASS scale score and VAS score frequencies in all children is shown in Fig. 5.1A and 5.1B. Both plots show that only a few patients had extremely low or high scores; most scores were distributed around the middle of the scale ranges. Fig. 5.1C and 5.1D show the scores for different seizure types (in the children with one seizure type only) for the parental HASS scale and the neurologists' VAS assessments, respectively.

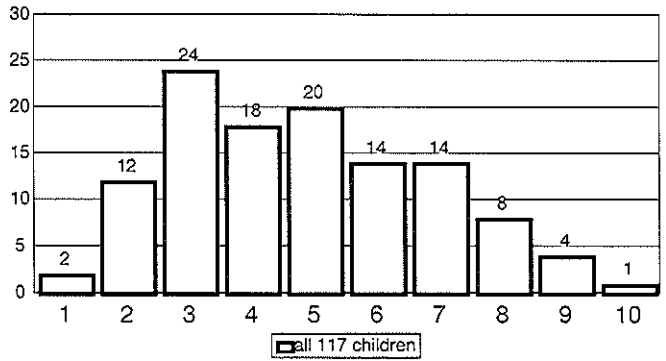
Fig. 5.1C and 5.1D demonstrate a considerable variability in seizure severity scores within one seizure type and considerable overlap in scores between seizure types.

HASS - parents' scores



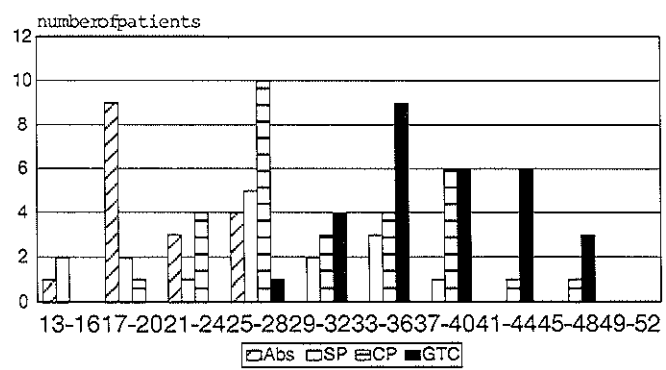
5.1 A

VAS - neurologists' scores



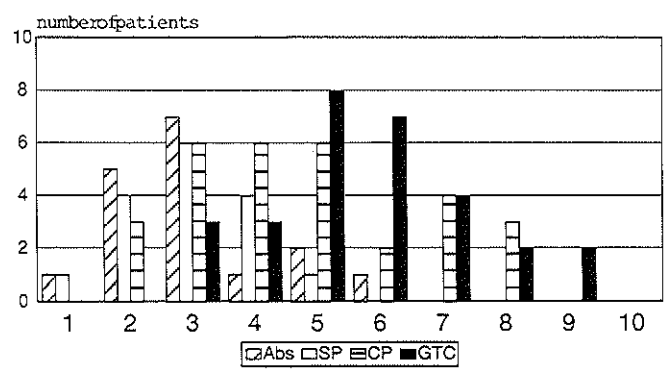
5.1 B

HASS - parents' scores by seizure type



5.1 C

VAS - neurologists' scores by seizure type



5.1 D

FIG. 5.1. Frequency distribution of seizure severity scores assigned by the parents using the Hague Seizure Severity Scale (HASS scale) (range: 13 (least severe) to 54 (most severe)) and by the neurologists using a Visual Analogue Scale (VAS) (range 1 (least severe) to 10 (most severe)). (A) HASS scale scores in all children. (B) VAS scores in all children. (C) HASS scale scores in four groups with single seizure types. (D) VAS scores in four groups with single seizure types. Abs=absences; SP=simple partial; CP=complex partial; GTC=primary or secondary generalized tonic clonic seizures.

Mean parental scores on the HASS scale per seizure type are shown in Table 5.3. The simple partial seizure group had obtained a higher mean score than the group with absence seizures, but the difference was not significant. The mean score in the complex partial seizure group was higher than the mean in the simple partial seizure group and lower than the mean for GTC seizures, the latter group showed little difference between primary and secondarily GTC seizures.

Mean VAS scores assigned by the neurologists per seizure type are also shown in Table 5.3. The absence and simple partial seizures were assigned a comparable low mean VAS score (2.9 and 3.2, respectively, on a 10-point scale). The complex partial seizures obtained an intermediate VAS rating (mean 4.6). The highest VAS scores were assigned to children with GTC seizures, again with little difference between primary and secondarily GTC seizures (mean 5.7 for both).

5.3.3 Comparison of parents' and neurologists' scores

We noted a statistically significant correlation ($r = 0.45$, $P < 0.001$) between the parental HASS scale score and the neurologists' VAS seizure severity rating (Fig. 5.2). After stratification for seizure type, the correlations between the parents' and neurologists' ratings were not significant and r values ranged from 0.10 to 0.26 (see Table 5.3).

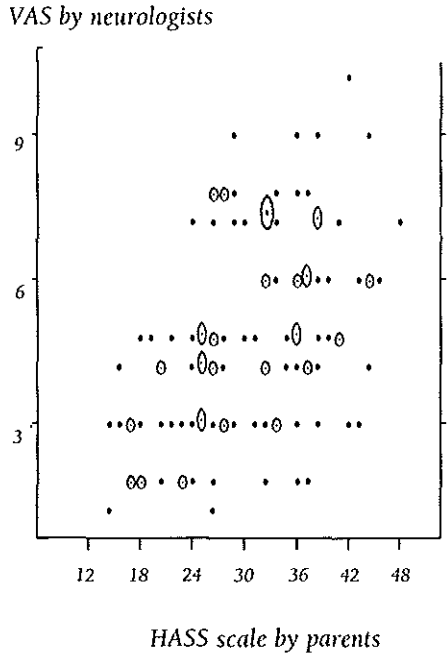


FIG. 5.2. Relation between parents' scores on the Hague Seizure Severity Scale (HASS scale, x-axis) and neurologists' scores of SS on a 10-point Visual Analogue Scale (VAS, y-axis) in 117 children (Pearson r=0.45). One case (solid circles), 2 cases (dotted circles), 3 cases (small dotted ovals), 4 cases (large dotted ovals).

5.3.4 Parental scores on the HASS scale and clinical data

We noted a significant correlation (r = -0.28) between seizure frequency and HASS scale score in the total group, indicating that the most frequent seizures tended to be the least severe (see Table 5.4). This finding is largely explained by the inclusion of children with absences. Children with absence seizures had high seizure frequencies as compared with children with other seizure types (Table 5.3), and the absences were assigned the lowest HASS scale score (mean 20.9). We noted no correlation exceeding r=0.14 between HASS scale score and seizure frequency after stratifying for seizure type. There was a significant correlation between age and HASS scale score (r=0.19). Table 5.3 shows that this could not be explained by differences in age between seizure types. Furthermore, the parents' HASS scale score did not correlate significantly with duration of epilepsy (see Table 5.4). We noted no significant difference in the mean HASS scale score between girls and boys, between children receiving special education (for mild to profoundly retarded children) and those attending normal schools, or between children receiving monotherapy and children receiving polytherapy.

5.3.5 Neurologists' scores on the VAS and clinical data

The VAS score was not correlated with seizure frequency. The VAS score correlated significantly with duration of epilepsy (r=0.28), but not with age (Table 5.4). Table 5.3 shows that this correlation was not explained by differences in duration of epilepsy between seizure types. Differences in VAS score were significant between children attending normal schools and those attending special schools (mean scores, 4.1 versus 5.7; P<0.001; t-test) and between children receiving monotherapy and those receiving polytherapy (mean scores, 3.3 versus 5.8; P<0.001; t-test). Differences between boys and girls were not significant.

5.4 DISCUSSION

We compared a parent-completed scale quantifying seizure severity in childhood epilepsy with clinical data, including a standardized seizure severity rating by the treating neurologist. The use of a seizure severity scale allows quantification of the variability in severity of seizures beyond fixed ratings based on seizure type. This appears to be relevant because scores on the parental HASS scale as well as on the neurologists' VAS showed considerable difference in seizure severity between children with identical seizure types.

SS can not be measured objectively, and opinions are necessarily included in its quantification, which raises the question of whose point of view ought to be be preferred in clinical trials and practice. Clinicians may prefer professional assessments of disease severity, claiming a higher degree of objectivity or scientific validity. However, because doctors rarely witness a child's seizures, the parents are probably the best judges of SS and the impact on their children. For this reason alone, it may be more appropriate to use a parent-completed rather than a physician-completed SS scale. These considerations prompted us to develop the parent-completed scale used in the present study. Nevertheless, because a SS scale will be used in a clinical context, we believed that it was important to compare parental ratings with a 'clinical global impression' by professionals and with other clinical data.

We used a VAS scale to quantify the clinicians' opinion of SS because it has the merit of simplicity [103] and has been used in previous studies for an assessment of SS [84,111]. We did not analyze the reliability of the VAS ratings, but the reliability of a one-item scale is inevitably inferior to that of a multiple-item test [103]. Despite these differences in scales, we think that a meaningful comparison of scores can be made, because both scales quantified SS.

Overall, the neurologists' score predicted < 20 % of the variability of the parents' score in the total group, and we noted even lower correlations after stratifying for seizure type. Furthermore, the parental HASS scale made a distinction between absences and simple partial seizures -although the difference in mean scores did not reach statistical significance-, and the neurologists' score on the VAS did not. We conclude that there was a substantial difference between SS ratings assigned by the parents and the neurologists in the present study. Our data do not suggest that this difference can be explained by a lack of validity of the HASS scale or VAS.

We noted significant differences in HASS scale and VAS scores between subgroups including, respectively, 1) absences and simple partial, 2) complex partial, and 3) generalized tonic-clonic seizures, that supported the validity of both measures. Furthermore, these data confirmed that parents correctly identified the appropriate seizure characteristics in their children. For the parental HASS scale, we noted no evidence of a substantial bias related to a variety of clinical variables, including seizure frequency after stratification for seizure type. Therefore, the parents were able to isolate SS from a range of variables, all of which may contribute to the 'overall severity of epilepsy' [51]. In contrast to the parents' score, the neurologists' score was not correlated with seizure frequency in the total group, although we had hypothesized that the most frequent seizures would be the least severe. Resistance to AED treatment may have influenced the neurologists' score, as the mean score of children receiving polytherapy was higher than that of children receiving monotherapy. The VAS scores were also higher for children attending special schools for retarded children as compared with scores of children with normal intellectual abilities.

We did not examine the psychosocial status of the parents. Psychosocial factors, such as depression or anxiety, may have influenced the parental ratings in our study. We previously reported low to moderate (between 0.16 and 0.38) correlations between scales measuring parent-perceived SS, severity of side-effects and severity of restrictions due to epilepsy [25]. Had these scores reflected the parents' anxiety to a large extent, more substantial correlations probably would have resulted.

Clinical trials in epilepsy using a traditional design, with seizure frequency as the only outcome variable often cannot assess differences in efficacy between AEDs. Therefore, the inclusion of a measure of SS may increase the sensitivity and relevancy to patients. Clinical trials that have included a measure of SS are rare. The HASS scale was based on the Liverpool Seizure Severity scale [15], a reliable and valid self-report scale for adults pertaining to QoL in epilepsy [14]. Used in a clinical trial, the Liverpool Seizure Severity scale enhanced the sensitivity of outcome assessment [105].

We are now evaluating scales in a comparable format addressing the sever-

ity of adverse effects of AEDs and restrictions in activities of daily life of children with epilepsy. Our goal is to combine these scales to quantify the parents' opinion on some of the most relevant disease-specific problems affecting QoL in children with epilepsy. Many researchers [12,33,35] have suggested that it is relevant to include scientific measures of the patients' opinion -often addressed as QoL measures- in clinical studies of patients with epilepsy. The HASS scale, however, reflects the parents' and not the child's opinion. The use of the parents as the source of information in the present study corresponds well to previous QoL research in children [93]. Because of their age-dependent understanding of disease and cognitive abilities, children represent a problematic group for use of self-report scales [35,93]. Children with mental retardation constitute another group that appears to be less accessible for use of self-report measures.

We suggest that the HASS scale could be a useful tool for clinical trials in children with recurrent seizures. In daily practice, the HASS scale could be useful to guide decisions regarding when to start treatment and how to respond to recurrences despite treatment or after discontinuation of drugs.

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Table 5.1 Items addressed in the Hague Seizure Severity scale

1. frequency of impairment ofconsciousness*
2. duration of impairment of consciousness
3. overall seizure severity
4. frequency of jerks or cramps
5. duration of jerks or cramps
6. noticeability of altered behaviour during seizure
7. frequency of confusion during or after attack
8. frequency of urinary incontinence during seizure
9. frequency of tongue or cheek-biting
10. frequency of other injury related to attack
11. frequency of postictal sleepiness
12. frequency of postictal nausea, headache or muscle pain
13. time to normal function after attack

*Frequencies represent the number of times a problem occurs as compared with the total number of seizures. All questions relate to the seizures in the previous three months. All items have 4 or 5 adjectival (subjective) response categories (e.g. always, usually, sometimes, never). Scoring for each item: 1 point for the most favourable answer, to 4 or 5 points for the most unfavourable answer.
Total scale score ranges from 13 (lowest seizure severity) to 54 (highest seizure severity).

Table 5.2. Demographic and clinical variables of 117 children

Mean age (SD)	9.7 (3.3) years
Sex	67 (57%) boys
Mean duration of epilepsy (SD)	4.2 (3.8) years
Epilepsy classification	*localization-related* - idiopathic with age-related onset: 16 (14%) - symptomatic: 46 (39%) *generalized* - idiopathic with age-related onset: 23 (20%) - symptomatic: 24 (21%) *unclassified* 8 (7%)
Two or more seizure types	18 (15%)
Number of AEDs per patient	no AED: 8 (7%) 1 AED: 67 (57%) 2 AEDs: 31 (26%) 3 AEDs: 10 (9%) 4 AEDs: 1 (1%)
Mental retardation[#]	45 (38%)

[#] *Mental retardation was based on schooling level.*

Table 5.3. Demographic and clinical variables, seizure severity and seizure type

	Absence	SP	Complex Partial	PGTC	SGTC
Number	17	16	30	13	16
Age mean	9.3 (2.9)	10.5 (3.1)	9.7 (3.2)	9.9 (3.5)	10.1 (3.5)
Duration of epilepsy	3.7 (4.0)	2.4 (3.2)	4.5 (3.8)	2.8 (2.5)	4.8 (4.2)
Seizure frequency	2049 (3540)	15 (29)	103 (252)	9 (12)	4 (6)
Score VAS	3.2 (1.6)	2.9 (1.2)	4.6 (2.0)	5.7 (1.9)	5.7 (1.4)
Score HASS scale	20.9 (4.2)	26.9 (7.5)	30.9 (6.9)	37.9 (6.6)	36.7 (4.5)
VAS/HASS scale r	0.25 (ns)	0.26 (ns)	0.25 (ns)	0.10 (ns)	0.10 (ns)

Only children with one single seizure type are included in this table.
Data are mean values with standard deviations between parentheses. SP=simple partial seizures. P(S)GTC=primary (secondary) generalized tonic-clonic seizures. Seizure frequency=the mean number of seizures in the previous three months. VAS score=the neurologists' rating of seizure severity on a 10-point Visual Analogue Scale. Score HASS scale=the score on the Hague Seizure Severity Scale (scale ranges 13-54). VAS/SS Scale r=Pearson correlation between VAS score and HASS scale score; ns=not significant.
Analysis of variance (ANOVA) showed that differences in age and duration of epilepsy were not significant between any two seizure types. Seizure frequency in the absence group was significantly different from that in all other groups. Other between-group differences in seizure frequency were not significant.

Table 5.4. Univariate analysis of correlation between clinical variables and parents' and neurologists' seizure severity score (Pearson r value) in 117 children

Parameter	Parents[$]	Neurologists[+]
Age	0.19 (p=0.037)*	-0.11 (p=0.239)
Duration of epilepsy	0.16 (p=0.094)	0.28 (p=0.003)*
Seizure frequency[#]	-0.28 (p<0.001)*	-0.03 (p=0.746)

[$] Parents' score on the Hague Seizure Severity scale

[+] Neurologists' rating of seizure severity on a 10-point Visual Analogue Scale.

* Significant at p<0.05

[#] Seizure frequency=mean number of seizures in the previous three months.

6 SUBJECTIVE SIDE-EFFECTS OF ANTIEPILEPTIC DRUGS: ASSESSMENT BY USING A PARENT-COMPLETED SCALE.

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Submitted.

6.0 ABSTRACT

Objective- To quantify the prevalence and severity of subjective side-effects (SE) as perceived by parents of children taking antiepileptic drugs (AEDs), and their association with clinical risk factors for SE.
Methods- We used a parent-completed 20-item scale (The Hague Side Effect Scale, HASES) in 115 children on AEDs aged 4-16 years. Results were compared with a control group of 25 children on medication for asthma. Furthermore, we studied the associations between parent-reported SE and clinical data, including number and dosage of AEDs, and the clinician's global evaluation of the severity of SE.
Results- In 82% of the children at least one SE was reported. Median scores on the HASES were not significantly different between children on AEDs and children on anti-asthma medication. There was no significant correlation between the parental HASES score and the clinicians' evaluation of the global severity of SE. There was no significant relationship between the HASES score and the dosage of AEDs, or the use of mono- or polytherapy. Neither age, sex, duration of epilepsy, presence of mental retardation, seizure activity or presence of a steady state AED regimen for 90 days were substantially associated with the HASES score.
Conclusion- In this sample, the prevalence of subjective SE was high. There was a lack of association between prevalence and severity of subjective SE as reported by the parents, and number or dosage of AEDs. However, in this observational study this may reflect adjustment of medication to the individual child's ability to tolerate AEDs. It remains questionable if the subjective SE as reported by the parents were causally related to the AEDs, at least they were not specific for children taking AEDs.

Keywords: antiepileptic drugs, side-effects, epilepsy, quality of life.

6.1 INTRODUCTION

Most children with epilepsy are treated with antiepileptic drugs (AEDs). AEDs are often associated with minor, subjective side-effects (SE).[2,69] Few studies provide details about prevalence and severity of such SE. Furthermore, most methods sections in publications about treatment with AEDs are rather vague about the assessments of SE.[67] Because subjective SE may influence clinical decisions and may undermine compliance, a valid and reliable tool for their quantification would seem useful. If patients are children with epilepsy, the ideal of self-report scales reflecting the patient's opinion about SE is often unrealistic. Especially, for young or mentally retarded children the parents may be the most reliable source of information.[35,93]

We have previously described a method for a standardized quantification of the prevalence and severity of subjective SE in children taking AEDs, proposing a scale for completion by the parents, the Hague Side-Effects Scale (HASES).[26] Items were contributed by child neurologists and parents of children using AEDs, and selected for the scale from a pilot pool on the basis of item analysis. The HASES comprises 20 symptoms relating to systemic toxicity and neurotoxicity, which were common in a pilot population of children using AEDs. The inclusion of items in the HASES was based on empirical findings in this pilot study and not on clinical perceptions, although we felt the scale's content validity was satisfactory. The HASES was reliable in terms of internal consistency and retest stability.[26]

We report the prevalence and severity of SE as measured using the HASES in children taking AEDs, and the association of the HASES score with clinical data. We focused on children with drug-resistant epilepsy. Patients with drug-resistant epilepsy may be at risk for SE, because they often are treated with high dosages or multiple AEDs. The use of high dosages and multiple AEDs is generally believed to increase the prevalence and severity of SE.[2,4,55,69,91,110]

6.2 PATIENTS AND METHODS

6.2.1 Design

Children were recruited from the outpatient child-neurology departments of three University Hospitals, a Paediatric Hospital and a General Hospital. Eight child neurologists provided patients. Children with epilepsy were eligible when they were aged 4 to 16 years, were treated with at least one AED and had not been seizure-free for more than one year. The neurologists selected parents with

sufficient written Dutch language skills to be able to complete a questionnaire. Most first generation immigrant parents were thus excluded.

A control group was selected of 25 age-matched children with asthma using only inhaled standard medication (corticosteroids and beta agonists) for this condition. It was hypothesized that such medication was unlikely to be causally related to SE as addressed in the HASES.

The study protocol was approved by the Ethical Committees of the participating centres.

6.2.2 Scale

The items addressed in the HASES are given in Table 6.1. All questions in the scale refer to symptoms attributed to the AED medication as recalled and perceived by the parents, in the previous three months. Each item includes the following four response categories: 1. no problem or not applicable or cannot be assessed because of impairment; 2. a mild problem; 3. a moderately serious problem; 4. a very serious problem. A simple scoring system was used, ranging from 1 point (no problem or not applicable or cannot be assessed) to 4 points (very serious problem) for each item. Hence, for children with concomitant impairments, it was possible that parents indicated that certain symptoms could be not applicable or could not be assessed. For example, when a child is unable to walk because of cerebral palsy, an AED cannot cause a disturbance of walking. In such children the impact of SE could thus be underestimated. On the HASES, the least severe score possible is 20 (indicating that none of the SE listed are perceived to be present), the most severe score 80 (all SE are very serious problems). To avoid investigator bias, parents completed the questions on the HASES at home. Parents were not instructed on how to interprete the meaning of items or response categories.

6.2.3 Clinical data and VAS

The medical records of all patients were reviewed for information about the following variables: age, sex, classification[29] and duration of epilepsy, time on present AED regime, name(s) and dosage(s) of AED(s), and body weight. In the questionnaire including the HASES, the parents were also asked to report their child's seizure frequency or the duration of remission from seizures, respectively. Compliance was not formally assessed by a protocol of serum drug level tests, but the clinician was asked if he or she had reasons to believe that compliance was poor, yes or no.

Because severity of SE will influence clinical decisions regarding medication, and because an objective assessment of the severity of SE as addressed in the HASES is lacking, we attempted to compare the parental ratings with the

neurologists' global evaluation of the severity of SE. The neurologist who treated the child rated the severity of SE on a 10-point Visual Analogue Scale (VAS)[103], ranging from 1 (no SE) to 10 (most severe SE imaginable).

6.2.4 Association between HASES score and clinical data

We examined three main hypotheses:

1) HASES scores would be significantly higher in children on AED treatment than in children on anti-asthmatic medication. The latter medication is believed to be only rarely associated with SE as addressed in the HASES.[77]

2) HASES score would be higher in children on polytherapy than on monotherapy. The common opinion in the literature is that polytherapy is a risk-factor for SE.

3) HASES scores would be positively correlated with relatively high dosages of an AED. Because children were using many different AEDs or combinations of AEDs, we computed a standardized dosage ratio. Average daily maintenance dosages (DMDs) in the study group were computed per AED in mg/kg. To be able to make comparisons between AEDs, we calculated the ratio of the prescribed DMD and the average DMD for each child. We subsequently computed the correlation between the HASES score and this ratio. Because the possibility of drug interactions makes it difficult to compare mono- and polytherapy dosages, we first analyzed the children on monotherapy alone. Subsequently, we performed the same analysis including the children on polytherapy, using the summated ratio of the different AEDs. A comparable approach was described in a previous study in adults on side-effects of AEDs.[65]

Furthermore, we examined the correlation of the HASES score with age, sex and duration of epilepsy. A lack of association would be supportive of the HASES' validity, as there is no logical reason for an association with these sources of variation. The neurologists' VAS rating was compared with HASES scores, as a simple quantification of the clinicians' opinion and not as a 'gold standard'. Finally, differences in HASES score were determined between children with normal intelligence versus mentally retarded children, because in retarded children especially cognitive and behavioural SE can easily be missed.[101] We compared scores between children with and without noticeable seizures in the past three months, because the effects of recurrent seizures may be difficult to separate from SE.[30,113] And we compared scores between children on a steady state AED regimen versus children with a new AED or increased dosage within 90 days before completion of the scale, because many SE occur predominantly at the start of new medication[69], even when hypersensitivity reactions and other idiosyncratic SE are left out of consideration.

6.2.5 Analysis

The statistical analysis was performed with standard non-parametric tests. For the analysis of correlations, Spearman's rank correlation coefficient was used. The Mann Whitney U test was used to examine group differences.

6.3 RESULTS

We selected 117 parents for the study, 115 parents completed and returned the questionnaire. The questionnaire was completed by the mother in 52, the father in 6, both parents in 54 and other primary caretakers in 3 cases. Demographic and clinical characteristics of the children are listed in Table 6.2. 97 Children (84%) had recurrent seizures for more than one year despite state-of-the-art treatment with AEDs. The epilepsy classification was dominated by symptomatic epilepsies. Almost half of the children were mildly to severely retarded. Only 26 children (23%) had been seizure-free in the previous three months. Only 2 children were judged to be noncompliant to the prescribed AED regimen. These children were not excluded.

SE (a score of more than 20 on the HASES) were reported in 94 children on AEDs (82%). Items obtained affirmative responses in 8% (double or blurred vision) to 49% (fatigue) (see Table 6.1). Fig 6.1 shows the range and skewed distribution of scores of the 115 children on AEDs. The median HASES score in children taking AEDs was 26.

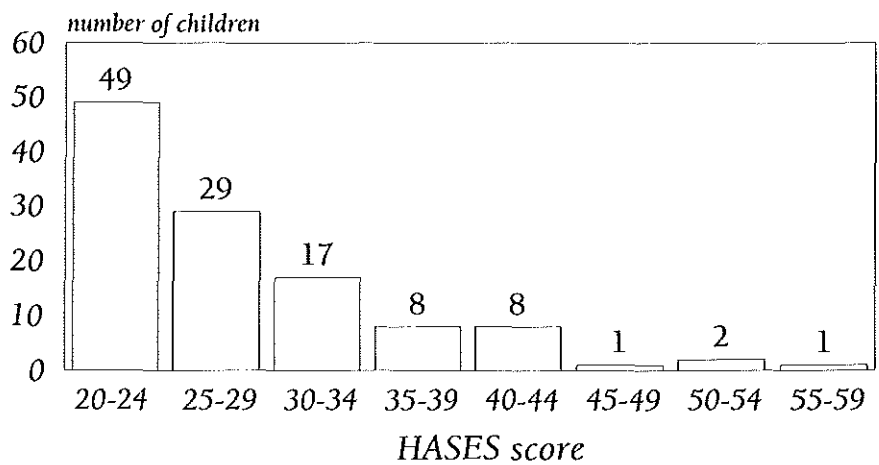

Figure 6.1 Distribution of score frequencies on the Hague Side-Effects Scale (HASES) in 115 children. Score range: 20 (least severe score, none of the listed side-effects is a problem) to 80 (most severe score possible, all 20 side-effects listed are very serious problems).

In the control group of 25 children with asthma, 22 (88%) reported one or more SE on the HASES, scores ranged from 20 to 43, and the median was 22. Median HASES score was not significantly different between children with epilepsy and asthma (Mann-Witney U test, $p = 0.15$).

Table 6.3 shows the distribution of AEDs and dosages. In 46 children polytherapy was used. The benzodiazepines and vigabatrin were (almost) exclusively prescribed in polytherapy regimens. As shown in Table 6.4, the ratio between prescribed DMD and mean DMD was generally lower for children on monotherapy as compared to children on polytherapy. Mono- and polytherapy groups were well matched with respect to age and gender. Duration of epilepsy was significantly longer in the children on polytherapy (mean 6.8 years) than on monotherapy (mean 3.4 years) (Mann-Whitney U test, $p < 0.001$).

The difference in HASES score between children on mono- and polytherapy was not significant (Table 6.5). HASES score was not associated with gender, mental retardation, being seizure-free for more than three months, or being on a stable AED regimen during the previous three months (Table 6.5).

No significant correlation between dosage and the HASES score was found either in the monotherapy or in the entire group, including the children on polytherapy (Table 6.6). Age and duration of epilepsy did not correlate significantly with the HASES score (Table 6.6).

The VAS score, reflecting the neurologist's perception of the severity of SE, did not correlate significantly with the parents' score on the SE scale (Table 6.6). A VAS score of 0 or 1 (indicating no or almost no SE) was given to only 17% of the sample. The median VAS score showed a significant difference between mono- and polytherapy groups (Mann Whitney U test, $p = 0.005$). Furthermore, the VAS score correlated significantly with the prescribed DMD/mean DMD ratio in the total group, but this correlation was not very strong (Spearman $r = 0.27$, $p = 0.014$).

6.4 DISCUSSION

The percentage of children taking AEDs reported to have SE ranges between about 50 and 75% [2,55,112], although in about 10% only, SE are considered intolerable.[55,100,112] Hence, the majority of reported symptoms attributed to the use of AEDs are probably mild and clinically acceptable. Drowsiness/sleepiness, fatigue and decreased concentration were the most frequently reported SE, which was in accordance with, for example, results of Verity et al[112], and supported our impression that the HASES has sufficient content validity.

In our study, parents reported subjective SE in more than 80% of their children. This equals the results of a large European study using a comparable (self-report) scale for adults taking AEDs; in this study 88% reported SE.[13] The use of a standardized questionnaire such as the HASES may account for the high percentage reporting SE, as a global, unspecified question may be less sensitive.[26] However, most children in our sample had a severe epilepsy in terms of resistance to AEDs. It is possible that the prevalence and severity of SE correlate with the extent to which seizures are drug-resistant: Drug-resistance may lead to high-dose monotherapy 'pushed to toxicity' or the use of a combination of AEDs. Thus, we examined if the HASES score was associated with the number and dosages of AEDs.

First of all, we found that polytherapy was not associated with a higher HASES score than monotherapy. However, in this observational study polytherapy may have been used only by children who tolerated it well. Further studies using the HASES in a blind, randomized comparison of mono- and polytherapy could solve this issue, which is sufficiently important to warrant further investigation. Recently, after more than a decade of general preference for monotherapy, some have advocated the use of 'rational polytherapy' with newly developed AEDs, and it is possible that in the future specific polytherapy regimens will be used more often and earlier in the course of treatment.

Alternatively, it is possible that not the number of AEDs but their (cumulative) dosages are associated with the severity of SE: high-dose monotherapy regimens may be as toxic as combinations of several AEDs in a low dosage. For this reason the relation between the dosage and HASES score was studied. Mean DMDs of each AED were in agreement with usual guidelines.[4] We did not find a simple relationship between dosage ratios and HASES score. In children on monotherapy we found no significant correlation between the dosage of an AED and the HASES score. Lammers et al[65] provided some evidence for a relationship between AED dosage and the severity of SE, but only in adults on polytherapy. Using a comparable approach in children on mono- and polytherapy, we found no such relationship. Again, the observational design of our study may have biassed our findings, as high dosages may have been prescribed only to children who seemed to tolerate them well. We are aware that widely different drug dosages may result in similar serum drug levels, and vice versa. We were not able to compare our data regarding SE with serum drug levels because for most children, recent values were not available.

We anticipated and found no relationship between age and sex and the HASES score. Duration of epilepsy was related to the number of AEDs used, but not to the HASES score. A new AED or increased dosage within the last three months was not associated with a higher HASES score. Hence, we found no evi-

dence for tolerance to SE as addressed in the HASES. Furthermore, we found no significant difference between children with normal intelligence and retarded children, with respect to the SE score. Thus, we found no evidence that SE in retarded children were underreported, or that the symptoms and signs reported as side-effects were part of an underlying encephalopathy. We found no evidence for confusion between SE and effects of (subtle) seizures, but the number of seizure-free children was small and we have not included EEG-monitoring to exclude 'subclinical' seizures in children who were seizure-free according to their parents.

Both the neurologists and the parents reported SE in > 80% of the children. However, the neurologist's VAS rating correlated poorly with the parents' score on the HASES. This does not, by itself, suggest that the HASES is not a valid tool for the quantification of the parents' opinion, or disprove a causal relation between parent-perceived SE and the use of AEDs. Furthermore, it makes it likely that the HASES contributed new information for the clinician. An interesting finding was that the neurologists' VAS rating of children on polytherapy was significantly higher than of children on monotherapy, and correlated with AED dosage. Although there is a possibility that the VAS rating by the neurologists in our study has a better discriminative ability than the HASES scale, an alternative explanation is that the neurologists were biased by the number and dosage of AEDs prescribed, for which they nor the parents were blinded.

Even if one accepts our claim that the HASES is a valid and reliable instrument to quantify the parents' opinion about SE, a clinician will need to know if a high score only points to parental concern or if it means that the dosage of AEDs needs to be adjusted. In the present study, a causal relationship between reported SE and the use of AEDs could not be established. We have not been able to include a control group taking placebo. It is well known that placebo's cause SE as well as pharmacologically active drugs. We have not included a control group of children not taking any medication, because our questionnaire specifically asks parents to report side-effects of medication, and not general signs or symptoms. However, the symptoms listed in the HASES are probably prevalent also among children who do not take medication and 'adverse nondrug reactions' have been noted in healthy, unmedicated adults.[30] The reported SE may be an effect of the chronic illness itself on the parents' perceptions. The lack of a significant difference in HASES median scores between the children taking AEDs and children receiving anti-asthma medication showed, at least, that the reported SE were not specific for children on AEDs. In a study by Austin et al[11] using a global 7-point scale to assess 'problems with SE', mothers reported more SE in children on anti-asthma medication as compared to children on AEDs. If this were true, our findings suggest that the HASES is more sensitive to SE associated with AEDs than

anti-asthma medication. Finally, some authors have suggested that a list of possible SE -such as the HASES- may actually cause SE[78], and others have not confirmed such an 'adverse effect of information'.[64] It is unclear, how these studies of adult self-reported SE relate to parental report of SE as in our study.

The subjective cognitive and behavioural SE addressed in the HASES were highly correlated with the other SE.[26] Especially cognitive and behavioural SE of AEDs are an area of concern to clinicians.[30] However, after reviewing the literature, Vermeulen and Aldenkamp concluded that there is no convincing evidence that AEDs in therapeutic dosages actually cause such SE.[113] In children, the impact of AEDs on formal tests of higher cognitive functioning is probably limited.[5] It would, nevertheless, be of interest to compare the HASES with formal neuropsychological assessments, if only to find out if the HASES could be useful as a screening tool to select candidates for formal testing. However, in adults, standardized neuropsychological assessments were poorly associated with subjective complaints.[114] Furthermore, such tests are not always appropriate for young or retarded children.

Many new AEDs are marketed with a claim that they cause less SE than the traditional AEDs and we may anticipate a tendency to accept fewer -subjective- SE for children taking AEDs in the future. SE of AEDs will no doubt continue to be an area of concern to parents and clinicians. In clinical practice, the HASES seems useful as an easily administered, reliable and very sensitive tool to quantify the parents perceptions regarding subjective SE in a standardized way.

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Table 6.1 Items addressed in the Hague Side Effects scale and responses by parents of 115 children taking antiepileptic drugs

	Items	Number (%) of 115 children reported to have a mild to very serious problem
1.	drowsiness/sleepiness	48 (42%)
2.	dizziness	16 (14%)
3.	uncertainty when walking	13 (11%)
4.	falling	10 (9%)
5.	sickness	19 (16%)
6.	difficulty with defecation	18 (16%)
7.	diarrhoea	11 (10%)
8.	shaking, trembling	17 (15%)
9.	speech difficulties	14 (12%)
10.	double or blurred vision	9 (8%)
11.	headache	40 (35%)
12.	fatigue	56 (49%)
13.	loss of appetite	29 (25%)
14.	depression	15 (13%)
15.	hyperactivity	34 (30%)
16.	temper tantrums, aggression	38 (33%)
17.	slowness	55 (39%)
18.	poorer school results	39 (34%)
19.	decreased concentration	51 (44%)
20.	behavioural disturbance	25 (22%)

Table 6.2 Demographic and clinical variables of 115 children taking antiepileptic drugs

Mean age (SD)	10.1 (3.4) years
Sex	61 (53%) boys
Mean duration of epilepsy (SD)	4.7 (3.8) years
No seizures in previous 3 months	26 (23%)
Epilepsy classification	*localization-related* - idiopathic with age-related onset: 13 (11%) - symptomatic: 47 (41%) *generalized* - idiopathic with age-related onset: 24 (21%) - symptomatic: 23 (20%) *unclassified*: 8 (7%)
Number of AEDs per patient	1 AED: 69 (60%) 2 AEDs: 30 (26%) 3 AEDs: 15 (13%) 4 AEDs:1 (1%)
Mental retardation	47 (41%)

Table 6.3 Number of children taking an AED, mean daily maintenance dosage (DMD) and range of dosages in mg/kg (N = 115)

AED	Monotherapy			Mono- and polytherapy		
	N	DMD (mg/kg)	Range	N	DMD (mg/kg)	Range
Valproate	23	21.7 (9.3)	8.0-39.0	52	23.8 (10.1)	2.4-43.5
Carbamazepine	27	13.0 (4.8)	5.3-27.3	52	15.7 (6.0)	5.3-28.6
Phenytoin	5	6.1 (1.7)	3.5-8.0	14	6.6 (1.8)	3.5-9.2
Ethosuximide	4	23.2 (3.4)	20.0-27.8	8	21.2 (3.3)	17.4-27.8
Clobazam	0			9	0.52 (0.5)	0.18-1.9
Clonazepam	0			4	0.05 (0.03)	0.02-0.08
Nitrazepam	0			2	0.58 (0.14)	0.44-0.72
Vigabatrin	3	50.7 (21.9)	32.6-75.0	21	42.0 (12.6)	22.7-75.0
Phenobarbital	2	9.2 (6.7)	4.4-13.9	3	6.8 (6.3)	2.0-13.9
Oxcarbazepine	5	33.5 (14.6)	11.8-48.7	9	31.8 (12.1)	11.8-48.7

DMDs are means (SD).

Note: 46 children were on polytherapy. Rescue medication was not included in the study.

Table 6.4 Distribution of number of children over prescribed DMD/mean DMD ratios and relation with number of AEDs

ratio	All N=115	Monotherapy N=69	Polytherapy N=46
0.01-0.33	0	0	0
0.34-0.66	16	15	1
0.67-1.00	25	24	1
1.01-1.33	20	18	2
1.34-1.66	10	8	2
1.67-2.00	11	3	8
2.01-2.33	6	1	5
2.34-2.66	8	0	8
2.67-3.00	6	0	6
3.01-3.33	6	0	6
3.34-3.66	4	0	4
3.67-4.00	0	0	0
4.01-4.33	0	0	0
4.34-4.66	2	0	2
>5.00	1	0	1

DMD, daily maintenance dosage (in mg/kg).

Table 6.5 Comparisons of scores on the HASES between groups (Mann Whitney U test)

	N	Median	p
girls	54	26	0.56
boys	61	25	
monotherapy	69	25	0.16
polytherapy	46	26.5	
normal intellect	68	26	0.95
mental retardation	47	25	
seizure-free >3 months	26	25	0.32
not seizure-free	89	26	
>90 days unchanged AED	61	25.5	0.85
New AED/increased dose	54	26	

HASES, The Hague Side-Effects scale

Table 6.6 Correlation of score on the HASES with clinical variables (Spearman r, N = 115)

	r	p
Prescribed DMD/mean DMD (monotherapy)	-0.11	0.38
Prescribed DMD/mean DMD (all children)	0.12	0.21
Age	-0.05	0.56
Duration of epilepsy	0.17	0.08
Neurologists' severity of SE score*	0.18	0.12

HASES, The Hague Side-Effects scale; SE, side-effects; DMD, daily maintenance dosage of an antiepileptic drug (in mg/kg). * On a 10-point Visual Analogue Scale.

7 DISABILITY DUE TO RESTRICTIONS IN CHILDHOOD EPILEPSY.

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7.0 SUMMARY

Parents and doctors impose restrictions on children with epilepsy to avoid seizure-related injuries. We intended to quantify disability due to such restrictions by using a newly developed parent-completed 10-item scale (The Hague Restrictions in Childhood Epilepsy scale, HARCES). Parents reported disability on at least one item of the HARCES in 83% of 122 children with epilepsy and a remission from seizures for less than one year. Psychometric analysis of the scale's reliability demonstrated good internal consistency and retest stability. Its validity was supported by the association between HARCES scores and the physicians' advice to impose restrictions. We found no substantial association with such variables as seizure type, short-term remission, or seizure activity. These findings suggest that in children with recurrent seizures, restrictions were probably not optimally adapted to seizure-related risks. A repeat test after one year showed that a seizure remission of more than one year substantially reduced restrictions, which is probably associated with an improvement in quality of life.

7.1 INTRODUCTION

Parents impose restrictions on their children with epilepsy to reduce the risk of seizure-related injuries and they are often adviced to do so by the treating physician. There is no doubt that such restrictions can adversely influence the development of children with epilepsy[109]. Clearly, for a child to lead a life as normal as possible, the 'pros and cons' of restrictions should be carefully balanced. The optimal balance, however, is hard to find, if only because little is known about the specific risks run by children with various forms of epilepsy and concomitant disorders. Because restrictions limit the child's ability to perform activities of daily life (ADL) in the manner or within the range considered normal for the child, they may cause disabilities as defined by the World Health Organization (WHO)[122] -see Table 7.1 for definitions.

Disabilities in children with epilepsy can sometimes be related to impairments (see Table 7.1) e.g. mental retardation or cerebral palsy, but most children with epilepsy have no such impairments. Sillanpää [99] reported that children with epilepsy had more disabilities than a control group. Disability was associated with impairments due to neurological comorbidity. For children without such impairments the difference from the control group in overall occurrence of disabilities was not significant. In the same study, however, all families subjectively experienced their child as disabled. We were interested to learn more about the relationship between the epilepsy itself and disability in children.

We developed a scale to quantify parent-perceived disability due to restrictions in childhood epilepsy and explored its association with various clinical variables, which we selected because we assumed they were associated with seizure-related risks.

7.2 METHODS

7.2.1 Content

We developed the Hague Restrictions in Childhood Epilepsy Scale (HARCES) in the following steps. First of all, 35 parents of children with epilepsy were asked to list the daily life activities which were limited by their child's epilepsy. Parents were instructed to focus on disabilities caused by the epilepsy, and to discount disabilities caused by other factors, such as mental retardation or cerebral palsy. A 10-item scale was developed, based on the parents' suggestions and a review of items by the participating neurologists. It was felt that most of the suggested items pertained to restrictions to avoid seizure-related injuries or other adverse

effects of seizures. Some items (addressing specific precautions and activities like swimming, riding a bicycle or physical excercise) were considered to be quite specific to epilepsy, other items seemed applicable to other childhood disorders as well (e.g. restrictions against 'stay[ing] the night with friends or relatives').

This 10-item scale included two global items: one for the amount of extra supervision needed and one for special precautions taken (such as wearing a helmet or special bathing cap), and addressed eight specific activities of daily life. The full scale is listed in Table 7.2. Each item has four adjectival response categories providing a score of 1 (most favourable) to 4 (most unfavourable) points per item. The HARCES' total score ranges from 10 (no disabilities) to 40 (most severe disabilities).

7.2.2 Patients and parents

Children and their parents were recruited from the outpatient populations of the departments of child neurology of two hospitals in The Hague (a children's hospital and a general hospital) and the University Hospitals of Rotterdam, Leiden and Utrecht.

We selected children aged 4 to 16 years with a diagnosis of epilepsy who had suffered at least one seizure in the previous year. Physicians were asked to recruit parents with sufficient Dutch reading skills to complete a questionnaire. Consequently, most first-generation immigrant parents, whose children were eligible, were excluded. Parents completed a mailed questionnaire at home. The questionnaire included the HARCES scale, the Hague Seizure Severity scale[26], and single items addressing duration of remission, estimated likelihood of a seizure occurring in the next month, patterns of timing and predictability of seizures, and parental level of concern about the child's epilepsy. All questions referred to the situation in the preceding three months.

The medical records of all patients were reviewed for information on the duration of epilepsy, treatment and compliance, mental retardation or cerebral palsy, and educational level (five categories of schools reflecting different levels of intellectual ability were used, ranging from normal schools to day-care centres for severely retarded children). The child's regular neurologist was asked if restrictions had been advised and to classify seizures and epilepsy according to the current ILAE classifications[28,29].

One hundred and twenty-four (124) parents were asked to complete the scale and the additional questionnaire, including the 35 parents who had participated in the pilot phase. The 87 parents of the children who had not been involved in the pilot testing phase, were sent a second questionnaire after one year, which was identical to the first and thus allowed for a repeat test comparison.

7.2.3 Psychometric analysis of the scale

Psychometric analysis included item-analysis, assessment of internal consistency and retest stability. We computed corrected item-total correlations (CITCs) and frequency distributions of answers. Crohnbach's alpha was computed as a measure of the scales' internal consistency. A scale has sufficient internal consistency for research purposes, when alpha is at least 0.8[108]. Furthermore, test-retest stability was assessed. Of 22 consecutive parents, 18 responded to an invitation to complete a repeat questionnaire 14 days after they had completed the first.

7.2.4 Statistical analysis

Because HARCES' scores were not normally distributed, standard non-parametric statistical methods were used. A significance level of $p < 0.01$ was chosen to reduce the chance of a type I error because multiple comparisons were made. Spearman's r_S was used as a measure of correlation. The Mann Whitney U test or Kruskal-Wallis one-way analysis of variance (with correction for ties) were used to compare group differences. To analyze differences between repeated measures, the Wilcoxon matched-pairs signed-ranks test was used.

7.3 RESULTS

Of 124 parents, 122 (98%) returned the questionnaire. Overall availability of data was excellent, and parents had no serious problems when completing the questionnaire.

7.3.1 Psychometric analysis of the HARCES

CITC's ranged from 0.44 to 0.82 and items produced affirmative responses in 25% (playing indoors) to 65% (swimming) (see Table 7.2 for a complete listing of responses). Alpha of the scale was 0.89. Retest r_S after 14 days was 0.93 N=18).

Figure 7.1 (on the next page) shows the skewed distribution of the scores. The median score was 16.0 and the scores ranged from 10 (in 21 children, reflecting no disability) to 35 (in two children, reflecting severe disability). Hence, in 101 of 122 (83%) children parents reported disability.

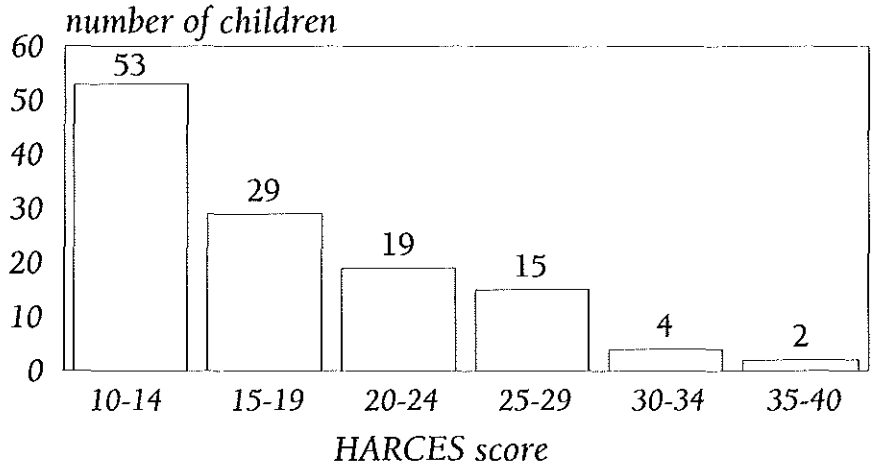

Figure 7.1. Distribution of score frequencies on the HARCES in 122 children. Scale range: 10 (least severe) to 40 (most severe score possible).

7.3.2 HARCES score and clinical variables

The majority of children included had a long history of epilepsy without remission and only 20 children had had epilepsy for less than one year (see Table 7.3 for demography and clinical variables). Only a few were not taking AEDs and more than one third were receiving polytherapy. Only two children were judged non-compliant with the prescibed AED regimen.

The results of a univariate analysis of the association between the score and clinical variables are shown in Table 7.4. Two factors were significantly associated with the disability score. When the neurologist had advised imposing restrictions, the median score was higher than when this was not advised (median 18 vs 13, p <0.001). Parent-estimated likelihood of a seizure occurring in the next months was significantly, but not very substantially, associated with the score (r_S= 0.28, p=0.002). The correlation between 'advice' and 'likelihood of seizure' was also not very substantial (r_S= 0.23, p=0.035). No significant influence was found for any of the other clinical variables. The difference in HARCES score between children with seizures for less than one year and more than one year was not significant (p=0.77).

The parents' own judgement of their 'level of concern about their child's epilepsy' was significantly correlated with the HARCES score (r_S= 0.42, p<0.001).

7.3.3 Repeated HARCES after one year

Of the 87 children selected for a repeat test after one year, one child had died, in one child the diagnosis of epilepsy had been rejected, and three were lost to follow-up. Thus, 82 parents were asked to complete a second questionnaire, and 78 (95%) responded. At the time of the second questionnaire, 51 children had suffered recurrent seizures without remission, 13 had achieved a remission between three months and one year and 14 had achieved a remission of > one year.

Overall, the correlation between the first and second HARCES score was high (r_S =0.75). There was no trend towards a lower or higher score after one year (Wilcoxon matched-pairs signed-ranks test, p=0.76; 27 repeat scores were higher, 25 were lower and 26 were equal). However, median scores on the HARCES were lower for children who had achieved a period of remission from seizures (> one year remission: median 11.5; remission > 3 months - 1 year: median 14; no remission: median 20, Kruskal-Wallis ANOVA, X^2=11.7, p=0.003).

7.4 DISCUSSION

Our study demonstrated parent-reported disability due to restrictions in 83% of 122 children with epilepsy and a remission of less than one year. The fact that all children were attending outpatient child neurology clinics, does not suggest that they were suffering from unusually severe epilepsies. In the Netherlands, children with epilepsy are not likely to be treated by a general practitioner. However, our sample included many children with epilepsy and a poor prognosis to achieve a complete remission within a short period, and is, therefore, representative only of a minority of a population-based sample of new onset epilepsies. Nevertheless, clinicians cannot predict the prognosis for quick and complete remission for most children with new onset epilepsy with great confidence. They will advice imposing restrictions on most of them, when they perceive a substantial risk of seizure-related injuries. In fact, we have not found a significant difference in HARCES scores between children with a history of less than and more than one year. To address the influence of a remission of more than one year, we performed a follow-up study.

The HARCES scale's reliability analysis demonstrated good internal consistency and retest-stability. Its validity was supported by its association with the physicians' advice to impose restrictions and lack of association with presence or absence of permanent impairments like mental retardation and cerebral palsy. These are well-recognized causes of disability which we did not intend to address with the HARCES.

The neurologists had advised imposing at least some restrictions in about two-thirds of the children. In these children, the median score on the HARCES was significantly higher than the median score of the remaining children. In our opinion, this finding emphasizes the responsibility of doctors when they counsel the parents about restrictions. The precise nature of the advise given, however, was not recorded; nor were the grounds on which the clinician based the advice.

From a clinical point of view, restrictions imposed on children with epilepsy should relate to a child's individual risk profile. A child will be more at risk of getting injured due to a seizure when seizures are frequent, severe or unpredictable. Unfortunately, little is known about the specific risks associated with such clinical variables or the influence of age and impairments on seizure-related risks.

Epidemiological studies assessing the risks of seizures in a population of children with epilepsy are rare. Beghi *et al.*[17] reported no difference for everyday life risks between patients with epilepsy aged between 5 and 68 years and healthy controls. In multi-handicapped adults with epilepsy closely observed in nursing homes during 13 months, seizure related injuries were rare and mild, serious injuries occurred in 0,09% of seizures and were related to atonic and generalized tonic-clonic (GTC) seizures[79]. In children over 5 years of age with epilepsy, drowning accidents occurred more often than in the general population[34]. Closer supervision may explain the lack of difference that was found in the frequency of submersion injuries in under 5-year-olds with and without epilepsy.

Despite the lack of specific risk profiles, most authors [4,41,56,85,106,109] agree about global guidelines of councelling about restrictions in childhood epilepsy. Activities for which restrictions are often advised are bathing, swimming, climbing and riding a bicycle. Everyday life at home should not be restricted, except for children with especially dangerous types of seizures[4]. Participation in sports and physical exercise is generally not discouraged. Parents must set the standard of acceptable risk and make their own judgements about restrictions[106]. Few authors indicate how long a period of remission would be sufficient to reduce or totally discard previously imposed restrictions. Some have suggested a remission of at least two months for low risk activities such as riding a bicycle, and of two years for high risk activities [109]. However, children are unlikely to perform high risk activities, such as driving a car or risky sports, anyway.

7.4.1 HARCES and clinical variables

Although short-term remission (between three and twelve months) made no significant difference on the HARCES score, a remission of > one year was associated with a lower median score. These data suggest that parents and doctors

awaited a long period of remission before restrictions were discarded. They support that 'one year remission' is a relevant measure of outcome in clinical studies of childhood epilepsy, probably associated with an improvement in the childrens quality of life. The parents' (subjective) perception of the likelihood of a seizure occurring in the next month was also significantly associated with the score on the HARCES, but the association was not very strong (r_S 0.28). We found no significant relationship between other a priori selected clinical variables and the HARCES score.

Overall, differences in median HARCES score between seizure types were not significant, although the highest median score was found for atonic seizures. The risk of seizure-related injuries associated with such seizure types as absences, simple and complex partial seizures is probably much smaller than the risk associated with GTC or atonic seizures [79]. The children with absences (without GTC seizures) obtained a median score on the HARCES which came remarkably close to the median score of children with GTC seizures. It is not within our competence to judge whether this points to overprotection of children with absences, although some of these children, when they become adults, may state that their parents have overprotected them[86]. We have not used seizure frequency as a variable in our study, because it is closely associated with seizure type: especially absences come in very high frequencies. However, in a study of children with epilepsy Austin *et al.*[11] found that a score reflecting participation in social activities did not correlate with seizure frequency.

It has been suggested that the age of the child[45] and presence of impairments[31,99] may influence the necessity of restrictions. It is possible that young or severely retarded children are closely supervised anyway and more limited in their daily activities, and that therefore the impact of epilepsy is smaller in these children. We have not found an association between age or impairments and the HARCES score. We have deliberately focused on disability caused by restrictions and not due to impairments.

We found a significant correlation with an item addressing 'level of concern', which at least suggests that further studies addressing the association between psychosocial variables and restrictions as measured using the HARCES may be fruitful. It is possible that the severity and nature of restrictions to some extent reflects the parents' anxiety or tendency to overprotect their children. Furthermore, parents may impose restrictions simply because their child has a disorder, regardless of disease-specific risks. In a study by Austin *et al.*[11] social activities' scores did not differ significantly between children with asthma and epilepsy. An extensive discussion of the psychosocial consequences of childhood epilepsy for the child and the family is beyond the scope of the present paper.

7.4.2 Suggested use of the HARCES

In addition to the lack of knowledge about the risks run by children with epilepsy, there is little information available about the efficacy of imposed restrictions in preventing injuries or death, or about the child's compliance with imposed restrictions. Nevertheless, doctors advise imposing restrictions in most cases and in our study this advice was shown to have a significant influence on the parents. Counselling about restrictions to impose on children with epilepsy should probably be repeated at regular intervals in any child with epilepsy, as during the course of treatment symptoms may change or remission may be achieved. The HARCES can be useful to help optimize the balance between risks and overprotection. At all times clinicians must be aware that parents may find themselves in a 'catch 22' situation[123] and should never be accused of overprotection or negligence.

We suggest the use of the HARCES as a measure of quality of life in studies of outcome in childhood epilepsy. We have developed similar subjective parent-completed scales addressing seizure severity and severity of side-effects[26]. In our opinion these scales address three important issues in the physical domain of quality of life. There is increasing awareness that such measures of quality of life may contribute to a more differentiated outcome assessment in (childhood) epilepsy [12,33,35]. Translated versions of the scales for severity of seizures, side-effects and restrictions are currently being validated in a United States population, including a comparison between the parents' and childrens perceptions[83]. A preliminary analysis suggested that children felt less restricted than their parents felt they were restricting them.

Acknowledgements

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Table 7.1 Definitions used in the study

Impairment: Any loss or abnormality of psychological, physiological or anatomical structure or function.

Disability: Any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being.

Handicap: A disadvantage for a given individual, resulting from an impairment or a disability, that limits or prevents the fulfilment of a role that is normal (depending on age, sex, social and cultural factors) for that individual.

World Health Organization (1980).[122]

Table 7.2 The HARCES and response percentages in 122 children

The following questions are about the restrictions placed on your child because of the epilepsy. If, for example, your child can ride a bicycle, but is not allowed to, because of the chance of a seizure, we call it a restriction resulting from the epilepsy. If your child can't ride a bike because of some other reason, (eg. being too small, or having a handicap), it does not count as such.

1. How much extra supervision is needed in your child's daily activities?

a. a lot	3
b. some	12
c. a little	40
d. none	44

2. Does your child require special precautions in daily activities? *(like wearing a helmet)*

a. always	6
b. usually	5
c. sometimes	18
d. never	71

3. Does the epilepsy influence the freedom of your child to play in the house? *(freedom means: the ability to do things in the normal way of a child without epilepsy)*

a. a lot	2
b. some	4
c. a little	20
d. not at all	75

4. Does the epilepsy influence the freedom of your child to play outside?

a. a lot	4
b. some	12
c. a little	30
d. not at all	55

5. Does the epilepsy influence the freedom of your child to go swimming?

a. a lot	20
b. some	22
c. a little	23
d. not at all	35

6. Does the epilepsy influence the freedom of your child to participate in sports activities (excluding swimming)?

a. a lot	5
b. some	8
c. a little	31
d. not at all	56

7. Does the epilepsy influence the freedom of your child in traffic (like riding a bicycle)?

a. a lot	12
b. some	16
c. a little	19
d. not at all	53

8. Does the epilepsy influence the freedom of your child to stay elsewhere overnight? *(with friends or family)*

a. a lot	10
b. some	17
c. a little	23
d. not at all	50

9. Does the epilepsy influence the freedom of your child to go to parties?

a. a lot	3
b. some	11
c. a little	25
d. not at all	62

10. Does the epilepsy influence the freedom of your child to participate in physical education?

a. a lot	10
b. some	8
c. a little	33
d. not at all	49

Table 7.3 Demographic and clinical variables of 122 children

Mean age (SD)	10,1 (3,3) years (range 4-16 years)
Sex	65 (53,3%) boys
Mean duration of epilepsy (SD)	4,6 (3,8) years
Epilepsy classification	*localization-related* - idiopathic with age-related onset: 16 (13%) - symptomatic: 48 (39%) *generalized* - idiopathic with age-related onset: 27 (22%) - symptomatic: 23 (19%) *unclassified*: 8 (7%)
AED treatment	no AED: 7 (6%) 1 AED: 69 (57%) >1 AEDs: 46 (38%)
Mental retardation	48 (39%)
Other impairments	14 (12%)

SD=Standard Deviation. AED= antiepileptic drug.
Mental retardation was based on schooling level and was sometimes accompanied by other impairments. 'Other impairments' refers to children without mental retardation, in most cases cerebral palsy.

Table 7.4 Score on the HARCES: relation with clinical data in 122 children.

Variable		Test result	Significance (P)
Clinical data:			
Seizure type*		X^2= 5,00	0,29*
simple partial (n=17)	median=12,5		
absences (n=18)	median=14		
complex partial (n=35)	median=17		
generalized tonic-clonic (n=34)	median=16		
atonic (n=13)	median=19		
Duration of epilepsy		r_S= 0,18	0,05*
Sex		Z=-0,61	0,54@
boys (n=65)	median=15		
girls (n=57)	median=17		
Age		r_S=-0,03	0,74*
Neurologic impairments		Z=-0,24	0,81@
yes (n=58)	median=16		
no (n=64)	median=15		
Schooling level'		r_S=-0,05	0,55*
Restrictions advised by neurologist		Z=-3,55	0,0004@
no (n=39)	median=13		
yes (n=79)	median=18		
Parent questionnaire:			
Predictability of seizures$			
aura, useful as warning signal		r_S=0,01	0,90*
provoking factors (watching TV, lack of sleep)		r_S=0,08	0,44*
timing at fixed part of day or night		r_S=-0,08	0,47*
clustering of seizures		r_S=-0,08	0,48*
Seizure control			
remission between 3 and 12 months		Z=-1,36	0,17@
yes (n=28)	median=15		
no (n=94)	median=16.5		
likelihood of a seizure in next month`		r_S=0,28	0,002*
Perceived seizure severity (scale)		r_S=0,16	0,13*

* Most bothersome seizure type classified in 117 children (seizures were unclassified in 5 children).

* Kruskal-Wallis analysis of variance with correction for ties.

' Spearman Rank Correlation (r_S).

@ Mann-Whitney U Test.

' Five categories of schools, reflecting intellectual ability.

` Single items with four subjective answering categories.

8 SUMMARY AND CONCLUSION

A brief summary of chapters 2-7 will be presented here, more extensive summaries can be found at the beginning of each chapter. Some concluding remarks are made, with suggestions for further studies.

Chapter 2 described a study based on the material of the Dutch Study of Epilepsy in Childhood (DSEC), following 494 children with newly developed epilepsy. It addressed the treatment strategies adopted by the participating child neurologists. In this cohort, two years after inclusion, 17% of the children with new onset epilepsy were not receiving treatment with AEDs. The impact of seizures in these children was probably limited and did not outweigh the possible adverse effects of treatment with AEDs. Treatment was initially withheld in 29% of the cohort; hence, in about half the children this 'wait-and-see' policy seems to have failed during the follow-up period. After two years, the first AED regimen had not provided acceptable control of seizures or had caused unacceptable side-effects in 40% of the children. Finally, about 10% had not achieved a substantial remission from seizures. We noted that in 15 of these 50 children who suffered recurrent seizures despite treatment with AEDs, the neurologist indicated that 'acceptable control' had been achieved.

These findings raised at least two questions: 1. Who judged whether the impact of seizures was acceptable or not, and, if not, who judged whether (more or different) AEDs were indicated to suppress seizures: the child, the parents or the doctor? 2. What were the motives for considering seizures and side-effects to be sometimes acceptable and sometimes not? The material of the DSEC, which included traditional outcome variables only, did not provide answers to these questions. They confirmed that a more complete approach towards outcome assessment in childhood epilepsy, including measures of subjective disease severity, may be rewarding. Clearly, it is important to monitor more than 'objective' variables like seizure frequency or duration of remission, or clinically intolerable side-effects. Chapters 3 to 7 describe our efforts to develop tools for this purpose.

In *chapter* 3, we reviewed scales which were developed by others to improve outcome assessment in epilepsy. In their present form, these scales for adults with epilepsy seemed inappropriate for children. Some basic differences in methodology between the scales were discussed. Physical issues, such as 'severity of seizures and side-effects' were identified as neglected areas in quality of life re-

search. We outlined the problems developing similar measures of outcome for children with epilepsy. We explained why we selected the parents as the source of information and not the child itself.

Chapters 4 and 7 describe the development of three scales addressing, respectively,

(1) Seizure severity (the Hague Seizure Severity scale, HASS). We used one of the reviewed scales for adults, the Liverpool Seizure Severity scale [15], as a basis for the development of this scale;
(2) Severity of side-effects of AEDs (the Hague Side-Effects scale, HASES);
(3) Severity of disability due to restrictions to avoid seizure-related injuries in children with epilepsy (the Hague Restrictions in Childhood Epilepsy scale, HARCES).

All three scales were developed using items contributed by neurologists as well as parents. The scales comprise subjective items to be completed by the parents. Because these scales reflect a broad approach towards outcome assessment in childhood epilepsy and because they quantify subjective perceptions rather than objective assessments, they can be classified as quality of life instruments. Nevertheless, they focus on clinical issues and should not be regarded as measures of overall quality of life or psychosocial outcome. A description of the psychometric analysis of the HASS and the HASES can be found in chapter 4, and of the HARCES in chapter 7, respectively. All three scales were reliable in terms of retest stability and internal consistency. Further studies included an assessment of the validity of these scales, especially by comparing them with clinical data.

In *chapters 5 and 6*, respectively, the HASS and the HASES are compared with clinical data, including the clinicians' global impressions of the severity of seizures and side-effects. Ratings of the parents and neurologists were not substantially correlated. Scores on the HASS were significantly different between various seizure types, but within one seizure type considerable variation in reported seizure severity was noted. Scores on the HASES did not differ significantly between children taking medication for epilepsy or asthma. We noted no difference in the severity of side-effects as addressed in the HASES between children receiving mono- or polytherapy, nor was there a correlation between dosage of AEDs and score on the HASES. We have not been able to confirm the validity of the HASES as a measure of side-effects, possibly due to limitations in our study design. The practical importance of the parents subjective assessments of side-effects, however, would seem to justify further controlled studies using the HASES.

In *chapter 7*, the HARCES is compared with clinical data. We describe a lack of influence of various clinical variables on restrictions as addressed in the

HARCES. Only a remission from seizures of more than one year was associated with a significant reduction in HARCES score.

One of the core messages of the chapters 5-7 is that these three scales add new information to traditional clinical data as well as the clinician's global impressions. Trials comparing AEDs typically yield equivocal results, and a broader assessment of outcome, e.g. by using the present scales, could be helpful. The usefulness of these scales for trials and clinical practice, however, still has to be established.

We need to assess sensitivity to (clinically relevant) change. In a follow-up study of children with recurrent seizures, we found no significant difference in seizure severity after one more year of therapy.[115] It is more likely that this finding points to the intractable nature of the seizures in this sample, rather than to insensitivity to change of the HASS. For this purpose, use of the scales in clinicals trials is being planned.

Furthermore, we are hopeful that our scales will prove to be useful in guiding or clarifying management decisions in the treatment of children with epilepsy, and, thus, be of help in answering some of the questions raised in Chapter 2. As such, the scales could be of use to clinicians in daily practice. For example, would it be possible to optimize the balance between risks and restrictions for children with epilepsy by using the HARCES as a basis for discussion and follow-up?

Another interesting question is how the parents' perceptions relate to those of their children. This is one of the goals of a study in the USA, which uses a translated version of our scales.[83] A preliminary analysis showed that parents' and childrens' perceptions were highly correlated, although children felt, in fact, less restricted than their parents believed they were restricting them. The second aim of this American study is to validate the English versions of the scales.

At present there is increasing interest in quality of life scales for epilepsy. We have developed the scales described in this thesis hoping that they will be used outside our own institutions. Therefore, we would stimulate initiatives from other researchers to use them. Copies of the scales will be provided on request; an (American) English version is available.

9 SAMENVATTING EN CONCLUSIE

Hieronder wordt een samenvatting gegeven van de volgende hoofdstukken uit dit proefschrift, gevolgd door een korte discussie:
Hoofdstuk 2: Een audit van behandelingsstrategie bij een groep kinderen bij wie de diagnose epilepsie voor het eerst wordt gesteld.
Hoofdstuk 3: Een overzicht van de literatuur met betrekking tot alternatieven voor de traditionele uitkomst-variabelen.
Hoofdstuk 4: De ontwikkeling en psychometrische analyse van schalen voor de 'ernst van aanvallen en bijwerkingen van anti-epileptica' (AEDs).
Hoofdstuk 5: De relatie tussen 'ernst van aanvallen' en diverse klinische variabelen.
Hoofdstuk 6: De relatie tussen 'ernst van bijwerkingen' en diverse klinische variabelen.
Hoofdstuk 7: De ontwikkeling en psychometrische analyse van een schaal voor 'ernst van beperkingen door epilepsie'. De relatie tussen deze schaal en diverse klinische variabelen.

9.1 Hoofdstuk 2: AUDIT VAN BEHANDELING VAN KINDEREPILEPSIE.

Dit hoofdstuk beschrijft de behandeling van epilepsie bij 494 kinderen uit het Zuid-Hollandse Kinderepilepsie Onderzoek (ZHKO). Van dit cohort werd aanvankelijk 29% niet met medicijnen behandeld, en na twee jaar was het percentage onbehandelde kinderen nog 17%. Bij deze kinderen waren de te verwachten gevolgen van de aanvallen dus kennelijk zo gering, dat zij niet opwogen tegen de verwachte bijwerkingen van AEDs. Ongeveer 40% van de kinderen met epilepsie moest stoppen met de medicatie van eerste keus, hetzij omdat de aanvallen onvoldoende werden onderdrukt, hetzij omdat de bijwerkingen onacceptabel waren. Na twee jaar had ca. 10% van de kinderen met medicatie geen langdurige remissie van aanvallen bereikt. Wij vonden aanwijzingen dat bij 15 van deze 50 kinderen zonder substantiële remissie desondanks toch een 'acceptabel' behandelingsresultaat was bereikt. Hiervoor werd een combinatie van 'harde data' (duur van remissie, ontbreken van verdere aanpassing van medicatie) en 'zachte data' (retrospectief oordeel van de neuroloog) nodig geacht.

Wie oordeelde in de praktijk van de studie of aanvallen of bijwerkingen

'acceptabel' waren: de arts, de ouders of het kind? Waarom waren aanvallen of bijwerkingen soms 'acceptabel' en soms niet? Deze vragen benadrukken dat de traditionele, relatief simpele manier waarop de toestand van de patiënt met epilepsie in het ZHKO kaart werd gebracht soms te beperkt is. De rapportage van vrijwel alle trials en audit studies geeft slechts informatie over aanvalsfrequentie (b.v. het aantal dat 50% reductie bereikt in aanvalsfrequentie) of duur van remissie. Informatie over 'acceptabele controle' van aanvallen, of 'acceptabele bijwerkingen' ontbreekt. Een belangrijke reden hiervoor is, dat het ingewikkeld is om zulke subjectieve zaken op een betrouwbare, valide en voor onderzoekers bruikbare wijze te kwantificeren. Toch is er een duidelijke trend in de klinische wetenschap, en zo ook in de epileptologie, om dit wel te proberen. Dit proefschrift geeft in de hoofdstukken 3 -7 een overzicht van de resultaten van een project met als doel om alternatieve uitkomstmaten te ontwikkelen, voor toepassing bij kinderen met (moeilijk behandelbare) epilepsie.

9.2 Hoofdstuk 3: LITERATUUROVERZICHT: Alternatieve uitkomstmaten bij epilepsie.

In de laatste tien jaar zijn er verschillende schalen ontwikkeld om beter in kaart te kunnen brengen wat de effecten zijn van epilepsie op het dagelijks leven. In dit overzicht beperk ik mij tot schalen die zich richten op de fysieke cq klinische gevolgen van epilepsie, met name de aanvallen en de bijwerkingen van medicijnen. De besproken schalen kunnen dus beschouwd worden als klinimetrische instrumenten. Vier schalen zijn in de literatuur goed beschreven: (1) De schalen van de Veterans Administration [32], die zich richten op aanvalsfrequentie en -ernst, respectievelijk bijwerkingen van AEDs. (2) De Chalfont Seizure Severity Scale.[10] (3) De Liverpool Seizure Severity Scale.[15] (4) De Epilepsy Surgery Inventory (ESI) en Quality of Life in Epilepsy (QOLIE) Scale.[116] Deze schalen zijn bedoeld voor epilepsie bij volwassen patiënten. Van deze schalen is de betrouwbaarheid en validiteit onderzocht en is sprake -zij het in beperkte mate- van klinische bruikbaarheid.

Deze schalen verschillen op ten minste twee belangrijke punten: het perspectief (Wie bepaalt de ernst van ziekteverschijnselen?) en de mate van specificiteit voor epilepsie. De schalen genoemd onder 1) en 2) zijn schalen die het perspectief van de dokter kiezen, met name de dokter beslist of iemand ergens last van heeft en hoe zwaar dat telt. Schalen 3) en 4) kiezen het perspectief van de patiënt. Dit is een essentieel verschil: wat dokters vinden van de ernst van ziekte kan sterk afwijken van wat de patiënt vindt. Een belangrijk fundament van 'kwaliteit van leven' onderzoek is, dat men in kaart brengt wat de patiënt zelf

vindt, of probeert dit zo dicht mogelijk te benaderen. Welk perspectief men prefereert zal vooral afhangen van het doel dat men met de schaal voor ogen heeft. Ten aanzien van het verschil in specificiteit kan het volgende worden gesteld: Schalen 1), 2) en 3) bevatten items die men kan opvatten als specifiek betrekking hebbend op epilepsie en de gevolgen daarvan; de schalen genoemd onder 4) bevatte veel items die men kan beschouwen als betrekking hebbend op de algemene gezondheid (generieke items). Generieke schalen hebben het voordeel dat men de gevolgen van verschillende aandoeningen kan vergelijken, maar als nadeel dat soms relevante specifieke gevolgen van een ziekte in zo'n schaal niet aan de orde komen. Epilepsie is bij uitstek een ziekte met veel unieke kenmerken, zodat een specifieke schaal hier belangrijke voordelen biedt.

9.3 Hoofdstukken 4-7: DE ONTWIKKELING VAN DRIE SCHALEN VOOR KINDEREN MET EPILEPSIE.

Ook voor kinderen met epilepsie is er behoefte aan alternatieve uitkomstmaten als aanvulling op de traditionele. In hoofdstuk 3 kwamen wij tot de conclusie dat de epilepsie op de kinderleeftijd zo veel specifieke verschillen met epilepsie bij volwassenen kent, dat men voor onderzoek bij kinderen niet zonder meer gebruik kan maken van de besproken schalen voor volwassen patiënten. Wij besloten tot de ontwikkeling van schalen voor (a) aanvalsernst, (b) ernst van bijwerkingen en (c) ernst van beperkingen door epilepsie. Doel van de schalen was om op gestandaardiseerde wijze het subjectieve oordeel over de epilepsie en de behandeling bij de behandelingsstrategie te kunnen betrekken. Omdat naar onze verwachting in de doelgroep veel kinderen niet in staat zouden zijn om zelf betrouwbare informatie te geven, hebben wij gekozen voor de ouders als bron van informatie. We kozen daarmee voor een opzet die aansloot bij algemene opvattingen over de manier waarop men aspecten van kwaliteit van leven van kinderen in kaart kan brengen. De schalen zijn zo gemaakt, dat het aan de ouders wordt overgelaten om aan te geven of bepaalde verschijnselen zich voordoen en -zo ja- hoe ernstig deze zijn.

Items voor een pilot studie werden zowel door clinici als ouders voorgesteld. De definitieve schalen werden geconstrueerd uit een verzameling van items, na analyse van materiaal uit de pilot studie. Vervolgens werden de schalen getest in een groep van ruim 100 kinderen tussen 4 en 16 jaar, waarvan 3/4 leed aan een moeilijk behandelbare epilepsie. Bijna de helft van deze groep was licht tot zeer ernstig geretardeerd, en een deel van deze kinderen had daarbij nog andere beperkingen. De groep die wordt beschreven in de hoofdstukken 4-7 verschilt dus van de populatie in hoofdstuk 2, waar het kinderen met een recent vastgestelde epilepsie betrof.

9.3.1 Hoofdstuk 4: DE ERNST VAN EPILEPTISCHE AANVALLEN

Aanvalsernst is een belangrijke aanvulling op aanvalsfrequentie: het heeft weinig betekenis om te weten dat een kind 5 aanvallen per maand heeft zonder daarbij over een indicatie van de ernst van de aanvallen te beschikken. Als indicatie voor aanvalsernst dient nu vaak de classificatie van het aanvalstype. Hieraan kleven echter belangrijke nadelen, die zijn besproken in hoofdstuk 3. De door ons ontwikkelde schaal voor aanvalsernst werd gebaseerd op de Liverpool Seizure Severity scale[15], die werd aangepast om beantwoording door de ouders mogelijk te maken en werd aangevuld met nieuwe items afkomstig van neurologen en ouders.

In Appendix 1A is de schaal (the Hague Seizure Severity scale, HASS) integraal opgenomen. De resultaten van psychometrische analyse van de HASS waren kort samengevat als volgt: Aantal items = 13. Laagste (beste) score 13; hoogste (slechtste) 54. Test-hertest betrouwbaarheid: Pearson r= 0.93. Interne consistentie: Crohnbach's alpha= 0.85. Frequentie distributie scores: normale verdeling.

Bij 117 kinderen met epileptische aanvallen vergeleken we de scores op de HASS met diverse klinische gegevens en een globaal oordeel over aanvalsernst door de neuroloog, middels een score op een visueel analoge schaal (VAS) van 1 (minst ernstig) tot 10 (meest ernstig). Zowel de score voor aanvalsernst van de ouders op de HASS als de score van de neuroloog op de VAS, toonde forse variatie binnen een aanvalstype en overlap tussen verschillende aanvalstypen. Scores waren voor beide schalen wel significant verschillend tussen groepen met (a) absences of enkelvoudig partiële aanvallen, (b) complex partiële aanvallen of (c) gegeneraliseerd tonisch-clonische aanvallen. De correlatiecoëfficiënt tussen de scores van de ouders en de neurologen was 0.45 in de groep als geheel, maar was niet groter dan 0.26 per groep met één aanvalstype. Er was geen substantiële correlatie tussen de HASS scores en aanvalsfrequentie, leeftijd, duur van de epilepsie of geslacht. Kinderen op polytherapie en kinderen met retardatie kregen van de neurologen, maar niet van de ouders, een hogere score voor aanvalsernst.

Conclusie: De HASS is een betrouwbare schaal voor het kwantificeren van de ernst van epileptische aanvallen bij kinderen. Hoewel de schaal is gebaseerd op een klinisch concept van aanvalsernst, laat de schaal de ouders veel ruimte om de eigen mening inzake aan- of afwezigheid van verschijnselen en hun ernst weer te geven. De correlatie met een globale score voor aanvalsernst door de neuroloog was zwak. Dit wijst er op, dat het subjectieve oordeel van de ouders een aanvulling is op het oordeel van de neuroloog. Geen van beide opvattingen kan worden aangemerkt als 'waar', in de zin van 'ontdaan van subjectiviteit'. Hierbij kan men overwegen dat ouders het meest frequent getuige zijn van de

aanvallen en de gevolgen hiervan voor hun kind, en dat hun opvattingen wellicht de manier waarop het kind met de aanvallen leert omgaan sterker beïnvloeden dan die van de neuroloog.

9.3.2 Hoofdstuk 5: DE ERNST VAN BIJWERKINGEN

De tweede schaal werd ontwikkeld met de bedoeling om de ernst van 'subjectieve' bijwerkingen te kwantificeren. In de meeste klinische publikaties wordt vooral de aandacht gericht op de positieve effecten van medicatie, en vormen de bijwerkingen een wat onderbelicht geheel, zowel in de 'Methods' als in de 'Results' sectie. Dit geldt met name voor de 'klinisch acceptabele' bijwerkingen, terwijl ouders en kinderen in de praktijk veelvuldig melding maken van bijwerkingen van AEDs. Vaak blijft het hierbij onduidelijk of deze bijwerkingen een causaal verband hebben met de AEDs in kwestie, en is de ernst van de gemelde bijwerkingen moeilijk of niet objectiveerbaar.

De schaal die wij maakten voor het kwantificeren van de ernst van bijwerkingen, the Hague Side Effects scale (HASES), kon niet op een bestaande schaal worden gebaseerd. Wij begonnen met een pilot-schaal, die uitvoerig werd aangepast na een eerste studie bij ca. 40 kinderen. Wij kozen voor 20 frequent gerapporteerde, onderling samenhangende bijwerkingen. In Appendix 1B is de HASES integraal opgenomen. De resultaten van psychometrische analyse van de HASES waren kort samengevat als volgt: Aantal items = 20. Laagste (beste) score 20; hoogste (slechtste) 80. Test-hertest betrouwbaarheid: Pearson r= 0.91. Interne consistentie: Crohnbach's alpha= 0.88. Frequentie distributie scores: scheve verdeling met veel lage en weinig hoge scores.

Bij 115 kinderen die AEDs gebruikten, vergeleken we de scores op de HASES met die van een controlegroep van 25 kinderen die behandeld werden met inhalatie medicatie voor astma (IMA). Voorts bestudeerden we de correlatie met diverse klinische gegevens zoals het aantal AEDs en de dosering, alsmede een globaal oordeel over de ernst van bijwerkingen door de neuroloog op een VAS. Bij 82% van de kinderen op AEDs en 88% van de kinderen op IMA werden één of meer bijwerkingen gerapporteerd. De mediane scores op de HASES waren 26 voor kinderen op AEDs en 22 voor kinderen op IMA (verschil niet significant). Er was geen significant correlatie tussen het oordeel van de ouders en dat van de neuroloog. Wij vonden geen significant verschil in mediane HASES score tussen kinderen op mono- of polytherapie, en geen significante correlatie met de dosering van AEDs. Factoren als leeftijd, geslacht, duur van epilepsie, mentale retardatie, klinische remissie van aanvallen, of recent starten met cq verhogen van de dosis van een AED waren niet substantieel van invloed op de HASES score.

Conclusie: De HASES meet op betrouwbare wijze de prevalentie en ernst van een aantal klachten die de ouders toeschrijven aan de door hun kinderen gebruikte AEDs. De subjectieve bijwerkingen van de medicatie, zoals vastgesteld met de HASES, waren echter niet specifiek voor kinderen op AEDs. We vonden geen aanwijzingen voor een causale relatie tussen AEDs en de gemelde bijwerkingen. De validiteit van deze schaal als maat voor de ernst van bijwerkingen kon dus niet worden bevestigd. Omdat de schaal beoogd opvattingen van de ouders te kwantificeren, kan de validiteit hiermede ook niet worden verworpen. Aangezien deze studie geen blinde en gerandomiseerde opzet kende is het mogelijk dat de negatieve resultaten het gevolg waren van aanpassing van dosis en aantal AEDs aan de tolerantie voor AEDs van het individuele kind. Gelet op het belang in de praktijk van de opvattingen van ouders inzake bijwerkingen, lijkt een gecontroleerde studie met de HASES zeer gewenst.

9.3.2 Hoofdstuk 6: DE ERNST VAN BEPERKINGEN

Een derde schaal werd ontwikkeld om de beperkingen te kwantificeren, die het gevolg zijn van de epilepsie. Zo adviseren clinici soms de ouders van een kind met epileptische aanvallen om het kind niet te laten fietsen of klimmen en om toezicht te houden bij activiteiten zoals zwemmen. Dergelijke beperkingen dienen vooral om schadelijke gevolgen van een aanval te voorkomen. Ze hebben ongetwijfeld ook nadelige neveneffecten, omdat ze de 'normale' activiteiten en zo de 'normale' ontwikkeling van een kind in de weg staan. Ook voor deze schaal zijn wij niet uitgegaan van een reeds bestaande schaal, en werd de inhoud van de schaal vooral bepaald door suggesties van ouders en analyse van gegevens uit een pilotstudie. De schaal richt zich dus op beperkingen die de ouders toepassen, en niet noodzakelijkerwijs op klinisch rationele beperkingen.

In Appendix 1C is de schaal (the Hague Restrictions in Childhood Epilepsy scale, HARCES) integraal opgenomen. De resultaten van psychometrische analyse van de HARCES waren kort samengevat als volgt: Aantal items = 10. Laagste (beste) score 10; hoogste (slechtste) 40. Test-hertest betrouwbaarheid: Pearson r= 0.93. Interne consistentie: Crohnbach's alpha= 0.89. Frequentie distributie scores: scheve verdeling, veel lage en weinig hoge scores.

Bij 122 kinderen met epileptische aanvallen in het voorafgaande jaar, vergeleken we de score op de HARCES met een aantal klinische variabelen. Na één jaar herhaalden we de meting met de HARCES bij 78 opeenvolgende kinderen.

De neuroloog had beperkingen geadviseerd bij 2/3 van de 122 kinderen. Kinderen aan wie een dergelijk advies was gegeven hadden een hogere score op

de HARCES (18 vs 13, p<0.001). Andere klinische en demografische factoren waren niet substantieel geassocieerd met de HARCES score, inclusief factoren als 'remissie van 3 tot 12 maanden', voorspelbaarheid van aanvallen, bijkomende beperkingen door retardatie of verlammingen, leeftijd of aanvalsernst (HASS). Na één jaar waren de mediane scores significant verschillend tussen kinderen met (a) een remissie >1 jaar, (b) remissie tussen 3 en 12 maanden en (c) geen remissie (11,5 vs 14 vs 20, p=0.003). In de groep als geheel waren de scores na één jaar sterk gecorreleerd met de eerste scores (r=0.75).

Conclusie: Wij vonden een significante invloed van het neurologisch advies inzake beperkingen op de activiteiten die in de HARCES aan de orde komen. Een remissie van meer dan één jaar was de enige klinische factor die met een lagere HARCES score was geassocieerd. Het is aannemelijk dat andere -niet onderzochte- factoren, zoals de mate van bezorgdheid van ouders, een belangrijke invloed hadden op het aantal en de ernst van beperkingen die aan kinderen met epilepsie werden opgelegd. De HARCES kan nuttig zijn om deze beperkingen te inventariseren en te bespreken, en voor het verbeteren van de balans tussen beperkingen en het risico op verwondingen of andere complicaties van epileptische aanvallen.

9.4 DISCUSSIE

Om de redenen voor keuzes bij de behandeling van epilepsie goed te begrijpen en de uitkomst van de behandeling optimaal in kaart te brengen, schieten de traditionele parameters tekort. Wij bespraken drie door ons ontwikkelde schalen die kunnen dienen als aanvulling op de traditionele klinische parameters bij onderzoek naar de uitkomst van behandeling van kinderepilepsie. De schalen voldeden aan basale psychometrische eisen voor betrouwbaarheid. De validiteit van deze schalen kwam aan de orde in aanvullende studies, waarbij een vergelijking werd gemaakt met de 'globale klinische indruk' van de neuroloog en met diverse klinische variabelen. Alle drie schalen voegen naar onze mening nieuwe informatie toe aan de bekende klinische parameters. De validiteit van deze informatie kon met name voor de schalen voor aanvalsernst en beperkingen worden onderbouwd. De schaal voor bijwerkingen voldoet in die zin wel aan de verwachting dat hij naar alle waarschijnlijkheid meet wat ouders vinden van bijwerkingen van AEDs, maar we konden niet waarschijnlijk maken dat de gerapporteerde bijwerkingen ook daadwerkelijk in een causale relatie met het gebruik van AEDs stonden.

De schalen werden onderzocht in een populatie waarin kinderen met een therapieresistente epilepsie domineerden. Voor een groep kinderen met een recent begonnen epilepsie zal in ieder geval de HASS vermoedelijk van minder

waarde zijn: De meeste van deze kinderen komen snel in een complete remissie. Wel zou de schaal kunnen dienen om de uitgangspositie van twee of meer groepen met elkaar te vergelijken.

Van geen van de schalen staat vast dat ze voldoende gevoelig zijn voor verandering, hetgeen een belangrijke eis is voor bruikbaarheid bij wetenschappelijk onderzoek. In de groep met persisterende epileptische aanvallen, werd na één jaar de HASS herhaald, en werd geen significant verschil gevonden in aanvalsernst.[115] Het is echter aannemelijk dat deze bevindingen wijzen op de 'onbehandelbaarheid' van de aanvallen bij deze groep kinderen, en niet op ongevoeligheid voor het meten van verandering van de HASS. Derhalve is het van belang de opbrengst van de HASS en de HASES verder te onderzoeken in vergelijkende studies van AEDs met een blinde en gerandomiseerde opzet. Het is met name van belang om na te gaan of de schalen kunnen bijdragen aan het vinden van een klinisch relevant verschil in effectiviteit of bijwerkingen tussen verschillende AEDs. Binnen enkele jaren verwachten wij hierover nadere gegevens te kunnen publiceren.

Op grond van leeftijd en communicatieve vaardigheden kwam zeker de helft van de kinderen in ons onderzoek niet voor zelf-rapportage in aanmerking. Het is uiteraard belangrijk om na te gaan, hoe kinderen die daartoe wel in staat zijn, er zelf over denken. Met een Amerikaanse vertaling van onze schalen, wordt inmiddels getracht om de mening van ouders en kinderen te vergelijken, in een populatie van patiënten uit New York.[83] De voorlopige conclusie van deze studie is, dat ouders en kinderen in hoge mate dezelfde mening zijn toegedaan, alleen schatten kinderen zelf de ernst van hun beperkingen lager in dan hun ouders.

De beperkingen van de traditionele manier om de resultaten van behandeling van epilepsie in kaart te brengen worden steeds meer erkend. De interesse in alternatieve methoden, zoals bechreven in dit proefschrift, neemt toe. Wij hopen dat onze schalen ook door anderen gebruikt zullen worden, en stellen ze om deze reden dan ook beschikbaar aan geïnteresseerde clinici en onderzoekers.

Dit hoofdstuk is deels gebaseerd op een artikel, dat is verschenen in Epilepsie Bulletin 1997;25:46-49.

APPENDIX 1A: HAAGSE SCHAAL VOOR DE ERNST VAN EPILEPTISCHE AANVALLEN (The Hague Seizure Severity scale)

Deze vragen gaan over de aanvallen die Uw kind had in de afgelopen drie maanden. Wilt U per vraag a.u.b. maar één antwoord omcirkelen?

1. Hoe vaak was er bewustzijnsdaling bij de aanvallen?
   a. altijd
   b. meestal
   c. soms
   d. nooit

2. Hoe lang vond u de bewustzijnsdaling dan meestal duren (gerekend vanaf het begin totdat uw kind weer bijkomt)?
   a. zeer lang
   b. lang
   c. kort
   d. zeer kort
   e. niet van toepassing, er was nooit bewustzijnsdaling bij de aanvallen

3. Hoe ernstig waren de aanvallen in het algemeen?
   a. zeer ernstig
   b. matig ernstig
   c. mild
   d. zeer mild

4. Traden er bij de aanvallen schokken of stijfkrampen op in de armen of benen?
   a. altijd
   b. meestal
   c. soms
   d. nooit

5. Hoe lang duurden meestal de schokken of stijfkrampen bij een aanval?
   a. zeer lang
   b. lang
   c. kort
   d. zeer kort
   e. niet van toepassing, geen schokken of stijfkrampen

6. Hoe opvallend waren de verschijnselen van een aanval?
   a. zeer opvallend, iedereen zal een aanval opmerken
   b. matig opvallend, de meeste mensen zullen een aanval wel opmerken
   c. weinig opvallend, de meeste mensen zullen een aanval niet opmerken
   d. niet opvallend, je moet goed opletten om een aanval te zien

7. Hoe vaak was uw kind verward tijdens of direct na een aanval?
   a. altijd
   b. meestal
   c. soms
   d. nooit

8. Hoe vaak plaste uw kind in zijn/haar broek bij een aanval?
   a. altijd
   b. meestal
   c. soms
   d. nooit
   e. onbekend, mijn kind heeft (nog) geen controle over het plassen

9. Hoe vaak beet uw kind tijdens een aanval op zijn/haar tong of wang?
   a. altijd
   b. meestal
   c. soms
   d. nooit

10. Hoe vaak raakte uw kind gewond bij een aanval, met uitzondering van de tongbeet?
    a. altijd
    b. meestal
    c. soms
    d. nooit

11. Was uw kind slaperig nadat de aanval over was?
    (Het maakt niet uit of dit het gevolg was van de aanval of van het eventueel gebruiken noodmedicatie als Stesolid.)
    a. altijd
    b. meestal
    c. soms
    d. nooit

12. Had uw kind na de aanval last van misselijkheid, hoofdpijn en/of spierpijn?
    a. altijd
    b. meestal
    c. soms
    d. nooit
    e. onbekend, mijn kind zou dit niet duidelijk kunnen maken

13. Hoe lang duurde het na de aanval totdat uw kind weer normaal actief kon zijn?
    a. zeer lang
    b. lang
    c. kort
    d. zeer kort of direct na de aanval

Alle items hebben 4 of 5 subjectieve respons-categorieën (b.v. altijd, meestal, soms of nooit). Score per item: 1 punt voor meest gunstige antwoord, tot 5 (vraag 2 en 5) of 4 (alle overige vragen) punten voor meest ongunstige antwoord.

APPENDIX 1B: HAAGSE SCHAAL VOOR BIJWERKINGEN (the Hague Side Effects Scale)

LEEST U A.U.B. EERST DEZE TOELICHTING!

De volgende vragen gaan over bijwerkingen van de medicijnen tegen epilepsie. Als uw kind last heeft van onzekerheid bij het lopen, en u denkt dat dat komt door de medicijnen, noemen we het een bijwerking. Als uw kind moeilijk loopt om een andere reden (bij voorbeeld een handicap of een gebroken been) telt dat niet als bijwerking.

Betekenis van de antwoorden:
a = ernstig
b = matig ernstig
c = mild
d = nee/niet van toepassing/niet te beoordelen i.v.m. handicap

Bemerkte U bij Uw kind in de afgelopen drie maanden de volgende bijwerkingen van de medicijnen tegen epilepsie? Wilt U per vraag a.u.b. maar één antwoord omcirkelen?

1	sufheid, slaperigheid	a. b. c. d.
2	duizeligheid	a. b. c. d.
3	onzekerheid bij lopen	a. b. c. d.
4	vallen	a. b. c. d.
5	misselijkheid	a. b. c. d.
6	moeizame ontlasting	a. b. c. d.
7	diarree	a. b. c. d.
8	beven, trillen	a. b. c. d.
9	moeite met spreken	a. b. c. d.
10	dubbelzien, wazig zien	a. b. c. d.
11	hoofdpijn	a. b. c. d.
12	vermoeidheid	a. b. c. d.
13	vermindering van eetlust	a. b. c. d.
14	depressiviteit	a. b. c. d.
15	druk gedrag, overbewegelijkheid	a. b. c. d.
16	driftbuien, agressie	a. b. c. d.
17	traagheid, loomheid	a. b. c. d.

18	verminderde schoolprestaties	a. b. c. d.
19	concentratiestoornis	a. b. c. d.
20	verstoord gedrag	a. b. c. d.

Als u bij uw kind nog bijwerkingen hebt bemerkt,
die niet zijn genoemd, kunt u die hieronder invullen:

21		a. b. c. d.

Alle items hebben de volgende subjectieve respons-categorieen: ernstig, matig ernstig, mild, nee/niet van toepassing/niet te beoordelen i.v.m. handicap. Score per item: 1 punt voor meest gunstige antwoord, tot 4 punten voor meest ongunstige antwoord.

APPENDIX 1C: HAAGSE SCHAAL VOOR BEPERKINGEN BIJ KINDEREN MET EPILEPSIE (the Hague Restrictions in Childhood Epilepsy Scale)

De volgende vragen gaan over de beperkingen die uw kind heeft door zijn/haar epileptische aanvallen. Wanneer uw kind wel kan fietsen, maar dat niet mag, vanwege de kans op een aanval, noemen we dat een beperking door de epilepsie. Wanneer uw kind niet kan fietsen om een andere reden (bij voorbeeld omdat hij/zij te klein is, of een handicap heeft) telt dat hier niet mee. Wilt U per vraag a.u.b. maar één antwoord omcirkelen?

1. Is er extra toezicht nodig bij de dagelijkse activiteiten van uw kind ivm. de kans op een aanval (de epilepsie)?
   a. zeer veel
   b. veel
   c. weinig
   d. geen

2. Worden er speciale maatregelen getroffen bij de dagelijkse activiteiten van uw kind vanwege de epilepsie (bij voorbeeld dragen van helm, speciale badmuts)?
   a. altijd
   b. meestal
   c. soms
   d. nooit

3. Heeft de epilepsie invloed op de mate van vrijheid die uw kind heeft om binnen (in huis) te spelen?
   a. zeer veel
   b. veel
   c. weinig
   d. geen

4. Heeft de epilepsie invloed op de mate van vrijheid die uw kind heeft om buiten (op straat) te spelen?
   a. zeer veel
   b. veel
   c. weinig
   d. geen

5. Heeft de epilepsie invloed op de mate van vrijheid die uw kind heeft om te zwemmen?

   a. zeer veel
   b. veel
   c. weinig
   d. geen

6. Heeft de epilepsie invloed op de mate van vrijheid die uw kind heeft om te sporten (met uitzondering van zwemmen)?

   a. zeer veel
   b. veel
   c. weinig
   d. geen

7. Heeft de epilepsie invloed op de mate van vrijheid die uw kind heeft om aan het verkeer deel te nemen (bij voorbeeld te gaan fietsen)?

   a. zeer veel
   b. veel
   c. weinig
   d. geen

8. Heeft de epilepsie invloed op de mate van vrijheid die uw kind heeft om te gaan logeren?

   a. zeer veel
   b. veel
   c. weinig
   d. geen

9. Heeft de epilepsie invloed op de mate van vrijheid die uw kind heeft om naar feestjes of partijtjes te gaan?

   a. zeer veel
   b. veel
   c. weinig
   d. geen

10. Heeft de epilepsie invloed op de mate van vrijheid die uw kind heeft om aan de gymles deel te nemen (bij voorbeeld in het wandrek te klimmen)?

a. zeer veel
b. veel
c. weinig
d. geen

Score per item: 1 punt voor meest gunstige antwoord, tot 4 punten voor meest ongunstige antwoord.

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12 LIST OF ABBREVIATIONS

Abs	absence (seizure)
AED	antiepileptic drug
CP	complex partial (seizure)
DSEC	Dutch Study of Epilepsy in Childhood
GTC	generalized tonic-clonic (seizure)
HARCES	The Hague Restrictions in Childhood Epilepsy Scale
HASES	The Hague Side-Effects Scale
HASS	The Hague Seizure Severity Scale
QoL	quality of life
SE	side-effect
SP	simple partial (seizure)
SS	seizure severity
VAS	visual analogue scale

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14 CURRICULUM VITAE

The author was born in Amsterdam on the 28th of January, 1962. From 1973 to 1979 he attended the 'Utrechts Stedelijk Gymnasium'. He studied medicine at the 'Vrije Universiteit' (Free University) of Amsterdam from 1979 to 1986, and received his medical degree cum laude. During his military service he was a resident in neurology at the 'Militair Hospitaal' (Military Hospital) in Utrecht. Subsequently, he was a resident in neurology at the Amsterdam 'Academisch Medisch Centrum' (University Hospital) and the 'Westeinde Ziekenhuis' (Westeinde Hospital) in The Hague. In 1990, he began his formal training in neurology at the 'Westeinde Ziekenhuis' (Head of Department: Dr. J.Th.J. Tans). He was registered as a neurologist in April, 1995. From January to September 1995, he was a full-time researcher supported by the Dutch National Epilepsy Fund and the 'Westeinde Ziekenhuis'. He was a resident in clinical neurophysiology at the 'Westeinde Ziekenhuis' (Head of Department: Dr. A.W. de Weerd) from September 1995 to December 1996. Since January, 1997, the author has been working as a neurologist/clinical neurophysiologist at the 'Ziekenhuis Gooi-Noord', in Blaricum.

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